Catalytic Functionalization of Carbon–Hydrogen and Carbon–Carbon Bonds in Protic Media

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Alkanes are by far the most abundant and the least reactive members of the hydrocarbon family; the known reserves of methane alone approach those of petroleum.[1] Consequently, the selective, catalytic, activation and functionalization of carbon–hydrogen and carbon–carbon bonds of alkanes, and of unactivated alkyl groups in general, to form useful functional organics constitutes a Holy Grail in chemistry.[2] Of particular importance are oxidations, since the majority of the commercially important organic chemicals (alcohols, aldehydes, ketones, acids) can, in principle, be derived from alkanes through one or more oxidative functionalization steps.[3]

The lack of reactivity of alkanes (and of unactivated alkyl groups) stems from their unusually high bond energies (C–H bond energy of methane 104 kcal/mol), and most reactions involving the homolysis of a C–H bond occur at fairly high temperatures or under photolytic conditions. Moreover, the selectivity in these reactions is usually low because of the subsequent reactions of the intermediate products, which tend to be more reactive than the alkane itself. Using methane as an example, its homolytic C–H bond energy is 10 kcal/mol higher than that in methanol. Therefore, unless methanol can be removed or protected as soon as it is formed, any oxidation procedure that involves hydrogen atom abstraction from the substrate would normally cause rapid overoxidation of methanol. To achieve the selective functionalization of alkanes, it is therefore necessary in most cases to promote a pathway that does not involve C–H bond homolysis as one of the steps. The problem is compounded by the fact that practical processes usually require the direct use of dioxygen as the oxidant. Because of its triplet electronic configuration, the reaction between dioxygen and alkanes most often involves unselective radical pathways.[4]

Apart from the selectivity with respect to the degree of oxidation, a second selectivity issue arises for C_3 and higher alkanes: the selectivity with respect to the particular C–H bond that is functionalized. Since the homolytic bond energies decrease in the order: primary C–H > secondary C–H > tertiary C–H bonds, radical pathways involving C–H bond homolysis almost always show a marked preference for the functionalization of tertiary C–H bonds. However, many commodity chemicals are terminally functionalized.[3]
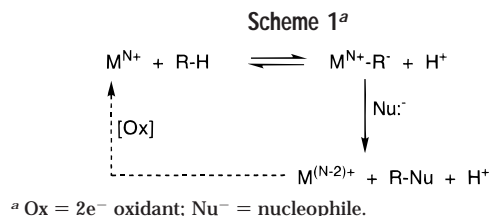
In principle, the above selectivity problems can be avoided in suitably designed metal-catalyzed oxidation procedures. Transition metals, particularly those whose most stable oxidation states differ by $2e^-$, often promote nonradical pathways even in the presence of dioxygen.[5] Moreover, since metal–carbon bond strengths parallel those of C–H bonds and because of unfavorable steric interactions between ancillary ligands and branched alkyl groups, the preferential functionalization of primary C–H bonds becomes possible.[6] As a bonus, metal ion catalyzed reactions usually operate at low temperatures (~100 °C or below).

While it is difficult to design a catalytic procedure for the selective functionalization of C–H bonds, it is harder still to achieve catalytic functionalization of C–C bonds, even though the C–C bonds are significantly weaker than C–H bonds. Two reasons are usually cited for the general lack of C–C activation[7] compared to corresponding C–H activation by metals. First, C–C bonds are sterically less accessible to transition metal centers surrounded by ligands. Second, metal–carbon bonds tend to be weaker than metal–hydrogen bonds, again due to steric repulsions between the ligands surrounding the metal and the alkyl group bound to it.[8] C–C cleavage is, however, commonly observed in the interaction of bare metal cations with alkanes.[9] In this case, there is no steric hindrance and the metal–carbon and metal–hydrogen bond strengths are comparable (approximately 60 kcal/mol).[9a,b,10]
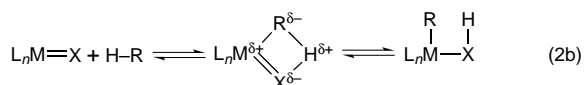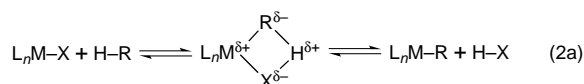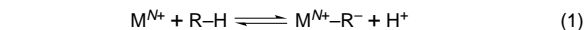
Below, we describe several metal-catalyzed systems for the activation and functionalization of C–H and C–C bonds of alkanes and unactivated alkyl groups in protic media. The account is based primarily on work performed in our laboratory, although related work reported by other groups is also discussed.

An important class of C–H functionalization reactions that proceed in protic solvents involves late transition metal ions as oxidants.[2a–d,11] An electrophilic pathway has been commonly invoked (though not proven unequivocally) for the C–H cleavage step in these reactions (see eq 1). A driving force for the reaction shown in eq 1 is the stabilization of the leaving group, H^+, by solvation in polar solvents. The related four-center electrophilic activation by transition, lanthanide, and actinide metal centers has also been reported (eq 2a,b).[2c,12] In these

Scheme 1[a]

$$M^{N+} + R\text{-}H \rightleftharpoons M^{N+}\text{-}R^- + H^+$$

[Ox] ↑ , Nu:⁻ ↓

$$M^{(N-2)+} + R\text{-}Nu + H^+$$

[a] Ox = 2e⁻ oxidant; Nu⁻ = nucleophile.

Scheme 2

$$CH_4 \xrightarrow{-e^-} [CH_4^{\bullet+}] \xrightarrow{-H^+} CH_3^\bullet \xrightarrow{-e^-} CH_3^+$$

$$CH_3^\bullet \underset{-Hg^I}{\overset{Hg^I}{\rightleftharpoons}} CH_3\text{-}Hg^{II}$$

$$CH_3^+ \xrightarrow{^-OSO_3H} CH_3OSO_3H$$

$$C_2H_6 \xrightarrow{-e^-} [C_2H_6^{\bullet+}] \xrightarrow{-H^+} C_2H_5^\bullet \xrightarrow{-e^-} C_2H_5^+$$

$$C_2H_5^+ \xrightarrow{^-OSO_3H} C_2H_5OSO_3H$$

$$[C_2H_6^{\bullet+}] \rightarrow CH_3^+ + CH_3^\bullet$$

$$CH_3^+ \xrightarrow{^-OSO_3H} CH_3OSO_3H$$

$$CH_3^\bullet \xrightarrow{-e^-} \xrightarrow{^-OSO_3H} CH_3OSO_3H$$

instances, a ligand on the metal (which may be an alkyl group) assists the reaction by acting as the base.

$$M^{N+} + R\text{-}H \rightleftharpoons M^{N+}\text{-}R^- + H^+ \qquad (1)$$

$$L_nM\text{-}X + H\text{-}R \rightleftharpoons L_nM^{\delta+}\underset{X^{\delta-}}{\overset{R^{\delta-}}{\diamond}}H^{\delta+} \rightleftharpoons L_nM\text{-}R + H\text{-}X \qquad (2a)$$

$$L_nM\text{=}X + H\text{-}R \rightleftharpoons L_nM^{\delta+}\underset{X^{\delta-}}{\overset{R^{\delta-}}{\diamond}}H^{\delta+} \rightleftharpoons L_nM\overset{R\quad H}{\underset{}{|\quad|}}X \qquad (2b)$$

