

Selective Intermolecular Carbon–Hydrogen Bond Activation by Synthetic Metal Complexes in Homogeneous Solution

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ARTHUR: Yes, we seek the Holy Grail (clears throat very quietly). Our quest is to find the Holy Grail.

KNIGHTS: Yes it is.

ARTHUR: And so we're looking for it.

KNIGHTS: Yes we are.

BEDEVERE: We have been for some time.

KNIGHTS: Yes.

ROBIN: Months.

ARTHUR: Yes...and any help we get is...is very...helpful.¹

Synthetic methods chemistry has undergone intense development during the past 50 years. As a result, nearly every class of organic compound can now be considered as a source of starting materials for selective conversion to members of other classes, as well as to a wide range of more complicated materials, such as polymers, biomolecules, and metal–organic compounds.

An important class of molecules that represents an exception to this generalization is alkanes, or saturated hydrocarbons. Among the thousands of reagents in the modern arsenal of synthetic organic methodology, few have been developed that are capable of carrying out selective chemistry on alkanes. The lack of reactivity of alkane C–H bonds is often attributed to their high bond energies (typically 90–100 kcal/mol) and very low acidity (difficult to measure directly but estimated to have $pK_a = 45\text{--}60$) and basicity.

The robust nature of alkanes presents both a fundamental and a practical challenge to chemists. At the fundamental level, carbon–hydrogen and carbon–carbon bonds are the most ubiquitous chemical linkages in nature. Elucidating the requirements necessary to effect their cleavage or their transformation

into other bonds lies at the heart of our understanding of chemical reactivity. On the more practical side, alkanes (especially methane) are abundant and relatively inexpensive. Methane is the primary constituent of natural gas, and alkanes typically make up about 50% of petroleum. Alkanes are a primary source of fuel, but they also constitute a significant fraction of the carbon pool that is potentially accessible for chemical synthesis. It is ironic that such an abundant resource is presently so difficult to utilize. Methane presents a special problem because of its location in remote places and its high volatility. Even its use as a fuel is restricted by the expense and danger of liquefying it and transporting it from discovery to utilization sites.

Despite the fact that C–H bonds are more difficult than other types of linkages to cleave, they are not completely inert. Alkanes have long been known to undergo a number of solution and gas-phase reactions that involve free radicals as intermediates, such as photochlorination, autoxidation, and combustion. More recently very powerful “super acids” have been developed that are capable of adding protons to alkanes; this work was recognized in a Nobel prize to George Olah. A critical feature of nearly all of these processes, however, is that they are relatively unselective. Two types of selectivity are at issue here. The first involves the capacity of a potential reagent to attack one type of C–H bond in preference to others. For example, free radical reagents exhibit some preference for reaction of tertiary C–H bonds over primary and secondary, but often the degree of selection is not high. Reagents that exhibit the reverse preference are extremely rare. A second type of selectivity is defined as the ability to convert an alkane into a functionalized product without having the product undergo even faster reaction than the alkane. A classic example of this is the oxidation of methane to methanol, which is often difficult to carry to high conversion without inducing substantial conversion of the methanol to more highly oxidized products including CO₂ and water.

One “Holy Grail” of C–H activation research, therefore, is not simply to find new C–H activation reactions but to obtain an understanding of them that will allow the development of reagents capable of *selective* transformations of C–H bonds into more reactive functionalized molecules. Although a few interesting organic and main group reagents have been discovered that show intriguing potential for meeting this goal, much of the activity in this field has been in transition

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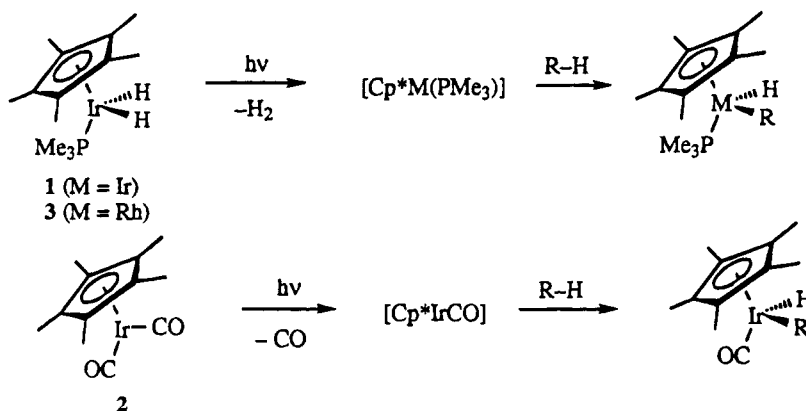
Robert G. Bergman was born in 1942 in Chicago, IL. He graduated from Carleton College in 1963 and received his Ph.D. in chemistry at the University of Wisconsin in 1966 under the direction of Jerome A. Berson. After a postdoctoral stay with Ronald Breslow at Columbia, he accepted his first academic position at the California Institute of Technology in 1967, where he worked in the area of organic reaction mechanisms. In 1978 he moved to Berkeley to accept a joint appointment as professor of chemistry at the University of California and principal investigator at the Lawrence Berkeley Laboratory. His research at Berkeley has focused on C–H activation reactions and the chemistry of nitrosyl complexes, heterobinuclear complexes, and complexes with metal–heteroatom bonds.

