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Designing Catalysts for Functionalization of Unactivated C–H Bonds Based on the CH Activation Reaction

BRIAN G. HASHIGUCHI, STEVEN M. BISCHOF,
MICHAEL M. KONNICK, AND ROY A. PERIANA*
The Scripps Energy & Materials Center, Department of Chemistry, The Scripps Research Institute, Jupiter, Florida 33458, United States

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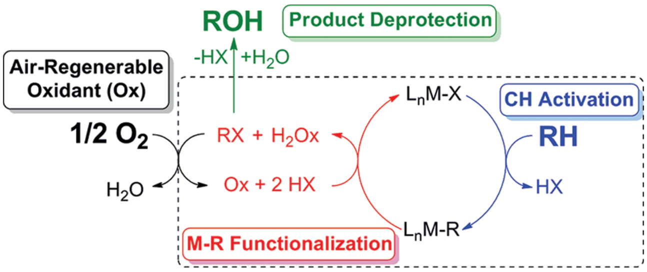

In an effort to augment or displace petroleum as a source of liquid fuels and chemicals, researchers are seeking lower cost technologies that convert natural gas (largely methane) to products such as methanol. Current methane to methanol technologies based on highly optimized, indirect, high-temperature chemistry (>800 °C) are prohibitively expensive. A new generation of catalysts is needed to rapidly convert methane and O_2 (ideally as air) directly to methanol (or other liquid hydrocarbons) at lower temperatures (~250 °C) and with high selectivity.

Our approach is based on the reaction between CH bonds of hydrocarbons (RH) and transition metal complexes, L_nM-X, to generate activated L_nM-R intermediates while avoiding the formation of free radicals or carbocations. We have focused on the incorporation of this reaction into catalytic cycles by integrating the activation of the CH bond with the functionalization of L_nM-R to generate the desired product and regenerate the L_nM-X complex. To avoid free-radical reactions possible with the direct use of O_2, our approach is based on the use of air-recyclable oxidants. In addition, the solvent serves several roles including protection of the product, generation of highly active catalysts, and in some cases, as the air-regenerable oxidant.

We postulate that there could be three distinct classes of catalyst/oxidant/solvent systems. The established electrophilic class combines electron-poor catalysts in acidic solvents that conceptually react by net removal of electrons from the bonding orbitals of the CH bond. The solvent protects the CH_3OH by conversion to more electron-poor $[CH_3OH_2]^+$ or the ester and also increases the electrophilicity of the catalyst by ligand protonation. The nucleophilic class matches electron-rich catalysts with basic solvents and conceptually reacts by net donation of electrons to the antibonding orbitals of the CH bond. In this case, the solvent could protect the CH_3OH by deprotonation to the more electron-rich $[CH_3O]^-$ and increases the nucleophilicity of the catalysts by ligand deprotonation. The third grouping involves ambiphilic catalysts that can conceptually react with both the HOMO and LUMO of the CH bond and would typically involve neutral reaction solvents. We call this continuum base- or acid-modulated (BAM) catalysis.

In this Account, we describe our efforts to design catalysts following these general principles. We have had the most success with designing electrophilic systems, but unfortunately, the essential role of the acidic solvent also led to catalyst inhibition by CH_3OH above ~1 M. The ambiphilic catalysts reduced this product inhibition but were too slow and inefficient. To date, we have designed new base-assisted CH activation and L_nM-R fuctionalization reactions and are working to integrate these into a complete, working catalytic cycle. Although we have yet to design a system that could supplant commercial processes, continued exploration of the BAM catalysis continuum may lead to new systems that will succeed in addressing this valuable goal.

Introduction

The majority of fuels, chemicals, and materials are derived from petroleum feedstocks. While there is a healthy discussion on how best to transition away from these nonrenewable resources, there is near unanimous agreement that developing a new generation of lower temperature, higher efficiency technologies to better utilize fossil fuels would be invaluable. Such technologies would minimize the use of our liquid petroleum feedstocks, limit emissions, and allow the use of cleaner resources such as natural gas. Fossil fuels

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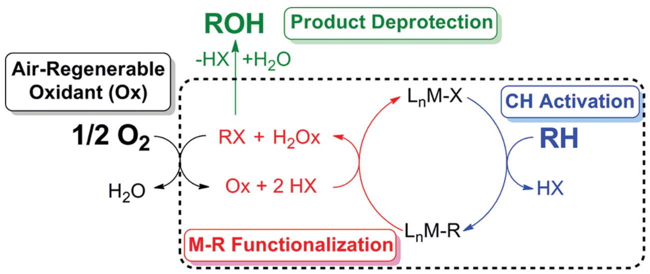
SCHEME 1. CH Activation/M−R Functionalization Catalytic Cycle[a]



[a]Reactions outside dotted box are external reactions.

are mostly composed of molecules containing C−H and C−C bonds. Current industrial processes used to functionalize CH bonds typically involve free radicals or carbocations and require high temperatures that increase costs and emissions. An important advance in the chemistry of the C−H bond was introduced in the early 1970s and later established as the "CH activation" reaction.[1−5] This attracted strong interest due to the possibility for C−H bond reactivity at remarkably high rates and selectivities at lower temperatures compared with classical free radical or carbocation reactions. Herein, we use "CH activation" to describe reactions between a C−H bond and a transition metal complex (L_nM-X) to generate discrete, "activated" L_nM-R intermediates that do not involve free-radicals, carbocations, or carbanions (Scheme 1).

As can be seen in Scheme 1, to utilize the CH activation reaction as the basis for catalysts for the overall conversion of hydrocarbons to useful products, a key requirement is the need for a subsequent step (referred to herein as "M−R functionalization") where the "activated" L_nM-R intermediate is functionalized and the catalyst regenerated. A potential issue that must be addressed is that the high catalyst reactivity required for reaction with the hydrocarbon can lead to the catalyst reacting preferentially with the desired, functionalized products (such as MeOH). These challenges, compounded by the simultaneous requirement for catalyst stability, compatibility between all catalytic steps, and the economic necessity to utilize O_2 (ideally as air) as the overall coreactant make the design of efficient CH functionalization catalysts for unactivated hydrocarbons one of the most daunting goals in chemistry today. In addition to utilizing CH activation, other strategies central to our approach are the indirect use of O_2 and a low-cost, reversible, product protection strategy (Scheme 1). This Account details our efforts to design and study a new generation of molecular catalysts for the selective, lower temperature functionalization of unactivated hydrocarbons (methane and benzene) based on the CH activation reaction.

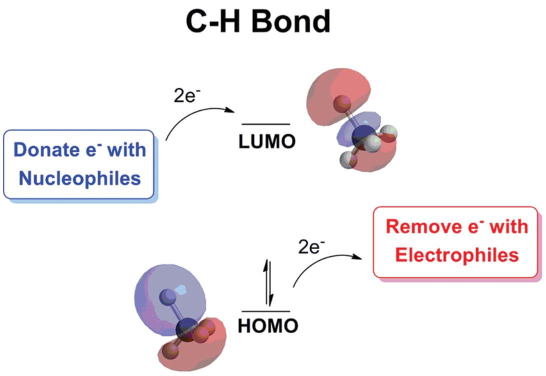


FIGURE 1. Orbital interaction to break a CH bond.

Electrophilic Catalysts

The first lower temperature CH functionalization of methane was reported by Shilov and co-workers $\sim$30 years ago.[6] While a CH activation/M−R functionalization mechanism was first proposed by Shilov, this became generally accepted in the 1980s as a result of work by Bergman[7] and Bercaw.[8] The Shilov systems were characterized by use of a prohibitively expensive oxidant (Pt^{IV}), slow reaction rates, unstable catalysts, and low methane conversion. However, these early systems provided a solid foundation for later studies. A simplified conceptual model for cleavage of the C−H bond is shown in Figure 1. As can be seen, removing electrons from the bonding orbitals with electrophiles can be expected to cleave the C−H bond. Extending on the Shilov system and early work with electrophiles,[9,10] we designed several systems based on the "soft"[11] redox-active cations, Hg^{II}, Pt^{II}, Pd^{II}, $Au^{I/III}$, and I^+, for the activation and functionalization of methane. In addition to the judicious choice of catalyst, an important key to the efficiency of these systems was the use of concentrated sulfuric acid, H_2SO_4, as a practical solvent that also served as a protecting group and air-regenerable oxidant (Scheme 1) for the overall conversion of methane to methanol. Methanol was specifically chosen because of the established technologies for the conversion to chemicals or fuels as well as the facile, reversible reactions, such as protonations or deprotonations, that could be utilized for product protection (*vide infra*). Experimental and theoretical studies are consistent with these systems operating by the CH activation/M−R functionalization catalytic sequence.

