MANGANESE CATALYZED SELECTIVE C(sp\(^3\))-H BONDS HALOGENATIONS

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Abstract

During the past three decades, manganese porphyrins and related Schiff bases have received considerable scrutiny due to their high reactivity toward functionalization of both unsaturated and saturated hydrocarbons. However, most of this work dealt with oxygenation reactions, particularly olefins epoxidation and C-H bonds hydroxylation. Only few reactions involving the catalytic incorporation of other groups, including chlorine, bromine, iodine and azide, have been achieved. On the other hand, halogenated organic compounds, including organochlorine and organofluorine molecules, play a very crucial role in organic chemistry, affording important components of a variety of biologically active molecules as well as pharmaceutical agents. Accordingly, the development of new chemoselective and regioselective approaches to the synthesis of alkyl halides remains an important challenge. In this dissertation, we will demonstrate several novel selective sp$^3$ C-H bonds halogenations catalyzed by manganese complexes.

In chapter 1, current studies on the functions and mechanisms of cytochrome P450s and metallloporphyrins are reviewed. The development of iron and manganese porphyrins catalyzed oxygenation reactions as well as the characterizations of important intermediates responsible for oxygen transfer, including oxoFe$^{IV}$ porpyrin cation radicals and oxoMn$^{V}$ porphyrin species, has also been reviewed. In chapter 2, we report a manganese porphyrin catalyzed selective aliphatic C-H chlorination reaction. This new chlorination system can be applied to simple hydrocarbons and complex substrates. In chapter 3, we report a manganese porphyrin catalyzed selective aliphatic C-H bonds fluorination reactions. The new fluorination system can be applied to different alkanes,
terpenoids and steroids. Mechanistic studies implicate a manganese difluoride intermediate that reacts with alkyl fluoride radicals generated by an oxoMn$^V$. In chapter 4, we report a manganese salen catalyzed reaction for the formation of benzylic fluorides directly from C-H bonds. This reaction does not require a directing group and uses simple and easily handled nucleophilic fluoride reagents. The success of this direct C-H fluorination reaction suggests a general strategy for late stage drug diversification and building block construction.
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Chapter 1.
Overview of Oxygenation Reactions Catalyzed by Metalloenzymes and Metalloporphyrins

1.1 Abstract
The heme-thiolate enzymes cytochrome P450s (CYPs) catalyze a variety of oxygenation reactions in biology. The enzymes contain an iron(III) protoporphyrin-IX in the active sites, which is responsible for the oxygenation reactivity. Understanding of the mechanisms of these reactions guides organic chemists to develop novel metalloporphyrins as catalysts for C-H oxidation reactions. In this chapter, we will review the development of iron and manganese porphyrins catalyzed oxygenation reactions as well as the characterization of important intermediates responsible for oxygen transfer, including oxoFe^{IV} porpyrin cation radical and oxoMn^{V} porphyrin species.

1.2 Cytochrome P450s (CYPs)
Cytochrome P450s (CYPs) are large family of cysteinato-heme enzymes that can be found in nearly all kinds of life, including mammals, bacteria, and plants. They are monooxygenases that employ molecular dioxygen (O_2) as the sole oxidant and formal equivalents of molecular hydrogen to catalyze a variety of oxygenation reactions in nature (Figure 1). These reactions include saturated carbon-hydrogen bonds hydroxylation, olefin epoxidation, aromatic rings oxidation, and heteroatoms oxidation. The substrates of CYP enzymes include lipids and steroidal hormones as well as different
xenobiotic such as the drug molecules. The reason that the enzymes are named as P450 is because they display an unusual strong absorption at 450 nm in the visible spectrum upon reduction in the presence of carbon monoxide when they were first discovered in particular cell fraction. Later study by Mason showed that this absorbance derives from the Cys-S-Fe$^{II}$-CO ligation of the heme.

![Figure 1](image_url)

**Figure 1.** Examples of reactions catalyzed by Cytochrome P450 enzymes

The consensus mechanism for CYP catalyzed oxidation reaction consists of 7 steps. (Figure 2) 1) First, the substrate binds to the resting low-spin ferric enzyme and displaces the axial water molecule. The binding leads to the change of the enzyme structure and converts the heme from the hexacoordinated low spin ($S = 1/2$) resting state to a pentacoordinated ($S = 5/2$) high-spin species. 2) The structural change makes the enzyme a better oxidant and induces the delivery of one electron from a redox partner,
generating the ferrous form of the enzyme, with a relatively slow rate constant \( k = 35 \text{ s}^{-1} \). The ferrous state form of CYP is an extremely powerful reducing agent. 3) Molecular dioxygen then binds to ferrous enzyme, forming a ferric superoxide complex. This oxygen-iron complex is relatively stable but can dissociate to an iron(III) and superoxide anion in a decoupling reaction pathway. 4) The second electron then transfers to P450 forming a nucleophilic iron-peroxo species, with a relatively slow step \( k = 17 \text{ s}^{-1} \). The generated negatively charged iron(III)-peroxo complex is then quickly protonated, producing the iron(III) hydroperoxo complex (Fe\( ^{III} \)-OOH). 5) The second protonation then occurs on the distal oxygen, leading to the cleavage of the O-O bond, producing a oxo iron(IV) porphyrin cation radical complex, also known as Compound I. 6) Compound I then abstracts a hydrogen atom from the substrate, resulting the formation of a substrate carbon radical and a oxo iron(IV) porphyrin speices, compound II. The radical then rapidly recombines, forming the final alcohol product and ferric enzyme. 7) The alcohol product then dissociates from the active site, and a water molecule coordinates to the heme center, generating the resting ferric enzyme.
Although the CYP compound I has been proposed as the key intermediates in the CYP catalyzed oxidation reactions for several decades, its isolation and characterization has only been achieved recently by Green et al.\textsuperscript{11} This CYP compound I complex was generated by reacting ferric CYP 119 with mCPBA in approximately 75% yield within 35 ms after mixing (Figure 3). The Mössbauer spectrum of CYP119 compound I is similar to that of chloroperoxidase compound I. In addition, CYP119 compound I can hydroxylate the C-H bonds of lauric acid with an extraordinary fast apparent rate constant ($k_{app} = 1.1 \times 10^7$ M$^{-1}$ s$^{-1}$), consistent with the high reactivity of CYP toward hydrocarbons.
Figure 3. UV/Vis spectra of CYP119 compound I obtained from the stopped-flow technique reported by Green et al.

Groves and coworkers have recently reported a highly reactive compound I of a heme thiolate peroxygenase from *Agrocybe aegerita* (*AaeAPO*). The UV–vis spectral features of *AaeAPO* compound I are similar to those of CPO compound I and the CYP compound I reported by Green. Reaction kinetics for *AaeAPO* compound I with a various substrates have revealed an informative correlation between the C–H BDE and the observed bimolecular rate constants. The *AaeAPO* compound II Fe$^{IV}$O–H BDE was estimated to be $\sim$103 kcal/mol.$^{12-14}$

The characterization of another important intermediate in CYP catalytic cycle, iron(IV)hydroxide complex, namely compound II has recently been reported by Green et al. This iron(IV)hydroxide complex in a P450 enzyme (CYP158) can be prepared in $>90\%$ yield from the reaction of CYP158 with $m$-CPBA in the pH range from 7-10. Using rapid mixing technologies in conjunction with Mössbauer, UV-vis, and x-ray absorption spectroscopies, the pKa value for this relatively stable complex has been
determined as 11.9. A higher $p$Ka value in Fe$^{IV}$-OH allows for a lower redox potential for the compound I oxidant that is responsible for C-H bond cleavage.

### 1.3 Radical rebound mechanism

There have been many studies in the oxygen transfer step in the CYP catalyzed hydroxylation reactions. Early studies suggested that the hydroxylation reactions followed a concerted insertion pathway based on the very small apparent kinetic isotope effects and frequent retention of stereochemistry. However, a large number of later experimental results indicate that the oxygen transfer does not proceed through a one-step, direct oxygen insertion pathway (Figure 3). In 1978, Groves et al. showed that the hydroxylation of norbornane by a reconstituted liver CYP accompanied by a significant amounts of epimerization at the carbon center. In addition, a large isotope effect ($k_H/k_D = 11.1 \pm 1$) was observed when exo, exo exo, exo-2,3,5,6-tetradueteronobornorane was used as a substrate. A similar value was also reported by Hjelmeland et al, who measured the primary kinetic isotope effect for benzylic hydroxylation using a symmetric substrate, 1,3-diphenylpropane-1,1-$d_2$, providing a value of $k_H/k_D = 11.18$. Moreover, allylic transportation is occasionally observed in the allylic hydroxylation reaction. Allylic arrangement of double bonds has been shown to occur during CYP catalyzed oxidation of 3,3,6,6-tetradeuteriocyclohexene, methylenecyclohexene, and $\beta$-pinene. These results all suggest that the C-H bond is half broken in a linear [O-H-C] transition state and that the oxygen transfer step proceeds via a free radical oxygen rebound mechanism, which was first proposed by Groves in 1978.
Figure 3. Epimerization, large isotope effect and allylic scrambling observed in CYP catalyzed hydroxylations.

In the radical rebound mechanism, the CYP compound I species abstracts a hydrogen atom from the substrate to give a carbon radical intermediate, which combines with the formal equivalent of iron-bound hydroxyl radical to give the final alcohol product (Figure 5).

Figure 4. Rebound mechanism proposed by Groves et al.

Experiments with radical clock substrates have provided strong support for the radical rebound mechanism. The oxidation bicyclo[2.1.0]pentane, the first radical clock used in the study of CYP, yielded a 7:1 mixture of unrearranged and rearranged products (Figure
This result indicates a recombination rate of $\sim 10^{10}$ s$^{-1}$ and a carbon radical life time of 50 ps.$^{23}$

Later in 2002, Groves and Ortiz de Montellano reexamined the mechanism of CYP catalyzed hydroxylation reactions using another diagnostic substrate, bicyclo[4.1.0]heptane (norcarane), which is capable of distinguishing between radical and cation intermediates (Figure 7). Oxidation of norcarane by four different CYP enzymes (P450cam, P450BM3, CYP2B1, and CYP2E1) all afforded detectable amounts of hydroxymethylcyclohexene, the product resulting from the radical intermediate. In agreement with the radical rearrangement observed for bicyclo[2.1.0]pentane, the maximum lifetime calculated for 2-norcaranyl radical is 16-52 ps. Although trace amounts of 3-cyclohepten-1-ol, the cation rearranged product, was also observed in the oxidation. It has been suggested that this cation product may derive from an electron transfer oxidation of the incipient carbon radical that competes with oxygen rebound.
In 2006, Groves and Austin examined a new diagnostic substrate, bicyclo[3.1.0]hexane, whose hydroxylated products give exceptionally resolved chromatography. Oxidation of bicyclo[3.1.0]hexane by two bacterial CYPs, CYP153A1 and CYP153A6 provided similar product distribution, with endo- and exo-2-bicyclohexanol as the major products. Importantly, the radical rearrangement product 3-hydroxymethylcyclopentene was detected in both cases and the products ratio indicates a rebound rate in the range of $10^{10} \text{s}^{-1}$.

In 2012, Groves and coworkers have investigated a purified a highly reactive form of non-heme diiron hydroxylase AlkB using a deuterated substrate, 3,3,4,4-norcarane-$d_4$ norcarane. A large kinetic isotope effect of ~20 has been observed for both C-H hydroxylation at C3 and desaturation pathway. These results indicate that C–H hydroxylation and desaturation follow analogous stepwise reaction channels via carbon radicals that diverge at the product-forming step.\textsuperscript{25}
1.3 Metalloporphyrins as model compounds for CYPs

Over the past three decades, synthetic metallopoprhyrins have been widely used as models compounds that can mimic the reactivities of CYP enzymes. These study have afforded important insights into the nature of the process of CYP.

1.3.1 Iron porphyrins as the catalysts for oxidation reactions

In 1978, Groves and coworker have reported the first catalytic alkane hydroxylation and alkene epoxidation catalyzed by a synthetic iron(III) porphyrin complex, Fe(TPP)Cl using iodosylbenzene (PhIO) as the oxidant (Figure 7). In the reactions, alkenes and alkanes were oxidized to the corresponding epoxides and alcohols, respectively. In a later article reported by Groves and Nemo, different iron porphyrins were used for hydrocarbon activation. The oxidation of cyclohexane with Fe(TTP)Cl catalyst afforded a 31% yield of cyclohexanol and 6% cyclohexanone. Hydroxylation of cis-decalin with Fe(TPP)Cl and iodosylbenzene yielded a mixture of 9:1 cis-9-decalol and trans-9-decalol, suggesting that the hydroxylation occurred majorly with retention of configuration at carbon center. In addition, a KIE number of 12.9 ± 1 was observed for cyclohexane hydroxylation, similar as what was found in the CYP catalyzed hydroxylation reactions, suggesting that a similar oxoFe(IV) porphyrin cation radical species may be involved in this reaction.
Figure 7. Olefin epoxidation and alkane hydroxylation catalyzed by a iron porphyrin Fe(TPP)Cl.

The first use a chiral iron porphyrin to carry out asymmetric epoxidation was reported in 1983 by Groves and Myers. Various substituted styrenes and aliphatic olefins were epoxidized with ee varying between 0% for 1-methylcyclohexene oxide and 51% for p-chlorostyrene oxide.\(^{32}\) The ee was improved to ~70% for epoxidation of cis-β-methylstyrene with the use of a very robust chiral vaulted binaphthyl porphyrin. More significantly, this catalyst can also be applied to catalytic asymmetric hydroxylation reactions, resulting in a ~70% ee for hydroxylation of ethylbenzene and related hydrocarbons.\(^{33,34}\)

In 1981, Groves and coworkers successfully isolated and characterized the first high-valent iron-oxo porphyrin complex, an iron(IV)-oxo porphyrin π cation radical species (Figure 8).\(^{35}\) This compound was prepared by the oxidation of Fe(TMP)Cl with 1.5 equiv. meta-chloroperbenzoic acid (\(m\)CPBA) in methylene chloride-methanol at -78°C. This high-valent iron porphyrin complex is reactive toward olefin and has a spectral
similar to those reported for horseradish peroxidase compound I. The NMR, visible, Mössbauer and EPR data clearly demonstrate that this complex is an iron(IV)-porphyrin cation π-radical structure. In addition, when this species was prepared in the presence of excess H$_2^{18}$O and treated with norbornene, 99% $^{18}$O was incorporated into the epoxide product. This result suggests that the compound I could readily exchange its oxygen atom with H$_2$O and also confirms that an oxo-Fe intermediate species is responsible for the oxygen transfer step.

![Figure 8. Characterization of an iron(IV)-porphyrin cation π-radical species](image)

Although the compound I model compounds exhibited a full range of oxygen transfer reactions, their low kinetic reactivities cannot explain how the CYP can generate sufficient reactive intermediates. This question was addressed when a highly reactive CYP model compound I, [O=Fe$^{IV}$-4-TMPyP]$^+$, was reported (Figure 10). This species was prepared by the oxidation of a water-soluble iron porphyrin, Fe$^{III}$-4-TMPyP, with
Monitoring the reaction of this compound I with xanthene using a single-mixing stopped flow experiment produced a ultra fast rate constant \( k = (3.6 \pm 0.3) \times 10^6 \text{ M}^{-1} \text{ s}^{-1} \). This rate constant is in orders of magnitude faster than that of the previously reported Fe(TMP)Cl analogue. The high reactivity observed with this model iron compound I is suggested to result from both the facilitated spin-state crossing phenomena during the reaction as well as a low-lying \( a_{2u} \) porphyrin HOMO.

![Figure 9](image)

**Figure 9.** A highly reactive CYP model compound I reported by Groves and Bell.

### 1.3.2 Manganese porphyrins catalyzed oxidations

Manganese porphyrins have been shown to have higher reactivity for C-H hydroxylation and olefin epoxidation than iron porphyrins. The first manganese porphyrin catalyzed hydrocarbon oxidation reaction was reported in 1980, using Mn(TPP)Cl as the catalyst.\(^{37}\) In that study, oxidation of cyclohexane with iodosylbenzene catalyzed by Mn(TPP)Cl afforded a 2.5 : 1 mixture of cyclohexanol and cyclohexyl chloride in a total 70% yield. Oxidation of a radical clock substrate, norcarane, provided significant amounts of radical rearranged products, suggesting the presence of a long-lived free alkyl radical. In
addition, epoxidation of cis-stilbene gave a mixture of 1.6:1 mixture of trans- and cis-epoxide, another indication of the radical nature of the reaction.

Although oxoMn\textsuperscript{V} porphyrin species have long been proposed as the intermediates for the oxidation reactions, their isolation and characterization was challenging due to the high reactivities and transient nature. Before the detection of an oxoMn\textsuperscript{V} porphyrin, direct evidence for an oxoMn\textsuperscript{V} salen complex was presented by Plattner \textit{et al.} using electrospray ionization mass spectrum technique.\textsuperscript{38}

The first direct detection of an oxoMn\textsuperscript{V} porphyrin intermediate was reported in 1997.\textsuperscript{39} This short-lived species was prepared by oxidation of Mn\textsuperscript{III}-TM-4-PyP with several oxidants including \textit{m}CPBA, HSO\textsubscript{5}\textsuperscript{−}, and ClO\textsuperscript{−} at pH=7.4 in aqueous solution with rapidly mixing stopped-flow spectrophotometry. Once formed, this intermediate species rapidly converted to oxoMn\textsuperscript{IV} by one-electron reduction. In the presence of H\textsubscript{2}\textsuperscript{18}O, the product epoxide was shown to contain 35\% 18O, consistent with an O-exchange-labile oxoMn\textsuperscript{V} intermediate.
Two years later, the first stable oxoMn\textsuperscript{V} porphyrin complex was reported by Groves and Jin\textsuperscript{40}. The stoichiometric oxidation of Mn\textsuperscript{III}-TM-2PyP with oxidants such as oxone, mCPBA, or ClO\textsuperscript{-} at pH=7.4 led to the formation of O=Mn\textsuperscript{V}TM-2PyP with a life-time of several minutes. The unusual stability of this oxoMn\textsuperscript{V} porphyrin species allows its characterization by \textsuperscript{1}HNMR spectra, which shows sharp resonance in the downfield region, clearly indicating the formation of a low-spin d\textsubscript{2} oxoMn\textsuperscript{V} proporphyrin species. The difference between the reactivity of O=Mn\textsuperscript{V}TM-2PyP and O=Mn\textsuperscript{V}TM-4PyP has also been studied. The half-life of O=Mn\textsuperscript{V}TM-2PyP (95 s) is about 200 times greater than that of its 4-PyP analogue. In addition, O=Mn\textsuperscript{V}TM-4PyP was found to be about 3 orders of magnitude less reactive than O=Mn\textsuperscript{V}TM-2PyP toward a range of oxidizable substrates. The difference between the reactivity of these two species is assigned to spin state crossing effects as suggested by Shaik and Schwartz\textsuperscript{41,42}. 