The most significant advantage of the C−H activation pathway shown in eq 1 is that the late transition metal electrophiles are compatible with oxidants, including dioxygen. Therefore, in principle, it should be possible to design a catalytic oxidation procedure that is based on an initial electrophilic C−H cleavage step, as is shown in Scheme 1, and was first demonstrated by Shilov and his colleagues using the Pt(II) ion as the C−H activating species (see below).[11b]

Reactions in Strongly Acidic Media

For two reasons, much of the work in the area has been carried out in strong acids. First, the conjugate bases of strong acids are poorly coordinating, thereby enhancing the electrophilicity of the metal ion. Second, the esterification of the alcohol, the primary product of alkane oxidation, protects it from overoxidation. One impressive achievement in this area is the Hg(II)-catalyzed oxidation of methane to methyl sulfate (CH_3OSO_3H) in 100% sulfuric acid at 180 °C, as described by Catalytica.[13] Both high selectivity and high conversion was achieved. The sulfuric acid served as both the solvent and the reoxidant for the metal. Although an electrophilic mechanism similar to Scheme 1 has been claimed, further studies indicate that a radical pathway, occurring at least in parallel, cannot be ruled out. For example, we have observed that a number of free-radical initiators, including $S_2O_8^{2-}$, also gave comparable stoichiometric yields of CH_3OSO_3H under conditions where mercury was not reoxidized by sulfuric acid.[14] The $S_2O_8^{2-}$ ion is an interesting case in point. We had earlier demonstrated that in water at 110 °C, $SO_4^-\bullet$ (generated from $S_2O_8^{2-}$) abstracted a hydrogen atom from methane or ethane to form the corresponding alkyl radical, which was then converted to, inter alia, the alcohol and the sulfate.[15] In the presence of added carbon monoxide, this radical was trapped efficiently and the resultant acyl radical was ultimately converted to a carboxylic acid. It is therefore possible that, as shown in Scheme 2,[14] one role of *all* the oxidants in sulfuric acid is to generate a methyl radical from methane by outer-

sphere electron transfer followed by proton loss. The methyl radical is eventually converted to CH_3OSO_3H. In the special case of Hg(II) as the oxidant, CH_3HgOSO_3H is formed by (reversible) recombination of methyl and Hg-(I) radicals. It may be noted that the proposed mechanism is similar to that suggested for some monooxygenases where both the alkyl radical and the alkyl cation, formed by electron transfers to high-valent iron−oxo species, have been implicated as intermediates.[16]
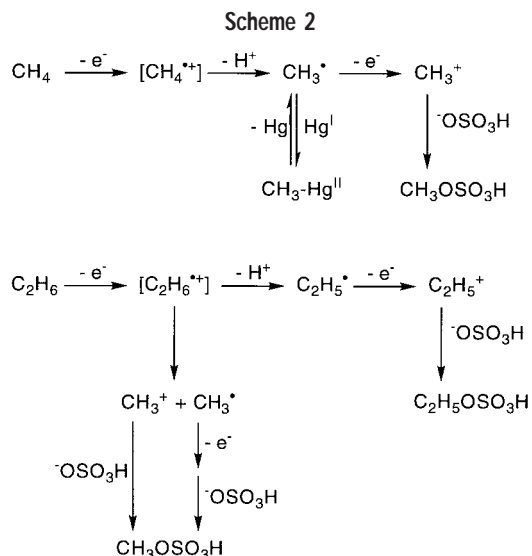
The mechanistic scenario outlined above finds support in the reactivity pattern observed with ethane.[14] The radical cation formed from ethane by electron transfer would be expected to fragment some of the time by C−C cleavage (Scheme 2). The direct precedent for such a step is Olah's observation of CH_3NO_2 as the principal product in the reaction of ethane with $NO_2^+PF_6^-$.[17] Indeed, the formation of CH_3OSO_3H was observed (up to 25% yield relative to oxidant) when ethane was contacted at 150−180 °C in 98% sulfuric acid with any one of a number of oxidants.

One possible argument against the mechanism shown in Scheme 2 is that the specific metal ions employed are not strong enough oxidants to effect a 1e⁻ oxidation of methane and ethane. However, highly electrophilic metal ions lacking donor ligands have reduction potentials significantly more positive than the corresponding ligated metal complexes. At the same time, there is a dramatic increase in oxidation potential for alkanes in strong acids.[18]

The radical-initiated functionalization of methane proceeds even more readily in fuming sulfuric acid (27−33% SO_3 content by weight was employed).[19] Thus, a variety of radical initiators were found to convert methane to CH_3SO_3H at 90 °C. For every initiator examined, the product concentration was many times the concentration of the initiator (>700 times in the case of $K_2S_2O_8$!). The preference for H-atom abstraction from methane rather than the methyl group of CH_3SO_3H by the chain carrier, $CH_3SO_3^\bullet$, may be ascribed at least in part to its electrophilic nature (the "polar effect"). At 170 °C, CH_3SO_3H was

quantitatively converted to CH_3OSO_3H even in the absence of an initiator. It was also possible to directly convert methane to CH_3OSO_3H by using a radical initiator and running the reaction at 170 °C.

A significant body of work on metal-mediated electrophilic C—H activations has also been carried out in perfluorocarboxylic acids. One noteworthy result in the area is the Pd(II)/Cu(II)-catalyzed carbonylation of alkanes, including methane, in trifluoroacetic acid as reported by Fujiwara.[20] In most cases, the oxidant was the $S_2O_8^{2-}$ ion. These and related reactions[21] build upon our earlier report on the Pd(II)-catalyzed electrophilic activation and conversion of methane to methanol by H_2O_2 in trifluoroacetic acid.[22]

