

Chapter 2

Alkane Functionalization via Electrophilic Activation

Jay A. Labinger

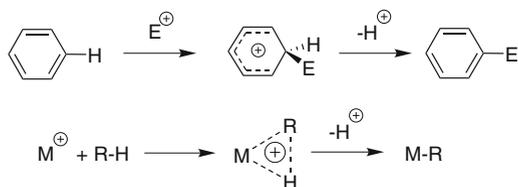
Abstract Electrophilic activation, which may be defined as the substitution of a transition metal center for a proton to generate a new metal–carbon bond, is the basis of a number of promising approaches to selective catalytic functionalization of alkanes. The field was introduced by the groundbreaking chemistry exhibited by aqueous chloroplatinum complexes, reported by Shilov in the early 1970s. Since then the field has expanded greatly, and electrophilic alkane activation has been demonstrated using a wide variety of species. These include ligand-supported platinum complexes; complexes of additional late transition metals, most commonly palladium but also iridium, gold and others; and even post-transition metals such as mercury. That body of work is surveyed here, with particular emphasis on mechanistic understanding, examples of actual functionalization at sp^3 -hybridized C–H bonds in alkanes and related compounds, and assessment of the further development that will be needed for practical applications.

2.1 Definition and Scope

What do we mean by electrophilic activation of alkanes? It *seems* as though the term should have mechanistic implications. The obvious antecedent is electrophilic substitution of arenes, which classically proceeds via a delocalized carbocationic Wheland intermediate, as shown in Scheme 1; the electrophile E^+ may be metal-centered, such as Hg^{2+} . Of course, there is no *classical* analog of the

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Scheme 2.1 Electrophilic mechanisms for substitution of an arene (top) and metallation of an alkane (bottom)

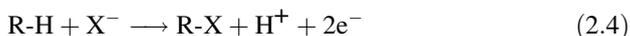
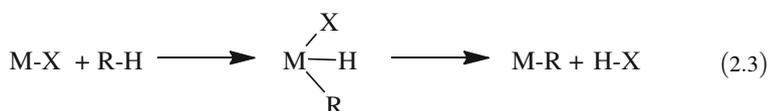
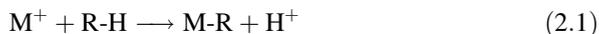


Wheland intermediate for alkane activation; but we now know that alkane σ complexes of transition metals are ubiquitous and, in many cases, remarkably stable, so the “non-classical” analog in Scheme 1 might be reasonable. But it appears that most if not all cases of alkane activation by transition metals *start* with formation of the σ complex, although they proceed therefrom in a variety of ways, rarely (if ever) exactly as in Scheme 2.1. Such a consideration would imply we should call *all* alkane activations electrophilic,¹ even oxidative additions which require very electron-rich metal centers, and which formally involve electron flow from the metal to the alkane. Clearly, then, it will be much more useful to use the term to signify stoichiometry, not mechanism.

Accordingly, for the purpose of this review, we define “electrophilic activation” as formation of an alkyl-metal complex according to Eq. 2.1. This chemistry was first established for aqueous chloroplatinate complexes—the so-called Shilov system—and has been extended to a number of late- and post-transition metal species, typically in protic and/or highly polar media. It should be emphasized that this is not, and cannot be, an unambiguous mechanistic designation. The proton may well be lost *along with* another ligand, a situation described by Eq. 2.2; but that stoichiometry also corresponds to the sigma bond metathesis reactions characteristic of d^0 early transition metal alkyl complexes [2]. Indeed, a similar route—sometimes termed a “sigma complex-assisted metathesis” or σ -CAM [3]—has been invoked for some late transition metal activations as well. Or the net stoichiometry of Eq. 2.2 may proceed via an oxidative addition/reductive elimination sequence (Eq. 2.3). But neither alkane activation by sigma bond metathesis at early transition metals nor oxidative addition at electron-rich late transition metal

¹ Periana and Goddard have recently offered an alternate perspective [1]. According to their theoretical studies, reactions may be classified as electrophilic, ambiphilic or nucleophilic based on the calculated transfer of charge from alkane to metal complex, or the reverse, in the transition state for C–H activation. Many of the systems classified as ambiphilic or nucleophilic involve simultaneous interaction of the C–H bond with both the metal center and another ligand, but even if only the metal center is involved, the net transfer can still be from metal to C–H bond, if π back-donation from a filled metal orbital to the C–H σ^* orbital is more important than donation from the C–H σ orbital to a vacant metal orbital. It is not clear how general or useful this approach might be (a possible illustration is discussed in Sect. 4.7); for one thing, a stated goal is to develop methods for combining C–H activations with compatible functionalization reactions, but (as we will see) in many cases the species that effects functionalization differs substantially from that responsible for the activation, so the nature of the activation (even assuming the methodology can accurately describe it) may well be entirely disconnected from potential functionalization chemistry. In any case, we will not make any use of these distinctions here.

centers commonly leads on to net alkane functionalization; the systems that favor those two pathways tend to be incompatible with many thermodynamically allowed transformations, particularly those involving oxidations [4]. In contrast, net overall oxidation often *can* be achieved via electrophilic activation (as defined by Eq. 2.1 or 2.2), often by reaction of the organometallic intermediate with a nucleophilic substituent, accompanied (at some point in the sequence) with a change in metal oxidation state, resulting in the overall stoichiometry of Eq. 2.4.



The main focus of this review is electrophilic functionalization of alkanes.² We will allow a rather loose definition of what counts as an alkane, generally including functionalization of a saturated (sp^3 -hybridized) C–H bond even though it may be part of a more complex molecule, so long as the chemistry involved could reasonably be applicable to simple alkanes. Reactions that *only* activate C–H bonds, without leading on to functionalization, will be considered only insofar as they shed important light on mechanism or reactivity patterns, with no attempt at comprehensive coverage (particularly of the *immense* body of literature concerning cyclometallation!). The same criterion will apply to the functionalization of aryl C–H bonds, for which there is a large body of recent work, especially involving *directed* activation by palladium (which effects a number of directed activations at sp^3 carbon as well see Sect. 4.1.2) [9]; only those examples that provide mechanistic lessons will be examined in any detail. The chapter is organized primarily according to the activating species, although in a few instances results are presented in the “wrong” section to facilitate comparisons.

² This subject has been reviewed before, far too often to cite all of them. Some particularly relevant ones; an earlier, but considerably shorter, review of electrophilic oxidations [5]; a much more thorough coverage of Pt-mediated C–H activation and functionalization [6]; a more recent review of oxidative functionalization of alkanes in protic media [7]; a general review of transition metal catalyzed oxidative functionalization of C–H bonds [8].

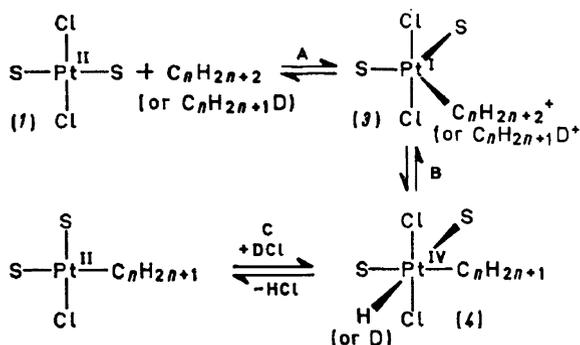
2.2 The Shilov System

C–H activation by a soluble transition metal complex was first reported by Garnett and Hodges in 1967: they found that a solution of $[\text{PtCl}_4]^{2-}$ in aqueous acetic acid, with added HCl, catalyzed H/D exchange between a variety of arenes and D_2O , at temperatures around 100–120 °C [10]. Exchange of aryl C–H bonds may not have appeared remarkable, possibly just another example of (reversible) electrophilic metallation of arenes as in Scheme 2.1; but the paper also noted some activity for exchange at the benzylic positions of toluene and mesitylene, and even in cyclohexane. More details on the aliphatic activations appeared shortly afterward, from Hodges [11] as well as the group of Alexander Shilov in the (then) USSR [12]. The first demonstration of actual functionalization came in a follow-up paper from the Shilov group: a combination of $[\text{PtCl}_4]^{2-}$ and $[\text{PtCl}_6]^{2-}$ in water or aqueous trifluoroacetic acid, under conditions similar to those used to effect H/D exchange, oxidized alkanes to a mixture of products, primarily alcohols and alkyl chlorides [13]. This combination of aqueous Pt(II) and Pt(IV) salts has become known as the Shilov system.

2.2.1 General Features

Shilov (in collaboration with his colleague Georgiy Shul'pin) has published comprehensive surveys of this chemistry as parts of two major review articles [14, 15] and two books [16, 17], the most recent dating from 2000; only highlights of the earlier work will be presented here. (Specific findings that are not explicitly referenced here have been taken from those surveys.) Initial studies by the Shilov group on the oxidations, and by both the Shilov and Hodges groups on H/D exchange, focused on two features of this novel chemistry: the effect of changing Pt speciation by varying $[\text{Cl}^-]$ and/or adding other anionic ligands, and the relative reactivities of different C–H bonds. In essentially all regards the two reactions show parallel features and trends, strongly indicating that they start off the same way, via C–H activation at a Pt(II) center. Reversal of that process results in H/D exchange, while Pt(IV) intervenes to divert some intermediate to a species leading to oxidative functionalization. The similarity of conditions to those needed for aryl H/D exchange suggests that arene and alkane reactions are closely related mechanistically. In general C–H bond reactivity follows the order primary > secondary > tertiary, which is the opposite of what would be predicted by considering bond strength; it is also the opposite of how one might guess a *mechanistically* electrophilic reaction would behave, since alkyl substitution is electron-releasing. Dependence of the rates of both H/D exchange and oxidation on $[\text{Cl}^-]$ implicated the reactivity order $[\text{PtCl}_4]^{2-} < [\text{PtCl}_3(\text{H}_2\text{O})]^- < [\text{PtCl}_2(\text{H}_2\text{O})_2] > [\text{PtCl}(\text{H}_2\text{O})_3]^+ > [\text{Pt}(\text{H}_2\text{O})_4]^{2+}$, which also seems incompatible with an electrophilic mechanism: the cationic species would be expected to be most electrophilic.

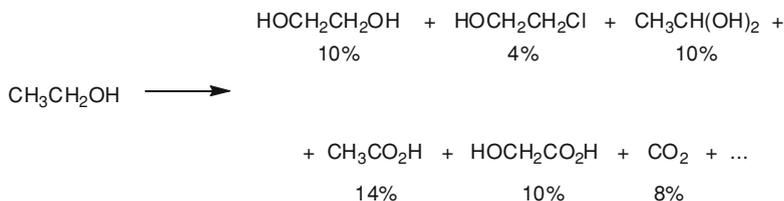
Scheme 2.2 Early mechanistic proposal for C–H activation by Pt(II). Reproduced from Ref. [11] with kind permission of © The Royal Society of Chemistry (1971)



Two additional observations gave important clues. C–H positions adjacent to quaternary centers are much less reactive, suggesting an important steric component in determining reactivity; and the distribution of $\text{C}_n\text{H}_{2n+2-x}\text{D}_x$ isotopologues was not statistical, but rather revealed a propensity for multiple exchange during each alkane–Pt encounter. To explain all of this, Hodges offered the C–H activation mechanism shown in Scheme 2.2 [11], which proceeds via rate-determining coordination of the alkane to Pt(II), followed by oxidative addition of a C–H bond to give an (alkyl)Pt(IV) hydride that can exchange with D^+ ; multiple exchange would be explained by assuming that intermediate **3** is sufficiently stable to allow steps **B** and **C** to take place (in both directions) a number of times before alkane dissociates (the reverse of step **A**). As we shall see, this proposal was in many ways remarkably prescient, especially considering that at the time there was no understanding at all of how an alkane might coordinate (Hodges described it as “electron transfer from delocalized molecular orbitals in the alkane to the platinum atom in the complex”), or how such an interaction could possibly give rise to a relatively long-lived species. Indeed, the feeling that such species were highly unlikely gave rise to alternate interpretations, involving intermediate olefin or carbene complexes, in a number of papers.

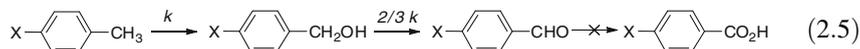
The preference for primary site oxidation is potentially useful, since many desirable alkane oxidation targets are those derived from terminal functionalization. For example, terminal alcohols used in detergents are currently obtained via hydroformylation of olefins; alkanes would constitute a much cheaper feedstock. As noted above, most oxidations involve homolytic pathways and disfavor the stronger C–H bonds. However, Shilov chemistry exhibits fairly modest selectivity: primary H/D exchange is perhaps a factor of 2–5 or so faster than at secondary positions [11].

Of even greater import is the relative reactivity of the initial alkane and its functionalization product. C–H bonds adjacent to oxygen-centered substituents, as well as most other functional groups likely to be introduced, are significantly weaker than those in simple alkanes, so that in traditional radical-based oxidations the products will be much more reactive than the starting material, severely limiting the yields attainable. For example, it has been estimated that these considerations would restrict the yield of methanol via *any* oxidation of methane that proceeds via a radical path to no more than a few percent, a prediction that so far has not been exceeded in



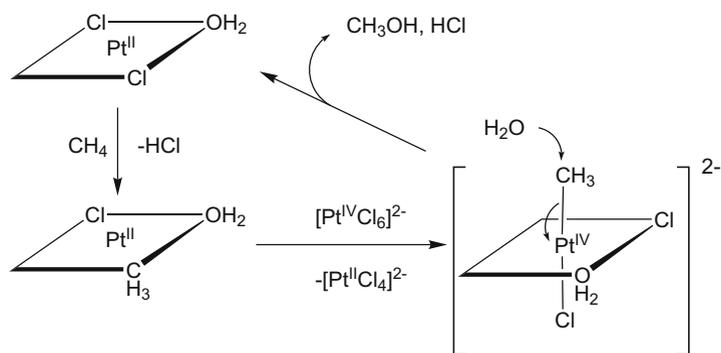
Scheme 2.3 Typical product distribution resulting from reaction of ethanol (at about 50 % conversion) under standard Shilov conditions

any reliable experimental report [18]. Since the selectivity trends for Shilov oxidation of alkanes argue strongly against anything resembling a radical mechanism, it seems possible that the same constraints might not apply. Experimental evidence that this is indeed so was first obtained for the oxidation of *p*-toluenesulfonic acid (a substrate chosen to permit detailed study in pure water, without the added complications of carboxylic acid co-solvents). Under the standard Shilov conditions, oxidation took place at the methyl group to give a mixture of the corresponding alcohol and aldehyde, but none of the carboxylic acid; analysis of the product distribution indicated that the methyl group is about 1.5 times as reactive as the hydroxymethyl group (uncorrected for statistical factors), as shown in Eq. 2.5. No significant oxidation at aryl positions was observed [19].

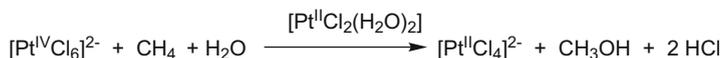


An even more dramatic demonstration of the unusual reactivity preferences demonstrated by this chemistry was obtained from the reaction of ethanol: all previously known oxidation methods lead to oxidation at the hydroxymethyl end of the molecule, to give acetaldehyde or acetic acid. In contrast, Shilov oxidation gave significant yields of the products resulting from oxidation at the methyl end—ethylene glycol and 2-chloroethanol—along with additional products attributable to initial hydroxymethyl oxidation and sequential further oxidation of the initial products (Scheme 2.3) [19]. Again, the product distribution turns out to be consistent with the methyl group being approximately 1.5 times as reactive as the hydroxymethyl group.

An estimate of the relative reactivity of methane and methanol, based on the attainable yields of the latter, and taking into account the limited solubility of the former, also gave a value on the order of 1.5 [20]. A more direct measurement was attempted by allowing the Shilov reaction of *both* methane and methanol to proceed to a steady-state product distribution, from which a reactivity ratio of about 0.17:1 was deduced [21]. However, that result is complicated by the tendency of platinum metal to precipitate from Shilov reactions, especially when carried out in pure water. (The use of a carboxylic acid co-solvent appears to retard Pt deposition considerably; a possible explanation will be discussed later.) Sen and others have shown that metallic platinum is an excellent catalyst for oxidation of alcohols by a



net reaction:



Scheme 2.4 Proposed three-step Shilov oxidation sequence for the oxidation of methane to methanol/methyl chloride

variety of oxidants, including $[\text{PtCl}_6]^{2-}$ [22], so that if colloidal (and hence not visible) Pt were present during this experiment (and, likewise, in any of those discussed above), the apparent reactivity of methanol would be artificially high. Hence the measured ratio must be taken as a lower limit; at a minimum we can say that for all of these experiments, C–H bonds in methyl and hydroxymethyl groups are of comparable reactivity. If that conclusion holds in general, then the yield (that is, one-pass conversion times selectivity) for direct oxidation of an alkane to an alcohol could be as high as $\sim 30\%$, an order of magnitude better than the quasi-theoretical limit for a radical mechanism [18]. Such findings understandably excited renewed interest in the potential of electrophilic functionalization methods.