\textbf{Figure 10.} Formation of O=Mn\textsuperscript{V}TM-4-PyP by mCPBA oxidation.
Oxo-hydroxo tautomerism was introduced by Meunier to explain the constant ratio of 0.5 for oxygen incorporation from solvent into oxidized substrates mediated by water soluble manganese porphyrins. This mechanism involves a coordinated water molecule on the metalloporphyrin catalyst and a rapid, prototropic equilibrium, which interconverts an oxo group on one face of the manganese porphyrin with an aqua or hydroxo group on the other face. A trans-dioxo manganese porphyrin was proposed as an intermediate (Figure 13).

In 2007, Groves and Spiro published the characterization of the trans-dioxo-Mn^V porphyrin complexes (Figure 12). These stable trans-dioxo complexes were prepared by oxidation of a variety of manganese(III) porphyrins in an alkaline solution using different oxidants, including mCPBA and H_2O_2. The ^1H NMR spectrum of [Mn^V(O_2)TMP]^+ shows a single and sharp resonance for the two methyl groups,
consistent with octahedral coordination of $D_{4h}$ symmetry. Raman spectra revealed symmetric $O=Mn=O$ stretching frequencies between 741 and 744 cm$^{-1}$ for different porphyrin complexes, comparable to $\nu$(Mn$^{IV}$=O) in oxoMn$^{IV}$ porphyrins. In addition, protonation of these unreactive species affords reactive intermediates that are able to efficiently epoxide cyclooctene, consistent with the transformation of an unreactive $trans$-dioxo species into a reactive oxo-hydroxo or oxo-aquo-Mn$^V$ speices.

Figure 12. $Trans$-dioxo manganese(V) porphyrin complexes

1.4 Development of manganese catalyzed C-H halogenation reactions

Although manganese porphyrins and related Schiff bases have received considerable scrutiny due to their high reactivities toward functionalization of both unsaturated and saturated hydrocarbons, most of this work dealt with oxygenation reactions, particularly olefins epoxidation and C-H bonds hydroxylation. Only few reactions involving the catalytic incorporation of other groups have been achieved. On the other hand, halogenated organic compounds, including organochlorine and organofluorine molecules, play a very crucial role in organic chemistry, affording important components of a variety of biologically active molecules as well as pharmaceutical agents. For many years it has been thought that halogenation reactions involving aliphatic C-H bonds were intrinsically
unselective, especially for complex molecules. However, highly selective chlorinations are now recognized in natural product biosynthesis that are mediated by metalloenzymes such as chloroperoxidases and the non-heme enzyme SyrB2. The development of a practical catalyst for such halogenations would offer numerous possibilities for late stage drug diversification or selective functionalization. In the following chapters, we will report three manganese catalyzed C(sp$^3$)-H bonds halogenation reactions, including a manganese porphyrin catalyzed C-H chlorination reaction, a manganese porphyrin catalyzed C-H fluorination reaction and a manganese salen catalyzed benzylic C-H fluorination reaction.

1.5 Conclusion

Heme thiolate enzymes, cytochrome P450s, have been the subjects of extensive studies due to their unusual abilities to catalyze the oxidation of variety of organic molecules. Mechanistic studies suggest that the oxidation reactions involve an oxo-iron(IV) porphyrin cation radical, compound I, which was recently characterized by EPR, Mössbauer and UV-Vis. The oxygen transfer step involves an initial hydrogen atom abstraction, followed by a radical recombination, also called as Groves Rebound Mechanism.

Different metalloporphyrins have been developed to mimic the oxidation activities of CYPs. By using PhIO as the oxidant, iron and manganese porphyrins have been shown to catalyze alkane hydroxylation and olefin epoxidation. The high valent reactive
intermediates, oxo-iron(IV) porphyrin cation radical and oxo-manganese(V) have both been synthesized and well-characterized.

1.6 References


Chapter 2.

Manganese Porphyrins Catalyze Selective Aliphatic C-H Bonds Chlorination

2.1 Abstract

In this chapter, we report a manganese porphyrin catalyzed selective aliphatic C-H chlorination reaction. In the presence of catalytic amounts of phase transfer catalyst and manganese porphyrin, Mn(TPP)Cl, reactions of sodium hypochlorite with different unactivated alkanes afforded alkyl chlorides as major products with trace amounts of oxygenation products. Substrates with strong C-H bonds, such as neopentane (BDE = ~100 kcal/mol), can be also chlorinated with moderate yield. Chlorination of a diagnostic substrate, norcarane, suggested a long life-time radical intermediate. Moreover, regioselective chlorination can be achieved by using a bulky catalyst, Mn(TMP)Cl. Chlorination of trans-decalin with 2 as the catalyst provided 95% selectivity for methylene-chlorinated products as well as a preference for C2 position. This new chlorination system can also be applied to complex substrates. When 5α-cholestane was used as the substrate, we observed the chlorination only at the C2 and C3 positions, corresponding to the least sterically hindered methylene positions in the A-ring. Similarly, chlorination of sclareolide affords mainly C2 position chlorinated product in a 42% isolated yield. The regioselectivity can be attributed to the non-bonded interactions between the alkyl groups on the substrates and the phenyl groups of the manganese porphyrins. A possible mechanism for this new transformation is proposed. Reaction of sodium hypochlorite with manganese(III) porphyrin affords a O=Mn\textsuperscript{V} complex, which abstracts a hydrogen atom from the substrate, resulting in a free alkyl radical and a Mn\textsuperscript{IV}-
OH complex. The latter then reacts with the hypochlorite anion, affording a Mn$^{IV}$-OCl species, which reacts with the free alkyl radical, affording the alkyl chloride.

2.2 Background

2.2.1 Organochlorine and organobromine compounds

Halogenated organic compounds play a very crucial role in organic chemistry, affording important components of a variety of biologically active molecules as well as pharmaceutical agents. Alkyl chlorides also find widespread use as intermediates in organic synthesis, such as in cross-coupling reactions. Accordingly, the development of new chemoselective and regioselective approaches to the synthesis of alkyl halides remains an important challenge.

Nature has found highly selective ways to incorporate halogen atoms into organic molecules using reactive metal-oxo intermediates within enzymes. These biological halogenations occur on variety organic scaffolds, including terpenoids, polyketides and nonribosomal peptides. Until now, there are more than 4000 known examples of naturally occurring organohalogen compounds, most of which are chlorinated and brominated compounds (ca. 120 iodinated, 2100 brominated, 2300 chlorinated, and 30 fluorinated compounds). Although a large number of synthetic halogenated organic molecules are harmful to the environment, some of the naturally occurring organohalogen compounds, such as chloromaphenicol (a bacteriostatic antimicrobial), chlortetracycline (a tetracycline antibiotic), and vancomycin (a glycopeptide antibiotic) (Figure 1), have substantial therapeutic significance.
2.2.2 Chloroperoxidase (CPO)

One of the most studied enzymes capable of incorporating of halogen atoms into organic compounds is the heme-containing enzyme chloroperoxidase (CPO) (Figure 2), which was initially isolated from the marine fungus *Caldariomyces fumago*. Since the discovery of CPO by Morris and Hager in 1966\textsuperscript{5,6}, this enzyme has been the subject of extensive

**Figure 1.** Structure of chlorine-containing natural products
investigations. In addition to the usual peroxidase and catalase reactivities exhibited by other peroxidase, CPO is unique in its ability to catalyze the oxidation of several halide ions, including Cl\(^{-}\), Br\(^{-}\) and I\(^{-}\) using hydrogen peroxide as well as the formation of corresponding carbon halogen bonds with halogen acceptors.

![Figure 2. Crystal structure of *Caldariomyces fungo* chloroperoxidase](image)

The mechanism of CPO catalyzed chlorination reaction has been extensively studied. To catalyze chlorination reactions, CPO employs hydrogen peroxide and chloride ion. The chlorination reaction by CPO is initiated by the coordination of hydrogen peroxide on the resting high-spin five-coordinate ferric state. The hydrogen peroxide adduct is then deprotonated to a transient peroxo-anion species. Heterolytic cleavage of O-O bond leads to the formation of an oxoFe\(^{IV}\) porphyrin cation radical species, also known as compound I. The compound I of CPO has been characterized by UV-Vis absorption\(^9\), resonance Raman\(^{10}\), electron paramagnetic resonance\(^{11,12}\), and Mössbauer spectroscopic measurement\(^{13}\). In the catalase mode, CPO compound I reacts with another equivalent of hydrogen peroxide, resulting in the formation of one equivalent dioxygen and starting
ferric resting state. In the peroxidase mode, CPO compound I abstract a hydrogen atom from the organic substrate (AH), forming a radical product (A) with concurrent reduction to oxoFe$^{IV}$ state, namely compound II. Green et al. has recently shown by X-ray absorption that CPO compound II is basic, as it is protonated under physiological pH, whereas compound II species of peroxidase and horseradish peroxidase is not, suggesting that the thiolate ligand in CPO may play an additional role in CPO chemistry.$^{14}$ Oxidation of another equivalent of substrate by compound II regenerates the starting ferric resting state. In the chlorination mode, CPO compound I oxidizes the halide ion forming a hypothetical ferric hypohalite adduct. The ferric hypohalite adduct can either react directly with the substrate forming the chlorinated product or release the free HOCl molecule, which is also able to chlorinate the substrate. Despite numerous investigations of CPO, the identification of the halogenation intermediates has remained elusive.

2.2.3 Iron(II) α-ketoglutarate dependent halogenase SyrB2

Very recently, Walsh and co-workers have reported a nonheme iron(II) α-ketoglutarate dependent halogenase SyrB2, which can facilitate chlorination of unreactive aliphatic compounds. Normally, SyrB2 performs chlorinating of the γ-carbon of L-Thr, a process involved in the biosynthesis of syringomycin E.$^{15}$ In addition to the mono-chlorination activity, SyrB2 can also catalyze tandem chlorination and bromination of its substrates. Crystal structure of SyrB2 reveals that, in contrast to the α-ketoglutarate-dependent dioxygenase, in which the iron(II) center is coordinated by three amino acid residues$^{16}$, the iron center of SyrB2 is coordinated by only two histidine residues and the carboxylate ligand of the facial triad is replaced by a chloride ion (Figure 3).$^{17}$
Based on the crystal structure, a possible mechanism for SyrB2 catalyzed chlorination reaction has been proposed \textcolor{red}{(Figure 4)}. The key intermediate in the catalytic cycle is a Cl-Fe$^{IV}$=O species, which activates a substrate by hydrogen atom abstraction to yield a Cl-Fe$^{III}$-OH complex and a substrate radical. The radical then rebounds to the chloride radical forming the alkyl chloride, similar as the oxygen rebound in the hydroxylase.
**Figure 4.** Mechanism of SyrB2 catalyzed C-H chlorination

### 2.2.4 Metalloporphyrin and salen complexes for halogenation reactions

During the past three decades, manganese porphyrins and related Schiff bases have received considerable scrutiny due to their high reactivities toward functionalization of both unsaturated and saturated hydrocarbons. However, most of this work dealt with oxygenation reactions, particularly olefins epoxidation and C-H bonds hydroxylation. Only few reactions involving the catalytic incorporation of other groups (Cl, Br, I, N₃) have been achieved in the presence of both iodosylarenes and halide or azide ions with manganese porphyrins as catalysts. In the early report by Groves and Kruper on the oxidation of norcarane catalyzed by manganese porphyrin, significantly amounts of rearranged and unrearranged chlorination products were detected in the reaction mixture (Figure 5). The fact that aliphatic chlorination is also observed in benzene with Mn(TPP)Cl as catalyst indicates the chlorine transfer from the metal center.

![Figure 5. Oxidation of norcarane reported by Groves and Kruper](image)

A nickel(salen) catalyzed hydrocarbon chlorination reaction has been reported by Ricci _et al._ (Figure 5). In this case, sodium hypochlorite was employed as the oxidant. Different hydrocarbons including cyclohexane and adamantane were converted to their
chlorinated analogues. The chloroalkanes/oxygenated hydrocarbons ratios range from 10 to 333. The reaction was likely propagated by chloroxy radical with nickel complex as initiator and therefore the substrate scope is limited to simple compounds.\textsuperscript{23}

\begin{figure}
\centering
\includegraphics[width=\textwidth]{figure.png}
\caption{Ni(salen) mediated C-H chlorination of hydrocarbons reported by Ricci \textit{et al.}}
\end{figure}

Very recently, Fujii has reported that an oxoiron(IV) porphyrin \(\pi\)-cation radical can be converted to iron(III) \textit{meso}-chloro-isoporphyrin in the presence of trifluoroacetic acid and chloride ion. More importantly iron(III) \textit{meso}-chloro-isoporphyrin has shown to be an excellent reactive agent for chlorinating aromatic compounds and olefins.\textsuperscript{24,25}

The development of metalloporphyrin-catalyzed C-H halogenation of unactivated C-H bonds could provide a significant new avenue for late stage drug diversification. Further, the realization of such a process could provide insight into the mechanisms of halogenating enzymes such as CPO and SyrB2.
2.3 Development of a manganese porphyrin catalyzed C-H chlorination reaction

2.3.1 Simple hydrocarbons chlorination catalyzed by manganese porphyrins

We have found that a biphasic system with catalytic amount of Mn(TPP)Cl, tetrabutylammonium chloride as phase transfer catalyst, and sodium hypochlorite transformed a variety of organic molecules to their chlorinated products. We first chose cyclic alkanes and substituted toluenes as substrates since they were well studied in metalloporphyrin catalyzed hydroxylation reactions. Reaction of sodium hypochlorite with these substrates under our standard chlorination conditions produced corresponding alkyl halides and benzyl halides, respectively, as the major products.

Table 1. Halogenations of substrates using Mn(TPP)Cl/NaOX/PTC at ambient temperature

<table>
<thead>
<tr>
<th>entry</th>
<th>substrates</th>
<th>product(^a)</th>
<th>yield(^b)</th>
<th>product(^c)</th>
<th>yield(^b)</th>
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<tbody>
<tr>
<td>1</td>
<td></td>
<td>Cl</td>
<td>69%</td>
<td>Br</td>
<td>56%</td>
</tr>
<tr>
<td>2</td>
<td></td>
<td>Cl</td>
<td>57%</td>
<td>Br</td>
<td>49%</td>
</tr>
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</table>
Chlorinations of cyclopentane, cyclohexane, cycloheptane and cyclooctane all afforded their corresponding mono-chlorinated products with good to moderate yields (Figure 7). The yields are based the amounts of sodium hypochlorite employed. Trace amounts of di-halogenated products were detected, probably due to the electronegativity of the halogen atom. When toluene derivatives are used as the substrate, benzylic positions are cleanly halogenated. For all of the substrates employed, the selectivity of chlorinations is more than 95%. Only trace amounts of alcohol, ketone and other chlorinated products were detected under optimal conditions. No significant differences in terms of yields or selectivities of chlorinations were found when Mn(TMP)Cl₂ was used as catalyst. Very interesting to note is that the chlorinations reaction can also occur when using a manganese Schiff base catalyst, which was initially developed by the Jacobsen group for asymmetric epoxidation reactions. Control reactions showed that chlorinations did not

<table>
<thead>
<tr>
<th></th>
<th>Structure 1</th>
<th>Structure 2</th>
<th>Yield 1</th>
<th>Yield 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>cyclopentane</td>
<td>cyclopentane-Cl</td>
<td>60%</td>
<td>47%</td>
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<tr>
<td>4</td>
<td>cyclohexane</td>
<td>cyclohexane-Cl</td>
<td>74%</td>
<td>53%</td>
</tr>
<tr>
<td>5</td>
<td>cycloheptane</td>
<td>cycloheptane-Cl</td>
<td>38%</td>
<td>35%</td>
</tr>
<tr>
<td>6</td>
<td>cyclooctane</td>
<td>cyclooctane-Cl</td>
<td>41%</td>
<td>37%</td>
</tr>
<tr>
<td>7</td>
<td>benzene</td>
<td>benzene-Cl</td>
<td>39%</td>
<td>30%</td>
</tr>
<tr>
<td>8</td>
<td>toluene</td>
<td>toluene-Cl</td>
<td>44%</td>
<td>41%</td>
</tr>
</tbody>
</table>

^a^ catalytic chlorination reaction.  
^b^ GC yield, based on oxidant consumed.  
^c^ catalytic bromination reaction.
occur in the absence of either the manganese porphyrins or phase transfer catalysts. The catalysts are stable under chlorination condition and UV/Vis measurements showed that the decrease of the Soret band (478 nm) is less than 10% after the reactions.

![Figure 7](image)

**Figure 7.** A typical GC trace of the chlorination reactions (cyclooctane as an example). The peak on the left is the residual starting material, cyclooctane. The peak on the right is the chlorination product, cyclooctyl chloride.

**2.3.2 Manganese porphyrins catalyzed C-H bonds bromination**

The chlorination reactions can be easily expanded to bromination reactions by using sodium hypobromite (NaOBr) as the oxidant (Table 1). All of the substrates employed are readily brominated in MnTPPCl/NaOBr/PTC system and trace amounts of oxygenation products were detected.
Bromination of cyclohexane provided cyclohexyl bromide as the main product with insignificant amounts of cyclohexyl chloride, suggesting that hypohalite is the major halogen source. The yields of brominations slightly decrease compared to chlorination reactions, probably due to the instability of sodium hypobromite at room temperature.  

Interestingly, even substrates with strong C-H bonds, such as neopentane (BDE = ~100 kcal/mol)\(^{26}\) can be chlorinated with a useful yield by using a bulky manganese porphyrin, Mn(TMP)Cl\(_2\), as the catalyst (Figure 6). Intrigued by the result of neopentane chlorination, we plan to halogenate substrates with stronger C-H bond. Considering that conversion of light hydrocarbons to their liquid derivatives could have great values, we first tested the bromination of ethane, the C-H bond of which is ~101 kcal/mol, with different manganese porphyrins as the catalysts. The ethane bromination reactions were set up with saturated ethane in dichloromethane-\(d_2\) and were subjected to \(^1\)HNMR analysis direct after the reactions were done. To our satisfaction, bromination of ethane with a electron-withdrawing manganese porphyrin, Mn(TDClP)Cl, as the catalyst, provided ethyl bromide as the major product with a turnover number of ~14 (Figure 9). Our ultimate goal is to activate methane, the C-H bond BDE of which is up to 105 kcal. Unfortunately, our attempt to chlorinate and brominate methane did not succeed no
matter what catalysts were used. We attribute the low reactivity of methane to the low pressure and resultant low solubility in dichloromethane.

![Figure 7](image_url)  
*Figure 7. $^1$H NMR of Mn(TDCIP)Cl catalyzed ethane bromination*

### 2.3.3 C-H chlorination of more complex compounds by manganese porphyrins

**Chlorination of trans-decalin by manganese porphyrins**

Intrigued by this unusual Mn-porphyrin catalyzed chlorination reaction, we then aimed to expand it to more complex molecules. We first chose trans-decalin as a model substrate, as this scaffold is ubiquitous in biological active molecules. Chlorination of trans-decalin with commonly used chlorinating agents such as N-chlorosuccinimide (NCS)$^{27}$ or hypochlorite acid$^{28}$ provided different products with poor regioselectivity and secondary/tertiary selectivity as $\sim 0.7$ and $\sim 0.3$, respectively, after statistically corrections.