Mercury Catalysts

The initial studies on HgX_2 salts were the basis for the subsequent discoveries in acidic media and the conceptual considerations that led to the discoveries presented here. One of the oldest known organometallic reactions is the facile electrophilic substitution of benzene by HgX_2 salts in acidic solvents (HX) to generate a stable Ph−Hg^{II} species.[12] This is not a CH activation reaction since the reaction involved direct attachment at the aromatic ring and not the CH bond. However, this highlighted that the reactivity of simple Hg^{II} cations, classified as "soft" in the early studies by Pearson,[9] could be increased by acidic solvents and that this system could lead to facile generation of M−C bonds. Interestingly, it was previously reported that gas phase reactions between methane and oleum over supported Hg salts between 100−450 °C yielded several products with CH_3−O, CH_3−S, and S−CH_2−S bonds.[13] Rudakov[14] also later reported that treatment of cyclohexane with concentrated H_2SO_4 containing $HgSO_4$ led to benzene. Unfortunately, we ignored these reports in the early phases of our work because we, as the authors of these reports, believed that these reactions were based on carbocation chemistry. We were also biased by the observations in the CH activation field that transition metals would be required.

The use of electrophilic cations in acidic media was also influenced by the reports of Sen[9] and Moiseev[10] on the stoichiometric reactions of methane with PdX_2 (eq 1) and CoX_3 (eq 2) salts in CF_3CO_2H to generate $CF_3CO_2CH_3$. These early studies suggested that the electron-withdrawing CF_3CO_2− group could "protect" the CH_3 group from further reaction, since it was presumed that the reaction proceeded by electrophilic CH activation. Subsequent studies using Pd^{II} and H_2O_2 demonstrated catalysis; however, the $CF_3CO_2CH_3$ product rapidly decomposed yielding ~5 TON under optimum conditions.[15] Our studies of the PdX_2 system confirmed the stoichiometric conversion of methane to $CF_3CO_2CH_3$. However, the reaction led to irreversible formation of Pd black (Pd^0) and low yields. In the case of the CoX_3 system, we found that the acidic solvent rapidly and irreversibly reduced $Co^{III}X_3$ to $Co^{II}X$, likely via eq 3.

$$CH_4 + H_2O_2 + (CF_3CO)_2O \xrightarrow[90\,°C]{Pd^{II}} CF_3CO_2CH_3 + H_2O + CF_3CO_2H \qquad (1)$$

$$CH_4 + 2Co^{III}(OCOCF_3)_3 \xrightarrow[180\,°C]{} CF_3CO_2CH_3 + 2Co^{II}(OCOCF_3)_2 + CF_3CO_2H \qquad (2)$$

$$2CF_3CO_2H + 2Co^{III}(OCOCF_3)_3 \rightarrow (CF_3COO)_2 + 2Co^{II}(OCOCF_3)_2 + 2H^+ \qquad (3)$$

To address these disadvantages, we considered whether the class of "soft", oxidizing inorganic cations that are reported to react with aromatics via electrophilic substitution could react with methane in H_2SO_4. Interestingly, these considerations led to the initial study of TlX_3 salts because (A) Tl^{III} is classified as a "soft", strong electrophile, (B) it readily reacts with aromatics to generate Tl^{III}−Ar species, (C) TlX_3 ($E°(Tl^{III/I})$ = 1.28 V) is a much stronger oxidant that $Hg^{II/0}$ ($E°$ = 0.91 V), $Pd^{II/0}$ ($E°$ = 0.92 V), or $Co^{III/I}$ ($E°$ = 0.74 V), and (D) the "inert pair effect" predisposes Tl^{III} to two-electron oxidations. The TlX_3 salt first examined was a 0.1 M solution of $Tl(CF_3SO_3)_3$ prepared in situ, by addition of Tl_2O_3 to neat CF_3SO_3H.[16] This solution was then heated in a high pressure metal reactor at 180 °C under 500 psig of methane for 2 h. Subsequent analysis revealed much higher levels of methanol than our analytical methods were calibrated to observe! Reactions using $^{13}CH_4$ confirmed a nearly quantitative yield of CH_3OH based on Tl(III) (eq 4).

$$Tl^{III}(OSO_3H)_3 + CH_4 \rightarrow CH_3{-}OSO_3H + Tl^{I}OSO_3H + H_2SO_4 \qquad (4)$$

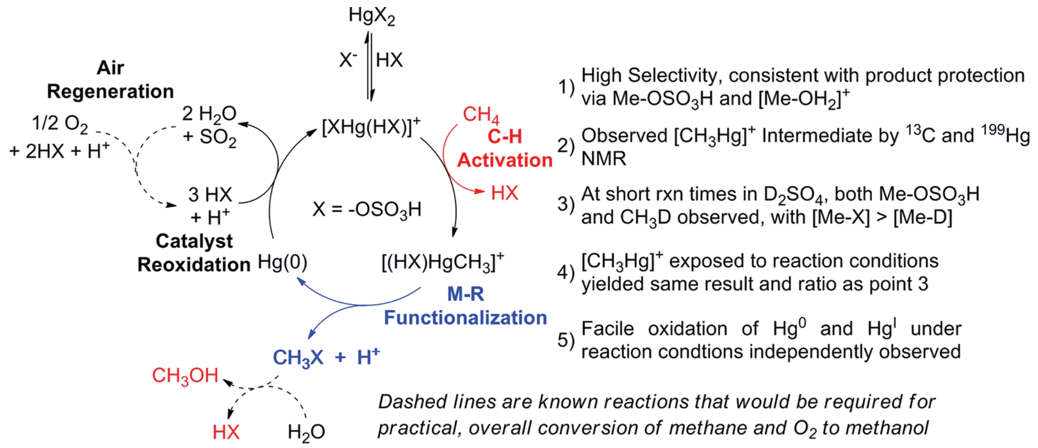
When attempts to make the reaction with catalytic TlX_3 were unsuccessful, we examined HgX_2 salts given the similarity in reactivity for arenes and the lower oxidation potential.[17] Initial experiments showed that $Hg(O_3SCF_3)_2$ in triflic acid also stoichiometrically converted methane to $CH_3OSO_2CF_3$ (eq 5). Upon switching to concentrated H_2SO_4, catalytic conversion of methane was observed. With ~50 mM $Hg(SO_4)_2$, the reaction produced ~1 M CH_3OSO_4H with 85% selectivity (major byproduct is CO_2) and ~50% yield based on added methane (eq 6). Studies showed that higher concentrations of methanol could not be obtained due to inhibition by the reaction products, water and methanol (in equilibrium with the ester CH_3OSO_3H and $CH_3OH_2^+$). Control reactions were consistent with a non-free-radical mechanism.

$$Hg(CF_3SO_3)_2 \xrightarrow[CF_3SO_3H]{CH_4} CF_3SO_3CH_3 + CF_3SO_3H + Hg^0 \qquad (5)$$

$$CH_4 + 2H_2SO_4 \xrightarrow{HgX_2} CH_3OSO_3H + 2H_2O + SO_2 \qquad (6)$$

We postulated that the reaction proceeds by (1) electrophilic activation of methane to generate $[CH_3Hg]^+$, (2) reductive functionalization to CH_3OSO_4H and Hg^0, and (3) subsequent oxidation of the Hg^0 by H_2SO_4 to regenerate the active catalyst (Scheme 2). Several key experiments provided evidence for this electrophilic CH activation mechanism (summarized in Scheme 2). Importantly, H_2SO_4 plays four key roles: (1) inexpensive, stable solvent; (2) activation of HgX_2 to generate the catalytically active $[XHg(HX)]^+$; (3) *in situ* protection of CH_3OH as $CH_3OH_2^+$; and (4) an air-regenerable oxidant. Several external experimental[18,19] and computational[20] studies are consistent with this general mechanism.

