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Discrete Molecular Catalysts for Methane Functionalization

Niles J. Gunsalus, Michael M. Konnick, Brian G. Hashiguchi, and Roy A. Periana*^[a]

Abstract: The implementation of selective, energy efficient, direct alkane oxidation chemistry could lead to a new paradigm in materials and energy technologies for the 21st century that is environmentally and economically superior to current processes. Such processes would allow the vast reserves of natural gas to be directly employed as feedstocks for fuels and chemicals. Molecular catalysts that activate and functionalize the C–H bonds of unactivated hydrocarbons are of particular interest, from both a scientific and economic viewpoint. This results from the unique properties of these engineered materials, which allow them to carry out oxidative hydrocarbon functionalization, with high atom and energy efficiency, under relatively mild conditions. Despite the large body of work on the activation of C–H bonds over the last three decades, relatively few catalyst systems based on this approach present a viable route to functionalize hydrocarbons. This dilemma is largely due to the large gaps in our fundamental knowledge to allow rational design of such catalysts. Addressed in this paper are some of the key challenges and approaches to the *de novo* design of alkane functionalization molecular catalysts based on the C–H activation reaction, with an emphasis on our own research.

Keywords: C–H activation · homogeneous catalysis · hydrocarbons · methane functionalization

1 Introduction

Petroleum feedstocks currently represent humanity's primary source of fuels, chemicals, and materials. However, the existing conversion technologies operate at high temperatures that lead to both excessive emissions and high capital costs. Between the consumption of this limited feedstock and concerns about the correlation of atmospheric CO_2 and rising global temperatures, a transition towards cleaner feedstocks and a new generation of more efficient, lower temperature technologies is vital to our planet's future.

Natural gas, the main component of which is methane (CH₄), is abundant in reserves worldwide, and has a larger energy to mass ratio than petroleum (oil). Unfortunately, direct transportation of gaseous CH₄ is more hazardous and expensive than for liquid petroleum, making its large-scale utilization less practical. CH₄ could be converted to a liquid product, such as methanol (CH₃OH) or diesel, which can then be transported using pre-existing infrastructure. However, the current industrial process for the conversion of CH₄ to these materials (i.e., the syngas process) is capital and energy intensive, requiring high temperatures (>800°C) and multiple steps. The development of a lower temperature, direct route to convert CH₄ to liquid products/intermediates (such as CH₃OH) would be ideal and could lead to a more efficient and atom-economic utilization of natural gas reserves. However, CH₄ is generally quite unreactive

(especially when compared with CH_3OH), making the design of systems which can selectively convert CH_4 to CH_3OH particularly challenging.

A potential solution to this challenge involves the design and use of discrete, molecular catalysts that functionalize the C–H bonds in CH₄ via the C–H activation reaction (Scheme 1). The C–H activation reaction involves the reaction between a C–H bond and a discrete metal complex (L_n M-X) to generate an organometallic species (L_n M-R) via a non-free radical pathway (Scheme 1, red pathway). Subsequently, this species can be oxidized (i.e., functionalized) to generate the desired product and regenerate the initial catalyst (Scheme 1, purple pathway). Two other important components of the approach shown include a reversible protection strategy (Scheme 1, green pathway) and the indirect use of O₂ (Scheme 1, black pathway). Product protection is a necessary component for the practicality of any system operat-

[[]a] N. J. Gunsalus, M. M. Konnick, B. G. Hashiguchi, R. A. Periana Scripps Energy and Materials Center Department of Chemistry The Scripps Research Institute 130 Scripps Way #3A1 Jupiter, Florida 33458 (USA) Phone: 561 228-2457 Fax: 561 228-3084 e-mail: rperiana@scripps.edu

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Niles J. Gunsalus was born in Stuart, Florida, USA (1987). After obtaining his B.S. degree from the University of South Florida in Tampa, Florida (2011), Niles began his graduate education at The Scripps Research Institute under the supervision of Prof. Periana. His Ph.D. work emphasizes utilizing the C— H activation reaction for the oxy-functionalization of hydrocarbons.

Michael M. Konnick was born near Scranton, Pennsylvania, USA (1980). After obtaining his B.S. degree from Bucknell University in Lewisburg, Pennsylvania (2002), he obtained his Ph.D. in chemistry (2009) with Prof. Shannon S. Stahl at the University of Wisconsin-Madison. Mike joined Prof. Periana's group at The Scripps Research Institute (2010), where he is currently a Senior Research Associate focusing upon the development of CH and CF functionalization methodologies.

Brian G. Hashiguchi was born in Seattle, Washington, USA (1979). He received his B.S. from Occidental College in Los Angeles, California (2002), and his Ph.D. (2008) under the supervision of Prof. Clark Landis at the University of Wisconsin-Madison. Brian joined Prof. Periana's group (2008) at The Scripps Research Institute, where he is currently a Staff Scientist focusing on the development of water soluble complexes for functionalization of small molecules.

Roy A. Periana was born in Georgetown, Guyana (1957). He received his B.S. degree in chemistry from the University of Michigan in Ann Arbor, Michigan (1979). Roy completed his Ph.D. work under the supervision of Prof. Robert G. Bergman at the University of California, Berkeley (1985). He has worked at Dow Chemical Company, Monsanto, Catalytica, Inc., and Catalytica Advanced Technologies. Following his tenure in industry, he has held various faculty appointments including the

University of Southern California and most recently, as the Director of the Scripps Energy and Materials Center at The Scripps Research Institute. His interests are on the low-temperature, selective, homogeneous activation and functionalization of small molecules (CH₄, CO₂, H₂O, N₂, and O₂) using transition metals.











Scheme 1. C-H activation/M-R functionalization catalytic cycle.

ing via a C-H activation sequence as it renders the generated products (such as CH₃OH) less reactive than the starting alkanes (CH₄), whereas for any economically practical large-scale industrial process, the use of O_2 as the terminal oxidant is a requirement. Realization of such a strategy could lead to a new generation of molecular catalysts competent for the low-temperature, selective functionalization of CH4 and other unactivated hydrocarbons. Progress and strategies towards the development of such systems is the focus of this mini-review. There are also systems which have been developed based on coordination and/or activation of an oxidizing reagent (so-called "oxygen activation") which then proceeds to functionalize alkane C-H bonds. Many examples within this class of systems have been shown to either react directly with C-H bonds to generate products or to generate free radicals or other high-energy species which rapidly react/functionalize C-H bonds. There are numerous reviews on this subject,^[1-5] and for reasons of brevity, such systems will not be discussed herein.

