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Edited by
Tharmalingam Punniyamurthy
and **Anil Kumar**

Transition-Metal-Catalyzed C-H Functionalization of Heterocycles

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Preface

Heterocycles are ubiquitous structural scaffolds in bioactive molecules, functional materials and natural products. The complexity in their structural aspect has ensured humanity with a series of diversified novel compounds, unveiling an array of reactivity and stability. Synthesis and modification of heterocyclic compounds is thus an ever-expanding field in synthetic chemistry. Over the past three decades, transition metal-catalyzed C-H bond functionalization has attracted considerable attention as an atom-economical and sustainable technology for the carbon-carbon and carbon-heteroatom bond formations. This approach has allowed rapid access to a library of functionalized heterocyclic compounds from simple substrates *via* divergent synthetic methodologies. The objective of this book is to focus on the developments in transition metal-catalyzed C-H functionalization of heterocycles. The methods described will allow for unprecedented disconnections in complex heterocyclic molecules. Through its eighteen chapters the reader would get an up-to-date of the C-H bond functionalization developed for a particular type of heterocycle. They are organized according to the type of heterocyclic structural frameworks.

A brief history of C-H activation and the mechanistic aspects of transition metal-catalyzed C-H bond activation reactions is presented in chapter 1.

In the subsequent chapter, the principal focus is on the developments of C-H arylation, alkenylation, alkynylation, alkylation, borylation, silylation and amidation of five-membered heterocycles with a single heteroatom *viz.* pyrroles, furans and thiophenes.

The transition metal-catalyzed C-H functionalization of five-membered heterocycles with two heteroatoms, *viz.* oxazoles, thiazoles, imidazoles, and pyrazoles has been emphasized in chapter 3. Key factors for the regioselectivity and mechanistic details are also demonstrated.

Chapter 4 pertinently focusses on the transition metal-catalyzed site-selective C-H functionalization of benzene core of indoles. The chapter is organized based on the site of functionalization and subdivided based on the type of reactions.

Chapter 5 details the site-selective C-2 and C-3 functionalization of indoles leading to the formation of carbon-carbon and carbon-heteroatom bonds, including arylation, alkenylation, allylation, alkylation, borylation, cyanation, amidation and annulation while the next chapter effectively describes the transition metal-catalyzed site-selective C-7 functionalization of indolines using diverse coupling partners.

The transition metal-catalyzed C-H bond functionalization of benzo-fused azoles with two or more heteroatoms is presented in chapter 7.

In chapter 8, the transition metal-catalyzed direct C(sp^2)-H bond functionalization of pyridine, quinoline, and isoquinoline derivatives is demonstrated in accordance with the mechanism and scope of the methodology.

In chapter 9, an in-depth discussion of the transition metal-catalyzed C-H bond functionalization of diazines and benzodiazines has been conferred. Mechanism of selected reactions and late stage C-H bond olefination of Gefitinib (an anticancer drug) are established. Subsequently, chapter 10 discusses the methods developed for the C-H bond functionalization of chromene derivatives using transition-metal-catalysts, also including some key mechanistic cycles.

In chapter 11, the C-H functionalization of imidazo-fused heterocycles under transition metal-catalysis has been relevantly disclosed along with the generalized mechanism.

Chapter 12 discusses the methodologies of transition metal-catalyzed dehydrogenative annulation of heterocycles leading to generation of fused heterocycles while in chapter 13, the transition metal-catalyzed C(sp^3)-H bond functionalization of saturated heterocycles has been covered at positions remote from the heteroatom.

In chapter 14, the methods for the asymmetric C-H bond functionalization of heterocycles have been discussed wherein, most of the reactions covered proceed through inner-sphere C-H activation mechanisms.

A concise overview of strategies for direct functionalization of nucleobases, including uracil, pyrimidine and purine with alkyl, alkenyl or (hetero)aryl groups is provided in chapter 15.

In chapter 16, different strategies to access C-aryl glycosides by C(sp^2)-H and C(sp^3)-H functionalization under the transition-metal-catalysis has been overviewed.

Synthesis of natural products and pharmaceutical drugs employing late-stage C-H functionalization strategy has been emphasised in chapter 17 whereas late-stage C-H functionalization of bioactive molecules, including marketed pharmaceuticals and agrochemicals, clinical candidates, and natural products using transition-metal-catalysis is described in the last chapter of the book.

The book is intended to be a valuable reference source for graduate students and researchers working in the field of organic synthesis and process development in academia and industry. The chapters written by an outstanding team of international authors will hopefully be an interesting read and meet the demand of all the readers concerned in further development of C-H functionalization reactions in the field of heterocyclic chemistry.

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1

Historical Perspective and Mechanistic Aspects of C–H Bond Functionalization

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1.1 Introduction

The C–H bond is the most common linkage in organic chemistry and, surely not entirely by coincidence, is also one of the least reactive groups. The bonds of carbon to hydrogen are, of course, terminal bonds in any organic molecule. Therefore, they cannot contribute to the complexity of a molecule in the same way as C–O, C–N, or, most importantly, C–C bonds. This terminal nature is shared, for the most part, with bonds to halogens or alkali metals, but (with the exception of C–F bonds) those bonds are generally far more reactive; indeed, in contrast with C–H bonds, bonds of carbon to halogens, and even more so to alkali (and other) metals, are viewed by organic chemists as particularly desirable points of opportunity to create new bonds and increase molecular complexity.

The standard graphical depiction of organic molecules indicates C–H bonds by default, highlighting that the ubiquitous C–H bond is the singular "unfunctional group" of organic chemistry. Thus, the ability to effect transformations of C–H bonds is potentially the most powerful class of reactions in organic chemistry. Yet for most of the history of organic chemistry the selective functionalization of the most common C–H bonds (sp^2 and especially sp^3) was considered a largely unrealistic goal – however desirable it might be – and was the subject of very little active pursuit.