We found that, interestingly, in our system with 1 as catalyst, chlorination of trans-decalin provided $95\%$ selectivity for methylene-chlorinated products *(Figure 8).*
Furthermore, to our delight, when the bulky catalyst 2 is used, 3a is observed as the major product, in which the least steric hindered position is chlorinated. Although a preference for secondary C-H bond oxidation has recently been noted by White\textsuperscript{29,30}, Costas,\textsuperscript{31,32} and Maruoka\textsuperscript{33}, the similar selectivity in chlorination has not been previously published. This result suggests that the regioselectivity of chlorination can be tuned by modifying the substitution on the porphyrin ring.

![Chlorination of trans-decalin catalyzed by two manganese porphyrins](image)

**Figure 8.** Chlorination of trans-decalin catalyzed by two manganese porphyrins

**Chlorination of 5α-cholestane and sclareolide by Mn(TMP)Cl**

We then examined the chlorination of 5α-cholestane, a saturated 27-carbon steroid precursor that contains a total of 48 unactivated C-H bonds. According to our trans-decalin results, we expected that the six tertiary sites would be sterically inaccessible for chlorination. The five member-ring would be steric hindered caused by the long side chain. Remarkably, despite 13 possible methylene sites of chlorination, we observed chlorination only at the C2 and C3 positions, corresponding to the least sterically hindered methylene positions in the A-ring (Figure 11A). Although an epimeric mixture was observed for the C3 chlorination, 4a was the major C2 chlorination, probably due to the 1,3-diaxial interactions. This example highlights the capacity of solely steric factor to produce selective chlorination of secondary C-H bonds.
Figure 9. Chlorination of complex molecules. A. Steric effect leads to selective chlorination of 5α-cholestane on C2 and C3 position. NMR yield. B. Combination of steric and electronic effects leads to the selective chlorination of sclareolide.

Regioselectivity through a combination of steric and electronic effects was demonstrated by Mn(TMP)Cl catalyzed chlorination of sclareolide, which is a sesquiterpene lactone natural product derived from various plant source including *Salvia sclarea*, *Salvia yosgadensis*, and cigar tobacco. Sclareolide is used as a fragrance in cosmetic and has been more recently marketed as a weight loss supplement. It has been utilized in a recent study by White et al., in which oxidation of sclareolide catalyzed by a bulky non-heme iron catalyst occurs only on C2 and C3 position. A similar result has also been reported by Costas et al. using several non-heme iron catalysts. The lactone group on the C ring serves as an electron-withdrawing group, which deactivates the B and C ring and leaves A ring the most accessible positions for C-H activation. As expected, this is the
case in our chlorination system. Interestingly, chlorination on the C2 position is 7 times more favored than C3 position, resulting in 5a being the major products in a 42% isolated yield (Figure 9B).

Regioselective chlorinations of unactivated methylene C-H bonds are rare with the few known examples involving the use of internal directing groups. The Ball group has reported a copper catalyzed remote sp$^3$ C-H chlorination of alkyl hydroperoxides. By using a simple ammonium chloride salt as the chlorine source, they were able to perform an intramolecular functionalization at a nonactivated δ carbon (Figure 12).

![Figure 12](image-url)

**Figure 12.** Remote sp$^3$ C-H chlorination mediated by copper species reported by Ball et al.

In our case, the regioselectivity derives from the geometry of substrates and catalysts, which is similar with the biomimetic controlled chemical selectivity. These results demonstrate that regioselective chlorination can be predictably achieved with catalyst 2.
The preference for methylene position can be explained by the non-bonded interactions between the substituents on the substrates and the pendant phenyl groups of the manganese porphyrins (Figure 13). However, a linear transition state geometry of H-atom abstraction cannot explain the interaction, as the tertiary C-H bonds could be abstracted by the reactive manganese oxo speices without difficulty (Figure 13A). On the other hand, a bent transition state of H-atom abstraction will result in significant interaction between the phenyl groups of porphyrins and the alkyl groups on the substrates (Figure 13B).

![Figure 13. Two possible C-H abstraction transition states](image)

2.4 Mechanistic studies of the Mn-catalyzed C-H bonds chlorination reaction

Intermediacy of free radicals

The high selectivity of halogenation motivated us to investigate the mechanism of this reaction. In normal Mn porphyrin catalyzed oxygenation reactions, radicals have been postulated to be the intermediates, which might be also the case in our chlorination system. Indeed, several lines of evidence implicated the presence of radicals in our
reactions. (Figure 10) The first indication of radical intermediates was found in the halogenation of norbornane. It is well-known that a process which gives rise to a norbornyl carbonium ion intermediate would give exclusively exo product, whereas free radical chlorination of norbornane gives predominantly exo-chloride with a discernible amounts of the endo-chloride. The appearance of both exo and endo chloride and bromide isomers in Mn porphyrin-catalyzed halogenation of norbornane implicates the production of norbornyl radical.

Figure 10. Evidence for radical intermediate

Further evidence for radical intermediate was obtained from chlorination of cyclooctane in the presence of radical scavenger. When an excellent radical scavenger such as bromotrichloromethane was used as the co-solvent with dichloromethane in the
chlorination of cyclooctane catalyzed Mn(TPP)Cl, cyclooctyl bromide was formed at the expense of cyclooctyl chloride. Since it is known that bromotrichloromethane reacts with radicals to form alkyl bromides, the presence of brominated product also indicates that radical is involved in the reaction.

The last line of evidence for radical intermediates was obtained by halogenation of norcarane. Boikess has examined the free radical chlorination of norcarane with molecular chlorine and the photoinduced reaction with tert-butyl hypochlorite. It was concluded that the cyclohexeyenyl methyl radical was the major rearrangement product of the 2-norcaranyl radical. In the chlorination of norcarane under standard conditions, 2-chloronorcarane and radical rearrangement product, cyclohexeyenyl methylchloride, were produced in 30% and 70%, respectively. Very interesting to note is that bromination of norcarane afforded the similar rearrangement/unrearrangement ratio. The observed product distribution indicates the presence of long-lived free radical intermediates. On the basis of the known rate constant \(k_r = 2 \times 10^8 \text{s}^{-1}\) for norcaranyl radical rearrangement, the apparent life time of the free radicals is calculated to be about 12 ns. Although the life-time of radicals appears too long to stay in the solvent cage waiting for the hypohalite anion to exchange with the hydroxide forming the Mn\textsuperscript{IV}-OCl species, we believe that part of the radicals could diffuse from the solvent cage and react with another equivalent of Mn\textsuperscript{IV}-OCl species.

Information concerning the nature of the reactive species in the chlorination reactions can be gained by comparing the kinetic isotope effect observed in our system with other
better-characterized systems. Such comparisons for reactions that involve H-atom abstraction are summarized in Table 2. It can be concluded from the comparisons that the reactive species in this system is not ClO•, Cl• or Br•, as these radicals could lead to smaller kinetic isotopic effect. Actually, the observed deuterium isotope effect listed in our system is similar with what was observed in Mn(TPP)Cl/PhIO system, in which O=MnV complexes have been proposed as the reactive species. The similarity in the KIE number between Mn(TPP)Cl catalyzed hydroxylation reaction and our chlorination reaction indicates that a common reactive species is involved.

Table 2 Comparison of kinetic isotope effects of various species in H-atom abstraction

<table>
<thead>
<tr>
<th>Reagent</th>
<th>Substrate</th>
<th>KIE</th>
</tr>
</thead>
<tbody>
<tr>
<td>ClO•</td>
<td>Toluene/toluene-d3</td>
<td>3.6</td>
</tr>
<tr>
<td>Cl•</td>
<td>Toluene/toluene-d3</td>
<td>1.3</td>
</tr>
<tr>
<td>Br•</td>
<td>Toluene/toluene-d3</td>
<td>4.9</td>
</tr>
<tr>
<td>Mn(TPP)Cl/PhIO(^a)</td>
<td>Cyclohexane/cyclohexane-d(_{12})</td>
<td>8.2±0.9</td>
</tr>
<tr>
<td>Mn(TPP)Cl/NaOCl/PTC</td>
<td>Cyclohexane/cyclohexane-d(_{12})</td>
<td>8.7±0.7</td>
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<tr>
<td>Mn(TPP)Cl/NaOCl/PTC</td>
<td>Toluene/toluene-d(_{3})</td>
<td>9.5±1.1</td>
</tr>
<tr>
<td>Mn(TPP)Cl/NaOBr/PTC</td>
<td>Cyclohexane/cyclohexane-d(_{12})</td>
<td>9.0±0.9</td>
</tr>
<tr>
<td>Mn(salen)/NaOCl/PTC</td>
<td>Cyclohexane/cyclohexane-d(_{12})</td>
<td>9.1±1.0</td>
</tr>
</tbody>
</table>

\(^a\) cited from Kruper thesis, University of Michigan.

Halogen source of the halogenation reactions
We then investigated how halogen was transferred to the products. In the usual manganese porphyrin catalyzed hydroxylation reaction, chlorinated products were sometimes observed as side products. The formation of alkyl chlorides from oxidation by PhIO/Mn(TPP)Cl system was postulated to result from either chlorine abstraction from dichloromethane or ligand-transfer chlorination of radical by Mn-porphyrin.\textsuperscript{45} The former is unlikely to be the major pathway in our system, because NaOBr can readily brominate different substrates and no chlorination products were observed in the bromination reaction when dichloromethane was used as the solvent.

\begin{figure}
\centering
\includegraphics[width=\textwidth]{figure11.png}
\caption{Two possible pathways for halogen transfer to the alkyl radical}
\end{figure}

In the latter case, the radical rebound to a Mn\textsuperscript{IV}-Cl complex, which is formed from replacement of hydroxide with a chloride ion, resulting in the chlorinated products and the starting manganese(III) catalyst (Figure 15, Pathway 1). The similar pathway has also been reported by Gross and his coworkers in the chlorine transfer from a dichloromanganese(IV) porphyrin complex to various olefins.\textsuperscript{46} However, our data are not supportive of this pathway, since when both chloride and bromide were present in the
NaOBr/MnTPPCl bromination system, only brominated products were produced and the yields of bromination reactions were not dependent on the presence of chloride.

Another halogen source that exists in our system is the hypohalite anion, which may exchange with hydroxide, forming a transient Mn$^{IV}$-OCl adduct. The radical then rebound to the Mn$^{IV}$-OCl, leading to chlorinated product and a Mn$^{V}=O$ complex (Figure 11, Pathway 2). We proposed that hypochlorite anion is responsible for the halogen transfer given the following consideration: (1) the bishypochloritomanganese(IV) porphyrin complex has been characterized and is able to transfer chlorine to unactivated hydrocarbon;\textsuperscript{47} (2) halogenation reaction by a mixture of sodium hypochlorite and sodium hypobromite solution produced both chlorinated and brominated products. Moreover, in the chlorination of cyclooctane reaction, we also noticed an intriguing phenomenon: the oxygenation products increased when the concentration of sodium hypochlorite decreased. Under standard reaction conditions, cyclooctyl chloride was produced as the major product with trace amounts of oxygenation products, whereas the selectivity of chlorination decreased to 78% when the concentration of sodium hypochlorite solution was diluted by 100 times. A similar phenomenon is also observed in NaOBr/MnTPPCl bromination system. Moreover, when 95% enriched O$^{18}$ Na$^{18}$OBr was used as oxidant, 90% O$^{18}$ was incorporated in the oxygenation products, indicating that the major source of oxygen in the oxygenation product was not from air. We assume that the reason for the hypochlorite dependent selectivity is that the ligand exchange rate is slow due to the low concentration of hypochlorite. In this scenario, oxygen rebound can compete with ligand exchange, resulting in the increase of oxygenation products.
Further evidence for the suggested metal bound hypochlorite species as halogen transfer reagent was provided by chlorination and bromination of norbornane by different catalysts (Table 5). It is well-known that, in the radical halogenation of norbornane, the exo/endo ratios of halogenated products are only related to the halogen source.\textsuperscript{48} Interestingly, when Mn(salen) was used as the catalyst in the chlorination and bromination of norbornane, the exo/endo ratios of halogenated products were significantly higher than when Mn(TPP)Cl or Mn(TMP)Cl are used as the catalysts. Importantly, studies on the mechanism of NaOCl/Mn(salen)Cl system by deuterium isotope effect, hypochlorite dependent selectivity, as well as intermediate study, showed that the reaction probably proceeded the same mechanism as Mn porphyrin catalyzed reactions. These results suggest that the manganese catalysts are involved in the halogen transfer step. Although Mn(TPP)Cl and Mn(TMP)Cl resulted in similar exo/endo ratio, this can be well explained by the long bond distance of O-X, which makes the chlorine or bromine atom far away from metal center.

Table 5. Chlorination and bromination of norbornane catalyzed by different catalysts\textsuperscript{a}

<table>
<thead>
<tr>
<th>Oxidant</th>
<th>Catalyst</th>
<th>Exo/endo ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sodium hypochlorite</td>
<td>Mn(TPP)Cl</td>
<td>9.5±0.5</td>
</tr>
<tr>
<td></td>
<td>Mn(TMP)Cl</td>
<td>9.8±0.4</td>
</tr>
<tr>
<td></td>
<td>Mn(salen)Cl</td>
<td>14±1.0</td>
</tr>
<tr>
<td>Sodium hypobromite</td>
<td>Mn(TPP)Cl</td>
<td>4.8±0.5</td>
</tr>
<tr>
<td></td>
<td>Mn(TMP)Cl</td>
<td>5.1±0.3</td>
</tr>
</tbody>
</table>
Chlorination of ethylbenzene.

When we tried to expand the chlorination reaction to substrates with weaker C-H bonds, such as ethylbenzene, however, the selectivity of chlorination decreased significantly. Under standard conditions, chlorination of ethylbenzene afforded 10% oxygenation products in addition to the usual chlorinated products. The ratio of oxygenation and chlorination products kept constant during the process of the reaction, suggesting that oxygenation products did not arise from hydrolysis of chlorinated products. Moreover, anaerobic reaction and O18 labeled experiment by using Na\textsuperscript{18}OBr/H\textsubscript{2}O\textsuperscript{18} showed that the alcohol product did not arise from the dioxygen trap reaction.

We interpret these results as evidence for the presence of both radical and carbocation intermediates in the ethylbenzene chlorination reaction. The carbocation intermediate, probably formed from further oxidation of the radical, can be trapped by water or hydroxide, resulting in alcohol products. The low ionization potential of the α-phenethyl radical results in a stronger tendency for the second electron transfer with respect to cyclic alkane. The carbocation intermediates have also been proposed in enzyme catalyzed hydroxylation reactions. Lipscomb and coworkers have reported that methane monooxygenase is capable of catalyzing the desaturation of ethylbenzene, which is rationalized by the formation of a substrate cationic intermediate.\textsuperscript{49} Although no desaturation products were detected in our system, it can be rationalized by the presence
of large amount of water and hydroxide anion, which could trap the carbocation intermediates efficiently.

### 2.5 Proposed mechanism of the Mn-catalyzed C-H bonds chlorination reaction

A likely mechanism for this new transformation is outlined in Figure 12. Basic sodium hypochlorite first oxidizes starting manganese(III) porphyrin to a Mn$^V$=O complex,\textsuperscript{50} which then abstracts a hydrogen atom from the substrate, resulting in a free alkyl radical and a Mn$^{IV}$-OH complex. The Mn$^{IV}$-OH complex then exchanges its ligand with another equivalent of hypochlorite anion, resulting in the formation of a Mn$^{IV}$-OCl complex. In the final step, radical abstracts halogen from the Mn$^{IV}$-OCl complex, forming the chlorinated product and regenerating Mn$^V$=O complex. We postulate that the coordinated hydroxide ligand lower the redox potential of the Mn$^{IV}$-OH intermediate, therefore slowing down the rebound rate of the alkyl radical, suppressing the formation of the alcohol products. Recently Sam P. de Visser has reported the DFT calculation on our chlorination mechanism, which predicts a halogenation mechanism in line with that proposed by experiments with an initial hydrogen atom abstraction followed by ligand exchange and halogen transfer.\textsuperscript{51}
2.6 Experimental section

Sodium hypochlorite (NaOCl, Aldrich) was standardized spectroscopically ($\lambda_{\text{max}} = 292$ nm, $\varepsilon = 350$ M$^{-1}$ cm$^{-1}$). Sodium hypobromite was prepared by mixing NaOCl with 10% excess sodium bromide (NaBr, 99.99% Aldrich) and was used immediately. 5,10,15,20-tetraphenylporphinatomanganese(III) chloride Mn$^{\text{III}}$(TPP)Cl was purchased from Aldrich. 5,10,15,20-tetramesitylporphyrinomanganese(III) chloride Mn$^{\text{III}}$(TMP)Cl was prepared by metallation of tetramesitylporphyrin. Bicyclo[4.1.0] heptane (norcarane) was prepared.
according to literature method. Dichloromethane (HPLC grade) was distilled from CaH₂. Water was distilled and deionized with a Millipore system. Other materials were purchased of the highest purity from Aldrich and used without further purification.

Instrumentation:
NMR spectra were obtained on a 500 MHz Varian INOVA spectrometer and are reported in ppm using solvent as an internal standard (CDCl₃ at 7.26 ppm). GC/MS analyses were performed on an Agilent 7890A Gas chromatography equipped with an Agilent 5975 mass spectrum detector. Internal standard was used for quantification.

Catalytic chlorination of simple hydrocarbons:
Under a nitrogen atmosphere, 2 mL NaOCl (0.33 M, pH = 11) was added to a solution of manganese porphyrin (0.013 mmol), tetrabutylammonium chloride (TBACl, 0.027 mmol), substrates (2 mmol) in 1 mL dichlormethane in a 4 mL sealed vial. The biphasic mixture was stirred smoothly under nitrogen. Reactions were run at ambient temperature and completion of the reactions was indicated by disappearance of the brown red color of high valent porphyrin and formation of the green color of manganese(III) species. The catalysts were removed by a short silica gel column eluted by CH₂Cl₂ and the solution was analyzed by GC/MS. Yield of chlorination was calculated based on oxidant added. The assignment of the products was based on the comparison of GC retention time and fragmentation with authentic samples. The products of trans-decalin chlorination were assigned by comparing the GC retention time with authentic samples, prepared by
treating corresponding alcohol with thionyl chloride. The ratio of equatorial: axial is ~1 for C1 and C2 chlorination.