2 Methane Functionalization

2.1 Stoichiometric Methane Functionalization – Early Investigations

2.1.1 Shilov chemistry: The First Example of Generating Methanol from Methane via C–H Activation

The direct and selective, metal-mediated activation of hydrocarbon C–H bonds, such as CH_4 , is a relatively challenging task. The first defined examples did not appear in the literature until the early 1970s.^[6-10] Although the facile electrophilic substitution of benzene by Hg^{II} salts in acidic media to give a stable Ph-Hg^{II} species has long been known,^[11] this early discovery is not formally referred to as a C–H activation reaction as it involves the attack by mercury on the aromatic π -system (and not the C–H bond). Nevertheless, this observation is significant, as it set the precedent for the facile generation of M–C

bonds and established that the electrophilic reactivity of "soft" cations could be increased in acidic media.^[12]

In 1972, Shilov and coworkers reported the first lowtemperature (100 °C) C–H functionalization of CH_4 ,^[13,14] where catalytic K₂PtCl₄, in the presence of stoichiometric K₂PtCl₆, was competent for the conversion of CH₄ to CH₃OH and CH₃Cl in acidic aqueous media (Eq. 1). While Shilov had originally proposed that the reaction proceeded via a C–H activation/functionalization mechanism, detailed study of the original system was difficult because of the multiple metal complex speciation and competing side reactions. As a result, several model systems were developed^[15–28] to investigate the mechanism. Mainly due to the work of Bergman,^[29] Bercaw,^[30] and Jones,^[31] it has become generally accepted that transition metal complexes are capable of interacting with alkane C–H bonds via a C–H activation mechanism.

$$CH_{4} + [Pt^{IV}CI_{6}]^{2} - \frac{cat. Pt^{II}CI_{2}(H_{2}O)_{2}}{HCI/H_{2}O, 100 \ ^{\circ}C} CH_{3}OH + [Pt^{II}CI_{4}]^{2} + 2HCI$$
(1)

The Labinger and Bercaw,^[32-38] as well as the Tilset,^[39-42] research groups have contributed substantially to understanding CH₄ functionalization/protonolysis in Shilov-type platinum systems through detailed study of the stoichiometric functionalization of Pt-Me intermediates. In a representative example, Luinstra, Labinger, and Bercaw^[32] demonstrated the synthesis and isolation of a Pt^{IV}-Me species, isolated as [NMe₄]₂⁺ [PtCl₅Me]²⁻, and studied the decomposition of this species to [PtCl_{4-x}- $(H_2O)_x]^{(2-x)-}$ and a mixture of CH₃OH and CH₃Cl in the presence of H_2O and Cl^- (Eq. 2). A competitive (H_2O vs. Cl⁻) nucleophilic attack at carbon of the Pt^{IV}-alkyl was proposed. The lack of observed CH4 in the reaction mixture indicated that protonation (microscopic reverse of C-H activation) did not occur from a Pt^{IV}-Me species. Further mechanistic evidence was provided in a study by Bercaw and coworkers,^[36] in which they observed the decomposition of a Pt^{II}-Me in the presence of various oxidants (Eq. 3). Notably, addition of Pt^{II}-Me to aqueous solutions containing Cl⁻ and oxidants, yielded a mixture of CH₄ and CH₃Cl. These two studies provided strong evidence that C-H activation in Shilov-type systems is carried out by Pt^{II}, and not Pt^{IV}. The Pt^{II}-Me species either undergoes protonolysis to give Me-H and Pt^{II}, or it is oxidized to Pt^{IV}-Me and subsequently functionalized.

The importance of the Shilov system should not be understated, as it was the first system for selective CH₄ functionalization under relatively mild conditions using well-defined, soluble species. Unfortunately, the use of Pt^{IV} as a non-regenerable oxidant, slow rates (a turnover frequency (TOF) of $<10^{-5}$ s⁻¹ at approximately 100 °C) and short catalyst life (TON < 20) made the Shilov system impractical for industrial applications. Nevertheless, it

of Chemistry C^г _ **A** CH₃OH + **B** CH₃CI

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(3)

$$[NMe_{4}]^{+}{}_{2} [PtCl_{5}Me]^{2-} \xrightarrow{C_{1}} H_{2}O, 25 °C \xrightarrow{A} CH_{3}OH + B CH_{3}CI + CCH_{4} + [NMe_{4}]^{+}{}_{2-x} [PtCl_{4-x}(H_{2}O)_{x}]^{(2-x)-}$$
(2)
$$[Pt^{II}(CH_{3})Cl_{3}]^{2-} \xrightarrow{Ox, H^{+}, CI^{-}} H_{2}O, 25 °C \xrightarrow{A} CH_{3}OH + B CH_{3}CI + C CH_{4} + [Pt^{II}Cl_{4-x}(H_{2}O)_{x}]^{2-x}$$
(2)

demonstrated the potential of the C–H activation approach to CH_4 functionalization and spawned a great deal of research effort in the field of C–H activation.

2.2 Catalytic Systems for Methane Functionalization utilizing Highly Electrophilic Metal Catalysts in Strong Acid Media

Due to the unreactive nature of CH₄ in comparison with its partially oxidized products (such as CH₃OH), a significant challenge in selective CH₄ functionalization is overoxidation to CO₂. Therefore, a key to designing a successful system for CH₄ functionalization lies in using an inexpensive and reversible product protection strategy that allows for selective functionalization of CH4 and not its oxidation products. Furthermore, to make such a process economically viable, such a system must be combined with an air-regenerable oxidant. Fortunately, SO₃ and its hydrated form (sulfuric acid or oleum), represents one of the world's largest commodity chemicals and is generated on a global scale in excess of 140 million metric tons per year.^[43] SO₃ is generated from the oxidation of SO₂ in air and, as such, meets the requirement of air-regenerable oxidant. Additionally, the major products generated from the oxidation of CH₄ in hot SO₃ are methyl bisulfate (CH₃OSO₃H) and methane sulfonic acid (CH₃SO₃H). These products are relatively stable to thermal decomposition under the reaction conditions, and significantly, are protected from further reaction with electrophilic reagents due to the electron-withdrawing nature of the sulfate group.