The challenge of functionalizing C–H bonds has been attributed most simplistically to their high bond strength, but this is certainly an incomplete explanation at best. The homolytic bond energy of H–F for example is far greater than that of typical C–H bonds yet no chemist would ever consider H–F to be unreactive. But a high homolytic bond strength combined with very low polarity and the absence of a lone pair of electrons begins to account for their general lack of reactivity. In comparing H–C bonds to other covalent H–element bonds, one observes that cleavage by polar reagents is generally uphill for C–H bonds.

Despite this general tendency to be unreactive, however, there are a fair number of reagents that will readily react with C–H bonds. O_2 is certainly cheap, abundant, and effective in this respect. But this leads to the next great obstacle toward achieving useful C–H bond functionalization: selectivity. The ubiquitous nature of C–H bonds means that there are often multiple, and often very similar, possible sites of initial attack. And if that challenge is somehow addressed, one then faces the unpleasant fact that an initial C–H bond functionalization generally leads to a molecular product with C–H bonds that are both (a) weaker than those of the starting material, and therefore typically more reactive with respect to homolytic cleavage, (b) more polar, and therefore typically more reactive in a heterolytic sense. Thus, even if one successfully and selectively functionalizes a C–H bond, secondary reactions lie waiting to prey upon the initial product.

Thus it is not surprising that for most of the 20th century useful examples of C–H bond functionalization were quite limited. But in part thanks to the groundwork laid at the end of that century in the field of organotransition chemistry, the past few decades have seen an explosion of examples of transition metal chemistry exploited to yield highly valuable and elegant organic transformation. This volume highlights many of the most elegant of such examples. In this introductory chapter we discuss the fertile ground from which they emerged. Our perspective has of course been shaped by that of many

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others in the field, including those put forth in numerous excellent reviews [1]. The diversity of these and other reviews reflects the remarkably interdisciplinary range of approaches and perspectives that have been brought to bear on the inspiring challenge of functionalizing C–H bonds.

1.2 Electrophilic C–H Bond Activation and Concerted Metalation Deprotonation

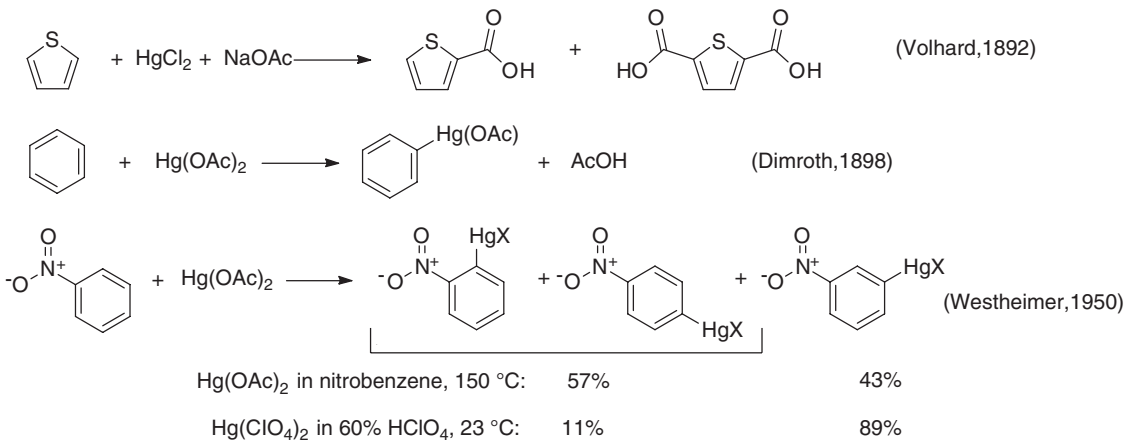
1.2.1 The (Very) Early Years - from Mercury to the Palladium Era

In the modern historiography and taxonomy of C–H bond activation, electrophilic chemistry is often considered the earliest class of mechanisms discovered, whereas concerted metalation deprotonation (CMD) is perhaps the most recent important example. The distinction between these two classes of mechanisms, however, is less clear upon careful consideration. In that context we note that this lack of a clear boundary between various classes of C–H activation extends well beyond this particular example; indeed, blurry lines are more the rule than the exception [2].

Although CMD was first described independently in 2005–2006 by Davies and Macgregor [3], Daugulis [4], Maseras and Echavarren [5], its importance was first particularly recognized and exploited by Fagnou [6]. However, despite being recognized relatively recently, CMD is perhaps the operative pathway for the first selective C–H bond functionalizations ever identified. The term is used to refer to a mechanism in which a C–H bond is associated with a vacant site on an electrophilic metal center (typically an electrophilic, late transition metal) through an initial sigma complex (3-center-2-electron bond). This leads to an acidification of the C–H bond, which enables a basic ligand, most classically a carboxylate, to abstract the hydrogen as proton and often dissociate synchronously with carbon-metal bond formation.

Selective functionalization of "unactivated" C–H bonds by a transition metal can arguably be dated back to 1891 [7]. BASF used fuming sulfuric acid to oxidize naphthalene to phthalic anhydride, a key intermediate for production of synthetic indigo dye [8]. During one batch, Eugene Sapper, the technician on duty, decided to stir the hot mixture of acid and naphthalene with the nearest object available – a mercury thermometer. The thermometer broke and the mercury entered the reactor, where it was quickly taken into solution. However unplanned, this procedural deviation sharply increased the yield of phthalic anhydride and was quickly commercialized by BASF. It also appears to have initiated academic research into reactions of mercury with aromatic compounds.

Thus in 1892, Jacob Volhard, then at Friedrichs-Universität Halle, discovered that aqueous mixtures of mercuric chloride and sodium acetate could mercurate thiophene *alpha* to sulfur [9]. With a bit of heating, both *alpha* positions could be substituted. This reaction, however, only afforded modest conversions, and it led to complex mixtures.



During his habilitation at the University of Tubingen in 1898, Otto Dimroth observed that boiling benzene with mercury(II) acetate resulted in the formation of phenylmercuric acetate [10]. Acetic acid was formed as the byproduct, accounting for the proton displaced from benzene. Phenol displayed even faster kinetics. It reacts with mercuric acetate at ambient temperature in aqueous media with a bias toward *ortho* mercuration. *Ortho* and *para* mercuration

of toluene was also observed [11]. Additionally, thiophene undergoes cleaner mercuration using Dimroth's conditions. Dimroth noted that this was a general electrophilic reaction for aromatic compounds, akin to sulfonation, nitration, and bromination [12].