**Catalytic chlorination of complex substrates**

5α-cholestane chlorination: Under a nitrogen atmosphere, 2mL NaOCl (0.33 M, pH = 11) was added to a solution of Mn(TMP)Cl (0.033 mmol), tetrabutylammonium chloride(TBAOCl, 0.027 mmol), cholestane (0.22 mmol) in 1mL dichlormethane in a 4ml sealed vial. The biphasic mixture was stirred smoothly under nitrogen. The aqueous layer was removed after 12 hours and another equivalent fresh oxidant was added under N2. The reaction was run for another 12 hours and the crude mixture was analyzed by NMR. The assignment of the products was based on the known chemical shift: 2α-Cl, 4.06 (t of t), 3β-Cl, 3.86 (t of t), 3α-Cl, 4.50 (sharp, m). The assignment was further confirmed by comparing the GC retention time and MS fragmentation with authentic samples, prepared by published procedure.
Figure S1. GC/MS trace of 5α-cholestane of chlorination
Figure S2. 1H NMR of 5α-cholestane chlorination

Sclareolide chlorination: Procedure is similar to the “cholestane chloriantion”, with the exception that products were purified by flash chromatography (5% EtOAc/hexanes) and starting material was recycled twice. $^1$H NMR (500MHz, CDCl3) δ 4.22 (tt, J=12.1, 4.2 Hz, 1H), 2.43 (dd, J=15.5, 14.8Hz, 1H), 2.27 (dd, J=16.1, 6.5Hz, 1H), 2.10 (dt, J=12.0, 3.4Hz, 1H), 2.05-1.96 (m, 3H), 1.90(dq, J=14.3, 3.7Hz, 1H), 1.70(td, J=12.6, 4.2Hz, 1H) 1.55-1.33(m, 6H), 1.12(dd, J=9.9, 2.8Hz, 1H), 0.96 (s, 3H), 0.96(s, 3H), 0.89(s, 3H)
A.

B.

Figure S3. $^1$H NMR of sclareolide chlorination

2.7 References


Chapter 3.

Oxidative Aliphatic C-H Fluorination Using Fluoride Ion Catalyzed By a Manganese Porphyrin

3.1 Abstract

The replacement of a fluorine atom for a hydrogen atom could have profound effects on the biological properties of organic molecules. As a result, organofluorine molecules are widely used as pharmaceuticals, agrochemicals, materials and imaging agents. Due to the importance of fluorine atom, over the past ten years, organic chemists have developed a variety of methods that can selectively construct carbon-fluorine bond. However, most of these methods dealt with the formation of aromatic C-F bonds, whereas few methods were available that can selectively convert unactivated aliphatic C-H bonds to C-F bonds. In this chapter, we report the first selective aliphatic C-H fluorination reaction catalyzed a bulky manganese porphyrin. The method use iodosylbenzene as an oxidant, the combination of tetrabutylammonium fluoride and silver fluoride as the fluorine source. Under mild conditions, various hydrocarbons, terpenoids and steroids can be selectively fluorinated. Mechanistic studies suggest that the reaction involves an oxoMn\textsuperscript{V} species responsible for the C-H abstraction and a \textit{trans}-difluoro-Mn\textsuperscript{IV} complex involved in the fluorine transfer step.
3.1 Background: organofluorine chemistry

3.1.1 Importance of the fluorine atom

In 1886, elemental fluorine was first isolated by a French chemist, Henri Môissan, through electrolysis of potassium fluoride in anhydrous hydrogen fluoride.\(^1\) This discovery was later awarded the Nobel Prize in 1906. At that time, no one could imagine the important application of this element one century later. Indeed, the development of fluorine chemistry started with the Manhattan Project in 1940s, which required the preparation of uranium hexafluoride (\(\text{UF}_6\)) from fluorhydric acid and elemental fluorine.\(^1\)

In the early 1950s, the organic chemistry of fluorine really emerged. During the studies of some fluorinated molecules such as fluorinated anesthetics and an antitumor drug molecule, 5-fluorouracil (Figure 1), medicinal chemists found out that incorporation of a fluorine atom into a molecule has dramatic effect on its biological activity.

![Figure 1. Structure of 5-fluorouracil](image)

5-fluorouracil is an antineoplastic agent, which shows high anticancer activity by inhibiting the enzyme thymidylate synthase. Since the synthesis of 5-fluorouracil in 1957, fluorine incorporation is commonly used in medicinal chemistry in order to affect the bioavailability, metabolic stability and protein interaction. The percentage of drug molecules containing at least one fluorine atom has increased from 2% in 1970 to 20% in 2010, with six drugs in the top 12 selling drugs, including Faslodex (anticancer),
Fluoxetine (antidepressant), Flurithromycin (antibacterial) and Efavirenz (antiviral) (Figure 2). In the agrochemical area, fluorinated compounds increases from 3% in 1970 to almost 30% in 2010.

![Examples of fluorine containing pharmaceuticals](image)

**Figure 2.** Examples of fluorine containing pharmaceuticals

The effects of fluorine on organic molecules mainly origin from the combination of the following properties of fluorine atom\(^1\): small size, very strong carbon-fluorine bond, strong electronegativity, and excellent overlap of the 2s or 2p orbitals with the corresponding orbitals of carbon. The van der Waals radius of fluorine (1.47 Å)\(^4\) is only 20% larger than that of hydrogen, making fluorine atom a excellent substitution for hydrogen atom. The BDE of CH\(_3\)-F is about 5 kcal/mol stronger than that of CH\(_3\)-H and therefore replacement of C-H bond with C-F bond can effectively block metabolic process via hydroxylation of C-H bonds. In addition, the incorporation of fluorine atom adjacent to functional groups such as hydroxyl and amino groups can affect the electronic
density on these groups, resulting in the decrease of the pKa value as well as Lewis basicity.

3.1.2 Organofluorine molecules and related enzymes in nature

Despite the great importance of fluorine atom, nature, however, is not good at utilizing this element. Although biochemistry has found highly selective ways to transform C–H bonds into alcohols, halides and olefins using reactive metal-oxo intermediates within enzymes, a notable exception is incorporation of fluorine atom. In contrast to more than 3000 thousands naturally occurring organochlorine molecules, there are only about 30 naturally occurring organofluorine compounds, 8 of which are fatty acids derivatives (Figure 3).

![Figure 3. Examples of naturally occurring fluorinated molecules](image)

Up till now, the only fluorinase enzyme that has been characterized form C-F bonds by nucleophilic displacement at the preactivated C center of S-adenosylmethionine(SAM) (Figure 1). Fluorinase, also known as 5’-fluoro-5’-deoxyadenosine synthase, was first isolated from bacterium *Streptomyces cattleya* by O’hagen and coworkers in 2002.\(^5,6\) This
enzyme can catalyze the formation of 5’-FDA from SAM and a fluoride ion. Observation from the isotopic labeling indicates that the fluorination reaction occurs with a stereochemical inversion of C5’ carbon, suggesting a $S_N2$ pathway for the fluorinase.

![Figure 1. Mechanism of fluorination by fluorinase](image)

Crystal structure of the fluorinase was reported by O’Hagen and Naismith et al. in 2004. Crystallography study shows that in the 5’-FDA structure Ser-158 forms two hydrogen bonds through the main chain NH and the side chain OH, to the organic-bound fluorine atom, suggesting a putative site for fluoride ion binding. In addition, there is no crystallographically located water hydrogen bonding to the fluorine atom. These results suggest that fluoride ion becomes completely dissociated from its hydrated water.

3.1.3 Fluorine in positron emission tomography

Positron emission tomography (PET) is a nuclear medical imaging technique that produces a three-dimensional image of functional process in vivo. To conduct a PET scan, a short-lived radioactive tracer isotope is chemically incorporated into a
biologically active molecule, which is then injected into the living subject. The radioactive tracer isotopes typically used in PET study include carbon-11 ($t_{1/2}=20$ min), nitrogen-13 ($t_{1/2}=10$ min), oxygen-15 ($t_{1/2}=2$ min), fluorine-18 ($t_{1/2}=110$ min) and rubidium-82 ($t_{1/2}=1.27$ min). One of the important reasons that $^{18}$F traces is advantageous is its longer half-life compared to other commonly used radionuclides. Therefore, PET imaging using $^{18}$F is developing rapidly in the area of medicinal chemistry. At present, the most frequently used radiotracers in PET scanning is 2-deoxy-2-[$^{18}$F]fluoro-D-glucose [$^{18}$F]FDG (Figure 5).

![Figure 5. Structure of 2-deoxy-2-[18F]fluoro-D-glucose](image)

Although $^{18}$F-PET technology has been used in oncology for decades, synthesis of complex $^{18}$F labeled tracers remains challenging. For $^{18}$F labeling, chemical challenge is due to the short life of the $^{18}$F, which means that the carbon fluorine bond formation reactions have to be in the late stage in the synthesis and be completed within very short amount of time. Recently, the Ritter group has reported a fluoride-derived electrophilic late-stage fluorination reagent for PET imaging (Figure 2). This protocol enables the synthesis of $^{18}$F-labeled functionalized molecules, which would be particularly difficulty to synthesize by conventional fluorination methods.
Figure 2. Fluoride derived electrophilic fluorination reagent for PET

3.2 Methods for constructing carbon-fluorine bonds

3.2.1 Aromatic carbon-fluorine bonds formation

Synthesis of aryl fluorides by conventional transition-metal catalyzed transformations is challenging. The difficulties associated with Ar-F bond formation is due to the high electronegativity, high reactivity and the high basicity of naked fluoride. In addition, reductive elimination of carbon-metal-fluorine complexes is much more difficult than those of C-C, C-O and C-O because of the strong metal fluoride bonds.

Strategies for aromatic fluorination developed over the past five years have provided novel and unprecedented access to complex aryl fluorides. In 2006, Sanford and coworkers reported the first example of a palladium catalyzed aromatic C-F bonds formation using a directing group strategy. The reactions were achieved under oxidizing conditions, using an electrophilic fluorination reagent, N-fluoro-2, 4, 6-
trimethylpyridinium tetrafluoroborate (Figure 3).\textsuperscript{10} A variety of phenylpyridine derivatives were fluorinated at the ortho positions with this protocol. It is believed that the nitrogen atom on the pyridine ring can coordinate with the palladium catalyst, leading to the activation of the C-H bonds through five or six-membered palladacyclic intermediates.

\begin{figure}[h]
\centering
\includegraphics[width=0.5\textwidth]{figure3.png}
\caption{Pd catalyzed C-H fluorination reaction developed by Sanford et al.}
\end{figure}

In 2009, the Yu group reported a similar palladium catalyzed electrophilic fluorination of N-benzyltriflamide derivatives with NMP (N-methylpyrrolidinoe) as a crucial promoter (Figure 8).\textsuperscript{11} A similar electrophilic fluorination reagent, N-fluoro-2,4,6-trimethylpyridinium triflate was used in this study. The triflamide directing group can be readily converted to various other useful functional groups, including cyanides, amines, aldehydes, azides and esters.

\begin{figure}[h]
\centering
\includegraphics[width=0.5\textwidth]{figure4.png}
\caption{Pd catalyzed C-H fluorination reaction developed by Yu et al.}
\end{figure}
In 2009, the Buchwald group reported the first palladium(0) catalyzed cross coupling reaction for aromatic fluoride formation (Figure 9). In that study, a large variety of aryl triflates were converted to the corresponding aryl fluorides with CsF as the nucleophilic fluorine source. The use of a bulky monodentate ligand, t-Bu-Brettphos was shown to be the key for the success for the Ar-F bond formation as this ligand can prevent the formation of a bridging fluorine in palladium intermediate which may inhibit the reductive elimination in the C-F bond formation step. Various substrates, including electron-poor, ortho, ortho-disubstituted arenes, as well as heterocycles are compatible with the reaction conditions.

![Figure 5. Pd-catalyzed fluorination of aryl triflates by Buchwald et al.](image)

The Ritter group at Harvard University has recently reported several important works on aryl fluoride bonds formation. In 2008, they reported the fluorination of arylboronic acids via stoichiometric palladium complexes. Later in 2009, this team reported the first silver mediated C-F bond formation. Arylstannes afforded the corresponding aryl fluorides when reacted with F-TEDA-PF$_6$ in the presence of silver triflate. The reaction can be applied to late-stage fluorination of complex bioactive molecules with a variety of functional groups, such as camptothecin and quinine, enabling access to complex aryl fluorides (Figure 10).
3.2.2 Aliphatic carbon-fluorine bonds formation

Traditional methods for introducing fluorine into a saturated framework require harsh conditions and highly toxic fluorine sources, such as elemental fluorine, that require specialized equipment and are not compatible with many typical substituents and functional groups.

Advances in the field of enantioselective organocatalytic fluorination have been reported that are capable of introducing a fluorine atom adjacent to a carbonyl group. In 2005, MacMillan et al. reported the first enantioselective organocatalytic fluorination of aldehyde. The use of imidazolidinone as an asymmetric catalyst has been found to mediate the fluorination of various aldehyde substrates with N-fluorobenzenesulfonimide (NFSI) serving as an electrophilic fluorine source (Figure 11).

![Figure 10. Ag-catalyzed late stage fluorination developed by Ritter et al.](image1)

![Figure 11. Organocatalytic fluorination of aldehyde reported by the MacMillan et al.](image2)
In 2010, Doyle and coworkers have reported an enantioselective ring opening of epoxides with fluoride ion using a chiral amine and chiral Lewis acid as cooperative catalysts. With benzoyl fluoride as a soluble, latent source of fluoride anion, a variety of five to eight membered cyclic epoxides can be converted to β-fluoroalcohols with up to 95% ee (Figure 6).  

\[ \text{Figure 6. Enantioselective ring opening of epoxides reported by Doyle et al.} \]

In 2009, a chemo-enzymatic fluorination strategy that combines initial cytochrome P450 mediated oxygenation with deoxofluorination by DAST has been reported by the Arnold group (Figure 13). This strategy was applied to a variety of biologically active molecules, including a non-steroidal anti-inflammatory drug molecule, ibuprofen derivate, achieving mono-and polyfluorination at unreactive sites.
Decarboxylative fluorination has also recently been reported to construct aliphatic C-F bonds. In 2012, the Sammis group has, for the first time, reported the transfer of fluorine atom to alkyl radicals, generated by thermolysis of the corresponding peresters through decarboxylation pathway. In the same year, the Li group reported a silver-catalyzed decarboxylative fluorination of aliphatic carboxylic acid (Figure 8). With AgNO₃ as the catalyst, Selectfluor as the fluorine source, a variety of aliphatic carboxylic acids undergo efficient decarboxylation, forming the corresponding alkyl fluorides in aqueous solution. Mechanistic study suggests that alkyl radicals are involved in the fluorination reactions.

**Figure 7.** Chemo-enzymatic fluorination of a pro-drug ibuprofen methyl ester

**Figure 8.** Ag-catalyzed decarboxylative fluorination reported by Li et al.
Since the appearance of our publication in 2012, several groups have reported catalytic methods for constructing aliphatic C-F bonds. The Lectka group have reported a aliphatic, benzylic and allylic C-H fluorination reaction using a polycomponent catalytic system involving commercially available Selectfluor, N-hydroxyphthalamide, an anionic phase transfer catalyst (KB(C₆F₅)₄), and a copper(I) bis(imine). The Li group has reported silver catalyzed intramolecular aminofluorination and phosphonofluorination of unactivated alkenes. The Doyle group has reported the first catalytic allylic C-H fluorination reaction using a nucleophilic fluoride source. With a Pd/Cr cocatalyst system, simple olefin substrates undergo fluorination with Et₃N·3HF in good yields with high branched : linear regioselectivity. In 2014, a photocatalyzed aliphatic fluorination was achieved by employing ultraviolet light and a photosensitizer, 1,2,4,5-tetracyanobenzene.

Despite these impressive progresses on fluorination, a method for the selective and efficient incorporation of fluorine at unactivated aliphatic C-H sites within a target molecule is singularly absent in the repertoire of chemical synthesis. The paradoxical challenge of achieving selective aliphatic fluorination lies in discovering a catalyst that is both highly reactive and predictably selective for activating these ubiquitous yet unactivated sp³ C–H bonds. A strategy was suggested to us by our recent discovery of an unusual methylene-selective C-H chlorination using the bulky manganese porphyrin catalyst, Mn(TMP)Cl, as aforementioned. We anticipated that site-selective fluorination could be achieved analogously if a suitable fluoride source could be found that redirected the biomimetic oxygen rebound scenario to fluorine, in the manner of halogenating
metalloenzymes such as SyrB2. Moreover, we sought a route that could use fluoride ion directly in a single-step process to empower $^{18}$F PET imaging applications to a wider variety of molecules. We report herein the first cases of manganese-catalyzed oxidative C-H fluorination using fluoride ion.

3.3 Development of a manganese porphyrin catalyzed aliphatic C-H fluorination reaction

3.3.1 Fluorination of small molecules catalyzed by Mn(TMP)Cl

We found that a variety of simple alkanes, as well as more complex molecules, can be fluorinated effectively in the presence of catalytic amounts of a manganese porphyrin, Mn(TMP)Cl. This oxidative aliphatic fluorination reaction is driven by iodosylbenzene as oxo-transfer agents, using a combination of silver fluoride/tetrabutylammonium fluoride trihydrate as the fluoride source.

We first carried out the fluorination reaction using a variety of simple hydrocarbons as substrates. The results for the initial exploratory reactions of a panel of simple alkanes are presented in Table 1. Typical cycloalkanes afforded mono-fluorinated products in 60-80% yield at ~70% conversion. Cyclohexane, cycloheptane and cyclooctane were converted to their monofluorinated products with ~50% yield. Two products, 1-fluoroadamantane and 2-fluoroadamantane, were detected in the adamantane fluorination reaction with a ratio of 1:1.4. Norbornane was fluorinated at the methylene position with an exo/endo ratio of 5.7. Interestingly, fluorination of norcarane, a radical clock substrate, provided a mixture of rearranged and unrearranged mono-fluorinated products with a
ratio of 1:2. There were negligible amounts of di-fluorides produced at this level of conversion, probably due to the electronic deficiency of the products caused by the fluorine atom.

In addition, we have carried a series of control experiments. No fluorination products were detected in control experiments that omitted the manganese porphyrin, PhIO or silver fluoride. When tetrabutylammonium fluoride was omitted in the reactions, large amounts of oxygenated products were detected. Moreover, ultra-dry conditions are not required. When the reaction was carried aerobically, the yield of fluorination decreased significantly and ketone compounds were detected as the major products.

### 3.3.2 Reaction scope of the manganese porphyrin catalyzed C-H fluorination

To further investigate substrate scope of the fluorination reaction, we prepared a series of cyclic organic compounds bearing different substituents, including esters, alcohols, ketones, and amides. As can be seen from Table 1, all of these substrates were fluorinated with moderate to good yields. Fluorination of methyl cyclohexylcarboxylate (entry 7) and methyl cyclohexanol (entry 8) afforded trans C3 fluoride as the major products. The slight preference for C3 over C4 is probably due to the release of the torisional strain between the bulky equatorial group (COOMe and Me/OH) and vicinal methylenes, generated by unfavorable 1,3-diaxial interactions at C1 and C3, upon C3 C-H oxidation. In addition, for the fluorination of methylcyclohexanol, fluorine atom is at the cis position of the hydroxyl group, suggesting that hydroxyl group may severe as a directing group for both the C-H activation and the fluorine transfer steps.
Five- and seven-membered ring containing molecules (entry 9, 10, 12) were all exclusively fluorinated at C3 and C4 position, respectively. Fluorination of cycloheptanone afforded the $\gamma$-fluorinated compound as the major product. The preference for $\gamma$ position over $\alpha$ and $\beta$ positions can be easily explained by the electronnегativity of the ketone group, which decrease the electron density on the $\alpha$ and $\beta$ methylene groups. This was also the case for O-benzoyl-cycloheptanol fluorination, suggesting the stereoelectronic effect on the selectivity of this novel fluorination reaction.