SCHEME 2. Proposed Mechanism for Functionalization of Methane with $Hg(OSO_3H)_2$ in H_2SO_4



1) High Selectivity, consistent with product protection via $Me\text{-}OSO_3H$ and $[Me\text{-}OH_2]^+$

2) Observed $[CH_3Hg]^+$ Intermediate by ^{13}C and ^{199}Hg NMR

3) At short rxn times in D_2SO_4, both $Me\text{-}OSO_3H$ and CH_3D observed, with $[Me\text{-}X] > [Me\text{-}D]$

4) $[CH_3Hg]^+$ exposed to reaction conditions yielded same result and ratio as point 3

5) Facile oxidation of Hg^0 and Hg^I under reaction condtions independently observed

Dashed lines are known reactions that would be required for practical, overall conversion of methane and O_2 to methanol

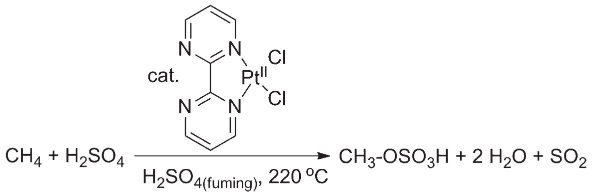
Despite the efficiency and potential practicality of this system, a key issue was the inhibition of the catalyst by the reaction products, which limited product concentrations to ~1 M. At this concentration, process economic studies showed that methanol separation by addition of water, subsequent product removal, and reconcentration of the solvent by distillation was prohibitively expensive. This inhibition was a result of the exponential drop in the solvent acidity (at ~80% H_2SO_4) and resulting increase in concentration of HSO_4^-. Since the HSO_4^- binds much more tightly than H_2SO_4, this increased the activation barrier for coordination and cleavage of CH_4 in the first coordination sphere of the Hg^{II} center.

Platinum Catalysts

Key challenges of early work reported by Shilov were the slow rates, unstable catalysts, and use of Pt^{IV} as the overall oxidant. In an attempt to address these issues, we began to examine the Pt-catalyzed functionalization of CH_4. Simple Pt salts were not effective in H_2SO_4 due to poor solubility, stability (due to Pt black formation), and selectivity. However, an early discovery revealed that the N-ligated complex, $(NH_3)_2PtCl_2$, was soluble in H_2SO_4 and an active catalyst for the functionalization of CH_4 (eq 7). Not unexpectedly, the catalyst was unstable and <20 turnovers of CH_3OH were observed before catalysis stopped as a result of $PtCl_2$ precipitation. To address this, we focused on chelating N-ligands. We focused on N-ligands because we anticipated stability issues with more typical ligands such as phosphines, cyclopentadienes, and carbon monoxide that were used in CH activation studies at that time.

$$CH_4 + H_2SO_4 \xrightarrow{(NH_3)_2PtCl_2} CH_3 - OSO_3H + 2H_2O + SO_2 \quad (7)$$

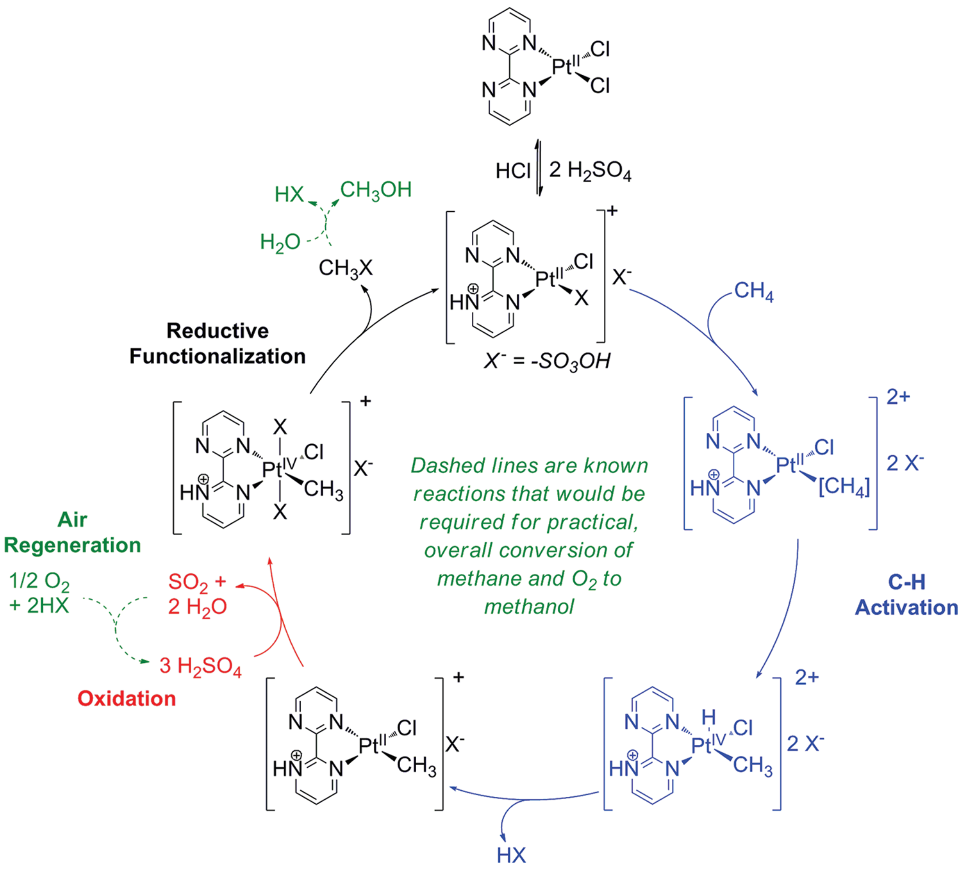
These studies led to the identification of the first example of an efficient, stable Pt-based catalyst, (κ^2-2,2′-bipyrimidyl)-platinum(II)dichloride, the so-called "Periana System" for the selective, high-yield functionalization of methane to ~1 M methanol in H_2SO_4 (eq 8).[21] Remarkably, stability was the result of oxidative dissolution of Pt^0 by H_2SO_4 facilitated by the bipyrimidine (bpym) ligand. In contrast to the HgX_2 system, the Pt-ligated system can operate in the presence of excess SO_3, without the formation of the undesirable C−S bonded product, CH_3SO_3H. The use of added SO_3 led to higher efficiency than the Hg system with yields of ~80% at ~90% selectivity to give a mixture of CH_3OSO_3H, CH_2OH^+, and CH_3OH. However, this system was also limited by product inhibition at ~1 M, resulting in poor process economics from the required product separation. A major disadvantage relative to Hg was the high cost of Pt and the requirement for 3 orders of magnitude increase in rate for practicality. Efforts continue in our laboratories to design catalyst systems that could utilize the practicality of H_2SO_4 while operating at high TOF and generating methanol at >1 M.



$$CH_4 + H_2SO_4 \xrightarrow[H_2SO_{4(fuming)},\ 220\ ^{\circ}C]{cat.} CH_3\text{-}OSO_3H + 2\ H_2O + SO_2 \quad (8)$$

We postulated that this system also proceeded by an electrophilic CH activation, $Pt-CH_3$ functionalization sequence (Scheme 3). Strong evidence was provided by carrying out the reaction in D_2SO_4 at low methane conversion where, in addition to oxygenated products, the isotopologues of methane, CH_nD_{4-n}, were observed as would be expected from reversible formation of $Pt^{II}-CH_3$. We anticipated that oxidation of $Pt^{II}-CH_3$ intermediate by H_2SO_4 to

SCHEME 3. Proposed Mechanism for the "Periana System" for Methane Oxidation



Pt^{IV}−CH$_3$ (and SO$_2$) followed by reductive functionalization would generate CH$_3$OSO$_4$H and regenerate the Pt^{II} catalyst. The expectation that product inhibition was also the result of the drop in solvent acidity and inhibition by HSO$_4^-$ is supported by recent computational studies (Figure 2).[22]

An important unresolved question about this system is why the catalyst is stable for extended periods. Studies show that under some conditions over 300 turnovers are observed without any loss in activity if acid concentration is maintained. This result is not consistent with the stoichiometric studies that show rapid and complete oxidization of Pt^{II} to (presumably) inactive Pt^{IV} by hot H$_2$SO$_4$. This is currently being studied in our laboratories.

