ACCOUNTS of chemical research

Article

pubs.acs.org/accounts

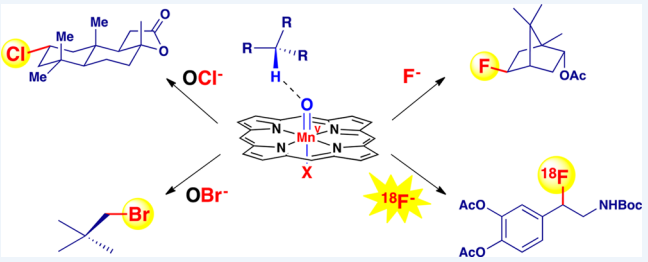
Manganese Catalyzed C−H Halogenation

Published as part of the Accounts of Chemical Research special issue "Earth Abundant Metals in Homogeneous Catalysis".

Wei Liu and John T. Groves*

Department of Chemistry, Princeton University, Princeton, New Jersey 08544, United States

CONSPECTUS: The remarkable aliphatic C−H hydroxylations catalyzed by the heme-containing enzyme, cytochrome P450, have attracted sustained attention for more than four decades. The effectiveness of P450 enzymes as highly selective biocatalysts for a wide range of oxygenation reactions of complex substrates has driven chemists to develop synthetic metalloporphyrin model compounds that mimic P450 reactivity. Among various known metalloporphyrins, manganese derivatives have received considerable attention since they have been shown to be versatile and powerful mediators for alkane hydroxylation and olefin epoxidation. Mechanistic studies have shown that the key intermediates of the manganese porphyrin-catalyzed oxygenation reactions include oxo- and dioxomanganese(V) species that transfer an oxygen atom to the substrate through a hydrogen abstraction/oxygen recombination pathway known as the oxygen rebound mechanism. Application of manganese porphyrins has been largely restricted to catalysis of oxygenation reactions until recently, however, due to ultrafast oxygen transfer rates.



In this Account, we discuss recently developed carbon−halogen bond formation, including *fluorination* reactions catalyzed by manganese porphyrins and related salen species. We found that biphasic sodium hypochlorite/manganese porphyrin systems can efficiently and selectively convert even unactivated aliphatic C−H bonds to C−Cl bonds. An understanding of this novel reactivity derived from results obtained for the oxidation of the mechanistically diagnostic substrate and radical clock, norcarane. Significantly, the oxygen rebound rate in Mn-mediated hydroxylation is highly correlated with the nature of the *trans*-axial ligands bound to the manganese center ($L-Mn^{V}=O$). Based on the ability of fluoride ion to decelerate the oxygen rebound step, we envisaged that a relatively long-lived substrate radical could be trapped by a Mn−F fluorine source, effecting carbon−fluorine bond formation. Indeed, this idea led to the discovery of the first Mn-catalyzed direct aliphatic C−H fluorination reactions utilizing simple, nucleophilic fluoride salts. Mechanistic studies and DFT calculations have revealed a *trans*-difluoromanganese(IV) species as the key fluorine transfer intermediate. In addition to catalyzing normal ^{19}F-fluorination reactions, manganese salen complexes were found to enable the incorporation of radioactive ^{18}F fluorine via C−H activation. This advance represented the first direct C_{sp^3}−H bond ^{18}F labeling with no-carrier-added [^{18}F]fluoride and facilitated the late-stage labeling of drug molecules for PET imaging. Given the high reactivity and enzymatic-like selectively of metalloporphyrins, we envision that this new Heteroatom-Rebound Catalysis (HRC) strategy will find widespread application in the C−H functionalization arena and serve as an effective tool for forming new carbon−heteroatom bonds at otherwise inaccessible sites in target molecules.

1. INTRODUCTION

The remarkable and varied oxygenation reactions catalyzed by the heme-thiolate monooxygenase cytochrome P450, particularly C−H hydroxylation, have intrigued chemists for more than four decades due to the centrality of these transformations to steroid biosynthesis and drug metabolism.[1,2] More recently, chloroperoxidase, nitric oxide synthase and the fungal hydroxylase APO have been shown to follow similar reaction pathways.[3−7] The active site of P450 contains an iron(III) protoporphyrin IX with an unusual cysteine thiolate as the axial ligand. The ferric protoporphyrin IX center is oxidized by dioxygen during turnover through multiple electron/proton transfer steps, forming a highly reactive oxoiron(IV) porphyrin cation radical intermediate, also known as compound I.[8] This reactive compound I species then transfers its oxygen atom to an organic substrate through a C−H abstraction and OH recombination scenario, affording an alcohol product in what has come to be called the oxygen rebound mechanism (Figure 1).[9,10]

Inspired by the reactivity of these P450 hydroxylases, the high utility of these transformations and the mysteries surrounding the nature of reactive intermediates and the chemical mechanisms, our group and numerous others have explored synthetic, model metalloporphyrins that have successfully mimicked many aspects of this remarkable reactivity.[11−13] The keys to understanding the mechanisms involved were early advances in chemical approaches to high-

Received: February 3, 2015
Published: June 4, 2015

DOI: 10.1021/acs.accounts.5b00062
Acc. Chem. Res. 2015, 48, 1727−1735

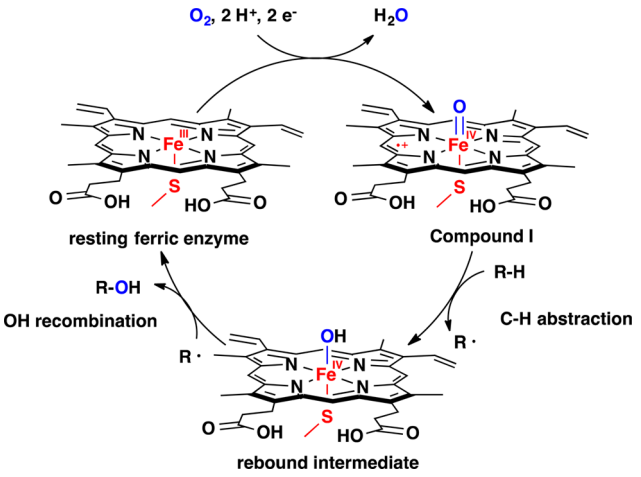


Figure 1. Oxygen rebound mechanism in P450-catalyzed C−H hydroxylation.

valent metalloporphyrin species.[14−16] Long ago, we reported the first example of iron porphyrin catalyzed hydroxylation of saturated C−H bonds using [Fe^{III}(TPP)Cl] as a catalyst in conjunction with iodosylbenzene as the terminal oxidant.[17] Our thinking at the time regarding the choice of that reagent was to find an oxidant of sufficiently high oxidation potential that might not support rapid, free radical chain reactions typical of peroxides. The insolubility of the iodosylbenzene polymer in organic media was a serendipitous side benefit that protected the metalloporphyrin catalyst from overoxidation. Two key advances at that time were the characterization of an oxo-iron(IV)porphyrin complex derived from the aerobic oxidation of an iron(II) precursor reported by Balch et al.[18] and our report of the characterization of a synthetic compound I, oxo-iron(IV)tetramesitylporphyrin cation radical.[19,20] These compounds were the first in the burgeoning bioinorganic model compound field to be characterized by proton NMR, EXAFS, and Mössbauer spectroscopies.[21−25] Since then, metalloporphyrin-catalyzed hydroxylations dominated the area of aliphatic C−H functionalization with a number of other significant advances.[11,13,19]