In many of the oxidation reactions carried out in perfluorocarboxylic acids, the corresponding anhydride was added to rapidly esterify the alcohol derived from the alkane. However, as with sulfuric acid, the mechanism of metal-mediated C—H activations in such solvent systems should be approached with caution. For example, we have discovered that in the presence of a radical initiator (e.g., H_2O_2), perfluorocarboxylic anhydrides act as oxidants toward ethane forming the mixed anhydride, $CH_3CH_2COOCOR_f$, and the ketone, $CH_3CH_2COR_f$, in varying ratios.[23] For a fixed amount of initiator, the amount of products formed increased with increasing amount of anhydride employed and was always higher than the initiator added. In particular, with $PbEt_4$ close to 500 equiv of products was formed from ethane for every equivalent of $PbEt_4$ employed!
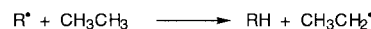
The mechanism of this curious reaction involves the formation of $C_2H_5{}^\bullet$ radical, which then attacks $(R_fCO)_2O$ at one of the carbonyl carbons to form an alkoxy radical (Scheme 3).[23] The attack by the $C_2H_5{}^\bullet$ radical occurs at the most electron-deficient site because of the alkyl radical's nucleophilic nature.[24] The alkoxy radical formed undergoes the well-known β-bond cleavage reaction. If the R_f—CO bond is cleaved, the product is the mixed anhydride. On the other hand, if the C(O)—O bond is broken, the ketone is produced. Both pathways produce the $R_f{}^\bullet$ radical: the first directly, and the second by formation and subsequent decarboxylation of the $R_fCO_2{}^\bullet$ radical. The $R_f{}^\bullet$ radical then continues the chain reaction by abstracting a hydrogen from C_2H_6, forming the $C_2H_5{}^\bullet$ radical and R_fH. Interestingly, unlike ethane, neither methane nor propane is able to participate in this reaction sequence, the former because the C—H bond of methane is too strong to undergo significant hydrogen-atom abstraction by the $R_f{}^\bullet$ radical and the latter because only primary alkyl radicals are sufficiently reactive to attack $(R_f-CO)_2O$.[23] Thus, our observation of Pd(II)-catalyzed conversion of methane to a methanol derivative by H_2O_2 in a trifluoroacetic acid/anhydride mixture was not complicated by the above reaction.[22,23]
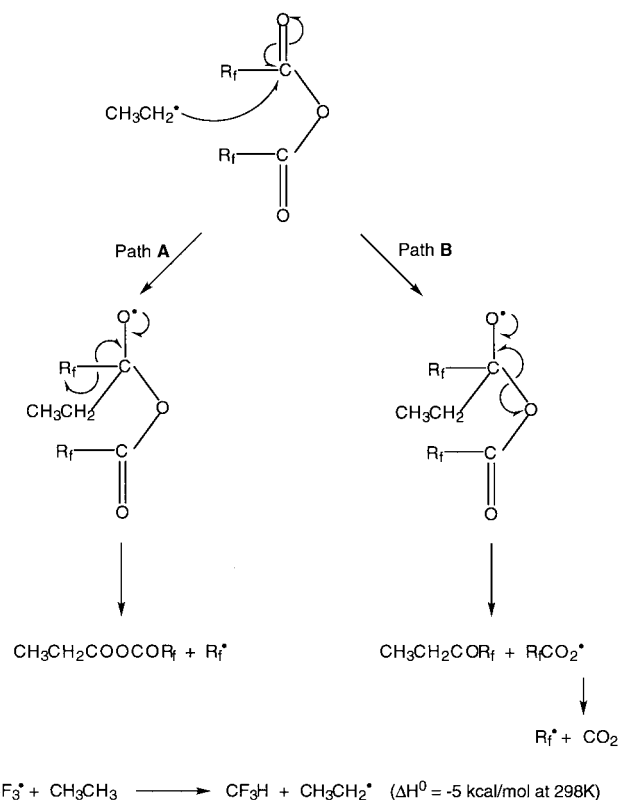
Reactions in Aqueous Medium

Electrophilic C—H activations can also be effected in water. At first glance, water would appear to be particu-

Scheme 3

Initiation:

$$R^\bullet + CH_3CH_3 \longrightarrow RH + CH_3CH_2{}^\bullet$$

Propagation:

Path A   Path B

$$CH_3CH_2COOCOR_f + R_f{}^\bullet \qquad CH_3CH_2COR_f + R_fCO_2{}^\bullet$$

$$R_f{}^\bullet + CO_2$$

$$CF_3{}^\bullet + CH_3CH_3 \longrightarrow CF_3H + CH_3CH_2{}^\bullet \quad (\Delta H^0 = -5 \text{ kcal/mol at 298K})$$

larly unpromising as a solvent for such reactions. Because of their extremely poor coordinating ability (no fully characterized alkane complex is known[25]), alkanes should not be able to compete with water for coordination sites. Moreover, the intermediate metal-alkyl species would be prone to hydrolytic decomposition. In one respect, however, water is almost an ideal medium for C—H functionalization: the O—H bond energy exceeds the corresponding C—H bond energy of even methane. Indeed, the selective oxidation of methane to methanol is carried out by methane monooxygenase in aqueous medium.[26]

Shilov and co-workers were the first to demonstrate metal-mediated alkane functionalization in water.[11b] They showed that simple Pt(II) complexes, such as $PtCl_4{}^{2-}$, will activate and oxidize the C—H bonds of alkanes. It is important to point out that, unlike with functional organics (see below), *the Shilov system exhibits little preference for attack on the primary C—H bond of alkanes, on a per-bond basis.* We,[27] as well as Bercaw and Labinger and Horváth,[28] have followed up on aspects of Shilov's work and have shown that a wide variety of substrates including methane can be functionalized with unusual selectivity through the mechanism outlined in Scheme 1. Thus, although the homolytic C—H bond energy of methane is 10 kcal/mol higher than that in methanol, a C—H bond of methanol would not be expected to be significantly

Scheme 4
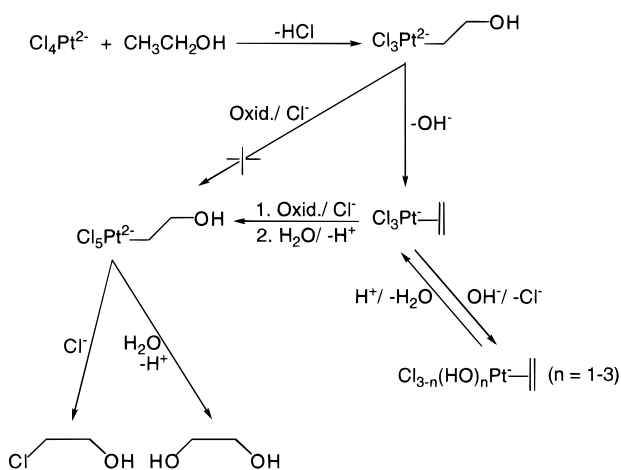
more susceptible to ***electrophilic*** cleavage than that of methane. Indeed, we have observed that, in water at 100 °C, the rate constant for the oxidation of methane to methanol by the $PtCl_4^{2-}/PtCl_6^{2-}$ combination [the Pt(IV) species acts merely as a reoxidant for the $Pt^0 \rightarrow Pt^{II}$ step; see Scheme 1] was only $^1/_7$ of that for methanol overoxidation by the same system.[27b] The observed similarity in rates is even more striking given the much higher binding ability of methanol to the Pt(II) center. Moving to substrates with C−H bonds somewhat weaker than that in methane resulted in actual ***reversal*** of commonly observed selectivity. Thus, the relative rate of C−H bond activation by the Pt(II) ion decreased in the order $H-CH_2-CH_3 > H-CH_2CH_2OH > H-CH(OH)CH_3$, i.e., an order that is exactly *opposite* of that expected on the basis of homolytic C−H bond energies.[27b] On a practical level, this showed that the direct conversion of ethane to ethane-1,2-diol is possible.