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Thomas H. Peterson was born in 1964 in Portland, OR. He did *not* receive his undergraduate degree at Carleton College. He obtained a B.A. degree in chemistry from Southern Oregon State College in 1987 and a Ph.D. in organic chemistry from Cornell University in 1993. His thesis work, under the direction of Barry K. Carpenter, was in the area of biradical kinetics. He is currently a NIH postdoctoral fellow with Robert Bergman at the University of California, Berkeley.

(1) Cleese, J.; Chapman, G.; Gilliam, T.; Idle, E.; Jones, T.; Palin, M. Excerpt from screenplay, “Monty Python and the Holy Grail”, 1974.

Scheme 1

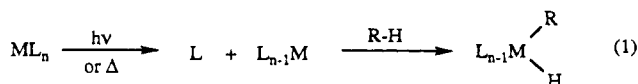


metal chemistry. The present Account therefore reflects this emphasis.

Because of space limitations we have had to substantially circumscribe the scope of this Account. We have chosen to focus on the reactions of saturated C–H bonds with soluble synthetic metal complexes in homogeneous solution. We have discussed our own work, but we have tried to cover the contributions of others as well. Although they will be mentioned briefly in passing, we have had to largely ignore the extensive fields of heterogeneous C–H activation by metal surfaces and reactions of alkanes with ions in the gas phase, and we mention only briefly the large field of biological C–H activation. We also focus primarily on intermolecular processes, because they are the most difficult to carry out, omitting discussion of intramolecular reactions involving interaction of C–H bonds and metal centers located in the same molecule. The bulk of the Account summarizes what has been learned so far about homogeneous metal-mediated C–H activation reactions and the Account concludes with our thoughts about the “Holy Grails” that workers in the C–H activation field would like to attain in the future.

Stoichiometric Reactions of Alkanes with Metal Complexes

Oxidative Addition of C–H Bonds to Late Transition Metal Centers. One of the most direct ways of obtaining fundamental information about C–H activation processes is to uncover and study direct stoichiometric reactions between metal centers and carbon–hydrogen bonds. The first reactions of this type that were observed were oxidative addition reactions of C–H bonds to late transition metal centers (i.e., those lying toward the right side of the transition series), leading to hydrido(alkyl)metal complexes (eq 1). This process, formally regarded as a two-



electron oxidation of the metal, requires that the metal possess (1) coordinative unsaturation enabling access to the metal valence orbitals, (2) electronic unsaturation for accommodation of the electrons supplied by the C and H ligands in the oxidative addition product, and (3) an accessible ($n + 2$) oxidation state.

This process was not directly observed with simple alkanes until 1981. However, a few intermolecular alkane C–H activation reactions, discovered earlier by workers such as Shilov and Crabtree and discussed later in this Account, were postulated to involve such oxidative addition steps leading to hydrido(alkyl)metal complexes as transient intermediates.

In the early 1980s, our research group and workers in the laboratories of Graham and Jones reported the first examples of oxidative addition of unactivated C–H bonds to transition metal centers that resulted in the direct observation of alkyl hydride products.^{2–6} Photolysis of $\text{Cp}^*(\text{PMe}_3)\text{IrH}_2$ (**1**),^{2,3} $\text{Cp}^*\text{Ir}(\text{CO})_2$ (**2**),⁴ or $\text{Cp}^*(\text{PMe}_3)\text{RhH}_2$ (**3**)^{5,6} ($\text{Cp}^* = \text{C}_5\text{Me}_5$) in a hydrocarbon solvent resulted in the loss of dihydrogen (complexes **1** and **3**) or CO (complex **2**) and C–H activation of the solvent (Scheme 1). However, the 16-electron Cp^*ML fragments ($\text{M} = \text{Ir}$, $\text{L} = \text{PMe}_3$, CO ; $\text{M} = \text{Rh}$, $\text{L} = \text{PMe}_3$) believed to be responsible for hydrocarbon oxidative addition were not directly observable.

Since then, a number of second- and third-row late transition metal complexes (e.g., $\text{L}_2\text{Pt}(\text{R})(\text{H})$, $\text{L}_4\text{Os}(\text{R})(\text{H})$, (arene)(CO)OsH₂, CpReL_3 , (tris(pyrazolyl)borate)RhL(carbodiimide), L_2PdBr_2) capable of undergoing reactions that result in oxidative addition of alkane C–H bonds have been reported. A single first-row example, $(\text{DMPE})_2\text{FeH}_2$ (DMPE = bis(dimethylphosphino)ethane), designed after seminal work in the C–H activation area carried out at DuPont on similar complexes in the iron triad in the 1970s, was also discovered. In each of these cases, reactive unsaturated fragments analogous to those illustrated in Scheme 1 were presumably generated by loss of ligands such as an alkane (RH), H₂, CO, Br₂, or $\text{P}(\text{CH}_3)_3$.^{7–11} The alkyl hydride products of alkane

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C–H insertion by third-row metal fragments are often stable at ambient temperatures and can be isolated. In contrast, rhodium and iron C–H activation products decompose rapidly at temperatures above -20°C .^{6,12}