Table 1. Manganese porphyrin-catalyzed fluorination of simple molecules. Reactions were run for 6 to 8 hours at 50 °C under N$_2$ in 3:1 CH$_3$CN/CH$_2$Cl$_2$ solvent, 1.5 mmol substrate, 4.5 mmol silver fluoride, 6 to 8 mol% catalyst, 0.3 equiv. tetrabutlammonium fluoride (TBAF) trihydrate and 6 to 8 equiv. iodosylbenzene. Yields were determined by integration of gas chromatography traces using naphthalene as the internal standard. Unless otherwise noted, all major fluorination products were isolated as single compounds.
<table>
<thead>
<tr>
<th>No.</th>
<th>Structure</th>
<th>Reaction</th>
<th>Yield/DR</th>
<th>Compound</th>
<th>Structure</th>
<th>Yield/DR</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="image1.png" alt="Structure 1" /></td>
<td><img src="image2.png" alt="Structure 2" /></td>
<td>2, 49% (73%)</td>
<td><img src="image3.png" alt="Structure 3" /></td>
<td><img src="image4.png" alt="Structure 4" /></td>
<td>C₄ 14%</td>
</tr>
<tr>
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<td><img src="image5.png" alt="Structure 5" /></td>
<td><img src="image6.png" alt="Structure 6" /></td>
<td>3, 51% (71%)</td>
<td><img src="image7.png" alt="Structure 7" /></td>
<td><img src="image8.png" alt="Structure 8" /></td>
<td>8, 46% dr=6:1</td>
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<tr>
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<td><img src="image10.png" alt="Structure 10" /></td>
<td>4, 55% (79%)</td>
<td><img src="image11.png" alt="Structure 11" /></td>
<td><img src="image12.png" alt="Structure 12" /></td>
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<td>5, 53% (74%)</td>
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<td><img src="image38.png" alt="Structure 38" /></td>
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<td><img src="image42.png" alt="Structure 42" /></td>
<td>11, 51% dr=1.5:1</td>
<td><img src="image43.png" alt="Structure 43" /></td>
<td><img src="image44.png" alt="Structure 44" /></td>
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<tr>
<td>12</td>
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<td><img src="image46.png" alt="Structure 46" /></td>
<td>12a, cis/trans=1:1</td>
<td><img src="image47.png" alt="Structure 47" /></td>
<td><img src="image48.png" alt="Structure 48" /></td>
<td>12b, C3 27%</td>
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</tbody>
</table>

*Rearranged product identified by the characteristic m-(CH₂F) peak in the mass spectrum.†Isolated as diastereomers.

### 3.3.3 Fluorination of complex molecules catalyzed by Mn(TMP)Cl

Having demonstrated that it is possible to redirect manganese-catalyzed hydroxylation to fluorination, we next aimed to apply this novel fluorination reaction to more complex molecules. We first chose *trans*-decalin as a model substrate, since we have shown previously that Mn(TMP)Cl can catalyze selective chlorination of this molecule. Interestingly, reaction of *trans*-decalin under our standard fluorination conditions...
afforded methylene fluorination products with a 3.5 to 1 preference for C2 over C1 (Figure 9). A similar regioselectivity was observed in the analogous, manganese-catalyzed chlorination reaction we have recently reported. The similarity in the product distribution indicates that a similar reactive oxo- or dioxo-manganese(V) intermediate was responsible for abstracting the hydrogen in both reactions.  

![Methylene selectivity](image)

**Figure 9.** Fluorination of trans-decalin catalyzed by Mn(TMP)Cl

Sclareolide, a plant-derived terpenoid with antifungal and cytotoxic activities, has recently been studied in several C-H activation reactions. Baran *et al.* have shown that amination of sclareolide catalyzed by a rhodium catalyst developed by the Dubois group, [Rh₂(esp)₂], provided C-2 aminated products with excellent selectivity.  

White and Chen have reported a 1.4/1 (C2/C3) selectivity in the a non-heme iron complex, Fe(PDP), catalyzed C-H oxidation reaction. Interestingly, it has also been shown that oxidation of sclareolide by a strong oxidant TFDO can also provide a mixture of C2 and C3 oxidation products with a ratio of 1:1.7.

We are gratified to find that fluorination of sclareolide using our standard conditions afforded C2 and C3 methylene-fluorinated products in an overall 58% yield (Figure 10). C2-fluorination was favored by nearly 3:1, probably due to the steric hindrance of the
gem-dimethyl groups at C4. The products could be separated chromatographically. By contrast, reaction of this molecule using Selectfluor\textsuperscript{32} afforded an intractable mixture.

**Figure 10.** Mn-catalyzed fluorination of sclareolide
Fluorine-substituted steroids, such as flumethasone and fluasterone, have been found to be beneficial in blocking metabolic pathways and $^{18}$F-fluorodihydrotestosterone has shown promise as a radiotracer for imaging prostate cancer in men. Because a direct, late-stage steroid fluorination protocol could greatly facilitate such applications, we sought to apply this manganese-catalyzed fluorination reaction to simple steroids. We examined the fluorination of 5α-androstan-17-one, which contains 27 unactivated $sp^3$ C-H bonds (Figure 17). Analysis of this molecule suggested that the carbonyl group would electronically deactivate ring D. Rings B and C are sterically hindered, leaving the methylene groups of A ring as the most likely sites for hydrogen abstraction. Consistent with this analysis, and despite the complexity of the molecule, remarkably, only the C2 and C3 positions in the A ring were fluorinated in an overall yield of 55% (78% of the product distribution at 70% conversion). The products of the reactions could be readily separated by column chromatography and structurally assigned by the diagnostic $^{19}$F-NMR spectrum and the characteristic proton J-couplings. A ~5:1 $\alpha/\beta$ diastereoselectivity was observed for both C2 and C3 positions, probably reflecting the steric effect of the axial methyl group at C10.

**Figure 17.** Mn-catalyzed fluorination of 5α-androstan-17-one

Reaction of bornyl acetate afforded a 55% yield of a single product, exo-5-fluoro-bornyl acetate (Figure 11). The characterization of this product was based on C-H correlation
NMR and $^{19}$F-NMR spectroscopy.\textsuperscript{35} We anticipated that the C5 position of camphor would also be accessible, in analogy to the selectivity of P450cam (CYP101).\textsuperscript{36} However, treating camphor under the standard fluorination conditions resulted in 95% recovered starting material. We attribute the low reactivity in this case to the electron withdrawing carbonyl group, which apparently deactivates the entire molecule toward fluorination. These results highlight the subtle electronic effects on both the reactivity and selectivity of the fluorination reaction.

\textbf{Figure 11.} Mn catalyzed fluorination of bornyl acetate

\textbf{3.4 Mechanism of the Mn-catalyzed aliphatic C-H fluorination reaction}

Clearly, this new fluorination protocol involves neither electrophilic nor nucleophilic fluorine chemistry. Rather, the data indicate a Mn-mediated radical pathway. We suggest the catalytic cycle shown in Figure 19, although there are numerous aspects of these transformations that will require further elucidation. Oxidation of the resting Mn(TMP)Cl catalyst in the presence of fluoride ion could afford a reactive oxomanganese(V) species\textsuperscript{29}, O=Mn\textsuperscript{V}(TMP)F, which then abstracts a substrate hydrogen atom to produce a carbon-centered radical and a HO-Mn\textsuperscript{IV}-F rebound intermediate.
The key step in forming the fluorinated products is the capture of the incipient substrate radicals either by HO-Mn$^{IV}$-F or a trans-difluoro-manganese(IV) species. There is no precedent for such a fluorine atom transfer. In this important regard the fluorination reaction differs from the manganese/hypochlorite chlorinating system we have described. Chloride ion is rapidly and reversibly oxidized to hypochlorite by oxoMn$^V$ porphyrins. Although HOF is known, there is no evidence that fluoride is oxidized in that way under these conditions. The importance of the hypochlorite in the Mn/-OCl case is illustrated by the observation of C-H bromination in the presence of hypobromite even with a large excess of chloride ion present. We attribute the unusual methylene selectivity observed in both the fluorination and chlorination reactions to stereoelectronically enforced steric clashes between the substrate and the approaching oxoMn$^V$ catalyst (Figure 13). The LUMOs in a low-spin, $d^2$ oxoMn$^V$ complex are expected to be the two, orthogonal Mn-O p* orbitals, which would direct the approach of the scissile C-H bond into a bent p*-approach trajectory.\textsuperscript{29,39} 

**Figure 12.** Proposed catalytic cycle of the Mn-catalyzed C-H fluorination reaction
We conducted a number of experiments to examine this mechanistic hypothesis. Initial C-H hydroxylation was ruled out by controls showing that cyclohexanol was oxidized to cyclohexanone and no cyclohexylfluoride was detected under the fluorination conditions. Also, the hydroxyl group of 1-methylcyclohexanol is stable to the reaction conditions (Table 1, entry 8). Deuterium kinetic isotope effects were evaluated by the reaction of a 1:1 mixture of cyclohexane and cyclohexane-d$_{12}$, producing an intermolecular competitive KIE of 6.1. A similar value (5.7) was observed with a mixture of ethylbenzene and ethylbenzene-d$_{10}$. The large KIE indicates that C-H bond cleavage is the rate-limiting step in the reaction, consistent with typical manganese porphyrin catalyzed hydroxylation reactions. Furthermore, fluorination of norcarane, a diagnostic radical clock substrate $^{40}$, afforded 2-fluoronorcaranes and a significant amount of the rearranged fluorinated product, 3-fluoromethylcyclohexene (7), which is indicative of a carbon radical ring-opening process (Table 1, entry 6). The 2:1 ratio of these cyclopropylcarbinyl and homoallyl fluorides indicates a short radical lifetime of 2.5 ns, given the ring-opening rate constant for the 2-norcaranyl radical of $2 \times 10^8$ M$^{-1}$ s$^{-1}$. 

**Figure 13.** Inferred stereoelectronics for H abstraction
The identification of trans-difluoroMn$^{IV}$ (TMP) as the likely fluorinating agent was made possible by its isolation and structural characterization (Figure 14). We were able to obtain pure crystals of the Mn$^{IV}$ (TMP)F$_2$ by treating Mn$^{IV}$ (TMP)Cl$_2$ with excess AgF. The molecular structure of this compound showed two axially bound fluoride ions with F-Mn$^{IV}$-F bond lengths of 1.7931(17) and 1.7968(16) Å. These distances are very close to those of diammonium hexafluoromanganate(IV), the only other fluoromanganese(IV) species to be structurally characterized to date.  

Figure 14. Molecular structure of trans-Mn$^{IV}$ (TMP)F$_2$ drawn at 50% probability of the electron density. Highlighted atoms are F (yellow), Mn (magenta) and N (blue) (hydrogen atoms omitted for clarity).

We found that stoichiometric amounts of Mn$^{IV}$ (TMP)F$_2$ could replace silver fluoride in a single-turnover C-H fluorination of cyclooctane using Mn(TMP)Cl and iodosylbenzene. A 43% yield of cyclooctyl fluoride was obtained based on added Mn$^{IV}$ (TMP)F$_2$. The
moderate fluoride formation is probably due to the instability of the high valent manganese species. Further, thermal decomposition of azo-bis-α-phenylethane to generate the α-phenethyl radical in the presence of Mn^{IV}(TMP)F₂ led to a 41% yield of 1-fluoroethylbenzene. These observations indicate that after initial hydrogen abstraction, Mn^{IV}(TMP)F₂ traps the substrate radicals in the fluorine delivery step. The role of silver fluoride in this scenario under catalytic conditions is to replenish the manganese(IV) fluoride during turnover. Although a direct reaction between the substrate radicals and AgF might also be considered, the reaction between AgF and phenethyl radicals generated in situ from azo-bis-α-phenylethane afforded only trace amounts of fluorinated products.

3.5 DFT calculation on the fluorine transfer step

We have explored the potential energy landscape and electronic structures of the intermediates and transition states proposed in Figure 22 using DFT computations and a polarizable continuum solvation model. We found that fluorine atom transfer from Mn(THP)F₂ to a cyclohexyl radical in the equatorial configuration was predicted to occur with a surprisingly low activation barrier of only 3 kcal/mol, very similar to the oxygen rebound barrier for hydroxylation reactions catalyzed by oxomanganese porphyrins. A slightly higher transition state was located for delivery of fluorine to a cyclohexyl radical in an axial configuration (4.2 kcal/mol). Further, the calculated barrier for fluorine transfer was ~3 kcal/mol lower for the trans-difluoroMn^{IV} species (Figure 15, X = F) than for the analogous hydroxy-fluoride (Figure 22, X= OH), implicating a much faster reaction rate for the difluoride. Consistent with this low barrier for fluorine transfer, the
transition state is very early in the reaction trajectory, showing an exceedingly long C—F distance of 2.48 Å and a Mn—F distance that is only very slightly elongated from the starting the manganese(IV) difluoride. The visible spectrum of the reaction mixture was complex, apparently due to the presence of several forms of the catalyst during turnover. However, the good yield of 1-fluoroethylbenzene from the generation of phenethyl radical in the presence of Mn(TMP)F$_2$ provides experimental support for these computational predictions that manganese(IV) fluorides of this type are excellent radical fluorinating agents.

Figure 15. Energy landscape for fluorine rebound to the cyclohexyl radical. (A) Schematic depiction of fluorine atom abstraction from X-MnIV-F by the cyclohexyl radical in the equatorial configuration and the influence of the axial ligand (X = OH and F) on the fluorine abstraction potential energy surface (enthalpies in kcal/mol at 298 K).
Bond distances shown are calculated for X = F. (B) Frontier orbital depiction of the transition state (TS) for fluorine transfer.

We are encouraged by the promising initial results described here for the selective fluorination of simple hydrocarbons, substituted cyclic molecules, terpenoids and steroid derivatives. The yields are sufficiently high and the techniques are sufficiently simple that the reaction can be performed without specialized apparatus or complicated precautions, other than normal care that should be taken whenever strong oxidants or fluoride-containing reagents are used. Given that the source of fluorine in this one-step, one-pot protocol is fluoride ion, we anticipate the potential application of these techniques to the incorporation of $^{18}$F into a wide variety of biomolecules and synthetic building blocks. Moreover, the isolation and structural characterization of the trans-difluoromanganese(IV) porphyrin, Mn$^{IV}$(TMP)F$_2$, suggest the existence of a rich chemistry of such transition metal fluorides for delivery of fluorine substituents.

3.6 Experimental section

**General information.** All fluorination reactions were run under nitrogen with no precautions taken to exclude moisture. All solvents were purified according to the method of Grubbs.$^{43}$ 5,10,15,20-tetramesitylporphyrinatomanganese(III) chloride Mn$^{III}$(TMP)Cl was prepared by metallation of tetramesitylporphyrin. Iodosylbenzene was prepared by hydrolysis of iodobenzene diacetate with sodium hydroxide solution. Bicyclo[4.1.0] heptane (norcarane) was prepared according to a literature method.$^{44}$ Other purchased materials were of the highest purity available from Aldrich and used
without further purification. GC/MS analyses were performed on an Agilent 7890A gas chromatograph equipped with an Agilent 5975 mass selective detector. \(^1\)H NMR spectra were obtained on a Varian INOVA 400 (400 Hz) or a Bruker 500 (500 MHz) spectrometer and are reported in ppm using solvent as an internal standard (CDCl\(_3\) at d 7.26). Data reported as: chemical shift (\(\delta\) or ppm), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), coupling constant (Hz); integrated intensity. Proton decoupled \(^{13}\)C NMR spectra were recorded on a Bruker 500 (125 MHz) spectrometer and are reported in ppm using solvents as an internal standard (CDCl\(_3\) at 77.15 ppm). \(^{19}\)F NMR spectra were obtained on a Varian INOVA 400 (375 Hz) spectrometer and are reported in ppm by adding external neat PhF (\(^{19}\)F, \(\delta\) -113.15 relative to CFCl\(_3\))

**General procedures for Mn(TMP)Cl catalyzed C-H bond Fluorinations**

An oven-dried 25 mL Schlenk flask equipped with a magnetic stir bar was charged with the following: Mn(TMP)Cl catalyst (13.2 mg, 0.015 mmol, 1 mol%), TBAF•3H\(_2\)O (0.3 mmol), AgF (4.5 mmol, 3 equiv.), substrate (1.5 mmol) and naphthalene (internal standard, 0.5 mmol). The flask was capped and purged with nitrogen for 5 min. Then, CH\(_3\)CN (1.5 mL) and CH\(_2\)Cl\(_2\) (0.5 mL) were added by syringe and the flask was heated at 50 °C in an oil bath. Iodosylbenzene (6-15 mmol, 4-10 equiv.) was added slowly to the reaction mixture in solid form over a period of 6-15 h. Significant decreases in yield were noted when the oxidants were added rapidly. Each addition of 1 equiv. oxidant was followed by Mn(TMP)Cl (13.2 mg, 1 mmol%) added dissolved in minimal amount of solvents. When the reaction was completed, the solution was allowed to cool to room temperature and was then passed through a short pad of silica gel (washing with
dichloromethane). The filtrate was analyzed by GC/MS and then concentrated under vacuum. The residue was separated by column chromatography.

**Table 1. Compound 7.** The reaction was run according to the general procedure above using methyl cyclohexanecarboxylate as a substrate. Purification by column chromatography (hexanes and then 5% EtOAc/hexanes). $^1$HNMR (500 MHz, CDCl$_3$) $\delta$ 4.85 (dt, $J$=47.7, 2.3 Hz, 1H), 3.61 (s, 3H), 2.67 (tt, $J$=11.6, 3.8 Hz, 1H), 2.11 (m, 1H), 1.89 (m, 2H), 1.72-1.38 (m, 5H). $^{13}$C APT NMR (125 MHz, CDCl$_3$) $\delta$ 176, 88.6, 51.8, 37.8, 33.1, 30.2, 28.1, 19.6. $^{19}$F NMR -183.0 ppm. MS (EI) m/z cal’d C$_8$H$_{13}$FO$_2$ [M]$^+$: 160.1, found 160.1.