Palladium Catalysts

As part of our studies to identify efficient reactions between electrophilic, "soft," redox active metal salts and CH$_4$ in H$_2$SO$_4$, PdX$_2$ was examined in detail. Unlike the Pt system, no ligands could be identified to prevent formation of Pd metal, and only low yields could be obtained due to formation of Pd^0. However, when experiments were carried out with ^{13}C-enriched CH$_4$ in addition to ^{13}CH$_3$OH, a persistent pair of doublets was observed in the ^{13}C NMR spectra of the crude reaction mixtures. This was eventually identified as ^{13}CH$_3$^{13}CO$_2$H,[23] where, remarkably, *both carbons originated from* ^{13}*CH*$_4$ (eq 9). This oxidative coupling of CH$_4$ occurs at greater than 90% selectivity and ~10% yield (based on methane) with H$_2$SO$_4$ as both the solvent and oxidant.

$$2CH_4 + 4H_2SO_4 \xrightarrow[180\,^{\circ}C]{Pd^{II}} CH_3CO_2H + 4SO_2 + 6H_2O \quad (9)$$

A non-free-radical, tandem catalysis mechanism was proposed based on detailed mechanistic studies using combinations of ^{13}C-labeled and nonlabeled CH$_4$, CH$_3$OH, and CO (Scheme 4). The two key mechanistic steps are the conversion of CH$_4$ to methanol via a CH activation reaction (path A), slow overoxidation of CH$_3$OH to generate low concentrations of CO (path B), and extraordinarily fast CO insertion into the Pd−CH$_3$ bond leading to HOAc (path D). To our knowledge, this is the first example of the direct condensation of two methane molecules to HOAc through a CH activation mechanism. This could potentially be a much less expensive route to HOAc than the current process based on reaction of CH$_3$OH and CO where both of these starting

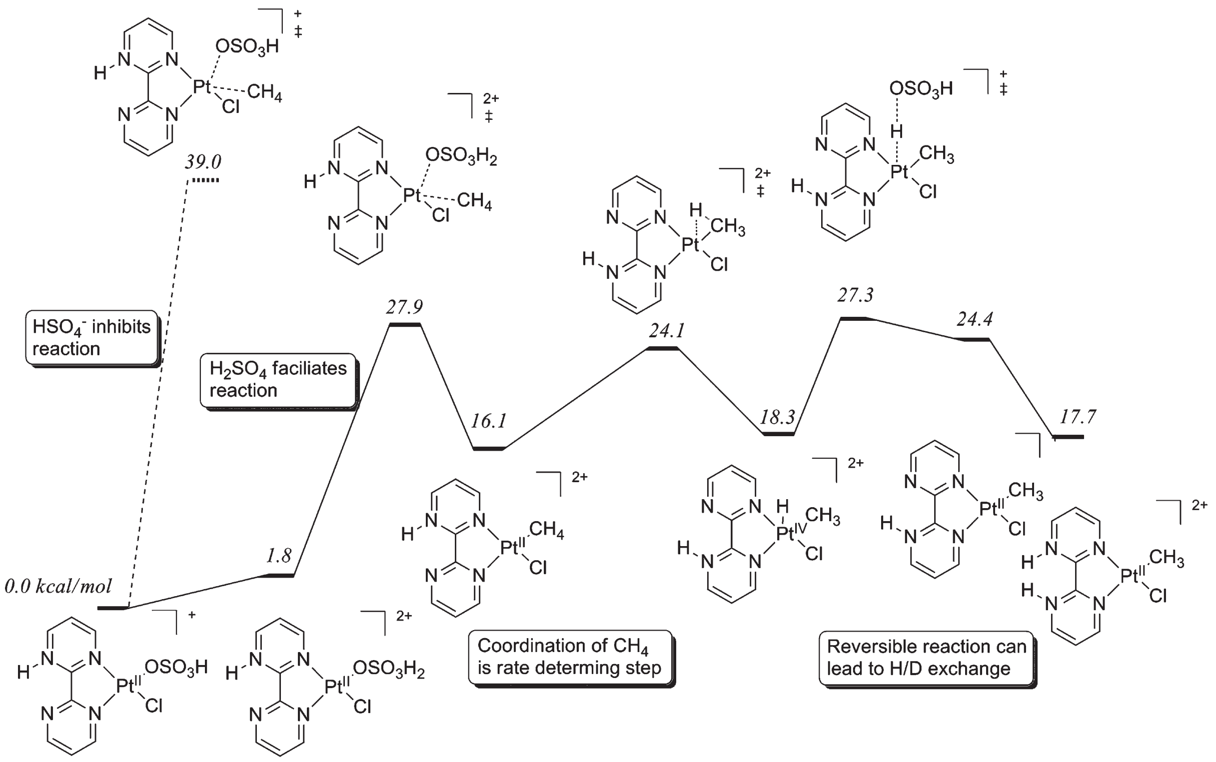
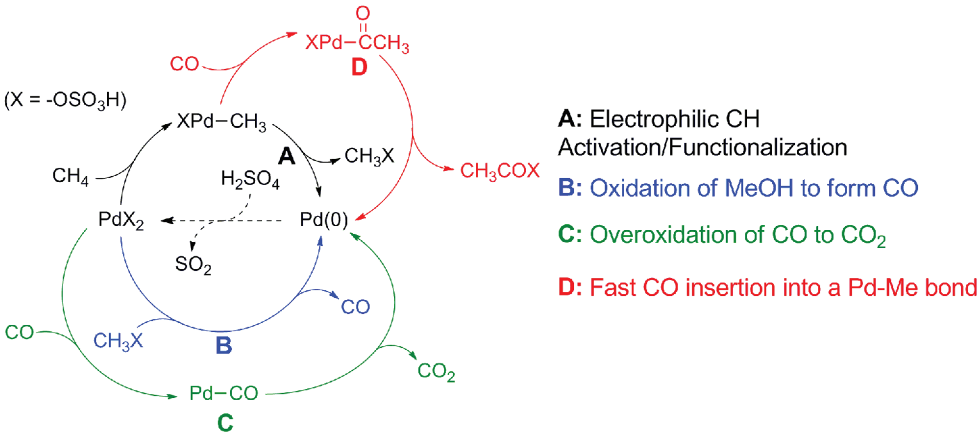


FIGURE 2. DFT studies for $[(Hbpym)PtClX]^+$ CH activation.

SCHEME 4. Palladium-Catalyzed Methane Functionalization to HOAc

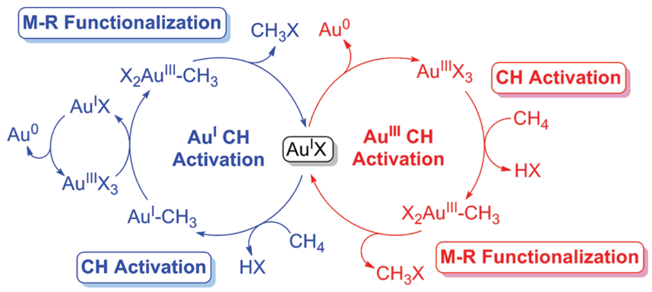


materials must first be generated by costly high-temperature reforming. Subsequent work by Bell and co-workers has confirmed the overall mechanism and shown that various additives can improve our original system.[24] Efforts are continuing in our laboratories to increase the efficiency of this process.

Gold Catalysts

As noted above, Hg^{II} (electronic configuration of $[Xe]4f^{14}5d^{10}$) and Pt^{II} ($[Xe]4f^{14}5d^{8}$) both reacted with CH_4 by CH activation. Consequently, we postulated that since the two “soft” common oxidation states of gold are isoelectronic with these metals, both could be capable of effecting CH activation. Experiments with AuX_3 ($X = HSO_4$) in H_2SO_4 or CF_3SO_3H confirmed that Au^{III} rapidly and selectively reacted with CH_4 to generate CH_3OH (eq 10). However, unlike the Hg^{II} and Pt^{II} systems, only stoichiometric reactions were observed because H_2SO_4 did not reoxidize the reduced gold metal.[25] As with the other electrophilic systems, the system required strongly acidic media. Later work showed that to catalyze the reaction, H_2SeO_4 (a stronger oxidant than H_2SO_4 but comparable in acidity) could be used to reoxidize Au^0. Using metallic gold as a catalyst precursor in a 3 M H_2SeO_4/H_2SO_4