2.2.1 Mercury-catalyzed Conversion of Methane to Methyl Bisulfate and Methane Sulfonic Acid

The facile reaction of Hg^{II} salts with benzene in weakly acidic media to generate a Ph- Hg^{II} species was described previously.^[11] CH₄, being a much weaker nucleophile than benzene, requires super acid solvents (e.g., H_2SO_4) to observe reactivity. This phenomena was first reported in a 1950 patent by Snyder and Grosse in which they observed the conversion of CH₄ into a mixture of oxidized products (Eq. 4).^[44]

$$CH_4 \xrightarrow{HgSO_4} X CH_3SO_3H + Y CH_3OSO_3H + Z CH_2(SO_3H)_2$$
(4)

The reaction between CH_4 and SO_3 was carried out between 100 °C and 450 °C in the presence of catalytic amounts of HgSO₄. A mixture of oxidized products were obtained (mostly CH_3OSO_3H , CH_3SO_3H , and $CH_2(SO_3H)_2$), with the ratio and components of the mixture primarily determined by reaction temperature and the ratio of CH_4 to SO_3 in the reactor. Under optimized conditions, the authors reported a selectivity ratio of 1.65 : 1 for the formation of CH_3OSO_3H over CH_3SO_3H , and an overall yield of 45% based on CH_4 .

2.2.2 Mercury-catalyzed Conversion of Methane Selectively to Methyl Bisulfate

The use of mercury catalysts for the selective oxidation of CH_4 to CH_3OH with high conversion was first reported by Periana and coworkers.^[45] Employing triflic acid as a solvent, the researchers demonstrated that mercuric triflate was stoichiometrically converted to methyl triflate. Mercuric triflate acted as a stochiometric oxidant, and because of the non-oxidizing nature of triflic acid, could not be regenerated from reduced Hg^0 under the reaction conditions. Utilization of concentrated H_2SO_4 (an oxidizing) solvent allowed for regeneration of Hg^{II} from Hg^0 , permitting the $Hg(SO_4)$ -catalyzed functionalization of CH_4 to produce CH_3OSO_3H with 85% selectivity when 50% of the added CH_4 was consumed (the yield of CH_3OSO_3H was 43% based on added CH_4). The major byproduct of the system was found to be CO_2 .

The researchers proposed that the reaction proceeds via an electrophilic activation of CH_4 by $Hg(OSO_3H)_2$. As demonstrated in Scheme 2, the resulting species, methyl mercury bisulfate (CH_3HgOSO_3H), functionalizes to CH_3OSO_3H and reduced [$Hg_2(OSO_3H)_2$]. The reduced mercury catalyst is then reoxidized by sulfuric acid to generate Hg^{II} . Evidence supporting this mechanism was provided by ¹³C and ¹⁹⁹Hg NMR studies of the reaction showing the ¹³CH₃HgOSO₃H intermediate. Further evi-



Scheme 2. Catalytic cycle for electrophilic C–H activation/functionalization of methane by $Hg(OSO_3H)_2$ in H_2SO_4 .

dence was provided by H/D exchange studies between CH_4 and D_2SO_4 in the presence of catalyst and the direct reaction of CH_3HgOSO_3H with H_2SO_4 to give CH_3OSO_3H and CH_4 (microscopic reverse of C–H activation). A study of the catalytic system, conducted by Bjerrum *et al.*, found that the reaction reaches equilibrium within one hour, with a final concentration of CH_3OSO_3H that is independent of catalyst concentration.^[46]

Computational studies on the mechanism of $CH_4 C-H$ activation by Hg^{II} have shown that the nature of the ligands coordinated to Hg greatly affect the activation barriers and reaction enthalpies.^[47] In the transition state, a bisulfate ligand on the catalyst is displaced and simultaneous CH_4 deprotonation and $Hg-CH_3$ bond formation occurs. The authors calculated that electronegative ligands facilitate the C–H activation of CH_4 by lowering the activation barrier between 6–12 kcalmol⁻¹. Placing electron donor groups on the spectator ligand stabilizes the interactions between CH_4 and mercury in the transition state.

Unfortunately, at product concentrations of ~1 M, catalytic productivity of the Hg system in sulfuric acid ceases and no more CH_4 is oxidized. This is attributed to dilution of the strong acid solvent and deactivation of the catalyst due to coordination of nucleophiles such as CH_3OH and H_2O . Additionally, product separation from the reaction mixture proves costly. The CH_3OSO_3H ester has a high boiling point and, as such, cannot effectively be separated from H_2SO_4 .^[48] While CH_3OH can easily be generated from CH_3OSO_3H and H_2SO_4 by simple dilution with H_2O , subsequent removal of water to concentrate the sulfuric acid for reuse is too costly and energy intensive for practical purposes.

Similar to the system developed by Periana et al., [45] Sen and coworkers^[49,50] have reported on a system using Hg^{II} salts for the oxy-functionalization of CH₄ and ethane in fuming H₂SO₄. The authors proposed a chain mechanism initiated by Hg^{II} and they claimed that the mercury salt is able to act as a one-electron oxidant (due to the acidic solvent and poor donor ligands) and generate a methyl radical. The methyl radical can then further react with bisulfate to give product. The authors stated that the methyl radical can reversibly combine with the catalyst to give the observed mercury species, CH₃HgOSO₃H, but that this species plays no role in the mechanism. This hypothesis is in stark contrast with that proposed by Periana and coworkers and is addressed here for that reason. While Sen provides evidence for the viability of a radical mechanism in this system, we hold the view that a C-H activation mechanism seems more likely due to the observation of H/D exchange between CH_4 and D_2SO_4 in the presence of mercury catalysts and that the reaction profile does not change in the presence of molecular oxygen (which is known to effect the reactivity or selectivity in radical reactions).

2.2.3 Mercury-catalyzed Conversion of Methane Selectively to Methane Sulfonic Acid

As was demonstrated in the original report by Snyder and Grosse,^[44] if free SO₃ is present in the reaction mixture, CH₃SO₃H can also be generated from reductive functionalization of the CH₃HgOSO₃H intermediate. Mukhopadhyay and Bell^[51] have demonstrated the selective formation of CH₃SO₃H in mercury-catalyzed oxidations of CH₄ conducted in fuming sulfuric acid. 92% selectivity for CH₃SO₃H and a TON of 60 was reported using Hg- $(CF_3SO_3)_2$ as a catalyst and running the reaction at $130^{\circ}C$ in the presence of O_2 . It was found that the yield of CH₃SO₃H increases rapidly without decreasing selectivity by increasing $[SO_3]$ up to 30 wt%. Further addition of SO₃ causes overoxidation to MeOSO₃H, thereby decreasing selectivity for CH₃SO₃H. This result is significant because the development of a process that generates CH₃SO₃H directly from CH₄ would be more economical than current methods.^[52] Notably, there is also precedent for the conversion of CH₃SO₃H into CH₃OH and SO₂.^[53]

