Perspectives on some challenges and approaches for developing the next generation of selective, low temperature, oxidation catalysts for alkane hydroxylation based on the CH activation reaction

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Abstract

The development of selective, energy efficient direct alkane oxidation chemistry could lead to a new paradigm in materials and energy technologies in the 21st century that is environmentally and economically superior and allow the vast reserves of natural gas to be employed directly as feedstocks for fuels and chemicals. The use of homogeneous catalysts that activate and functionalize the CH bonds of unactivated hydrocarbons is of particular interest from a scientific as well as an economic viewpoint. This results from the strong potential for these catalysts to carry out oxidative hydrocarbon conversions with high atom and energy efficiency and under mild conditions. Despite the large body of work on the CH activation reaction that has been produced over the last three decades, to date relatively few catalyst systems that are based on this approach have been developed that allow the functionalization of hydrocarbons and there are still large gaps in our fundamental knowledge of how to rationally design such catalysts. Addressed in this paper are some of the key challenges and approaches to the de novo, rational development of the next generation of organometallic, alkane functionalization catalysts based on the CH activation reaction with emphasis on our own research.
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1. Introduction

The conversion of fossilized hydrocarbons to energy and materials is a foundational technology. While it is important that we consider a switch to future alternatives, such as the proposed hydrogen-based economy, it is critical that as a bridge to this long term future, we develop more environmentally benign, greener technologies for these essential fossil fuel based processes that will continue to be important in the next decade. As shown in Fig. 1, the key objectives of such greener processes must be to minimize emissions and capital while maximizing energy and materials output. Importantly, reducing dependence on petroleum and increasing use of under-utilized, abundant natural gas would facilitate this movement to these greener technologies while extending the life time of these limited fossilized resources.

Alkanes from natural gas and petroleum are among the world's most abundant and low-cost feedstocks. Currently petrochemical technologies to convert these feedstocks to energy, fuel and chemicals operate at high temperatures and utilize multiple steps that lead to inefficient, capital intensive processes. The development of low temperature, selective, direct alkane oxidation chemistry could lead to a new paradigm in petrochemical technology that is environmentally cleaner, economically superior and allow the large reserves of untapped remote natural gas to be valorized as primary feedstocks for fuels and chemicals [1]. Alcohols are among the highest volume commodity chemicals and most versatile feedstocks [1b]. A primary reason that technologies for direct, selective hydroxylation of alkanes to alcohols remain a challenge is that the current commercial catalysts for alkane oxidation (typically solid metal oxides) are

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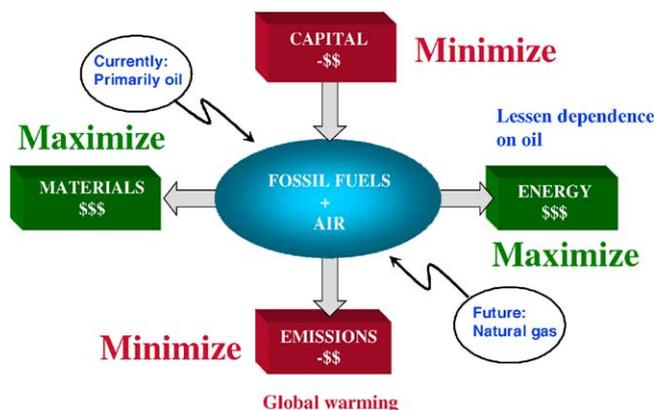 *E-mail address:* rperiana@usc.edu (R.A. Periana).

Fig. 1. Oxidative conversion of fossil fuels is a foundational technology.

not sufficiently active for the functionalization of alkane CH bonds and high temperatures and harsh conditions must be employed that lead to low reaction selectivity [1a].

The development of next generation catalysts that would allow the selective hydroxylation of methane and higher alkanes to alcohols at low temperatures (∼200–250 °C) in inexpensive reactors, with fewer steps and in high yields could provide a basis for this paradigm change in the petrochemical industry. Examples of the products that could be dramatically impacted by such low temperature, hydroxylation catalysts are shown in Fig. 2.

Significant advances in the chemistry of the hydrocarbons have been made since the 1970s. Particularly relevant to the development of low temperature, selective, heteroatom hydrocarbon functionalization catalysts has been the discovery of homogeneous metal complexes that cleave the CH bonds of unactivated hydrocarbons at low temperatures and with extraordinary selectivity, Fig. 3 [2,3]. Thus, studies

have shown that primary CH bonds are more reactive than tertiary, aromatic more reactive than aliphatic and important to the challenge of selective oxidation of methane to methanol, the CH bonds of alcohols are less reactive than those of the parent alkanes. Since this discovery, there has been and continues to be intense interest in incorporating the CH activation reaction into catalytic cycles to convert hydrocarbon to more useful functionalized products. However, to date relatively few catalyst systems that are based on the CH activation reaction have been developed that allow the functionalization of hydrocarbons [4–10] and there are still large gaps in our fundamental knowledge of how to design such catalysts [2,3]. In this article, the focus is discussion of some of the challenges and approaches to developing the next generation of alkane hydroxylation catalysts based on the CH activation reaction with emphasis on our research.

2. General catalyst requirements

In considering the de novo design of any new catalyst it is important to note that to be useful, all catalysts must meet some minimum performance requirements related to catalyst stability, rate and selectivity. Importantly, as illustrated in Fig. 4, effective catalysts must *simultaneously* meet *all three* of these performance requirements; meeting any one or two would not lead to useful catalysts. This represents a key challenge to the rational design of *any* efficient catalyst because these requirements related to catalyst rate, stability and selectivity are all interdependent on the molecular structure and composition of the catalyst and reaction system. This is a useful consideration because a common approach to de novo catalyst design is to attempt to meet these three
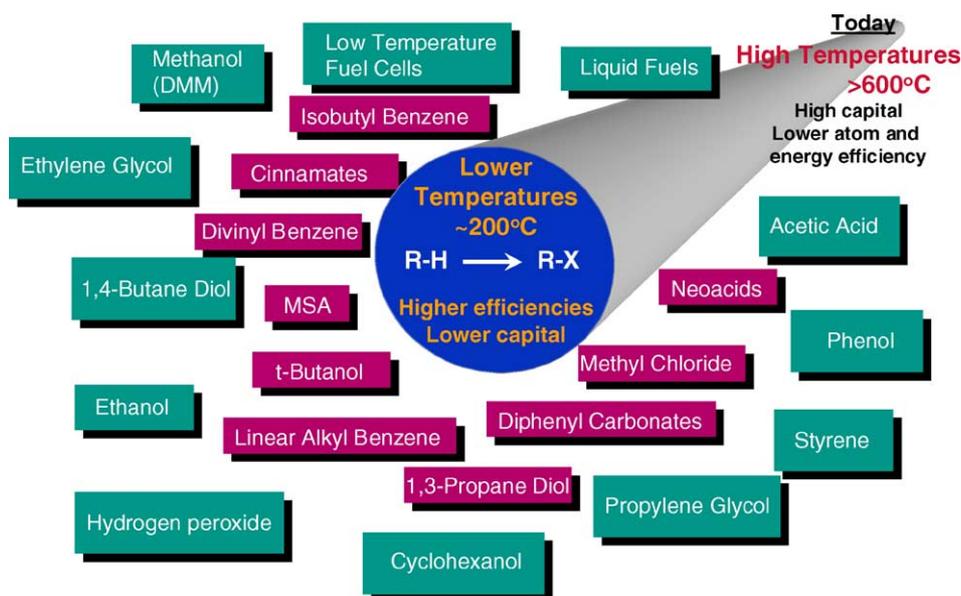

Fig. 2. Examples of products potentially impacted by next generation, low temperature, selective, hydrocarbon oxidation catalysts.
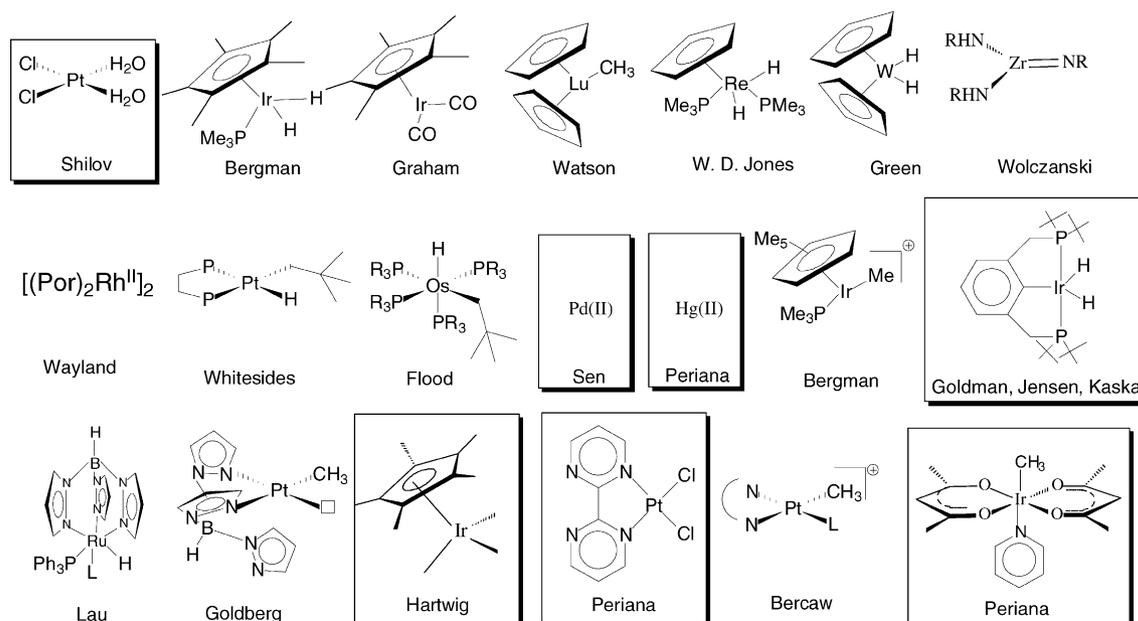
Fig. 3. Examples of some of the reported CH activation systems with catalytic systems that generate functionalized products highlighted.

requirements by a sequential focus in research: e.g. focusing on meeting the rate or selectivity requirements by modifying the catalyst structure and composition and then after that target is met, attempting to modify the catalyst to meet the other two performance requirements.

Such a sequential approach to catalyst design may not be the most efficient because focused structural, compositional and reaction system modifications to meet one requirement can lead to catalyst motifs that cannot be efficiently (or indeed at all) modified to meet the other performance requirements. This emphasizes that an effective strategy to developing useful catalysts should involve *simultaneous* consideration of all structure–function relationships that relate to stability, rate and selectivity in the design of the catalyst and reaction system. This can be challenging because such an approach can severely restrict the range of catalyst structures and compositions to be examined.

3. Why CH activation based catalysts?

3.1. CH activation as an inner-sphere reaction

Homogeneous transition metal catalysis has had a substantial impact on organic chemistry. From polymerizations to hydrogenations there are few aspects of organic chemistry that have not been touched by this field of research. The majority of these catalytic reactions take place in the inner or first coordination sphere of the homogeneous metal catalyst and in many cases lead to the formation of organometallic, M–C, intermediates. The advantage of these inner-sphere, organometallic reactions is that the reactant of interest is bound to the catalyst center during conversion to products and as a result, the catalyst can effectively mediate both rate and selectivity in the conversion of the reactants to desired products.