But even at this early stage of investigation, there are hints that electrophilic aromatic substitution could not be the entire story. That would not account for the *ortho*-selectivity in the mercuration of nitrobenzene [12], which overrides the *meta*-directing tendency of the nitro group. Additionally, in 1907, Reissert reported [13] that the methyl group of nitrotoluene could be mercurated – an sp^3 C–H bond functionalization.

These early examples remained curiosities for some time, and were seldom the preferred way to access organomercury compounds. Indeed, in 189 pages of preparations of organomercury compounds in Goddard and Goddard's 1928 textbook *Organometallic Chemistry* [14], only a handful of preparations involve direct reaction on C–H bonds [15]. And from a theoretical point of view, mechanistic understanding would await the development of physical organic chemistry methods.

Starting in the 1920s, significant research was done on the regiochemistry of mercuration of aromatic systems. In 1921, Dimroth studied the mercuration of nitrobenzene, anisole, and phenetole [16]. Burton, Hammond, and Kenner described the orientation of products obtained from mercuration of *o*-nitrotoluene [17]. Samuel Coffey conducted more detailed studies on the mercuration of nitrobenzene and nitrotoluene [18] and noted deviations from the expected *meta* substitution pattern. Henry and Sharp described the regioselectivity of mercuration of alkylphenols and alkylphenolaldehydes [19]. Frank Whitmore was particularly prolific in this area during his stay at Northwestern University from 1920 to 1929, reporting the mercuration of a suite of aromatic systems [20].

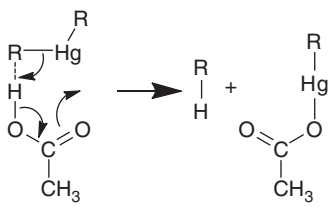
These early experiments did not consider the intimate role of the anion in forming carbon-mercury bonds. That is, it was assumed that mercuric acetate, mercuric perchlorate, or mercuric acid with perchloric acid catalyst all effected the same transformation. The general assumption was indeed that mercuration occurred simply through electrophilic aromatic substitution. A progression of investigations beginning in the 1950s, however, led to the acceptance of a concerted TS with the acetate ligand of $Hg(OAc)_2$ intimately involved in deprotonation concomitant with carbon-mercury bond formation.

In 1950, Frank Westheimer and William Klapproth found that in the mercuration of nitrobenzene with $Hg(OAc)_2$ at 150°C, the *ortho* and *para* products (57%) are formed in preference to the *meta* (43%) product [21]. Mercury perchlorate however conformed to the expected *meta*-orienting patterns of the nitro group. The anion mattered.

After some preliminary studies [22], Herbert C. Brown came into agreement with Westheimer and Klapproth, articulating a difference between $Hg(OAc)_2$ and $Hg(ClO_4)_2$, when he wrote:

> The results indicate that the attacking species in the uncatalyzed [i.e. without perchloric acid] reaction is a less selective agent than that involved in the perchloric acid-catalyzed reaction [23].

Due to the relatively low proportion of *ortho* product in the mercuration of toluene, Brown noted that the TS must be sterically demanding [24]. Winstein and Traylor elaborated on this observation by studying the kinetics of the reverse reaction, acetolysis of diphenylmercury [25], and proposed a cyclic, concerted TS involving proton transfer to the alkyl ligand concomitant with acetate coordination to mercury. Transition states know no direction, and so this arguably represents the first portrayal of a mechanism which aligns with the modern understanding of the concerted metalation-deprotonation.



Kresge and Brennan in 1966 arrived at a similar description of the key TS along the path to carbon-mercury bond formation through kinetic isotope effect (KIE) measurements [26]. In the mercuration of benzene by $Hg(OAc)(ClO_4)$, they observed a KIE of 6.0. They interpreted this to indicate that proton transfer from an intermediate sigma complex is the rate-limiting step of mercuration, and furthermore that the acetate group serves as the proton acceptor and

dissociates in concert. They left open the possibility that proton transfer may occur through a cyclic TS or to the solvent medium.

Attention to kinetic isotope effects led to an interesting connection. In 1968, Davidson and Triggs surveyed a series of transition metal and post-transition metal acetates [27] – mercury (II), thallium (III), lead(IV), gold(III), palladium(II), platinum(II) – in the metalation of benzene. In some cases, metal aryl complexes could be isolated whereas in others they decomposed to biphenyl – an oxidative cross coupling reaction with precipitation of metal. And along the way, they explicitly identified similarities between the mechanisms of C–H activation by mercury(II) acetate and palladium(II) acetate:

> It is clear that there is a strong resemblance between palladation and mercuration especially on account of the large primary isotope effect (k_H/k_D = ca. 5.0). The steady-state treatment, if correct, implies that transfer of a proton from some intermediate containing a benzene molecule and palladium(II) ion is rate-determining.

Strong support for Winstein and Traylor's proposed mechanism eventually arrived in 1980 with the work of Roger Roberts and colleagues [28]. Building on prior low-temperature nuclear magnetic resonance (NMR) studies of arenemercurinium intermediates in sulfur dioxide by George Olah in 1976 [29], they proposed two consecutive pre-equilibria followed by a slow carbon-mercury bond forming step.

$$ArH + HgX_2 \rightleftharpoons [\pi\ \text{complex}] \rightleftharpoons [\sigma\ \text{complex}]^+[X^-] \rightarrow \text{arylmercury product}$$