2.2.4 Platinum-catalyzed Conversion of Methane Selectively to Methyl Bisulfate in SO_3/H_2SO_4

Combining knowledge gained through the mercury chemistry^[45] with the original Shilov system^[13] for the C–H activation of CH₄, Periana and coworkers developed a ligated Pt^{II} complex, κ^2 -(2,2'-bipyramidal)Pt^{II}Cl₂ (1, Scheme 3), for catalytic C–H activation/M-R functionalization in strongly acidic solvents.^[54]

Using the ligated complex, the life of the catalyst was greatly extended under the reaction conditions, and high yields of oxy-functionalized products were obtained. Similar to the previously developed mercury system,^[45] this so-called "Periana-Catalytica system" utilizes sulfuric acid as solvent, oxidizing reagent, and product protectant. The oxy-functionalized products varied from CH₃OSO₃H, to protonated methanol, to methanol, depending on the concentration of H_2SO_4 (Eq. 5), which decreased as the reaction proceeded. When the reaction was run in oleum, 90% CH₄ conversion was observed, with 81% selectivity for methanol derivatives. The only observed byproduct of the system was CO_2 . In contrast to the mercury system, the Periana-Catalytica system requires higher temperatures (~220°C) to achieve similar reaction rates and volumetric productivity, but gives higher yields based on CH₄ of oxy-functionalized products (72% vs 43% in the mercury system), with the primary reason being that the Periana-Catalytica system is capable of operating in oleum (102% sulfuric acid) without generating CH₃SO₃H.

Much like the mercury system, the Periana-Catalytica system becomes inactive at product concentrations of approximately 1 M. This inhibition has been attributed to a drop in solvent acidity as CH_3OH and H_2O are formed in the reaction mixture; these product species strongly co-



ordinate to the Pt catalyst, rendering it inactive. Product separation is also an issue (similar to that observed previously with the mercury system), and it was determined that 2–3 volumes of H_2O must be added to the reaction mixtures to facilitate product separation. Unfortunately, the removal of water from the sulfuric acid for reuse, and the relatively high cost of the Pt catalyst, made the overall process economically prohibitive relative to the existing syngas technology.

Nevertheless, the Periana-Catalytica system is considered significant in the field of C-H activation/M-R functionalization of CH₄ due to the relatively high rates, volumetric productivity, selectivity, and stability of the catalyst under the reaction conditions (over 300 turnovers have been observed at 200-250 °C without catalyst deactivation), leading to extensive further studies which have included theoretical work to elucidate the mechanistic details of the process.^[55-59] While it was initially thought that the high efficiency of 1 was due to the development of a system where Pt^{II} catalysis (Scheme 3, k_1 , k_2 and k_3) can occur much faster than catalyst deactivation (via Pt^{II} to Pt^{IV} oxidation, Scheme 3, k₄), further studies by Periana and coworkers determined that formation of 4 does occur rapidly, and that the stability of the system is actually derived from the ability of 4 to readily oxidize 2 to 3 (Scheme 3, k_5) and regenerate the active Pt^{II} catalyst, 1, through a "self-repair" mechanism.^[60] This led Periana



Scheme 3. Proposed Pt(II) C–H activation mechanisms in the Catalytica system. All species possess an outer-sphere anion (HSO4⁻ or CI) which have been omitted for clarity.

and coworkers to propose that it is not only beneficial, but necessary, to design systems which contain this "selfrepair" mechanism when reduced-state catalysts are utilized because the oxidation of the active catalyst is inevitable.

In an attempt to improve the water tolerance of the Periana-Catalytica system, Tang and coworkers reported on the use of Pt^{II} compounds (PtCl₂, K₂PtCl₄ and H₂PtCl₆) in ionic liquids and 96 % sulfuric acid for the activation/functionalization of CH₄ (Eq. 6).^[61] The platinum salts of the original Shilov system that were not compatible with sulfuric acid and were insoluble in water, were found to readily dissolve into ionic liquids and C–H activation/functionalization catalysis was observed. While these systems were found to be more water tolerant, they were not nearly as productive as the original Periana-Catalytica system.

$$CH_{4} \xrightarrow{Catalyst} CH_{3}X$$

$$H_{2}SO_{4} (96\%), \text{ ionic liquid;} 200 ^{\circ}C - 220 ^{\circ}C$$

$$Catalyst = PtCl_{2}, PtO_{2}, K_{2}PtCl_{4}, H_{2}PtCl_{6}$$

$$X = OH, ^{+}OH_{2}, OSO_{3}H$$
(6)

Palkovits and coworkers utilized a covalent triazinebased framework (CTF) containing numerous bipyridyl structure units to develop a heterogeneous analogue of the Periana-Catalytica System.^[62] Treatment of the CTF with K₂[PtCl₄] in water resulted in a solid-supported, insoluble variant of the Periana catalyst (Eq. 7). The authors reported that subjection of this species to similar reaction conditions to the original report,^[54] resulted in yields of CH₃OH that were comparable with the homogeneous system. As in the Periana-Catalytica System, selectivity for CH₃OH formation was above 75% and the major byproduct was CO₂. While the catalytic activity and overall yields of CH₃OH were not improved relative to the original system, the authors were able to demonstrate catalyst recyclability over five consecutive runs without significant loss in activity (TON > 250). Interestingly, catalytic activity in the first run was significantly less (TON=26) than the consecutive runs and the authors attributed this to rearrangement of the solid-supported Pt under reaction conditions leading to the catalytically active species.

Covalent, triazine-based

$$K_2[PtCl_4] \xrightarrow{\text{framework (CTF)}} "K_2[PtCl_4]-CTF"$$
(7)

2.2.5 Iodine-catalyzed Methane Functionalization using SO₃

In an effort to extend the use of electrophiles in strongly acidic media, Periana and coworkers discovered that elemental iodine catalyzed the oxidation of CH_4 to

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CH₃OSO₃H in H₂SO₄/oleum at 195 °C.^[63] The reaction was inoperable without SO₃ present or in less than 98% H₂SO₄. The authors report a 53% conversion of CH₄ with 95% selectivity for CH₃OSO₃H in concentrations up to one molar. Only very low levels of CO_2 (<1% based on added CH₄) were detected in the gas phase of the reaction mixture and there was no detectable concentration of CH₃SO₃H or CH₃I. Notably, running the reactions in the presence of O_2 did not affect yield or selectivity of the reaction, probably excluding a free-radical mechanism. Initially the authors reported reaction rates and product selectivity that were indicative of first-order dependence on both CH₄ and I₂, but follow-up studies by Jarosin'ska et al. suggest that the reaction displays $\frac{1}{2}$ -order dependence on I₂.^[64] In addition to I₂, it has been demonstrated by Bjerrum and coworkers that KI, I₂O₅, KIO₃, KIO₄ and even CH₃I are also capable of catalyzing the oxidation of CH₄ under similar conditions with comparable yields and selectivities.^[65] The authors proposed this indicated that all of these iodine sources were precursors to a common active species. They were also able to optimize the temperature of the reaction as a balance between maximum catalyst activity and minimum product overoxidation. Thus, it was discovered that running the reaction at 180°C led to 57% conversion of CH₃OH (a 4% increase over the original report) and a total CH₃OH concentration of ~6 M! Essentially all of the SO_3 in the reaction was consumed.