SCHEME 5. Gold-Catalyzed Methane Functionalization



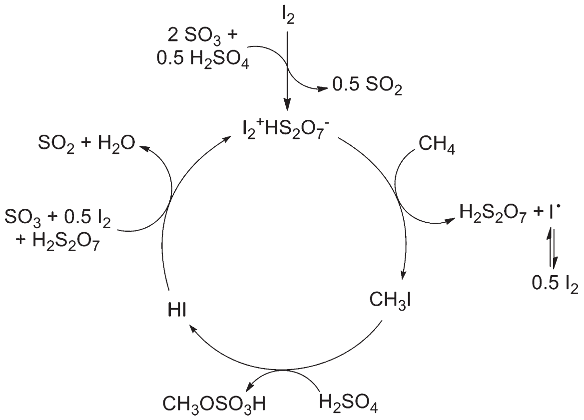
solution led to a TON = 32 in 2 h and 11% CH_4 conversion in 81% selectivity to CH_3OSO_3H. Control reactions (added O_2) excluded a radical mechanism, and DFT calculations support electrophilic CH activation of CH_4 for both Au^{III} and Au^I (Scheme 5).

$$3CH_4 + 2Au^{III}X_3 + 3H_2O \xrightarrow[\substack{H_2SO_4\\ 180\,°C}]{} 3CH_3OH + 6HX + 2Au^0 \qquad (10)$$

Iodine Catalysts

Following the success of the previous "soft" (metallic) cationic electrophiles in strong acid solvents, we reasoned that the characteristic blue species, $I_2{}^+HS_2O_7{}^-$, known to form upon addition of I_2 to oleum[26] could exhibit similar CH activation chemistry given the cation size and electrophilicity. This was indeed the case,[27] and treatment of CH_4 with $H_2SO_4/SO_3/I_2$ mixtures at 195 °C led to the catalytic generation of CH_3OSO_3H and methane oxidation occurs with 53% conversion at >95% selectivity (eq 11). CH_3OSO_3H was obtained up to [1 M] with a TOF of 3.3×10^{-2} s^{-1} and a volumetric productivity of $\sim 10^{-7}$ mol^{-1} cm^{-3} s^{-1}. Importantly, no MeI or CH_3SO_3H was observed. We proposed the mechanism shown in Scheme 6. Recent theoretical calculations are consistent with I^+ $HS_2O_7{}^-$ as the active catalyst.[28]

SCHEME 6. Methane Oxidation by I_2 in H_2SO_4/SO_3



$$CH_4 + 2SO_3 \xrightarrow[\substack{H_2SO_4/O_3\\ 195\,°C}]{\text{cat. } I_2} CH_3OSO_3H + SO_2 \qquad (11)$$

In considering the results, it is apparent that the electrophilic systems that were found to react with methane presented a potential dilemma; the requirement for strongly acidic solvents to activate the catalyst as well as protect the product could also lead to the inhibition of the catalyst as a result of the drop in solvent acidity as the reaction proceeded. Of course, it could not be predicted that all the systems would give a maximum of ~1 M and that this concentration would lead to expensive separations. One solution we considered

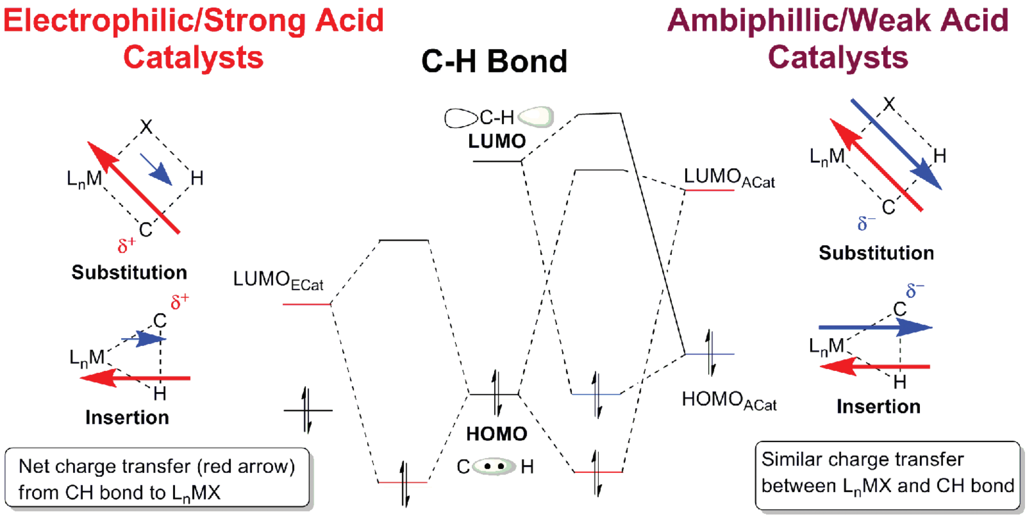
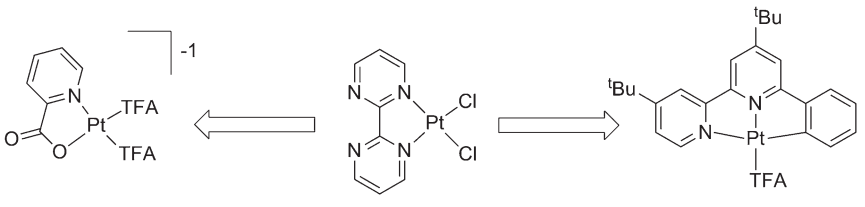


FIGURE 3. Conceptual comparison of electrophilic and ambiphilic catalysts.



[(pic)Pt(TFA)$_2$]$^{-1}$ **(bpym)PtCl$_2$** **(NNC)Pt(TFA)**

FIGURE 4. Increasing the electron density of the (bpym)PtCl$_2$ system.

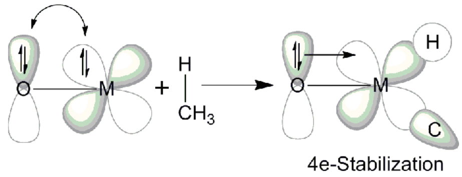


FIGURE 5. Possible π-donation effects of O-donor ligands.

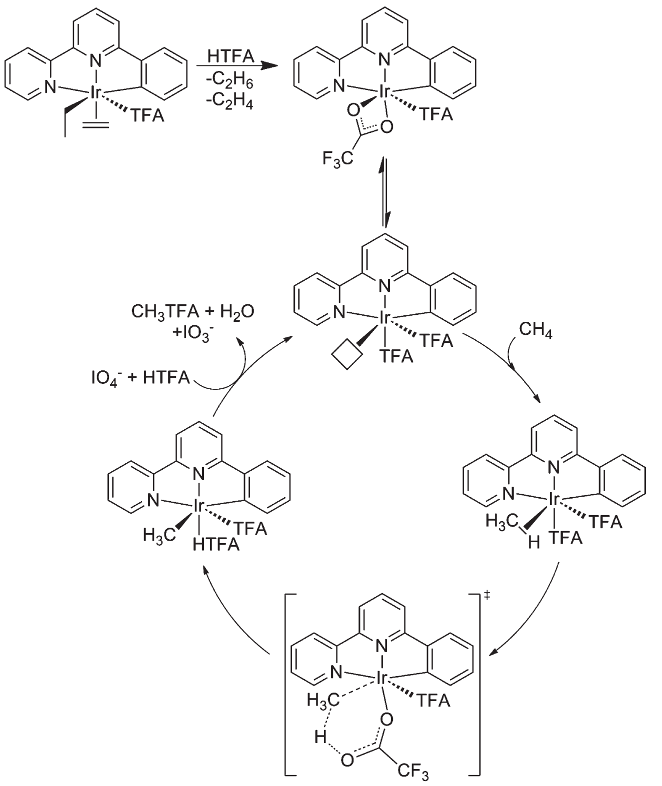
is to design catalysts that are not as strongly electrophilic and could operate in weaker acids where separation is more practical. However, as one moves to less electrophilic systems, it is likely that back-donation from the metal to the LUMO of the C$-$H bond would be required to compensate for the weaker metal ion electrophilicity (Figure 3). Discussion of such "ambiphilic" systems in weak acids are presented below.

Ambiphilic/Weak Acid Systems

In an attempt to reduce the electrophilicity of the Pt center, we examined the use of stronger σ-donor ligands (Figure 4). One example involved exchanging the bpym ligand for the better donor κ^2-*N,O*-picolinate (pic) to give [(pic)Pt(TFA)$_2$]$^{-1}$.[29] This complex was found to carry out H/D exchange reactions with benzene ~300 times faster than (bpym)Pt(TFA)$_2$ in CF_3CO_2H, which is a weaker acid than H_2SO_4. However, the complex was found to be too thermally unstable (>90 °C) to functionalize benzene or methane.