Among the variety of known metalloporphyrin complexes, manganese derivatives are of particular interest due to their high reactivity toward functionalization of both unsaturated and saturated hydrocarbons as well as more complex molecules. We found that catalytic amounts of a manganese porphyrin, Mn(TPP)Cl, in the presence of iodosylbenzene mediated the efficient oxygenation of cyclohexane to afford cyclohexanol as the major product.[26] Mechanistic studies suggested an oxomanganese(V) species as the key reactive intermediates, which were later characterized by UV−vis,[27] ^{1}H NMR,[28] IR, and Raman spectroscopy.[29] Mechanistic studies showed that the reactive oxomanganese(V) species could abstract a hydrogen atom readily from a substrate C−H bond, forming a substrate-derived radical and an hydroxomanganese(IV) intermediate.[14] The incipient carbon radical then recombines with the HO-Mn^{IV}(por) intermediate, affording the alcohol product. Oxygenation of the mechanistically diagnostic substrate, norcarane, signaled the formation of a carbon-centered radical rather than a carbocation and indicated that the radical recombination step was very fast, up to 10^{10} s^{-1}.[26]

Due to the fast radical recombination rate for [R·HO−Mn^{IV}(por)], it was reasonable to believe that any transformations that involved O═Mn^{V}(por) intermediates would necessarily lead to the formation of oxygenated products.

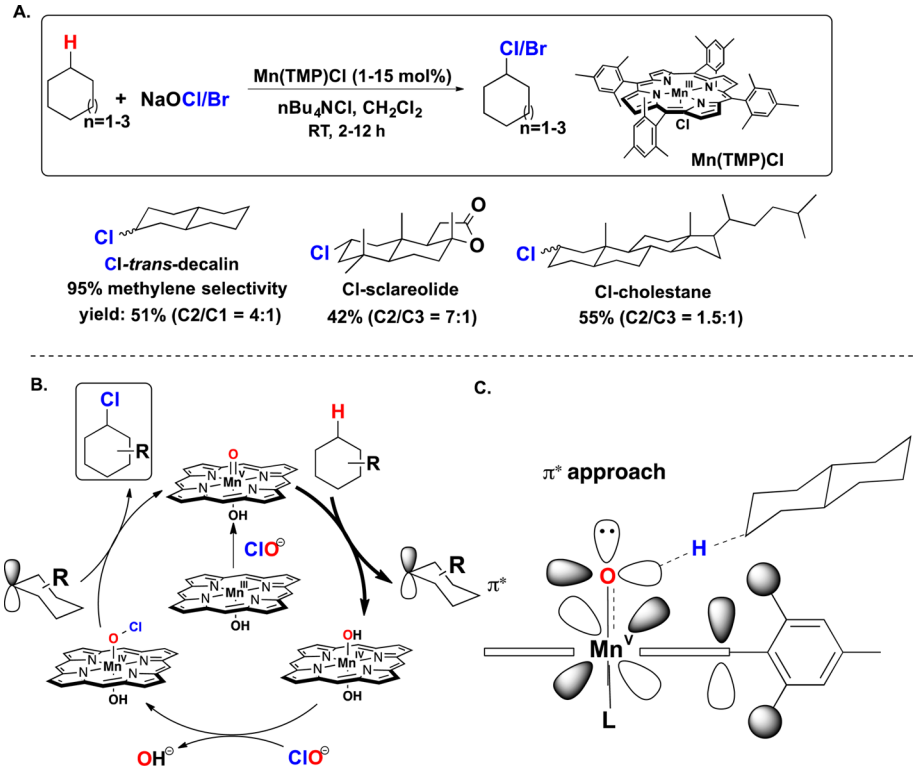


Figure 2. Manganese porphyrin catalyzed aliphatic C−H chlorination. (A) Regioselective chlorination and bromination of complex molecules. (B) Proposed catalytic cycle for the Mn-chlorination system. (C) Inferred stereoelectronics for C−H abstraction step.

DOI: 10.1021/acs.accounts.5b00062
Acc. Chem. Res. 2015, 48, 1727−1735

Indeed, there have been only rare reports of the incorporation of other functional groups (Cl, Br, I, N_3) into C−H bonds using stoichiometric amounts of manganese porphyrins.[26,30] In particular, the ability of manganese porphyrins to halogenate C−H bonds had been overlooked for many years. Very recently, we found that in addition to catalyzing oxygenation reactions, manganese porphyrins and related salen complexes are also capable of catalyzing carbon−halogen bond formation in preparatively significant yields. In this Account, we review our recent progress in transforming the manganese porphyrins from catalysts of oxygenation reactions to synthetic halogenases for carbon halogen bond formation. Most notably, C−H *fluorination* protocols were discovered that employed manganese fluoride catalysts, and with that, new strategies for late-stage drug diversification and for ^{18}F labeling.

2. Mn PORPHYRIN CATALYZED C−H CHLORINATION REACTIONS

The C−H halogenation story began in 2010, when we found that manganese porphyrins are also effective catalysts for the selective chlorination of aliphatic C−H bonds.[31] System optimization led to a biphasic system with Mn(TPP)Cl as the catalyst with tetrabutylammonium chloride as a phase transfer catalyst and aqueous sodium hypochlorite as chlorination reagent. Under these conditions a variety of organic molecules, including simple hydrocarbons and complex bioactive molecules, could be converted to their monochlorinated analogues with remarkable efficiency. Notably, only trace amounts of oxygenated products were detected in the reaction mixture. The C−H halogenation procedure differs only in this two-phase solvent system aspect from methods using bleach and manganese porphyrins to mediate C−H hydroxylation.[32] We now know that oxomanganese(V) porphyrins are capable of oxygenating even chloride ions,[33,34] and that there has been an unrecognized, rapid, reversible oxygen atom transfer equilibrium under typical reaction conditions (eq 1):

$$X{-}Mn^{V}{=}O + Cl^{-} \leftrightarrows X{-}Mn^{III}{-}OCl \quad (1)$$

Substrates containing even very strong C−H bonds, such as neopentane (BDE = ∼100 kcal/mol), could be chlorinated with this manganese−hypochlorite catalytic system. Significantly, substrate selectivity was shown to derive from the nature of the manganese catalyst, ruling out freely diffusing chlorine species as the active oxidant. This aliphatic C−H chlorination was readily expanded to C−H bromination by using sodium hypobromite as the halogen source. The recent emergence of very versatile cross-coupling procedures involving alkyl halides makes this C−H bromination pathway an attractive course to place substituents at otherwise inaccessible portions of target compounds.

Regioselective chlorination was achieved with a sterically bulky porphyrin, Mn(TMP)Cl, as the catalyst (Figure 2A). Remarkably, chlorination of a model substrate, *trans*-decalin, with Mn(TMP)Cl afforded 95% *secondary* chlorides with a 4:1 C2/C1 selectivity, even in the presence of a weaker methine C−H bond at the ring junction position. Such *methylene selectivity* had never been observed before in traditional radical chlorination reactions, in which common chlorination reagents N-chlorosuccinimide (NCS) or hypochlorous acid are employed. More complex molecules, such as the saturated steroid, 5α-cholestane, and a terpenoid natural product, sclareolide[35,36] were chlorinated selectively at the least sterically hindered and most electron-rich methylene sites.