Thorough mechanistic understanding of this chemistry is obviously a desirable target. The conditions of the reaction (especially when pure water is used as the solvent, rendering most substrates insoluble and promoting deposition of Pt metal), along with the general inability to observe any reaction intermediates, make it necessary to use indirect methods to get at many of the most interesting details; a less-detailed model for the overall reaction was formulated at early stages. As noted above, the close parallels between H/D exchange and oxidation strongly support the hypothesis that both begin the same way, with activation of the C–H bond at a Pt(II) center (exactly *how* that takes place will be addressed in the following section). The independent synthesis of (alkyl)Pt(IV) complexes can be achieved, most readily by the oxidative addition of alkyl iodides to $[\text{PtCl}_4]^{2-}$; the insolubility of PtI_2 drives ligand redistribution to afford $[\text{RPtCl}_5]^{2-}$ (or $[\text{RPtCl}_4(\text{H}_2\text{O})]^-$, depending on exact conditions). The latter species, when exposed to Shilov conditions, undergo reductive elimination to ROH/RCl plus Pt(II), at a rate fully compatible with that of the overall oxidation of alkanes. All of this leads directly to the three-step sequence (exemplified for methane oxidation) in Scheme 2.4.

2.2.2 Mechanistic Details

Although the above scheme has held up through the ensuing years, it is incomplete: there are multiple possibilities for the precise mechanism (or, perhaps, mechanisms) involved in each of these three sequential steps. In the next three sections we will examine how the steps have been studied separately in order to elucidate their mechanisms in detail, followed by a brief revisit to consider how they fit together to account for the overall behavior of the intact Shilov system.

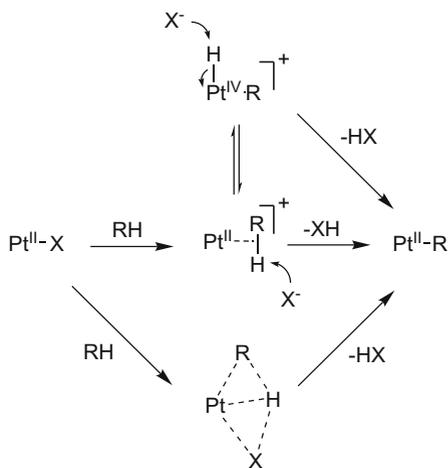
2.2.2.1 C–H Activation

The close similarity between the H/D exchange and Shilov oxidation processes, in terms of kinetics, site preferences, and other parameters, strongly implies that this first step is both rate- and selectivity-determining, and hence essential to understand as thoroughly as possible. It is also the most *difficult* to study, however, since the reaction of Pt(II) with RH to give RPt(II) cannot be isolated from the rest of the steps. Hence most of the detailed mechanistic studies have involved model complexes, an approach which is always subject to uncertainty, as the changes needed to generate a model for which the necessary observations can be made may well also cause the mechanism to change. Nonetheless, an extensive body of investigations on such models has led to a mechanistic picture that is (at least) self-consistent, as well as accounting reasonably well for the more limited set of findings on the actual Shilov system. As before, we will only highlight some of the more revealing experiments here; a much more extensive review of C–H activation at Pt has appeared [23].

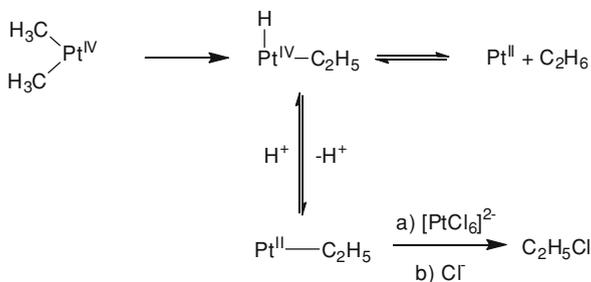
Two clearly differing mechanisms for C–H activation at Pt(II) have been considered from the beginning: oxidative addition, an established process for late-transition metal centers, followed by proton loss; or direct deprotonation of a σ -alkane complex, by analogy to the well-known acidity of σ -dihydrogen complexes. The so-called σ -CAM mechanism, in which the hydrogen is abstracted by a ligand on Pt, may be considered as a close variant of direct deprotonation. Scheme 2.5 shows these three alternatives; the σ -alkane complex is shown as a likely intermediate on the oxidative addition route, and might well be on the σ -CAM route as well.

The fact that most well-defined examples of oxidative addition involve very electron-rich metal centers—*not* an obvious characteristic of these Pt(II) species—was taken by some as an argument for direct deprotonation; but as noted above, experimental evidence on the actual system proved elusive. In one study, Zamashchikov examined the behavior of the (dimethyl)Pt(IV) complex $[\text{PtCl}_4(\text{CH}_3)_2]^{2-}$, which under Shilov-like conditions (aqueous chloride solution containing $[\text{PtCl}_6]^{2-}$ at 95 °C) decomposes to give ethane and ethyl chloride (as well as methyl chloride and methane). Those two products were also generated by Shilov oxidation of ethane, and comparison of the isotope effects on the product distributions in the two cases implicated a common intermediate, which

Scheme 2.5 C–H activation at Pt(II) by oxidative addition (top), direct deprotonation (middle), or σ -CAM (bottom) routes



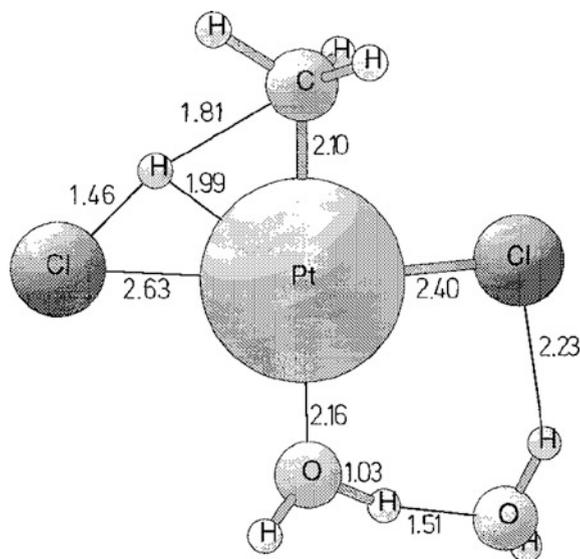
Scheme 2.6 Reactions used to argue for the oxidative addition mechanism



(they argued) had to be the oxidative addition adduct (Scheme 2.6), since they assumed σ -alkane complex formation would not be subject to any isotope effect [24]. However, there is considerable evidence in other systems that invalidates the latter assumption, so this attempt at a direct answer does not necessarily hold up.

Computational methods have been brought to bear on this question, but they are problematic. In aqueous media, the contributions of solvation and specific hydrogen bonding interactions will surely be very important, and it is not clear how reliable the methodology for handling them is likely to be. In an early study, Siegbahn and Crabtree examined the activation of methane by *cis*- $\text{PtCl}_2(\text{H}_2\text{O})_2$ by DFT, and found the lowest overall activation energy for a σ -CAM-like route; the calculated transition state (Fig. 2.1) includes specific solvation by a water molecule in the secondary coordination sphere, hydrogen bonded to both coordinated water and chloride. While the calculated transition state for an oxidative addition route came out very close in energy, the authors preferred the σ -CAM, feeling that a Pt(IV) intermediate was unlikely [25]. Subsequent calculations by Ziegler included all possible chloro(aquo)Pt(II) species; they concluded that the neutral $\text{PtCl}_2(\text{H}_2\text{O})_2$ is the most reactive, but depending on conditions it may be present in

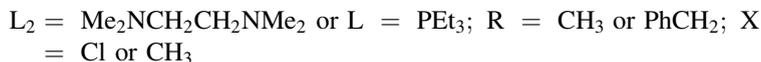
Fig. 2.1 Calculated transition state for activation of methane by $\text{PtCl}_2(\text{H}_2\text{O})_2$. Reprinted from Ref. [25] with kind permission of © The American Chemical Society (1996)



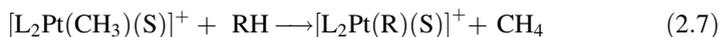
such low concentration that most of the activation proceeds via anionic $[\text{PtCl}_3(\text{H}_2\text{O})]^-$. Coordination of methane by associative displacement of water was calculated to be the rate-determining step; the actual C–H activation (assumed to be oxidative addition) had a much lower barrier [26].

In the absence of a direct experimental approach, researchers turned to indirect methods—specifically, examination of the microscopic reverse reaction, protonolysis of an (alkyl)Pt(II) complex. It was hoped that the alternatives (which correspond to running the reactions in Scheme 2.5 from right to left) could be more conclusively distinguished, perhaps even by observation of an intermediate. Here too there is a problem, though: the postulated Pt(II) complexes $[\text{PtCl}_3\text{R}]^{2-}$ are quite unstable. Attempts to synthesize such a species, either by methylation of $[\text{PtCl}_4]^{2-}$ or by reduction of $[\text{PtCl}_5(\text{CH}_3)]^{2-}$, were unsuccessful, leading to decomposition, formation of dimethyl species, and/or instantaneous liberation of methane by protonolysis. (There was one exception: reduction of $[\text{PtCl}_5(\text{CH}_3)]^{2-}$ by cobaltocene in a *nonprotic* solvent gave a mixture of salts including the desired species, which was used in studies described below) [27]. Hence model complexes were required even for this indirect approach.

The reaction summarized in Eq. 2.6 was carried out for several ligands L (amines and phosphines were used) under a variety of conditions of solvent, temperature and acid, with two key findings. First, several cases generated an NMR-observable alkyl(hydrido)Pt(IV) species, which was stable at low temperature and decomposed to alkane on warming; second, in deuterated acidic media many of the reactions displayed multiple H/D exchange in both the liberated alkane and the remaining unreacted alkyl group(s) [28].

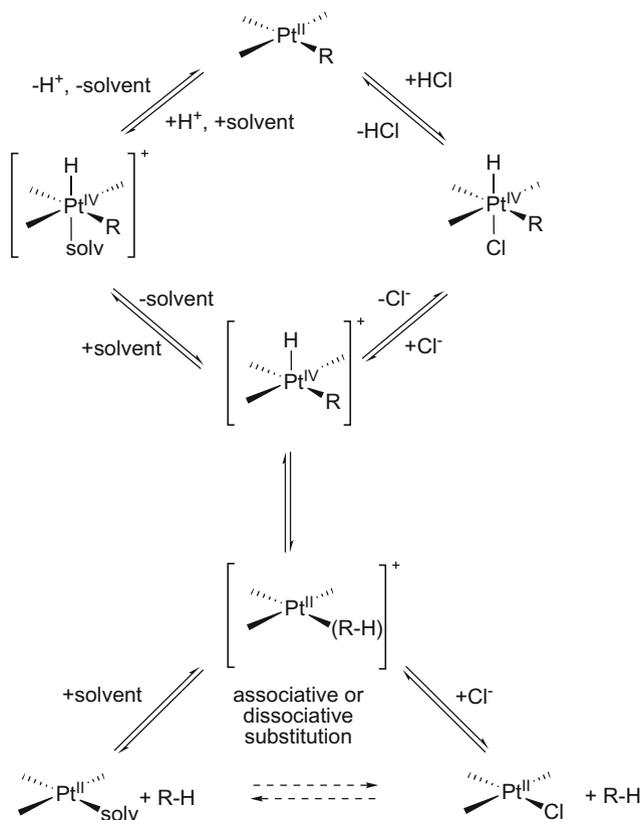


These findings point clearly to the overall reaction network shown in Scheme 2.7; both σ -alkane complex and alkyl(hydrido)Pt(IV) species are intermediates (to account for the H/D exchange), but proton loss takes place from the latter. If microscopic reversibility applies, then, C–H activation in the Shilov system would proceed by the oxidative addition route (reading Scheme 2.7 from bottom to top). But *does* it apply? The model complexes used in these studies do not themselves exhibit C–H activation chemistry, and it is certainly conceivable that the introduction of ligands perturbs the system sufficiently to alter the mechanism, so uncertainties remain. At a minimum, a system that *does* effect C–H activation and exhibits the same behavior needed to be demonstrated. That was eventually achieved for several model Pt(II) complexes, all having a common feature: at least one readily displaceable ligand, usually a solvent molecule, to facilitate the initial coordination of the alkane. That process corresponds to the step shown in the lower left corner of Scheme 2.7 (reading up). The reaction shown schematically in Eq. 2.7 was accomplished first for S = pentafluoropyridine [29]; subsequently the introduction of trifluoroethanol as solvent[30] led to an extremely versatile and richly informative model system. And there are even some cases, notably that of Scheme 2.8, where a *stable* alkyl(hydrido)Pt(IV) can be obtained via C–H activation [31].

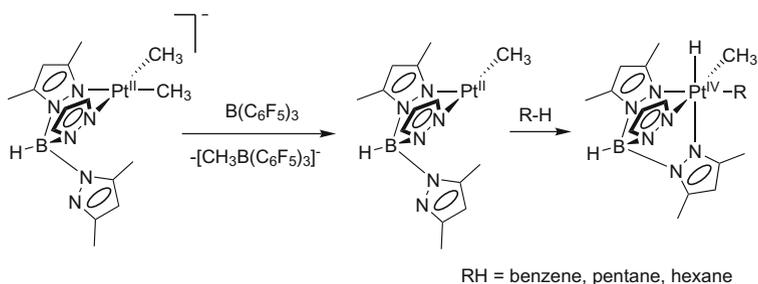


A number of studies on the trifluoroethanol-based system have significantly increased our detailed understanding of the C–H activation process. The dependence of the rate of benzene activation on the electronic and steric nature of the diimine ligands in Scheme 2.9 [32], along with the observation of extensive H/D scrambling in both the initial protonolysis of the dimethyl compound and the subsequent C–H activation, demonstrates that the rate-determining step in alkane activation³ is coordination of the alkane to give the σ -complex; (reversible) C–H cleavage to give the alkyl(hydrido)Pt(IV) complex is faster. Experiments on these model systems further indicate that alkane (or arene) coordination proceeds via *associative* displacement of solvent [32, 33].

³ For benzene activation the C–H activation step may be rate-determining, in cases where the steric constraints are not too severe; presumably the much more favorable interaction arene-metal π complex, compared to the σ alkane complex, lowers the barrier to complexation below that of C–H cleavage. This situation does not appear to arise in alkane activation by Pt(II); it is usually straightforward to decide which step is rate-determining by examining isotope exchange.

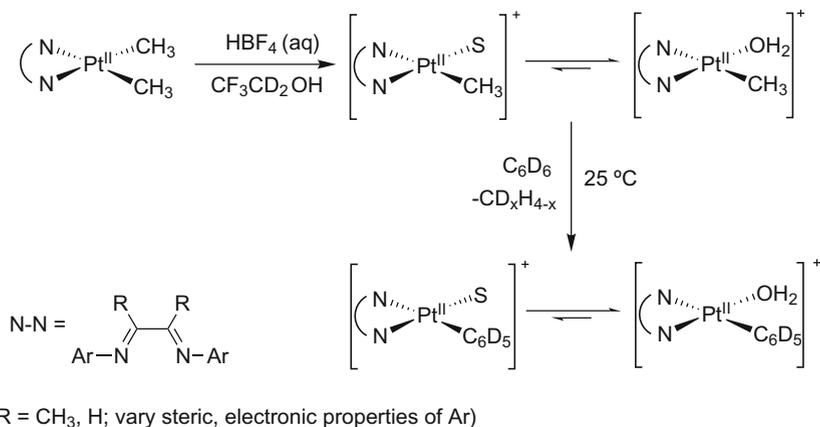


Scheme 2.7 Mechanism for protonolysis of (alkyl)Pt(II) complexes



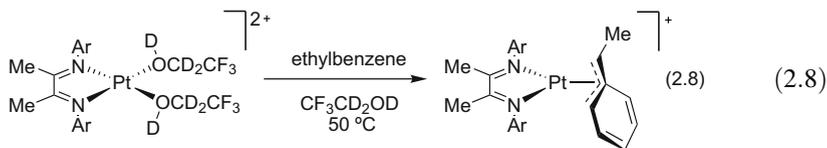
Scheme 2.8 Formation of a stable alkyl(hydrido)Pt(IV) complex via oxidative addition of alkane

Another important conclusion from this study is that electronic effects are manifested primarily in how tightly the ligand to be displaced is bound to the metal. This helps resolve some of the observations that appear at first to be at odds with the description of this chemistry as “electrophilic” (although it should be

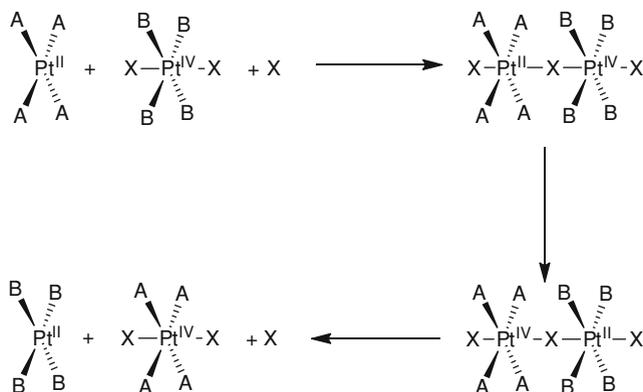


Scheme 2.9 Trifluoroethanol-based model for C–H activation studies

pointed out, once again, that we are not necessarily ascribing any mechanistic content to the term). Whereas one might expect the most electrophilic complexes—those with the highest positive charge and/or most electron-withdrawing ligands—to be the most reactive, in fact that is rarely what is found. Most of the reactivity trends in Scheme 2.9, as the N–N ligand is varied, reflect changes in the equilibrium between the aquo and solvento complexes (only the latter reacts with C–H bonds), rather than affinity for the hydrocarbon substrate [32]. Likewise, dicationic disolvento complexes can be generated; these would be expected to be much more electrophilic, and they *do* exhibit C–H activation, but only at benzylic or allylic positions (e.g., Eq. 2.8), not with simple alkanes; furthermore, the reactions are considerably slower than those of the analogous monocations of Scheme 2.9 [34]. It is clear that facile “displaceability” of a ligand is a crucial element of an efficient alkane functionalization system.