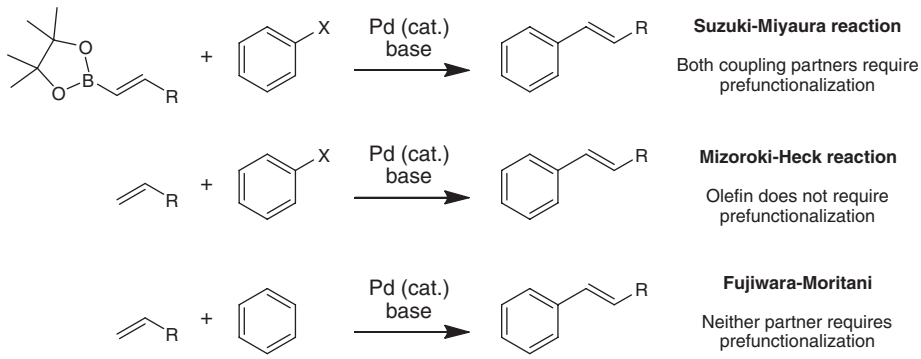
The term sigma complex as used by Roberts refers to a Wheland intermediate, rather than the 3-center-2-electron bonding of metal interactions with C–H bonds. The formation of the π complex is accompanied by a modest entropy loss, and is unaffected by added trifluoroacetate anion in the case of $Hg(TFA)_2$. This argues against ionization as a requirement for reaction. The subsequent steps are associated with a large decrease in entropy to reach the key TS (−20.3 eu±3.0 eu and −31.8 eu±1.9 eu for benzene and toluene, respectively) with rigid geometric requirements. They additionally observed a large primary KIE (k_H/k_D) of approximately 6 and 7 for benzene and toluene, respectively – indicating rate-limiting proton transfer in the TS (which they concluded was the breakdown of a sigma complex). Hammett analysis indicated a modest buildup of charge in the TS. These factors led them to question whether a discrete sigma complex need be invoked. Instead, the experimental evidence all seemed to agree with the cyclic TSe described by Winstein and Traylor, which resembles the current definitional model of concerted metalation deprotonation.

In revisiting these experiments, it's difficult if not impossible to completely separate concerted metalation deprotonation from proton transfer to solvent, or proton transfer via solvent shuttling. These minor differences in the pathway of proton transfer span either side of the definition of concerted metalation deprotonation and electrophilic insertion. As a credit to the researchers who developed this model, none asserted one pathway (intramolecular versus intermolecular proton transfer) over the other – instead, they left open the possibility for both. Likewise, this work preceded the direct observation of agostic bonding, non-classical dihydrogen complexes, and C–H sigma complexes. These are species that are now recognized as preliminary metal-substrate interactions that are central to C–H activation.

1.2.2 Modern Concerted Metalation Deprotonation

The use of mercury reagents is no longer preferred, and in most cases has been superseded by superior methods (with less toxic reagents), and in particular those based on palladium. Early work in cross-coupling, including by Richard Heck [30], utilized arylmercury salts, but the same cross-couplings can be accomplished using organozinc, organomagnesium, and organotin (albeit still toxic) reagents. Organoboron reagents have become particularly preferred with the advance of catalytic C–H borylation methodology. Direct arylation strategies – with transition metals other than mercury – are being heavily researched to eliminate the need for pre-functionalized coupling partners, with a focus on eliminating the organometallic coupling partner. In some instances, the electrophile can be replaced as well, leading to the concept of dehydrogenative cross-coupling [31].

The archetypical dehydrogenative cross-coupling, and certainly the most influential work in concerted metalation deprotonation, is the Fujiwara-Moritani reaction [32]. This is the palladium(II) carboxylate-catalyzed hydroarylation of alkenes followed by β-hydride elimination to form styrene and stilbene derivatives.



The reaction was discovered by Yuzo Fujiwara in 1967, while completing his doctorate at Osaka University in the group of Ichiro Moritani, during the course of studies on the stereochemistry of nucleophilic attack on palladium olefin complexes [33]. In the initial example, the complex (di-μ-chloro*bis*(styrene)dipalladium(II)) was treated with acetic acid in benzene, leading to *trans*-stilbene formation and *alpha* phenethyl acetate. Their early description of this process appears to have been influenced by prior work on nucleophilic addition and oxidation of palladium olefin complexes [32a]. Whereas the key role of the acetate anion was quickly appreciated in this oxidative cross-coupling [32c], the connection to the emerging mechanistic understanding of the role of acetate in mercuration may not have been recognized right away.

The substrate scope of the Fujiwara-Moritani reaction is fairly broad [34] and it is generally conducted at moderate temperatures (80–110°C). Yields tend to be modest, <50%, and side reactions (alkene dimerization, acetoxylation) also occur. Monosubstituted and disubstituted olefins, and even ethylene can be used [32c]. Electron-deficient alkenes such as acrylonitrile, methyl acrylate, and acrolein are tolerated [35]. Benzene, toluene, xylenes, naphthalene, furan, thiophene, selenophene, and ferrocene [35, 36] are all viable aromatic coupling partners. Anisole, chlorobenzene, and nitrobenzene may also be used [37] and, as in the case of mercuration, the regioselectivity of substitution is not as sensitive to substituent directing effects as conventional electrophilic aromatic substitution reactions. On this basis, Fujiwara and colleagues considered the possible involvement of palladium(II) aryl complexes as intermediates. They further identified a first-order dependence on each of the components of the reaction – the olefin, palladium(II) acetate, and the aromatic ring. With the benefit of hindsight, this would align with the models developed by Olah and Roberts for mercuration: initial reversible formation of a palladium(II) aryl complex (direct arylation) followed by rate-limiting olefin insertion. But as it turns out, direct palladation of arenes using palladium(II) acetate exists on a continuum of reactivity between classical depictions of electrophilic aromatic substitution and concerted metalation deprotonation. Metalation may occur through a mechanism similar to electrophilic aromatic substitution – with nucleophilic attack on an electrophilic metal center to form a Wheland intermediate. But with electron-deficient arenes and with relatively acidic protons, proton transfer becomes rate-limiting. In this case, carbon-palladium bond formation occurs in concert with proton transfer to ligand [38]. Recently, such a concerted pathway has been observed experimentally using time-resolved infrared spectroscopy [39].