Intrigued by this novel catalytic halogenation activity of manganese porphyrins, we then examined the mechanism of the C−H chlorination reaction. Substrate-derived alkyl radicals were implicated as the reactive intermediates as evidenced by the formation of a rearranged product in the chlorination of a radical clock probe, norcarane, consistent with the initial report.[26] A large kinetic isotopic effect (KIE = 8.7 ± 0.7) was observed, indicating C−H abstraction as the rate-limiting step. The magnitude of the KIE also rules out other possible C−H abstraction agents, such as ClO· or Cl·, since these radicals are known to display a much smaller KIE. Indeed, the observed KIE in our Mn-hypochlorite system is similar to what we observed for Mn(TPP)Cl/PhIO C−H hydroxylations in which $O{=}Mn^{V}$(por) complexes have been shown to be the reactive species. In addition, monitoring the reaction mixture by UV−vis spectroscopy indicated the involvement of $O{=}Mn^{V}$(por)−OH or $[O{=}Mn^{V}(por){=}O]^{-}$ intermediates as the main hydrogen abstracting species.[29]

Based upon this evidence, we proposed a catalytic cycle for the manganese chlorination system. First, the resting manganese(III) porphyrin is oxidized by the basic sodium hypochlorite, affording a reactive $O{=}Mn^{V}$(por)−OH or $[O{=}Mn^{V}(por){=}O]^{-}$ intermediate. The highly reactive $O{=}Mn^{V}$(por) species is capable of abstracting a hydrogen atom selectively from the substrate, generating a substrate derived alkyl radical and a HO-Mn^{IV}(por) intermediate. The HO−Mn^{IV} intermediate then exchanges the hydroxyl ligand with hypochlorite anion, forming a ClO−Mn^{IV}(por) adduct which then transfers the chlorine to the alkyl radical, affording the final chlorinated product (Figure 2B). The bulk of the manganese catalyst inventory is expected to be this manganese-(IV) hypochlorite species under turnover conditions, similar to the mechanism of C−H chlorinations mediated by alkyl hypochlorites. Our rationale for the unique least-hindered-methylene selectivity derives from expected nonbonded catalyst−substrate interactions resulting from the approach of the scissile C−H bond to the vacant (Mndπ-Opπ)* LUMO frontier orbital of the $O{=}Mn^{V}$ intermediate. This arrangement and a collinear hydrogen abstraction trajectory would enforce a steric confrontation between the approaching substrate and the meso substituents on the porphyrin ring (Figure 2C).

3. EFFECT OF AXIAL LIGANDS ON THE OXYGEN REBOUND STEP

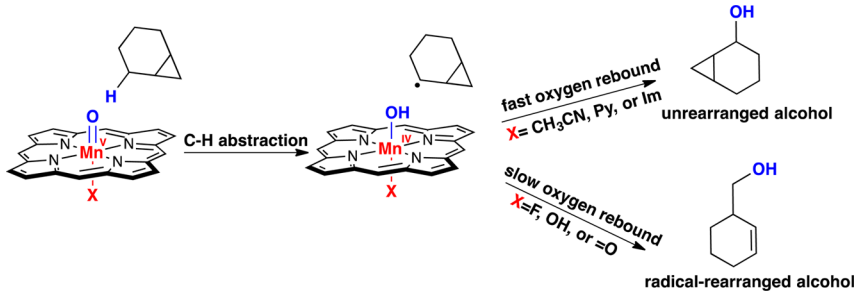
Despite extensive evidence supporting the proposed catalytic cycle, one major concern about this mechanism is why the incipient substrate radicals do not recombine with the HO−Mn^{IV}(por) intermediate after the hydrogen abstraction step. As is typical for manganese porphyrin catalyzed C−H hydroxylation reactions, the short-lived alkyl radical formed upon $O{=}Mn^{V}$(por) mediated hydrogen abstraction, will recombine with a rate constant up to 10^{10} s^{-1} (eq 2):

$$R\cdot + HO{-}Mn^{IV}(por) \rightarrow R{-}OH + Mn^{III}(por) \quad (2)$$

This oxygen rebound mechanism has proved to be ubiquitous in many other metal-oxo mediated oxygen transfer reactions. Clearly, the novel Mn-chlorination reactions discussed above indicate that there is a previously unknown switch that can redirect the substrate radicals from the fast hydroxyl transfer recombination pathway to transfer chlorine or bromine instead. We anticipated that elucidating the nature of this switch could

DOI: 10.1021/acs.accounts.5b00062
Acc. Chem. Res. 2015, 48, 1727−1735

Scheme 1. Effect of Axial Ligands on the Oxygen Rebound Step



dramatically expand the reaction scope of manganese porphyrins.

We noticed that one major difference between this Mn-chlorination reaction and the more usual Mn-hydroxylation reactions is the presence of a hydroxo axial ligand coordinated on the manganese center in the chlorination system due to high basicity of the aqueous sodium hypochlorite solution. Hydroxide coordination to the intermediate manganese(IV) center was signaled by UV−vis detection of a six-coordinate $[O{=}Mn^{IV}(TMP){-}OH]^-$ species (λ_{max} = 425 nm) during turnover conditions. This complex had been well characterized by us much earlier.[37] We reasoned that the species responsible for C−H scission derived from the $[O{=}Mn^{V}(por){-}OH_2]^+ \leftrightarrows O{=}Mn^{V}(por){-}OH \leftrightarrows [O{=}Mn^{V}(por){=}O]^-$ equilibrium, and decomposed to the long-lived manganese(IV) species during typical UV−vis experiment time frames. In the course of further optimization, we serendipitously observed that the addition of strongly ligating imidazole or pyridine to the chlorination system significantly suppressed the chlorinated products and led to the formation of oxygenated products instead. Based on the observation of this significant axial ligand effect, we speculated that the coordination of a hydroxide ligand might increase the energetic barrier of the oxygen rebound step. To test this hypothesis, we studied the effect of different axial ligands on manganese porphyrin catalyzed oxidation and rearrangement of norcarane. In the absence of other additives, oxidation of norcarane under *m*CPBA/Mn(TPP)OAc conditions afforded 1-norcaranol as major product with only trace amounts of radical rearranged product, 1-cyclohexene-3-methanol. Interestingly, the amount of rearranged product significantly increased when either tetrabutylammonium hydroxide or tetrabutylammonium fluoride was added to the reaction mixture. This result clearly indicated that hydroxide and fluoride ligands dramatically decreased the radical recombination rate depicted in Scheme 1. With these strong donor ligands, oxygen rebound was apparently slower than cage escape of the 2-norcaranyl radical and its known rearrangement rate (10^8 s^{-1}).[38,39]

4. C_{sp^3}−F BOND FORMATION VIA DIRECT C−H ACTIVATION

Inspired by the regioselectivity of the Mn-chlorination system as well as the effect of fluoride anion on the radical rebound step, we considered the possibility that the radicals generated via selective hydrogen abstraction might be efficiently trapped by a Mn−F species forming fluorinated products in the presence of appropriate fluoride sources. Indeed, fluorine transfer to alkyl radicals from an electrophilic fluorination reagent, NFSI, had recently been reported by Sammis and co-workers.[40] A direct aliphatic C−H fluorination reaction, if it could be discovered, would be a novel and very powerful C−H fluorination protocol with many possible applications, such as in the late-stage drug and agro-chemical diversification. In addition, since the fluorine source utilized in an Mn−F reaction is nucleophilic fluoride ion, we anticipated that such a C−H fluorination reaction would have the potential for translation to ^{18}F chemistry and PET imaging.