There are many definitions of "CH activation". As shown in Fig. 5, in this discussion we define CH activation as a facile CH cleavage reaction with an "MX" species that pro-

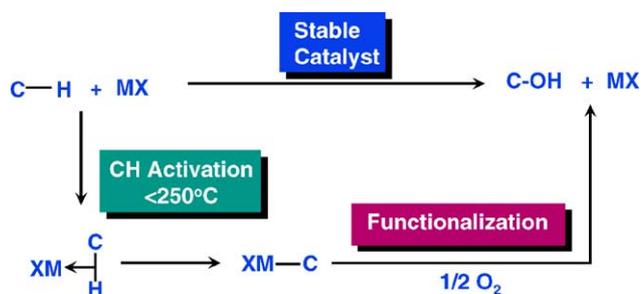
Fig. 4. Key requirements for any efficient catalyst.

Fig. 5. General scheme for oxidation catalysis based on CH activation.

ceeds by coordination of an alkane to the inner-sphere of "M" (either via an intermediate "alkane complex" or a transition state) leading to a M–C intermediate. Important to this definition is the requirement that during the CH cleavage the hydrocarbonyl species remains in the inner-sphere and under the influence of "M". Theoretical studies as well as experimental studies support this view that classically unreactive CH bonds can be cleaved by such inner-sphere mechanism [11]. This emphasis on inner-sphere coordination is based on the presumption that cleavage reactions of the CH bond that proceed in this manner, with strong interaction between the CH bond and "M", can be expected to show unique high selectivity and activities.

As might be expected from the wide variety of complexes that cleave CH bonds by such an inner-sphere reaction there are several recognized mechanistic classifications as shown in Fig. 6. As can be seen, these are all related by the requirement that the alkane coordinate to the inner-sphere of the metal center either as an intermediate or in a transition state leading to the formation of organometallic M–C intermediates. The specifics of the actual mode of cleavage depend on the electronic configuration of the metal, the X group and various variations of these classifications have been observed. Of these, the most common modes are electrophilic substitution (ES), oxidative addition (OA) and sigma bond metathesis and in all cases unique CH cleavage selectivity patterns are observed [3]. To utilize the

unique properties of the CH activation reaction (as defined above) the M–C species must be more easily functionalized than the CH bond to yield a useful C–X product with regeneration of the MX species. Ideally, to maintain high reaction selectivity and catalyst control it may be desirable that this functionalization also occur within the inner-sphere of "M".

3.2. Comparison of CH activation to other inner-sphere reactions

This cleavage of the CH bond mediated via the formation of a M–C species can be contrasted to other reactions of alkane CH bonds such as metal mediated generation of alkyl free radicals, acid or base catalyzed generation of carbocations or carbanions that are not as selective. In these processes, unlike the CH activation reaction as defined above, the reactive alkyl fragments that are generated are not under the influence of the catalyst (because they are not strongly bound to the catalyst center) and consequently, can exhibit intrinsic reactivities that are generally undesirable. This may be a reason that the commercially available oxidation catalysts based on metal oxides and utilized at high temperatures are not selective for the conversion of methane to methanol: such catalysts may operate by the generation of free radical species that exhibit intrinsic reactivity that cannot be controlled by the catalyst.
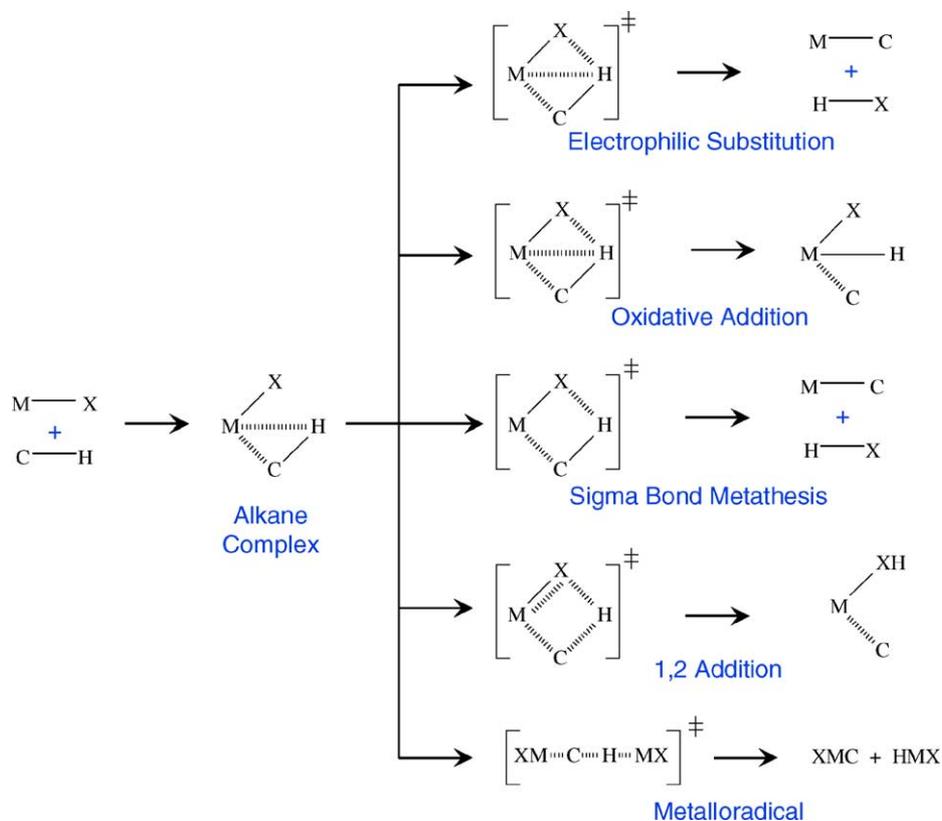

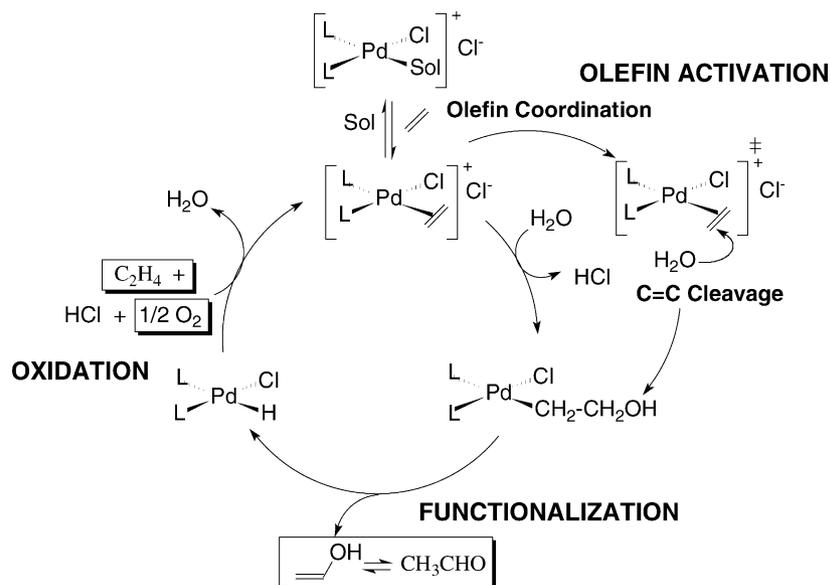Fig. 6. Classification of various modes of CH activation.

Fig. 7. Mechanism of the Wacker system highlighting key steps.

To illustrate the potential advantage of this inner-sphere CH activation chemistry, an analogy can be made between CH activation by coordination of an alkane CH bond to a metal center and the known catalysis resulting from coordination of olefins via the CC double bond, albeit the nature of the orbitals involved in bonding are quite different. It is well know that coordination of olefins to specific metal centers can activate the olefin to nucleophilic attack and conversion to organometallic, M–C type intermediates. These M–C intermediates can then be more readily converted to functionalized products than the uncoordinated olefin. A classic example of this in oxidation catalysis is the Wacker oxidation of ethylene to acetaldehyde. In this reaction, catalyzed by Pd(II) as shown in Fig. 7, ethylene is activated to attack by water by inner-sphere coordination to the electrophilic Pd(II) center. This leads to facile formation of an organometallic, palladium alkyl intermediate that is subsequently oxidized to acetaldehyde and the reduced catalyst reoxidized to complete the catalytic cycle. The Wacker reaction is very rapid and selective and it is possible to carry out the reaction is aqueous solvents. This is largely possible because of the favorable thermodynamics for coordination of olefins to transition metals that can be competitive with coordination to the water solvent. The reaction is very selective presumably because the bonds of the product (potentially reactive CC double bonds are still available from tautomerization of the acetaldehyde, Fig. 7) are not as readily activated. The most likely explanation is that the product forms much less stable olefin complexes to electrophilic Pd(II) due to the presence of the electron withdrawing OH group. With the discovery of the Wacker reaction, the earlier processes based on classical chemistry, acid catalyzed hydration of ethylene to ethanol, followed by high temperature, free radical auto-oxidation, is no longer practiced.

The useful comparison between the Wacker process and alkane CH activation is that all the inner-sphere steps identified in the Wacker reaction (activation, functionalization and reoxidation) can also be seen in catalytic, alkane CH activation and functionalization systems that operate with electrophilic catalysts. Thus, the coordination of the double bond of the olefin to electrophilic Pd(II) followed by cleavage of the coordinated double bond by nucleophilic attack of water can be compared to CH activation of CH_4 by an electrophilic substitution pathway.

Thus, as shown in Fig. 8, in the CH activation by an ES pathway the coordination of the CH of the alkane to an electrophilic center followed by loss of a proton can also be described as attack of a nucleophile, "sol", on the coordinated CH bond that leads to CH cleavage and generating an intermediate E-CH3 species. While this is a valid comparison,
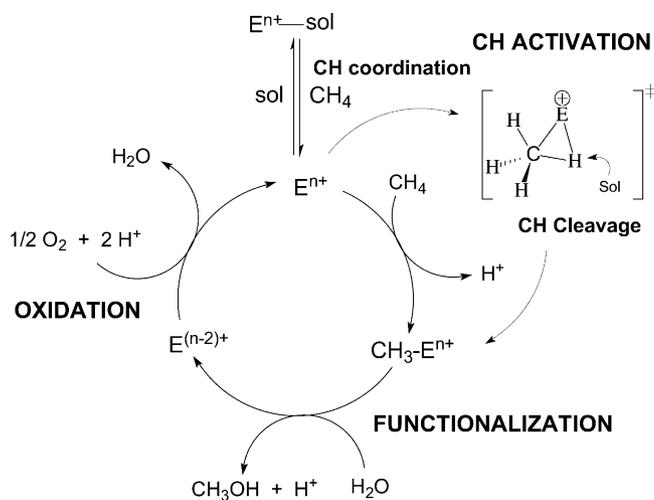

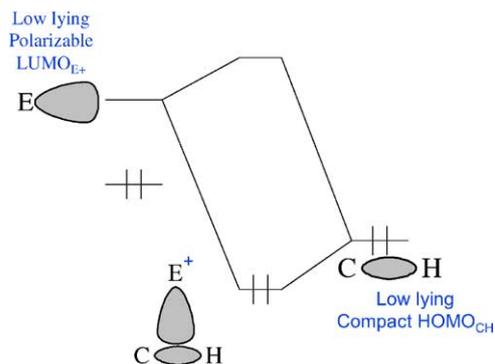Fig. 8. Electrophilic activation of methane by "soft" electrophiles.