The preferential oxidation of the methyl group of ethanol by the $PtCl_4^{2-}/PtCl_6^{2-}$ combination in water at 90 °C was first reported by Bercaw and Labinger[28a] and subsequently confirmed by us, who observed the exclusive oxidation of the methyl group in ethanol resulting in the formation of ethane-1,2-diol as the sole product.[27a,b] The mechanism of this transformation is shown in Scheme 4.[27e,28d]

Invoking the intermediacy of a similar alkene complex in the oxidation of *n*-propanol would lead to the prediction of propane-1,2-diol as the preferred oxidation product. Indeed, the oxidation of the propene complex, $[PtCl_3(C_3H_6)]^-$, resulted in the formation of mostly propane-1,2-diol, along with some 1-chloro-2-propanol and a trace of 2-chloro-1-propanol.[27e] On the other hand, the dominant product obtained from *n*-propanol by using the Shilov system was propane-1,3-diol.[27a,b,d,28a] In fact, by using the Shilov system, the remote oxidation of highly flexible linear and branched alkyl chains becomes possible with unprecedented regioselectivity. The order of reactivity is α-C−H $\ll$ β-C−H $<$ γ-C−H $<$ δ-C−H for alcohols and α-C−H $\ll$ β-C−H $<$ γ-C−H $\geq$ δ-C−H for carboxylic acids, sulfonic acids, and phosphonic acids.[27a,c,d] There are several noteworthy points regarding the remote oxida-

tions. First, the Pt(II) ion does not discriminate between primary, secondary, and tertiary C−H bonds; the distance between the existing functionality and C−H bond being attacked is all that is important. In a separate experiment, the same system showed no preference in the hydroxylation of the primary versus the secondary C−H bond of propane (on a per-hydrogen basis). The above trend is inconsistent with an H-atom abstraction step given that the homolytic C−H bond energies decrease in the order primary C−H $>$ secondary C−H $>$ tertiary C−H. In addition, an α-C−H bond in alcohols is especially weak due to the stabilization of the radical derived therefrom by donation of electron density from the neighboring oxygen atom. The second trend of note is that only hydroxylation or its equivalent oxidation level was observed; there was no overoxidation to the aldehyde or the carboxylic acid functionality. Thus, a precise control with respect to the oxidation level was achieved.
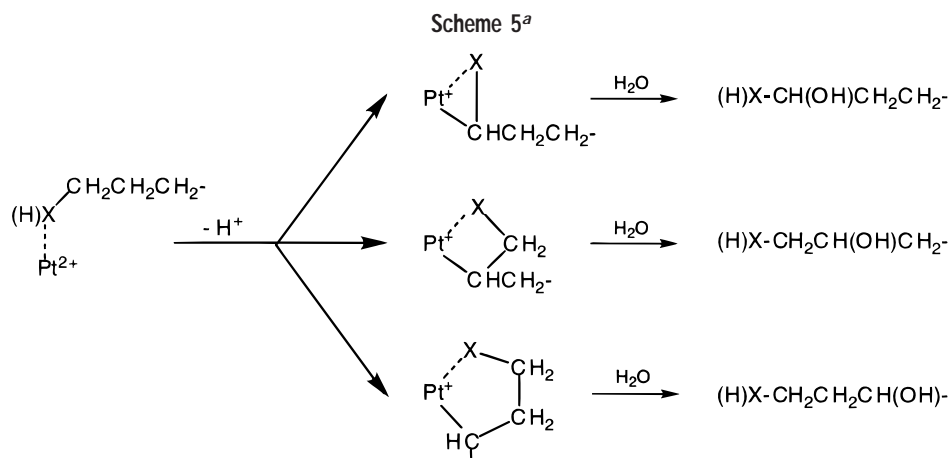
The simplest explanation for the observed regioselectivity is the "chelate effect" (Scheme 5).[27a,c,d] The functional group on the organic substrate would be expected to coordinate to the electrophilic Pt(II) center. As a result, an intermediate metallacycle will be formed following an electrophilic C−H activation step. The observed order of reactivity then is a function of the ring strain present with a five-membered ring being favored over a four-membered analogue, which in turn was favored over a highly strained three-membered metallacycle. The preference for hydroxylation is a result of the strained transition state that was involved in the activation of a C−H bond α to the hydroxyl group (see Scheme 5). Note that the selective functionalization of remote C−H bonds by the Fe^+ ion through a similar chelate effect has been observed in the gas phase.[9c,d]

While it has been generally assumed that heterolytic C−H bond cleavage is involved in the Shilov system (eq 1), the possibility that C−H activation proceeds through an oxidative addition step resulting in the intermediacy of a Pt(IV)(alkyl)(hydride) has been raised on the basis of studies of model systems.[29]

The activation and functionalization of C−H bonds by the Pt(II) ion is particularly attractive because of the unusual regioselectivity, high oxidation level specificity, and the mildness of reaction conditions. Nevertheless, thus far it suffers from one crippling drawback: dioxygen cannot be used efficiently as the reoxidant for the Pt^0 formed from Pt(II) during substrate oxidation.[30]

Artificial Monooxygenases

Recently, we have reported two catalytic systems that *simultaneously* activate dioxygen and alkane C−H and C−C bonds, resulting in the direct oxidations of alkanes. In the first system, metallic palladium was found to catalyze the oxidation of methane and ethane by dioxygen at 70−110 °C in the presence of carbon monoxide.[31] In aqueous medium, formic acid was the observed oxidation product from methane while acetic acid, together with some formic acid, was formed from ethane.[31a] *No* alkane

Scheme 5[a]

$$Pt^+ \cdots X,\ \overset{|}{C}HCH_2CH_2- \quad \xrightarrow{H_2O} \quad (H)X\text{-}CH(OH)CH_2CH_2-$$

$$(H)X \cdots Pt^{2+},\ CH_2CH_2CH_2-$$

$$\xrightarrow{-H^+}$$

$$Pt^+ \cdots X,\ CH_2,\ \overset{|}{C}HCH_2- \quad \xrightarrow{H_2O} \quad (H)X\text{-}CH_2CH(OH)CH_2-$$

$$Pt^+ \cdots X,\ CH_2,\ CH_2,\ H\overset{|}{C} \quad \xrightarrow{H_2O} \quad (H)X\text{-}CH_2CH_2CH(OH)-$$

[a] X = ligating atom; note that in acids there is an extra atom between X and the C—H bond being attacked.

Scheme 6[a]

$$CO \xrightarrow{[Pd]} CO_2 \qquad S \xrightarrow{[Pd]} S_{OX}$$
$$H_2O \qquad H_2 \qquad H_2O_2$$
$$O_2 \quad [Pd]$$
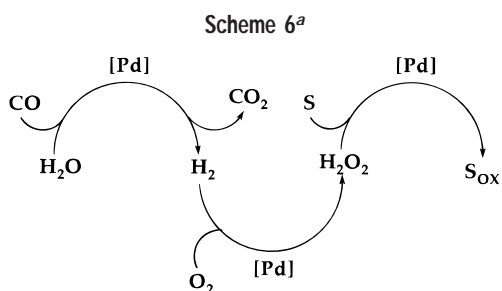
[a] S = substrate; S_{OX} = oxidized substrate.

oxidation was observed in the absence of added carbon monoxide. The essential role of carbon monoxide in achieving "difficult" alkane oxidation was shown by a competition experiment between ethane and ethanol, in both the presence and absence of carbon monoxide.[32a] In the absence of added carbon monoxide, only ethanol was oxidized. When carbon monoxide was added, almost half of the products were derived from ethane. Thus, the more inert ethane was oxidized *only* in the presence of added carbon monoxide.