The question of the relative reactivity of different C–H bonds can also be addressed using these model systems. An anhydrous version of the system shown in Scheme 2.9 reacts readily with a variety of alkanes and cycloalkanes according to Eq. 2.9, with rapid β -hydrogen elimination following C–H activation; the rate constant for the various substrates (after correction for statistical factors) varies only slightly [35]. The same model complex was used to determine the relative reactivity of methane (using ¹³C labeling) and methanol (Scheme 2.10), giving a ratio of rate constants k_2/k_1 around 1.3, [36] on the same order as that estimated for



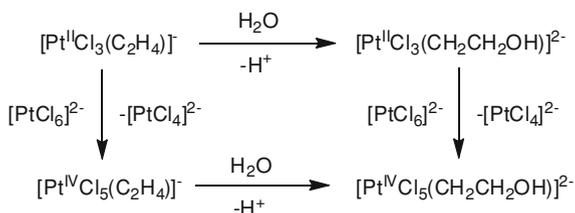
Scheme 2.11 Schematic representation of the inner-sphere mechanism for Pt(II)-Pt(IV) redox reactions

be able to compete under Shilov oxidation conditions. It is not at all obvious why it should be so fast. The “standard” mechanism for a redox reaction between Pt(II) and Pt(IV) is via a 2-electron, inner-sphere pathway, as in Scheme 2.11; the requirement for an additional X^- ligand in the symmetric bridged transition state is responsible for the commonly observed third-order kinetics [37]. Such a mechanism has been demonstrated for N-ligated complexes of the sort used for the model studies described in the previous section [38–40].

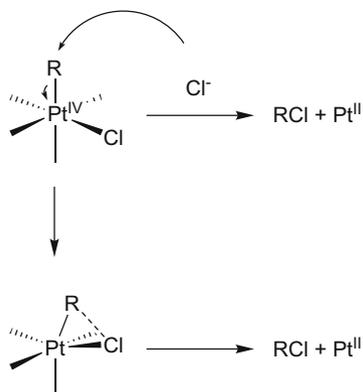
An example more closely relevant to the actual Shilov system, the self-exchange between $[\text{PtCl}_4]^{2-}$ and $[\text{PtCl}_6]^{2-}$, was examined by following the exchange of isotopically labeled Cl [41]; although rigorous quantitative comparison is not possible because of the complexity of the systems, the upper limit of that self-exchange rate would be far too slow (by at least several orders of magnitude) to compete with the lowest estimate of the rate of protonolysis. Of course, one *would* expect the reaction of $[\text{PtCl}_3\text{R}]^{2-}$ with $[\text{PtCl}_6]^{2-}$ to be faster (but how much faster?). First, there is a substantial driving force (absent in self-exchange) due to the replacement of Cl by R, which makes the Pt(II) complex more electron-rich and more susceptible to oxidation, as has been documented by both electrochemical data and reactivity trends in a model system [38]. Also, the greater *trans* effect of R should accelerate formation of the bridged species, a process that in effect amounts to nucleophilic attack on square planar Pt(II). Another possibility, however, is that the reaction involves *alkyl* transfer rather than electron transfer—although here too it is far from clear why that should be a fast process.

These two alternatives may be distinguished by labeling the respective Pt centers and determining which one the R group ends up on. For model systems, electron transfer is easily demonstrated by using different ligands on the Pt(II) and Pt(IV) reacting partners [38], but for the actual Shilov system, where RPt(II) is not readily available and all the other ligands are (freely exchanging) chloride and water, isotopically labeled Pt is required. The first such study took advantage of the observation that Zeise’s salt, $[\text{PtCl}_3(\text{C}_2\text{H}_4)]^-$, is oxidized by $[\text{PtCl}_6]^{2-}$ to a

Scheme 2.12 Alternate pathways for oxidation of Zeise's salt to an (alkyl)Pt(IV) species



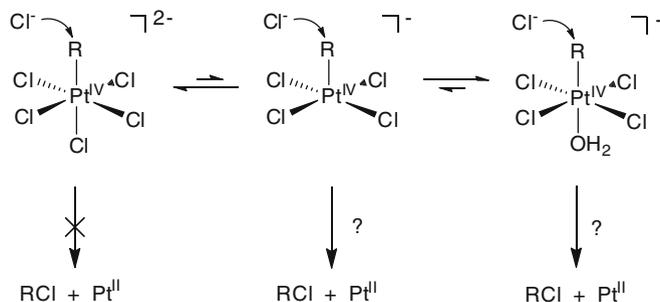
Scheme 2.13 Alternative $\text{S}_{\text{N}}2$ (top) and intramolecular reductive elimination (bottom) routes for liberation of RCl from RPt(IV)



(2-hydroxyethyl)Pt(IV) species. There are two possible routes for that reaction: prior nucleophilic attack of water on the coordinated olefin to give (2-hydroxyethyl)Pt(II) which undergoes oxidation; or initial oxidation to a Pt(IV) ethylene complex that reacts with water (Scheme 2.12); only the former would be a true analog of the redox step of the Shilov system. Kinetics established that the former path is indeed followed, and use of enriched $[\text{}^{195}\text{PtCl}_6]^{2-}$ led to *no* enrichment in the (2-hydroxyethyl)Pt(IV) product, arguing for the electron transfer route [42]. Subsequently an analogous experiment, in which the insoluble $[\text{PtCl}_3\text{R}]^{2-}$ salt mentioned in the previous section was oxidized by $[\text{}^{195}\text{PtCl}_6]^{2-}$, led to the same conclusion [27].

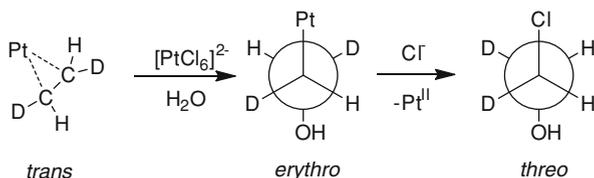
2.2.2.3 C-X Bond Formation

Two issues pertain to the liberation of RX ($\text{X} = \text{OH}, \text{Cl}$) from (alkyl)Pt(IV). First, does the product form via intramolecular reductive elimination of RX , or by external nucleophilic attack of X at R , with Pt(II) as the leaving group (Scheme 2.13)? Second, does the reaction take place from the intact six-coordinate Pt(IV) complex, or from a five-coordinate intermediate species generated by prior ligand dissociation (as is common to many reductive elimination processes)? Since (as noted earlier) representative (alkyl)Pt(IV) complexes can be independently synthesized and are quite stable, this step has proven the most amenable to direct study.



Scheme 2.14 Possible intermediates in liberation of RCl by nucleophilic attack; kinetics rules out the first, but does not distinguish between the other two

Scheme 2.15 Experiment demonstrating inversion of stereochemistry in formation of RCl from RPt(IV)



Early studies strongly supported nucleophilic attack; perhaps most telling was the observation that an external nucleophile, such as Br^- , is incorporated into RX *much faster* than it exchanges into a position *cis* to R in RPt(IV) [43]. The kinetics are also consistent with nucleophilic attack: the dependence of the rate of disappearance of RPt(IV) on chloride concentration takes the form shown in Eq. 2.10, while the proportion of $\text{RCl}:\text{ROH}$ increases with $[\text{Cl}^-]$. The appearance of $[\text{Cl}^-]$ in the denominator suggests that the reaction proceeds via a five-coordinate intermediate; but in fact the kinetics are equally consistent with nucleophilic attack occurring at a six-coordinate complex with an aquo (but *not* a chloride) ligand *trans* to the R group (Scheme 2.14). While there is no way to distinguish between these two possibilities, the former seems clearly favored by the fact that it is the microscopic reverse of the first step of many examples of oxidative addition of methyl halide to square-planar, four-coordinate d^8 complexes [42].

$$\frac{-d[\text{RPt}^{\text{IV}}]}{dt} = \frac{k_1[\text{Cl}^-] + k_2[\text{H}_2\text{O}]}{1 + K[\text{Cl}^-]} \quad (2.10)$$

Conclusive evidence supporting the nucleophilic attack mechanism was obtained from a stereochemical study. A stereolabeled (alkyl)Pt(IV) complex was synthesized by the oxidation of Zeise's salt (as in Scheme 2.12) prepared from *trans*-1,2-dideuterioethylene; the resulting (mostly) *erythro* isomer of the (2-hydroxyethyl)Pt(IV) complex reacts with Cl^- to liberate *threo*-2-chloroethanol (Scheme 2.15), demonstrating inversion of configuration, as expected for $\text{S}_{\text{N}}2$ [42].

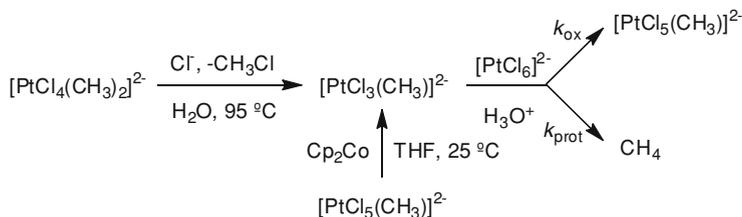
2.2.2.4 Global Mechanism Considerations

From the work summarized in the three preceding sections, we can say with confidence that the three-step sequence originally proposed for the Shilov system (Scheme 2.4) stands on very firm ground, and can fill in many of the finer mechanistic details for each of the three steps. How do they fit together to account for overall behavior? As already noted, the close similarity between Shilov oxidation and Pt(II)-catalyzed H/D exchange, in terms of both rates and selectivities for different C–H bonds, implies that the first step, C–H activation, is rate-determining for oxidation. That conclusion is consistent with *most* observations, but there are a couple of apparently discordant findings. Most notably, Shilov and coworkers reported that a solution used for oxidation of methane, after cooling, exhibited the NMR signal of $[\text{PtCl}_5(\text{CH}_3)]^{2-}$ [44]; if both steps 2 and 3 are significantly faster than step 1, one would not expect any significant buildup of that intermediate. (Indeed, a later examination under actual reaction conditions, using pressure-resistant NMR tubes, found no evidence of that NMR signal [45]).

Another is found in the kinetics for the oxidation of acetic acid to chloroacetic acid: the rate is independent of $[\text{Pt(IV)}]$, as expected if step 1 is rate-limiting, but only up to 100 °C; at higher temperatures (and at low $[\text{Pt(IV)}]$ levels) the rate law includes a term first-order in $[\text{Pt(IV)}]$ [46]. The implication is that the activation energy for step 2 is lower than that for step 1, so that as the temperature is raised step 1 speeds up more and step 2 becomes rate-limiting. In the high-temperature regime the activation energy was measured to be around 9 kcal/mol [46], similar to the value of 7 kcal/mol determined for Pt(II)-Pt(IV) redox in a model system [38] and for the $[\text{PtCl}_4]^{2-}/[\text{PtCl}_6]^{2-}$ self-exchange reaction [38, 41].

As previously noted, the oxidation of RPt(II) (step 2) must be faster than protonolysis (reverse of step 1) for overall oxidation to succeed. The *relative* rates of those two processes have been estimated by two different procedures (both alluded to above). The (dimethyl)Pt(IV) complex shown in Scheme 2.6, besides undergoing C–C reductive elimination to give ethane, reacts in aqueous Cl^- at 95 °C to generate (transiently) the key (methyl)Pt(II) intermediate. If that reaction is carried out in the presence of varying concentrations of $[\text{PtCl}_6]^{2-}$ and H^+ , the ratio of the rate constants for oxidation and protonolysis can be obtained straightforwardly from the relative amounts of (methyl)Pt(IV) (which is itself unstable to the reaction conditions, but the methyl chloride thus liberated can be measured) and methane produced [43]. A similar experiment can be carried out at lower temperature, by dissolving solid $[\text{PtCl}_3(\text{CH}_3)]^{2-}$ (part of the salt mixture obtained by reducing $[\text{PtCl}_5(\text{CH}_3)]^{2-}$ with cobaltocene) in aqueous $[\text{PtCl}_6]^{2-}/\text{H}^+$ [27]. The relative rate constants thus determined are (Scheme 2.16): $k_{\text{ox}}/k_{\text{prot}} \sim 20$ at 95 °C [43, 47] and near one at room temperature [27, 47]. By extrapolation, oxidation should be even more dominant around 120 °C, more typical of Shilov conditions.

The fact that the rate constant ratio increasingly favors oxidation as the temperature rises, along with the earlier report that oxidation becomes rate-limiting at higher temperatures, implies that the activation energies are in the order: C–H



Scheme 2.16 Reactions used to determine relative rates of oxidation and protonolysis of an (alkyl)Pt(II) complex at elevated and room temperatures

activation (step 1) > oxidation (step 2) > protonolysis (reverse of step 1). That may not be unreasonable; one might expect protonolysis to have a low activation barrier. It should be noted, however, that these two studies were carried out in different media, water and aqueous acetic acid respectively. That could well have a significant impact on the oxidation step, since a reaction requiring two negatively charged species to get together should be facilitated by the more polar medium. This may account for a significant difference in behavior: whereas Shilov oxidation in acetic acid is accompanied by a substantial amount of H/D exchange [14–17], in water no H/D exchange takes place until after deposition of Pt metal has been observed [45, 48]. Thus, although protonolysis and oxidation may take place at comparable rates in acetic acid, in water protonolysis is always much slower than oxidation until the appearance of Pt metal, which may catalyze the exchange reaction itself and/or signal the point where the concentration of Pt(IV) has been reduced enough to allow protonolysis to compete.

This effect may also explain why the two media differ in the propensity to deposit Pt metal, which is much less pronounced in acetic acid than in water. Although Pt(II) can on its own disproportionate to Pt(IV) and Pt(0) under some conditions, it seems more likely that the appearance of Pt metal in the Shilov system results from oxidation of RPt(II) by inorganic Pt(II) (Eq. 2.11), which as discussed above should be thermodynamically more favorable than disproportionation. Since this redox reaction, like the previous one, involves two negatively charged participants, it could be much more important in water than in acetic acid. (The reaction of “purely” aqueous Pt(II) with hydrocarbons was examined by means of inverted micelles, as an alternative to the use of aqueous acetic acid; H/D exchange appears to behave more or less similarly, but formation of metallic Pt is observed [49].) An analog of the experiment portrayed in Scheme 2.16 indicated that $[\text{PtCl}_4]^{2-}$ is *not* capable of oxidizing $[\text{PtCl}_3(\text{CH}_3)]^{2-}$ competitively with protonolysis at room temperature [27], but if the same temperature trends hold here as for oxidation by $[\text{PtCl}_6]^{2-}$, at operating Shilov temperatures Eq. 2.11 could well be a competent mechanism for Pt metal formation.



In the following sections we will examine potential applications, of both the original Shilov system and modifications thereof, within the context of this well-delineated mechanistic framework.

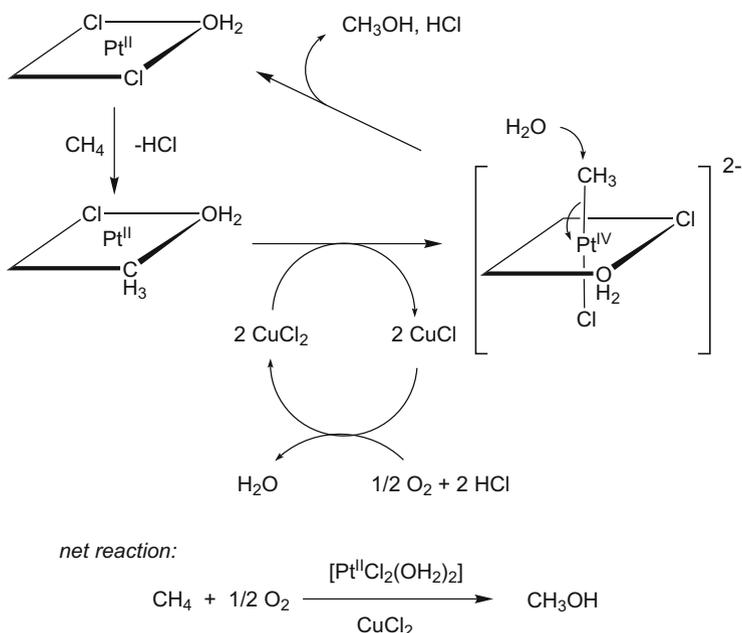
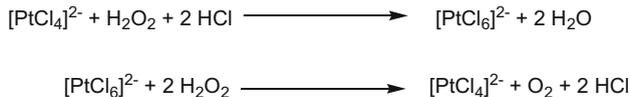
2.2.3 Potential Applications

Beyond the fundamental interest in Shilov oxidation as an unusual reaction, does it present any practical opportunities? If we are interested in large-scale applications, such as direct conversion of methane to methanol, we obviously need to replace Pt(IV) with something *much* cheaper—preferably O₂—as the stoichiometric oxidant. On the other hand, it is conceivable that the original Shilov system might be a useful tool in the laboratory-scale synthesis of complex products by functionalization at a saturated position, but only if sufficiently high selectivity can be achieved.