Fig. 9. Orbital interaction between the low lying compact HOMO of a CH bond and the low lying, polarizable LUMO of a "soft" electrophile.

it would be expected that as the CC double bond is considerably more electron rich than that of an alkane CH bond, that more reactive electrophiles would be required for similar coordination and cleavage of the CH bond. Frontier orbital considerations of this interaction between the CH bond and electrophiles, Fig. 9, would indicate, given the low energy, σ-symmetry and low polarizability of the $HOMO_{CH}$ that "soft", electrophiles characterized by low lying, polarizable LUMOs with σ-symmetry would be effective for this mode of CH activation.

This has been found to be the case with the "soft", powerful electrophilic species, $[XHg]^+$, generated by dissolving HgX_2 salts in strongly acidic solvent such as sulfuric acid or Triflic acid. These species have been found to react readily with methane via CH activation and are among the most effective catalysts for the conversion of methane to methanol in 96% sulfuric acid solvent [5]. Thus at $\sim$180 °C with a 20 mM concentration of $Hg(HSO_4)_2$ in sulfuric acid, methanol concentration of $\sim$1 M with yields of over 40% based on added methane, at methanol selectivities >90% have been observed by the reaction shown in Eq. (1).

$$CH_4 + H_2SO_4 \xrightarrow{Hg(II)/H_2SO_4} CH_3OH + H_2O + SO_2 \qquad (1)$$

As shown in Fig. 10, the reaction mechanism is proposed to occur by an electrophilic substitution pathway that involves coordination of methane to the inner-sphere of the poorly coordinated XHg^+ species (solvated by liquid sulfuric acid) either via a transition state or intermediate methane complex and subsequent loss of a proton to generate a $[CH_3–Hg]^+$ intermediate. The $[CH_3–Hg]^+$ intermediate is converted to methanol and the reduced catalyst is reoxidized.

Interestingly, given the poor basicity of the sulfuric acid solvent, the coordination of the CH bond to $[XHg]^+$ followed by "nucleophilic attack" by sulfuric acid shows that the coordinated methane must be considered quite an acidic species as this is, in effect, the protonation of sulfuric acid (albeit it is likely that low concentration of HSO_4^- or water may be involved). Similar increases in acidity of hydrogen upon coordination to electrophilic metal centers have also been reported [12].
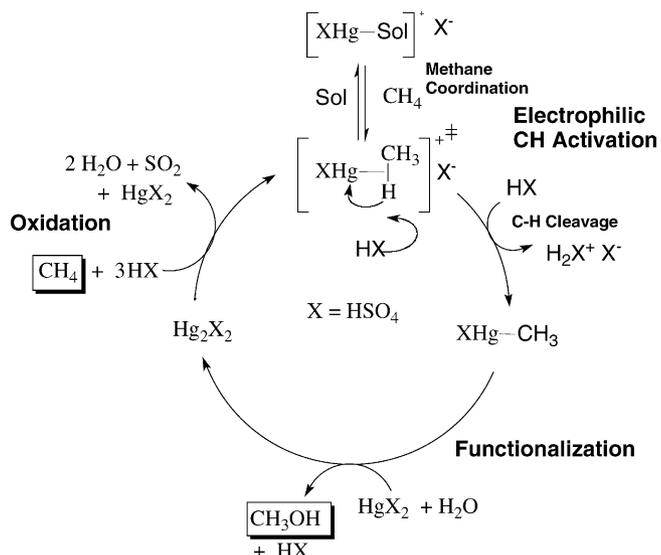

Fig. 10. Proposed electrophilic CH activation mechanism for the oxidation of methane to methanol by the $Hg(II)/H_2SO_4$ system.

This system illustrates the advantages of developing catalysts based on CH activation as both the reaction rate and selectivity can be attributed directly to the relative rates of CH activation of the CH bonds present in the reaction system by the poorly solvated $[XHg]^+$ catalyst. In the case of methane, theoretical calculations show that the poorly solvated species, $[XHg]^+$ reacts with a $\sim$29 kcal/mol barrier via a transition state in which methane is coordinated to a two-coordinate cationic mercury species, $[XHgCH_4]^+$, that losses a proton to the solvent to generate CH_3HgX. This correlated well with the experimental activation barrier of $\sim$28 kcal/mol and the direct observation of $[HgCH_3]^+$ as an intermediate in the catalytic cycle [5], Both theoretical calculations and experimental investigations also show that the $[HgCH_3]^+$ species readily reacts to generate methanol and the reduced catalyst is rapidly reoxidized by hot sulfuric acid. The basis for the high selectivity, also confirmed by theoretical and experimental results, is that the active catalyst $[XHg]^+$ reacts at least 1000 times faster with the CH bonds of methane compared to those of CH_3OH, which exist primarily as the protonated or sulfated forms, $[CH_3OH_2]^+$ or CH_3OSO_3H, respectively, in sulfuric acid solvent. This greater reactivity of the methane CH bonds compared to those of methanol can be traced to substantially lower reactivity of the electrophilic $[XHg]^+$ catalyst with the CH bonds of methanol, which due to the electron withdrawing effect of protonation or sulfation are substantially less electron rich than those of those of methane.

3.3. Key advantage of CH activation is high selectivity and rates

These considerations emphasize a key reason for focus on the CH activation reaction (as an inner-sphere reaction as defined above) as the basis for developing the next gen-

eration of selective hydroxylation catalysts: the reaction can allow the cleavage of CH bonds with extraordinary selectivity and rates. If we presume that these high selectivities and rates will not be lost when coupled to efficient M–C functionalization, this then provides a compelling rationalization for designing oxidation catalysts based on the CH activation (as defined above as an inner-sphere process) reaction. Strategically, this restriction of the reaction mechanism to a CH activation pathway could greatly simplify de novo catalyst design as this can effectively fix the catalyst structure–selectivity (and potentially rate) relationship and allows for focus on structure-stability and structure-rate modifications with a high probability that the resulting catalyst could be made stable, selective and rapid. Of course, this places severe restrictions on the catalyst structures and compositions that will be examined, but as shown in Fig. 3, there is a wide variety of motifs that show activity for the CH activation reaction.

4. Some key challenges and approaches to catalyst design

4.1. Key challenge is simultaneous design of rapid, stable CH activation systems coupled to oxidative functionalization reaction

If we assume that catalysts based on CH activation can be selective and rapid, the key challenges that remain are to identify the requirements for designing *stable* catalysts while maintaining high alkane oxidation *rates* at low temperatures. These general requirements can be broken into more specific requirements as follows: (A) A reactive species must be generated that reacts rapidly with the CH bond via the CH activation reaction without the need for high energy conditions (as this is uneconomical), or high energy (and expensive) reagents and, critically, that is not inhibited in the presence of competing reactants (typically the oxidant), the solvent (desirably a species such as water), or product (methanol). (B) The CH activation reaction should be coupled in a catalytic cycle to an oxidative functionalization reaction that generates methanol, regenerates the catalyst and utilizes only air, or an air-recyclable oxidant and be compatible with all reagents required for the CH activation reaction. (C) The catalyst should be stable (not destroyed) to the reaction system.

The *simultaneous* requirement of these catalyst functions could provide an explanation to why, despite the large number of systems known to cleave CH bonds by the CH activation reaction, only relatively few systems are shown to function as catalysts to convert methane to methanol and none of them meet the target guidelines discussed below. While various reasons can be attributed to this lack of efficient catalytic systems, key reasons are lack of stability and/or no efficient functionalization reactions. Thus, for systems that can be classified as operating by the Metallorad-

ical, 1,2-addition and sigma bond metathesis pathways, no efficient functionalization pathways have yet been identified that generates useful products while regenerating the catalyst. The other two classifications, oxidative addition and electrophilic substitution have been successfully coupled to functionalization pathways that regenerate the catalyst. Indeed, all the active catalysts shown in Fig. 3 that generate functionalized products operate either via ES or OA pathways. However, in general these catalytic systems still suffer primarily from either poor rates and/or stability issues and have not met the performance goals required to be useful.

Meeting the two requirements of increasing rate and stability of CH activation based functionalization catalysis represents a significant challenge given the state of knowledge in the field. However, a useful strategy for the rational design of new catalysts could be based on selected, structurally and compositionally flexible motifs that can be expected to be thermally stable to the protic, oxidizing conditions required for functionalization and that can be expected to operate via the CH activation reaction. With such selected, stable motifs in hand, efforts could then be focused on modifications to increase rates and coupling of the CH activation and oxidative functionalization steps with some confidence that the catalyst will be sufficiently stable to show useful chemistry or catalysis.

4.2. Stable catalyst motifs for CH activation

Examining the known catalyst systems shown in Fig. 3 for some common property that leads to their effectiveness as catalysts reveals that stability is an important feature. Thus, while all these systems operate by two different pathways, ES or OA, an important common characteristic is structural motifs that primarily impart stability. In the case of the Pd(II) and Hg(II) cationic systems that operate in strongly acidic media by ES mechanisms, the stability is imparted by the simplicity of these catalysts that minimize the probability of degradation of complex catalytic structures. The primary mode of decomposition of these catalysts is irreversible formation of the reduced metallic state or other inactive states such as polymeric salts. In the case of Pd(II) this is a significant issue as Pd black is quite stable. However, in the case of Hg(II) salts in sulfuric acid media [5], this is not an issue as the reduced metal or oxidation states, $Hg_2(II)$, can readily be reoxidized to the active catalytic state, Hg(II).