The mechanism put forth by Periana and coworkers proposed that $I_2^+HS_2O_7^-$ acts as the active catalyst (Scheme 4). Evidence for the activity of this species was provided via a stoichiometric reaction of $I_2^+[Sb_2F_{11}]^-$ with CH_4 in oleum to give CH_3OSO_3H in 30% yield at 50°C. As in the catalytic system, the stoichiometric reaction fails to give CH_3OSO_3H in the absence of SO_3 . In the proposed mechanism, CH_4 reacts with $I_2^+HS_2O_7^-$ to generate CH_3I and $\frac{1}{2}$ I_2 . The reaction between CH_3I and



Scheme 4. Proposed mechanism for iodine-catalyzed methane functionalization in H_2SO_4/SO_3 .

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 H_2SO_4 generates CH_3OSO_3H and HI. The catalyst, I_2^+ $HS_2O_7^-$, is regenerated via SO_3 oxidation of I_2 and $H_2S_2O_7$ to give water and SO_2 . Further evidence for this mechanism is provided by the reaction of methyl iodide in oleum at 150 °C, where CH_3OSO_3H is formed quantitatively and the solution turns blue, the characteristic color of I_2^+ .

In contrast to the I_2^+ species described by the Periana group, an I⁺ cation was proposed as the active species by Davico.^[66] Davico's opposition to the original hypothesis proposed by Periana was based on gas-phase reactions and *ab initio* calculations carried out on I_2^+ and I^+ with CH₄. Davico demonstrated that I_2^+ did not react with CH₄ at any measurable rate and all of the products generated from such a reaction were computationally determined to be energetically inaccessible. Furthermore, reaction of I^+ with CH_4 was found to occur quite readily. These data led to the proposal that I⁺ directly inserts into CH_4 to give a species, CH_3IH^+ . It should be noted that such gas phase calculations should be cautiously accepted as the original system studied by Periana and coworkers is in a highly polar H₂SO₄ medium with oleum present, and the results are in disagreement with the stoichiometric reaction of $I_2^+[Sb_2F_{11}]^-$ with CH_4 under those conditions. Nevertheless, the $\frac{1}{2}$ order dependence on iodine reported by Jarosin'ska suggests that further studies are needed to determine the active catalytic species.

2.2.6 Methane Functionalization in H_2SO_4/SO_3 Catalyzed by Gold

There are known examples of aurophilic microbes, *Micrococcus luteus*, that accumulate gold from their surrounding environment.^[67] These organisms utilize gold in a membrane bound protein, an NADH oxidase, known as "Au-protein", which is competent for the oxidation of CH₄ to CH₃OH and other, oxidized organic products using NADH, K₃Fe(CN)₆, and O₂ as cofactors. This precedent, by its nature, has inspired interest in the examination of gold catalysts for CH₄ functionalization in several research programs.^[68–75]

In a collaborative effort, the groups of Periana and Goddard reported on the first example of a gold catalyst designed for the oxy-functionalization of CH_4 .^[76] Initial investigations revealed that Au_2O_3 was competent for the stoichiometric activation and functionalization of CH_4 in 96% H_2SO_4 or triflic acid at 180 °C. Au^{III} was reduced to elemental Au^0 in the reaction and could not be reoxidized under these conditions. Switching to a stronger oxidizing media, H_2SeO_4 , it was found that gold could be reoxidized to Au^{III} and catalysis of CH_4 activation/functionalization was achieved. Adding elemental gold to a reaction mixture of CH_4 in 3 M H_2SeO_4/H_2SO_4 , a TON of 32 was achieved in 2 hours. CH_4 conversion was calculated to be 11% with 81% selectivity for CH_3OSO_3H . Addition of 2 wt% SO₃ to the reaction mixture was found to increase

both yield and selectivity to 28% and 94%, respectively. Notably, the presence of O_2 did not affect the rate or outcome of the reaction, probably excluding a free radical pathway. DFT calculations revealed that electrophilic C–H activation by Au^I or Au^{III} could both be viable pathways. Both pathways, Au^I and Au^{III} facilitated C–H activation, are demonstrated in Scheme 5.



Scheme 5. Gold-catalyzed methane functionalization facilitated by Au $^{\rm l}$ or Au $^{\rm III}$

Inspired by the aurophilic microbes, Shilov and coworkers investigated CH_4 oxidation utilizing mixtures of gold and several different bioflavonoids.^[72,73] In a representative example, 0.2 μ M HAuCl₄ and 1 μ M quercetin in a 3:7 EtOH:H₂O solvent generated CH₃OH from CH₄, with up to 60 turnovers in 48 hours at room temperature. The catalytically active species was proposed to be a quercetin-gold complex containing gold in three different coordination sites (Scheme 6). The proposed mechanism is demonstrated in Scheme 7 and was based on the requirement of NADH, Fe^{III}, and O₂ as cofactors for the reaction to proceed.

Several computational studies were conducted after this work, probing the use of gold complexes with oxygen-containing ligands for C–H activation.^[68,69,74,75,77] These studies found that, in aqueous solvent environments, barriers for CH₄ activation by gold catalysts are usually greater than 35 kcalmol⁻¹ with cationic Au^{III} complexes being the exception, demonstrating lower activation barriers.

2.2.7 Palladium-catalyzed Methane Functionalization in SO_3 $/H_2SO_4$

In a report by Sen *et al.*, $Pd(SO_4)_2$ was shown to oxy-functionalize CH₄ to CH₃OSO₃H in fuming sulfuric acid.^[49,50] The reaction showed selective formation of CH₃OSO₃H and reactions were not reported to contain CH₃SO₃H, characteristic of previously developed Pd reactions based on radical processes. Reactions run in H₂SO₄ containing 30 wt% SO₃ at 160 °C were shown to have a TON of 15 under optimized conditions. Michaliewicz *et al.* further optimized this process with the replacement of palladium

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Scheme 6. Proposed, catalytically-active, gold-quercetin complex containing gold in three different coordination sites.