2.2.3.1 Alternate Oxidants

There are fairly severe constraints on possible choices for an alternate stoichiometric oxidant in a large-scale alkane functionalization process. First, it must be very cheap; for production of a fuel/commodity chemical such as methanol, it is most unlikely that anything but O₂ will be cheap enough. Unfortunately, unlike Pd (see below), it does not appear that any of the intermediate Pt species can be directly oxidized by O₂, so the oxidant will have to be regenerable by O₂ under reaction conditions. Second, while it has to oxidize the (alkyl)Pt(II) intermediate, it must not be strong enough to oxidize *inorganic* Pt(II), since the mechanism requires the latter for C–H activation. And finally, the rate of oxidation of (alkyl)Pt(II) must be extremely fast to compete with protonolysis. Given the particular mechanism of the Pt(II)-Pt(IV) redox process, it is not obvious what other oxidants could be equally fast.

In earlier work several oxidants were found to achieve some catalytic oxidation, although even the best results gave only a handful of turnovers. Some, such as chlorine [45] or peroxydisulfate [50], are clearly too expensive and *not* regenerable with O₂. Other systems use catalytic amounts of oxidants, such as CuCl₂ [51] or polyoxometalates [52, 53], which (at least in principle) *can* be reoxidized by dioxygen, making the latter the stoichiometric oxidant. Indeed, with Cu(II) under elevated O₂ pressures, ethanesulfonic acid (a water-soluble alkane surrogate) can be oxidized to 2-hydroxyethanesulfonic acid with a significant number (50 or more) of turnovers. Several other substrates, including methanesulfonic acid (which is somewhat less reactive, probably reflecting the effect of the fairly strong electron-withdrawing substituent), propanesulfonic acid, ethylphosphonic acid, and propionic acid, could be similarly oxidized to hydroxy compounds [54]. If this modified Shilov system could operate on methane, the overall reaction would

**Scheme 2.17** Modified Shilov mechanism with Cu(II)/O₂**Scheme 2.18** Disproportionation of H₂O₂ accompanies its use as an oxidant in the Shilov system

amount to direct oxidation of methane to methanol by dioxygen (Scheme 2.17). Recently a Pt/Fe(III)/O₂ combination (discovered using a microfluidic screening device) showed some success for selective methane oxidation, giving up to 50 turnovers of a mixture of methanol and formic acid [55].

With most of these alternative oxidants (but not Cu(II)/O₂; see below) the catalyst dies in the same manner as the original Shilov system, by deposition of Pt metal, resulting in degradation of both activity and selectivity, since as noted earlier the latter is a good catalyst for alcohol oxidation. In one study, which used electrochemically regenerated polyoxometalate, the selectivity for oxidation of *p*-toluenesulfonic acid to the corresponding benzylic alcohol decreased steadily as the number of turnovers increased, accompanied by the appearance of Pt metal [56].

Hydrogen peroxide has also been shown to function as an alternative oxidant in the Shilov system, despite its being able to oxidize inorganic Pt(II), because it also functions as a reductant; the combination of steps in Scheme 2.18 maintains a

sufficient steady-state concentration of Pt(II) to allow C–H activation and functionalization to take place [57]. The downside, of course, is that large quantities of H_2O_2 are consumed; clearly this inefficiency would prevent any practical applications.

The ability of Cu(II) to function as an “appropriate” oxidant for Shilov chemistry was further tested by carrying out the competitive reactions of Scheme 2.16 using CuCl_2 instead of $[\text{PtCl}_6]^{2-}$. Somewhat surprisingly, the former turns out to be an even *faster* oxidant: at 95 °C, the ratio of the rate constant for oxidation to that for protonolysis of $[\text{PtCl}_3(\text{CH}_3)]^{2-}$ is around 200, an order of magnitude higher! Effective competitive oxidation was also observed for FeCl_3 and the polyoxometallate $[\text{H}_3\text{PMo}_9\text{V}_3\text{O}_{40}]^{3-}$, both of which exhibit reactivity approximately equal to that of $[\text{PtCl}_6]^{2-}$. Even more importantly, the competitive experiment can be performed using only a stoichiometric amount of Cu(II) under an O_2 atmosphere, and the same relative reactivity is observed, demonstrating that the recycle of Cu(I) to Cu(II) is fast compared to substrate oxidation [47].

Clearly fast oxidation is not a consequence of something special about the redox mechanism of Scheme 2.11. Indeed, Cu(II) seems much more likely to act as a *one*-electron oxidant, which would require a stepwise mechanism and a (presumably highly unstable) Pt(III) intermediate. Conceivably two-electron oxidation could be achieved via a pre-formed multimetallic complex involving two or more Cu(II) centers; however, fast oxidation is also observed using $[\text{IrCl}_6]^{2-}$ [47], and it seems extremely unlikely that this Ir(IV) species could function in anything other than a stepwise, one-electron mode (the oxidation of $[\text{PtCl}_4]^{2-}$ by $[\text{IrCl}_6]^{2-}$ has been shown to go by consecutive one-electron steps [58]). It thus appears that the (kinetically) facile oxidation of $[\text{PtCl}_3(\text{CH}_3)]^{2-}$ is not dependent upon any particular mechanism, and sufficient reactivity to compete with protonolysis can be achieved with a fairly wide range of (thermodynamically) competent oxidants.

Since Cu(II) is so effective an oxidant, and since when run under O_2 the effective concentration of oxidant should not decrease over time (until the O_2 is mostly consumed), one would think that this modification of the Shilov system should *not* deactivate by precipitation of metallic Pt. Indeed that appears to be the case—no appearance of Pt(0) was reported in the above-described study [54]—but nonetheless this catalytic system, comprised of Pt(II), Cu(II) and O_2 , *does* deactivate. In later work (which found up to 100 turnovers for oxidation of the methyl group of *p*-toluenesulfonic acid) it was determined that the deactivation results from complete conversion of Pt(II) to Pt(IV) [59], a reaction also observed in the experiments measuring the relative rate of RPt(II) oxidation by Cu(II)/ O_2 [47]. But Cu(II) by itself can't be capable of oxidizing inorganic Pt(II), since as discussed above that would preclude catalysis altogether; the reverse reaction, oxidation of CuCl by $[\text{PtCl}_6]^{2-}$, has been demonstrated and studied kinetically [60]. It must be the case, then, that the combination of Cu(II) and O_2 generates an oxidant that is thermodynamically stronger than Cu(II) alone and kinetically faster than O_2 alone, possibly a copper-peroxide complex. If not for this additional complication, the Pt(II)/Cu(II)/ O_2 system could well comprise a practical catalyst for selective functionalization of certain C–H bonds.

2.2.3.2 Selective Transformations

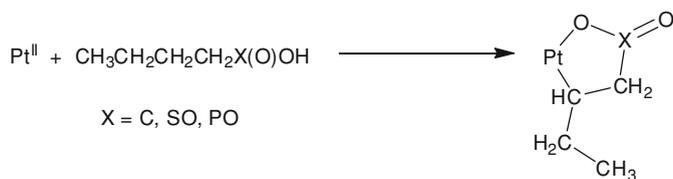
While there remain major barriers to practical implementation of the Shilov system for functionalization of alkanes and related molecules, as discussed in preceding sections, it is certainly possible that useful applications might arise, given the right combination of desired target and available precursor. Almost certainly these would involve small-scale processes, where low catalytic efficiency and the cost of the oxidant need not be fatal flaws. Even then, we will normally want to functionalize at a particular position with high selectivity, and that will be attainable only in special cases: where potentially competing sites are deactivated by steric and/or electronic factors, or where a substituent on the substrate can lead to directed activation by coordinating to Pt. A few suggestive examples have been reported and are summarized here.

The formation of (some) ethylene glycol from ethanol was mentioned earlier; since the initial product of Shilov oxidation of ethane should be ethanol (along with ethyl chloride, depending on conditions), the direct conversion of ethane to ethylene glycol should be possible. That has been demonstrated, although no estimate of selectivity or yield was made [61]; but the earlier findings on ethanol oxidation show that there is little discrimination between C–H bonds, and coupled with the propensity for overoxidation—especially after Pt metal has begun to deposit—selectivities must be well below 50 %. Of course, one might *want* the “overoxidized” product: oxidation of ethane using a combination of Pt(II) and Pt(0) gave primarily acetic acid (along with some glycolic acid), although less than one equivalent was obtained [62]. While it is possible to deactivate C–H bonds by steric crowding or electronegative substitution, there is no obvious indication that particular bonds can be *activated*; for example the benzylic and terminal methyl C–H bonds in *p*-ethylbenzenesulfonic acid are about equally reactive [48].

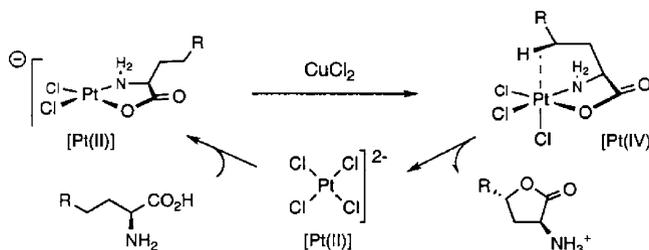
As we move away from actual alkanes to more complex molecules, some degree of selectivity can be achieved by directed functionalization of potentially chelating substrates. Sen has shown that oxidation of alcohols, as well as carboxylic, sulfonic, and phosphonic acids, tend to give preferential reaction at sites that would lead to favorably sized rings upon C–H activation if the original functional group is also coordinated to Pt (Scheme 2.19). For carboxylic acids the typical selectivity order is $\alpha\text{-CH} \ll \beta\text{-CH} < \gamma\text{-CH} \sim \delta\text{-CH}$ [63].

In related chemistry, Sames has found that amino acids can be selectively hydroxylated by either the original or the Cu(II)-modified Shilov system. Thus valine is converted to hydroxyvaline (obtained as the lactone) in up to 50–60 % yield and 20 turnovers. Selectivity was proposed to arise via preferential attack at the γ position of valine coordinated through *both* O and N (Scheme 2.20). With other amino acids some pyrrolidine products were also obtained, via competing functionalization at the δ position followed by intramolecular S_N2 attack by N (either directly as shown in Scheme 2.21, or perhaps subsequent to formation of a chlorinated intermediate) [64].

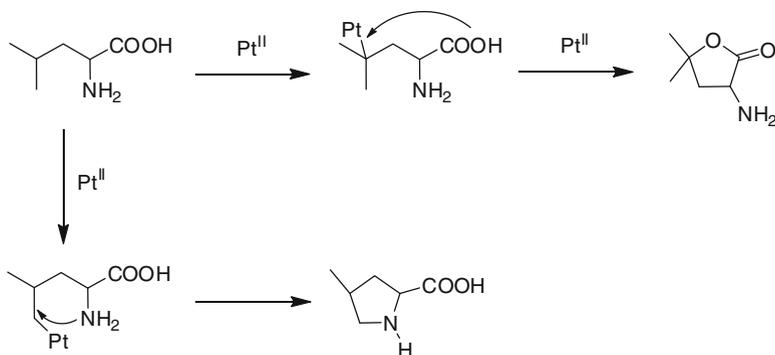
The most elaborate example (we have gotten very far away from simple alkanes here!), from the same group, makes use of one of the Shilov models discussed



Scheme 2.19 Selective functionalization of organic acids via chelation

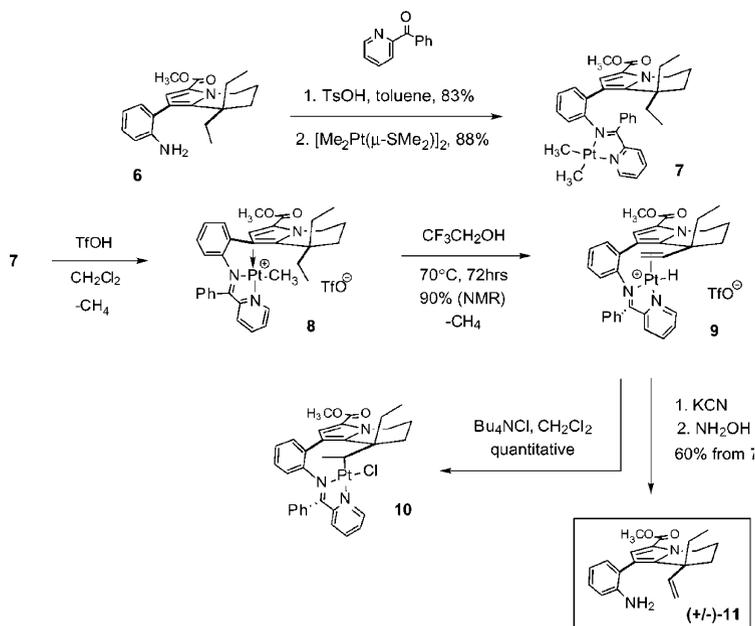


Scheme 2.20 Proposed mechanism for selective oxidation of valine. Reprinted from Ref. [64] with kind permission of © The American Chemical Society (2001)



Scheme 2.21 Competing γ (top) and δ (bottom) functionalization of leucine

earlier: a substituted aniline containing the C–H group to be activated (the terminal end of an ethyl group) was incorporated into an imine ligand that could be coordinated to a PtMe₂ group. After protonolytic cleavage of one of the Pt–Me bonds, the resulting reactive Pt(II) center was in just the right position to selectively activate the target saturated C–H bond, resulting in an (alkyl)Pt(II) species. The latter spontaneously underwent β -hydride elimination, followed by detaching the resulting olefin—the desired product—from Pt (Scheme 2.22). This highly selective functionalization was a crucial step in the total synthesis of the antitumor agent rhazininilam [65].



Scheme 2.22 Selective functionalization of a C–H bond by Pt(II) in the total synthesis of a complex natural product. Reprinted from Ref. [65] with kind permission of © The American Chemical Society (2002)

Electrophilic C–H activation has been increasingly used as a solution to complex organic synthesis problems, most commonly involving Pd; some examples (but by no means a comprehensive survey) will be presented in Sect. 2.4.1.2.

2.3 Other Platinum-Based Functionalizations

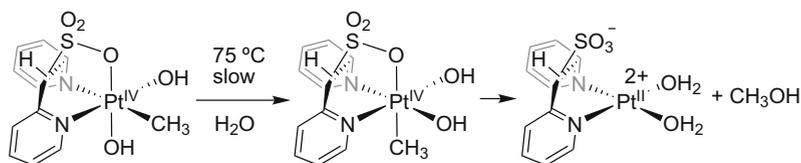
A priori there is no reason at all why the original Shilov system should be best suited for alkane functionalization, but few attempts at modification by introducing new ligands to the Pt coordination sphere have led to improvement—with one very notable exception.

2.3.1 Ligand-Substituted Complexes

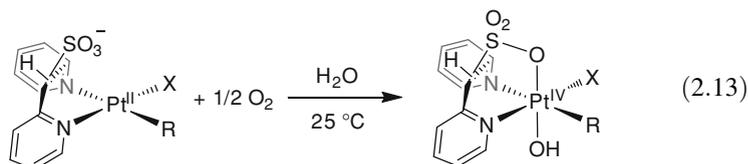
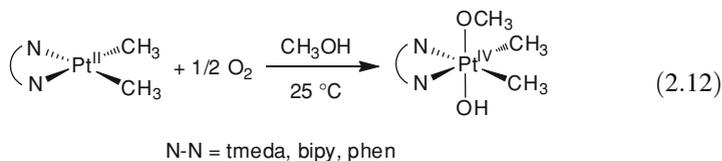
As indicated earlier, there is a *very* large body of work on C–H activation by ligand-substituted Pt(II) complexes [23], but not so many examples of functionalization. Since C–H activation, the first step of the Shilov cycle, appears to

be rate-determining under most or all conditions, one should look first at the effect of ligands on that step. Early work by Shilov's group included substitution of various anions for chloride; the rate of H/D exchange correlates fairly well *inversely* with their *trans*-directing power: $\text{CN}^- < \text{NO}_2^- < \text{I}^- < \text{Br}^- < \text{Cl}^- < \text{F}^-$ [16, 17]. Since a variety of studies strongly indicate that displacement of water by the C–H bond of the alkane is rate-limiting for both H/D exchange and oxidation, that finding at first seems a bit surprising: a better *trans*-directing ligand might be expected to facilitate ligand substitution. DFT calculations suggest that such a simple correlation is not to be expected, as the predicted barriers depend strongly on solvation factors as well as the relative abundance of Pt(II) species and which ligand is replaced; for really strong *trans*-directing ligands such as cyanide or neutral amines and phosphines, the C–H activation barrier increases and becomes rate-limiting [66, 67]. Indeed, generally the addition of “good” ligands to the Shilov system completely inhibits C–H functionalization. Amino acids seem to be one exception: in addition to the intramolecular functionalizations discussed in the preceding section, substitution of $[\text{Pt}(\text{glycinato})\text{Cl}_2]^-$ for $[\text{PtCl}_4]^{2-}$ in a standard Shilov reaction leads to (small) improvements in both activity and selectivity [68].

The inclusion of ligands in the Shilov system can be expected to affect the rates of all the steps differently; the effect upon the second and third steps, oxidation and C–X bond formation, can be particularly important if either one becomes rate-limiting for a particular catalytic reaction, as is certainly possible. (We will see an example in the following section.) One would expect that replacement of one or more electron-withdrawing chlorides by better-donating N- and P-centered ligands would facilitate oxidation, and that generally seems to be borne out. Of particular interest is the fact that some relevant Pt(II) complexes can be oxidized to Pt(IV) by O_2 ; examples include those shown in Eqs. 2.12 [69, 70] and 2.13 [71]. In the former the presence of *two* electron-releasing methyls along with the N–N ligand is required for the facile oxidation; in the latter, the availability of a “dangling” sulfonate group that can serve in chelate mode as the sixth ligand in the Pt(IV) product presumably provides the additional boost needed when the Pt(II) complex contains only one methyl group. No clearcut demonstration of a ligated system that sequentially effects both C–H activation and aerobic oxidation has been achieved, however. A possible example is the combination of $[\text{Pt}(\text{Mebpym})\text{Cl}_2]^+$ (where Mebpym is derived from the bipyrimidine ligand discussed in the next section by methylation at one of the non-coordinated N centers) and the polyoxometalate $\text{H}_5\text{PV}_2\text{Mo}_{10}\text{O}_{40}$, supported on silica; that system was reported to catalyze oxidation of methane at 50 °C by O_2 , giving some methanol and (mostly) acetaldehyde, with up to 30 turnovers [53]. The formation of acetaldehyde, a quite unexpected product, has not been completely explained.



