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

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CONSPECTUS

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 O2 (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, LnM–X, to generate activated LnM–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 LnM–R to generate the desired product and regenerate the LnM–X complex. To avoid free-radical reactions possible with the direct use of O2, 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 CH3OH by conversion to more electron-poor [CH3OH2]+ 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 CH3OH by deprotonation to the more electron-rich [CH3O]− 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 CH3OH 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 LnM–R functionalization 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
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 (\(\text{L}_n\text{M–X}\)) to generate discrete, “activated” \(\text{L}_n\text{M–R}\) 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” \(\text{L}_n\text{M–R}\) 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 \(\text{O}_2\) (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 \(\text{O}_2\) 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.
Catalysts for Functionalization of Unactivated C–H Bonds

Hashiguchi et al.

酸性溶媒（HX）を生成する安定なPh–HgII種。12
このもはや一CH Activation反応としてこの反応
に直接関与するアトミック環とCH bond. しかし、この高調度化が単なるHgII種、"soft"とされる在近年の研究で
考えられるが、酸性溶媒とこの系が核チタニウム生成に
イオン化合物の酸化がHgII/0（E° = 0.91 V）、PdII/
(E° = 0.92 V)、またはCoII/III (E° = 0.74 V)、および基準双電子反応が
Prussian Blue (eq 5)。これを酸性フタル酸に

\[
\text{Hg(CF}_3\text{SO}_3\text{)}_2 + \text{CH}_4 \rightarrow \text{CF}_3\text{SO}_3\text{CH}_3 + \text{CF}_3\text{SO}_3\text{H} + \text{Hg}^0
\]

(5)

We postulated that the reaction proceeds by (1) electrophilic activation of methane to generate [CH3Hg]+, (2) reductive functionalization to CH3OSO4H and Hg0, and (3) subsequent oxidation of the CH3 group.

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 H2SO4. Interestingly, these consider
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 recondensation of the solvent by distillation was prohibitively expensive. This inhibition was a result of the exponential drop in the solvent acidity (at ∼80% H2SO4) and resulting increase in concentration of HSO4⁻. Since the HSO4⁻ binds much more tightly than H2SO4, this increased the activation barrier for coordination and cleavage of CH4 in the first coordination sphere of the HgII center.

**Platinum Catalysts**

Key challenges of early work reported by Shilov were the slow rates, unstable catalysts, and use of PtIV as the overall oxidant. In an attempt to address these issues, we began to examine the Pt-catalyzed functionalization of CH4. Simple Pt salts were not effective in H2SO4 due to poor solubility, stability (due to Pt black formation), and selectivity. However, an early discovery revealed that the N-ligated complex, (NH3)2PtCl2, was soluble in H2SO4 and an active catalyst for the functionalization of CH4 (eq 7). Not unexpectedly, the catalyst was unstable and <20 turnovers of CH3OH were observed before catalysis stopped as a result of PtCl2 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.

\[
\text{CH}_4 + \text{H}_2\text{SO}_4 + (\text{NH}_3)_2\text{PtCl}_2 \rightarrow \text{CH}_3\text{Cl} + \text{N}_2 + 2\text{HCl}
\]

(7)

These studies led to the identification of the first example of an efficient, stable Pt-based catalyst, (κ²-2,2'-bipyrimidyl)-platinum(II)dichloride, the so-called “Periana System” for the selective, high-yield functionalization of methane to ∼1 M methanol in H2SO4 (eq 8). Remarkably, stability was the result of oxidative dissolution of Pt0 by H2SO4 facilitated by the bipyrimidine (bpym) ligand. In contrast to the HgX2 system, the Pt-ligated system can operate in the presence of excess SO3, without the formation of the undesirable C–S bonded product, CH3SO3H. The use of added SO3 led to higher efficiency than the Hg system with yields of ∼80% at ∼90% selectivity to give a mixture of CH3OSO3H, CH2OH⁺, and CH3OH. 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 H2SO4 while operating at high TOF and generating methanol at >1 M.

\[
\text{CH}_4 + \text{H}_2\text{SO}_4 + \text{PtCl}_2 \rightarrow \text{CH}_3\text{OSO}_3\text{H} + \text{CH}_2\text{OH}^+ + \text{SO}_2 + \text{HCl}
\]

(8)