Studies indicated that the overall transformation encompasses three catalytic steps in tandem (Scheme 6).[31a] The first is the water gas shift reaction involving the oxidation of carbon monoxide to carbon dioxide with the simultaneous formation of dihydrogen. It is possible to bypass this step by replacing carbon monoxide with dihydrogen. The second catalytic step involves the combination of dihydrogen with dioxygen to yield hydrogen peroxide[33] (or its equivalent). The final step involves metal-catalyzed oxidation of the substrate by hydrogen peroxide (or its equivalent).

Since the above catalytic system is able to effect the oxidation of molecules as unreactive as methane under unusually mild conditions, the deep oxidation of a number of hazardous organics was also examined.[32] These included benzene, phenol and substituted phenols, aliphatic and aromatic halogenated compounds, organophosphorus, and organosulfur compounds. In each case, deep oxidation to carbon monoxide, carbon dioxide, and water occurred in high yields, resulting in up to several hundred turnovers over a 24 h period.[32]

Returning to the partial oxidation of alkanes in aqueous medium, while acetic acid was formed in good yield from ethane, the analogous formation of formic acid from methane proceeded only in low yield because of the general instability of the latter acid under the reaction conditions. Since formic acid is a much less desirable product from methane than is methanol, we examined the possibility of halting the oxidation of methane at the methanol stage.

Simply changing the solvent in the Pd-based catalytic system from water to a mixture of water and a perfluorocarboxylic acid (some water was necessary for the reaction; see Scheme 6) had no significant effect on product composition: formic acid was still the principal product from methane. However, the addition of copper-(I) or -(II) chloride to the reaction mixture had a dramatic effect. Methanol and its ester now became the preferred products, with virtually no acetic and little formic acid being formed![31b] The activation parameters for the overall reaction determined under the condition when the rate was first-order in both methane and carbon monoxide were $A = 2 \times 10^4\ s^{-1}$ and $E_a = 15.3$ kcal mol^{-1}. Since methyl trifluoroacetate is both volatile and easily hydrolyzed back to the acid and methanol, it should be possible to design a system where the acid is recycled and methanol is the end product.

In the second (slower) system, RhCl$_3$, in the presence of several equivalents of Cl$^-$ and I$^-$ ions, was found to catalyze the direct functionalization of methane in the presence of carbon monoxide and dioxygen at 80–85 °C.[34] The reaction proceeded in water to give acetic acid as the principal product.[34a] However, a much higher rate was observed in a 6:1 (v/v) mixture of perfluorobutyric acid and water, with the products being methanol and acetic acid.[34b] As shown in Figures 1 and 2, it is possible to selectively form *either* methanol *or* acetic acid by a simple change in the solvent system. The ratio of alcohol derivative to the corresponding higher acid may be assumed to be a function of the relative rates of nucleophilic attack versus carbon monoxide insertion into a common Rh–alkyl bond (i.e., k_{Nu}/k_{CO}; see Scheme 7). While, to a first-order approximation, k_{CO} was likely to be
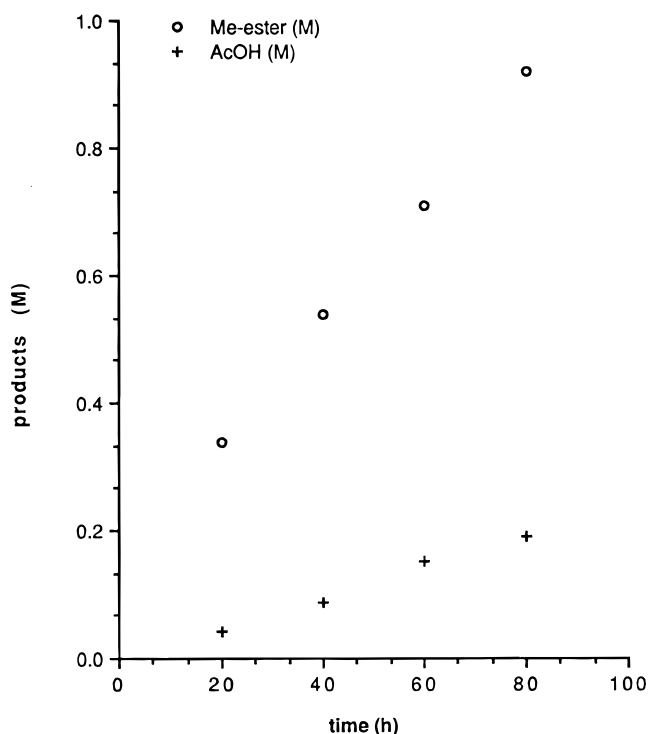
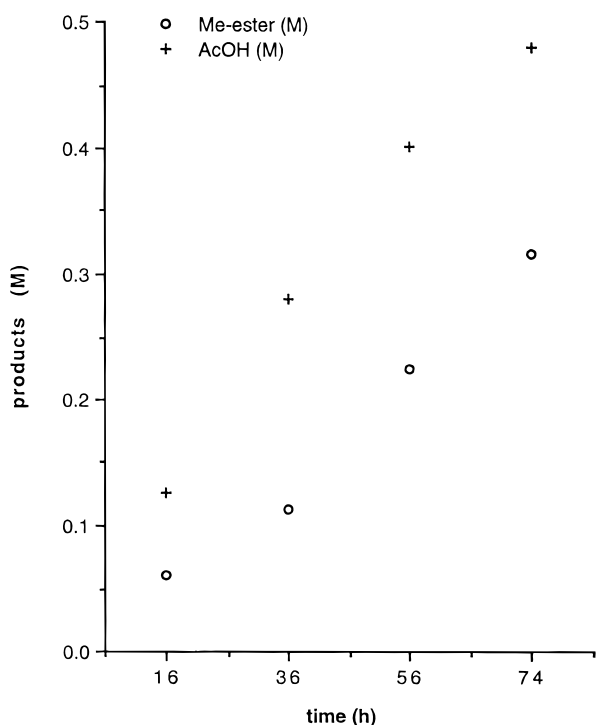**FIGURE 1.** Plots of products formed from methane versus time. Reaction conditions: $RhCl_3 \cdot 3H_2O$ (5 mg, 0.005 M), KI (10 mg, 0.017 M), and NaCl (15 mg, 0.073 M) in 3.5 mL of a 6:1 (v/v) mixture of $C_3F_7CO_2H$ and D_2O; CH_4 (1000 psi), CO (300 psi), and O_2 (100 psi), 80 °C.

FIGURE 2. Plots of products formed from methane versus time. Reaction conditions: $RhCl_3 \cdot 3H_2O$ (5 mg, 0.005 M), KI (10 mg, 0.017 M), and NaCl (15 mg, 0.073 M) in 3.5 mL of a 5:1:1 (v/v) mixture of $C_3F_7CO_2H$, $(CF_3)_2CHOH$, and D_2O; CH_4 (1000 psi), CO (200 psi), and O_2 (75 psi), 80 °C.

independent of the solvent, k_{Nu} would depend on the nature of the nucleophile derived from the solvent.