This continuum was uncovered during a renaissance of interest in direct metalation strategies in the early 2000s that was driven in large part by the lab of Keith Fagnou at the University of Ottawa. In their initial studies of direct arylation reactions, they observed that electron-deficient arenes underwent palladation with palladium(II) acetate at similar – if not faster – rates than electron rich arenes. The importance of carboxylate was likewise identified in early reaction screening. In a 2006 paper [38], they observed that increasing fluorine substitution on a benzene ring *increased* the rate of biaryl formation in a cross coupling with palladium(II) acetate, in a trend that paralleled the acidity of the fluoroarene. Using density functional theory (DFT) calculations, they identified a concerted TS similar to the one depicted by Winstein and Traylor in 1955. Similar findings were obtained in contemporaneous experimental and computational work by Maseras and Echavarren [5]. MacGregor also reported the same concerted mechanism, in a system that benefited from chelation assistance [3].

This was quickly recognized by Fagnou and colleagues as an approach complementary to electrophilic aromatic substitution. Using palladation, even electron-poor arenes and heterocycles were amenable to palladium-catalyzed C–C coupling reactions. As was noted in the earliest studies of concerted metalation deprotonation in the context of mercuration, nitrobenzene yielded to C–H activation by palladium(II) acetate [40]. So too did N-oxides of pyridine, pyrazine,

quinoline, and other azines [41]. Swapping palladium(II) acetate with palladium(II) pivalate was also rewarded with higher activities [42]. This was soon employed in intramolecular sp^2- sp^3 cross coupling reactions [43].

Since this seminal work, there has been a surge in applications of CMD and it likely stands as the dominant and most versatile mode of C–H activation in synthetic organic chemistry. But it's also reasonable to wonder what took so long. First, advances in computational chemistry put the concerted TS (proposed decades earlier) on a firm footing. Secondly, the field was primed for advances in organometallic catalysis. C–H activation itself had been well recognized and reached a degree of maturity by the 1990s [1a]. Breakthroughs in cross-coupling [44] illustrated the power of organopalladium species. But thirdly, and perhaps just as importantly, was the naming of the concept. By coining the name concerted metalation deprotonation, a specific mechanistic motif was consolidated under a simple descriptive name, helping to focus and inspire a remarkably productive race for its development as a tool in organic synthesis.

1.2.3 Classic Electrophilic C–H Activation

The term electrophilic C–H activation has acquired two related definitions. In the context of aromatic systems, it is the formation of a carbon-metal bond through nucleophilic attack of the aromatic system on a metal center – typically a high oxidation state, late transition metal. This is reminiscent of classical understandings of electrophilic aromatic substitution (SEAr), with formation of a Wheland intermediate followed by proton transfer to restore aromaticity. This is embodied by the auration of arenes. In the second sense, with initial precedent set by the discoveries of Alexander Shilov in the 1960s, it entails direct reaction of a high oxidation state, late transition metal center with a C–H bond (including sp^3 C–H bonds) followed by deprotonation.

1.2.3.1 Electrophilic Auration of Arenes

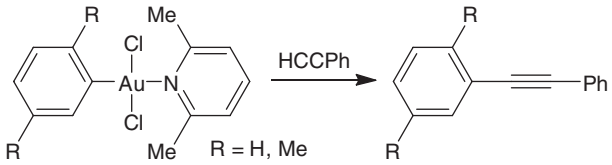
In 1926, after just a year of doctoral studies under Morris S. Kharasch at the University of Maryland, Horace S. Isbell [45] submitted a dissertation on the preparation of organogold compounds. Some of this was an extension of earlier reports using Grignard reagents to nucleophilically attach alkyl groups to gold centers by displacement of halides [46]. But another remarkable portion described the direct, rapid formation of aryl gold complexes from aqueous solutions of gold(III) chloride in contact with benzene [47]. Hydrogen chloride is immediately evolved as a byproduct, followed by precipitation of gold(I) chloride. Chlorination of benzene is the result; but along the way, phenyl auric dichloride may also be isolated as an intermediate during this process. Other compounds with "active" hydrogen atoms, such as malonic acid, are also chlorinated in this way. And if the reaction is conducted in the presence of chlorine gas, gold(II) chloride can be reoxidized to gold(III) chloride, rendering the process catalytic.

Research into the organometallic chemistry of gold(III) advanced slowly for many years. We posit that it failed to attract the interest of the wider chemistry community for a few reasons. The price of gold is certainly high among them, particularly if it doesn't offer a compelling advantage over stoichiometric mercury(II) or differentiate itself from cheaper Lewis acid catalysts like aluminum(III) and iron(III) in aromatic functionalization. Secondly, strongly coordinating motifs such as nitrile groups [48] tend to intercept the gold center and inhibit ring auration thus limiting substrate scope. The same is true for other coordinating species, particularly water [49]. Thirdly, gold displays some "Goldilocks" behavior. Electron-poor systems, such as nitrobenzene, are unreactive; and very electron rich systems, such as aniline, form unstable products. Lastly, the dramatic success of palladium catalysis, with its diversity of mechanisms and applications, from the 1950s through the early 2000s may have stunted research into other precious metal catalysts.

Maturation in thinking about organometallic chemistry was required to fully appreciate the value of gold. For example, the susceptibility to coordination can be used advantageously, such as in the directed auration of substituted pyridines [50]. In the absence of such pre-coordination, auration of aromatics displays a regioselectivity pattern consistent with nucleophilic aromatic substitution, with gold preferentially reacting with positions with higher electron density [51]. This is not at all a shortcoming. This strong regioselective preference on the basis of well-known orienting principles of aromatic systems has come to be an attractive feature of gold's C–H activation chemistry. It is complementary to palladium with its generally poorer regioselectivity in aromatic C–H activation.

Expanding the scope of auration required a more careful analysis of reaction intermediates. Kerk and Boersma discovered that the products of auration under Kharasch and Isbell's conditions were dimeric [49]. Parkin and Liddle found that these dimers could be converted to monomers by sigma-coordinating ligands such as phosphines and pyridines [52]. This proved key to unlocking catalytic transformations of gold. An early demonstration of this was by Fuchita and coworkers in

2001 [51], who found that 2,6-lutidine stabilizes monomeric adducts formed from the reaction of gold(III) chloride with substituted aromatics. In each case, only a single regioisomeric product was observed, which was isolable and could even be handled in air. Subsequent reaction of these arylgold intermediates with phenylacetylene afforded diaryl acetylenes in an oxidative cross-coupling reaction.