Scheme 2.23 Liberation of methanol from (methyl)Pt(IV) proceeds via isomerization to place a labile ligand *trans* to the methyl group

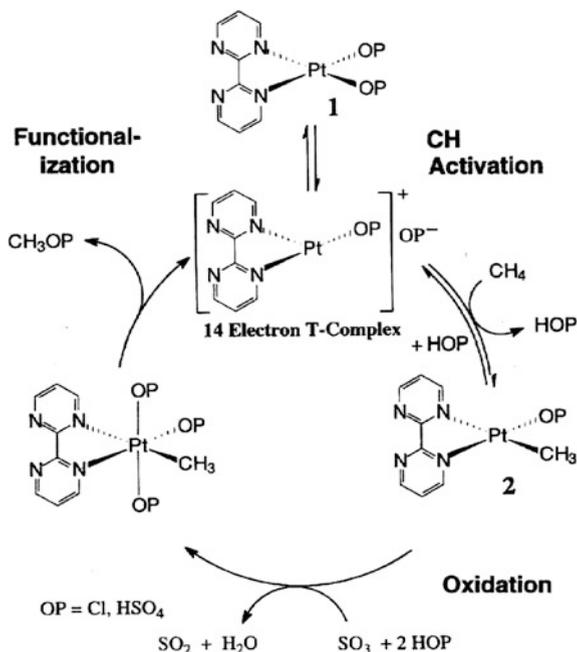


In contrast to the oxidation step, incorporation of strongly-binding ligands—especially chelators—may well be detrimental for the final C-X bond forming step. In most or all cases where the mechanism of that step has been elucidated, a vacant site *trans* to the Pt–C bond is required for nucleophilic attack by X at the R group, which will be more difficult or even impossible if that position is occupied by a good ligand. That situation is most clearly manifested by Vedernikov’s Pt(IV) complex shown in Eq. 2.13 (where X = OH), which undergoes loss of methanol in water, but only at elevated temperature, and mechanistic examination shows that the net reductive elimination is preceded by geometrical isomerization, to get the methyl group *trans* to the labile sulfonate ligand (Scheme 2.23) [72]. Clearly there are a number of factors, including geometric ones, that will need to be considered in designing complexes for Shilov-like catalytic alkane functionalization.

2.3.2 The Catalytica System

There *is* one highly successful variant of Shilov chemistry based on ligand-substituted Pt(II): the 1998 report of Pt-catalyzed selective oxidation of methane to methyl bisulfate [73], an advance upon the earlier Hg-based system (Sect. 2.4.6), was and remains the most impressive achievement of high selectivity, conversion and yield in functionalization of a simple alkane. Whereas, as noted above, ligands generally are detrimental to the original Shilov system (which operates around 120 °C in water or aqueous acetic acid), that does not appear to

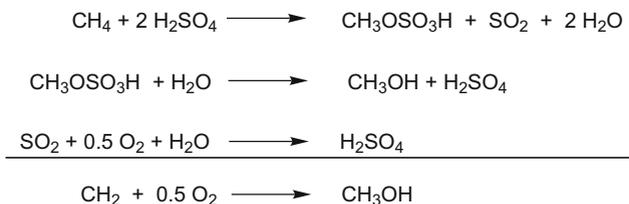
Scheme 2.24 Originally proposed mechanism for oxidation of methane by the Catalytica system. Reprinted from Ref. [73] with kind permission of © The American Association for the Advancement of Science (1998)



be the case under more extreme conditions: a number of bis(N-ligated)Pt(II) complexes—even the simplest example, $\text{Pt}(\text{NH}_3)_2\text{Cl}_2$ —are moderately active for methane oxidation in concentrated sulfuric acid at 180 °C, oxidizing methane according to Eq. 2.14, with initial turnover rates on the order of 10^{-3} /s. While the simple ammine complex is only marginally stable to the reaction conditions, decomposing in less than an hour, the analogous bipyrimidine (bpym) complex (shown in Scheme 2.24) persists indefinitely. Indeed, it is not only kinetically inert but thermodynamically stable: it is readily generated by adding either PtCl_2 or Pt metal to a hot solution of bpym in concentrated H_2SO_4 .



The mechanism originally proposed for this reaction (Scheme 2.24) is closely analogous to that of the Shilov system, with a couple of differences. First, as shown in the scheme, a dissociative route for activation of methane was suggested (without any specific experimental support), in contrast to the associative pathway established for several Shilov models. The question of which of the alternate paths the actual C–H bond cleavage follows (see Scheme 2.5 above) was left open. More importantly, in this system the rate-limiting step appears to be oxidation of Pt(II) to Pt(IV), rather than C–H activation, as indicated by the much greater extent of H/D exchange than in the Shilov system; indeed, the (bpym)Pt(II) complex can effect exchange without any oxidation at all by either going to a lower temperature (< 150 °C) or substituting non-oxidizing triflic acid as the reaction medium.



Scheme 2.25 Combined process for conversion of methane to methanol based on the Catalytica system

The Catalytica system achieves up to 90 % methane conversion with 81 % selectivity to methyl bisulfate, an overall yield of 72 %, far higher than any other reports. Based on considerations discussed above, such a result requires that the relative C–H bond reactivity of CH_4 : $\text{CH}_3\text{OSO}_3\text{H}$ be on the order of 100 :1, in contrast to the typically \sim 1:1 ratios observed for alkanes:alcohols in the Shilov system as well as models. (Unfortunately a direct comparison cannot be made using the models, as was done for methane and methanol, since methyl bisulfate will methylate model Pt(II) complexes instead of undergoing C–H activation.) Presumably this is a consequence of the strongly electron-withdrawing nature (and perhaps some steric contribution as well) of the sulfate substituent.

Although methyl bisulfate is not in itself a desirable product, it can be readily hydrolyzed to methanol; also the SO_2 byproduct can be reoxidized to H_2SO_4 by O_2 . Hence this new reaction, coupled with two very old ones, comprises the net catalytic conversion of methane plus dioxygen to methanol (Scheme 2.25), with parameters of conversion and selectivity that appear potentially compatible with practical application. Unfortunately, more detailed analysis shows that the process will almost certainly *not* be close to competitive with the existing route from methane via syngas to methanol [74, 75], for several reasons. First, the rates are *far* too low: turnover frequencies on the order of 1/s are normally the minimum required for practical processes, and that is three orders of magnitude higher than the best results found here. Next, the chemistry only works in highly concentrated (fuming) sulfuric acid, and since water is a byproduct, the medium would need to be “regenerated” after a short time. Additionally, the complexity and cost of moving large quantities of sulfuric acid through a system consisting of three separate reactions is so high that it outweighs the advantages of high-yield, moderate temperature direct methane conversion. The bpym and related Pt complexes have been supported on solid polymers in an attempt to facilitate catalyst separation and recycling, which is one (but probably not the most important) of the process problems, with some success at reproducing the performance of the homogeneous system [76]. Furthermore, it seems very unlikely that this chemistry could be used for functionalizing anything *but* methane, as the products of more complex alkanes will almost certainly be unstable to the harsh reaction conditions.

Accordingly, most of the subsequent effort on this and related reactions has focused on better understanding of the mechanism and the factors controlling reactivity, which could lead to potentially more practical systems. Much of that work has been

computational, with the earliest work on the simpler ammine complex $\text{Pt}(\text{NH}_3)_2\text{Cl}_2$ suggesting that an H_2SO_4 -solvated species, $[\text{Pt}(\text{NH}_3)_2(\text{OSO}_3\text{H})(\text{OSO}_3\text{H}_2)]^+$, is a likely candidate for the C–H activating species via displacement of the sulfuric acid by methane; σ -CAM appeared to be more likely than oxidative addition for the actual C–H cleavage step [77]. A following study on the same system concluded that NH_3 displacement might be involved instead [78]. Subsequently several groups have focused on the “real” Catalytica catalyst, the (bpym)Pt complex, but their work has not yet converged on a single preferred mechanism, with differing conclusions about the coordination of the Pt(II) species responsible for C–H activation, the detailed mechanism of the latter, and the question of whether or not the distal (non-coordinated) nitrogens in the bpym ligand are protonated. The calculations do generally agree with some aspects of the originally proposed mechanism: that methane coordination rather than C–H bond cleavage is rate-determining for C–H activation, and that oxidation of Pt(II) to Pt(IV) by sulfuric acid (or, more probably, SO_3) is rate-determining for the overall catalytic oxidation. References to this work may be found in a very useful recent review of computational work on C–H activation in general [79].

Goddard has argued for the utility of computational “screening” to search for ways to overcome the limitations of catalytic systems that may be revealed by experimental and theoretical studies [80]. Applying this approach to methane oxidation, it was predicted that changing bpym to a monoanionic ligand such as picolinate should reduce the barrier to methane coordination, the rate-determining step for C–H activation, and experimental studies indeed showed such a complex was more active for H/D exchange in benzene than its bpym analog [81]. This counts only as a partial validation, so far, because the picolinate complex is not stable at temperatures (>100 °C) needed to activate methane (for either H/D exchange or oxidation). The problem of deactivation by water has also been addressed: experimentally it has been found that the addition of ionic liquids improves water tolerance, although at considerable cost in performance [82]; calculations do not establish exactly how the effect operates [83].

2.4 Functionalization by Other Metal (and Non-Metal) Centers

It may be useful first to review what the various Pt-based systems for electrophilic functionalization of C–H bonds have in common, and what differences might be expected when we switch to other metals. The chemical properties exhibited by complexes in the various oxidation states, as well as the ease of moving between oxidation states, play a central role. For Pt, oxidation states 0, +2 and +4 are all reasonably stable, with no great kinetic or thermodynamic barriers between them. We observe net electrophilic chemistry—the (reversible) reaction between Pt and RH to give RPt and H^+ —in the +2 state, but the nucleophilic chemistry that accomplishes functionalization takes place only in the +4 state. Oxidation in effect thus amounts to an “umpolung” of the Pt–C bond, from $\text{Pt(II)}^{\delta+}\text{—R}^{\delta-}$ to $\text{Pt(IV)}^{\delta-}\text{—R}^{\delta+}$. Clearly it is

crucial that the interconversion between oxidation states be facile; more particularly, as discussed earlier, it must be substantially easier to oxidize RPt(II) than its inorganic precursor. All of this is accomplished by the Shilov and Catalytica systems. On the negative side, the Pt(0) state is easily accessible—indeed, for simple chloro-Pt species, the redox potentials for the Pt^{0/II} and Pt^{II/IV} couples are about equal—and Pt(0) once formed is hard to reoxidize, the most common cause of deactivation for the Shilov system. (The latter problem does not apply to the Catalytica system, but there are other limitations, as we have seen.)

For other metals, then, we need to consider how these requirements are satisfied: whether an oxidation state higher than the one responsible for the C–H activation is accessible; if not, whether both electrophilic activation and nucleophilic (or some other mode of) functionalization can be achieved at a single oxidation state; whether the catalyst can be too easily trapped in an inactive form. Other issues include substitutional lability—coordination of the C–H bond is often rate-determining—and, of course, cost, if practical applicability is the goal.

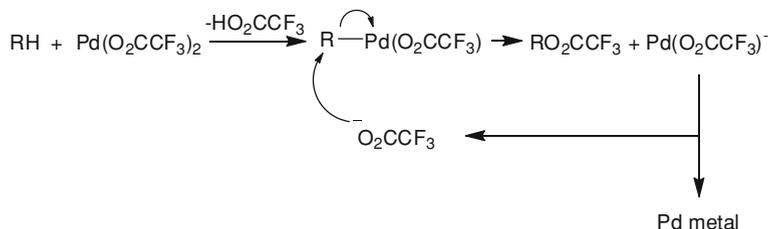
2.4.1 Palladium

Based on general periodic trends, oxidation of Pd(II) to Pd(IV) will be more difficult, for any given species, than the Pt analog. On the other hand, based on experience, it is generally easier to catch Pd(0) before it aggregates and reoxidize it to Pd(II) than to do the same for Pt(0). We might expect, then, that electrophilic functionalizations based on a Pd^{0/II} cycle would prevail, in contrast to the Pt^{II/IV} cycles discussed in the previous section. As we shall see, that mechanism does operate, but not in all cases: many functionalizations at *sp*³ C–H bonds appear to involve Pd(IV) intermediates [84, 85]. Also direct oxidation by O₂ appears to be much more common for Pd than for Pt, a significant potential advantage [86].

2.4.1.1 Alkane Oxidation

While there is no good example of a palladium analog of the Shilov system (i.e., C–H activation by a Pd salt in aqueous solution), in strong acid solution Pd salts do activate alkanes, often at temperatures considerably lower than those required for Pt in the Catalytica system. The first clear demonstration was reported by Sen, who found that Pd(OAc)₂ reacts with adamantane or methane in trifluoroacetic acid (TFA) at 80 °C, to give the corresponding alkyl trifluoroacetate in better than 50 % yield (based on Pd), accompanied by deposition of Pd metal [87]. It should be noted, however, that there have been subsequent reports of difficulty in reproducing these yields, especially for methane.⁴ One potential ambiguity is the

⁴ See papers cited in references [5] and [6].



Scheme 2.26 Proposed mechanism for oxidation of alkanes by Pd(II) in TFA

use of acetate salts as precursors: methyl trifluoroacetate can be produced by the reaction of acetate with TFA, probably via a radical process, so any reaction that yields no more than two moles of product per $\text{Pd}(\text{OAc})_2$ is open to some question, in the absence of labeling studies.

The proposed mechanism involves electrophilic activation of the C–H bond by Pd(II), followed by nucleophilic attack as in the Shilov mechanism (Scheme 2.26). (There is no real evidence that would exclude intramolecular reductive elimination as an alternate mechanism for the last step.) Sen observed no H/D exchange for adamantane, which seems rather surprising: that means that the (alkyl)Pd(II) intermediate must be more susceptible to nucleophilic cleavage (if that is what is happening) by trifluoroacetate (not the world's best nucleophile!) than to electrophilic cleavage by H^+ . The latter is the reverse of the C–H activation step, which is more facile for Pd(II) than for Pt(II), and $\text{RPt}(\text{II})$ doesn't undergo nucleophilic attack at all. Why do we have such a dramatic reversal of trends? There do not appear to be any computational studies that might clarify this issue.

By analogy to the Wacker reaction, in which a Pd(II) salt oxidizes ethylene to acetaldehyde *stoichiometrically* (with Pd(0) deposition) or *catalytically*, in the absence or presence of an oxidant that can recycle Pd(0) to Pd(II) respectively, catalytic alkane oxidation under the above conditions ought to be possible. This has been achieved: addition of H_2O_2 as oxidant to a solution of $\text{Pd}(\text{O}_2\text{CC}_2\text{H}_5)_2$ (the propionate salt was used as precursor to avoid the ambiguity of acetate-derived product) in TFA at 90°C gave $\text{CH}_3\text{O}_2\text{CCF}_3$ in up to 5 turnovers, based on Pd [88]. There is still some ambiguity, however: some $\text{CH}_3\text{O}_2\text{CCF}_3$ was observed even in the absence of any Pd salt, and it has been suggested that this chemistry does *not* involve electrophilic activation of a C–H bond at Pd(II), but rather oxidation by trifluoroperacetic acid formed in situ, possibly catalyzed by Pd(II). For example, the reported oxidation of cyclohexane by $\text{H}_2\text{O}_2/\text{TFA}$, catalyzed by Rh or Ru salts, has been shown to work equally well in the absence of any metal at all [89].

More recently this chemistry was reexamined with benzoquinone/ O_2/NaNO_2 as a combined reoxidizing system, with up to 5 turnovers to $\text{CH}_3\text{O}_2\text{CCF}_3$ achieved; a labeling study was carried out to exclude the possibility that some of the product arose from the $\text{Pd}(\text{OAc})_2$ precursor [90]. Somewhat surprisingly, a nearly 100 % yield of product based on Pd was reported in the absence of added oxidant, much better than the original report or any other reexamination. (It is not clear whether

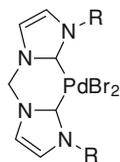


Fig. 2.2 Structure of methane-activating Pd(NHC)₂ complexes (R = Bu^t, Me)

the labeling study was done for the stoichiometric reaction.) These results seem reasonably unequivocal, but given the afore-mentioned problems of reproducibility, this apparently facile electrophilic activation of methane by Pd(II) in TFA at relatively mild temperatures may still be open to some question.