**Table 1. Compound 8.** The reaction was run according to the general procedure above using methyl cyclohexanol as a substrate. Purification by column chromatography (hexanes and then 10% ethyl acetate/hexanes). $^1$HNMR (500 MHz, CDCl$_3$) $\delta$ 4.86 (dtt, $J$=48.1, 5.3, 2.9 Hz, 1H), 2.50 (d, $J$=10.7 Hz, 1H), 1.97 (m, 1H), 1.84 (m, 2H), 1.64 (m, 2H), 1.41 (m, 3H), 1.14 (s, 3H). $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 91.6, 42.8, 38.4, 30.4, 29.7, 16.7. $^{19}$F NMR -179.2 ppm. MS (EI) m/z cal’d C$_7$H$_{13}$FO [M]$^+$: 132.1 found 132.1.

**Table 1. Compound 9.** The reaction was run according to the general procedure above using methyl cycloheptanone as a substrate. Purification by column chromatography (hexanes and then 4% ethyl acetate/hexanes). $^1$HNMR
(500 MHz, CDCl$_3$) δ 4.75 (dtt, J=45.6, 7.4, 2.7 Hz, 1H), 2.73, (m, 1H), 2.49, (m, 1H), 2.40 (m, 1H), 2.30 (ddd, J=15.4, 9.2, 2.5 Hz, 1H), 2.08-1.76 (m, 5H). 1.58 (m, 1H). $^{13}$C APT NMR (125 MHz, CDCl$_3$) δ 91.7, 43.5, 36.4, 35.4, 29.7, 17.6. $^{19}$F NMR -175.3 ppm.

MS (EI) m/z cal’d C$_7$H$_{11}$FO [M]+: 130.1, found 130.1.

Table 1. Compound 10. The reaction was run according to the general procedure above using N-Methyltrifluoroacetylecyclopentylamine as a substrate. Purification by column chromatography (hexanes and then 4% ethyl acetate/hexanes). $^{1}$HNMR (500 MHz, CDCl$_3$) δ 5.13-4.39 (m, 2H), 2.93 (d, 3H), 2.23 (ddddd, J=35.8, 15.9, 10.6, 5.0 Hz, 1H), 2.07 (m, 1H), 1.96-1.71 (m, 3H), 1.67-1.49 (m, 1H). $^{13}$C APT NMR (125 MHz, CDCl$_3$) δ 157.2, 116.5, 94.5, 56.4, 54.0, 36.7, 35.5, 32.9, 29.0, 27.5, 25.8. $^{19}$F NMR -68.7 (s), -70.2 (s), -168.8 (m) ppm. MS (EI) m/z cal’d C$_7$H$_{11}$FO [M]+: 213.1, found 213.1.

Table 1. Compound 12. The reaction was run according to the general procedure above using cycloheptyl benzoate as a substrate. Purification by column chromatography (hexanes and then 1% ethyl acetate/hexanes). isolated as a mixture of cis and trans products. $^{1}$HNMR (500 MHz, CDCl$_3$) δ 7.96 (m, 2H), 7.49 (m, 2H), 7.38 (m, 1H), 5.20-4.70 (m, 2H). 2.50-1.50 (m, 10H). $^{19}$F NMR -164.6, -166.7 ppm. MS (EI) m/z cal’d C$_{14}$H$_{17}$FO$_2$ [M]+: 236.1, found 236.1.

Table 1. Compound 11a (cis). The reaction was run according to the general procedure above using cyclohexylacetate as a substrate. Purification by
column chromatography (1% ethyl acetate/petroleum ether). $^1$H NMR (500 MHz, CDCl$_3$) δ 4.75-4.57 (m, 2H), 1.99 (s, 3H), 1.93 (m, 2H), 1.74 (m, 2H), 1.68-1.57 (m, 4H). $^{13}$C APT NMR (125 MHz, CDCl$_3$) δ 170.7, 88.7, 70.6, 28.9 26.6, 21.5. $^{19}$F NMR -180.4 ppm. MS (EI) m/z cal’d C$_8$H$_{12}$O$_2$ [M-HF]$^+$: 140.1, found 140.1.

**Table 1. Compound 11b (cis).** $^1$H NMR (500 MHz, CDCl$_3$) δ 4.65 (m, 1H), 4.48 (dt, J=48.0, 10.1, 4.4 Hz, 1H), 2.28 (m, 1H), 2.04-1.93 (m, 2H), 1.98 (s, 3H), 1.81 (m, 2H), 1.60-1.40 (m, 3H), $^{13}$C APT NMR (125 MHz, CDCl$_3$) δ 170.5, 89.5, 69.9, 37.9, 31.5, 30.5, 21.4, 18.8. $^{19}$F NMR -180.4 ppm. MS (EI) m/z cal’d C$_8$H$_{12}$O$_2$ [M-HF]$^+$: 140.1, found 140.1.

Compound 11a (trans) and Compound 11b (trans) were isolated as an inseparable mixture. $^1$H NMR (500 MHz, CDCl$_3$) δ 5.07-5.46 (m, 2H), 1.97 (s, 3H), 1.95-1.32 (m, 8H). $^{19}$F NMR -180.0, -181.1 ppm.

Reaction was run according to the general procedure above using bornyl acetate as a substrate. After the reaction was over, the mixture was subjected to the workup protocol outlined in the general procedure and purified by column chromatography using DCM:hexanes (1:4) as eluent. Colorless oil. $^1$H NMR (500 MHz, CDCl$_3$) δ 4.71 (d, J=9.7 Hz, 1H), 4.56 (ddd, J=60, 7.6, 2.3 Hz, 1H), 2.33 (m, 2H), 2.05-1.95(m, 1H) 1.98 (s, 3H), 1.63 (dd, J=35.3, 15.4 Hz, 1H), 0.97 (s, 3H), 0.85 (s, 3H), 0.83 (s, 3H), 0.68 (dd,
J=14.5, 3.4 Hz, 1H). $^{13}$CAPT NMR (125 MHz, CDCl$_3$) δ 95.8 (d, 186 Hz), 77.6, 50.5 (d, 17.6 Hz), 37.5 (d, 18.0 Hz), 32.2 (d, 11.1 Hz), 21.3, 20.2, 19.4, 12.6. $^{19}$F NMR -158.2 ppm. MS (El) m/z cal’d C$_{12}$H$_{19}$FO$_2$ [M]$^+$: 214.1, found 214.1.

![Image of NMR spectrum]

**Figure 16.** 1H-13C HSQC NMR spectroscopy of bornyl acetate fluorination product.

Reaction was run according to the general procedure above using 5α-Androstan-17-one as a substrate. After the reaction was over, the mixture was subjected to the workup protocol outlined in the general procedure and purified by column chromatography (hexanes and then 30% DCM/hexanes). The assignment of the product structures was
based on the diagnostic F-NMR spectrum. 2α (-172.4 ppm, dm), 2β (-172.8 ppm, qt), 3α (-181.5 ppm, qt), 3β (-168.3 ppm, dm). The major product 3α-fluoro-5α-Androstan-17-one was isolated by a second column chromatography (4% ethyl acetate/hexanes).

\(^1\)HNMR (500 MHz, CDCl\(_3\)) \(\delta\) 4.75 (dm, J=48.7, 2.5 Hz, 1H), 2.37 (dd, J=19.1, 8.9 Hz, 1H), 2.01 (dt, J=19.4, 9.1 Hz, 1H), 1.85 (m, 2H), 1.73 (m, 2H), 1.60 (m, 3H), 1.53-1.32 (m, 6H), 1.28-1.09 (m, 6H) 0.95 (m, 1H), 0.79 (s, 3H), 0.74 (s, 3H). \(^13\)C APT NMR (125 MHz, CDCl\(_3\)) \(\delta\) 221.6, 89.4, 54.2, 51.4, 47.8, 39.4, 35.9, 35.0, 33.9, 32.4, 31.5, 30.8, 28.0, 27.1, 21.8, 20.1, 13.9, 11.2. \(^19\)F NMR -181.5 ppm. MS (EI) m/z cal’d C\(_{19}\)H\(_{29}\)FO \([\text{M}]^+\): 292.2, found 292.2.

Reaction was run according to the general procedure above using sclareolide as a substrate. After the reaction was over, the mixture was subjected to the workup protocol outlined in the general procedure and purified by column chromatography (hexanes and then 10% EtOAc/hexanes). The assignment of the product structures was based on the diagnostic F-NMR spectrum. 2α (-180.3 ppm, dm), 2β (-172.6 ppm, qt), 3α (-187.8 ppm, qt), 3β (-185.6 ppm, dm). The major 2α-fluoro isomer could be isolated a white solid on a second column chromatography. \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 4.83 (dtt, J=48.0, 11.3, 4.6 Hz, 1H), 2.45 (dd, J=16.2, 14.7 Hz, 1H), 2.27 (dd, J=15.8, 6.5 Hz, 1H), 2.12-1.85 (m, 6H), 1.70 (td, J=12.6, 4.1 Hz, 1H), 1.43-1.30 (m, 6H), 0.99 (s, 3H), 0.95 (s, 3H), 0.89 (s, 3H). \(^19\)F NMR -180.3 ppm. MS (EI) m/z cal’d C\(_{16}\)H\(_{25}\)FO \([\text{M}]^+\): 268.2, found 268.2.
Computational details

The geometry optimizations and zero-point vibrational energy (ZPVE) were carried out using the B3LYP\textsuperscript{45-47} functional with the 6-31G**\textsuperscript{48,49} basis set for all atoms except Mn. For Mn the first two shells of core electrons were described by the Los Alamos angular momentum projected effective core potential (ECP) using the double-$\zeta$ contraction of valence functions\textsuperscript{50} (denoted as LACVP**) leading to 15 explicit electrons for neutral Mn. In order to obtain a more accurate electronic energy, we performed single-point energy calculations using a larger basis set, where Mn was described with the triple-$\zeta$ contraction of valence functions augmented with two f functions\textsuperscript{51} (the core electrons were described by the same ECP), with the other atoms described with the 6-311++G**\textsuperscript{52,53} basis set.

Solvation energies \( G_{\text{solv}} \) were calculated using the Poisson-Boltzmann self-consistent polarizable continuum method\textsuperscript{54,55} implemented in Jaguar to represent CH3CN (dielectric constant = 36.7 and effective radius = 2.23 Å). The solvation calculations used the B3LYP/LACVP** level of theory and the gas-phase optimized structures. Enthalpies are

\[
H_{298K} = E_{\text{elec}} + G_{\text{solv}} + \text{ZPVE} + \sum \frac{\hbar \nu}{e^{\hbar \nu/kT} - 1} \frac{n}{2} kT,
\]

where ZPVE is the zero-point vibrational energy, \( n = 12 \) accounts for the potential and kinetic energies of the translational and rotational modes, and \( T = 298 \text{ K} \).

All calculations performed with the Jaguar package\textsuperscript{56}. 
3.7 References:


Chapter 4.

Manganese Catalyzed Oxidative Benzylic C-H Fluorination using Fluoride Ion

4.1 Abstract
Benzylic C-H bonds are ubiquitous in bioactive molecules, including amino acids, steroids and terpenoids. The substitution of these benzylic C-H bonds with C-F bonds could have profound effects on the biological activities of these molecules via blocking the possible cytochrome P450 metabolism. In this chapter, we report a manganese salen catalyzed direct benzylic C-H bonds fluorination using iodosylbenzene as an oxidant and triethylamine trihydrofluoride as the fluoride source. This protocol can be applied to molecules containing various functional groups and bioactive molecules such as ibuprofen, vitamin E and homophenylalanine derivatives.

4.2 Background: molecules containing benzylic C-F bonds and methods for benzylic C-F bonds formation
As aforementioned, fluorinated organic compounds are extremely important as pharmaceuticals, fine chemicals and materials. In the context of C(sp^3)-F containing molecules, the benzylic fluoride fragment could be an effective substitute for benzylic C-H groups in many bioactive molecules. Benzylic C-H bonds and C-OH bonds are ubiquitous in bioactive molecules including amino acids, steroids, terpenoids as well a variety of other important drug molecules (Figure 1). Replacement of hydrogen with fluorine atom at the benzylic position may potentially inhibit the cytochrome P450 oxidation, and thereby increasing the lifetime of a drug molecule.
Methods for benzylic C-F bonds formation

Traditionally, benzylic fluorides can be prepared by halogen exchange, electrochemical methods, and the dehydroxy-fluorination of benzylic alcohols with diethylaminosulfur trifluoride (DAST) and bis(2-methoxy-ethyl)aminosulfur trifluoride (Deoxo-Fluor).4-9

Diethylaminosulfur trifluoride (DAST) and its thermally more stable analogue N,N-bis(2-methoxyethyl)aminosulfur trifluoride (Dexo-fluor) are commonly used fluorination reagents, which convert alcohols to the corresponding alkyl fluorides as well as aldehydes and unhindered ketones to germinal difluorides. Middleton et al. has shown in very early study that benzyl alcohols reacts with DAST and Deoxo-fluor in dichloromethane or trichlorofluoromethane forming benzyl fluoride.4 Recently, DAST has been successfully used by Grynszpan et al. in the synthesis of a series of haptens (Figure 2).10 Although the yield for the fluorination step is low (30%), this example
highlights the fluorination ability of DAST in the presence of various functional groups (Figure 2).

Figure 2. An example of benzylic fluorination using DAST reported by Grynszpan et al.

Electrochemical fluorination is generally carried out in organic solvents containing HF salts. In 2002, the Fuchigami group has reported an anodic fluorination of toluene, ethylbenzene and cumene derivatives. The fluorination reactions were performed in acetonitrile with tetraethylammonium tetrahydrogen pentafluoride as both the electrolyte and the fluorination reagent. Anodic benzylic fluorination occurred excepted for certain cumene derivatives. The yield of the fluorination reaction greatly depended on the stability of the corresponding benzylic cations. In 2012, this group reported the selective electrochemical fluorination using the alkali metal fluoride KF under mild conditions (Figure 1). The use of poly(ethylene glycol) addressed the problem of the low solubility of KF in organic solvents. Anodic fluorination of a model substrate triphenylmethane in the presence of PEG 200 provided the fluorinated products with >90% yield at 40 °C. In contrast, when 18-crown-6 ether was used as the additive, the anodic fluorination
proceeded in much lower yield, suggesting that PEG 200 not only increased solubility of KF in acetonitrile, but also accelerated the anodic fluorination rate.

\[ \text{Figure 1. Electrochemical fluorination using KF reported by Fuchigami} \]

Despite of these important discoveries, most of these methods require pre-functionalization at the benzylic positions and often suffer from elimination by-products. Further, the fluorine source is often incompatible with the preparation of $^{18}$F-labeled compounds, which requires fluoride ion as the fluorine source.

Recently, organometallic methods have been employed to prepare benzylic fluoride compounds. Vigalok et al. have reported a reagent dependent formation of benzylic C-F bonds in a Pt complexes (Figure 4).\textsuperscript{11} Cyclometalated platinum (II) complexes (C-P)Pt(Mesity)Py undergoes oxidative addition when treating with N-fluoro-2,4,6-trimethylpyridinium, affording C-C coupling products, whereas benzylic fluorination of
the mesityl group was observed when XeF$_2$ was used as the electrophilic fluorination reagent.

Figure 2. Reagent dependent benzylic C-F bond formation in Pt complex reported by Vigalok

The Sanford group has reported a palladium catalyzed benzylic fluorination reaction of a series of 8-methylquinoline derivatives (Figure 5).$^{12}$ The combination of silver fluoride and a hypervalent iodine oxidant was used in this transformation. The pyridine groups in the molecules served as the directing groups, which coordinate on the palladium catalysts at the beginning of the catalytic cycle, resulting in the activation of the benzylic C-H bonds at 8 position. Preliminary mechanistic studies of the reaction suggested the involvement of a Pd$^{IV}$-F complex, generated by the oxidation of Pd$^{II}$ species with hypervalent iodine in the presence of fluoride source. Although ArIF$_2$ is also observed during the reaction, their results suggest that this species may not be the primary active fluorinating reagent.
Figure 3. Palladium catalysed benzylic C-H fluorination using fluoride reported by Sanford et al.

In 2013, several works on direct benzylic C-H bond fluorination have been published. The Lectka group reported an iron catalyzed benzylic C-H fluorination using an inexpensive iron (II) salt, iron (II) acetylacetonate Fe(acac)$_2$, and commercial available Selectfluor as an electrophilic fluorination reagent (Figure 6A).$^{13}$ The Inoue group reported a metal-free benzylic fluorination using $N,N$-dihydroxypyromellitimide as a catalyst and Selectfluor as the fluorine source (Figure 4B).$^{14}$ Several aliphatic molecules, including cyclohexane and adamantane derivatives, can be fluorinated using this protocol. Mechanistic study suggests that the reaction is initiated by H-atom abstraction at the electron-rich positions by $N$-oxyl radical, generated by $N,N$-dihydroxypyromellitimide, and the resulting carbon radical reacts with Selectfluor, forming fluorinated products.
Figure 4. Direct benzylic C-H fluorination. A. Iron catalyzed direct benzylic fluorination reported by Lectka et al. B. Metal free benzylic C-H fluorination mediated by NDHPI reported by Inoue et al.

In addition to benzylic C-F bond formation, the reactivity of benzylic fluorides in transition metal catalyzed cross coupling reactions has also been studied. Gouverneur and coworkers have recently shown that benzylic fluorides are indeed good substrates for palladium catalyzed Tsuji-Trost reaction (Figure 7). This reaction is indeed the first example of palladium catalyzed cross coupling of benzylic fluorides with C-, N-, O- and
S-nucleophilic. The leaving group ability of fluoride at benzylic positions is between –OCO₂CH₃ and CH₃CO₂ groups, similar to the allylic fluorides under palladium catalysis.

\[
\begin{array}{c}
\text{R}^1 \quad \text{R}^2 \\
\text{F} \\
\text{R}^1 \quad \text{R}^2
\end{array}
\xrightarrow{\text{Pd(0) catalyst}}
\begin{array}{c}
\text{R}^1 \quad \text{R}^2 \\
\text{Nu} \\
\text{R}^1 \quad \text{R}^2
\end{array}
\]

**Figure 5.** Palladium catalyzed cross coupling of benzylic fluorides

Given the potential importance of benzylic fluorides and the paucity of current preparative methods, a general, transition metal-catalyzed direct C-H fluorination at benzylic positions with a nucleophilic fluorine source would be highly desirable. Such a method could be of great value for both radiolabelling applications of biomolecules and structure-activity relationship studies of drug candidates.

### 4.3 Development of a manganese catalyzed benzylic C-H fluorination reaction

#### 4.3.1 Initial results of the benzylic C-H fluorination reaction

As aforementioned, we have found an efficient process for the conversion of unactivated aliphatic C-H bonds to C-F bonds that employed a manganese porphyrin catalyst 1, with silver fluoride/tetrabutylammonium fluoride trihydrate (TBAF•3H₂O) as the fluorine source. The reaction is believed to proceed through a catalytic cycle involving a novel *trans*-difluoro manganese(IV) species, which efficiently transfers a fluorine atom to
short-lived alkyl radicals generated by a reactive oxoMn\textsuperscript{V} intermediate.\textsuperscript{17,18} An intriguing and particularly useful aspect of this C-H fluorination was a marked preference for methylene C-H bonds in carbocyclic rings, apparently due to steric and stereoelectronic effects.