Scheme 7[a]

[a] Nu = OH, $C_3F_7CO_2$.
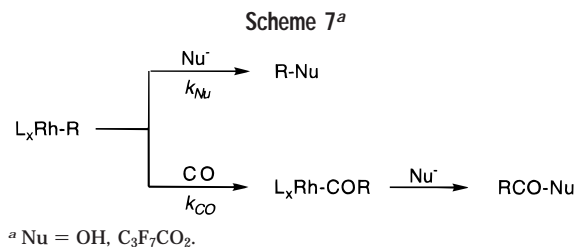
Presumably, the perfluorobutyrate ion is a better nucleophile than water since more of the alcohol derivative was formed in a perfluorobutyric acid−water mixture than in pure water. This also explains why acetic acid was once again the major product when the perfluorobutyrate ion was tied up as the ester (Figure 2). Consistent with the mechanistic scenario shown in Scheme 7 was also the observation that the ratio of acetic acid to methanol derivative formed from methane increased with increasing pressure of CO, although the overall reaction was sharply inhibited at high CO pressures.

The Pd/Cu and the Rh-based systems show similar selectivity patterns that are, for the most part, without precedent. For example, in both cases, methane was *significantly more reactive* (at least 5 times) than methanol.[31b,34] However, this does not take into account the increase in the C−H bond energy when methanol is converted to the ester (the following C−H bond energy data illustrate the point: H−CH$_2$OH, 94 kcal/mol; H−CH$_2$-OCOC$_6$H$_5$, 100.2 kcal/mol). For the Rh-based system, even methyl iodide was found to be less reactive than methane![34b]

A more interesting reactivity pattern exhibited by these two systems is their preference for C−C cleavage over C−H cleavage for higher alkanes.[31b,34b] Indeed, we are unaware of any other catalytic system that effects the oxidative cleavage of alkane C−C bonds under such mild conditions. For example, the Rh-based system converted ethane to a mixture of methanol, ethanol, and acetic acid (Figure 3), with the ratio of products formed through C−H versus C−C cleavage approximately 0.6 on a per-bond basis.[34b] As with methanol, control experiments indicated ethane was more reactive than ethanol. Additionally, neither ethanol nor acetic acid was the precursor to methanol. Finally, even part of the acetic acid was formed by initial C−C cleavage of ethane followed by carbonylation of the resultant C$_1$ fragment. For C$_4$ and higher alkanes, C−C cleavage products were *virtually all* that were observed; especially noteworthy was the formation of ethanol from *n*-butane, which indicates that vicinal diols were not the precursors to the C−C cleavage products.[31b,34b] The above reactivity profile exhibited by the two systems, together with other observations, appears to be inconsistent with the intermediacy of *free* alkyl radicals in the oxidation process.

A curious aspect of the Pd/Cu and Rh-based systems is that, apart from their ability to simultaneously activate both dioxygen and alkane, both require a coreductant (carbon monoxide).[31,34] Thus, there is a striking resemblance with monooxygenases.[35] In nature, while the dioxygenases utilize the dioxygen molecule more ef-
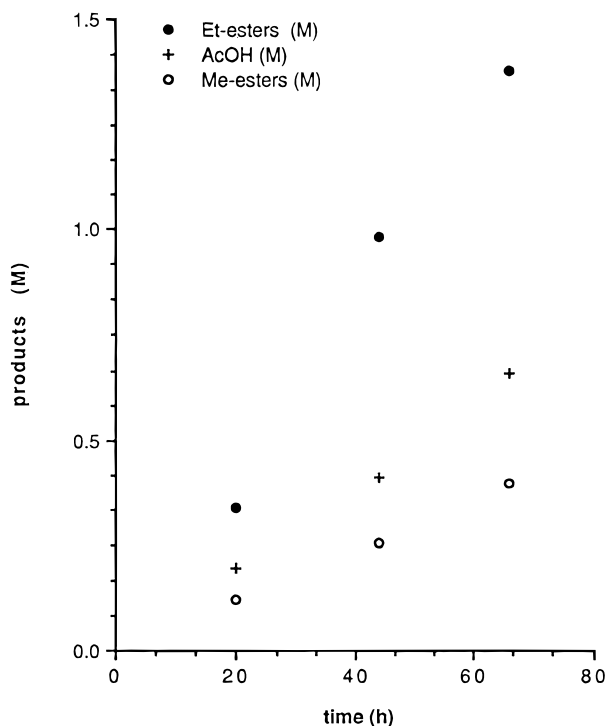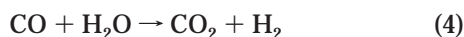
FIGURE 3. Plots of products formed from ethane versus time. Reaction conditions: $RhCl_3 \cdot 3H_2O$ (5 mg, 0.005 M), KI (10 mg, 0.017 M), and NaCl (15 mg, 0.073 M) in 3.5 mL of a 6:1 (v/v) mixture of $C_3F_7CO_2H$ and D_2O; C_2H_6 (550 psi), CO (150 psi), and O_2 (50 psi), 80 °C.

ficiently, it is the monooxygenases that carry out "difficult" oxidations, such as alkane oxidations. In the latter, one of the two oxygen atoms of dioxygen is reduced to water in a highly thermodynamically favorable reaction and the free energy gained thereby is employed to generate a high-energy oxygen species, such as a metal−oxo complex, from the second oxygen atom (eq 3). Several other systems, including the "Gif" system, are also designed on this premise.[36] In at least the metallic Pd-based system,[31] the coreductant, carbon monoxide, was employed to generate dihydrogen (eq 4), the latter being formally equivalent to $2H^+ + 2e^-$ that is employed in the biological systems (cf. eqs 3 and 5).

$$O_2 + 2H^+ + 2e^- \rightarrow H_2O + [O] \qquad (3)$$

$$CO + H_2O \rightarrow CO_2 + H_2 \qquad (4)$$

$$O_2 + H_2 \rightarrow H_2O + [O] \qquad (5)$$

How general is this requirement for a coreductant (e.g., CO or H_2) in achieving "difficult" catalytic hydrocarbon oxidations by dioxygen? Our own work has provided two examples of catalytic systems that operate in this manner (i.e., as monooxygenase analogues).[31,34] There have been other recent publications on catalytic systems for the oxidation of hydrocarbons, including olefins and aromatics, that also call for either CO or H_2 as the coreductant.[36b,37] While, from a practical standpoint, it is more desirable for both oxygen atoms of O_2 to be used for substrate oxidation, there appears to be no currently

known catalytic system that operates as an artificial "dioxygenase" under mild conditions toward "difficult" substrates, such as those possessing unactivated primary C−H bonds.