Scheme 7. Gold-catalyzed functionalization of methane with NADH, K_3 Fe(CN)₆ and molecular oxygen.

sulfate by metallic palladium.^[78] The authors report a TON of 47 in just two hours under comparable conditions (Eq. 8).

$$CH_4 \xrightarrow[-30]{\text{cat. Pd}(SO_4)_2 \text{ or } Pd^0} \rightarrow CH_3OSO_3H$$

$$30 \text{ wt\% } SO_3, H_2SO_4$$

$$160 ^{\circ}C \qquad (8)$$

2.2.8 Methane Functionalization to Acetic Acid, Catalyzed by Palladium in H_2SO_4

In an interesting and unexpected extension of the Sen system, Taube, Periana, and coworkers showed the use of $Pd(SO_4)_2$ to generate acetic acid from CH_4 without added CO in 96% H_2SO_4 .^[79] Acetic acid formation was the result of oxidative condensation of two molecules of CH_4 , as was revealed by studies using ¹³C labeled CH_4 . A calculated yield of 10% acetic acid based on CH_4 was reported with 90% selectivity.

The reaction was proposed to proceed through a twostep, non-radical mechanism demonstrated in Scheme 8. First, CH_4 undergoes C–H activation mediated by X_2Pd^{II} to generate XPd^{II} - CH_3 . Some of this species undergoes reductive elimination to CH_3OSO_3H . The formed CH_3OSO_3H undergoes inorganic Pd^{II} -facilitated overoxidation to CO, which oxidatively adds and inserts into a Pd–C bond of XPd^{II} – CH_3 to give a Pd-acyl intermediate. Reductive elimination from the Pd-acyl species gives acetic acid and Pd^0 . Addition of CO to the reaction was



Scheme 8. Proposed mechanism for Pd-catalyzed functionalization of methane to acetic acid in H_2SO_4 . Key processes include: A) electrophilic C–H activation/reductive functionalization (black pathway); B) oxidation of methanol to form CO (red pathway); C) CO insertion into the Pd^{II}-Me intermediate/reductive functionalization (blue pathway); and D) overoxidation of CO to CO₂ (grey pathway).

found to inhibit catalyst activity, leading to reduced yields of acetic acid.

A major drawback of this system is the formation of Pd black (Pd⁰). As CO concentrations increased, so did the rate of reduction of the active Pd^{II} catalyst. Reoxidation of the formed Pd⁰ by SO₃ is slow and serves as a turn-over-limiting step in this process. In an extension of this work, Bell and coworkers^[80,81] confirmed the mechanism originally proposed by Periana *et al.* The researchers also found that the overall efficiency of the system could be improved with the inclusion of O₂^[81] or a combination of O₂/Cu^{II.[80]} The researchers reported higher TOFs and final acetic acid concentrations that were slightly higher than in the original system. The proposed mechanism of the reaction was further confirmed through DFT calculations conducted by Bell and Chempath.^[82]

2.2.9 Challenges with using Electrophilic Catalysts in Strongly Acidic Media

Studies conducted on the Periana-Catalytica and related systems suggest that highly electrophilic, C–H activation catalysts are severely inhibited by mild electron donors (which includes the reaction products of CH_3OH and H_2O), resulting in maximum product concentrations of approximately 1 M. Consequently, at this concentration, the separation of the products from the reaction mixture is too expensive for commercial viability. For a system to be industrially practical, concentrations of at least 1 M must be attainable and product separation from the reaction mixture must be inexpensive. With solution-phase

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 CH_4 concentrations in the millimolar range, this necessitates the catalyst being 100–1000 times more reactive with CH_4 than with the resulting functionalized product. In the previously described systems, this reactivity pattern was achieved through the use of highly electrophilic C–H activation catalysts combined with product protection by a strongly electron withdrawing sulfate group. Other systems were designed using less electrophilic catalysts in weaker acid media in an attempt to resolve these issues.

2.3 Catalytic Systems for Methane Functionalization utilizing Ambiphilic Metal Catalysts in Weaker Acid Media

Goddard, Periana, and coworkers have used computations to probe the extent of electrophilicity of various transition-metal complexes.^[83] Using density functional theory, the authors were able to quantify the direction and magnitude of charge transfer between metal complexes and alkyl C–H bonds in the transition state. It was found that metal-mediated C–H activation of alkanes did not necessarily adhere to the classic electrophilic activation paradigm. As an alternative, the authors proposed a continuum that ranged from highly electrophilic C–H activation through highly nucleophilic C–H activation. Figure 1 graphically depicts the charge-transfer (CT) differences between these systems.



Figure 1. a) A depiction of insertion and substitution transition states used to probe the charge-transfer continuum; and b) a generalized depiction of the CT continuum of C–H bond activation for insertion.

2.3.1 Iridium-catalyzed Functionalization in HTFA using Periodate

Quantum mechanical rapid prototyping (QMRP), a methodology developed by Goddard and coworkers, allows for rapid, computational sampling of different catalytic conditions in which the metal, oxidation state, ligands, and solvent can all be rapidly varied to test conditions. Using this technique, Goddard, Periana, and coworkers designed a complex based on iridium, **5**, for C–H activation in trifluoroacetic acid (HTFA) media (Scheme 9).^[84] The complex showed catalytic activity for H/D exchange, an indication of C–H activation between CH₄ and TFA-d₁, in experiments conducted between 105 °C and 135 °C; a barrier of 24 ± 3 kcalmol⁻¹ was determined. Unfortu-



Scheme 9. Catalytic cycle for the iridium-catalyzed functionalization of methane in HTFA.

nately, the barrier for functionalization of the activated Ir-CH₃ complex required heating the reaction to 180° C, and at temperatures above 150°C, the catalyst was shown to gradually lose activity. Thus, under optimum conditions, a maximum TON of 6.3 was observed with 5 in HTFA using KIO₄ as the terminal oxidant. The proposed mechanism (Scheme 9) involves protonolysis and loss of ethane and ethylene from 5 and simultaneous coordination of OTFA to give 6; opening up a coordination site gives the proposed active catalyst, 7. Methane undergoes C-H activation with 7 (proceeding through 8 and 9) to give 10. Ir-Me functionalization of 10 is facilitated by KIO₄ and HTFA to give methyl trifluoroacetate (CH_3OTFA) and regenerate the active catalyst, 7. Attempts at running the reaction in acetic acid resulted in no observed H/D exchange even at 180°C, and was likely due to the stronger coordinating effects of the acetate anion.