Unsaturated transition metal centers capable of activating strong C–H bonds are exceptionally reactive. Reactions of these species with alkanes appear to be characterized by rapid rates (low energy barriers) for C–H oxidative addition such that they often cannot be observed directly with conventional spectroscopic methods. Consequently, the fragments typically react with almost every C–H bond, requiring that studies detailing the mechanisms of these transformations be effected in suitable inert media. Some nonreactive solvents that have been employed include the noble gases Kr and Xe^{13–18} and perfluorinated alkanes.⁴

Mechanistic studies have shown these processes to exhibit primary kinetic isotope effects for C–H oxidative addition that lie in the range 1.5–2.0, indicating an early transition state for the reaction.^{3,8,13,15,19} However, little is known about the roles played by alkane complexes (sometimes called “ σ -complexes” because of their analogy to π -complexes) in determining the kinetic selectivity exhibited by a reactive metal fragment. These complexes, which arise from interaction of the C–H bonding electrons with an unfilled metal orbital (4), are analogs of dihydrogen and agostic complexes.²⁰ The intervention of alkane complexes in both C–H activation and reductive elimination reac-



tions has been postulated in several experimental papers.^{21–23} These postulates have found support in a number of theoretical studies,^{24–27} in which methane–metal σ -complex formation has been calculated to be exothermic by 10–14 kcal/mol. Alkane–metal complexes (often referred to as “solvates”) have been directly observed in several non-C–H-activating systems. One of the only cases in which alkane–metal complexes have been observed directly in a C–H-activating process is the Cp*Rh(CO) system investi-

gated in our collaborative flash kinetic study with C. B. Moore and his co-workers, utilizing liquid xenon and liquid krypton as inert solvents.^{13,15} This work provided infrared frequencies for the noble gas solvates Cp*Rh(CO)(Xe) and Cp*Rh(CO)(Kr) as well as for alkane complexes Cp*Rh(CO)(RH), where RH = cyclohexane, *n*-propane, and neopentane. These studies also allowed direct measurement of a 4.6 kcal/mol activation energy for conversion of the Rh(I) cyclohexane complex Cp*Rh(CO)(C₆H₁₂) into its C–H-activated Rh(III) product Cp*Rh(CO)(C₆H₁₁)(H).

While alkane complexes with complexation energies estimated to be on the order of 10 kcal/mol have been observed spectroscopically for larger alkanes (e.g., cyclohexane, neopentane),^{13–15} the corresponding methane complexes have not been observed in solution.¹⁵ This “size effect” seems not to have been examined by theorists. If it is real, it may be that theoretical methods (which typically predict significant binding energies for metal–methane complexes) overestimate the metal–alkane binding energy. Clearly, calculations involving the formation of complexes between larger alkanes and unsaturated transition metal fragments would be important to help understand the effect of alkane size on binding energetics.

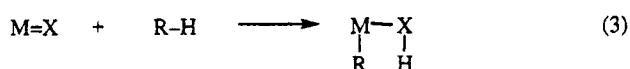
The low kinetic barriers associated with oxidative addition of alkanes and arenes to reactive metal fragments often lead to little or no kinetic selectivity in intermolecular C–H activation experiments, although intermolecular activation is favored over cyclometalation in most of the cited examples. Measured selectivities are scarce in the literature, but reported examples generally show higher preferences for aryl and primary alkyl C–H bonds (i.e., PhH > primary alkyl > cycloalkyl).^{3,8,9,28,29} This contrasts with selectivities observed for radical reactions which show the reverse trend.

The stoichiometric conversion of C–H activation products to functionalized organic compounds is potentially one step along the road to development of catalytic C–H activation processes. However, such reactions have been reported in only a few cases^{3,6,12} (however, see later sections on catalytic reactions). In our laboratory we have found that sequential treatment of Cp*(PMe₃)Ir(R)(H) complexes with bromoform followed by mercuric chloride resulted in transmetalation to an organomercury compound, which was subsequently converted to an alkyl bromide by treatment with bromine. Similarly, reaction of analogous rhodium complexes with bromoform at -60°C , followed by treatment with Br₂ at room temperature, afforded bromoalkane. The reaction of (DMPE)₂Fe(pentyl)(H) with bromine yielded 1-bromopentane directly.

Addition of Alkanes to M–X Bonds. A second important class of C–H activation reactions involves addition of C–H bonds across M–X bonds, rather than to the metal atom itself (eqs 2 and 3).^{30–35} These reac-

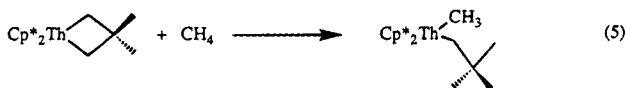
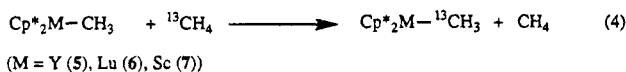
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tions lead to products in which only one of the alkyl or hydrogen fragments is directly attached to the metal after the "activation" process. The reactions shown in eqs 2 and 3 typically involve early transition, lanthanide, or actinide metal complexes, but a few similar processes have been discovered which involve late transition metal complexes.