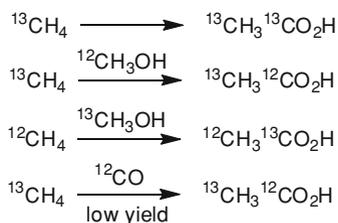
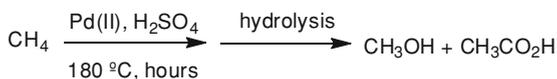
Sen has discovered an alternate alkane oxidation system involving palladium, but in this case *metallic* Pd. In combination with CuCl₂, light alkanes are oxidized by O₂ in the presence of CO, in aqueous TFA, at 90 °C [91, 92]. There is no indication that Pd(0) is oxidized during reaction; rather the proposed mechanism involves a Pd-catalyzed water gas shift reaction to generate H₂, which reacts with O₂ (again Pd-catalyzed) to form H₂O₂, which oxidizes alkane. Although there is unquestionably interesting chemistry going on, it probably does *not* involve electrophilic alkane activation, and will not be further discussed here.

A ligated Pd complex has also been found to effect this chemistry: the chelated bis(N-heterocyclic carbene) complex shown in Fig. 2.2 catalyzes the oxidation of methane to methyl trifluoroacetate by K₂S₂O₈, in TFA at 80–90 °C, with up to 30 turnovers achieved in 14 h [93]. The performance was significantly better than that of the simple Pd(OAc)₂ salt under the same conditions, indicating that the intact complex and not a decomposition product is the catalytically active species; indeed, the stability of the complex to the reaction conditions is notable, as the Pt analog decomposes immediately in TFA.

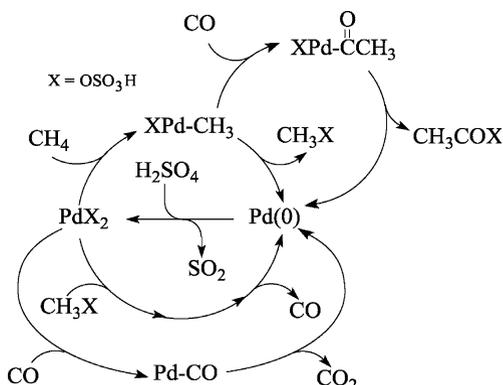
Under the more stringent Catalytica-like conditions, Pd(II) clearly does activate methane, but not exactly like Pt. Surprisingly, in addition to methyl bisulfate a significant amount of acetic acid (after hydrolysis), up to 3–4 turnovers per Pd, can be obtained [94]. Labeling studies showed that both carbon atoms come from methane, excluding the possible involvement of a contaminant. When labeled methanol was included in the reaction mixture, the label showed up *only* in the carboxylate end of the product (Scheme 2.27). The proposal was that the immediate precursors to acetic acid are methane and CO, the latter formed by oxidation of methanol; in agreement, some carboxylate-labeled acetic acid was obtained when the reaction was run under an atmosphere of labeled CO. Addition of CO also increased the selectivity to acetic acid *relative* to methyl bisulfate, but decreased the absolute yield (of both products), evidently because CO promotes reduction of catalyst to Pd(0) which deposits as Pd black.

These results may be explained by the “tandem” catalytic scheme shown in Scheme 2.28. Reaction begins with the electrophilic activation of methane by Pd(II) (upper left of the scheme), leading to (methyl)Pd(II) which can undergo competitive nucleophilic attack by bisulfate, giving methyl bisulfate (which becomes methanol

Scheme 2.27 Outcome of selective labeling experiments in the Pd-catalyzed oxidation of methane to acetic acid



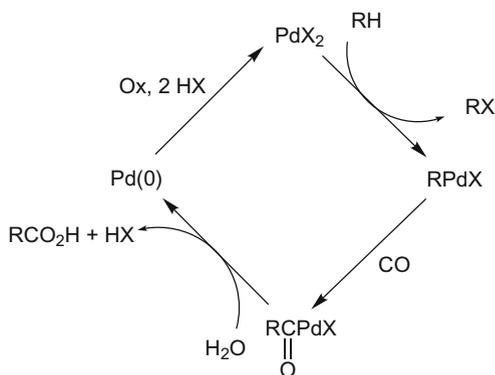
Scheme 2.28 Proposed mechanism for conversion of methane to acetic acid. Reprinted from Ref. [94] with kind permission of The American Association for the Advancement of Science (2003)



after hydrolysis) and Pd(0); or CO insertion, giving (acetyl)Pd(II), the precursor to acetic acid. The CO is formed in turn by Pd-catalyzed oxidation of methyl bisulfate or some other intermediate; besides inserting into the methyl-Pd bond, it can be oxidized to CO₂ along with Pd(0) formation. Pd(0) is reoxidized to Pd(II) by sulfuric acid; as in the Catalytica system that appears to be the rate-limiting step, and (unlike the Catalytica system) cannot keep up with reduction, so that the catalyst is deactivated over a few hours (faster with added CO) by Pd metal deposition.

Bell et al. subsequently reinvestigated this chemistry; while they were unable to reproduce the claimed yields under the original conditions, they found that carrying the reaction out under a methane-dioxygen atmosphere, with [95] or without added Cu(II), led to a significant increase in acetic acid yield—up to 14 turnovers per Pd—accompanied by (and surely due to) substantial inhibition of Pd metal formation [96]. This is consistent with the earlier conclusion that reoxidation by sulfuric acid is rate-limiting; indeed, these studies agreed in most regards with the previously proposed mechanism, with a couple of refinements. In particular, methyl bisulfate yields were dramatically higher in >100 % sulfuric acid, probably resulting from competing insertion of SO₃ into the methyl-Pd bond to give methanesulfonic acid, which has independently been shown to convert to methyl bisulfate under these conditions. An electrophilic mechanism was proposed in a

Scheme 2.29 Plausible mechanism for palladium-catalyzed oxidative carbonylation of alkanes. (HX = TFA; Ox = $K_2S_2O_8$, Cu(II), O_2)



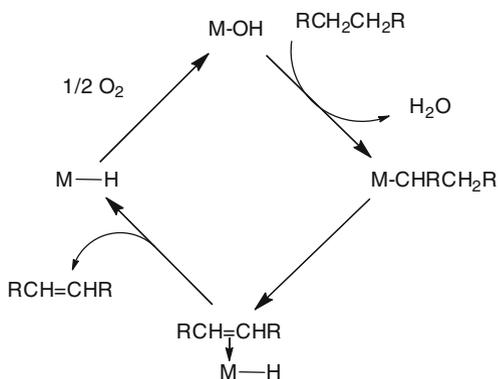
recent report of oxidation of methane to methyl bisulfate over a *heterogeneous* catalyst, 5 % Pd/C [97]; however, as the reaction was carried out in oleum (50 % SO_3), it seems more likely that it proceeds via methanesulfonic acid, which can be formed under these (and even milder) conditions without any electrophilic activation at all (see Sect. 2.4.6)

While the preceding chemistry amounts to accidental oxidative carbonylation of methane, intentional oxidative carbonylation has also been pursued. Whereas direct carboxylation of an alkane with CO_2 (Eq. 2.15) is thermodynamically disfavored (as is simple carbonylation, Eq. 2.16), coupling carbonylation to oxidation (shown for a generic two-electron oxidant M^{2+} in Eq. 2.17) can make the overall process thermodynamically allowed. Following earlier work on oxidative carbonylation of arenes, Fujiwara showed that palladium salts can catalyze the conversion of methane and other light alkanes, as well as cyclohexane, to the corresponding carboxylic acids [98, 99]. Under the first conditions studied (TFA solution, 20–40 atm CO, 80 °C, $K_2S_2O_8$ as oxidant) up to 20 turnovers (based on Pd) of cyclohexanecarboxylic acid were obtained; later it was found that the addition of catalytic amounts of Cu(II) increased the yield to 200 turnovers (although the efficiency based on oxidant was less than 50 %) [100]. The mechanism, while not fully delineated, could involve the sequence of steps in Scheme 2.29 (which is quite similar to that of the top half of Scheme 2.28).



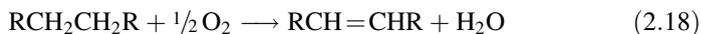
For methane, yields of acetic acid were significantly lower (up to 15 turnovers using $K_2S_2O_8$); it was found that O_2 could be substituted as oxidant, but with still lower yields [101]. Copper was required—indeed, for methane, copper alone worked as well as or better than reactions with palladium. This result and several others seem inconsistent with the assumption that electrophilic activation at Pd is responsible for this chemistry. It was found that CO_2 can be substituted for CO,

Scheme 2.30 Possible cycle for catalytic oxidative dehydrogenation of an alkane via electrophilic C–H activation



with comparable yields of acetic acid; it is far from clear how that finding could be accommodated in the proposed mechanism. Furthermore, $VO(acac)_2$ was found to be a much better catalyst for methane oxidative carbonylation; that almost certainly will *not* operate by an electrophilic mechanism, but rather by a radical pathway [102]. Certainly there could be more than one mechanism for this transformation, but the possibility that apparent electrophilic reactivity might actually be due, in whole or in part, to radical mechanisms (especially when reagents such as $K_2S_2O_8$ are involved) must always be kept in mind.

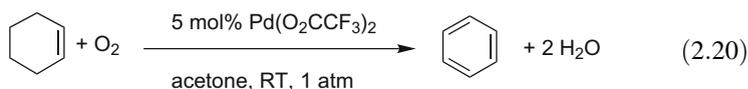
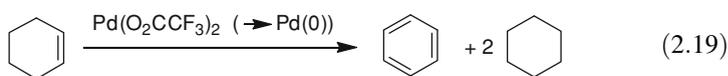
For alkanes other than methane, an alternative to oxygenation—perhaps a more likely one, especially in acidic media where alcohols will not be stable—is oxidative dehydrogenation. The chapter in this volume by Brookhart and Goldman covers the general topic of alkane dehydrogenation; most examples involve either thermal dehydrogenation, which is thermodynamically disfavored at temperatures accessible to homogeneous catalysts, or transfer dehydrogenation, for which a sacrificial—usually expensive—hydrogen acceptor is required. Oxidative dehydrogenation (Eq. 2.18) offers a means of overcoming both of those problems, both being thermodynamically favored and employing a cheap (even free, if air can be used) hydrogen acceptor. It has been studied extensively over traditional heterogeneous catalysts at elevated temperature, but CO_x is always a major byproduct; practically useful selectivities have not been achieved. Scheme 2.30 shows a plausible sequence, consisting of electrophilic activation, β -hydrogen elimination, and (in either order) dissociation of olefin and oxidation of $M-H$, that could lead to low-temperature, highly selective oxidative dehydrogenation.



The oxidative aromatization of cyclohexanes, effected by $Pd(OAc)_2$ and $Na_2Cr_2O_7$, in TFA at 90 °C, was offered as an early example of electrophilic activation leading to oxidative dehydrogenation [103]. Cyclohexane itself did not react, but substituted cyclohexanes did, although yields were less than stoichiometric in Pd (up to 54 % for conversion of tetralin to naphthalene, the best case). Isotopic labeling experiments indicated that cleavage of a tertiary C–H bond was

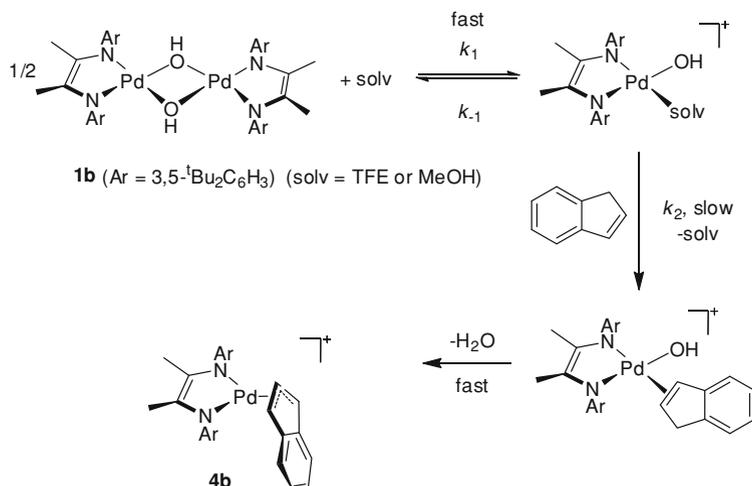
the initial, rate-limiting step (for tetralin it would be a benzylic C–H bond), which might appear more consistent with homolytic C–H cleavage; on the other hand, the intermediacy of free cyclohexenes was ruled out, so organopalladium intermediates (however generated) must be involved.

Cyclohexene can be aromatized under considerably milder conditions (unsurprisingly). Disproportionation of cyclohexene to benzene plus cyclohexane—a transfer dehydrogenation—in the presence of palladium trifluoroacetate (Eq. 2.19) had been previously reported, but was proposed to involve Pd metal (deposited almost immediately) as a heterogeneous catalyst [104]. Under an atmosphere of O₂, in contrast, oxidative dehydrogenation is observed: at room temperature, cyclohexene is converted to benzene (plus water) by 5 mol % Pd(O₂CCF₃)₂ in acetone, in up to 25 % conversion and 100 % selectivity (Eq. 2.20). Several lines of evidence strongly indicated that this reaction is strictly homogeneous. Substituted cyclohexenes could be similarly aromatized, but neither cyclohexane nor tetralin underwent this reaction [105].



A similar result was obtained with a ligand-substituted Pd(II) catalyst: the hydroxy-bridged dimeric diimine complex shown in Scheme 2.31 catalyzes the oxidative dehydrogenation of cyclohexene at 60 °C in trifluoroethanol solution, again achieving up to 25 % conversion with 100 % selectivity. Mechanistic studies on the C–H activation of indene, which leads to a stable allylic Pd(II) complex (Scheme 2.31) rather than any catalysis, indicate that electrophilic C–H activation takes place at monomeric, monocationic Pd(II) centers produced via solvent-induced dissociation [106]. This may be contrasted to the Pt analog, for which activation of cyclohexene gives a stable cyclohexenyl complex, and the main active species is the dication, [(diimine)Pt(H₂O)₂]²⁺ [107]. It is not clear why different pathways are followed.

One might question whether reaction at an allylic C–H bond is truly representative of electrophilic activation: certainly there are many examples in the literature of interconversion between metal olefin complexes and metal allyls that do not look at all like electrophilic activation. Nonetheless, although these Pd (and Pt) complexes have not yet been shown to activate alkanes, closely related analogs (discussed earlier) do; it seems quite plausible that a more reactive version of these systems may be found to catalyze oxidative dehydrogenation of alkanes. Some oxidative dehydrogenation has been reported in Shilov chemistry, but except in cases where arenes (benzene, naphthalene) are generated, (alkene)Pt(II) complexes, in only small amounts, were obtained [16, 17].



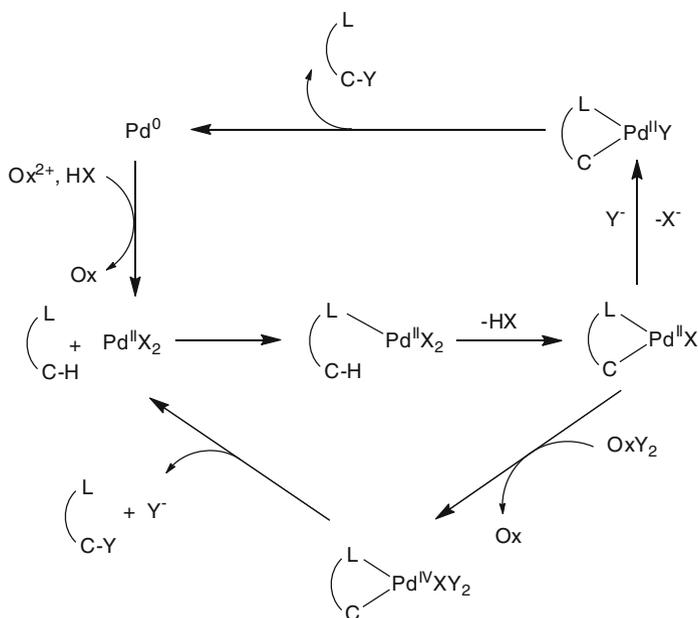
Scheme 2.31 Mechanism of electrophilic activation of an allylic C–H bond by a hydroxy-bridged dimeric Pd(II) complex

We will not consider Pd-catalyzed allylic oxidation of olefins, a topic that has received considerable attention of late [108], because there does not appear to be any likelihood of applying that chemistry to alkane functionalization (even though there are undoubtedly *some* mechanistic connections to the chemistry presented here).

2.4.1.2 Directed Functionalization

While cross-coupling reactions undoubtedly comprise the most important role of catalysis by palladium in organic synthesis, directed functionalization of C–H bonds, both aromatic and aliphatic, is becoming increasingly prominent. Obviously we are not dealing with simple alkanes here: these are reactions in which a molecule is coordinated to Pd, via a good ligating center (most often nitrogen), bringing the Pd center in proximity to the targeted C–H bond, which undergoes cyclometallation to give a C–Pd bond; the latter can then be functionalized by means of a variety of transformations. There are several good recent reviews devoted entirely [9] or in part [84, 85] to this topic, so only a few of the more informative points will be highlighted here.

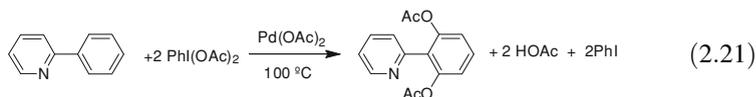
Two generic mechanisms are shown in Scheme 2.32. In each case the reaction starts with C–H activation, presumed to be electrophilic in nature (computational studies have been reported only for aryl C–H bonds [109]). The top cycle proceeds via Pd^{0/II} species, in which the functional group Y is attached to the carbon center that has undergone electrophilic activation at Pd(II) via reductive elimination; the resulting Pd(0) is reoxidized to complete the catalytic cycle. In the bottom one, the cyclometallated intermediate itself is oxidized to Pd(IV), which undergoes reductive elimination to give the functionalized product and regenerate Pd(II).