2.3.2 Palladium-catalyzed Methane Functionalization to MeOTFA using H_2O_2 in HTFA

Sen and coworkers in 1987 demonstrated that $Pd(OAc)_2$ was competent to stoichiometrically react with alkanes (including CH_4) in trifuoroacetic acid to give alkyl trifluoroacetates (Eq. 9), and an electrophilic C–H activation reaction was proposed.^[85,86] The authors were able to

achieve a 60% yield of CH₃OTFA ester based on added Pd^{II}, using approximately 55 bar of CH₄ at 80°C. According to the authors, HTFA was chosen as a solvent for several reasons: (i) the relatively poor basicity of the CF₃COO⁻ anion; (ii) high ligand lability of $M-O_2CF_3$ bonds leads to a highly electrophilic Pd^{II} species; and (iii) the solvent lacks C–H bonds.

$$CH_4 + Pd(OAc)_2 \xrightarrow{CF_3CO_2H} CH_3OTFA + Pd^0 + 2HOAc$$
80 °C (9)

Sen and coworkers showed that the system could be made catalytic when trifluoroacetic anhydride was used as a solvent and H_2O_2 was employed as the terminal oxidant.^[87] CH₃OTFA was generated from CH₄ with a catalyst TON of 5.3 after two hours. Unfortunately, increasing reaction times only resulted in lower yields of the product, presumably due to product instability under the reaction conditions. This was attributed to hydrolysis of the CH₃OTFA ester followed by overoxidation of (the now unprotected) CH₃OH.

Following this work by Sen, several other Pd^{II} complexes were reported^[88-92] as efficient catalysts for CH_4 functionalization in HTFA/TFAA. The first of these reports, by Muehlhofer and coworkers, demonstrated that, with Pd-bis-N-heterocyclic carbene (NHC) complex **12a**, a TON of 20 was achieved after 7 hours at 90 °C using $K_2S_2O_8$ as the terminal oxidant (Figure 2).^[88] Strassner and coworkers^[90] investigated the effect of the bite angle in these bis-chelating carbene species by varying the number of methylene linkers (**13**, Figure 2). It was found that **13a** (n=2) had the highest activity for CH_4 functionalization to MeOTFA with a reported maximum TON of 33 under similar conditions.

Further exploration of this area by Strassner^[89-91] led to the recent development of a series of Pd–NHC complexes in which one of the NHC ligands was replaced by pyrimidine.^[91] In this study, **14** was shown to exhibit higher activity than the previously developed Pd-bis NHC complexes (**11–13**), demonstrating a TON of 41 under similar reaction conditions. The origin of the increase in activity, whether due to changes in ligand structure or the Pd counter anion, is not clear.

A recent, detailed computational study on Pd–NHC complexes conducted by Strassner *et al.* suggests that C– H activation is carried out by cationic palladium(II).^[92] This Pd^{II}-CH₃ species is subsequently oxidized to a Pd^{IV}-CH₃ which undergoes reductive elimination to give MeOTFA and regenerate cationic palladium(II) (Scheme 10).

Ingrosso and coworkers also reported the use of Pd complexes for the conversion of CH₄ to CH₃OTFA in TFA/TFAA using H₂O₂ as oxidant (Eq. 10).^[93] Utilizing hexafluoroacetylacetonate ligated Pd^{II}, the authors were able to achieve a TON of 50 running the reaction at 50 °C



Figure 2. Pd-carbene complexes developed for methane functionalization.



Scheme 10. Catalytic cycle for chelating, bis(NHC) palladium-catalyzed functionalization of CH_4 to CH_3OTFA reported by Strassner.

for 4 hours. Interestingly, the authors also reported copper complexes comprised of the same ligands that were competent for CH_4 conversion (Eq. 11). Although they were only capable of achieving a TON of 12 under optimal conditions, and the reaction was proposed to proceed via activation of trifluoroperacetic acid rather than C–H activation, the result is nonetheless significant because it utilizes relatively inexpensive copper as the catalyst.

$$CH_4 \xrightarrow[]{\text{cat. Pd(hfacac)}_2, H_2O_2}{\text{HTFA/TFAA, 50 °C}} CH_3 OTFA$$
(10)

$$CH_4 \xrightarrow{\text{cat. Cu(hfacac)}_2(H_2O)_2, H_2O_2} CH_3 OTFA$$

$$HTFA/TFAA, 75 °C (11)$$

2.3.3 Systems which use O₂ Directly

Although examples of selective CH₄ functionalization where O_2 is used directly as the oxidant are rare, and the mechanisms of such processes are only vaguely understood, they are elegant in their simplicity and represent significant progress in hydrocarbon oxy-functionalization processes. One example is a system designed by Jasra and coworkers in which the authors observe CH4 hydroxylation with a binuclear, bridged Ru^{III} complex, $[(HSalen)_2Ru_2(\mu-O)(\mu-CH_3COO)_2]$.^[94] Running the reaction in a 1:1 mixture of acetone:H₂O (Eq. 12), a reported TON of 54 was achieved at 30°C using an oxygen pressure of 5 bar. It has been proposed that the reaction proceeds via Ru activation of O₂, which then reacts with CH₄ to generate CH₃OH. Radical mechanisms were ruled unlikely in this system through studies involving radical traps.

$$CH_4 + O_2 \xrightarrow{\text{cat. } [(\text{HSalen})_2 \text{Ru}_2(\mu-\text{O})(\mu-\text{CH}_3\text{COO})_2]} Acetone:H_2O (1:1), 30 \text{ °C} CH_3OH$$
(12)

Bao and coworkers recently reported observing catalytic turnover with the previously described $Pd(OAc)_2$ system designed by Sen, using a three-cycle redox couple reaction for the regeneration of Pd^{II} from Pd^0 in HTFA.^[95] The authors reported yields of CH₃OTFA in concentrations up to 106 µmol in 10 hours at 80 °C using a Pd^0/Pd^{II} , p-benzoquinone/hydrobenzoquinone, NO/NO₂/ O₂ triple redox cycle (Scheme 11). This work has been expanded upon by Yuan and coworkers^[96-98] who utilized molybdovanado-phosphoric acid in place of NO₂.



Scheme 11. Pd^{II} regeneration from Pd^0 through a redox-couple mediated oxidation.