Metal-Alkyl σ -Bond Metathesis. Early transition, lanthanide, and actinide metal alkyl and hydride complexes capable of activating C-H bonds as shown in eq 2 have been actively studied for the past 20 years.³⁰ Initial investigations were prompted by Erker's discovery of a zirconium benzyne complex capable of activating arene C-H bonds.³⁶ Watson observed the first examples of "early" metal alkane activation processes in 1983 (eq 4) with the scrambling of $^{13}\text{C}_4$ into soluble yttrium (5) and lutetium (6) metal complexes $\text{Cp}_2\text{M}-\text{CH}_3$.^{37,38} Soon after Watson's discovery, several similar systems capable of methane activation were developed and studied in detail (eqs 4 and 5).³⁹⁻⁴³



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Significant work has been aimed at understanding the mechanisms of these activations.³⁰ The exchange processes typically occur at formally d^0 metal centers, suggesting that oxidative addition to the metal, as described for late metals in the Oxidative Addition section above, was not a viable mechanism. Kinetic studies on these reactions demonstrate first-order rate dependence upon the concentrations of both the metal complex and the alkane as well as large, negative entropies of activation. These suggest an associative mechanism and significant organization in the transition state.⁴⁴ In addition, activated deuterated alkane substrates show rather large primary kinetic deuterium isotope effects³⁰ ($k_H/k_D = 3-6$), which can be interpreted as evidence for significant C-H bond cleavage in the transition state. These mechanistic data are supportive of a $2 + 2$ σ -bond metathesis mechanism³⁰ involving a four-center transition state, 9.

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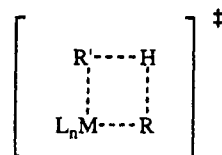
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(44) Some systems are complicated by a first-order pathway involving activation of a Cp^* methyl group to form a cyclometalated complex in the rate-determining step. The cyclometalated complex then reacts with the alkane in a subsequent step.

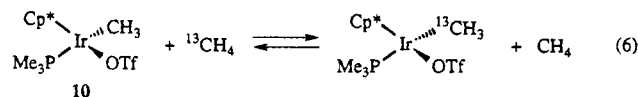


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Such σ -bond metathesis mechanisms have been suggested previously for the H/D scrambling of metal-hydride species and the hydrogenation of metal-alkyl bonds^{45,46} and are supported by theoretical calculations.^{47,48} The presence of intermediates on the pathway to σ -bond metathesis, primarily metal-alkane complexes similar to those involved in late transition metal C-H oxidative addition reactions, has been discussed as a possibility.⁴⁷ Kinetic evidence in support of such intermediates in these systems is not yet available.

In contrast to the behavior of highly reactive unsaturated late metal fragments, these σ -bond metathesis processes can exhibit marked kinetic selectivities. Studies have shown that both electronic and steric considerations are important in determining the substrate reactivity. Bercaw⁴⁰ and Marks⁴² have shown that C-H bonds with more s-orbital character react faster than those with more p-orbital character ($sp > sp^2 > sp^3$). With sp^3 -hybridized C-H bonds, σ -bond metathesis reactions show selectivity toward less-hindered primary sites (cyclohexane is often used as a solvent due to its inert nature).

In addition to these electron deficient metal systems, recent results in our laboratory indicate that late transition metal systems may also be capable of alkane activation by a σ -bond metathesis mechanism.⁴⁹ As seen in eq 6, the overall exchange of labeled methane into the iridium methyl triflate complex, 10, is formally the same as that discussed above. In addition to alkanes, this system can also



mediate the activation of functionalized substrates (i.e., ethers, aldehydes, ketones, acetates). Although these processes are of potential synthetic utility, they are typically not compatible with the oxophilic electron deficient systems above. Mechanistically, we have not yet been able to distinguish between the σ -bond metathesis mechanism and an Ir(III)/Ir(V) oxidative-addition/reductive-elimination mechanism.

Metal-Imide C-H Activation and Related Systems. As shown in eq 3, C-H bonds can be activated using metal-nitrogen double bonds. First discovered for arene C-H bonds,³⁵ this chemistry has been extended to the activation of alkane C-H bonds by Wolczanski.³³ Zirconium,^{33,50} titanium,³¹ tantalum,³² and vanadium³⁴ systems have all been demonstrated

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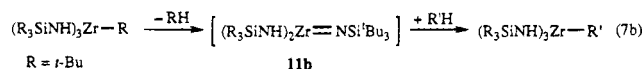
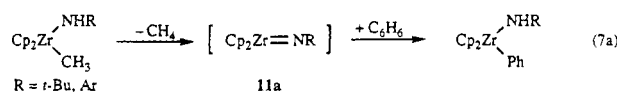
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to be capable of activating the C–H bonds of methane and other alkanes. In analogy to the metal–alkyl C–H activation systems described above, the activation of C–H bonds by imidometal species is believed to occur through a four-center transition state. However, in these systems the C–H bond adds across the metal–nitrogen multiple bond to generate an (alkyl)-(amido)metal species.