The primary issue with the Shilov system [9], $PtCl_2$-$(H_2O)_2$, which is proposed to operate via an oxidative addition pathway [2c], is also catalyst instability due to irreversible decomposition to Pt metal or insoluble, polymeric Pt salts such $(PtCl_2)_n$. This can be addressed by the use of ligands as has been done with the high yield, $Pt(bpym)Cl_2/H_2SO_4$ system [5]. This system is stable and active for the conversion of methane to methanol in concentrated sulfuric acid (Eq. (2)) and yields of over 70% methanol (based on methane) with selectivities of >90%
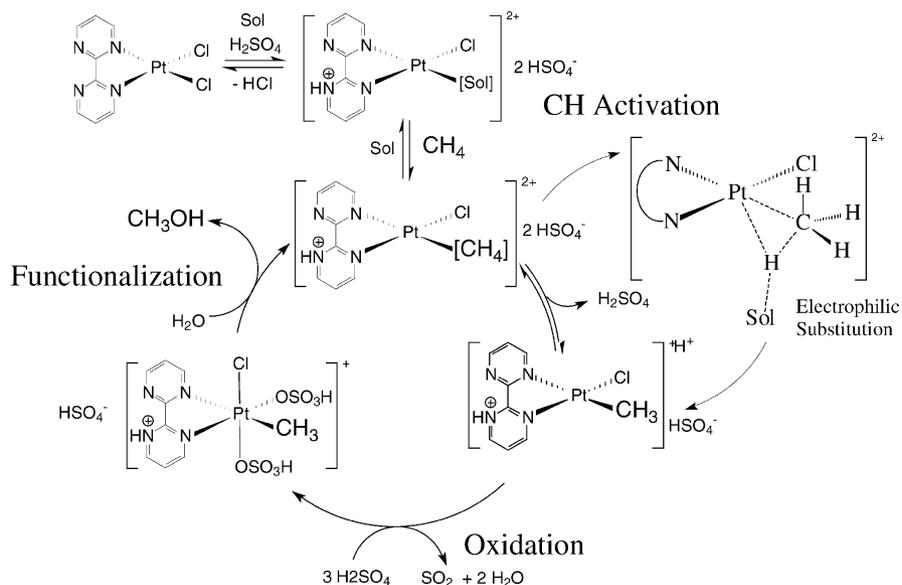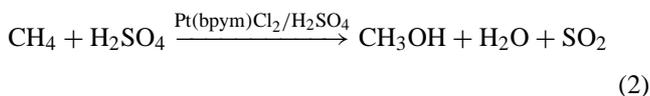
Fig. 11. Proposed electrophilic substitution of CH activation mechanism for the Pt(bpym)Cl$_2$/H$_2$SO$_4$ system for methane oxidation to methanol.

and turnovers of >300 have been observed

$$CH_4 + H_2SO_4 \xrightarrow{Pt(bpym)Cl_2/H_2SO_4} CH_3OH + H_2O + SO_2$$

(2)

In this system, experimental and theoretical studies show that this complex is stable to high thermal and strong acid solvents due to its unique structure and composition of the bpym (bipyrimidine) ligand [5,11]. Theoretical and experimental studies show that the bpym ligand is protonated in strongly acidic media and that this imparts both thermal and acid stability by stabilizing the active Pt(II) oxidation state to irreversible formation of insoluble (PtCl$_2$)$_n$ or Pt black formation. This has been shown to be due to the presence of the two nitrogens in the same aromatic ring in the bipyrimidine ligand that allows electronic communication between these centers. Consistent with this, replacement of the bpym ligand with simpler NH$_3$ ligands [5a] lead to systems that are active for the catalytic oxidation of methane to methanol but are unstable and lead to catalyst decomposition. Theoretical studies [11] confirm the experimental observations that Pt(NH$_3$)$_2$Cl$_2$ is thermodynamically *less* stable than (PtCl$_2$)$_n$ whereas the protonated Pt(bpym)Cl$_2$ complex, [(Hbpym)PtCl$_2$]$^+$ is thermodynamically *more* stable to this decomposition product. Theoretical and experimental studies show that this system also operates via an ES reaction pathway as shown in Figs. 11 and 12. This switch to an ES pathway, whereas the proposal is that the Shilov Pt(II) system operates via an OA pathway, is due to the increased electrophilic of the metal imparted by the protonation of the bpym ligand.

Catalysts based on ES pathways are not the only stable, active systems that operate by alkane CH activation and functionalization. In the case of the (PCP)IrH$_2$ system, which is the one of the most efficient system known for the

low temperature dehydrogenation of alkanes (conversion of alkanes to olefins) [6] has been shown to operate by an OA, β-hydride elimination sequence. This catalyst is quite stable and reaction of alkanes can be carried out at reasonable rates at temperatures above 200 °C where both transfer hydrogenation (transfer of hydrogen to an olefin as hydrogen acceptor) and "acceptorless" dehydrogenation (loss of hydrogen gas) is observed [5d]. While many systems are known that can cleave CH bonds by OA mechanism and may also be capable of β-hydride elimination reactions, it is likely that an important property of the catalyst is the unique, high thermal stability imparted by the tridentate, PCP ligand and strong Ir–C and Ir–P bonds.

Given the ubiquity of the OA mechanism, most of the systems shown in Fig. 3 operate by this mechanism, it would be desirable to identify complexes that operate via this mechanism and that are stable to the protic, thermal, oxidizing conditions required for functionalization of alkanes to alcohols. This could lead to new catalytic systems for the hydroxylation of alkanes that are based on this mode of CH activation. In such an effort to develop new stable motifs that operate via the OA pathway and that may lead to the development of new, stable oxidation catalysts, we have been exploring the use of O-donor ligands with metals known to facilitate the OA pathway. Thus, the simple O-donor Ir(III) system shown in Fig. 13 is thermally stable to protic media such as boiling acetic or triflouroacetic acids for days. Importantly, these complexes have now been shown to activate both arene and alkane CH bonds at temperatures above 150 °C [13]. In the presence of olefins and arene hydrocarbons, the complex catalyzes the anti-Markovnikov addition of arene CH bonds to olefins. The reaction mechanism has been elucidated, Fig. 14, by both theoretical [14] and experimental studies [14] and proceeds via a transition state or intermediate with OA character. We are examining the use
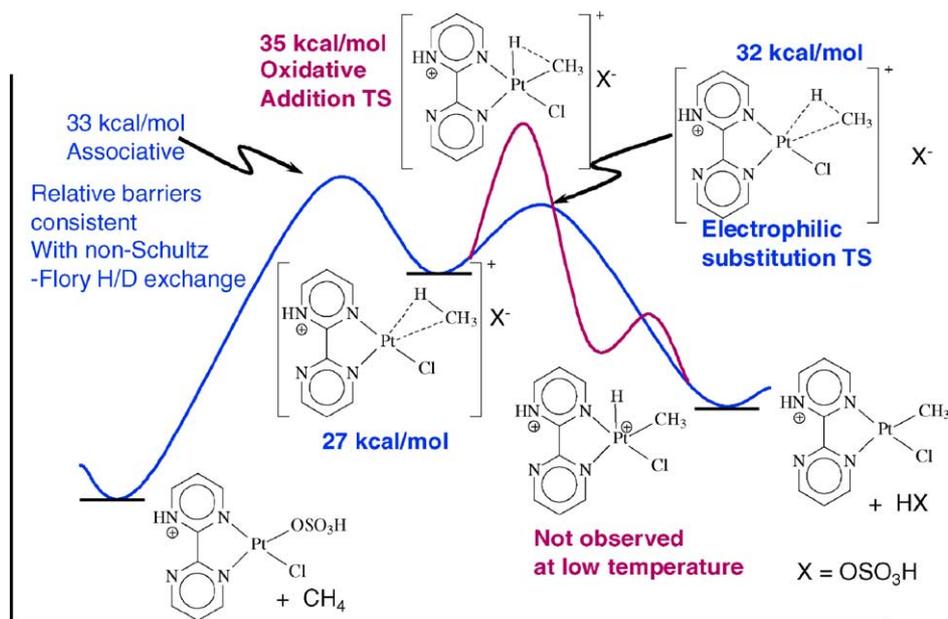
Fig. 12. Theoretical studies showing the relative energies of the ES and OA pathways for CH activation with $[(Hbpym)PtClX]^+$.

of these O-donor and related motifs for developing catalysts based on coupling the CH activation and functionalization reactions.

4.3. Slow rates of CH activation based catalysts

4.3.1. Catalyst inhibition by ground state stabilization

As shown above, Fig. 3, many systems that activate CH bonds are now known and it is possible that if these systems can be made stable that some could be used as the basis for development of catalysts for alkane oxidation. In most cases, the CH activation rates of these systems are quite rapid when rates are extrapolated to temperatures of ~200 °C. Indeed, in some cases CH activation has even been observed at temperatures below room temperature. On the basis of these observations and assuming that stable motifs can be identified that would facilitate CH activation and functionalization, it might be considered that acceptable catalysis rates can be
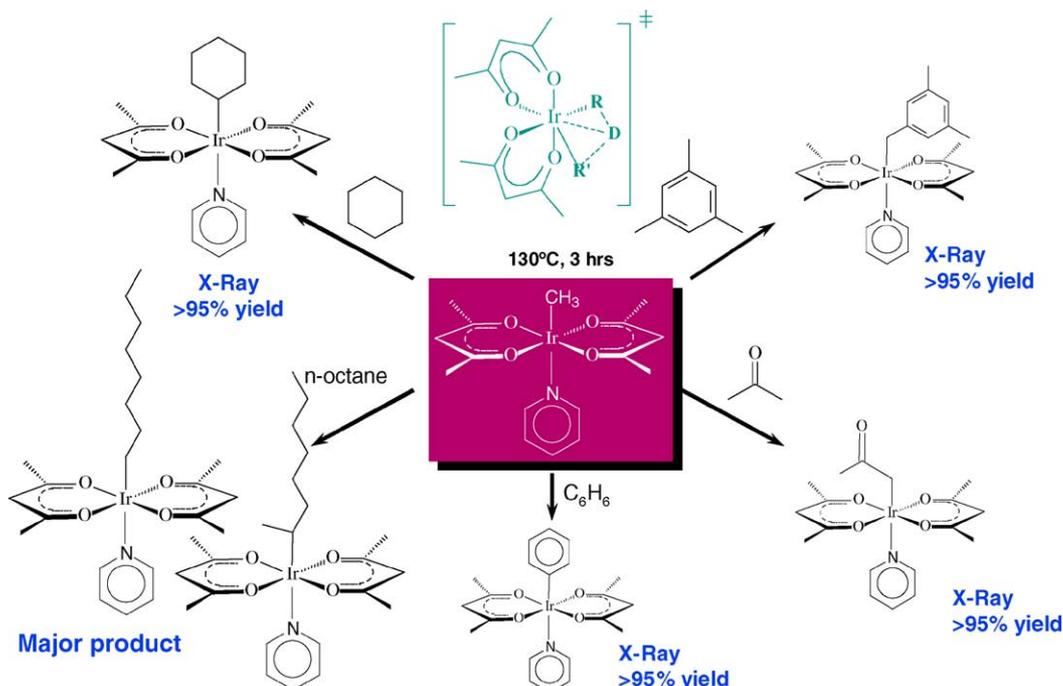

Fig. 13. Alkane and arene CH activation by O-donor Ir complexes that operate via an OA mechanism.
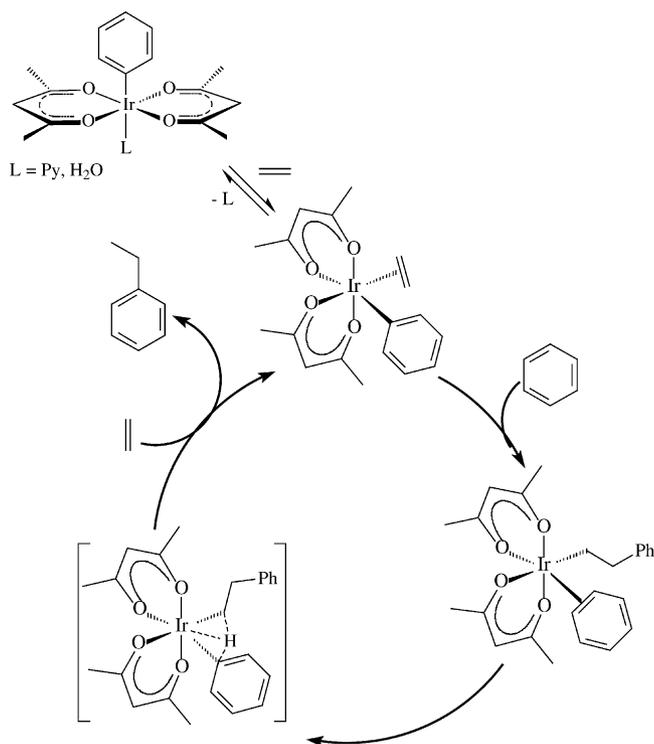
Fig. 14. Proposed mechanism for the hydroarylation of olefins catalyzed by the O-donor Ir(III) catalyst, (acac)$_2$Ir(Ph)(Pyr).