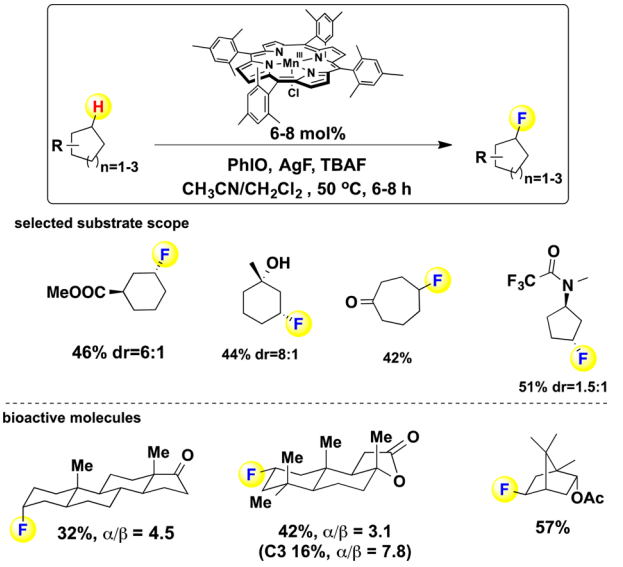
The replacement of hydrogen by fluorine has profound effects on the biological properties of organic molecules due to the strong C−F dipole and the ability to act as a hydrogen bond acceptor. Fluorinated analogues are often more potent due both to stronger target binding and slower oxidative metabolism. As a result, organofluorine molecules are widely used as pharmaceuticals, agrochemicals, material chemistry and imaging agents. Currently, 20% of pharmaceuticals and 30% agrochemicals contain at least one fluorine atom.[41] Due to the importance of fluorine substituents, organic chemists have devised a variety of methods to construct carbon−fluorine bonds over the past decade.[42] Because of the prevalence of fluorinated arenes and heterocycles in drug development, numerous transition metal catalyzed aromatic C−F bond formation reactions have been reported.[43] On the other hand, the direct conversion of unactivated C_{sp^3}−H bonds to C_{sp^3}−F bond remained a highly attractive but elusive prospect, since the fluorine atom must be incorporated in a regioselective manner despite of the ubiquity of C_{sp^3}−H bonds in organic molecules.[44]

After extensive screening of fluoride salts as well as oxidants, we found that a variety of simple alkanes as well as more complex molecules could be fluorinated efficiently under mild conditions in the presence of catalytic amounts of the bulky manganese porphyrin, Mn(TMP)Cl (Scheme 2).[45] Initially, oxidative aliphatic C−H fluorination used a combination of silver fluoride and tetrabutylammonium fluoride trihydrate as the fluoride source in conjunction with iodosylbenzene as terminal oxidant. Typical cycloalkanes afforded *mono*-fluorinated products in 60−80% yield at ∼70% conversion. A series of cyclic compounds containing common functional groups, such as esters, alcohols, ketones, and amides were all selectively fluorinated at otherwise inaccessible C−H positions. This novel fluorination reaction was also applied to more complex molecules. For example, fluorination of the terpenoid natural product sclareolide afforded C2 and C3 methylene-fluorinated products in an overall 58% yield with C2-fluoride favored by nearly 3:1, analogous to the C−H chlorination discussed above.

Detailed mechanistic studies including DFT computations in collaboration with Goddard group suggested that the mechanism of this Mn-fluorination stands in contrast to typical electrophilic or nucleophilic fluorine chemistry. Rather, the mechanistic investigation indicated a Mn-mediated radical

DOI: 10.1021/acs.accounts.5b00062
Acc. Chem. Res. 2015, 48, 1727−1735

Scheme 2. Manganese Porphyrin-Catalyzed Selective Aliphatic C−H Fluorination



pathway involving a fluorine atom transfer. We proposed the catalytic cycle shown in Figure 3A. First, oxidation of the starting Mn^{III}(TMP)Cl catalyst in the presence of fluoride ion affords a reactive oxomanganese(V) species, O=Mn^{V}(TMP)F, which then abstracts a hydrogen atom from the substrate to produce a carbon-centered radical and a HO−Mn^{IV}−F intermediate. The radical is then captured by the F−Mn^{IV}−F species, generated from the reaction between HO−Mn^{IV}−F and AgF. DFT calculation showed that fluorine atom transfer from a simple *trans*-difluoro model, Mn(THP)F_2, to a cyclohexyl radical in the equatorial configuration occurs with a remarkably low activation barrier of only 3 kcal/mol (Figure 3B).

Concurrently, Lectka reported an aliphatic C−H fluorination reaction using a poly component catalytic system involving commercially available Selectfluor, *N*-hydroxyphthalimide, an anionic phase transfer catalyst ($KB(C_6F_5)_4$), and a copper(I) bis(imine).[46] Since then, a variety of other systems have been reported that can selectively construct C_{sp^3}−F bonds via direct C−H activation, reflecting the high current interest in this field.[47−51]

5. DIRECT BENZYLIC C−H FLUORINATION

We sought to expand the Mn−F reaction scope to benzylic C−H fluorination given that benzylic C−H bonds are ubiquitous in bioactive molecules and that incorporation of a fluorine atom at benzylic position can block phase I metabolism of these molecules. The recent upsurge in fluorination chemistry has revealed a number of direct benzylic C−H fluorination methods, such as an iron catalyzed benzylic C−H fluorination using an inexpensive iron(II) salt, $Fe(acac)_2$, and Selectfluor as an electrophilic fluorination reagent.[52] The Inoue group reported a metal-free benzylic fluorination using *N*,*N*-dihydroxypyromellitimide as the catalyst and Selectfluor as the fluorine source.[47] Photoredox benzylic C−H fluorination methods have also been reported recently.[53,54]

When the Mn-catalyzed aliphatic fluorination protocol was applied to substrates containing benzylic C−H bonds, significant amounts of oxygenated side products were observed in the reaction mixture at first.[55,56] Our rationale for the byproducts formation was the relatively low oxidation potential of the benzyl radicals, which leads to a rapid carbon radical rebound to the Mn^{IV}−OH intermediate. Upon screening other ligand systems, we found that benzylic fluorides could be formed efficiently with minimal amounts of oxygenation byproducts when a manganese salen complex was employed as the catalyst. High functional group tolerance was demonstrated with this method (Scheme 3). Various bioactive molecules including a nonsteroidal anti-inflammatory drug (ibuprofen methyl ester), a vitamin E analogue (δ-tocopherol acetate), a commercial perfume component (celestolide), and a non-natural amino acid derivative (homophenylalanine) were all selectively fluorinated at benzylic positions in useful yields under mild conditions. In addition, readily detectable enantioselectivity was observed with celestolide as the substrate and a chiral manganese salen catalyst, providing strong support for a manganese-bound fluorine source, Mn−F, in the fluorine transfer step. Another important aspect of this reaction is that potassium fluoride could be used as the sole fluorine source in conjunction with a phase transfer catalyst, 18-crown-6. This viability of KF was an important practical advance for potential application of this technique in the ^{18}F labeling reactions.