References

(1) (a) Axelrod, M. G.; Gaffney, A. M.; Pitchai, R.; Sofranko, J. A. In *Natural Gas Conversion II*; Curry-Hyde, H. E., Howe, R. F., Eds.; Elsevier: Amsterdam, 1994; pp 93−101. (b) Masters, C. D.; Root, D. H.; Attanasi, E. D. *Science* **1991**, *253*, 146−52. (c) Starr, C.; Searl, M. F.; Alpert, S. *Science* **1992**, *256*, 981−87.

(2) Recent reviews: (a) Sen, A. In *Applied Homogeneous Catalysis with Organometallic Compounds*; Herrmann, W. A., Cornils, B., Eds.; VCH: Weinheim, Germany, 1996; Vol. 2, pp 1081−92. (b) Crabtree, R. H. *Chem. Rev.* **1995**, *95*, 987−1007. (c) Arndtsen, B. A.; Bergman, R. G.; Mobley, T. A.; Peterson, T. H. *Acc. Chem. Res.* **1995**, *28*, 154−62. (d) Labinger, J. A. *Fuel Process. Technol.* **1995**, *42*, 325−38. (e) Fierro, J. L. G. *Catalysis Lett.* **1993**, *22*, 67−91. (f) Srivastava, R. D.; Zhou, P.; Stiegel, G. J.; Rao, V. U. S.; Cinquegrane, G. *Catalysis (London)* **1992**, *9*, 183−228. (g) Olah, G. A.; Molnár, A. *Hydrocarbon Chemistry*; Wiley: New York, 1995.

(3) Collins, D. E.; Richey, F. A. In *Riegel's Handbook of Industrial Chemistry*; Kent, J. A., Ed.; Van Nostrand-Reinhold: New York, 1992; pp 800−62.

(4) Reviews: (a) Parshall, G. W.; Ittel, S. D. *Homogeneous Catalysis*; Wiley: New York, 1992; pp 237−68. (b) Howard, J. A. In *Free Radicals*; Kochi, J. K., Ed.; Wiley: New York, 1973; Vol. II, pp 3−62.

(5) Reviews: (a) Drago, R. S. *Coord. Chem. Rev.* **1992**, *117*, 185−213. (b) Simándi, L. I. *Catalytic Activation of Dioxygen by Metal Complexes*; Kluwer Academic: Dordrecht, The Netherlands, 1992; pp 74−108.

(6) (a) Bryndza, H. E.; Fong, L. K.; Paciello, R. A.; Tam, W.; Bercaw, J. E. *J. Am. Chem. Soc.* **1987**, *109*, 1444−56. (b) Bergman, R. G. *Science* **1984**, *223*, 902−8.

(7) Recent representative publications: (a) Perthuisot, C.; Edelbach, B. L.; Zubris, D. L.; Jones, W. D. *Organometallics* **1997**, *16*, 2016−23. (b) Yang, X.; Stern, C. L.; Marks, T. J. *J. Am. Chem. Soc.* **1994**, *116*, 10015−31. (c) Gozin, M.; Weisman, A.; Ben-David, Y.; Milstein, D. *Nature* **1993**, *364*, 699−701. (d) Rondon, D.; Chaudret, B.; He, X.-D.; Labroue, D. *J. Am. Chem. Soc.* **1991**, *113*, 5671−76. (e) Hartwig, J. F.; Andersen, R. A.; Bergman, R. G. *J. Am. Chem. Soc.* **1989**, *111*, 2717−19. (f) Bunel, E.; Burger, B. J.; Bercaw, J. E. *J. Am. Chem. Soc.* **1988**, *110*, 976−78. (g) Crabtree, R. H.; Dion, R. P.; Gibboni, D. J.; McGrath, D. V.; Holt, E. M. *J. Am. Chem. Soc.* **1986**, *108*, 7222−27. (h) Suggs, J. W.; Jun, C.-H. *J. Am. Chem. Soc.* **1986**, *108*, 4679−81. (i) Watson, P. L.; Roe, D. C. *J. Am. Chem. Soc.* **1982**, *104*, 6471−73. (j) Dufaud, V.; Basset, J.-M. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 806−10.

(8) (a) Halpern, J. *Inorg. Chim. Acta* **1985**, *100*, 41−48. (b) Halpern, J. *Acc. Chem. Res.* **1982**, *15*, 238−44.

(9) Reviews: (a) Armentrout, P. B. In *Selective Hydrocarbon Oxidation and Functionalization*; Davies, J. A., Watson, P. L., Greenberg, A., Liebman, J. F., Eds.; VCH: New York, 1990; pp 467–533. (b) Armentrout, P. B.; Beauchamp, J. L. *Acc. Chem. Res.* **1989**, *22*, 315–21. (c) Eller, K.; Schwarz, H. *Chem. Rev.* **1991**, *91*, 1121–77. (d) Schwarz, H. *Acc. Chem. Res.* **1989**, *22*, 282–87.

(10) Simoes, J. A. M.; Beauchamp, J. L. *Chem. Rev.* **1990**, *90*, 629–88.

(11) Reviews: (a) Sen, A. *Platinum Metals Rev.* **1991**, *35*, 126–32. (b) Shilov, A. E. *Activation of Saturated Hydrocarbons by Transition Metal Complexes*; Reidel: Dordrecht, The Netherlands, 1984; Chapt. V.

(12) Reviews: (a) Rothwell, I. P. In *Selective Hydrocarbon Oxidation and Functionalization*; Davies, J. A., Watson, P. L., Greenberg, A., Liebman, J. F., Eds.; VCH: New York, 1990; pp 43–78. (b) Watson, P. L. In *Selective Hydrocarbon Oxidation and Functionalization*; Davies, J. A., Watson, P. L., Greenberg, A., Liebman, J. F., Eds.; VCH: New York, 1990; pp 79–112. (c) Jordan, R. F. *Adv. Organomet. Chem.* **1991**, *32*, 325–87. Specific recent examples: (d) Holtcamp, M. W.; Labinger, J. A.; Bercaw, J. E. *J. Am. Chem. Soc.* **1997**, *119*, 848–49. (e) Schaller, C. P.; Cummins, C. C.; Wolczanski, P. T. *J. Am. Chem. Soc.* **1996**, *118*, 591–611. (f) Arndtsen, B. A.; Bergman, R. G. *Science* **1995**, *270*, 1970–72.

(13) Periana, R. A.; Taube, D. J.; Evitt, E. R.; Löffler, D. G.; Wentrcek, P. R.; Voss, G.; Masuda, T. *Science* **1993**, *259*, 340–343. Also see: Snyder, J. C.; Grosse, A. V. U.S. Patent 2,493,038, 1950.

(14) Sen, A.; Benvenuto, M. A.; Lin, M.; Hutson, A. C.; Basickes, N. *J. Am. Chem. Soc.* **1994**, *116*, 998–1003.

(15) Lin, M.; Sen, A. *J. Chem. Soc., Chem. Commun.* **1992**, 892–93.

(16) (a) Valentine, A. M.; Wilkinson, B.; Liu, K. E.; Komar-Panicucci, S.; Priestley, N. D.; Williams, P. G.; Morimoto, H.; Floss, H. G.; Lippard, S. J. *J. Am. Chem. Soc.* **1997**, *119*, 1818–27. (b) Newcomb, M.; Le Tadic-Biadatti, M.-H.; Chestney, D. L.; Roberts, E. S.; Hollenberg, P. F. *J. Am. Chem. Soc.* **1995**, *117*, 12085–91.