Fig. 15. Generalized energy diagram for CH activation via alkane coordination and CH cleavage showing ground state stabilization.

readily obtained by simply basing catalyst designs on the CH activation reaction. Importantly, this is not the case and other considerations are important.

The CH activation is typically a rapid reaction only when the reaction is carried out by the generation of high energy species and where the reaction system is carefully chosen such that the alkane is the most (or only) reactive species present. Under these circumstances it is understandable that the CH activation reactions observed are rapid. Unfortunately, under conditions where products such as alcohols can be produced, typically in the presence of protic, oxidizing higher temperature conditions, many of these catalysts, even if they can be made stable, could exhibit very low rates.

One fundamental reason for this is that the alkane CH bond, unlike CC double bonds of olefins or other functional groups, are among the poorest known ligands and unlikely to compete well with other more ligating species for coordination to the metal center. Indeed, this may well be the "Achilles heel" of catalyst development based on the CH activation reaction. Consistent with the poor ligating capability of alkanes, other than by spectroscopic methods and mechanistic studies, only one experimental observation of a transient alkane complex, and that by low temperature NMR, has been reported [15,16]. The coordination of an alkane to the first coordination sphere of a metal center in the CH activation reaction (either leading to an intermediate alkane complex or a transition state that leads directly to CH cleavage) can be viewed as inner-sphere ligand displacement or interchange mechanism where the alkane in
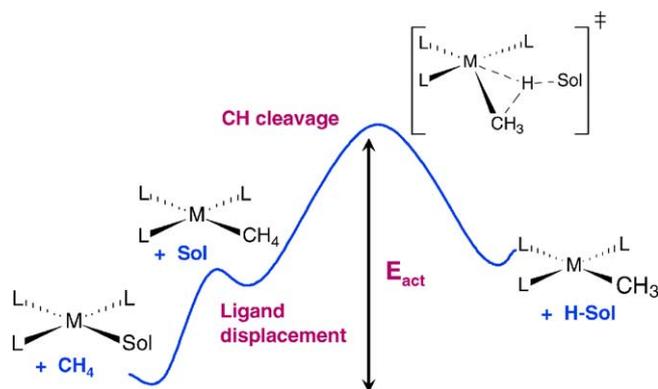
one of the ligands and the other is the ligand initially occupying that coordination site. In general this ligand to be displaced by the alkane, shown as "Sol" in Fig. 15, will be the most nucleophilic (ligating) species present in the reaction system and can be either reactants other than the alkane, solvent or the products. There is some debate as to whether this ligand exchange involving the alkane is dissociative or associative [17,3]. This depends on the binding constant of the ligand being displaced by the alkane but given the poor binding characteristics of alkanes, it is reasonable that there is will be substantial dissociative character to the displacement reaction in all cases except with extremely poor ligands.

These considerations point a fundamental issue that must be overcome in developing catalyst systems based on the CH activation reactions: inner-sphere ligand displacement mechanisms with alkanes (whether associative or dissociative) leading to weakly bound, intermediate alkane complexes, or directly to a transition state leading to CH cleavage, can be expected to be subject to severe ground state inhibition in most media that would be useful for oxidation catalysis. This ground state stabilization fundamentally arises from strong binding of other possible ligands to the catalyst in the reaction system. This leads to drop in energy of the catalyst resting state and as can be seen from Fig. 15, the more stable this state the higher the expected activation barrier for CH activation.

For example, it is challenging to imagine how methane coordination could occur to sufficient extent to allow efficient catalysis in a solvent such as liquid water, given the excellent coordinating properties of water that would lead to stable water complexes and extensive ground state inhibition. This is heightened by the poor solubility of methane in most useful media and the high concentration of the solvent. Of course, the reaction does not have to be carried out in solvents as ligating as water. However, if the objective is the hydroxylation of methane to methanol, then at a minimum (if as desired, the catalyst is expected to operate at high turn over numbers before separation of product) methanol, which can be expected to bind more tightly to the catalyst

than methane, will be present in the system and catalyst inhibition may be observed.

As might be anticipated this issue of ground state inhibition is observed in many catalytic alkane functionalization systems that operate by the CH activation reaction. Thus, of the systems that are known or likely to activate and hydroxylate alkanes by the CH activation reaction, the Shilov, Sen and Periana systems, this issue of inhibition is present. Thus, for the Sen Pd(II) and Periana Hg(II) and Pt(bpym)Cl$_2$ systems shown in Fig. 3, independent of stabilities, the slow rates or eventual inhibition of these catalyst systems that prevent their utility can be traced to water (or methanol) binding that leads to ground state inhibition. Other CH activation/functionalization systems that operate by mechanisms other than ES, such as the Kaska/Goldman/Jensen system [6] for the dehydrogenation of alkanes to olefins that operate by an OA mechanism, this inhibition is observed. In this case, this reaction cannot be carried in the presence of ethylene, an ideal, inexpensive, hydrogen acceptor due to ground state inhibition from olefin binding. The slow rates of the Shilov system that is proposed to operate by an OA mechanism is also most likely due to strong ground state inhibition from water binding.

We have been examining two approaches to this problem: (A) use of strongly acidic solvents and (B) altering the electronics of the metal center so as to minimize this ground state inhibition. The fundamental idea behind the use of an acidic solvent (this can be Lewis, or Bronsted acid) is that in principle, the strongest base that can exist in such a solvent is the conjugate base of the acid. In the case of a strong acid, both the acidic and the conjugate base will be weakly basic and expected to be poorly coordinating. This will minimize ground state stabilization by the solvent and the conjugate base. Critically, this use of a strong acid as a solvent rather than in stoichiometric amounts relative to the catalyst is central to preventing catalyst inhibition by products or reactants as these materials will also be present in large excess over the catalyst in any useful catalyst system.

4.3.2. Use of acidic solvents to minimize catalyst inhibition by ground state stabilization

The general use of Lewis or Bronsted acids to facilitate coordination of reactants is a well-known phenomenon in coordination chemistry [18]. Indeed, some of the most active systems reported for the stoichiometric CH activation can be seen as complexes that have been activated by addition of a Lewis acid. Thus, one of the most active complexes know for catalytic CH activation developed by Bergman and coworkers [19], [Cp*Ir(PMe)$_3$Me(CH$_2$Cl$_2$)]$^+$[MeB(C$_6$F$_5$)$_3$]$^-$, is generated by reaction of the Lewis acid, B(C$_6$F$_5$)$_3$, with Cp*Ir(PMe)$_3$Me$_2$ in the poorly coordinating solvent, CH$_2$Cl$_2$. One reason that this complex is quite reactive with methane (at $-10\,^\circ$C) is that all the possible competing ligands in the reaction system [MeB(C$_6$F$_5$)$_3$]$^-$ and CH$_2$Cl$_2$, are poorly coordinating species that minimize ground state stabilization and allow methane to effectively compete for

coordination to the metal center. While this strategy of stoichiometric use of weakly coordinated complex can lead to very active catalysts in reactions where no strongly coordinating reactants, solvents, or products are present, such catalysts could not be expected to remain active in the presence of stoichiometric or greater amounts of coordinating species such as water or methanol. In the presence of these materials the weakly coordinated groups will be readily displaced, resulting in severe ground state inhibition of the catalyst. Consequently, this approach of stoichiometric use of weakly coordinating groups would not be suitable for catalytic systems where the desired product is methanol and many catalyst turnovers are required.

One approach that could be considered is to run the reaction in liquid B(C$_6$F$_5$)$_3$ as solvent because under these conditions any methanol produced would form a strong acid–base adduct with the excess B(C$_6$F$_5$)$_3$. Under these conditions the methanol would be unavailable for coordination to the metal thereby preventing product coordination by methanol and subsequent ground state inhibition. The key issue with this strategy is that B(C$_6$F$_5$)$_3$ is expensive and most likely it would not be cost effective to attempt to separate the MeOH:B(C$_6$F$_5$)$_3$ complex and recycle the B(C$_6$F$_5$)$_3$. However, if the Lewis acid utilized is inexpensive and thermally robust, this could be potentially useful strategy.

This is the essential idea behind the use of inexpensive sulfuric acid solvent for facilitating the selective oxidation of methane [5]. Liquid sulfuric acid, at concentrations $> \sim 85\%$, is a polar, strongly Lewis acidic, poorly nucleophilic liquid in which the strongest nucleophile (or ligand) that can exist, HSO$_4^-$, is substantially less coordinating that water or methanol. Above this concentration of acid solvent, any water or methanol generated (or any other species more basic than HSO$_4^-$) is essentially fully protonated and not available for coordination to the metal center, minimizing catalyst inhibition by ground state inhibition. Below this acid concentration the solvent acidity drops rapidly [20] and water or methanol can become available for coordination to the metal center leading to inhibition of the CH activation reaction.

The key challenge to utilizing this strategy is the identification of catalysts, reactants and products that are thermally stable in such a medium. Both methane and methanol are thermally stable in sulfuric acid at temperature below 250$\,^\circ$C and we have identified several catalyst systems that are stable in this media for the selective oxidation of methane to methanol. As noted above both the Hg(II) and Pt(bpym)Cl$_2$ system have been found to be an efficient catalyst for methane oxidation to methanol at $\sim 200\,^\circ$C in this solvent as both are very stable in this media. Consistent with the concept of basicity leveling, theoretical studies show that, at sulfuric acid concentrations $> 90\%$, the ground state of these catalysts, [(Hbpym)PtCl(HSO$_4$)]$^+$ and Hg(HSO$_4$)$_2$, are coordinated to weakly binding HSO$_4^-$ that is most likely extensively hydrogen bonded to solvent H$_2$SO$_4$ molecules as shown in Fig. 16 for the Pt(bpym)Cl$_2$/H$_2$SO$_4$ system. As
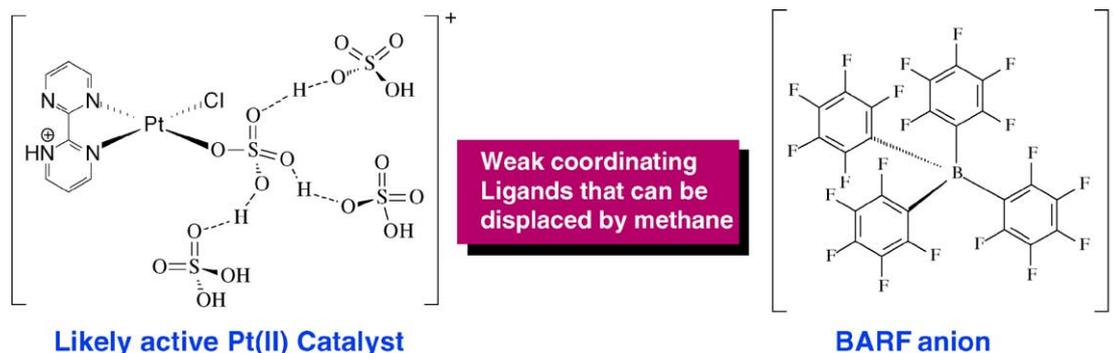
Fig. 16. Comparison of the likely active catalyst in the Pt(bpym)Cl$_2$/H$_2$SO$_4$ system with the weakly coordinating BARF anion.

can be seen, this weakly coordination of HSO$_4^-$ in sulfuric acid leads to a highly dispersed anion that is similar to the weakly coordinating anion, [B(C$_6$F$_5$)$_3$Me]$^-$ and that can be expected to be displaced by methane more readily than water.