6. DIRECT BENZYLIC C−H ^{18}F FLUORINATION FOR PET IMAGING

Positron emission tomography (PET) is a nuclear imaging technique that is widely used in oncology, cardiology,

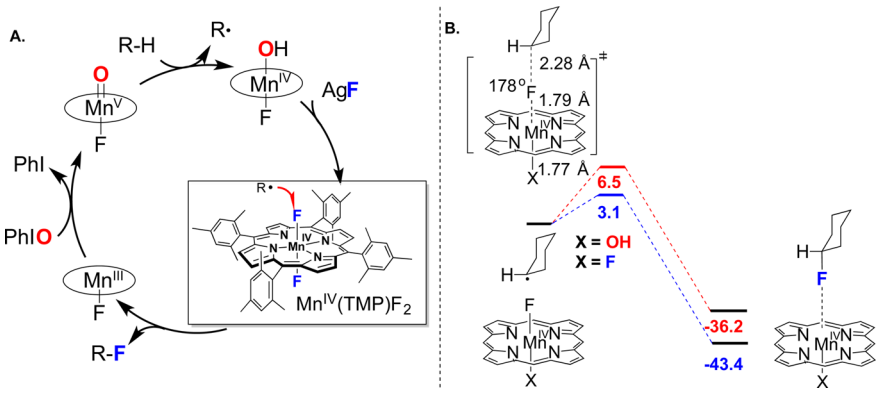
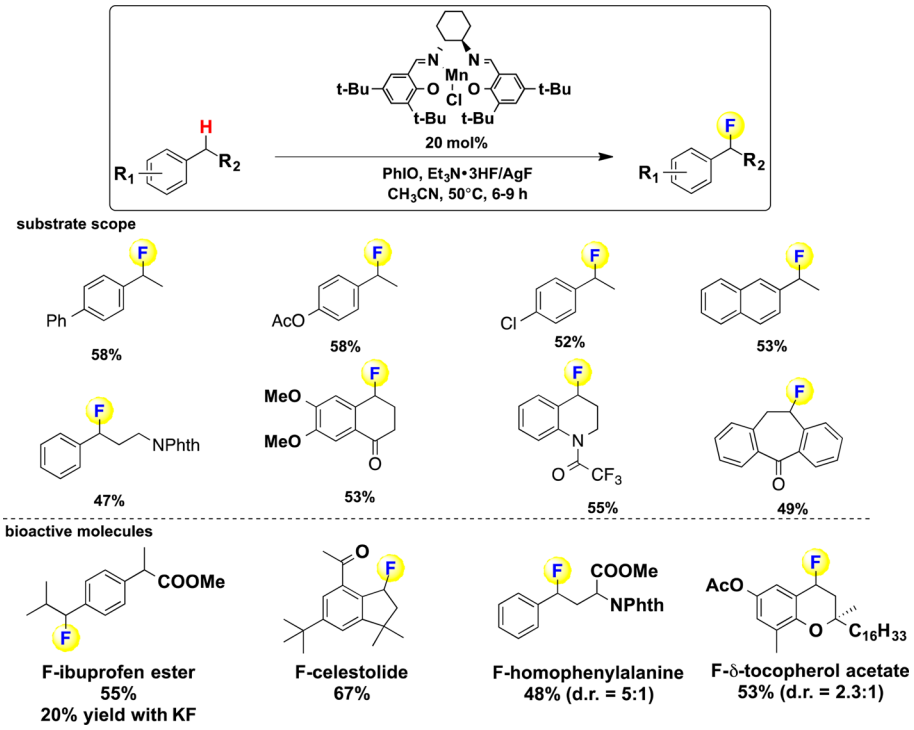


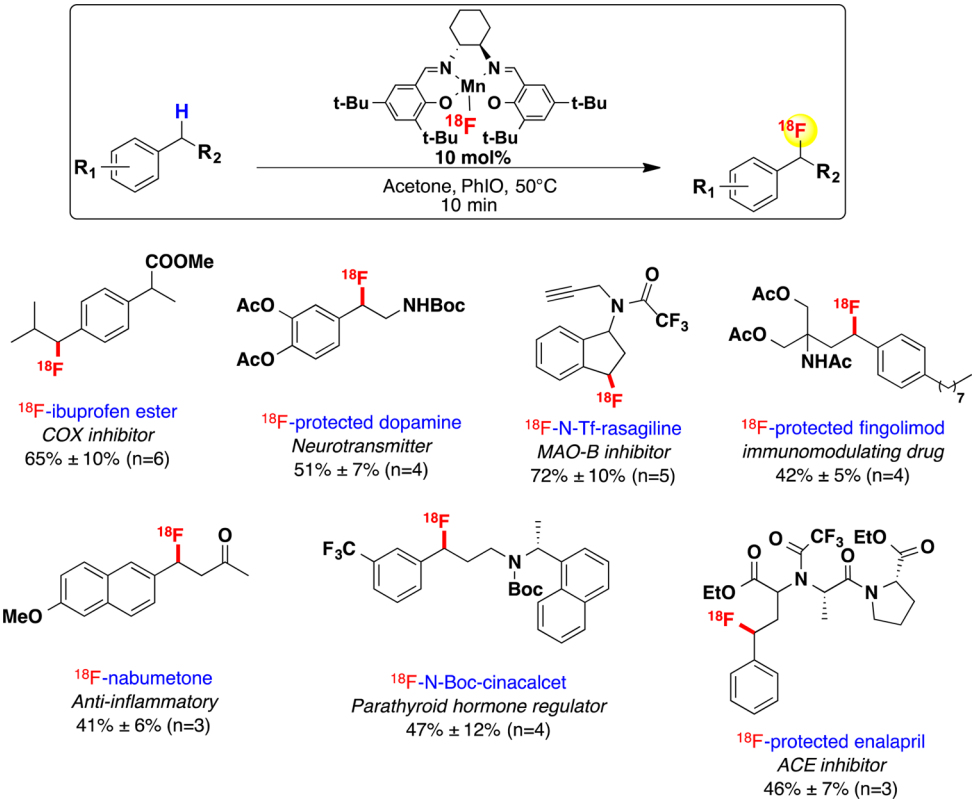
Figure 3. (A) Proposed catalytic cycle for the Mn-catalyzed C−H fluorination reaction. (B) Energy landscape and calculated transition state structure for fluorine rebound to cyclohexyl radical in the equatorial configuration using [Mn(THP)] as a simplified model structure.

DOI: 10.1021/acs.accounts.5b00062
Acc. Chem. Res. 2015, 48, 1727−1735

Scheme 3. Manganese Salen Catalysed Benzylic C−H Fluorination



Scheme 4. Benzylic C−H ^{18}F Labeling Mediated by a Manganese Salen Complex



neuroscience and pharmacokinetic studies.[57] Among all of the commonly used PET radioisotopes, ^{18}F is the preferred radionuclide due to its suitable half-life (110 min) for synthesis and low positron energy that is needed for high-resolution imaging (~1 mm). Currently, 2-[^{18}F]fluoro-2-deoxy-D-glucose ([^{18}F]FDG) is the most widely used PET radiotracer, primarily for oncology imaging. Due to the importance of ^{18}F containing radio-tracers in clinical and research domains, many new strategies have recently been developed that can introduce ^{18}F into complex molecules.[58−61] However, despite these signifi-

DOI: 10.1021/acs.accounts.5b00062
Acc. Chem. Res. 2015, 48, 1727−1735

cant advances, current methods for incorporating ^{18}F at a C_{sp^3} position is still dominated by traditional nucleophilic substitutions with ^{18}F fluoride reacting with a precursor molecule bearing a suitable leaving group at the target site. A major drawback of this conventional approach is that the preparation of the precursor molecules usually requires multistep synthesis, significantly increasing the effort required and limiting the number of PET tracer molecules that can be considered during development.