When we applied this fluorination protocol to substrates containing benzylic C-H bonds, such as 4-ethylbiphenyl (3), we observed the formation of the benzylic fluorinated product 3a in 44% yield as expected. However, analysis of the reaction mixture revealed that nearly equal amounts of oxygenated compounds (benzylic alcohol and ketone) were also formed (Table 1, Entry 1). Since the reactions were conducted under anaerobic conditions, the oxygen in these by-products must derive from the oxidant, PhIO, or water. Our rationale for the formation of the oxygenation products is that the relatively low ionization potential of the incipient benzylic radical leads to a rapid carbon radical rebound to the Mn\textsuperscript{IV}-OH intermediate.\textsuperscript{19}

4.3.2 Reaction optimization on the Mn catalyzed benzylic C-H fluorination

Accordingly, we sought a catalyst system that might display complementary selectivity to that of the manganese porphyrin catalysts and mediate benzylic C-H fluorinations. Upon screening over a number of other ligand systems, we found that a manganese salen complex (2), originally developed by Jacobsen \textit{et al.} for oxygen transfer,\textsuperscript{20} did favour the
efficient formation of benzylic fluorides while effectively suppressing the oxygenation products observed with 1, albeit in a relatively low conversion (Table 1, Entry 2). After further screening of reaction conditions, we discovered that triethylamine trihydrofluoride (TREAT•HF)\textsuperscript{21} is a superior fluorine source for this reaction compared to the combination of TBAF•3H\textsubscript{2}O/AgF in terms of the selectivity for fluorination over oxygenation (Table 1, Entry 3). TREAT•HF is a colorless liquid, which has a shelf life of at least one year and is reported not to corrode borosilicate glassware.\textsuperscript{21}

Table 1. Effect of catalyst and fluorine source on the benzylic fluorination reaction

<table>
<thead>
<tr>
<th>entry</th>
<th>catalyst</th>
<th>equiv. of fluorine source</th>
<th>conv. (%)\textsuperscript{a}</th>
<th>yield (%)\textsuperscript{b}</th>
<th>-F:-O\textsuperscript{a}</th>
</tr>
</thead>
<tbody>
<tr>
<td>1\textsuperscript{c}</td>
<td>10% 1</td>
<td>0.2 TBAF•3H\textsubscript{2}O 3 AgF</td>
<td>94</td>
<td>44</td>
<td>1:1</td>
</tr>
<tr>
<td>2\textsuperscript{c}</td>
<td>10% 2</td>
<td>0.2 TBAF•3H\textsubscript{2}O 3 AgF</td>
<td>50</td>
<td>40</td>
<td>5:1</td>
</tr>
<tr>
<td>3</td>
<td>10% 2</td>
<td>1.5 TREAT•HF</td>
<td>42</td>
<td>37</td>
<td>12:1</td>
</tr>
<tr>
<td>4</td>
<td>20% 2</td>
<td>1.5 TREAT•HF</td>
<td>75</td>
<td>59\textsuperscript{d}</td>
<td>6:1</td>
</tr>
<tr>
<td>5\textsuperscript{c}</td>
<td>20% 2</td>
<td>0.5 TREAT•HF 3 AgF</td>
<td>81</td>
<td>60</td>
<td>5:1</td>
</tr>
</tbody>
</table>

[a] Determined by GC/MS. [b] Determined by \textsuperscript{19}F NMR using fluorobenzene as an internal standard. [c] Reactions were carried out excluding of light. [d] Isolated yield based on starting material.

Upon optimizing the catalyst load, we found that in the presence of 20 mol% 2, fluorination of 3 afforded the benzylic fluoride 3a in 59% yield (Table 1, Entry 4, Method A). The combination of TREAT•HF and AgF also served as a good fluorine
source, although slightly diminished selectivity for fluorination was observed in this case (Table 1, Entry 5, Method B). Control reactions in the absence of the Mn-salen catalyst showed none of the fluorinated product. No aromatic fluorination was observed in any of the cases examined. Approximately 5% of the gem-difluoride product was observed in the crude reaction mixture for 3. In most cases, the catalysts are consumed at the end of the reaction.

4.3.3 Reaction scope of the manganese salen catalyzed benzylic C-H fluorination

With optimized reaction conditions in hand, we then investigated the scope of this fluorination protocol. As can be seen from Table 2, the method has a broad scope and exhibits high functional group tolerance. Substrates containing amide, ether, ester, carbonyl, halide, imide and aryl groups were mono-fluorinated efficiently at benzylic sites. For compounds that contain electron-withdrawing groups adjacent to the benzylic positions, the combination of AgF and triethylamine trihydrofluoride was found to be advantageous (Method B). The fact that a variety substrates containing halogen atoms was tolerated is of interest because this strategy could provide sites for further modification of the fluorinated motif. Moreover, a wide array of ring systems, most of which are important scaffolds in biologically active molecules, such as tetrahydronaphthahlene, indan, tetrahydroquinoline and dibenzocycloheptene were all successfully fluorinated.

Table 2. Substrate scope of the Mn-salen catalyzed benzylic fluorination

<table>
<thead>
<tr>
<th>R1</th>
<th>R2</th>
<th>R2</th>
<th>R1</th>
</tr>
</thead>
<tbody>
<tr>
<td>H</td>
<td></td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>20 mol%</td>
<td>PhIO, CH3CN, 50 YC</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

(method a yield b)
4.3.4 Benzylic fluorination of bioactive molecules

Encouraged by the generality of the reaction, we next turned our attention to the late stage fluorination of drug-like compounds. To demonstrate this potential, several biologically active molecules, including a nonsteroidal anti-inflammatory drug (ibuprofen methyl ester), a vitamin E analog (δ-tocopherol acetate), a commercial perfume
component (celestolide) and a non-natural amino acid derivative (homophenylalanine), were subjected to this Mn(salen) fluorination procedure (Figure 6).

We first examine the fluorination of a non-steroidal anti-inflammatory drug derivative, ibuprofen methyl ester. Fluorination of this molecule has previously been reported by Arnold group using a chemo-enzymatic method. In that study, benzylic fluoride and aliphatic fluoride products can both be prepared by using two different cytochrome P450 enzymes. Although there are two benzylic C-H positions in this molecule, the one adjacent to the ester group should be electronic deactivated and therefore should be unreactive under our fluorination conditions. Consistent with our analysis, fluorination of ibuprofen methyl ester with Mn(salen)Cl afforded 17 as the product with 55% yield.

Celestolide, also known as indane musk, is an important commercially fragrance. Introduction of a fluorine atom into this molecule may probably affect its physical properties such as the volatility. Traditional method, such as treatment of the corresponding benzylic alcohol with DAST, may not provide its benzylic fluorinated product, as the ketone group will probably react with DAST forming germinal difluoride complex. To our satisfaction, by treating celestolide under our standard fluorination conditions, we successfully obtained its benzylic fluorinated product in 67% yield.

Incorporation of non-natural amino acid into proteins has recently been the subject of extensive studies. Therefore, preparation of fluorinated amino acids has also been widely studied. There are two natural amino acids containing benzylic C-H bonds,
phenylalanine and tyrosine, which may potentially be the substrates of our benzylic fluorination reactions. In order to test whether our protocol can be applied to the synthesis of fluorinated amino acid, we prepared the protected version of phenylalanine by converting the amine group to imide group and carboxylic acid to ester group. Unfortunately, fluorination of protected phenylalanine with our standard fluorination conditions only affords less than 5% fluorinated products. We attributed the low reactivity to the two strong electron-withdrawing groups, ester and imide, adjacent to the benzylic positions.

**Figure 6.** Benzylic fluorination of bioactive molecules

Although being disappointed of the low reactivity of phenylalanine derivatives, we are wondering whether introduction of one more methylene group between the benzylic position and the amino acid groups may diminish the electron-withdrawing effect. To test this hypothesis, we prepared the protected version of a non-natural amino acid, homo-
phenylalanine, with the same protecting groups. Upon treating this substrate under our fluorination conditions, to our satisfaction, we are able to obtain its benzylic fluorinated products in 48% yield with a diastereoselectivity of 5:1. Similarly, fluorination of a form of vitamin E, δ-tocopherol acteate afforded the benzylic fluoride product in 53% yield with a diastereoselectivity of 2.2:1.

4.3.5 Fluorination of ibuprofen ester with KF as the fluoride source

We realized that for potential application of this C-H fluorination to $^{18}$F PET imaging, it would be desirable to replace TREAT•HF or AgF with potassium fluoride, as it is one of the most common fluoride source in the PET study. In addition, short reaction time are required due to the short half-life of $^{18}$F (110 min). We have found conditions that meet these two important criteria. Treating ibuprofen methyl ester with 20 mol% 2 as the catalyst, potassium fluoride as the sole fluorine source, 18-crown-6 as the phase transfer catalyst as well as silver triflate, afforded the corresponding benzylic fluoride analog in 20% yield within 30 min (Figure 7). The role of 18-crown-6 in this reaction is to increase the solubility of KF in acetonitrile and the role of silver triflate is to react with fluoride ion forming silver fluoride in situ, which can facilitate the fluorination reaction. Further development along these lines and the application of flow techniques are under way.

![Figure 7. Fluorination of ibuprofen methyl ester with KF as the fluoride source](image-url)
4.4 Mechanism of the manganese salen catalyzed benzylic fluorination reaction

A likely mechanism for this benzylic fluorination, depicted in Figure 10, is analogous to the Mn-porphyrin case we have described.\(^{16}\) The starting Mn\(^{\text{III}}\) (salen)\(F\) or Mn\(^{\text{III}}\) (salen)\(F_2\) catalyst, formed in situ, is oxidized to Mn\(^{\text{V}}\)(O)(salen)F, which then abstracts hydrogen from the substrate, forming the benzyl radical and a manganese(IV) species. In the fluorine transfer step, the radical reacts with the Mn\(^{\text{IV}}\)(salen)\(F_2\) affording the fluorinated products. This step also regenerates the resting Mn\(^{\text{III}}\) catalyst.

![Figure 8. Proposed catalytic cycle for the benzylic C-H fluorination](image)

While further work is required to elucidate the mechanistic aspects of this reaction more fully, several preliminary observations warrant comment. First, the ESI mass spectrum of the starting catalyst/fluoride mixture showed a large peak at m/z 637.5 (Figure 11),
which is the mass of Mn\textsuperscript{III}(salen)F\textsubscript{2}\textsuperscript{-}, supporting the coordination of fluoride to the manganese center.

![Negative mode ESI-MS spectrum of [Mn\textsuperscript{III}(salen)F\textsubscript{2}]\textsuperscript{-}](image)

**Figure 9.** Negative mode ESI-MS spectrum of [Mn\textsuperscript{III}(salen)F\textsubscript{2}]\textsuperscript{-}

Second, a significant kinetic isotope effect (5.6±0.6) was observed for a 1:1 mixture of ethylbenzene and ethylbenzene-\textsubscript{d\textsubscript{10}} as the substrate. A similar KIE value (4.6±1.0) was observed by Katsuki et al. for a manganese(salen)-catalyzed C-H hydroxylation reaction,\textsuperscript{29} suggesting a common Mn\textsuperscript{V}(O)(salen) intermediate and a similar transition state for C-H bond cleavage. Analysis of compounds 8 and 18 by chiral HPLC (Figures S2 and S3) showed that readily detectable enantioselectivities were achieved (11% and 20\% ee, respectively). Compound 18 could be obtained in 40\% ee at -40°C in ~5% yield. The relatively low enantioselectivities observed are probably due to a very early transition state for the fluorine transfer step and a linear Mn-F-C geometry (top-on approach) as indicated by DFT calculations on a related manganese porphyrin system.\textsuperscript{16} C-H hydroxylations mediated by chiral Mn(salen) complexes also show modest ee.\textsuperscript{29} By contrast, the high enantioselectivities observed for olefin epoxidation by manganese salen catalysts have been attributed to a side-on approach of the substrate \pi-bond to the
manganyl group of the catalyst, thus increasing the steric contacts during the oxygen atom transfer from Mn\(^V\)=O\(^{30}\). Despite the modest enantiomeric ratios for C-H fluorination, the observation that the asymmetric Mn catalyst can afford the observed degree of stereoinduction provides strong support for a manganese-bound fluorine source in the fluorine transfer step.

In conclusion, we have presented here a general Mn-catalyzed method for the formation of benzylic fluorides directly from C-H bonds. In contrast to previous efforts in this area, the reaction does not require a directing group and uses simple and easily handled nucleophilic fluoride reagents. The success of this direct C-H fluorination reaction suggests a general strategy for late stage drug diversification and building block construction. On going efforts in our laboratory seek to probe the mechanism of the current reaction and to evaluate the potential of this transformation for PET imaging applications.

Since our work was published in 2013, several other groups have also reported several direct benzylic C-H fluorination methods. Lectka and coworkers have explored in detail the iron-catalyzed benzylic fluorination of substrates containing aromatic rings and electron-withdrawing groups positioned β to one another, thus providing direct access to β-fluorinated adducts\(^{31}\). The Chen group has reported a visible light-promoted diarylketone-catalyzed selective benzylic mono- and difluorination reaction. They have shown that visible light can activate diarylketones to abstract a benzylic hydrogen selectively\(^{32}\). In 2014, Sammis and Paquin have reported the first example of a
photoredox catalytic method for the formation of benzylic C-F bonds. Mechanistic studies of the reaction using transient absorption spectroscopy suggest the involvement of a key single-electron transfer from the $^3$MLCT (triplet metal-to-ligand charge transfer) state of Ru(bpy)$_3^{2+}$ to Selectfluor.$^{33}$

### 4.5 Detailed procedures for the fluorination reaction

**PhIO:** PhIO is prepared by the hydrolysis of PhI(OAc)$_2$ in excess 4N NaOH solution (ca. 5 equivalent) for 4 h in a beaker. After suction filtration and washing with large amount of water until the filtrate become neutral, solid, yellow PhIO was obtained. Leave the PhIO solid in the funnel overnight with suction pump connected for complete dryness. Grind the solid PhIO into powder and store in a refrigerator. PhIO should be used within 2 months. ▲ CRITICAL Choose a large magnetic stir bar (e.g. 10 × 70 mm) as the solution will become a slurry within 1 h of hydrolysis.

**Reaction setup ● TIMING 15 - 20 min**

1 Weigh 4-acetyl-6-tert-butyl-1,1-dimethylindan (Celestolide) 500 mg, Mn(salen)Cl 260 mg (20 mol%) and AgF 780 mg (3 equiv.) into a 25 mL Schlenk tube flask. Place a Teflon-coated magnetic stir bar in the flask. Cap the flask with a rubber septa. As AgF is light sensitive, weighing AgF should be carried as quickly as possible and in an area of low light intensity. The color of AgF will change to dark if the weighing step takes too much time.

2 Connect the Schlenk flask to the Schlenk line. Evacuate the flask for 2 min and back-fill it with nitrogen for 1 min. Repeat the pump-backfill cycle 3 times. As AgF is light
sensitive, all operations should be done in dark places. Normally, turning off the light of the hood and wrapping the bottom of the flask with aluminum foil is sufficient to avoid the decomposition of AgF.

3 Add 130 μL TREAT·HF into a 4 mL vial. Cap it and add 1.0 mL dry and degassed CH₃CN (from the solvent system) via syringe through the septum into the vial. Swirl the vial to obtain a clear solution. Flush N₂ into the vial for 4 min. During all of these processes, the vial should be under a positive pressure of N₂.

Note: TREAT·HF is used as received. This procedure is intended for substrates that are solids. Liquid substrates can be dissolved in CH₃CN and dispensed via syringe.

4 Transfer the CH₃CN solution of TREA·HF into the Schlenk flask using a 1 mL syringe with needle. Wash the syringe with additional 0.5 mL CH₃CN and transfer it into the reaction vessel as well. During the transfer, keep the Schlenk flask and the vial under positive N₂ pressure.

5 Submerge the bottom portion of the Schlenk flask in a preheated 50 °C water bath. Set the speed of stirring to ~600 rpm. Avoid stirring too vigorously, because the reaction mixture, especially AgF, will spill onto the wall of the flask.

Fluorination of 4-Acetyl-6-tert-butyl-1,1-dimethylindan (celestolide), timing: 6 – 8 h.
CRITICAL: During the fluorination, the Schlenk flask should be connected to the N\textsubscript{2} flow. Control the on/off of N\textsubscript{2} flow with stopcock. Turn on the stopcock \textbf{only} when adding iodosylbezene.

6 Weigh 1.100 g PhIO (1 equiv.) in the 4 mL vial.

7 Add the 1 equiv. PhIO into the Schlenk flask in small portions within 1 h. Detail procedure for each addition: (i) connect the Schlenk flask to N\textsubscript{2} by turning the stopcock; (ii) take a small portion of PhIO using the bottom part of a disposable glass pipette; (iii) quickly open the rubber septa and add the PhIO into the reaction mixture using the glass pipette; (iv) cap the flask with rubber septa and keep the N\textsubscript{2} flow for 1 more minute before closing the N\textsubscript{2} by turning the stopcock. CRITICAL: Every portion is approximately 70 – 80 mg. The time interval between each portion is about 4 min.

8 Repeat step 7 until all of the PhIO has been added. CRITICAL: As the reaction progresses, the solvent volume may decrease, add 0.5 mL CH\textsubscript{3}CN into the reaction mixture for every 2 equiv. of added PhIO.

9 After the addition of 4 equiv. of PhIO, for every 0.5 - 1 equiv. of newly added PhIO, use microliter syringe to take aliquot (ca. 5 µL) of the reaction mixture Dilute the aliquot with 1 mL DCM and pass through a 3 cm plug of silica gel eluting with excess DCM (ca. 10 mL). The resulting solution is used for monitor the reaction by GC/MS as described in
the Equipment Setup. CRITICAL: Stop the stirring when taking the aliquot to avoid the clogging of the syringe.

10 The reaction would be stopped when there is no further increase in yield with newly added PhIO. The flask is removed from the bath and allowed to cool to room temperature. ▲ CRITICAL The stop point is different from substrate to substrate, typically ranging from 4–9 equiv. of PhIO. For celestolide, the stopping point was around 5 equiv. of PhIO.

Purification of the product ● TIMING 1 – 1.5 h.

11 Dilute the reaction mixture with DCM (10 mL) and filter through a thin (2 cm) pad of silica gel using a Büchner funnel attached to a round bottom flask. Wash the reaction vessel and funnel with excess DCM (50 mL) which is also collected in the round bottom flask. CRITICAL: This step is to remove the insoluble species in the reaction mixture. It is common that the color of filtrate is red due to the presence of catalyst, which will be removed in the later purification steps.

PAUSE POINT: The filtrate can be stored overnight in a sealed round bottom flask (RBF) in the cold (0 to -20 °C).