Efforts at improving stability while increasing the electron density led to synthesis and study of the thermally, protic-, and air-stable ligated Pt^{II} complex with the 3-6-phenyl-4,4′-di-*tert*-butyl-2,2′-bipyridine (NNC) ligand (Figure 4). However, while this complex was stable at 180 °C in CF_3CO_2H and active for CH activation of benzene and methane (TON = 61 for H/D exchange), no oxy-functionalization reaction with methane was observed. The likely fundamental reason for this was that increasing the electron density at the metal center while facilitating CH activation also led to unfavorable thermodynamics for reductive functionalization. The DFT calculations are consistent with this interpretation.

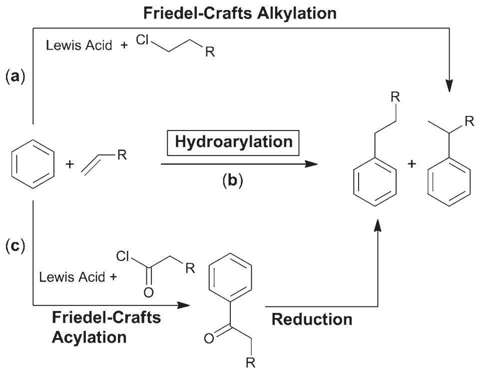
SCHEME 7. (NNC)Ir Oxy-Functionalization of Methane



Interestingly, substituting Ir^{III} for Pt^{II} with the same NNC ligand showed accessible barriers for methane activation in DFT calculations, as well as possible pathways for functionalization of the M$-$CH$_3$ intermediate with strong oxidants.[30] Catalytic methane CH activation was observed at 180 °C in CF_3CO_2H and calculated barriers of 24 ± 3 kcal mol^{-1} were consistent with experiment. In agreement with our expectations, these ambiphilic systems were more active than the Pt(bpym)X$_2$ system in weaker acids. The Ir(NNC) catalyzes MeTFA (TON = 6.3) formation using KIO_4 with a CH_4 atmosphere (35.5 bar) for 3 h at 180 °C (Scheme 7). Higher temperatures or reaction times did not improve yields. Further study revealed that the system was thermally unstable above 150 °C over long reaction times.

Continuing the study of ambiphilic systems, we expanded our study to other N-, O-, P-, and C-donor ligands. We were

SCHEME 8. Comparison of Friedel–Crafts Alkylation (a), Hydroarylation of Olefins (b), and Friedel–Crafts Acylation/Clemmenson Reduction (c)

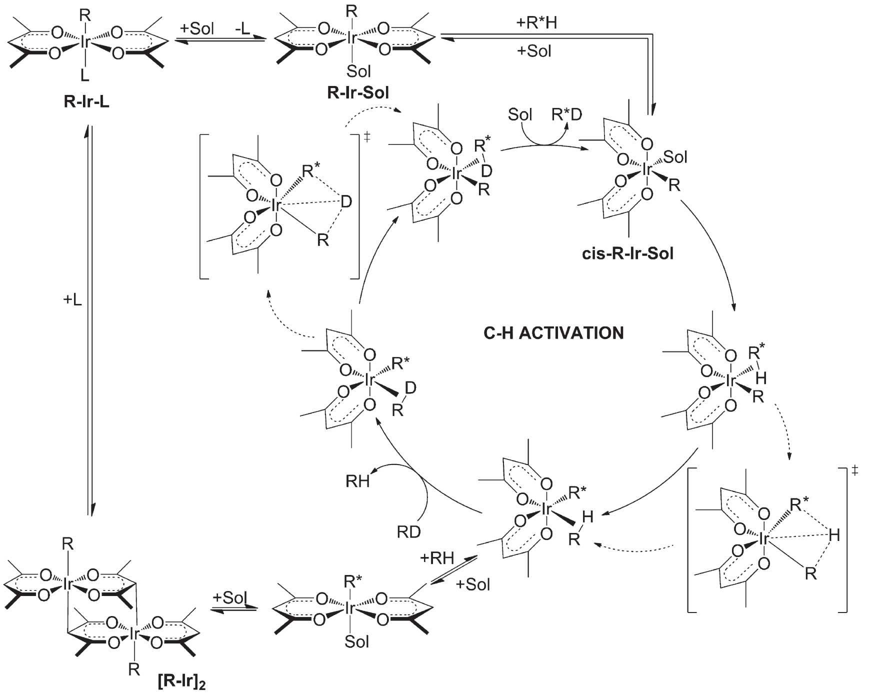


particular interested in O-donor ligands because they may help to stabilize higher oxidation states by "hard"/"hard" interactions or π-donation to the metal center during CH cleavage (Figure 5). Another advantage of O-donor ligands is that the electronegative oxygen is weakly σ-withdrawing and the reduced electron density at the metal center could minimize irreversible reactions such as β-hydride eliminations that are observed in very electron-rich or electron-deficient systems.

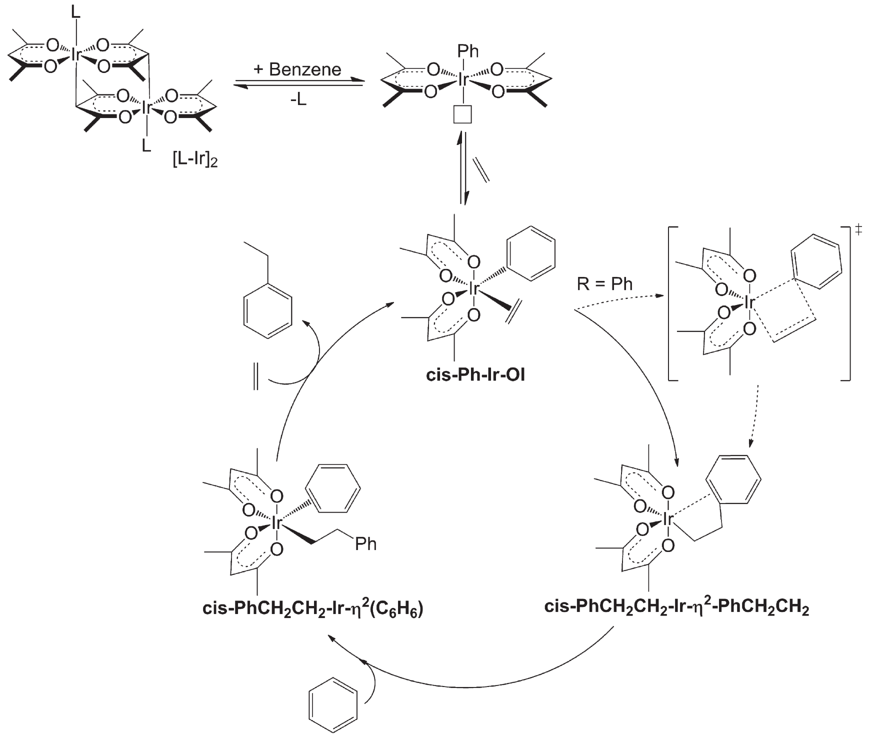
In order to identify catalysts capable of CH activation under less acidic conditions, a variety of complexes were systematically examined for H/D exchange between CH_3CO_2D and benzene. A peculiar result that attracted our attention was that tris(acetylacetonato-*O,O*) iridium(III), (acac-*O,O*)$_3$Ir^{III}, showed some activity. This complex is a very stable, coordinatively saturated complex and should be inert. Upon closer examination, the activity was found to result from Ir-based impurities. Interestingly, during attempts to improve yields of (acac-*O,O*)$_3$Ir, Bennett and Mitchell found a more labile bis(acetylacetonato-*O,O*) iridium(III) complex that we speculated could be a contaminant of commercial samples of (acac-*O,O*)$_3$Ir.[31] Guided by this possibility, we prepared a class of air-, water-, and acid-stable (acac-*O,O*)$_2$Ir^{III}(R)(L) compounds, where R = alkyl or aryl. Remarkably, these air, acid, and thermally stable complexes showed high activity for activation of sp^2 CH bonds and moderate reactivity with some sp^3 C–H bonds. Indeed, (acac-*O,O*)$_2$Ir^{III}(R)(L) was found to be one of the most stable arene CH activation catalysts in nonacidic media with TONs up to ~4500 in air. In addition, extraordinarily high rates of CH activation (TOFs of ~7 s^{-1} at 180 °C) were observed in CH_3CO_2H. However, no reactivity with methane or other unactivated alkane substrates could be observed in acidic media due to thermal instability of the catalyst ($T_{1/2} = 2$ h at 180 °C in CH_3CO_2H).[32]