There has been particular success in the past 20 years in catalytic arylation and oxidative arylation using gold(III) catalysts [53].

1.2.3.2 The Shilov Reaction

The pathway for the emergence of the direct electrophilic activation of C–H bonds was paved by Garnett and Hodges [54] in 1967 who used the system ($K_2PtCl_4/CH_3COOH/H_2O$) to catalyze an H/D exchange of a range of aromatic hydrocarbons with isotopic water. To quote their paper [54a],

> The results of this work are of importance to fundamental catalysis since the present system constitutes the homogeneous analog of the conventional heterogeneous method which utilizes prereduced group VIII transition metals as catalysts, platinum being the most active.

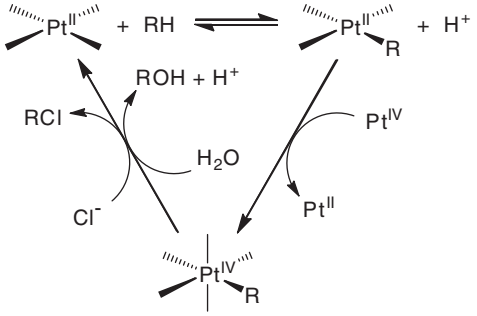
They went on to state that the chemistry of adsorbed molecules and that of inorganic coordination compounds are very much interrelated via the formation of a π-complex. Their report provides an efficient and rapid method of labeling organic compounds with deuterium and tritium and is significant due to the use of milder conditions which homogenous catalysis offers, leading to the foundation for similar labeling processes of other compounds.

A few years later, in 1971, Hodges and co-workers reported that alkanes H/D exchange of alkanes was also effected under these conditions [55]. And quite notably, the order of reactivity of C–H bonds was primary>secondary>tertiary – a trend in which the *stronger* C–H bonds are *more* reactive, opposite expectation and trends shown by other reagents that can react with alkanes (e.g. radical), but a trend that ultimately was discovered to be characteristic of C–H activation by transition metal complexes. The work of Garnett and Hodges however had already caught the attention of Alexander Shilov whose group reported in 1969 [56], that exchange of deuterium and hydrogen takes place when methane or ethane was heated with K_2PtCl_4 in a D_2O/CD_3CO_2D mixture under relatively mild conditions. Methane, notably, has the strongest C–H bond of any alkane. Most importantly, the Shilov lab soon reported actual functionalizations of light alkanes to give the corresponding alkyl chlorides and alcohols [57].

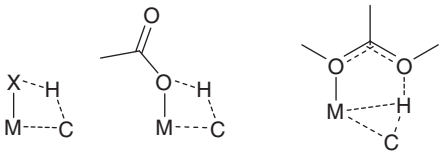
$$CH_4 + [PtCl_6]^{2-} + H_2O\,(Cl^-) \xrightarrow[H_2O,\ 120\ ^\circ C]{[PtCl_4]^{2-}} CH_3OH\,(CH_3Cl) + [PtCl_4]^{2-} + 2\ HCl$$

The use of Pt^{IV} as a stoichiometric reagent would seem to defeat the economic value of using platinum(II) catalytically, as well as leading to confusion at a purely scientific level. Nevertheless, the efficiency of this system in carrying out selective C–H activation of the most inert of C–H bonds under mild conditions was clearly revolutionary, and 'Shilov chemistry' has certainly proven to be one of the most influential developments in the field of C–H activation [58].

Extensive mechanistic investigations of Shilov and related Pt^{II}-based systems have since been conducted [59], particularly by Labinger and Bercaw [1b, 60]. In the first step of the mechanistic cycle, methane undergoes C–H activation by a platinum(II) complex to form a methylplatinum(II) intermediate. The product then undergoes oxidation to yield a methylplatinum(IV) species. Nucleophilic attack then occurs at the methyl group by H_2O, resulting in the reduction of the platinum center back to give back the platinum(II) species. This generalized mechanism set the basis for various other C–H functionalization reactions involving a platinum center.



The nature of the C–H activation, the initial step in the Shilov cycle was the subject of a seminal computational study by Siegbahn and Crabtree in 1996 [61]. The authors considered that the platinum(II) center might undergo C–H oxidative addition, followed by deprotonation. This was, however, calculated to have a barrier higher – although not so much higher that it could be ruled out definitively – than an alternative pathway in which, methane, coordinated to $Pt(II)Cl_2(OH_2)$, transfers a proton to a neighboring chloride. The authors referred to this as a "σ-bond metathesis". Their nomenclature however may reflect the limited categories of the time recognized for C–H activation reactions. The term σ-bond metathesis (discussed below) had been used to refer to reactions of the type M–X+A–Y=M–Y+A–X (A=H for the most part). Clearly the term is appropriate in such cases, as they are (stoichiometrically) simple examples of two σ-bonded species exchanging partners. In the Siegbahn-Crabtree pathway, however, the chloride that accepts the proton never departs; instead, it loses the proton to solvent and thus the term σ-bond metathesis seems less than ideal. It is our view that CMD would have been a better description, but the term CMD had yet to be coined. Even more descriptive would be a term later coined by Davies and Macgregor, "ambiphilic metal ligand activation" or AMLA[1g]. Most precisely by this nomenclature system, this is an AMLA(4) process, where the number in parentheses refers to the number of atoms involved in the proton-transfer TS, as distinguished from a classic carboxylate-assisted CMD which is an AMLA(6) process.



AMLA(4) AMLA(6)

AMLA (ambiphilic metal ligand activation) TSs

Platinum(II) is required to effect the C–H activation step, but the next step, conversion to a Pt(IV) alkyl is required to achieve functionalization. Platinum(IV) is likely unable to effect C–H activation, at least in part because of difficulty accessing a vacant coordination site. This could be envisioned to occur via either transfer of the alkyl from platinum(II) to platinum(IV), or via electron-transfer from the platinum(II) alkyl. Labeling experiments with isotopically enriched ^{195}Pt demonstrate that the reaction proceeds through electron transfer [60g].