One possible approach to address this prefunctionalization issue is to develop strategies for direct C−H radiofluorination that could circumvent the complex precursor synthesis. A major obstacle to catalytic ^{18}F fluorinations, however, is the miniscule amounts of fluoride that are actually present (typically nanomoles). In this context, we have successfully translated our benzylic C−H ^{19}F fluorination system to a facile, no-carrier-added, ^{18}F labeling protocol that allows efficient late-stage labeling of a variety of bioactive molecules via direct activation of benzylic C−H bonds (Scheme 4).[62] This novel oxidative C−H ^{18}F fluorination is mediated by manganese salen complexes ligated with the tosyl anions and is driven by iodosylbenzene as the terminal oxidant. Under typical reaction conditions, the ^{18}F fluoride efficiently displaces the tosyl group at the manganese center, forming an ^{18}F−Mn^{III}(salen) complex. This ^{18}F bound manganese salen species then smoothly transferred the ^{18}F fluoride to the substrate derived radical, which is formed via C−H abstraction by the O═Mn^{V}(salen) intermediate in spite of the very low concentration of total fluoride in the reaction mixtures. This labeling method displayed high functional group tolerance. A variety of known drug molecules such as a celecoxib analogue (COX inhibitor), rasagiline (MAOB inhibitor), papaverine (PDE inhibitor), and dopamine (neurotransmitter) have all been selectively labeled with ^{18}F with radiochemical yields up to 70%, easily exceeding the required activity levels for clinical development. Notably, the tedious and time-consuming aqueous $K^{18}F$ dry-down step that is required by ^{18}F labeling chemistry, is not necessary with this new procedure. We found that ^{18}F fluoride (up to 1 Ci) was efficiently eluted directly from an anion exchange cartridge with an acetone solution of Mn(salen)OTs. The Mn(salen)^{18}F catalyst solution obtained in this manner could be used without further processing for ^{18}F-labeling C−H fluorination reactions.

7. SUMMARY AND OUTLOOK

We have outlined a new strategy for constructing C-halogen bonds using manganese complexes as catalysts. These reactions are based on the generation of long-lived substrate radicals via selective C−H abstraction by reactive O═Mn(V) intermediates. These substrate radicals then undergo an uncommon heteroatom (F, Cl, or Br) rebound step, forming halogenated products in contrast to the conventional oxygen rebound pathway. The key factor that switches the radical from oxygenation to heteroatom rebound lies in the nature of the axial ligands at manganese center. Stronger donor ligands such as fluoride and hydroxide create a significant kinetic barrier for the oxygen rebound step.

The Heteroatom-Rebound Catalysis (HRC) strategy described in this Account has already been applied to a wide range of halogenation reactions, including direct C_{sp^3}−H chlorination, bromination, fluorination and ^{18}F labeling. Based on this strategy, our group has, very recently, successfully developed methods for decarboxylative fluorination and direct C−H azidation using manganese complexes as catalysts.[63,64] We expect further developments, the emergence of other carbon−heteroatom processes and even carbon−carbon bond formation reactions. New catalysts and methodologies based on this strategy are currently being explored in our laboratory.

AUTHOR INFORMATION

Corresponding Author

*E-mail: jtgroves@princeton.edu.

Notes

The authors declare no competing financial interest.

Biographies

Wei Liu received his Ph.D. in 2014 at Princeton University with Prof. John T. Groves, where he was working on new synthetic strategies for C-halogen bond formation reactions using manganese complexes as catalysts. He then spent a year in the Groves group as a postdoctoral fellow developing novel ^{18}F labeling methods. He is planning to move to the bay area working as a joint-postdoctoral fellow between Prof. Christopher Chang at UC Berkeley and Prof. David Wilson at UCSF.

John T. Groves is currently the Hugh Stott Taylor Chair of Chemistry at Princeton University. He was an early pioneer in the use of diagnostic substrates as probes of redox enzyme mechanism and the preparation of high-valent metalloporphyrins as heme protein active site models while at the University of Michigan. That work from the 1970s led to the elucidation of the oxygen rebound mechanism of cytochrome P450 as well as the first syntheses and characterizations of ferryl, manganyl, and chromyl porphyrins. He is a fellow of the American Academy of Arts and Sciences, a fellow of the Royal Society of Chemistry, and a member of the National Academy of Sciences and has received the ACS Award in Inorganic Chemistry for 2015.

ACKNOWLEDGMENTS

Deepest thanks are due to all the co-workers from the Groves laboratories, both at the University of Michigan, for the earliest work, and Princeton. In particular, we thank those involved in the metalloporphyrin and P450/APO studies referred to in this Account for their invaluable intellectual and experimental contributions. We are especially indebted to Xiongyi Huang for his contributions to the development of this Mn−F chemistry, including the structural characterization of the manganese(IV) difluoride catalyst. Mn-porphyrin research was supported by the U.S. National Science Foundation Award CHE-1148597 and the Center for Catalytic Hydrocarbon Functionalization, an Energy Frontier Research Center, U.S. Department of Energy, Office of Science, Basic Energy Sciences, under Award No. DE SC0001298. P450 and APO enzymology was supported by the National Institutes of Health (2R37 GM036298).

REFERENCES

(1) Groves, J. T. Enzymatic C−H Bond Activation: Using Push to Get Pull. *Nat. Chem.* **2014**, *6*, 89−91.

(2) Ortiz de Montellano, P. R. Hydrocarbon Hydroxylation by Cytochrome P450 Enzymes. *Chem. Rev.* **2010**, *110*, 932−948.

(3) Yosca, T. H.; Rittle, J.; Krest, C. M.; Onderko, E. L.; Silakov, A.; Calixto, J. C.; Behan, R. K.; Green, M. T. Iron(IV)hydroxide pK_a and the Role of Thiolate Ligation in C−H Bond Activation by Cytochrome P450. *Science* **2013**, *342*, 825−829.

(4) Green, M. T.; Dawson, J. H.; Gray, H. B. Oxoiron(IV) in chloroperoxidase compound II is basic: Implications for P450 chemistry. *Science* **2004**, *304*, 1653−1656.