Interestingly, (acac-*O,O*)$_2$Ir^{III}(R)(L) was found to readily catalyze hydroarylation between olefins and arenes to generate predominately primary alkyl-arenes (anti-Markovnikov product, Scheme 8, path B).[33] This was a

SCHEME 9. H/D Exchange Catalyzed by (acac-*O,O*)$_2$Ir^{III}(R)(L)



SCHEME 10. Hydroarylation Catalyzed by (acac-*O,O*)$_2$Ir(III)(R)(L) Complexes



significant result because typical Friedel–Crafts reactions generate the branched (Markovnikov) product via Scheme 8, path A, and synthesis of linear alkyl-arenes typically requires two steps (Scheme 8, path C). This selectivity for the anti-Markovnikov product was strongly indicative of a non-Friedel–Crafts mechanism. Also consistent with a non-Friedel–Crafts mechanism in these Ir-catalyzed systems were (A) that the monoalkylated products were less reactive than the parent aromatics and (B) that the reactions were uneffected by added water. We initially speculated that both the H/D exchange and hydroarylation reactions proceeded via CH activation to generate an Ir–Ph intermediate (Scheme 9).[34] The mechanism for the C–C bond formation was later confirmed by both experimental[35] and theoretical[36,37] work to proceed by rate-determining olefin insertion into an Ir–Ph bond (Scheme 10).

These results showed that stable, ambiphilic metal complexes capable of CH activation could operate in weaker acids than H_2SO_4. Indeed, almost all of the systems developed were more active for CH activation in CF_3CO_2H than the original Pt(bpym)X_2 system. However, a key issue with these systems seemed to be poor thermal stability and activity for the subsequent M–R functionalization step. For example, in the bis-(acac-*O,O*) iridium(III) system, the rate-determining step is insertion of the olefin rather than the CH activation step. The Pt and Ir(NNC) systems also did not show efficient functionalization and exhibited rapid deactivation. Although further research will continue on ambiphilic systems, we are also working to develop new mechanisms and reactions for CH functionalization based on more nucleophilic CH activation systems.

Nucleophilic Catalysts

An important basis for the efficiency of the electrophilic catalysts was that the strongly acidic solvents played the essential roles of facilitating both CH activation and functionalization steps as well as protecting the product by increasing its electrophilicity (as $CH_3OH_2^+$ or CH_3OSO_3H). This led us to examine the possibility that basic solvents could play similar roles with nucleophilic catalysts. One key basis for activation of the electrophilic catalyst by the acid solvents was protonation of noninnocent ligands to increase metal-center electrophilicity. Conversely, we postulated that inexpensive basic solvents (such as NaOH/H_2O) would enhance metal-centered nucleophilicity via deprotonation of protic, noninnocent ligands (Figure 6). Additionally, it is plausible that deprotonation of CH_3OH to generate CH_3O^- (where -O^- is a strong donor group) would lead to product

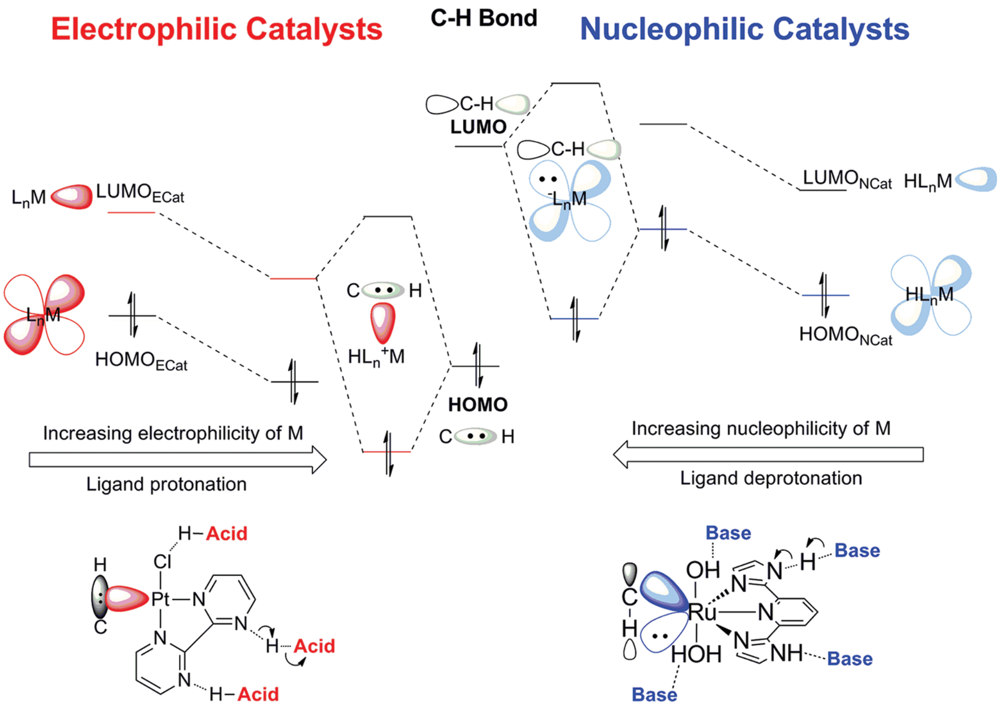


FIGURE 6. Frontier molecular orbital diagram of electrophilic and nucleophilic catalysts.

protection from nucleophilic CH activation if negative charge builds up on the carbon during CH cleavage (Figure 7).

On initial consideration, it would seem that coordination of the CH bond to a metal center would be untenable in strongly basic media because poorly nucleophilic alkane CH bonds would have to compete for coordination with strong bases such as OH^-. This concern is clearly demonstrated with electrophilic metal cations (Hg^{2+}, Pt^{2+}, etc.) that are strongly inhibited even by small amounts of water. Thus, we anticipated that any new CH activation system designed to operate in strongly basic media should be based on more nucleophilic metals to the left of Pt (Ir, Rh, Os, Ru, Re, etc.). Interestingly, while many examples of CH activation with these metals exist,[1] there are almost no examples of facile M–R functionalization to generate C–O functionalized products. Consequently, it was important to identify new oxy-functionalization reactions of $M-CH_3$ species with this class of metals. The lower, more labile oxidation states expected to be active for CH activation are not oxidizing, and two-electron reductive functionalization reactions (observed in more electrophilic systems) are unlikely to occur. Thus, new mechanisms not requiring reduction at the metal would be required. A key insight was the well-known reaction of alkyl borons, X_2B-CH_3, reacting with O-donors (H_2O_2, pyridine oxide, etc.) to generate C–O products by a Baeyer–Villiger (BV)-type O-atom insertion without any formal reduction at the boron. In a search for models of this reaction in organometallic chemistry, we demonstrated that $R-ReO_3$ (where R = alkyl[38] or aryl[39]) complexes undergo similar facile, nonreductive oxy-functionalization via a BV-type O-atom transfer reaction giving the corresponding alcohols (Scheme 11). Significantly, these and other[40] M–R functionalization reactions with more electropositive metals were compatible with and, in some cases, accelerated by aqueous OH^-. This is a minimum requirement to use these reactions in basic media.

$$CH_3OP_{EWG} \xrightleftharpoons{P_{EWG}} CH_3OH \xrightleftharpoons{P_{EDG}} CH_3OP_{EDG}$$

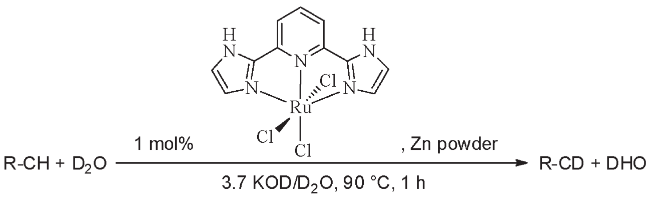
Protected in electrophilic reactions

Protected in nucleophilic reactions

EWG = electron-withdrawing group
EDG = electron-donating group

FIGURE 7. Possible strategies to protect methanol.