Calculations show that replacement of the HSO$_4^-$ ligand by methane in the Pt(bpym)Cl$_2$/H$_2$SO$_4$ system is uphill 24 kcal/mol with a barrier of ∼33 kcal/mol. This is comparable to the ∼28–30 kcal/mol barrier obtained experimentally for the CH activation step by carrying out the reaction in D$_2$SO$_4$ and monitoring the rate of H/D exchange between methane and the solvent. Interestingly, the calculations as well as experimental results indicate that in the Pt(bpym)X$_2$ system that operates via an ES mechanism, the formation of this methane complex, rather than the CH cleavage step, is the rate determining step as shown in Fig. 12. Importantly, as a result of the large excess of solvent sulfuric acid (the catalyst concentration is typically 5–50 mM), substantially more than one equivalent of methanol can be generated in this system before catalyst inhibition due to water or methanol binding slows reaction to impractical rates. Thus, with a catalyst concentration of 50 mM, and starting with 100% sulfuric acid solvent, ∼300 turnovers have been demonstrated with the generation of >1.5 M methanol at ∼80% conversion of methane with >90% selectivity to methanol. At these high levels of water and methanol concentrations, Eq. (2), the activity of water and methanol are considerably higher because the sulfuric acid concentration is reduced. Experimental studies show that at acid concentrations below 80% sulfuric acid the reaction rates are too low to be useful (∼10^{-7} s^{-1}) at 200 °C. In this acid concentration range, the CH activation step is rate limiting and is at least 1000 times slower than at 96% sulfuric acid solvent concentration. The basis for this large difference in rate can be explained by theoretical calculations, Fig. 12, that show that the water complex (which is expected to be formed at lower concentrations of acid), [(Hbpym)PtCl(H$_2$O)]$^{2+}$ is ∼7–8 kcal/mol more stable than the [(Hbpym)PtCl(HSO$_4$)]$^+$ complex. Consistent with the expected dependence on solvent acidity, as can be seen from Fig. 17 the drop off in rate below 85% sulfuric acid solvent correlates well with the solvent acidity.

Critically, while the use of sulfuric acid allows the catalytic reaction to proceed efficiently, the rapid inhibition of the catalysts by water or methanol below 90% sulfuric acid leads to uneconomical catalyst rates (for the Pt system) and high separation costs for the methanol (for both the Pt and Hg systems). Calculations show that if catalyst inhibition can be minimized to allow an ∼5 M solution of methanol to be obtained, with an overall catalyst TOF of ∼1 s^{-1} that a process based on the use of sulfuric acid could potentially be useful.

4.3.3. Structure and composition catalyst modifications that minimize catalyst inhibition by ground state stabilization

The other approach to overcoming the inhibition of the catalyst from ground state inhibition that we have been investigating is to tune the electronics of the metal complex to prevent coordination. In general, CH activation by the OA mechanism is generally observed with more electron rich metals. Given the known propensity of such metal to bind olefins, a possible issue is strong ground state inhibition if olefins are utilized as reactants or can be formed during reaction, e.g., by β-hydride eliminations reactions. The thermally and protic stable O-donor ligated Ir(III) complexes
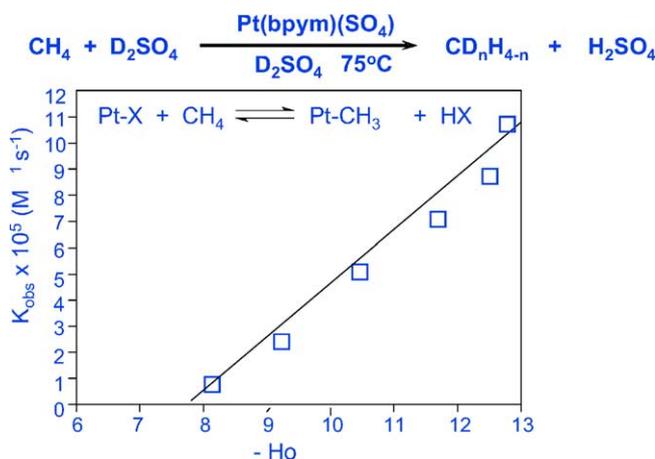

Fig. 17. Correlation of CH activation rates (measured by H/D exchange rates) with solvent acidity, H_0.

(acac)$_2$Ir(Ph)(Py) (that, as noted above, Fig. 13, activates alkane CH bonds by an OA mechanism) is one of the first catalyst reported for the anti-Markovnikov hydroarylation of olefins such as propylene with benzene to give predominantly *n*-propyl benzene [13]. Interestingly, in spite of the OA mechanism [14] the catalyst is not prohibitively inhibited even in the presence of olefins such as ethylene and catalyses the hydrophenylation of ethylene with benzene even in the presence of 300 psig of ethylene, albeit at 200 °C [13]. Additionally, no olefinic products such as styrene that could be expected from facile, β-hydride elimination reactions are produced in the reactions with ethylene. Mechanistic and theoretical studies show that this is due to substantially reduced olefin binding resulting from the electronegative O-donor ligands and lower electron density at the metal center [13,14].

To examine this further we examined a model system to determine if the reduction in electron density at the metal would *prevent* β-hydride elimination or make it *reversible*. As can be seen from Fig. 18, treatment of the pure ^{13}C isotopomer, (acac)$_2$Ir(^{13}CH$_2$CH$_3$)(Py) (A) with C$_6$D$_6$ leads to formation of (acac)$_2$Ir(CH$_2$^{13}CH$_3$)(Py) (B) as well as two products resulting from CD activation of C$_6$D$_6$, ^{13}CH$_3$CH$_2$D and ^{13}CH$_2$DCH$_3$; no free or coordinated olefin products are observed. These results are consistent with theoretical calculations that suggest that β-hydride elimination is reversible due to poor olefin binding and is unproductive due to faster rates of CH activation than loss of olefinic products. It is important to note however, that this decreased inhibition by

olefins is accompanied by a significant drop in CH activation reaction rates; thus while these O-donor system require heating to 150 °C for CH activation to be observed electron rich systems such as [Cp*(PMe$_3$)Ir(CH$_3$)(CH$_2$Cl$_2$)]$^+$ can be observed to react at −10 °C. This interplay between rate and functionality is to be expected and must be balanced in catalyst design.

4.4. Coupling CH activation with functionalization

4.4.1. Functionalization by formal reductive eliminations

If stable motifs can be identified that would allow CH activation to occur under conditions required for functionalization, i.e. at higher temperatures and in the presence of an oxidant, without being inhibited or destroyed by the reactants or products of the reaction, then the focus can become oxidative conversion of the M–C intermediate. As indicated above, to maintain the influence of the catalyst on both the conversion of the cleavage of the CH bond as well as the functionalization to the desired C–X product, the C fragment of the M–C intermediate should also ideally be functionalized while remaining in the inner-sphere of the metal. This requirement for an inner-sphere process leading to conversion of M–C to CX can be contrasted to other processes that can lead to C–X formation via, e.g. homolysis of the M–C bond to free radical species, C$^\bullet$, that could exhibit intrinsic, unselective reactivity that maybe undesirable. It is anticipated that in the functionalization step there could be a greater degree of electron transfer involved as the
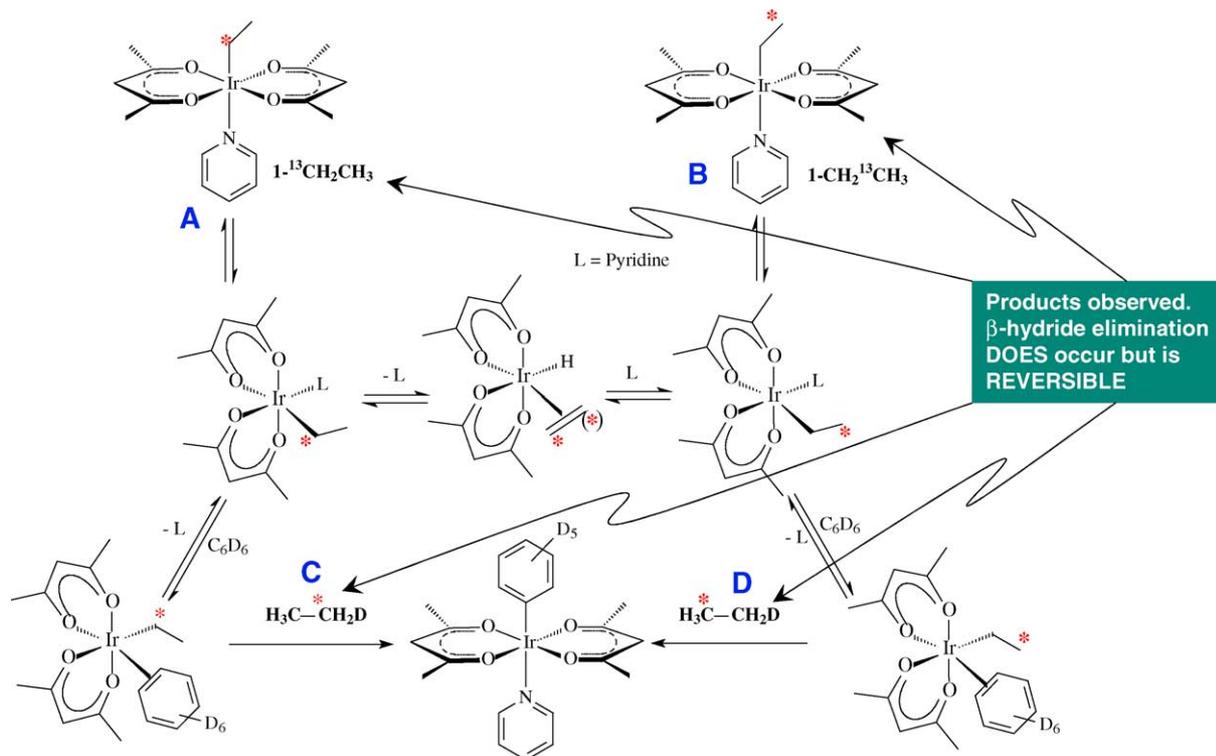

Fig. 18. Isotopic labeling experiment suggesting that β-hydride elimination is reversible and unproductive with O-donor Ir(III) complex.

formal oxidation state of the carbon fragment in the M–C intermediate will increase by two units due to the formal assignment of oxidation states to M–C and C–X species, where X is a heteroatom. This is of course a formalism, but it likely reflects some degree of reality. Depending on the actual extent of electron transfer, the driving force and structural changes around the M fragment, this reaction could be a facile or a challenging step. The facile, inner-sphere reactions that we have developed for the functionalization of M–C species to CX products are: (A) formal reductive elimination and (B) oxidative insertion reactions (such as CO insertions).