12 Concentrate the solution under reduced pressure using a rotary evaporator at a temperature of 25 °C.
13 Purify the crude product by flash chromatography on silica gel (RediSep $R_f$ normal-phase flash column, 40-gram) using a mixture of hexane and ethyl acetate. Retention time: PhI at 5 min., substrate at 15 min., product at 16 min and by product at 26 min.

14 Collect the fractions that contain the pure product into a round-bottom flask as determined by GC/MS and remove the solvent using a rotary evaporator at a temperature of 25 – 30 °.

15 Check structure and purity of product by NMR and GC/MS using the methods mentioned in equipment setup section.

4.6 Experimental section

GC/MS analyses were performed on an Agilent 7890A gas chromatograph equipped with an Agilent 5975 mass selective detector. A representative method for monitoring the reaction is as follows: (i) 50 °C oven temperature upon injection, (ii) hold at 50 °C for 2 min, (iii) increase the temperature to 250 °C for 20 min, (iv) hold at 250 °C for 2 min.

General information.

All fluorination reactions were run under nitrogen atmosphere with no precautions taken to exclude moisture. All solvents were purified according to the method of Grubbs.\textsuperscript{34} Iodosylbenzene was prepared by hydrolysis of iodobenzene diacetate with sodium hydroxide solution.\textsuperscript{35} Other purchased materials were of the highest purity available from Aldrich and used without further purification. GC/MS analyses were performed on an
Agilent 7890A gas chromatograph equipped with an Agilent 5975 mass selective detector. $^1$H NMR spectra were obtained on a Varian INOVA 400 (400 MHz) or a Bruker 500 (500 MHz) spectrometer and are reported in ppm using solvent as an internal standard (CDCl$_3$ at δ 7.26 ppm). Data reported as: chemical shift (δ ppm), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), coupling constant (Hz); integrated intensity. $^{13}$C NMR spectra were recorded on a Bruker 500 (125 MHz) spectrometer and are reported in ppm using solvents as an internal standard (CDCl$_3$ at 77.15 ppm or Acetone-$d_6$ at 29.92 ppm). $^{19}$F NMR spectra were obtained on a Varian INOVA 400 (375 Hz) spectrometer and are reported in ppm by adding external neat PhF ($^{19}$F, δ -113.15 relative to CFCl$_3$). High-resolution mass spectra were obtained from the Princeton University mass spectrometer facility by electrospray ionization (ESI). High-performance liquid chromatography (HPLC) was performed on an Agilent 1200 series instrument with a binary pump and a diode array detector, using a Chiracel OJ-H (25 cm x 0.46 cm) column.

**General procedure for benzylic C-H bonds fluorinations catalyzed by manganese salen (2)**

An oven-dried, 5 mL Schlenk flask equipped with a stir bar was place under an atmosphere of N$_2$. Catalyst (2, 100 mg, 0.16 mmol, 20 mol%), substrate (0.8 mmol), TREAT•HF (0.2 mL, 1.2 mmol, 1.5 equiv.) (Method A) or AgF (300 mg, 2.4 mmol, 3 equiv.) and TREAT•HF (0.066 mL, 0.4 mmol, 0.5 equiv.) (Method B) were then added, followed by degassed CH$_3$CN (0.5 mL). The reaction mixture was then heated to 50°C. Under a stream of N$_2$, iodosylbenzene (4.8 - 6.4 mmol, 6 - 8 equiv.) was added slowly to
the reaction mixture in solid form over a period of 6-8 h. Significant decreases in yield were noted when the oxidants were added rapidly. The reaction was monitored by GC/MS analysis. After the addition of iodosylbenzene was complete, the solution was allowed to cool to room temperature and diluted with 2 mL hexanes. Products were separated from the reaction residue by silica gel column chromatography.

Procedure for the fluorination using KF: An oven-dried, 5 mL Schlenk flask equipped with a stir bar was placed under an atmosphere of N₂. Mn(salen)Cl (100 mg, 20 mol%), ibuprofen methyl ester (176 mg, 0.8 mmol), anhydrous KF (186 mg, 3.2 mmol, 4 equiv.), AgOTf (411 mg, 1.6 mmol, 2 equiv.), 18-Crown-6 (633 mg, 2.4 mmol, 3 equiv.) were then added followed by degassed CH₃CN. The reaction mixture was then stirred vigorously at 60°C for 5 minutes. Iodosylbenzen (704 mg, 3.2 mmol, 4 equiv.) was then added within 25 minutes (~140 mg every 5 minutes.). After the addition is completed, the reaction mixture was directly analyzed by ¹⁹F NMR using fluorobenzene as an internal standard.

![Compound 3a, Method A. Purification by column chromatography (hexanes).](image)

¹H NMR (500 MHz, CDCl₃) δ 1.60 (dd, J = 23.8, 6.4 Hz, 3H), 5.59 (dq, J = 47.7, 6.4 Hz, 1H), 7.42 – 7.22 (m, 4H), 7.57 – 7.45 (m, 5H); ¹³C NMR (125 MHz, CDCl₃) δ 22.9, 90.7, 125.8, 127.1, 127.3, 127.5, 128.8, 140.7, 140.5, 141.3; ¹⁹F NMR -166.6 ppm; MS (El) m/z cal’d C₁₄H₁₃F [M]⁺: 200.1, found 200.1.
**Compound 4, Method A.** Purification by column chromatography (10% EtOAc/hexanes). $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 1.66 (dd, $J$ = 23.9, 6.4 Hz, 3H), 2.32 (s, 3H), 5.64 (dq, $J$ = 47.6, 6.4 Hz, 1H), 7.20 – 7.04 (m, 2H), 7.46 – 7.35 (m, 2H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 21.5, 23.0, 90.5, 121.8, 126.5, 139.0, 150.6, 169.6; $^{19}$F NMR -166.4 ppm; MS (EI) m/z cal’d C$_{10}$H$_{11}$FO$_2$ [M]$^+$: 182.1, found 182.1.

**Compound 5, Method B.** Purification by column chromatography (hexanes). $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 1.54 (dd, $J$ = 23.8, 6.4 Hz, 3H), 5.52 (dq, $J$ = 47.5, 6.4 Hz, 1H), 7.34 – 7.15 (m, 4H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 23.3, 90.5, 126.8, 128.9, 134.1, 140.0; $^{19}$F NMR -166.4 ppm; MS (EI) m/z cal’d C$_8$H$_8$ClF [M]$^+$: 158.3, found 158.3.

**Compound 6, Method B.** Purification by column chromatography (hexanes). $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 1.65 (dd, $J$ = 23.9, 6.4 Hz, 3H), 5.62 (dq, $J$ = 47.5, 6.4 Hz, 1H), 7.32 – 7.18 (m, 2H), 7.62–7.47 (m, 2H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 23.0, 90.4, 122.2, 127.0, 131.6, 140.5; $^{19}$F NMR -168.5 ppm; MS (EI) m/z cal’d C$_8$H$_8$BrF [M]$^+$: 202.0, found 202.0.
**Compound 7, Method B.** Purification by column chromatography (hexanes). $^1$H NMR (500 MHz, CDCl$_3$) $\delta$1.63 (dd, $J = 23.9$, 6.4 Hz, 3H), 5.59 (dq, $J = 47.5$, 6.4 Hz, 1H), 7.20 – 7.06 (m, 2H), 7.80 – 7.70 (m, 2H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 23.1, 90.5, 93.8, 127.3, 137.7, 141.3; $^{19}$F NMR -168.7 ppm; MS (EI) m/z cal’d C$_8$H$_8$FI [M]$^+$: 250.0, found 250.0.

**Compound 8, Method A.** Purification by column chromatography (hexanes). $^1$H NMR (500 MHz, CDCl$_3$) $\delta$1.84 (dd, $J = 23.8$, 6.4 Hz, 3H), 6.37 (dq, $J = 46.7$, 7.0 Hz, 1H), 7.58 – 7.44 (m, 3H), 7.62 (d, $J = 7.1$ Hz, 1H), 7.91-7.82 (m, 2H), 8.02 (d, $J = 7.6$, 1H); $^{13}$C NMR (125 MHz, Acetone-$d_6$) $\delta$ 21.7, 88.6, 122.4, 123.4, 125.3, 125.8, 126.3, 128.7, 128.8, 130.0, 133.9, 137.3; $^{19}$F NMR -170.2 ppm; MS (EI) m/z cal’d C$_{12}$H$_{11}$F [M]$^+$: 174.1, found 174.1.

**Compound 9, Method A.** Purification by column chromatography (hexanes). $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 1.74 (dd, $J = 23.8$, 6.5 Hz, 3H), 5.80 (dq, $J = 52.0$, 6.3 Hz, 1H), 7.55–7.45 (m, 3H), 8.00–7.73 (m, 4H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 23.1, 91.4, 123.3, 124.2, 126.2, 127.7, 128.1, 128.4, 128.8, 133.0, 133.1, 138.8; $^{19}$F NMR -167.4 ppm; MS (EI) m/z cal’d C$_{12}$H$_{11}$F [M]$^+$: 174.1, found 174.1.
**Compound 10, Method B.** Purification by column chromatography (10% EtOAc/hexanes). \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 2.40 – 2.02 (m, 2H), 2.63 – 2.45 (m, 2H), 3.70 (s, 3H), 5.53 (ddd, \(J = 47.9, 7.6, 5.0\) Hz, 1H), 7.52 – 7.34 (m, 5H); \(^{13}\)C NMR (125 MHz, CDCl\(_3\)) \(\delta\) 29.5, 32.3, 51.8, 93.4, 125.4, 128.4, 128.5, 139.6, 173.3; \(^{19}\)F NMR -178.1 ppm; MS (EI) m/z cal’d C\(_{11}\)H\(_{13}\)FO\(_2\) [M]\(^+\): 196.1, found 196.1.

**Compound 11, Method B.** Purification by column chromatography (10% EtOAc/hexanes). \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 2.69 – 2.00 (m, 2H), 3.92 (td, \(J = 7.2, 2.4\) Hz, 2H), 5.56 (ddd, \(J = 47.9, 8.6, 4.2\) Hz, 1H), 7.44 – 7.29 (m, 5H), 7.77 – 7.67 (m, 2H), 7.85 (m, 2H); \(^{13}\)C NMR (125 MHz, CDCl\(_3\)) \(\delta\) 34.6, 35.7, 92.6, 123.2, 125.6, 128.5, 128.6, 132.0, 134.0, 139.3, 168.3; \(^{19}\)F NMR -175.7 ppm; MS (EI) m/z cal’d C\(_{17}\)H\(_{14}\)FNO\(_2\) [M]\(^+\): 283.1, found 283.1.

**Compound 12, Method B.** Purification by column chromatography (3%-20% EtOAc/hexanes). \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 2.53 (m, 3H), 3.00 – 2.86 (m, 1H), 3.96 (s, 3H), 4.00 (s, 3H), 5.70 (dt, \(J=51.1, 4.5\) Hz, 1H), 7.00 (s, 1H), 7.54 (s, 1H); \(^{13}\)C
NMR (125 MHz, CDCl\textsubscript{3}) $\delta$ 30.0, 33.7, 56.2, 56.3, 88.0, 108.4, 109.5, 125.3, 135.0, 150.0, 154.0, 195.8; $^{19}$F NMR -169.6 ppm; HRMS (ESI) m/z cal’d C\textsubscript{12}H\textsubscript{14}FO\textsubscript{3} [M+H]\textsuperscript{+}: 225.0927, found 225.0924.

\[ \text{Compound 13, Method A.} \] Purification by column chromatography (10% EtOAc/hexanes). $^1$H NMR (500 MHz, CDCl\textsubscript{3}) $\delta$ 2.28 – 2.06 (m, 2H), 2.46 – 2.32 (m, 2H), 3.60 (ddd, $J$ = 14.1, 12.3, 2.6 Hz, 1H), 4.17 – 3.96 (m, 1H), 5.48 (ddd, $J$ = 50.9, 4.2, 2.5 Hz, 1H), 7.23 (t, $J$ = 7.4 Hz, 1H), 7.37 – 7.31 (m, 1H), 7.43 (d, $J$ = 7.7 Hz, 1H). 7.80 (br, 1H); $^{13}$C NMR (125 MHz, CDCl\textsubscript{3}) $\delta$ 30.8, 41.1, 84.4, 116.4, 124.1, 126.7, 129.68, 129.71, 130.7, 136.5, 155.5; $^{19}$F NMR -68.8, 151.4 ppm; MS (EI) m/z cal’d C\textsubscript{11}H\textsubscript{19}F\textsubscript{4}NO [M]\textsuperscript{+}: 247.1, found 247.1.

\[ \text{Compound 14, Method A.} \] Purification by column chromatography (4% EtOAc/hexanes). $^1$H NMR (500 MHz, CDCl\textsubscript{3}) $\delta$ 3.86 – 3.34 (m, 2H), 5.86 (ddd, $J$ = 47.6, 9.7, 2.2 Hz, 1H), 7.70 – 7.19 (m, 6H), 8.28 – 7.93 (m, 2H); $^{13}$C NMR (125 MHz, CDCl\textsubscript{3}) $\delta$ 41.0, 90.5, 126.4, 127.5, 128.9, 130.2, 130.5, 130.6, 132.7, 132.8, 134.2, 136.2, 138.6, 139.2, 194.3; $^{19}$F NMR -168.8 ppm; MS (EI) m/z cal’d C\textsubscript{15}H\textsubscript{17}FO [M]\textsuperscript{+}: 226.1, found 226.1.
**Compound 15, Method A.** Purification by column chromatography (10% EtOAc/hexanes). Isolated as a mixture of diastereomers. \(^1\)H NMR (500 MHz, CDCl\(_3\)) 2.50 – 1.85 (m, 4H), 5.75 – 5.34 (m, 1H), 6.16 (m, 1H), 7.56 – 7.19 (m, 7H), 8.11 – 7.84 (m, 2H); \(^{19}\)F NMR -160.4 (major), -161.2 ppm (minor); MS (EI) m/z cal’d C\(_{17}\)H\(_{15}\)FO\(_2\) [M]+: 270.1, found 270.1.

**Compound 16, Method B.** Purification by flash column chromatography (5% EtOAc/hexanes). Isolated as a single diastereomer. \(^1\)H NMR (500 MHz, CDCl\(_3\)) 1.23 (s, 9H), 2.37 (dddd, \(J = 24.1, 15.1, 6.4, 4.7\) Hz, 1H), 2.83 (dddd, \(J = 22.6, 15.1, 7.0, 2.4\) Hz, 1H), 6.15 (dd, \(J = 57.4, 6.3, 2.4\) Hz, 1H), 6.42 (m, 1H), 7.50 – 7.37 (m, 3H), 7.55 (m, 1H); \(^{13}\)C NMR (125 MHz, CDCl\(_3\)) \(\delta\) 27.1, 38.7, 40.6, 75.7, 94.5 125.4, 125.7, 129.4, 130.5, 140.2, 142.4, 178.5; \(^{19}\)F NMR -164.1 ppm; MS (EI) m/z cal’d C\(_{14}\)H\(_{17}\)FO\(_2\) [M]+: 236.1, found 236.1.

**Compound 17, Method B.** Purification by column chromatography (10% EtOAc/hexanes). \(^1\)H NMR (500 MHz, CDCl\(_3\)) 0.77 (d, \(J = 6.9\) Hz, 3H), 0.94 (d, \(J = 6.8\) Hz, 3H), 1.42 (dd, \(J = 7.3, 4.7\) Hz, 3H), 2.01 (dh, \(J = 16.8, 6.7\) Hz,
1H), 3.58 (s, 3H), 3.66 (q, \( J = 7.2 \) Hz, 1H), 5.00 (dd, \( J = 47.0, 6.9 \) Hz, 1H), 7.23 – 7.13 (m, 4H); \(^{13}\)C NMR (125 MHz, CDCl\(_3\)) \( \delta \) 17.6, 18.4, 18.6, 34.2, 34.4, 45.2, 52.1, 99.3, 126.46, 126.52, 127.5, 138.3, 140.7, 175.0; \(^{19}\)F NMR -179.0 ppm; MS (EI) m/z cal’d C\(_{14}\)H\(_{19}\)F\(_2\) [M]+: 238.1, found 238.1.

**Compound 18, Method A.** Purification by column chromatography (5% EtOAc/hexanes). \(^1\)H NMR (500 MHz, CDCl\(_3\)) 1.34 (s, 3H), 1.37 (s, 12H), 2.39 – 2.06 (m, 2H), 2.65 (s, 3H), 6.44 (ddd, \( J = 53.9, 5.9, 1.5 \) Hz, 1H), 7.43 (t, \( J = 1.5 \) Hz, 1H), 7.77 (d, \( J = 1.7 \) Hz, 1H); \(^{13}\)C NMR (125 MHz, CDCl\(_3\)) \( \delta \) 28.6, 29.0, 31.4, 31.5, 35.2, 42.7, 48.4, 93.9, 123.6, 125.7, 134.8, 135.2, 154.2, 155.9, 199.9; \(^{19}\)F NMR -158.6 ppm; MS (EI) m/z cal’d C\(_{17}\)H\(_{23}\)FO [M]+: 262.2, found 262.2.

**Compound 19, Method B.** Purification by column chromatography (5%-10% EtOAc/hexanes). Isolated as a mixture of diastereomers. \(^1\)H NMR (500 MHz, CDCl\(_3\)) 3.07 – 2.59 (m, 1H), 3.67 (s, 3H), 5.18 – 5.00 (m, 1H), 5.93 – 5.20 (m, 1H), 7.40 – 7.07 (m, 5H), 7.74 (ddd, \( J = 34.5, 5.5, 3.1 \) Hz, 4H); \(^{19}\)F NMR -176.2 (major), -180.2 (minor) ppm; MS (EI) m/z cal’d C\(_{19}\)H\(_{16}\)FNO\(_4\) [M]+: 341.1, found 341.1.
Compound 20, Method A.

Purification by column chromatography (5%-10% EtOAc/hexanes). major isomer: $^1$H NMR (500 MHz, Acetone-$d_6$) 2.27 – 0.73 (m, 43H), 2.75 (s, 1H), 5.48 (dt, $J = 52.9, 5.2$ Hz, 1H), 6.88 – 6.66 (m, 2H); $^{13}$C NMR (125 MHz, Acetone-$d_6$) $\delta$ 15.24, 19.13, 19.22, 20.04, 21.06, 22.06, 22.44, 24.21, 24.53, 24.65, 27.80, 31.46, 32.40, 32.64, 37.11, 37.14, 37.26, 38.66 39.20, 76.65, 84.19, 119.40, 121.35, 124.76, 127.20, 143.37, 148.98, 169.06; $^{19}$F NMR -159.9 ppm; HRMS (ESI) m/z cal’d C$_{29}$H$_{47}$FNaO$_3$ [M+Na]$^+$: 485.34069, found 485.34140.
Chiralcel OJ-H, 2% hexanes/isopropyl, 1mL/min

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**Totals:** 1372.32373 168.71878

**product from the reaction, 20% ee**
Figure S2. HPLC trace of compound 18.

References