These reactions are presumed to proceed by mechanisms similar to the ones shown for our and Wolczanski's zirconium complexes in eqs 7a and 7b. Rate-determining alkane elimination (the reverse of alkane activation) to generate the reactive imido species is

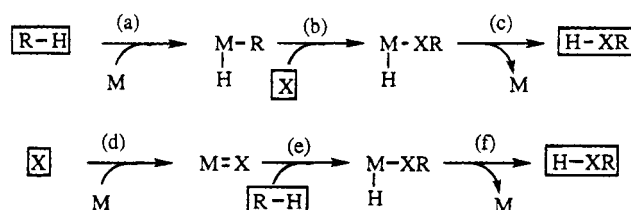


suggested to occur via a four-center transition state. Thus, these reactions are characterized by first-order kinetics and small, negative entropies of activation.^{31–33,50,51} The intermediate imido species **11a** or **11b** then activates the C–H bond of the substrate. Like the systems discussed above, Wolczanski's reactions exhibit a high degree of selectivity toward primary alkyl–hydrogen bonds. Another similarity is the rather high kinetic deuterium isotope effects observed for the activation of arenes and methanes: e.g., $k_{\text{H}}/k_{\text{D}} = 5.1$ (for CH_2D_2) and $k_{\text{H}}/k_{\text{D}} = 4.0$ (for CH_4/CD_4). While theoretical work by Cundari has indicated that methane complexation stabilizes a model zirconium–imido complex by approximately 9 kcal/mol,^{52,53} Wolczanski's recent inter- and intramolecular isotope effect studies do not support the existence of these methane adducts in his imidozirconium system.⁵⁰

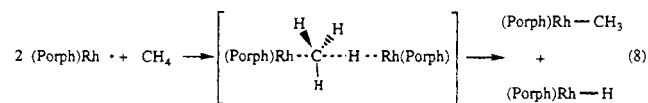
Although there are several examples of metal alkylidenes (carbon analogs of metal imides) that activate C–H bonds intramolecularly,³⁰ no examples of intermolecular C–H activation of alkanes by metal–alkylidene species are known. The reverse process, α -elimination of dialkyl species to form metal alkylidenes and free alkanes, is well documented, however.^{11,54} No early metal oxo complexes are known to activate alkyl hydrogen bonds. However, manganese(III) and iron(II) porphyrin species modeled after cytochrome P-450 are converted to Mn(V) and Fe(IV) metal–oxo species in the presence of oxidizing agents such as H_2O_2 and PhIO . These late metal oxo complexes capable of activating C–H bonds will be discussed later in this Account.

Alkane Activation by Metalloradicals. Although it involves metal rather than organic radicals, one other important reaction that should be mentioned in this section is the unique porphyrin-based C–H activation system discovered by Wayland and his group. These researchers have found that paramagnetic substituted porphyrin Rh(II) complexes react with methane and certain other hydrocarbons between 23 and 120 °C to give equimolar amounts (in the

Scheme 2



methane example) of $\text{Rh}-\text{CH}_3$ and $\text{Rh}-\text{H}$ complexes.^{55,56} In contrast to both the late transition



metal oxidative addition and early metal $\text{M}=\text{X}$ complexes, none of the porphyrin complexes investigated showed any reaction with benzene over a period of several weeks at 80 °C. This and other evidence suggests that these reactions take place via a linear, termolecular transition state in which two metal centers participate cooperatively, one attacking the methane carbon center and the other abstracting a methane hydrogen. To our knowledge this type of reaction has so far been found only in this rhodium porphyrin system. It would be interesting to know whether other paramagnetic complexes exist that will activate alkanes by this double-attack mechanism.

Metal-Catalyzed Functionalization of Alkanes

While the stoichiometric activation of C–H bonds with homogeneous metal complexes has been successfully achieved in the past decade, this represents only the first step toward the rational development of *catalytic* methods for alkane functionalization. Two of the most general non-free radical schemes for catalytic C–H functionalization are illustrated in Scheme 2. The first involves (a) activation of alkane, (b) addition of functionality X, and (c) elimination of product. The second route requires (d) initial metal-mediated generation of a reactive functional group $\text{M}=\text{X}$, (e) addition of a C–H bond across the $\text{M}=\text{X}$ bond, and (f) product elimination. Many of the compounds described in the previous sections that activate alkanes do not provide routes to these other steps; indeed only in rare cases can the metal mediate stoichiometric functionalization.^{3,6}

The most widely employed alkane functionalization catalysts are heterogeneous metal surfaces. While a discussion of the chemistry of these systems is outside the scope of this Account, it is notable that these catalysts are the only ones to have made their way into industrial alkane functionalization processes. Examples include alkane cracking, methane-to-alcohol synthesis, and the conversion of *n*-butane to maleic anhydride.⁵⁷ Nevertheless, heterogeneous alkane functionalization reactions are typified by stringent conditions and either poor (e.g., cracking) or poorly understood (*n*-butane to maleic anhydride) selectivity, which

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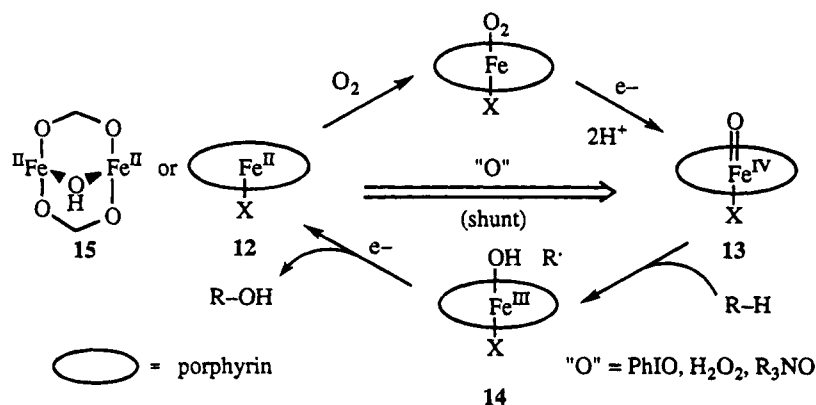
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Scheme 3



makes them either difficult to control or hard to generalize to a wide range of substrates.