The electron-transfer pathway leads to the challenge of avoiding oxidation of the lower oxidation state species prior to alkylation. This problem was initially circumvented, albeit impractically, with the use of platinum(IV) as the oxidant – in that case, any oxidation of unmethylated platinum(II) is a degenerate reaction.

The final step involves formation of a bond between carbon and a heteroatom (O or Cl) at the Pt(IV) methyl complex. This step involves nucleophilic attack at the carbon center; several studies have shown that there occurs an inversion of stereochemistry at the carbon center [60c, 60d]. Although the pictorial mechanism depicts the attack to be occurring at a six-coordinate platinum species, there is reason to believe that the nucleophile attacks at a five-coordinate platinum species [1b].

1.2.3.3 Post-Shilov Electrophilic Activation

The use of an alternative to platinum(IV) as the terminal oxidant in platinum(II)-catalyzed methane functionalization was first reported by Periana and co-workers at Catalytica [62]. The reaction between methane and fuming sulfuric acid was

catalyzed by a platinum(II) bipyrimidine complex to give methyl bisulfate in 72% yield at 220°C. The oxidant was the sulfuric acid solvent (which may be formally viewed as SO_3 plus H_2O). The bisulfate anion gave rise to the methyl ester. The ester, in contrast with methanol, was found to be stable under the reaction conditions as it is resistant to oxidation and to further attack by the electrophilic catalyst because it is particularly electron-poor [58c, 62].

$$CH_4 + 2\,H_2SO_4 \rightarrow CH_3OSO_3H + 2\,H_2O + SO_2$$

The ester could be hydrolyzed to give methanol and regenerate sulfuric acid. The oxidation of SO_2 to give SO_3 (which is perhaps the largest-scale chemical reaction practiced industrially) would complete the cycle with O_2 as the ultimate oxidant in the process. Perhaps the biggest obstacle to practical application of this process is not strictly chemical, but separation of the water from the concentrated sulfuric acid [58c].

Apart from platinum, several palladium-based systems have also been developed for oxidation of methane and some lower alkanes. Sen and co-workers reported a bimetallic electrophilic system, comprising Pd/C and $CuCl_2$ using trifluoroacetic acid and water as solvents, that could oxidize methane to methanol and methyl trifluoroacetate in the presence of oxygen and carbon monoxide (used as a co-reductant) [63]. The exact mechanism of this reaction is not very clear, but the studies suggest that free alkyl radicals are probably not involved in this type of reaction.

Fujiwara and co-workers had also reported the oxidation of methane to acetic acid with CO, using a system of $Pd(OAc)_2$ and/or $Cu(OAc)_2$ in trifluoroacetic acid with potassium peroxodisulfate as oxidant. Among the co-catalysts, $Cu(OAc)_2$ seemed to be the most effective in converting methane to acetic acid [64].

A report by Strassner showed that palladium(II) *N*-heterocyclic carbene complexes were able to convert methane to methyl trifluoroacetate in the presence of trifluoroacetic acid and trifluoroacetic acid anhydride using potassium peroxodisulfate as oxidant. Use of peroxydisulfate gives rise to the possibility of a radical pathway; indeed, in the absence of a metal complex, the oxidant itself could convert methane to alcohol via a radical pathway, albeit at higher temperatures [65].

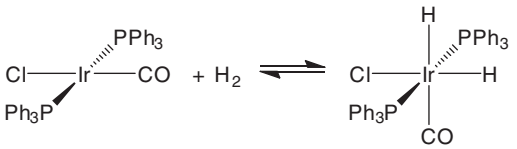
The strategy of using H_2SO_4 to serve as solvent, nucleophile, oxidant, and protecting group, had been applied by Periana prior to the development of the platinum-based Catalytica system. The greatest success was found with mercury(II), but thallium(III) and palladium(II) were also found to be effective [66]. A one-pass methyl bisulfate yield of 43% was obtained at 180°C. Ess and co-workers investigated this system computationally [67]. In contrast with platinum(II), C–H oxidative addition, to either mercury(0) or mercury(II) was found to be definitively not viable. Rather they calculated a low-energy TS for C–H activation in which methane, coordinated to mercury(II), is deprotonated by a non-coordinating oxygen atom of a (κ^1) coordinated bisulfate anion. This TS is completely analogous with the CMD TSs of palladium(II) systems (AMLA(6) in the Davies-Macgregor classification scheme [1g]). A TS that was very slightly (not meaningfully) lower in energy was calculated in which the proton was transferred from coordinated methane to a weakly coordinated bisulfate oxygen atom ligand (AMLA(4) [1g]).

1.3 Oxidative Addition

1.3.1 Stoichiometric Oxidative Addition of C–H Bonds

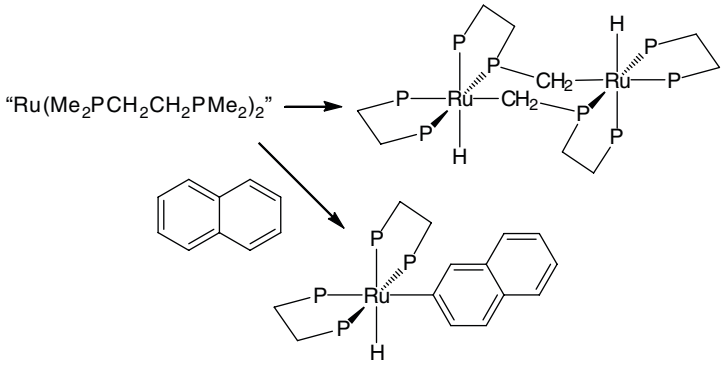
Oxidative addition may be defined as any reaction in which the addition of one or more ligands to a metal center results in an increase in formal oxidation state of the metal center; for example addition of H^+ which increases the formal oxidation state by 2 units. The most common usage, however, is for the net insertion of a metal center (regardless of the mechanism) into a bond X–Y to give M(X)(Y) where X and Y each acquire a formal charge of −1 and thus the charge of M is increased by 2.

Oxidative addition rose to prominence in organometallic chemistry with the 1962 report of H_2 adding, reversibly, to Vaska's Complex [68].