We postulated that this system also proceeded by an electrophilic CH activation, Pt–CH3 functionalization sequence (Scheme 3). Strong evidence was provided by carrying out the reaction in D2SO4 at low methane conversion where, in addition to oxygenated products, the isotopologues of methane, CH3D₄, were observed as would be expected from reversible formation of Pt⁰–CH₃. We anticipated that oxidation of Pt²⁺–CH3 intermediate by H2SO4 to
Pt\textsuperscript{IV}–CH\textsubscript{3} (and SO\textsubscript{2}) followed by reductive functionalization would generate CH\textsubscript{3}OSO\textsubscript{4}H and regenerate the Pt\textsuperscript{II} catalyst. The expectation that product inhibition was also the result of the drop in solvent acidity and inhibition by HSO\textsubscript{4}\textsuperscript{−} is supported by recent computational studies (Figure 2).\textsuperscript{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\textsuperscript{II} to (presumably) inactive Pt\textsuperscript{IV} by hot H\textsubscript{2}SO\textsubscript{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\textsubscript{4} in H\textsubscript{2}SO\textsubscript{4}, PdX\textsubscript{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\textsuperscript{0}. However, when experiments were carried out with \textsuperscript{13}C-enriched CH\textsubscript{4} in addition to \textsuperscript{13}CH\textsubscript{3}OH, a persistent pair of doublets was observed in the \textsuperscript{13}C NMR spectra of the crude reaction mixtures. This was eventually identified as \textsuperscript{13}CH\textsubscript{3}13CO\textsubscript{2}H,\textsuperscript{23} where, remarkably, both carbons originated from \textsuperscript{13}CH\textsubscript{4} (eq 9). This oxidative coupling of CH\textsubscript{4} occurs at greater than 90% selectivity and \textit{∼}10% yield (based on methane) with H\textsubscript{2}SO\textsubscript{4} as both the solvent and oxidant.

\[
\text{2CH}_4 + 4\text{H}_2\text{SO}_4 \xrightarrow{\text{Pd}^{0} / 180^\circ\text{C}} \text{CH}_3\text{CO}_2\text{H} + 4\text{SO}_2 + 6\text{H}_2\text{O} \quad (9)
\]

A non-free-radical, tandem catalysis mechanism was proposed based on detailed mechanistic studies using combinations of \textsuperscript{13}C-labeled and nonlabeled CH\textsubscript{4}, CH\textsubscript{3}OH, and CO (Scheme 4). The two key mechanistic steps are the conversion of CH\textsubscript{4} to methanol via a CH activation reaction (path A), slow overoxidation of CH\textsubscript{3}OH to generate low concentrations of CO (path B), and extraordinarily fast CO insertion into the Pd–CH\textsubscript{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\textsubscript{3}OH and CO where both of these starting
Catalysts for Functionalization of Unactivated C-H Bonds

Hashiguchi et al.

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. Efforts are continuing in our laboratories to increase the efficiency of this process.

Gold Catalysts

As noted above, Hg
II [electronic configuration of \(\{\text{Xe}\}4f^{14}5d^{10}\)] and Pt
II [\(\{\text{Xe}\}4f^{14}5d^{8}\)] both reacted with \(\text{CH}_4\) 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 AuX₃ (X = HSO₄) in \(\text{H}_2\text{SO}_4\) or CF₃SO₃H confirmed that Au
III rapidly and selectively reacted with \(\text{CH}_4\) to generate \(\text{CH}_3\text{OH}\) (eq 10). However, unlike the Hg
II and Pt
II systems, only stoichiometric reactions were observed because \(\text{H}_2\text{SO}_4\) did not reoxidize the reduced gold metal. As with the other electrophilic systems, the system required strongly acidic media. Later work showed that to catalyze the reaction, \(\text{H}_2\text{SeO}_4\) (a stronger oxidant than \(\text{H}_2\text{SO}_4\) but comparable in acidity) could be used to reoxidize Au
⁰. Using metallic gold as a catalyst precursor in a 3 M \(\text{H}_2\text{SeO}_4/\text{H}_2\text{SO}_4\)
solution led to a TON = 32 in 2 h and 11% CH4 conversion in 81% selectivity to CH3OSO3H. Control reactions (added O2) excluded a radical mechanism, and DFT calculations support electrophilic CH activation of CH4 for both AuIII and AuI (Scheme 5).

\[
3\text{CH}_4 + 2\text{Au}^{\text{III}}X_3 + 3\text{H}_2\text{O} \rightarrow 3\text{CH}_3\text{OH} + 6\text{HX} + 2\text{Au}^0 \quad \text{H}_2\text{SO}_4 \quad 180 \degree \text{C}
\]  

(10)