In addition to heterogeneous C-H-activating systems, several important homogeneous metal-mediated alkane functionalization processes are known. In this section we will summarize information that is available about the most important of these.

Radical-Based Alkane Functionalization. *Biochemical Alkane Oxidation.* Nature performs ambient temperature alkane functionalization continually, and sometimes with great selectivity, through the use of oxygenase enzymes.⁵⁸⁻⁶⁰ Those belonging to the monooxygenase cytochrome P-450^{58,59} and methane monooxygenase (MMO) families have received a significant amount of attention. These enzymes catalyze the incorporation of molecular oxygen into alkane C-H bonds with the concomitant loss of water and oxidation of NADPH or NADH. In the case of cytochrome P-450, the enzyme active site has been found to contain an iron porphyrin complex with sulfur-bound cysteine (12), which mediates the cleavage of O₂ to generate an iron-oxo complex (13) (Scheme 3). This oxo complex is considered to be the active oxidant of alkane C-H bonds.

As is typical of much classical alkane chemistry, the generally accepted mechanism for this process involves the intermediacy of alkyl radicals. Intermediate 13 is proposed to abstract a hydrogen atom from R-H, generating a caged hydroxoiron(III) complex/alkyl radical pair (14). This is followed by an "oxygen rebound" step in which the carbon radical recombines with the hydroxide. As might be expected of processes that generate R[•], cytochrome P-450 oxidations typically favor oxidation of the weaker tertiary C-H bonds over secondary or primary.

Methane monooxygenase enzymes are active in bacterial oxidation of methane to methanol.^{61,62} The structure of the oxygenating catalyst has recently been crystallographically determined to contain a diiron system with two bridging carboxylate groups and a bridging hydroxide (15).^{63,64} There is mounting evi-

dence that the mechanistic steps by which oxygenation occurs are similar to that for the iron-heme P-450 systems (Scheme 3).⁶⁵⁻⁶⁸ The hydroxylation of methane to methanol by MMO is quite specific, but more complicated substrates, such as linear alkanes, typically give product mixtures.

Biomimetic Alkane Oxidation. The efficiency of biological oxygenase systems has stimulated a significant body of research devoted to developing both structural and functional mimics designed to oxidize alkanes.^{59,69} Groves discovered the first example of metalloporphyrin (iron tetraphenylporphyrin) catalyzed oxidation in 1979, in which cyclohexane was oxidized to cyclohexanol using iodosobenzene as a sacrificial oxidant.⁷⁰ Subsequently oxygenation of alkanes has been observed with a number of metalloporphyrin systems, with manganese porphyrins often the most efficient.⁷¹ The oxygen atom sources employed in these systems have included iodosobenzene, peroxides, amine oxides, and, in a few cases, O₂.^{72,73} These processes are considered to proceed by a mechanism similar to the enzymatic systems in which the oxidant "shunts" the metal to 13. However, both yields and product distributions vary significantly with oxygen-transfer reagent, suggesting that a common oxometal complex is unlikely. In general these systems are neither as efficient nor as selective toward alkanes as the natural systems, and more significant efforts have lately focused upon their use as olefin epoxidation catalysts.^{74,75}

In addition to these porphyrin-based monooxygenases mimics, a number of non-porphyrin systems perform similar alkane oxidation functions. It has been known since the last century that iron salts catalyze the oxidation of alkanes by peroxides (Fenton

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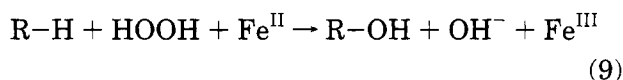
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oxidations).^{76,77} These processes are considered to involve the iron-catalyzed homolysis of hydrogen peroxide followed by hydrogen abstraction and radical recombination (eq 9). Because the metals are involved only in the generation of hydroxyl radicals, and the chemical properties and (relatively nonspecific) selectivities observed are those characteristic of this intermediate, this class of reactions is normally not considered to be a true metal-mediated C–H activation process.



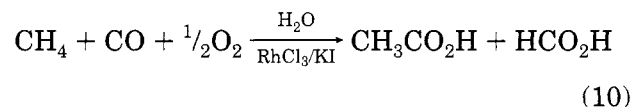
A significant extension of these iron-catalyzed oxidations was first observed in 1983 by Barton and co-workers, who used iron powder and dioxygen in pyridine solvent to effect the facile oxidation of adamantane to adamantanone.⁷⁸ Subsequent studies on several variations of this system (christened "Gif" oxidations by Barton for his location at Gif-sur-Yvette where the discovery was made) have demonstrated that iron salts in the presence of a reducing agent, or in combination with peroxides, can effect the catalytic oxidation of alkanes, sometimes with interesting selectivities. Addition of anion salts (e.g., $\text{X}^- = \text{Cl}^-$, Br^- , N_3^- , SCN^-) to these systems has been found to lead to the catalytic formation of the corresponding alkyl-X compounds.^{79,80} The mechanism of these oxidations is still a matter of some debate.^{81–83} Nevertheless, there appears to be strong evidence for at least partial involvement of hydrogen abstraction by alkoxy radicals, followed by iron-mediated functional group transfer.⁸¹