DOI: 10.1021/acs.accounts.5b00062
Acc. Chem. Res. 2015, 48, 1727−1735

(5) Alderton, W. K.; Cooper, C. E.; Knowles, R. G. Nitric oxide synthases: Structure, function and inhibition. *Biochem. J.* **2001**, *357*, 593−615.
(6) Wang, X. S.; Peter, S.; Kinne, M.; Hofrichter, M.; Groves, J. T. Detection and Kinetic Characterization of a Highly Reactive Heme-Thiolate Peroxygenase Compound I. *J. Am. Chem. Soc.* **2012**, *134*, 12897−12900.
(7) Wang, X. S.; Peter, S.; Ullrich, R.; Hofrichter, M.; Groves, J. T. Driving Force for Oxygen-Atom Transfer by Heme-Thiolate Enzymes. *Angew. Chem., Int. Ed.* **2013**, *52*, 9238−9241.
(8) Rittle, J.; Green, M. T. Cytochrome P450 Compound I: Capture, Characterization, and C-H Bond Activation Kinetics. *Science* **2010**, *330*, 933−937.
(9) Hjelmeland, L. M.; Aronow, L.; Trudell, J. R. Intramolecular Determination of Primary Kinetic Isotope Effects in Hydroxylations Catalyzed by Cytochrome-P-450. *Biochem. Biophys. Res. Commun.* **1977**, *76*, 541−549.
(10) Groves, J. T.; McClusky, G. A.; White, R. E.; Coon, M. J. Aliphatic Hydroxylation by Highly Purified Liver Microsomal Cytochrome-P-450—Evidence for a Carbon Radical Intermediate. *Biochem. Biophys. Res. Commun.* **1978**, *81*, 154−160.
(11) Che, C. M.; Lo, V. K. Y.; Zhou, C. Y.; Huang, J. S. Selective functionalisation of saturated C−H bonds with metalloporphyrin catalysts. *Chem. Soc. Rev.* **2011**, *40*, 1950−1975.
(12) Meunier, B.; de Visser, S. P.; Shaik, S. Mechanism of oxidation reactions catalyzed by cytochrome P450 enzymes. *Chem. Rev.* **2004**, *104*, 3947−3980.
(13) Meunier, B. Metalloporphyrins as Versatile Catalysts for Oxidation Reactions and Oxidative DNA Cleavage. *Chem. Rev.* **1992**, *92*, 1411−1456.
(14) Groves, J. T.; Watanabe, Y. Heterolytic and Homolytic O−O Bond-Cleavage Reactions of (Acylperoxo)Manganese(III) Porphyrins. *Inorg. Chem.* **1986**, *25*, 4808−4810.
(15) Groves, J. T.; Watanabe, Y. Reactive Iron Porphyrin Derivatives Related to the Catalytic Cycles of Cytochrome-P-450 and Peroxidase—Studies of the Mechanism of Oxygen Activation. *J. Am. Chem. Soc.* **1988**, *110*, 8443−8452.
(16) Brothers, P. J.; Collman, J. P. The Organometallic Chemistry of Transition-Metal Porphyrin Complexes. *Acc. Chem. Res.* **1986**, *19*, 209−215.
(17) Groves, J. T.; Nemo, T. E.; Myers, R. S. Hydroxylation and Epoxidation Catalyzed by Iron-Porphyrine Complexes—Oxygen-Transfer from Iodosylbenzene. *J. Am. Chem. Soc.* **1979**, *101*, 1032−1033.
(18) Chin, D. H.; Lamar, G. N.; Balch, A. L. On the Mechanism of Autoxidation of Iron(III) Porphyrins—Detection of a Peroxo-Bridged Iron(III) Porphyrin Dimer and the Mechanism of Its Thermal-Decomposition to the Oxo-Bridged Iron(III) Porphyrin Dimer. *J. Am. Chem. Soc.* **1980**, *102*, 4344−4350.
(19) Groves, J. T. High-valent iron in chemical and biological oxidations. *J. Inorg. Biochem.* **2006**, *100*, 434−447.
(20) Groves, J. T. Models and Mechanisms of Cytochrome P450 Action. In *Cytochrome P450*, 3rd ed.; Ortiz de Montellano, P. R., Ed.; Springer: New York, 2005; pp 1−43.
(21) Groves, J. T.; Quinn, R.; McMurry, T. J.; Lang, G.; Boso, B. Iron(IV) Porphyrins from Iron(III) Porphyrin Cation Radicals. *J. Chem. Soc., Chem. Commun.* **1984**, 1455−1456.
(22) Pennerhahn, J. E.; Eble, K. S.; McMurry, T. J.; Renner, M.; Balch, A. L.; Groves, J. T.; Dawson, J. H.; Hodgson, K. O. Structural Characterization of Horseradish-Peroxidase Using EXAFS Spectroscopy—Evidence for Fe=O Ligation in Compound-I and Compound-II. *J. Am. Chem. Soc.* **1986**, *108*, 7819−7825.
(23) Boso, B.; Lang, G.; McMurry, T. J.; Groves, J. T. Mössbauer-Effect Study of Tight Spin Coupling in Oxidized Chloro-5,10,15,20-Tetra(Mesityl)Porphyrinatoiron(III). *J. Chem. Phys.* **1983**, *79*, 1122−1126.
(24) Jayaraj, K.; Gold, A.; Austin, R. N.; Ball, L. M.; Terner, J.; Mandon, D.; Weiss, R.; Fischer, J.; DeCian, A.; Bill, E.; Muther, M.; Schunemann, V.; Trautwein, A. X. Compound I and compound II analogues from porpholactones. *Inorg. Chem.* **1997**, *36*, 4555−4566.
(25) Jayaraj, K.; Gold, A.; Austin, R. N.; Mandon, D.; Weiss, R.; Terner, J.; Bill, E.; Muther, M.; Trautwein, A. X. Compound-I and Compound-II Analogs of a Chlorin. *J. Am. Chem. Soc.* **1995**, *117*, 9079−9080.
(26) Groves, J. T.; Kruper, W. J.; Haushalter, R. C. Hydrocarbon Oxidations with Oxometalloporphinates—Isolation and Reactions of a (Porphinato)Manganese(V) Complex. *J. Am. Chem. Soc.* **1980**, *102*, 6375−6377.
(27) Groves, J. T.; Lee, J. B.; Marla, S. S. Detection and characterization of an oxomanganese(V) porphyrin complex by rapid-mixing stopped-flow spectrophotometry. *J. Am. Chem. Soc.* **1997**, *119*, 6269−6273.
(28) Jin, N.; Groves, J. T. Unusual kinetic stability of a ground-state singlet oxomanganese(V) porphyrin. Evidence for a spin state crossing effect. *J. Am. Chem. Soc.* **1999**, *121*, 2923−2924.
(29) Jin, N.; Ibrahim, M.; Spiro, T. G.; Groves, J. T. Trans-dioxo manganese(V) Porphyrins. *J. Am. Chem. Soc.* **2007**, *129*, 12416−12417.
(30) Hill, C. L.; Smegal, J. A.; Henly, T. J. Catalytic Replacement of Unactivated Alkane Carbon Hydrogen Bonds with Carbon−X Bonds (X = Nitrogen, Oxygen, Chlorine, Bromine, or Iodine)—Coupling of Intermolecular Hydrocarbon Activation by MnIII-tppx Complexes with Phase-Transfer Catalysis. *J. Org. Chem.* **1983**, *48*, 3277−3281.
(31) Liu, W.; Groves, J. T. Manganese Porphyrins Catalyze Selective C−H Bond Halogenations. *J. Am. Chem. Soc.* **2010**, *132*, 12847−12849.
(32) Depoorter, B.; Ricci, M.; Bortolini, O.; Meunier, B. Catalytic Hydroxylation of Saturated-Hydrocarbons with the Sodium Hypohalite Manganese Porphyrin System. *J. Mol. Catal.* **1985**, *31*, 221−224.
(33) Umile, T. P.; Wang, D.; Groves, J. T. Dissection of the Mechanism of Manganese Porphyrin-Catalyzed Chlorine Dioxide Generation. *Inorg. Chem.* **2011**, *50*, 10353−10362.
(34) Umile, T. P.; Groves, J. T. Catalytic Generation of Chlorine Dioxide from Chlorite Using a Water-Soluble Manganese Porphyrin. *Angew. Chem., Int. Ed.* **2011**, *50*, 695−698.
(35) Chen, M. S.; White, M. C. Combined Effects on Selectivity in Fe-Catalyzed Methylene Oxidation. *Science* **2010**, *327*, 566−571.
(36) Schmidt, V. A.; Quinn, R. K.; Brusoe, A. T.; Alexanian, E. J. Site-Selective Aliphatic C−H Bromination Using N-Bromoamides and Visible Light. *J. Am. Chem. Soc.* **2014**, *136*, 14389−14392.
(37) Groves, J. T.; Stern, M. K. Synthesis, Characterization, and Reactivity of Oxomanganese(IV) Porphyrin Complexes. *J. Am. Chem. Soc.* **1988**, *110*, 8628−8638.
(38) Austin, R. N.; Deng, D. Y.; Jiang, Y. Y.; Luddy, K.; van Beilen, J. B.; Ortiz de Montellano, P. R.; Groves, J. T. The diagnostic substrate bicyclohexane reveals a radical mechanism for bacterial cytochrome P450 in whole cells. *Angew. Chem., Int. Ed.* **2006**, *45*, 8192−8194.
(39) Cooper, H. L. R.; Mishra, G.; Huang, X. Y.; Pender-Cudlip, M.; Austin, R. N.; Shanklin, J.; Groves, J. T. Parallel and Competitive Pathways for Substrate Desaturation, Hydroxylation, and Radical Rearrangement by the Non-heme Diiron Hydroxylase AlkB. *J. Am. Chem. Soc.* **2012**, *134*, 20365−20375.
(40) Rueda-Becerril, M.; Sazepin, C. C.; Leung, J. C. T.; Okbinoglu, T.; Kennepohl, P.; Paquin, J. F.; Sammis, G. M. Fluorine Transfer to Alkyl Radicals. *J. Am. Chem. Soc.* **2012**, *134*, 4026−4029.
(41) Purser, S.; Moore, P. R.; Swallow, S.; Gouverneur, V. Fluorine in medicinal chemistry. *Chem. Soc. Rev.* **2008**, *37*, 320−330.
(42) Furuya, T.; Kamlet, A. S.; Ritter, T. Catalysis for fluorination and trifluoromethylation. *Nature* **2011**, *473*, 470−477.
(43) Grushin, V. V. The Organometallic Fluorine Chemistry of Palladium and Rhodium: Studies toward Aromatic Fluorination. *Acc. Chem. Res.* **2010**, *43*, 160−171.
(44) Rozen, S. Elemental Fluorine as a Legitimate Reagent for Selective Fluorination of Organic-Compounds. *Acc. Chem. Res.* **1988**, *21*, 307−312.
(45) Liu, W.; Huang, X. Y.; Cheng, M. J.; Nielsen, R. J.; Goddard, W. A.; Groves, J. T. Oxidative Aliphatic C-H Fluorination with Fluoride