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The reaction of CH_4 with CO and O_2 is a thermodynamically favorable process and there are several systems that have been developed to facilitate this transformation. Sen and coworkers reported the first of such systems using RhCl₃ in water.^[99] The proposed reaction pathway involves C–H coordination of CH₄ by the rhodium catalyst (**17**, Scheme 12) followed by C–H activation to give



Scheme 12. Proposed Mechanism for Rh-catalyzed functionalization of methane to acetic acid using CO and O_2 .

a Rh-Me intermediate, **19**. This step is followed by insertion of CO (Scheme 12, blue pathway) to generate an Rh-COCH₃ intermediate which can then be hydrolyzed by water to generate CH₃COOH. **19** was also shown to react directly with HX to generate CH₃OH products (Scheme 12, red pathway). The authors performed extensive studies, including isotopic labeling studies, to show that the Rh–CH₃ intermediate was indeed generated from CH₄. The authors also noted a substantial increase in rate in the presence of Cl⁻ and I⁻ and no observable change in rate in the presence of radical sources. Work by Sen,^[100] and later Chepaikin^[101–105] and coworkers, found that rate and selectivity were highly dependent on solvent effects. This reaction has been studied computationally through DFT studies by Ziegler and coworkers.^[106]

Similar to the system described above, Fujiwara and coworkers reported on a system for the conversion of CH₄, CO, and O₂ (or $K_2S_2O_8$) to acetic acid in the presence of Pd^{II} catalysts in HTFA solvent.^[107–110] Although the authors also reported on the use of Cu^{II} systems, the proposed mechanism proceeded via radical pathways and will not be further discussed. The Pd system was pro-

posed to operate by a C–H activation mechanism resembling an electrophilic substitution. The reaction was optimized to generate 0.14 mmol of acetic acid using 15 bar O₂, 20 bar CH₄, 15 bar CO, and 0.05 mmol of both Cu and Pd catalyst in HTFA at 80 °C for 20 hours (Eq. 13). The increased rate in the simultaneous presence of Cu and Pd was attributed to the formation of a Pd^{II}-Cu^{II} complex with increased electrophilicity. Other groups^[111–113] have extended this reactivity to Pt^{II} salts, but they were found not to be as effective as the former Pd^{II} salts for the oxidative carbonylation of CH₄.

$$CH_4 + CO \xrightarrow[HTFA, 80 °C]{O_2 \text{ or } K_2S_2O_8} CH_3CO_2H$$
(13)

2.3.5 The Significance and Outlook of Weakly Electrophilic/ Ambiphilic Systems

It is now clear that weakly electrophilic (or ambiphilic) systems can undergo C–H activation/M–R functionalization of inactivated C–H bonds in media less acidic than 98% H₂SO₄. Unfortunately, it still remains a major challenge to develop systems that operate in weaker acids than HTFA.

3 Outlook

Product protection is a crucial aspect to any strategy for CH₄ functionalization. Without adequate protection, the functionalized products of CH_4 (such as CH_3OH) are not likely to be stable under the reaction conditions and will give undesired, overoxidation products (such as CO₂). In highly electrophilic systems, the use of superacid solvents protected CH₃OH from further oxidation through in situ ester generation. Ambiphilic systems, while being able to operate in weaker acid media, seem to lack adequate protection to prevent overoxidation, as extended reaction times generally resulted in diminished yields and selectivities of desired products. In considering the electronic continuum discussed previously,^[83] it seems reasonable that transitioning to nucleophilic systems in strongly basic media could provide adequate product protection (deprotonation) to prevent further reactivity. While there are examples of CH₄ C-H activation using these more nucleophilic metals,^[8,114–126] examples of saturated hydrocarbon functionalization are limited,^[115,122-126] and the use of these metals for C-H activation in highly basic environments is essentially non-existent.

One example of alkane functionalization using nucleophilic C–H activation catalysts was reported by Chen *et al.*^[126] The authors reported on the use of Cp^{*}Rh(η^4 -C₆Me₆) (Cp^{*}=penta-methyl cyclopentadiene) to catalyze the formation of linear alkylboranes from n-alkanes and borane reagents(Eq. 14). The reaction between *n*-octane and 4,4,5,5-tetramethyl-1,3,2-dioxaborolane (HBpin) in the presence of a 5 mol% catalyst was shown to generate *n*-octylBpin in 65% yield upon heating to $150 \,^{\circ}$ C for 14 hours, demonstrating high selectivity for primary C–H bonds.

$$\begin{array}{c} \text{Cat. Rh or Ir} \\ \text{R}^{-}\text{H} + \begin{array}{c} \text{HBpin} \\ (\text{or [Bpin]}_2) \end{array} \xrightarrow{\Delta} \\ \text{R}^{-}\text{Bpin} + \begin{array}{c} \text{H}_2 \\ (\text{or HBpin}) \end{array} \end{array} \tag{14}$$

Periana and coworkers^[127] have shown the first example of a nucleophilic C–H activation under basic conditions. The authors reported a Ru^{II} complex, (IPI)Ru^{II} (IPI=2,6diimidazoylpyridine), which was shown to catalyze H/D exchange with aromatic C–H bonds in a basic environment (Eq. 15). Ligand deprotonation was proposed to play a major role in facilitating reactivity of the catalyst with the high-lying, π -type, antibonding orbitals of the C– H bond. Importantly, Periana and coworkers found that C–H activation activity increased with increasing basicity. The catalyst was also shown to catalyze H/D exchange with some aliphatic substrates; however, no report of H/D exchange at CH₄ has been reported with this class of system to date.

R-H
$$\xrightarrow{\text{cat. } (H_2|P|)\text{Ru}^{III}\text{Cl}_3, \\ \text{excess } Zn^0} \xrightarrow{\text{R-D}} \text{R-D} \qquad \begin{pmatrix} H & H \\ N & N \\ N & N \\ N & N \\ H_2|P| \end{pmatrix} \qquad (15)$$

Efficient, low-temperature functionalization of CH₄ is considered to be one of the most valuable, yet challenging goals in chemistry. CH₄ functionalization via C-H activation using discrete, molecular catalysts shows great potential in solving this problem, and to date, highly electrophilic catalysts in strong acid solvents have shown the most promise in achieving highly selective CH₄ functionalization combined with high volumetric productivity. For this reason, these systems have been the most extensively studied. In investigating the limitations of these systems as product concentrations increase and acidity decreases, it becomes apparent that new methods and systems need to be developed. The exploration of ambiphilic catalysts in less acidic media, as well as nucleophilic catalysts in basic media, has shown that these systems are competent for C-H activation/functionalization. While much progress has been made since the discovery of the C-H activation reaction in the early 1970s, it is imperative that we continue to push the boundaries of our knowledge and design new systems for the conversion of CH₄ and other hydrocarbons that will allow us to meet the increasing energy demands of an ever-increasing, energy-intensive, globalized society.

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