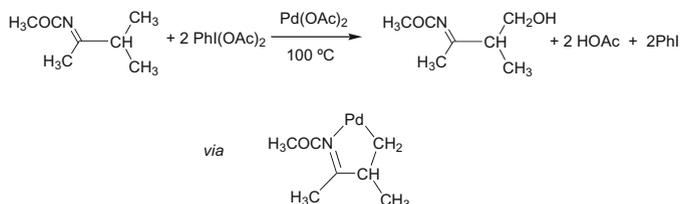


Scheme 2.32 Alternate mechanisms for directed oxidative functionalization of C–H bonds by Pd(II)

Other variants are also possible. As we shall see, whereas $\text{Pd}^{0/\text{II}}$ cycles appear to operate for most or all of the alkane oxidations discussed in the preceding section, $\text{Pd}^{\text{II}/\text{IV}}$ or other routes involving oxidation of an organopalladium species predominate in this chemistry.

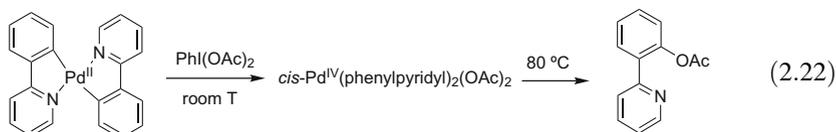
The “classic” example of Pd-catalyzed directed functionalization is the oxidation of phenylpyridine by $\text{PhI}(\text{OAc})_2$ to the 2,6-diacetylated derivative (Eq. 2.21). In this case an aryl C–H bond is involved, but the reaction may be readily generalized to a wide variety of coordinating/directing ligating groups (various N-heterocycles, imines, oxime ethers, etc.) and, more relevant to our topic, to aliphatic sp^3 C–H bonds. Regioselectivity—the “directed” part of the descriptor—is established at the C–H activation stage, and appears to arise from two factors: a preference for reaction at primary C–H bonds (consistent with trends we have already seen for other cases of electrophilic activation), along with a preference for 5-membered rings in the cyclopalladated intermediates [9]. An illustrative example is shown in Scheme 2.33.



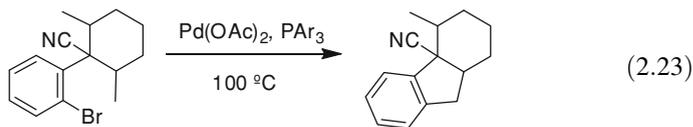


Scheme 2.33 Selectivity results from preference for primary C–H activation and a 5-membered palladacycle

Strong support for a Pd^{II/IV} mechanism was obtained by starting with a pre-formed bis(phenylpyridyl) Pd(II) metallacycle, which is oxidized by PhI(O₂CR)₂ to give a *stable* (at room temperature) Pd(IV) derivative that decomposes smoothly to the phenylpyridyl ester and Pd(II) (Eq. 2.22) [110]. The mechanism for C–O bond formation appears to be intramolecular reductive elimination from a cationic 5-coordinate intermediate [111]. (Recall that *external* nucleophilic attack has been found to operate for Pt(IV) in the Shilov system, but this difference is perhaps not so surprising, as an aryl–M bond might reasonably be expected to be less susceptible to nucleophilic attack. Comparably detailed mechanistic understanding for alkyl activations is not yet available.) Recently, however, a related reaction was shown to proceed via a bimetallic Pd(III) intermediate [112], different from *both* of the alternatives shown in Scheme 2.32. It seems most likely that a number of detailed mechanisms are accessible; the one preferred will depend on a number of factors.

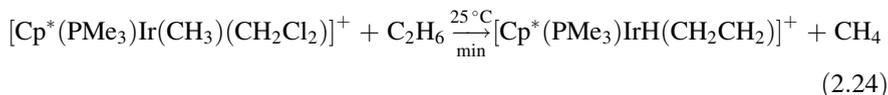


The acetoxy functionality may be installed at aliphatic C–H positions using other oxidants (by operating in acetic acid as solvent), including peroxides and even, for one particular class of substrate (8-methylquinolines), dioxygen. Similar reactions have been demonstrated for a wide variety of other functional groups: C–S bonds using ArSO₂Cl; C–X bonds using N-halosuccinimides, CuX₂, or XOAc; C–N and C–C bonds using various reagents. Directed dehydrogenation has also been reported [113]. The mechanism is not necessarily the same in all cases—some may well involve Pd^{0/II} cycles—and few if any of the functionalizations are universally applicable—some are (so far) limited to *sp*² C–H bonds and/or intramolecular bond formation [9]. Nonetheless, the potential of this methodology for complex organic synthesis is clear; for example (Eq. 2.23) a C–C bond can be established between centers generated by C–H and C–Br activation at Pd [114]. The utility for functionalization of actual alkanes, though, remains to be demonstrated.



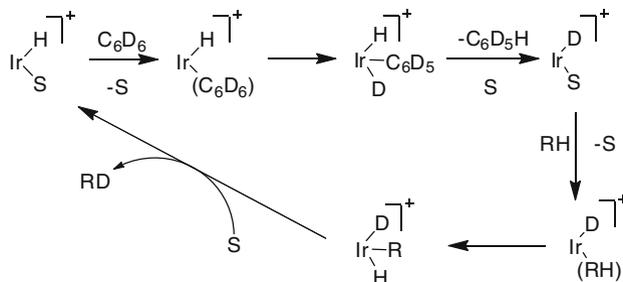
2.4.2 Iridium

The earliest well-defined reports of alkane activation involved iridium complexes; those were clearly *not* examples of electrophilic activation, but rather oxidative addition to Ir(I) [115, 116]. Somewhat later work, also from Bergman's group, does fit the definition used here: the Ir(III) complexes $\text{Cp}^*(\text{PMe}_3)\text{IrMe}(\text{OTf})$ and $[\text{Cp}^*(\text{PMe}_3)\text{IrMe}(\text{CH}_2\text{Cl}_2)]^+$ activate a variety of C–H bonds, including those of alkanes, with loss of methane. The resulting alkyls exhibit interesting chemistry, such as β -hydride elimination to give stable (unfortunately so, precluding the possibility of catalytic alkane dehydrogenation) olefin hydride complexes, as in Eq. 2.24 [117, 118].



The reactions appear to proceed via an alkane complex of the 16-electron cationic intermediate $[\text{Cp}^*(\text{PMe}_3)\text{IrMe}]^+$. One might think that an oxidative addition/reductive elimination sequence would be less likely for an $\text{Ir}^{\text{III/V}}$ couple (and cationic, in addition) than for the previously studied $\text{Ir}^{\text{I/III}}$ couple (which involved a similar ligand set), preferring an alternative sigma-bond metathesis or σ -CAM route. On the other hand, oxidative addition/reductive elimination does operate in the Shilov system (or, at least, in models thereof; see above), which involves lower oxidation states ($\text{Pt}^{\text{II/IV}}$) but much less electron-donating ligands than the Cp^*/PMe_3 combination. In fact, a variety of experimental indications (none completely unequivocal) [119] along with computational studies [120, 121] support the oxidative addition/reductive elimination route.

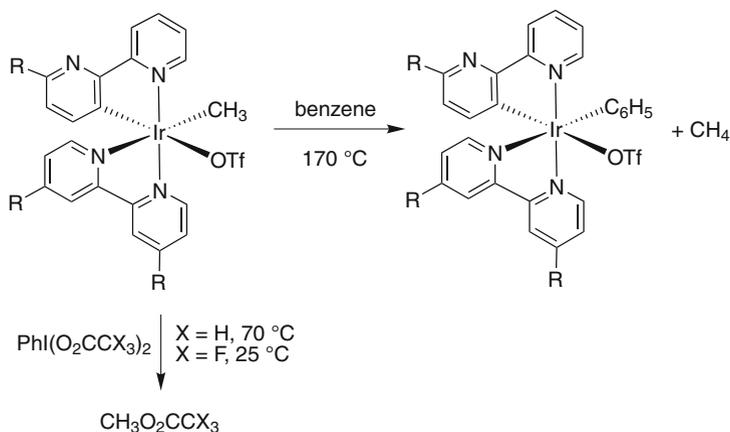
The analogous hydrido complex, $[\text{Cp}^*(\text{PMe}_3)\text{IrH}(\text{CH}_2\text{Cl}_2)]^+$, was found to catalyze isotopic exchange between C_6D_6 and a wide variety of C–H bonds, including alkanes (methane, ethane, cyclohexane), which could be substantially deuterated in a few hours at $-20\text{ }^\circ\text{C}$. Toluene undergoes exchange at both arene and benzylic positions; the *m*- and *p*-sites exchange rapidly even at $-84\text{ }^\circ\text{C}$ (the *o*-position is unreactive) while the methyl group requires $-20\text{ }^\circ\text{C}$. Ferrocene and even decamethylferrocene are quite reactive as well; diethyl ether and THF, less so. Presumably the mechanism here as well involves oxidative addition/reductive elimination, as sketched out in Scheme 2.34 [122].



Scheme 2.34 Proposed mechanism for H/D exchange catalyzed by a cationic Ir(III) hydride complex

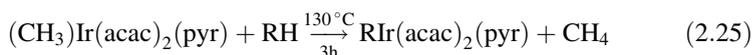
Alternatively, H/D exchange of C–H positions in water-soluble substrates can be achieved with D_2O , using $Cp^*(PMe_3)IrCl_2$ as catalyst, although considerably more stringent conditions (hours at $135\text{ }^\circ C$) are required; a mechanism analogous to that for H/D exchange in the Shilov system was proposed [123]. The catalyst is not stable but disproportionates by ligand redistribution; studies on related complexes in which the phosphine ligand is covalently linked to the Cp ring did not succeed in the main goal of retarding decomposition, but did indicate that more electron-donating ligands accelerate reaction [124]. That would be consistent with the proposed mechanism, if C–H activation is rate-limiting. A related NHC complex catalyzes H/D exchange with CD_3OD or CD_3COCD_3 as deuterium source, but the scope is apparently more limited, as no simple alkanes were reported to react [125, 126].

Periana has studied C–H activation at a variety of Ir(III) centers. The earliest reports were on $Ir(acac)_3$, which catalyzes hydroarylation of olefins via an (aryl)Ir(III) intermediate generated by C–H bond activation. Computational studies implicate a mechanism described as “oxidative hydrogen migration,” a sort of hybrid mechanism, wherein H is bonded strongly to the metal, as in oxidative addition, but also interacts weakly with both carbon centers, as in sigma bond metathesis, in the transition state [127]. This Ir complex has not been found to activate sp^3 C–H bonds; however, a closely related methyl compound does (Eq. 2.25), reacting with linear and cyclic alkanes as well as mesitylene (at the benzylic position) [128]. Detailed mechanistic studies were reported for activation of benzene, where the oxidative hydrogen migration mechanism seemed to be preferred again [129], but not for the alkane activations. The closely related bis(tropolonate) complex undergoes the same reactions with mesitylene and cyclohexane, but nearly an order of magnitude more rapidly than does $(CH_3)Ir(acac)_2(pyr)$ [130]. The methoxy complex $(CH_3O)Ir(acac)_2(pyr)$ activates benzene to give the phenyl derivative, as well as catalyzing H/D exchange between benzene and water. Here the more “classical” sigma bond metathesis was calculated to be the lowest energy pathway; the favorable O–H interaction in the transition state (stronger than the C–H interaction in the transition state for activation by the methyl complex) and/or the disfavoring of Ir(V) by the more



Scheme 2.35 C–H bond activation and C–O bond formation at an Ir(III) center

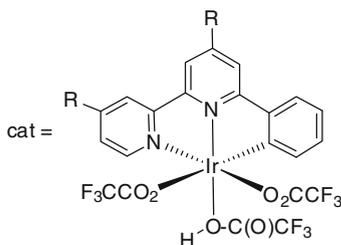
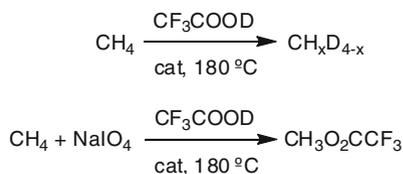
electronegative methoxy group were offered as possible reasons for the difference in C–H activation mechanism [131].



More recent studies have moved away from acac and other O-centered ligands to less electron-withdrawing N- and C-centered ligands. This reflects the possibility, noted earlier in work on Shilov models and also predicted by computational “screening”[80], that the most electrophilic metal center may well not make the optimal C–H functionalization catalyst, even if the C–H activation is electrophilic in nature, because displacement of water or other ligands by alkane may become the most difficult step in the cycle. The (N,N)-(N,C)-coordinated Ir(III) complex shown in Scheme 2.35 activates benzene (but not aliphatic C–H bonds) as well as catalyzing H/D exchange between benzene and acids; it also reacts with the strong oxidants $\text{PhI}(\text{O}_2\text{CCX}_3)$ ($\text{X} = \text{H}, \text{F}$) to cleave the Ir–C bond and form the corresponding methyl ester. The last reaction corresponds to the final step in a (hypothetical) catalytic methane oxidation; the detailed mechanism is not known [132].

The next-generation species suggested by computational screening, based on the (NNC)-ligand shown in Scheme 2.36, likewise catalyzes H/D exchange, but in this case will do so for methane and other alkanes as well as benzene. Calculations favor an electrophilic (or sigma bond metathesis) mechanism for the C–H activation step, with the H being removed by a departing trifluoroacetate; but the oxidative hydrogen migration route, in which the H moves to the phenyl group of the tridentate ligand, was not much higher in energy. Of greatest interest is the report that the complexes *catalyzes* methane oxidation by NaIO_4 , giving up to 6 turnovers of methyl trifluoroacetate per Ir in 3 h at 180 °C [133]. This appears to be a nice validation of the computationally-informed design approach, but there is one caveat. The paper notes the presence of a “background” reaction between

Scheme 2.36 H/D exchange and methane oxidation catalyzed by a (NNC)-coordinated Ir(III) complex



methane and periodate; the amount of product in the absence of Ir (given in the SI) is fully half of that obtained with Ir. Since there is no information on how the Ir-free reaction works (some sort of radical chemistry seems most likely), we must remain open to the possibility that the Ir “catalyst” is not actually effecting C–H activation by an electrophilic (or any other) route, but rather promoting the “background” mechanism in some fashion.

2.4.3 Rhodium

There is considerably less literature about rhodium than iridium, for reasons that are not clear. Only a few examples—none of them entirely unambiguous—of electrophilic activation have been reported. The earliest work involves a supported complex: methane reacts with a bis(allyl)Rh(III) center attached to silica at 100 °C, to give Rh hydride species along with C₃ and some C₄ hydrocarbons; labeling studies establish that the 4th carbon in the latter came from methane. The analogously supported (SiO)-RhHCl center reacts with methane to give methyl chloride and a (tentatively identified) (methyl)Rh(III)hydride; any of these supported species serves as a pre-catalyst for chlorination of methane at 100 °C. Electrophilic activation of methane at Rh(III) was proposed, even though the distribution of chlorinated methanes obtained was not substantially different from that expected for free-radical chlorination [134].

Sen found that RhCl₃ in a mixed H₂O/C₃F₇CO₂H solvent catalyzes methane oxidation by O₂ at 80–85 °C; additional Cl[−] and I[−] in solution and CO in the gas phase are required as well. The main products are methanol (in part obtained as the perfluorobutyrate ester) and acetic acid; overall rates on the order of 3 turnovers/h could be obtained. The only byproduct observed was formic acid. (It is not clear whether an attempt was made to detect formation of CO_x from methane, which

would require labeling.) The obvious possibility that acetic acid arises via Monsanto-like carbonylation of intermediate methanol (with the aid of iodide) was ruled out by labeling, implicating a mechanism wherein a (methyl)Rh(III) intermediate undergoes competitive nucleophilic attack (by water or perfluorobutyrate) and CO insertion [135]. Calculations suggest that the (methyl)Rh(III) species is generated by oxidative addition to a Rh(I) complex, $[\text{RhI}_2(\text{CO})_2]^-$, which could certainly be generated under reaction conditions [136]. Reactions of ethane and higher alkanes do not seem entirely in accord with this proposal, however: they also undergo oxidation, but substantial amounts of C–C cleavage products are obtained, especially for butane and above. Also, surprisingly, propane showed a 5:1 preference (statistically corrected) for reaction at the secondary C–H bond (giving isopropyl esters and acetone) than at the primary position, the opposite of the predominant trend for electrophilic activations. The role of CO was also unclear: obviously it is needed for the carbonylation products, but no simple oxidation takes place in the absence of CO; it was suggested that the combination of CO and water leads to H_2O_2 as in the metallic Pd system discussed earlier.