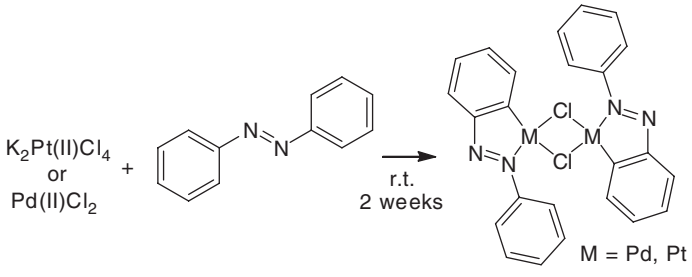
This reaction caused some consternation in the chemical community which had generally regarded H_2 addition (e.g. to olefins) as a reduction (the confusion, which occasionally still arises, derives from the ambiguity of assigning negative or positive charges to H). As inorganic chemists think in terms of electronic structure, however, and the relationship between hydrides and the corresponding halides for example is very clear, Vaska correctly argued that H_2 addition should be viewed as (formally) oxidative [68, 69]. Much more questionable, however, was Vaska's extension of this argument to H_2 addition being oxidative in a *physical* sense – even though much of his own very rigorous data suggested the opposite [69]. Complexes that are more electron-rich generally have a greater tendency to undergo additions that are physically oxidative, e.g. halogenation. But Ir–H bonds are not particularly polar and therefore other factors determine the relative thermodynamics of H_2 addition to different complexes. In retrospect, it is clear that the thermodynamics of H_2 addition were in many cases *less* favorable for those derivatives of Vaska's complex that are more electron-rich [69, 70]. Nevertheless for many years it was accepted that complexes that are more electron-rich would undergo any oxidative addition more favorably. In the context of oxidative addition of C–H bonds; this proved to be misleading. At the very least it contributed to a failure to see the close relationship between various types of reactions that resulted in C–H bond cleavage and metal-carbon bond formation, in particular oxidative addition and electrophilic addition.

The first example of oxidative addition of C–H bonds is often attributed to Chatt in 1965 [71], shortly after Vaska's report. He found that gen erating Ru(0)$(dmpe)_2$ resulted in addition of both C–H bonds of naphthalene and those of the phosphinomethyl groups [72].

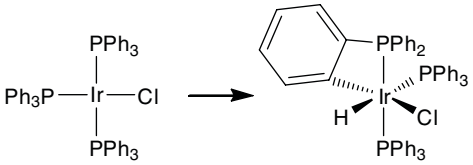


This surely seemed to support the notion that very electron-rich complexes were key to activating inert C–H bonds. But, ironically enough, it was much later found by Roddick that $Ru[(C_2F_5)PCH_2CH_2P(C_2F_5)_2]_2$, a much less electron-rich analogue of Ru$(dmpe)_2$, was apparently more reactive toward the addition of C–H bonds [73].

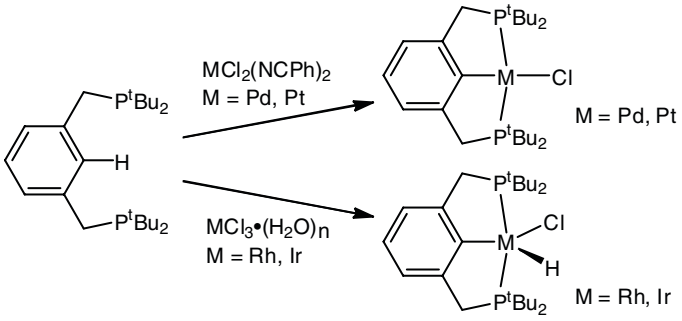
The year 1965 also saw the report by Cope and Siekman of a cyclometalation of an azobenzene (i.e. the activation of one of the *ortho*-phenyl C–H bonds) [74]. Whereas the net reaction is not an oxidative addition, and it might perhaps best be described as electrophilic activation, in retrospect at least the possibility of C–H addition followed by loss of HCl can certainly be considered. The value of *ortho* directing groups and the ambiguity between the usual categories of C–H addition seems to have been foreshadowed by this discovery decades before these concepts came to the fore.



Most of the early examples of C–H activation involved aryl C–H bonds or intermolecular additions, or frequently both (e.g. cyclometalation of a PPh_3 ligand) [75, 76].

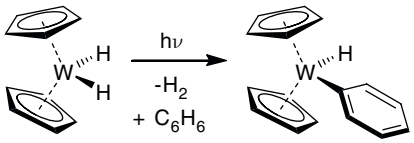


A particularly notable class of such reactions was discovered by Shaw. With 1,3-*bis*[(di-t-butyl)phosphino)methyl] benzene, cyclometalation gives rise to an extremely stable pincer structure. Complexes of nickel, palladium, platinum, rhodium, and iridium were all synthesized via cyclometalation of the diphosphine [77].



These complexes and derivatives thereof would ultimately play a supporting role for a vast range of catalytic and other valuable reactions, including many examples involving oxidative addition of unactivated C–H bonds [78].

An important example of intermolecular oxidative addition of a C–H bond was reported in 1970 by Green, who found that benzene undergoes C–H addition to Cp_2W. This fragment, which has a valence electron count (VEC) of 16e, was generated from Cp_2WH_2 either by photolysis [79] or by hydrogenation of olefin [80] (two approaches that were subsequently employed countless times in the field of C–H activation). Note that whereas 16e square planar species like Vaska's Complex do not add unactivated C–H bonds, and even add H_2 relatively slowly and reversibly (i.e. not very exergonically), Cp_2W appears to add the benzene C–H bond too rapidly to allow its observation and the thermodynamics of addition are too favorable to allow rapid reversibility.



In 1982 Bergman [81] and Graham [82] independently reported pentamethylcyclopentadienyl (Cp*) iridium complexes that effected the first well characterized examples of oxidative addition of alkane C–H bonds. Thus C–H bond activation had finally been achieved to give well characterized products, with the corresponding metal carbon bonds, without assistance through coordination at another site or the help of π electrons. This breakthrough captured the imagination of the chemical community and brought C–H activation to the forefront unlike any prior reaction.