(17) Olah, G. A.; Lin, H. C. *J. Am. Chem. Soc.* **1971**, *93*, 1259–61.

(18) Review: Fabre, P.-L.; Devynck, J.; Trémillon, B. *Chem. Rev.* **1982**, *82*, 591–614.

(19) Basickes, N.; Hogan, T. E.; Sen, A. *J. Am. Chem. Soc.* **1996**, *118*, 13111–12.

(20) (a) Taniguchi, Y.; Yamaoka, Y.; Nakata, K.; Takaki, K.; Fujiwara, Y. *Chem. Lett.* **1995**, 345–46. (b) Nakata, K.; Yamaoka, Y.; Miyata, T.; Taniguchi, Y.; Takaki, K.; Fujiwara, Y. *J. Organomet. Chem.* **1994**, *473*, 329–34. (c) Nakata, K.; Miyata, T.; Jintoku, T.; Kitani, A.; Taniguchi, Y.; Takaki, K.; Fujiwara, Y. *Bull. Chem. Soc. Jpn.* **1993**, *66*, 3755–59.

(21) (a) Yamanaka, I.; Soma, M.; Otsuka, K. *Chem. Lett.* **1996**, 565–66. (b) Nomura, K.; Uemura, S. *J. Chem. Soc., Chem. Commun.* **1994**, 129–130. (c) Vargaftik, M. N.; Stolarov, I. P.; Moiseev, I. I *J. Chem. Soc., Chem. Commun.* **1990**, 1049–50.

(22) (a) Reference 11a. (b) Kao, L.-C.; Hutson, A. C.; Sen, A. *J. Am. Chem. Soc.* **1991**, *113*, 700–1.

(23) Hogan, T.; Sen, A. *J. Am. Chem. Soc.* **1997**, *119*, 2642–46.

(24) Motherwell, W. B.; Crich, D. *Free Radical Chain Reactions in Organic Synthesis*; Academic Press: London, 1992; pp 4–7.

(25) Review: Hall, C.; Perutz, R. N. *Chem. Rev.* **1996**, *96*, 3125–46.

(26) Reviews: (a) Liu, K. E.; Lippard, S. J. *Adv. Inorg. Chem.* **1995**, *42*, 263–89. (b) Feig, A. L.; Lippard, S. J. *Chem. Rev.* **1994**, *94*, 759–805. (c) Que, L. In *Bioinorganic Catalysis*; Reedijk, J., Ed.; Marcel Dekker: New York, 1993; pp 347–93.

(27) (a) Sen, A.; Lin, M.; Kao, L.-C.; Hutson, A. C. *J. Am. Chem. Soc.* **1992**, *114*, 6385–92. (b) Reference 14. (c) Kao, L.-C.; Sen, A. *J. Chem. Soc., Chem. Commun.* **1991**, 1242–43. (d) Basickes, N.; Sen, A. *Polyhedron* **1995**, *14*, 197–202. (e) Hutson, A. C.; Lin, M.; Basickes, N.; Sen, A. *J. Organomet. Chem.* **1995**, *504*, 69–74.

(28) (a) Labinger, J. A.; Herring, A. M.; Lyon, D. K.; Luinstra, G. A.; Bercaw, J. E.; Horváth, I. T.; Eller, K. *Organometallics* **1993**, *12*, 895–905. (b) Luinstra, G. A.; Labinger, J. A.; Bercaw, J. E. *J. Am. Chem. Soc.* **1993**, *115*, 3004–5. (c) Luinstra, G. A.; Wang, L.; Stahl, S. S.; Labinger, J. A.; Bercaw, J. E. *Organometallics* **1994**, *13*, 755–56. (d) Luinstra, G. A.; Wang, L.; Stahl, S. S.; Labinger, J. A.; Bercaw, J. E. *J. Organomet. Chem.* **1995**, *504*, 75–91.

(29) (a) Wick, D. D.; Goldberg, K. I. *J. Am. Chem. Soc.* **1997**, *119*, 10235–36. (b) Stahl, S. S.; Labinger, J. A.; Bercaw, J. E. *J. Am. Chem. Soc.* **1996**, *118*, 5961–76. (c) Zamashchikov, V. V.; Popov, V. G.; Rudakov, E. S. *Kinet. Katal.* **1994**, *35*, 436–42. (d) Theoretical study: Siegbahn, P. E. M.; Crabtree, R. H. *J. Am. Chem. Soc.* **1996**, *118*, 4442–50.

(30) (a) Freund, M. S.; Labinger, J. A.; Lewis, N. S.; Bercaw, J. E. *J. Mol. Catal.* **1994**, *87*, L11–15. (b) Geletii, Yu. V.; Shilov, A. E. *Kinet. Katal.* **1983**, *24*, 486–89.

(31) (a) Lin, M.; Sen, A. *J. Am. Chem. Soc.* **1992**, *114*, 7307–8. (b) Lin, M.; Hogan, T. E.; Sen, A. *J. Am. Chem. Soc.* **1997**, *119*, 6048–53.

(32) (a) Hogan, T.; Simpson, R.; Lin, M.; Sen, A. *Catal. Lett.* **1996**, *40*, 95–99. (b) Hogan, T.; Simpson, R.; Lin, M.; Sen, A. *Catal. Lett.* **1997**, *49*, 59–63.

(33) Gosser, L. W. U.S. Patent 4,681,751, 1987.

(34) (a) Lin, M.; Sen, A. *Nature* **1994**, *368*, 613–15. (b) Lin, M.; Hogan, T. E.; Sen, A. *J. Am. Chem. Soc.* **1996**, *118*, 4574–80. (c) Also see: Chepaikin, E. G.; Boyko, G. N.; Bezruchenko, A. P.; Lescheva, A. A.; Grigoryan, E. H. *J. Mol. Catal. A* **1998**, *129*, 15–18.

(35) Recent reviews on monooxygenases and their synthetic analogues: (a) *Metalloporphyrins in Catalytic Oxidations*; Sheldon, R. A., Ed.; Marcel Dekker: New York, 1994. (b) *Metalloporphyrins Catalyzed Oxidations*; Montanari, F., Casella, L., Eds.; Kluwer: Dordrecht, The Netherlands, 1994. (c) Reference 26.

(36) (a) Barton, D. H. R.; Doller, D. *Acc. Chem. Res.* **1992**, *25*, 504–12. (b) Tabushi, I. *Coord. Chem. Rev.* **1988**, *86*, 1–42.

(37) Representative examples: (a) Otake, M. *Chemtech* **1995**, 36–41. (b) Miyake, T.; Hamada, M.; Sasaki, Y.; Oguri, M. *Appl. Catal. A: General* **1995**, *131*, 33–42. (c) Teranishi, T.; Toshima, N. *J. Chem. Soc., Dalton Trans.* **1995**, 979–85. (d) Wang, Y.; Otsuka, K. *J. Catal.* **1995**, *155*, 256–67.