DOI: 10.1021/acs.accounts.5b00062
Acc. Chem. Res. 2015, 48, 1727−1735

Ion Catalyzed by a Manganese Porphyrin. *Science* **2012**, *337*, 1322−1325.
(46) Bloom, S.; Pitts, C. R.; Miller, D. C.; Haselton, N.; Holl, M. G.; Urheim, E.; Lectka, T. A Polycomponent Metal-Catalyzed Aliphatic, Allylic, and Benzylic Fluorination. *Angew. Chem., Int. Ed.* **2012**, *51*, 10580−10583.
(47) Amaoka, Y.; Nagatomo, M.; Inoue, M. Metal-Free Fluorination of C(sp(3))-H Bonds Using a Catalytic N-Oxyl Radical. *Org. Lett.* **2013**, *15*, 2160−2163.
(48) Braun, M. G.; Doyle, A. G. Palladium-catalyzed allylic C-H fluorination. *J. Am. Chem. Soc.* **2013**, *135*, 12990−12993.
(49) Bloom, S.; Knippel, J. L.; Lectka, T. A photocatalyzed aliphatic fluorination. *Chem. Sci.* **2014**, *5*, 1175−1178.
(50) Kee, C. W.; Chin, K. F.; Wong, M. W.; Tan, C. H. Selective fluorination of alkyl C-H bonds via photocatalysis. *Chem. Commun.* **2014**, *50*, 8211−8214.
(51) Xia, J. B.; Ma, Y.; Chen, C. Vanadium-Catalyzed C(sp3)-H Fluorination Reactions. *Org. Chem. Front.* **2014**, *1*, 468−472.
(52) Bloom, S.; Pitts, C. R.; Woltornist, R.; Griswold, A.; Holl, M. G.; Lectka, T. Iron(II)-Catalyzed Benzylic Fluorination. *Org. Lett.* **2013**, *15*, 1722−1724.
(53) Xia, J. B.; Zhu, C.; Chen, C. Visible light-promoted metal-free C−H activation: diarylketone-catalyzed selective benzylic mono- and difluorination. *J. Am. Chem. Soc.* **2013**, *135*, 17494−17500.
(54) Bloom, S.; McCann, M.; Lectka, T. Photocatalyzed benzylic fluorination: shedding ″light″ on the involvement of electron transfer. *Org. Lett.* **2014**, *16*, 6338−6341.
(55) Liu, W.; Groves, J. T. Manganese-Catalyzed Oxidative Benzylic C−H Fluorination by Fluoride Ions. *Angew. Chem., Int. Ed.* **2013**, *52*, 6024−6027.
(56) Liu, W.; Huang, X. Y.; Groves, J. T. Oxidative aliphatic C−H fluorination with manganese catalysts and fluoride ion. *Nat. Protoc.* **2013**, *8*, 2348−2354.
(57) Phelps, M. E. Positron emission tomography provides molecular imaging of biological processes. *Proc. Natl. Acad. Sci. U. S. A.* **2000**, *97*, 9226−9233.
(58) Lee, E.; Kamlet, A. S.; Powers, D. C.; Neumann, C. N.; Boursalian, G. B.; Furuya, T.; Choi, D. C.; Hooker, J. M.; Ritter, T. A Fluoride-Derived Electrophilic Late-Stage Fluorination Reagent for PET Imaging. *Science* **2011**, *334*, 639−642.
(59) Lee, E.; Hooker, J. M.; Ritter, T. Nickel-Mediated Oxidative Fluorination for PET with Aqueous [F-18] Fluoride. *J. Am. Chem. Soc.* **2012**, *134*, 17456−17458.
(60) Brooks, A. F.; Topczewski, J. J.; Ichiishi, N.; Sanford, M. S.; Scott, P. J. H. Late-stage [F-18]fluorination: new solutions to old problems. *Chem. Sci.* **2014**, *5*, 4545−4553.
(61) Liang, S. H.; Vasdev, N. C(sp(3))-F-18 Bond Formation by Transition-Metal-Based [F-18]Fluorination. *Angew. Chem., Int. Ed.* **2014**, *53*, 11416−11418.
(62) Huang, X. Y.; Liu, W.; Ren, H.; Neelamegam, R.; Hooker, J. M.; Groves, J. T. Late Stage Benzylic C−H Fluorination with [F-18]Fluoride for PET Imaging. *J. Am. Chem. Soc.* **2014**, *136*, 6842−6845.
(63) Huang, X.; Bergsten, T. M.; Groves, J. T. Manganese-catalyzed late-stage aliphatic C-H azidation. *J. Am. Chem. Soc.* **2015**, *137*, 5300−5303.
(64) Huang, X.; Liu, W.; Hooker, J. M.; Groves, J. T. Targeted fluorination with the fluoride ion by manganese-catalyzed decarboxylation. *Angew. Chem., Int. Ed.* **2015**, *54*, 5241−5245.

DOI: 10.1021/acs.accounts.5b00062
Acc. Chem. Res. 2015, 48, 1727−1735