One of the simplest systems that illustrates the formal reductive elimination pathway is the Hg(II)/H$_2$SO$_4$ system [5]. As noted above, this system operates by an ES CH activation reaction mechanism as shown above in Fig. 10. As can be seen in Fig. 10, the MC intermediate resulting from CH activation, [CH$_3$Hg]$^+$HSO$_4^-$ undergoes a formal reductive elimination to generate CH$_3$OSO$_3$H and Hg(0). It is interesting to speculate on how the methanol is formed in this reaction. It is well know that Hg(II) with strong field ligands such as CH$_3^-$ adopts a linear, two coordinate geometry. Consequently, a concerted reductive elimination is unlikely. On the basis of preliminary theoretical and experimental studies, we can speculate that the reaction occurs by solvent assisted heterolysis of the [CH$_3$–Hg]$^+$ species with simultaneous capture of the departing electrophilic CH$_3$ fragment by H$_2$SO$_4$ (or HSO$_4^-$ and H$_2$O which can be expected to be present in concentrated sulfuric acid at 180 °C) as shown in Fig. 19 to generate CH$_3$OSO$_3$H or CH$_3$OH and Hg(0) (which is not observed as Hg(II) is observed to react rapidly with Hg(0) in a coproportionation reaction to generate Hg$_2$(II) which is observed). The reaction is presumably aided by the polar sulfuric acid solvent but as this is not strong nucleophilic, the reaction is most likely largely dissociative in character. The driving force for this reaction must be the relatively high oxidation potential for Hg(II)/Hg(0) which in sulfuric acid is greater than the standard potential of 0.85 V. We initially speculated that this heterolysis may be aided by free Hg(II) in an electrophilic substitution to directly generate Hg$_2$(II) (which we observe in solution) and CH$_3$X as shown in Fig. 19. However, kinetic studies on [CH$_3$Hg]$^+$ in hot sulfuric acid show that the rate of formation of CH$_3$OH is independent of the concentration of added Hg(II). The Hg$_2$(II) species are rapidly reoxidized to Hg(II) by hot H$_2$SO$_4$.
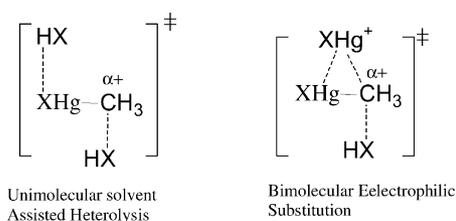
This Hg(II) system is interesting in that the higher oxidation state seems to be the active catalyst (or species) for the CH activation. Thus, studies show that Hg$_2$(II) is not active for CH activation. Thus the properties of Hg(II) that leads to this efficient reaction with methane in strongly acidic media can be described as "soft", "redox active" and electrophilic. These properties are shared by the third row elements on the middle to right of the periodic table due to the high Z_{eff}, high principal quantum number and large size. Predictably, we have found that Tl^{III}, Au^{III}, Pt^{II} and Pd^{II} are all active species for reaction with methane in concentrated H$_2$SO$_4$ and are inhibited below ∼85% sulfuric acid presumably due to ground state stabilization as discussed above.

The reactions with Tl^{III} is stoichiometric but cleanly converts methane to methanol by the general reaction shown in Eq. (3):

$$TlX_3 + CH_4 \rightarrow CH_3X + TlX + HX, \quad \text{where } X = HSO_4 \tag{3}$$
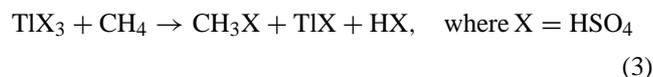
The reaction with Au(III) is interesting in that Au(0) is generated with clean formation of CH$_3$X by the stoichiometry shown in Eq. (4):

$$2AuX_3 + 3CH_4 \rightarrow 3CH_3X + 2Au(0) + 3HX \tag{4}$$
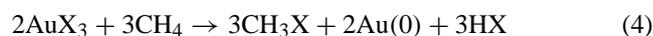
Since Au(I) is isoelectronic with Hg(II), and Au(III) is isoelectronic with Pt(II), and both Hg(II) and Pt(II) have been found to be active, it is possible that both Au(I) and Au(III) could be capable of CH activation of methane in strong acids by an ES mechanism. As shown in Fig. 20, catalytic cycles can be written with either Au(I) or Au(III) involved in the CH activation reaction followed by oxidation and functionalization steps that lead to irreversible formation of Au(0). Preliminary theoretical studies suggest both mechanisms are energetically plausible. We have attempted to study the discrete reaction of CH$_3$AuX$_2$ by synthesizing this species in strongly acidic media. Thus far attempts to generate such species without soft ligands such as PR$_3$ have led to decomposition to Au(0).

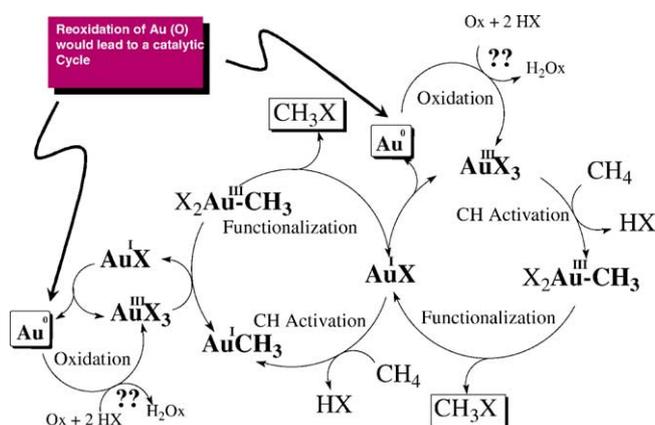Fig. 19. Possible mechanisms for the functionalization of [CH$_3$Hg]$^+$.

Fig. 20. Proposed mechanism for the oxidation of methane with Au(III) and Au(I).
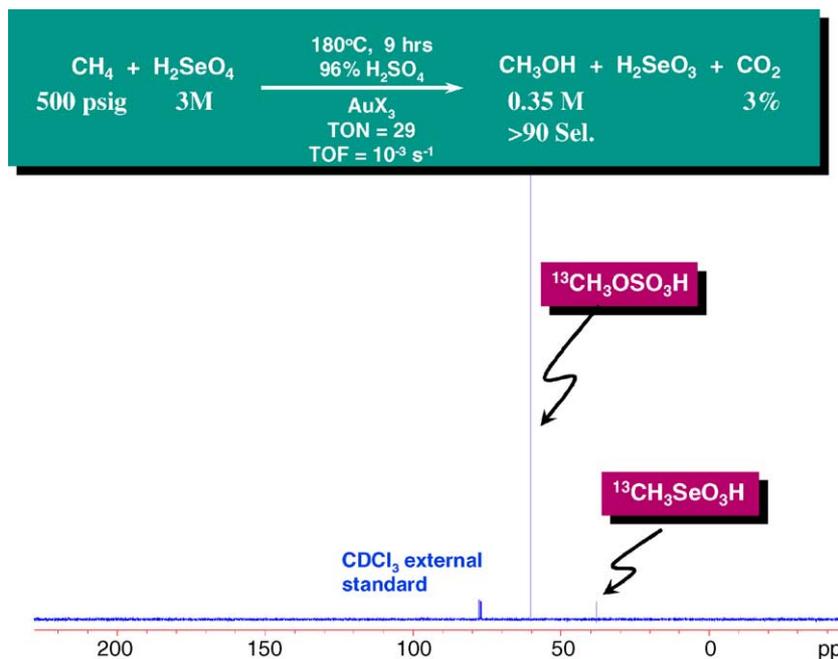
Fig. 21. ^{13}C NMR of the crude reaction mixture of methane with H_2SeO_4 dissolved in H_2SO_4.

As noted in Fig. 20, if the Au(0) could be reoxidized it seemed possible to make the systems catalytic. In considering possible oxidants it was necessary to ensure that the reoxidation reaction would not destroy the methanol product and that the acidity of the solvent would not be reduced by the presence of the oxidant. A good choice is H_2SeO_4, selenic acid. This acid is almost as strong as sulfuric acid but is a much more powerful oxidant and importantly is known to dissolve gold metal. Using this reagent we have now found that the Au(III) system can be made catalytic and we have observed ~30 turnovers to generate a 0.35 M methanol solution with a TOF of $\sim 10^{-3}$ s^{-1} at 500 psig of CH$_4$ at 180 °C as shown in Fig. 21.

The reaction is quite clean as shown by the ^{13}C NMR of crude reaction mixture from the reaction carried out with 100% enriched ^{13}CH$_4$.

4.4.2. Functionalization by oxidative insertion

One of the key issues with using strongly acid solvents to generate products such as methanol is the high affinity with the solvent that can lead to costly separation unless high concentrations of the product can be obtained. An approach that we are exploring is to generate products that can potentially be more readily removed from strongly acid media, such as carboxylic acid. The simplest target could be acetic acid generated by oxidative carbonylation in sulfuric acid by the reaction and proposed mechanism shown in Fig. 22.

We have recently found that this reaction is feasible and can be carried out with both the acid and thermally stable Pt(bpym)Cl$_2$/H$_2$SO$_4$ system as well as with Pd(II) in sulfuric acid [21]. The reaction with Pd(II) is very interesting because while this system can catalyze the addition oxidative insertion of CO into a CH bond of methane, it is also the first system, to our knowledge that efficiently couples two methane molecules to generate acetic acid, *without the need for added CO*. Thus as shown in Fig. 23, reaction of ^{13}CH$_4$ with Pd(II) dissolved in H_2SO_4 cleanly leads to CH$_3$CO$_2$H as the major product. The reaction is reasonably efficient and ~12% yield of acetic acid based on added methane with a selectivity of ~90% to acetic acid an be obtained. The reaction stops after with time after ~20 turnovers presumably due to catalyst deactivation and the formation of Pd(0).