**Iodine Catalysts**

Following the success of the previous "soft" (metallic) cationic electrophiles in strong acid solvents, we reasoned that the characteristic blue species, I2⁺HS2O7⁻, known to form upon addition of I2 to oleum26 could exhibit similar CH activation chemistry given the cation size and electrophilicity. This was indeed the case,27 and treatment of CH4 with H2SO4/SO3/I2 mixtures at 195 °C led to the catalytic generation of CH3O⁻SO3H and methane oxidation occurs with 53% conversion at >95% selectivity (eq 11). CH3OSO3H was obtained up to [1 M] with a TOF of \(3.3 \times 10^{-2} \text{ s}^{-1}\) and a volumetric productivity of \(~10^{-7} \text{ mol}^{-1} \text{ cm}^{-3} \text{ s}^{-1}\). Importantly, no MeI or CH3SO3H was observed. We proposed the mechanism shown in Scheme 6. Recent theoretical calculations are consistent with I⁺HS2O7⁻ as the active catalyst.28

\[
\text{CH}_4 + 2\text{SO}_3 \underset{\text{cat. I}_2}{\overset{\text{H}_2\text{SO}_4/\text{O}_3}{\rightarrow}} \text{CH}_3\text{OSO}_3\text{H} + \text{SO}_2
\]  

(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 \(~1 \text{ M}\) and that this concentration would lead to expensive separations. One solution we considered...
Catalysts for Functionalization of Unactivated C-H Bonds
Hashiguchi et al.

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)$_2$. This complex was found to carry out H/D exchange reactions with benzene ~300 times faster than (bpym)Pt(TFA)$_2$, which is a weaker acid than H$_2$SO$_4$. 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 PtII 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$_3$CO$_2$H 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.

Interestingly, substituting IrIII for PtII 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. Catalytic methane CH activation was observed at 180 °C in CF$_3$CO$_2$H 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(bpy)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
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 CH3CO2D and benzene. A peculiar result that attracted our attention was that tris(acetylacetonato-O,O) iridium(III), (acac-O,O)3IrIII, 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)3Ir, 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)3Ir.31 Guided by this possibility, we prepared a class of air-, water-, and acid-stable (acac-O,O)2IrIII(R)(L) compounds, where R = alkyl or aryl. Remarkably, these air, acid, and thermally stable complexes showed high activity for activation of sp2 CH bonds and moderate reactivity with some sp3 C–H bonds. Indeed, (acac-O,O)2IrIII(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 CH3CO2H. However, no reactivity with methane or other unactivated alkane substrates could be observed in acidic media due to thermal instability of the catalyst (T1/2 = 2 h at 180 °C in CH3CO2H).32

Interestingly, (acac-O,O)2IrIII(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
Catalysts for Functionalization of Unactivated C-H Bonds

Hashiguchi et al.

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 unaffected 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). The mechanism for the C–C bond formation was later confirmed by both experimental and theoretical 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 H2SO4. Indeed, almost all of the systems developed were more active for CH activation in CF3CO2H than the original Pt(bpym)X2 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 CH3OH2+ or CH3OSO3H). 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/H2O) would enhance metal-centered nucleophilicity via deprotonation of protic, noninnocent ligands (Figure 6). Additionally, it is plausible that deprotonation of CH3OH to generate CH3O− (where −O− is a strong donor group) would lead to product
Catalysts for Functionalization of Unactivated C-H Bonds

Hashiguchi et al.

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\(_2\)B–CH\(_3\), reacting with O-donors (H\(_2\)O\(_2\), 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.

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 \(\sigma\)-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

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

FIGURE 7. Possible strategies to protect methanol.
of these nucleophilic catalysts facilitated reaction with the high-lying, antibonding \( \pi \)-type orbitals of the \( \text{CH} \) bond. This contrasts with the electrophilic systems involving reaction with low-lying, \( \text{C}^\sigma/\text{C}_0^\sigma \)-orbitals that are enhanced by ligand protonation. We refer to this spectrum of catalyst activations as base or acid modulated (BAM) catalysis.

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 \( \pi \)-nucleophilic 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).

Initial observations suggest that the reactivity of base-activated catalysts could be further enhanced at higher base concentrations because the activity of \( \text{OH}^- \) is known to increase exponentially at high concentrations.\(^{46}\) This phenomenon would parallel the reactivity seen in strongly acidic solvents such as \( \text{H}_2\text{SO}_4 \) using \text{Hg} and Pt catalysts, where the activity increases exponentially at higher \( \text{H}^+ \) 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 amphiphilic 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 N₂ and CO₂. Perhaps, in an environment where all the long-standing challenges in CH₄, N₂, CO₂, and O₂ are being simultaneously addressed, the combined insights could provide the solution to these valuable goals.

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**BIOGRAPHICAL INFORMATION**

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**FOOTNOTES**

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Catalysts for Functionalization of Unactivated C-H Bonds

Hashiguchi et al.

16 Unpublished results.