With the feasibility of nucleophilic M–R functionalization reactions established, attention turned to designing nucleophilic CH activation catalysts that operated in basic media. To minimize inhibition by strong σ-donors, hydroxyl groups on the metal catalysts must be strong bases themselves.[41] This eventually led to the design of a protic, ligated Ru^{III} complex,[42] which upon reduction yields a $(IPI)Ru^{II}$ motif (where IPI = 2,6-diimidizoylpyridine) that was a competent catalyst for H/D exchange that we proposed to result from nucleophilic CH activation in basic media (eq 12).[43] As shown, ligand deprotonation of these nucleophilic catalysts facilitated reaction with the high-lying, antibonding π-type orbitals of the CH bond. This contrasts with the electrophilic systems involving reaction with low-lying, C–H σ-orbitals that are enhanced by ligand protonation. We refer to this spectrum of catalyst activations as base or acid modulated (BAM) catalysis.



(12)

As can be seen in Figure 8, the H/D exchange reaction is accelerated by increasing solvent basicity.[43] We reasoned that the observed acceleration is likely a result of reversible deprotonation of the IPI ligand, coordinated water, or coordinated hydroxides, which would increase electron density on the Ru center and facilitate CH activation by enhancing the π-nuclophilic character of the catalyst (Scheme 12).[44] As shown by Basolo,[45] ligand deprotonations are known to facilitate ligand loss by the "conjugate base mechanism", and this is the likely basis for CH coordination to the metal center that is required for CH activation (Figure 9).

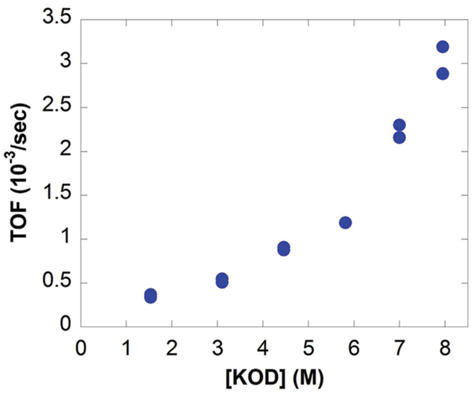


FIGURE 8. Base accelerated CH activation.[43]

$$\mathrm{HL_nMX} + \mathrm{OH^-} \xrightleftharpoons{\text{Fast}} [\mathrm{L_nMX}]^- + \mathrm{H_2O}$$

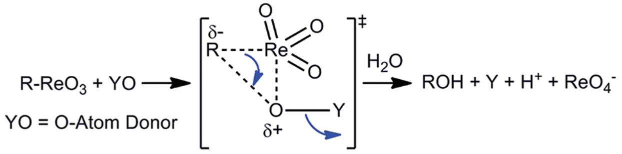
$$[\mathrm{L_nMX}]^- \xrightarrow{\text{Slow}} \mathrm{L_nM} + \mathrm{X^-}$$

$$\mathrm{L_nM} + \mathrm{Y^-} + \mathrm{H_2O} \xrightarrow{\text{Fast}} \mathrm{HL_nMY} + \mathrm{OH^-}$$

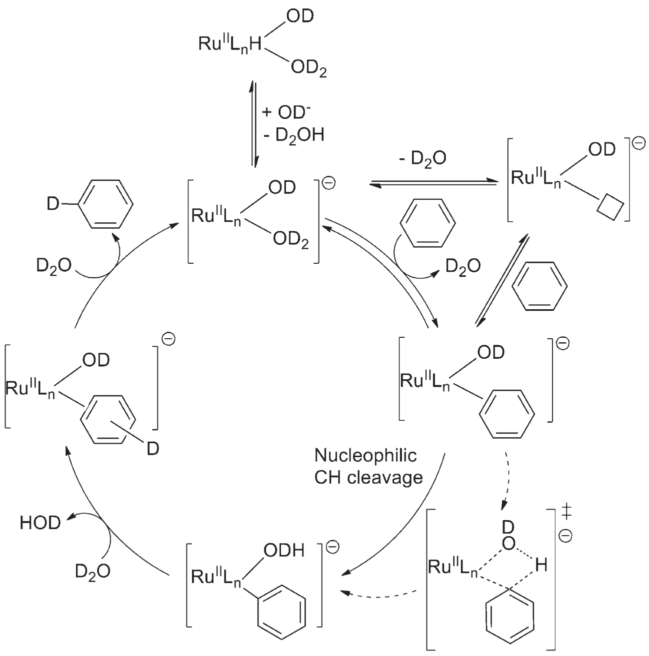
$$\text{Net RXN: } \boxed{\mathrm{HL_nMX} + \mathrm{Y^-} \xrightarrow{\mathrm{OH^-}} \mathrm{HL_nMX} + \mathrm{X^-}}$$

FIGURE 9. Base catalyzed ligand exchange by the Basolo conjugate base mechanism.[45]

SCHEME 11. Baeyer–Villiger-Type M–R Functionalization



SCHEME 12. Nucleophilic H/D Exchange



Initial observations suggest that the reactivity of base-activated catalysts could be further enhanced at higher base concentrations because the activity of OH$^-$ is known to increase exponentially at high concentrations.[46] This phenomenon would parallel the reactivity seen in strongly acidic solvents such as H_2SO_4 using Hg and Pt catalysts, where the activity increases exponentially at higher H$^+$ activity.[47] These results demonstrate that alkane and arene CH functionalization in basic media may prove feasible. Key challenges will be to develop even more active and stable systems that integrate catalyst life, stability, and rates into an operational system. It will be critical to ensure that any new system provides adequate product protection for high selectivity and that all catalytic steps are compatible.

Conclusion

Methods to efficiently functionalize hydrocarbons, in particular methane, without high temperature reforming remain one of the most valuable goals in chemistry. To date, electrophilic catalysts in strongly acidic solvents are the most efficient systems reported for the direct oxy-functionalization of methane. However, due to the strong acid requirement of these systems and the inherent drop in acidity and deactivation upon generation of the reaction products, sufficiently high product concentrations could not be obtained for practicality. As less electrophilic systems were examined, other interesting chemistry including an anti-Markovnikov hydroarylation catalyst and a new ambiphilic methane functionalization catalyst were discovered. Ongoing exploration has led to the discovery that CH activation and M−R functionalization reactions based on more electron-rich metals can be accelerated by basic solvents. This shows that there could be the potential to design new classes of nucleophilic catalysts that, in a manner analogous to the rate enhancements seen in the electrophilic systems with strong acids, could be designed to operate and accelerate in strongly basic media. Although we have yet to design a catalyst to supplant current systems, we believe that exploring the continuum of BAM catalysis could lead to new systems with the potential for practicality. Indeed, many of the concepts outlined in BAM catalysis can be readily applied to the challenges in the conversion of other small molecules such as N_2 and CO_2. Perhaps, in an environment where all the long-standing challenges in CH_4, N_2, CO_2, and O_2 are being simultaneously addressed, the combined insights could provide the solution to these valuable goals.

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BIOGRAPHICAL INFORMATION

Brian G. Hashiguchi was born in Seattle, Washington (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 currently is a Staff Scientist focusing on the development of water-soluble complexes for functionalization of small molecules.

Steven M. Bischof was born in Minneapolis, Minnesota (1983). He received his B.A. degree from St. John's University in Collegeville, Minnesota (2006). Steven's graduate education began at the University of Southern California in Los Angeles, California, followed by relocation (2007) to The Scripps Research Institute under the supervision of Prof. Periana. His Ph.D. work emphasizes using CH activation for the oxy-functionalization of hydrocarbons.

Michael M. Konnick was born near Scranton, Pennsylvania (1980). After obtaining his B.S. degree at Bucknell University in Lewisburg, Pennsylvania (2002), he obtained his Ph.D. in chemistry (2009) with Prof. Stahl at the University of Wisconsin—Madison. Mike joined Prof. Periana's group at The Scripps Research Institute (2010), where his research and interests focus upon small molecule functionalization, chemical kinetics, and reaction mechanisms.

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 The University of Southern California and most recently as the Director of the Scripps Energy & Materials Center at The Scripps Research Institute. His interests are on the low-temperature, selective, homogeneous activation and functionalization of small molecules (CH_4, CO_2, H_2O, N_2, and O_2) using transition metals.

FOOTNOTES

*To whom correspondence should be addressed. E-mail: rperiana@scripps.edu.
The authors declare no competing financial interest.

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