Metal-Based Alkane Functionalization. In contrast to the alkane activation systems outlined above, many (or possibly all) of which involve the intermediacy of radicals, several transition metal alkane transformation systems have been uncovered in which both C–H bond cleavage and functionalization are believed to occur at the metal center. Because they are non-radical based, these systems typically exhibit selectivities different from those mentioned above and often result in preferential activation of thermodynamically stronger primary C–H bonds. Such processes typically involve late metal systems, largely because the metal center not only must catalyze the activation of the C–H bond but also must be compatible with the functionalizing substrate.

Alkane Oxidations. One of the oldest examples of metal-mediated functionalization is the oxidation of alkanes by platinum chloride salts. The addition of alkanes, including methane, to a mixture of H_2PtCl_6 and Na_2PtCl_4 was noted by Shilov in the 1960s to lead to the generation of both alkyl halides and alcohols.^{84,85} It has subsequently been noted that Pt(II) will perform

this oxidation by itself,⁸⁶ and in the presence of oxidant, a small number of catalytic turnovers have been noted.⁸⁷ Labinger and Bercaw have extended this process to the hydroxylation of functionalized systems (e.g., the activation of the β -carbon in ethanol to give ethylene glycol⁸⁸) and have investigated the mechanism of the process.^{89,90} Their results suggest that initial reaction of Pt(IV) with the C–H bond generates an alkylplatinum intermediate, which then undergoes nucleophilic attack at carbon by either chloride or hydroxide. While the direct oxidation of alkanes with Pt salts is limited in its catalytic ability, the activation of alkanes with similar palladium systems in the presence of carbon monoxide has been reported to result with high turnover numbers in carboxylated products.^{91,92}

The carboxylation of methane to acetic acid was observed recently by Sen and co-workers to be catalyzed by RhCl_3 under aqueous conditions with the use of O_2 as the oxidant (eq 10).⁹³ It is thought that this reaction proceeds via a Rh-CH_3 complex, analogous to the Pd systems above, though little direct mechanistic information is available. Unfortunately, no mention was made of the yield of acetic acid based on methane consumed (i.e., how much acetic acid relative to overoxidized products such as CO and CO_2 was formed), which would affect the potential utility of the reaction.



In addition to alkane carboxylation, photochemical conversions of alkanes to aldehydes have also been observed. These reactions were first catalyzed by $\text{ClRh}(\text{PMe}_3)_2\text{CO}$ (**16**) in the presence of pentane and CO to yield exclusively 1-hexanal (eq 11).^{94,95} Recent mechanistic studies by Goldman have provided evidence that the CO-dissociated species, although present, is not the C–H-activating intermediate. Goldman has suggested that the primary photoprocess in this system involves direct C–H oxidative addition to the four-coordinate Rh(I) center to generate a six-coordinate complex, which then undergoes CO insertion in a subsequent step.⁹⁶

Alkane Dehydrogenation. In addition to the processes discussed above that involve the metal-mediated insertion of a functional group into the C–H

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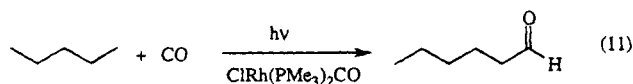
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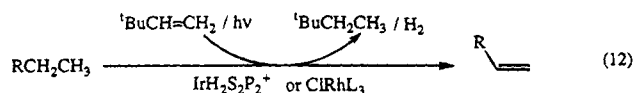
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bond, the conversion of alkanes to olefins by metal complexes also represents their formal functionalization, in this case through the removal of H₂. This process was first noted by Crabtree in 1979 to occur stoichiometrically with [IrH₂(PPh₃)₂(acetone)₂]⁺X⁻.⁹⁷ Subsequent studies showed that addition of 3,3-dimethylbutene to this system, to act as a "hydrogen collector" and thus drive the endothermic loss of H₂, resulted in the catalytic generation of dehydrogenation products.⁹⁸



Alkane dehydrogenation was also observed to be mediated by RhCl(PMe₃)₂CO (**16**) photochemically, the complex described in the alkane oxidation section above that leads to alkane carbonylation under photochemical conditions. This reaction, reported by both Tanaka⁹⁹ and Saito,¹⁰⁰ leads again to the generation of monoalkenes with turnovers ranging up to several hundred.¹⁰¹

Mechanistically, this process is considered to proceed by photochemical extrusion of CO, followed by thermal steps that involve C-H oxidative addition, β-hydride elimination, and finally dissociation of the product olefin. Goldman has recently taken advantage of the reversibility of the hydrogen-for-CO ligand substitution to develop a method for the *thermal* dehydrogenation of alkanes catalyzed by **16** and related systems.¹⁰² In this reaction dihydrogen and 3,3-dimethylbutene are added to the system, providing a catalytic dehydrogenation with the sacrificial olefin serving to remove H₂. This system is more active than that observed by Crabtree, and the use of [RhL₂Cl]₂ leads to turnovers of several hundred/hour. As with other dehydrogenation systems, selectivity for various C-H bonds is generally lacking, and clean olefin synthesis requires the use of cyclic alkanes.