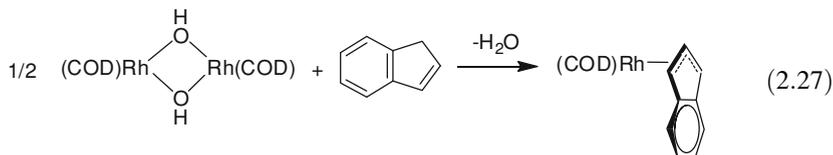
Russian workers (simultaneously and subsequently) examined this system in greater detail. In $\text{H}_2\text{O}/\text{TFA}$ higher rates are obtained, with maximum turnovers to methanol (and methyl trifluoroacetate), acetic acid, and formic acid at 95 °C around 12, 6 and 9 per hour respectively; substantial CO_2 formation was also measured, but shown to arise entirely from CO oxidation. *No* H/D exchange with solvent was detected, a possible argument against *any* (methyl)Rh intermediate, although no such strong conclusion was drawn; on the other hand, several lines of evidence implicated the important participation of a good oxidant, H_2O_2 or HOI [137]. ^{18}O -labelling studies proved particularly telling: in the presence of H_2^{18}O (which rapidly exchanges into TFA), there is much less $\text{CF}_3\text{C}^{16}\text{O}^{18}\text{OCH}_3$ and $\text{CF}_3\text{C}^{18}\text{O}_2\text{CH}_3$ than the amount of label in the TFA, ruling out a mechanism involving nucleophilic attack by trifluoroacetate (or water) on a (methyl)Rh intermediate. In contrast, label from $^{18}\text{O}_2$ showed up in the product in about the same proportion as in the reagent, implying that the C–O bond is formed from O_2 or a derivative (such as H_2O_2) thereof. The authors were not ready to completely rule out a mechanism involving C–H activation at Rh, offering possible schemes that might account for the observations, but suggested that activation at an O-centered species, such as a (peroxo)Rh complex, seems most likely [138]. Inclusion of this chemistry as an example of electrophilic alkane functionalization must thus be considered at best equivocal.

Rhodium(III) porphyrin complexes such as $\text{Rh}(\text{ttp})\text{Cl}$ (ttp = tri-*p*-tolylporphyrin) react with cyclic and linear alkanes at 120 °C or higher to give the corresponding alkyls, $\text{Rh}(\text{ttp})\text{R}$; with linear alkanes, only primary alkyl products are obtained. The hydride $\text{Rh}(\text{ttp})\text{H}$ was found to be a viable intermediate, and mechanisms involving electrophilic activation by that species (the reaction is accelerated for porphyrins bearing electron-withdrawing substituents), following either an oxidative addition/reductive elimination sequence or sigma bond metathesis, were proposed. However, the Rh(II) dimer $(\text{Rh}(\text{ttp}))_2$ was also found as an intermediate, so the two-center one-electron oxidative addition mechanism

established by Wayland (Eq. 2.26) [139] was offered as a parallel path [140]. It seems more likely that *only* the latter is followed, since reaction of a solution of cyclohexane in benzene gives the cyclohexyl but no phenyl product. One would expect benzene to be at least as reactive as an alkane in either of the routes suggested for electrophilic activation (and certainly the phenyl product should be stable if formed), whereas aryl C–H bonds are known to be unreactive by Wayland’s mechanism.



The hydroxo-bridged dimer $[(\text{COD})\text{Rh}^{\text{I}}(\mu\text{-OH})]_2$ was investigated for comparison to the (dicationic) diimine-Pd and –Pt analogs discussed above, with the idea that displacement of solvent by a C–H bond would be more facile for this uncharged system. The latter *does* appear to be the case, but increased reactivity does not result; rather there is a switch of rate-determining step, from coordination of substrate for Pd and Pt, to C–H bond cleavage for Rh. As a consequence only the highly reactive C–H bond of indene can be activated (Eq. 2.27), and the reaction is *slower*, not faster, than the corresponding Pd case [141]. The exact nature of the C–H activation process is not clear.



2.4.4 Gold

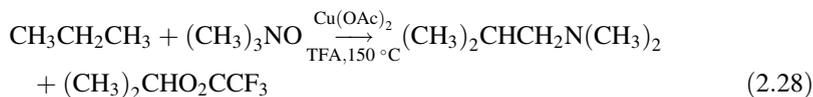
While there are a number of examples of C–H activation and functionalization involving gold complexes, most are limited to arenes and other unsaturated centers [142]. The clearest example of electrophilic functionalization of an alkane by gold is Periana’s demonstration that Au(III) exhibits reactivity akin to the Catalytica system. In strong acid (sulfuric, triflic), at 180 °C, methane is stoichiometrically oxidized to the corresponding methyl ester, with deposition of metallic gold; H_2SO_4 (or SO_3) is not able to keep gold in solution by reoxidation. However, the addition of selenic acid (which is known to oxidize gold) effects catalytic oxidation, with turnover frequencies around $10^{-3}/\text{s}$ and up to 30 total turnovers. (Again, it should be noted that there is a significant background reaction: selenic acid in sulfuric acid oxidizes methane in the absence of gold, at a rate about 1/5 of the gold-catalyzed process.) While little experimental evidence bearing on mechanism is available, computational studies suggested functionalization takes place by nucleophilic attack on (methyl)Au(III), and found that several different mechanisms for reaching the

latter—activation at Au(III); activation at Au(I) by either electrophilic substitution or oxidative addition/reductive elimination, followed by oxidation of (methyl)Au(I) to (methyl)Au(III)—all appear to be energetically feasible [143]. Comparing the three metallic systems for oxidation of methane in sulfuric acid—the (bpym)Pt(II) complex (see above), Hg(II) (see below), and Au—shows that they all operate with similar rates (~ 3 turnovers per hour at 180 °C for Hg and Au; ~ 10 at 200 °C for Pt) and achieve similar maximal product concentrations (~ 0.5 – 1.5 M), corresponding to only tens of total turnovers [144].

There is an intriguing report of gold-dependent biological oxidation of methane to methanol by the microorganism *Micrococcus luteus*; electrophilic activation at Au(III) was proposed as a possible mechanism, but there is no supporting evidence [145]. Both Au(I) and Au(III) complexes have been reported to catalyze alkane oxygenation by H₂O₂; at 75 °C in acetonitrile, cyclooctane was oxidized to a mixture of the hydroperoxide, alcohol and ketone, with a total of 520 turnovers after 144 h. Both the appearance of the hydroperoxide as a product and the selectivities observed with linear alkanes (oxidation at tertiary > secondary > primary positions) strongly implicate a radical mechanism, rather than anything to do with electrophilic activation [146].

2.4.5 Copper

Electrophilic arene activation by Cu is fairly common, although detailed mechanistic understanding is quite limited [147], but there do not appear to be any well-substantiated examples of alkane activation. As noted in the section on Pd, there are a number of combined Pd/Cu oxidation catalysts, some of which work nearly as well (or even better) with Cu alone. That *could* be taken as an indication that both operate by similar mechanisms, but it could also suggest that electrophilic activation is not involved for *either* Cu *or* Pd. An example is the aminomethylation of alkanes by trimethylamine *N*-oxide, in which a mixture of alkyldimethylamine and alkyl trifluoroacetate is obtained (Eq. 2.28). Cu alone gives the highest absolute yield of amine, but the combined catalyst gives the highest ratio of amine to ester [148]. Although an alkylcopper intermediate was proposed, a radical mechanism seems more probable (which does not necessarily rule out an alkylcopper intermediate), since a radical scavenger substantially inhibited product formation; also the preferential oxidation of the secondary C–H position is more consistent with radical than electrophilic activation. (Methane could not be oxidatively aminomethylated, although some oxidation to methyl trifluoroacetate was observed.) The oxidation of alkanes by H₂O₂, catalyzed by a tetranuclear Cu(II) cluster complex, is almost certainly radical in nature [149].



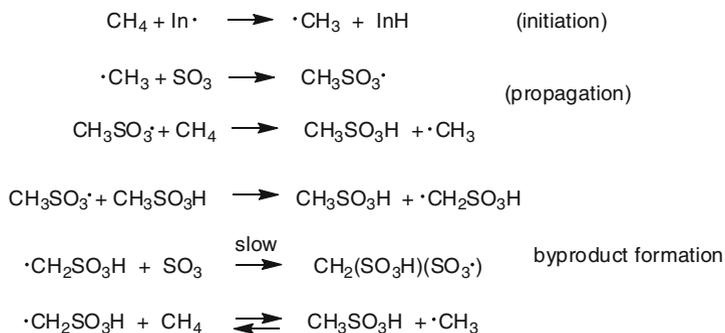
2.4.6 Mercury

The Pt-based Catalytica system (Sect. 2.3.2 above) was discovered as a follow-on to an earlier report from the same group, that mercuric salts catalyze oxidation of methane to methyl bisulfate in concentrated sulfuric acid at 180 °C [150]. (Closely related chemistry, at higher temperature, had been reported previously in the patent literature [151]). A similar mechanism was proposed, involving electrophilic activation of methane by Hg(II). The presumed next step, nucleophilic C–Hg bond cleavage by bisulfate, would generate Hg(0), which was never observed; but its reoxidation by sulfuric acid and/or comproportionation with Hg(II) to give Hg(I) should both be rapid; the corresponding reaction in (non-oxidizing) triflic acid gives a stoichiometric amount of methyl triflate along with mercurous triflate. Independently-synthesized CH₃Hg(OSO₃H) reacts at 180 °C in sulfuric acid to give both methyl bisulfate (at a rate consistent with the overall catalytic process) and methane (the reverse of electrophilic activation), all supporting the proposed mechanism. The best methane yields obtained, around 43 %, are not so high as those obtained with Pt, but still impressive.

An alternate view of this chemistry was offered by Sen, who examined the reaction of methane in sulfuric acid with Hg(II) as well as other 1e⁻ (K₂S₂O₈, Ce(IV)) and 2e⁻ (Pd(II)) oxidants and found that they *all* gave CH₃OSO₃H, although the yield exceeded stoichiometry with respect to oxidant only with Hg(II). Sen postulated that all these systems follow the same mechanism, which surely could not involve electrophilic activation in all cases, and therefore must consist of generation of methyl radicals, via H-atom abstraction and/or stepwise electron transfer followed by loss of proton. The methyl radical would be the precursor to product, possibly by further oxidation to the carbocation which is trapped by bisulfate. The fact that methyl bisulfate also appeared as the major product obtained from ethane oxidation, via C–C cleavage, was taken to support the electron transfer mechanism [21].

Several additional observations also bear upon the mechanistic issues. Although formation of some CH₃Hg(OSO₃H) was observed at lower temperatures, the inability to synthesize that species by reaction of methyl bisulfate and either Hg(I) or Hg(II) was taken as evidence that it does *not* form via electrophilic activation of methane at Hg(II), but rather via coupling of CH₃• and Hg(I). Methanesulfonic acid (CH₃SO₃H, MSA) was a minor product in some reactions, but control experiments were reported to demonstrate that it does not convert further to CH₃OSO₃H under reaction conditions. (As noted earlier, and discussed below, that conclusion was not correct.) Sen acknowledged that the high selectivity to the latter product requires that the C–H bond in methane be considerably more reactive than that of CH₃OSO₃H, which is not obviously consistent with a radical mechanism, but argued that it could be so, as a consequence of the electronegativity of the sulfonate group [21].

In a subsequent paper, however, Sen found that MSA is the main product at 90 °C with either Hg(II) or K₂S₂O₈ as promoter; furthermore, MSA *is* oxidized to methyl bisulfate at 160 °C in fuming sulfuric acid, even without any other oxidant present [152]. Subsequently Bell extended this chemistry to other promoters [153],



Scheme 2.37 Radical mechanism for oxidation of methane to MSA

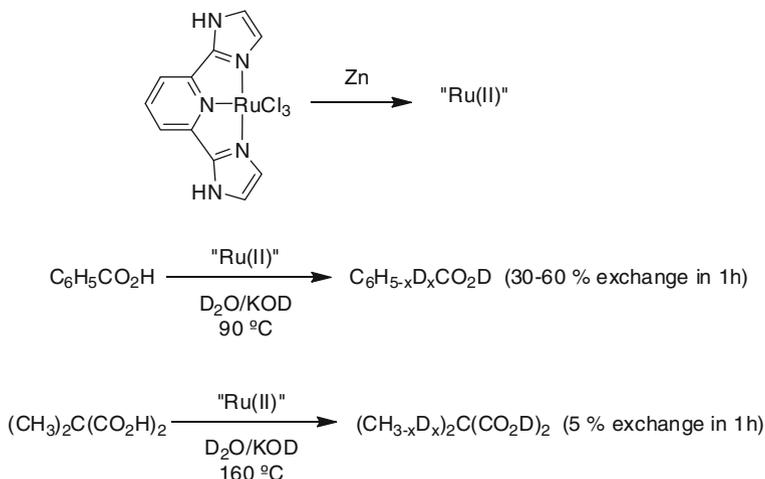
including catalyzed oxidations by O_2 [154]. These observations clearly indicate that a radical-based route for oxidizing methane to methyl bisulfate via MSA is viable, perhaps as in Scheme 2.37. It is possible to account for the good selectivity without arguing that the C–H bond in MSA is much less reactive than that of methane (as Sen does); instead it could be that $\cdot\text{CH}_2\text{SO}_3\text{H}$ is generated, but it does not readily couple with SO_3 (some $\text{CH}_2(\text{SO}_3\text{H})_2$ is observed as a byproduct under many conditions [153]), so most of it is quenched by reaction with methane.

Nonetheless, it seems very likely that the catalytic electrophilic mechanism does operate as well for $\text{Hg}(\text{II})$ (and others, particularly $\text{Pd}(\text{II})$), since considerably higher production of methyl bisulfate relative to additive are obtained than with radical initiators. The failure to generate the (methyl) $\text{Hg}(\text{II})$ species by alkylation of $\text{Hg}(\text{I})$ or $\text{Hg}(\text{II})$ does not really prove anything; indeed, if C–O bond formation results from nucleophilic attack of bisulfate on (methyl) $\text{Hg}(\text{II})$, the *correct* attempt at its preparation (the microscopic reverse) would be the reaction of a methylating agent with $\text{Hg}(\text{O})$.

This chemistry has been incorporated into a heterogeneous catalyst: a mixture of methane and O_2 was passed over a bed of BaSO_4 nanotubes impregnated with metal ($\text{Pt}(\text{II})$, $\text{Hg}(\text{II})$, $\text{Ce}(\text{IV})$ or $\text{Pb}(\text{IV})$) sulfate salts and concentrated sulfuric acid at 170–230 °C. Up to 50 % methane conversion was achieved, with up to 60–70 % selectivity to methanol (it was not clear whether the product stream underwent hydrolysis before analysis). All four different metals behaved approximately the same, which seems more consistent with a radical than an electrophilic activation mechanism [155].

2.4.7 Miscellaneous

Among the promoters for methane oxidation in oleum, iodine (which can be added in various chemical forms) has been found to be unexpectedly effective [156, 157]. It is not clear whether this is electrophilic or radical chemistry; a gas-phase experiment implicates electrophilic activation at I^+ as the most probable route [158], but the chemistry in sulfuric acid could certainly be quite different.



Scheme 2.38 Ru(II)-catalyzed H/D exchange via “nucleophilic” activation

Periana and Goddard have attempted to instantiate their prediction of possible “nucleophilic” activation [1] with ruthenium: the (NNN)-ligated Ru(III) complex shown in Scheme 2.38 can be reduced to a (presumed) Ru(II) species that catalyzes H/D exchange of aromatic C–H bonds, as well as certain aliphatic ones (more slowly), in the presence of strong base [159]. The proposed mechanism includes a C–H bond cleavage step that closely resembles sigma bond metathesis; although termed nucleophilic by the authors, it fits (stoichiometrically) the definition of electrophilic activation employed here. No alkane activation or any functionalization was reported.

An uncharacterized product obtained from the reaction of nickelocene with LiAlH_4 was reported to react with methane at 70°C , giving H/D exchange with D_2 ; alcoholysis of the resulting (also uncharacterized) solid with EtOD gave CH_3OD [160]. An unspecified C–H activation at a Ni center was proposed, but no followup work has appeared.

Lastly, one might consider Basset’s supported organometallic chemistry as electrophilic functionalization: Zr(IV), Ta(V) and W(VI) alkyl and/or hydride species, attached to silica, alumina, or other oxide surfaces via M–O bonds, react with alkanes via sigma bond metathesis, leading to transformations such as alkane hydrogenolysis and alkane metathesis [161]. Strictly speaking these are not functionalizations, as no functional groups are introduced, but they do represent rare examples of productive (if not yet practical) alkane transformations at early transition metal centers.

2.5 Conclusions and Prospects

We have seen that electrophilic activation by a number of late transition metal species can serve as the basis for functionalization of saturated C–H bonds. These reactions can be quite facile, some taking place even below room temperature,

although in other cases severe conditions are required. Most of the well-defined chemistry involves Pt, Pd or Ir centers; there are a number of examples with other metals that *may* proceed by this route, but the evidence is at least somewhat inconclusive: alternate mechanisms, most probably radical in character, could also account for some or all of the observations. Indeed, for at least some reactions there is good reason to believe that two (or more?!) parallel mechanisms might operate simultaneously; the Hg-catalyzed oxidation of methane in sulfuric acid may be such a case.

Up to now the best examples of utility are in the realm of directed functionalization of C–H bonds that are part of a more complex molecule—i.e., not for simple alkanes. For the latter, the only transformations with really useful conversions and selectivities are those of methane in strong acids, but as discussed earlier, even these are not practical, and it is not obvious whether the difficulties are surmountable; furthermore, they are almost certainly unsuited to higher alkanes. There have been a few interesting examples involving the latter, such as the Shilov oxidation of ethane to ethylene glycol, but the selectivities are not as good, and (like the Catalytica methane oxidation) rates are far too slow. Oxidative dehydrogenation looks like an attractive opportunity for selective alkane functionalization, but as yet it has not been demonstrated for an actual alkane.

Despite these (so far) limited accomplishments, the prospects for this approach to alkane functionalization are quite encouraging. We understand a lot (though by no means all that we would like) about the mechanisms, and factors controlling reactivity, for a number of prototypical reactions. With the range of metals and ligands available, and the powerful experimental and computational tools that have been developed, a practical application of electrophilic functionalization of alkanes may well appear in the not too distant future.

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