We are currently studying this reaction mechanism and we believe that the reaction proceeds via an ES CH activation reaction, potentially involving Pd(CO)$_x$$^{2+}$ species that may be generated by slow overoxidation of the methanol from the oxidation of methane. Evidence for this is that added ^{13}CO as well as added ^{13}CH$_3$OH (in separate experiments) reacts with ^{12}CH$_4$ to generate ^{12}CH$_3$^{13}CO$_2$H. Additionally, addition of ^{12}CH$_3$OH to a ^{13}CH$_4$ reaction mixture generated primarily ^{13}CH$_3$^{12}CO$_2$H. Interestingly, while low levels of CO (added or produced by in situ methanol oxidation) is effective for the generation of acetic acid, addition of higher concentrations of CO essentially shuts down the reaction and rapid formation of Pd black and CO$_2$ is observed. These observations are all consistent with the propose mechanism is shown in Fig. 24. Central to this proposal is that there are several parallel reaction steps proceeding as might be expected for a formal eight electron coupling of two methane molecules to acetic acid. The observation that the reaction is effectively stopped by high concentrations of CO but facilitated by low levels of CO can be explained if the rate limiting step is reoxidation of Pd(0) by sulfuric acid. From independent experiments we have found that under high CO
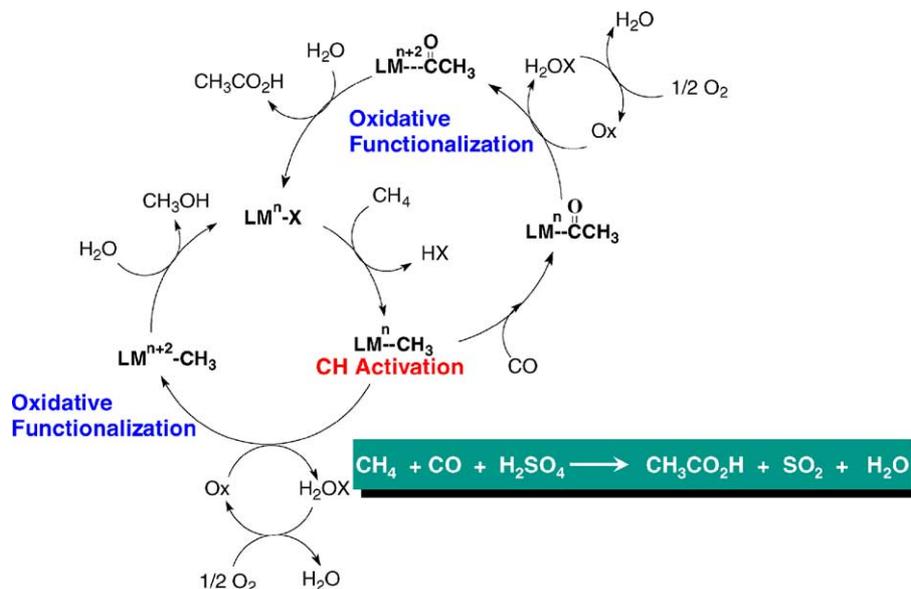
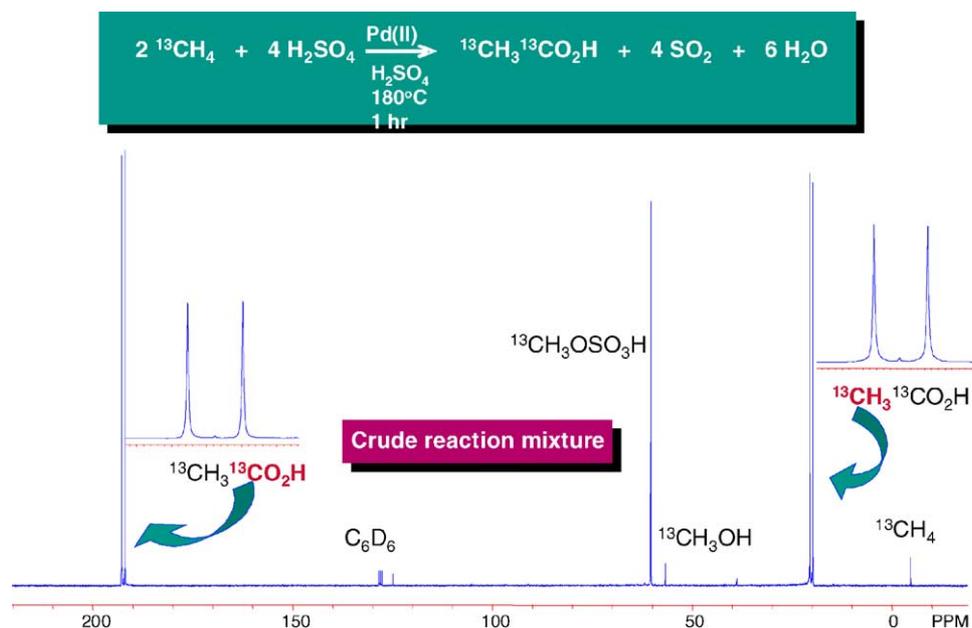Fig. 22. Plausible mechanism for the oxidative carbonylation of methane via the CH activation reaction.

Fig. 23. ^{13}C NMR of the crude reaction mixture from the oxidation coupling of methane to acetic acid catalyzed reaction by Pd(II)/H$_2$SO$_4$.

conditions the rate of formation of Pd(0) is much higher for the reoxidation and the reaction rate drops due to loss of the Pd(II) catalyst. Under low CO conditions, the rates of Pd(0) reoxidation and Pd(II) reduction (from reactions with methane, methanol and CO) are balanced and the reaction can be maintained. These results are intriguing and suggest that CO insertion is particularly facile under these conditions of CH activation. This could suggest that oxidative carbonylation of alkanes may be a particularly effective means of coupling CH activation with a useful M–C functionalization reaction.

5. Some performance guidelines for homogeneous catalysts for selective low temperature oxidation of methane to methanol

Meeting the challenge of developing the next generation of catalysts based on the CH activation reaction (or other pathways) for methane (or other alkane) conversion will require continued fundamental knowledge to be acquired by basic research and to be used in the design of these new catalysts. An important additional consideration is that while the main thrust of research to develop new catalysts is still
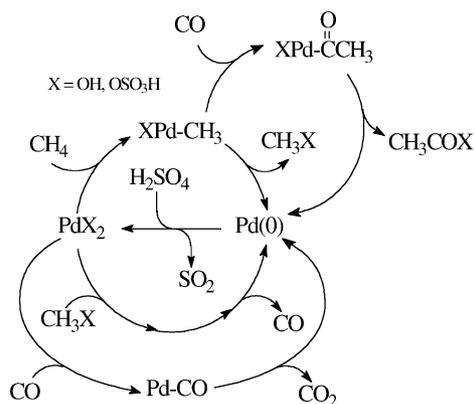
Fig. 24. Proposed tandem catalysis mechanism for the oxidative condensation of methane to acetic acid with Pd(II)/H$_2$SO$_4$.

largely in the area of fundamental research, as the field advances it could be of benefit if the fundamental thrust can be coupled with real world considerations that will ultimately be required to develop the next generation catalyst for selective, low temperature, alkane oxidation processes.

In practice, any methane to methanol commercial process will most likely be run in a continuous manner with reactants being continuously added and products removed from the reactor for separation and recycle. If new, low temperature catalysts soluble in a liquid phase can be developed, process consideration suggests that inexpensive, continuous, gas–liquid reactor systems could be utilized for this process. However, in the research laboratory, reactions are typically carried out in stirred, gas–liquid, batch reactors (reactions run for a fixed time with a fixed amounts of reactants introduced at the beginning of the reaction). It is useful to consider the performance targets of catalysts in this mode of reaction that could be used to quantify the effectiveness of any new catalyst systems being developed in research laboratories for possible production of methanol.

The guidelines shown below are obtained from two process economic considerations: (A) the optimum volumetric productivity (STY, space time yield) of inexpensive reactors which is a balance between efficient reactor usage and efficiency/cost of heat and mass transfer and (B) the percent of the total costs catalyst costs related to methanol production. While the STY value can vary with different products and process designs, a useful target value, based on engineering comparison of large scale, low value-added commodity products generated in inexpensive, gas–liquid reactor designs is $\sim 10^{-6}$ to 10^{-7} mol/cm^3 s. The catalyst costs are roughly broken into capital (related to total cost of the all the catalyst present in the plant) and working (generally related to regeneration costs) costs. Economic considerations that set a maximum to these costs to ~ 1–3%, lead to the useful guideline that the maximum catalyst concentrations should be ~ 1–10 mM and (based on typical regeneration costs and noble metal catalysts) with a catalyst TON of $\sim 10^5$ to 10^6. The STY and catalyst concentration are related to the catalyst rate in turnover frequency units (TOF) as shown in

Eq. (5):

$$STY = TOF \times [Cat] \qquad (5)$$

Critically, the only economically feasible raw materials for the conversion of methane to methanol are air and natural gas. For a high volume, low added-value product there is a significant cost difference between air and oxygen (even in the pressures of these required) and it would be desirable to utilize air but this is not always feasible depending on whether N$_2$/CH$_4$ separations would be required. These cost considerations rule out the use of expensive oxidants such as H$_2$O$_2$ and require that any alternative oxidants utilized in new low temperature processes must be regenerated by air, without excessive consumption of methane, as part of the process.

Some general guidelines for a potentially economical catalyst for the low temperature, oxidative conversion of methane to methanol, tested in a stirred, gas–liquid, batch reactor are: (A) the catalyst concentration should be ~ 1–5 mM concentration for good economics based on the cost (including regeneration) of typical ligated, noble metal catalysts; (B) the reaction should be carried out at ~ 150–250 °C (~ 220 °C preferred so that heat of reaction can be utilized in the plant), (C) the catalyst should be sufficiently stable to demonstrate TON (turnover-number) of ~ 300 in the research laboratory (TON of $\sim 10^4$ to 10^6 will most likely be required, before regeneration, for an economical process), (D) the reaction pressure should be ~ 300–600 psig (above these pressures the reactors can be excessively expensive), (E) the reaction should be highly selective for methanol (>95% to maximize the carbon yield), (F) allow a reactor volumetric productivity (space time yield) of methanol of $\sim 5 \times 10^{-7}$ mol/cm^3 s with (G) $\sim 75\%$ conversion of the limiting reagent (either methane or the oxidant). To achieve these performance targets in one batch reaction requires a selective, active, stable catalyst that operates with a TOF, turnover frequency, of ~ 0.5 s^{-1}.

To put these targets guidelines into a experimental perspective, in a typical gas–liquid, batch reactor (with a 2:1 gas:liquid ratio, for example) with good gas–liquid mixing (that results in a well-mixed gas–liquid phase of 1.3 times the volume of the unmixed liquid phase), with a catalyst concentration of ~ 5 mM, a maximum reactor pressure of 500 psig, using a methane/oxygen gas mixture of $\sim 3\%$ pure oxygen (in an industrial type reactor the O$_2$ would be introduced continuously so as to avoid explosive mixtures), a reaction temperature of 220 °C and exhibiting a methanol selectivity of 95%, meeting the STY target of 5×10^{-7} mol/cm^3 s requires that >75% oxygen gas (the limiting reagent) be consumed in 10 s of reaction time! This consumption of 75% of the O$_2$ will only result in 1 TON of the catalyst and to demonstrate that the catalyst is stable, the reactor should be recharged with O$_2$ and the reactions repeated for 300 times with the same catalyst/solvent system (without removal of methanol) to demonstrate that a TON of 300 is possible. Importantly, during these sequential reactions the selectiv-

ity to methanol should remain at 95%. After these numbers of reactions the concentration of product would be $\sim$1.4 M assuming a catalyst TOF of 0.5 s^{-1}.

Of course, these values represent guidelines that are meant to provide some level of calibration of what may be required for commercial success. As consideration of Eq. (3) shows, if a less expensive catalyst is utilized that allows a higher concentration of catalyst to be utilized, the requirement for activity can be reduced assuming that the STY target remains the same. In the final evaluation, these values will depend on the actual system developed as well as the end use of the product methanol, e.g., whether it will be used for the chemical or fuel markets. The performance guidelines shown above are based on developing a methanol process that may be sufficiently economical to be used in the fuel markets.

Acknowledgements

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