Mercury and Mercuric Salts in Alkane Functionalization. A metal that has achieved increased prominence in C-H activation chemistry recently is mercury. One example is the triplet mercury-photo-sensitized activation of alkanes, leading to dimerization and direct functionalization. Although this reaction is not photocatalytic (i.e., the quantum yield is not above 1.0), the process does not consume mercury and so it is catalytic in metal. Crabtree has made a persuasive case that the simplicity of the system greatly enhances its utility.

The photosensitization process is thought to proceed by photoexcitation of a Hg atom, which quickly crosses over to its lowest triplet state. Because the triplet lies

112 kcal/mol above the ground state, it has sufficient energy to cause homolytic cleavage of unactivated C-H bonds, leading to alkyl radicals and hydrogen atoms.^{103,104} The alkyl radicals then dimerize, leading to coupled products. As expected for such radical reactions, selectivities strongly favor tertiary C-H bonds and exhibit high primary isotope effects.

Crabtree has recently revived research in this area by carrying out experiments under preparative conditions in the presence of equilibrating vapor and liquid phases. Under these conditions mercury sensitization takes place only in the gas phase, and the alkane dimerization products are not converted to higher molecular weight oligomers because they condense to less volatile liquids, physically removing them from exposure to light in the vapor-phase reaction zone.^{105,106} This process has been successfully employed to prepare a number of cycloalkane dimers, as well as dimers and cross-products involving alcohols, ethers, and silanes.

Activation of primary C-H bonds, such as those of methane, is generally difficult with triplet mercury, but Crabtree has recently reported that addition of ammonia (N-H bond strength 107 kcal/mol) to Hg/CH₄ systems leads to methane activation and imine formation.^{107,108} This is considered to result from a strong bonding interaction between amines and mercury (Hg^{*}-NH₃), which leads to efficient energy transfer and N-H bond homolysis. The H^{*} and NH₂^{*} radicals can then abstract hydrogen from methane and through radical recombination yield imine products. This amine system has also been applied to the efficient amination of cycloalkanes.

Very recently a new non-photochemical methane activation method based on mercury salts has been reported. Periana has found that Hg(II) salts in CF₃-SO₃H (trifluoromethanesulfonic or "triflic" acid) catalyze the conversion of methane to methyl triflate (which can be subsequently hydrolyzed to methanol) in high yield and selectivity under relatively mild conditions.¹⁰⁹ The key to this system seems to be the electron-withdrawing character of the triflate group, which stabilizes the initial product and prevents its overoxidation to formaldehyde, formic acid, and CO₂. It seems likely that analogous non-mercury-based methods will follow this initial discovery. Although no information is yet available as to whether selective catalytic oxygenation of higher hydrocarbons can be carried out using this method, it constitutes a novel approach that holds out real promise for direct industrial-scale conversion of methane to methanol.

The Future

As we hope has been made clear in the foregoing discussion, many things have been learned about C-H activation during the past 15 years, but a significant number of "Holy Grails" remain to be found. We

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emphasize that these research targets include those that are both basic and applied. Moving from relatively fundamental to more practical goals, we cite the following challenges as a hopefully stimulating, but certainly noninclusive, list.

The C–H activation research area needs a better understanding of the factors that control the rate, selectivity, isotope effects, and stereochemistry of C–H activation processes and of the nature and role of alkane complexes. We require better insight into why some metals undergo C–H activation and why some do not, and an improvement in the level of reliability associated with theoretical predictions of energy surfaces for C–H activation, especially for relatively complex molecules. Still perplexing is the relationship of heterogeneous and biological catalysts to those that can be prepared in the laboratory, as well as the challenge of synthesizing soluble complexes that will mimic the C–H activation behavior of their solid and biological relatives.

Exploratory goals include the search for new types of C–H activating systems. Wayland's termolecular rhodium porphyrin reactions, our late transition metal Ir(III) apparent σ -bond metathesis reactions, and Periana's Hg(II)/CF₃SO₃H systems are examples of new types of C–H activation reactions that have come to light relatively recently. We expect that the search for analogues of these reactions, as well as for completely new classes of C–H activation processes, will be fruitful. We also anticipate the appearance of new

ligands that will convert nonreactive metals into reactive ones, allow conversion of C–H-activated products into functionalized organic compounds (e.g., oxidation-resistant ligands), and provide methods for carrying out enantioselective C–H activation.

Although progress has been made on the development of catalytic alkane functionalization methods, the community still awaits the development of truly robust, high-yield, high-turnover catalysts for alkane functionalization that can be employed on a large scale. The triflic acid system (perhaps with some metal other than mercury) may ultimately result in an effective methane-to-methanol process, but different types of catalysts will probably be required to convert higher hydrocarbons selectively into, for example, primary alcohols. Within this general goal lie methods for selective conversion of C–H activated metal complexes to functional groups of choice and conversion of methane to longer-chain hydrocarbons for use as synthetic intermediates or liquid fuels. We have no doubt that substantial progress will be made on the search for these "Holy Grails" as this field continues to expand.

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