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Iron(II)-Catalyzed Site-selective Functionalization of Unactivated C(sp^3)–H Bonds Guided by Alkoxyl Radical

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Abstract: *An alkoxyl radical-guided strategy for site-selective functionalization of unactivated methylene and methine C–H bonds enabled by an Fe(II)-catalyzed orchestrated redox process is described. The mild, expeditious, and modular protocol allows for efficient remote aliphatic fluorination, chlorination, amination, and alkynylation of structurally and electronically varied primary, secondary, and tertiary hydroperoxides with excellent functional group tolerance. The application in one-pot 1,4-hydroxyl-functionalization of non-oxygenated alkane substrates initiated by aerobic C−H oxygenation is also demonstrated.*

Direct functionalization of ubiquitous alkyl C–H bonds streamlines existing chemical synthesis and unlocks unique synthetic planning.[1] Unfortunately, achieving site-selective intermolecular functionalization of a single unactivated C(sp^3)–H bond in a complex molecule remains a critical challenge. Given the omnipresence of hydroxy groups in organic molecules, radical transposition processes mediated by alkoxyl radicals, such as 1,5-H atom transfer (1,5-HAT), provide an attractive option for remote aliphatic functionalization in a rational and selective manner.[2] Despite this longstanding mechanistic precedent, the majority of alkoxyl radical induced 1,5-HAT reactions leads to cyclization instead of intermolecular functionalizations.[3,4] Moreover, the majority of intermolecular studies involve substitution of activated C(sp^3)–H bonds adjacent to a heteroatom.[5] Surprisingly few intermolecular functionalization reactions of unactivated C(sp^3)–H bonds have been disclosed to date, and each system is typically suitable for a single class of transformation.[6,7] Therefore, developing a general, mild, and modular method for alkoxyl radical-guided conversion of unactivated C(sp^3)–H bonds into a variety of valuable functional groups is highly desirable.

While several types of masked alcohols have been used as alkoxyl radical precursors, alkyl hydroperoxide is chosen for this study based on three basic criteria including accessibility, handleability, and atom economy.[8] Primary, secondary, and tertiary hydroperoxides are bench-stable and can be prepared by substitution reactions of corresponding alcohol with hydrogen peroxide with good functional group compatibility.[9,10] The proposed set of events is outlined as below: alkyl hydroperoxides undergo one-electron reduction by a suitable base metal catalyst furnishing alkoxyl radicals for atom transfer functionalization, and concurrently generated high-valent base metal species is reduced by a suitable terminal reductant for the redox cycle. One main obstacle to designing this process is the simultaneous presence of both reductant and oxidant in the reaction medium, and their direct quenching with each other is usually kinetically favorable. Accordingly, one essential prerequisite should be met: the expected redox cycle must be much faster than the undesired quenching.

The site-selectivity of present C(sp^3)–H fluorination is predominantly dictated by the innate substrate reactivity, and substitution typically occurs at an electron-rich, sterically accessible bond.[11] Selective fluorination of a specified unactivated C(sp^3)–H bond remains a fundamental challenge. Existing directed protocols still lack substrate generality, and suffer from extra efforts for subsequent directing group manipulation, the use of noble transition metal, harsh conditions, and moderate yields.[12,13] To our knowledge, alkoxyl radical guided site-selective fluorination of unactivated C(sp^3)–H bonds of simple alkanes has never been reported to date. Inspired by the pioneering work of $FeSO_4$-mediated alkyl hydroperoxide-directed remote desaturation,[14] Fe(TPP)Cl (**2a**) was selected as base metal catalyst for the fluorination of primary alkyl hydroperoxide **1a** with *N*-fluorobenzenesulfonimide (NFSI) for reductant search (Table 1). Preliminary screening revealed the ability of $NaBH_4$ as a stoichiometric reductant affording the expected *δ*-C–H fluorinated **3a** in 16% yield within 5 min (entry 1).[10] However, the process was accompanied by byproduct **3a'** in 72% yield that seemingly arises by three possible pathways: (1) direct quench of hydroperoxide with reductant; (2) undesired heterolytic O–O bond cleavage;[15] (3) H-abstraction prior to fluorination. Further investigations of borohydride salts identified $LiBH_4$ to be optimal for suppressing **3a'**, providing **3a** in an improved yield of 45% (entries 1-4).[10] Other earth-abundant metal catalysts such as [Fe(Pc)Cl] (iron(III) phthalocyanine chloride) furnished inferior result (entry 5).[10] Next, systematic catalyst modification was performed with the hope to further enhance chemoselectivity by suppressing the potential heterolytic O–O bond cleavage resulting in **3a'**. Fine-tuning of the electronic nature of porphyrin ligand identified electron-rich Fe(TNP)Cl (**2e**) to be the superior catalyst giving **3a** in 62% yield (entries 6-9).[10] Moreover, when 4-methoxyphenol was introduced, the undesired **3a'** was suppressed to a satisfied extent, and expected **3a** was isolated in 73% yield (entries 10-12).[10,16] Other fluorinating reagents like Selectfluor and FP were inferior to NFSI (entries 13 and 14). Other organic peroxides like **1a'** and **1a''** proved to be ineffective alkoxyl radical precursors (entry 15).

We next evaluated the scope of this alkoxyl radical directed aliphatic fluorination protocol (Scheme 1a). The reaction proved general for a broad range of structurally and electronically varied primary (**3a**-**3d**), secondary (**3h**-**3q**), and tertiary hydroperoxides (**3r**, **3s**, and **3u**-**3z**), with selective and predictable fluorine incorporation at δ-methylene or methine site of linear alkane substrates in high efficiency.[17] Secondary and tertiary δ-C–H bonds originating from carbocycles of various sizes were also viable targets, as demonstrated by the formation of **3e**-**3g** and **3t**.[17] The iron-catalyzed redox process has an excellent functional group tolerance,

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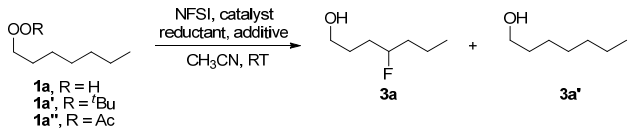
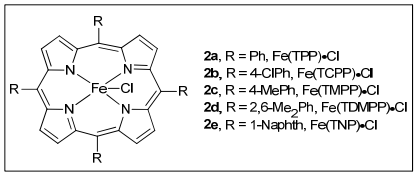
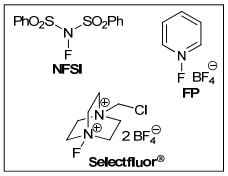
Table 1: Optimization of the reaction conditions.[a]



Entry	Catalyst	Reductant	Additive	Yield (%)[b] **3a/3a'**
1	**2a**	$NaBH_4$	—	16 / 72
2	**2a**	$NaBH_3CN$	—	10 / 77
3	**2a**	$(CH_3)_4NBH_4$	—	21 / 70
4	**2a**	$LiBH_4$	—	45 / 46
5	Fe(Pc)·Cl	$LiBH_4$	—	20 / 68
6	**2b**	$LiBH_4$	—	9 / 75
7	**2c**	$LiBH_4$	—	49 / 40
8	**2d**	$LiBH_4$	—	52 / 34
9	**2e**	$LiBH_4$	—	62 / 27
10	**2e**	$LiBH_4$	imidazole	64 / 26
11	**2e**	$LiBH_4$	PhOH	67 / 20
12	**2e**	$LiBH_4$	(4-MeO)PhOH	73 / 12
13[c]	**2e**	$LiBH_4$	(4-MeO)PhOH	60 / 29
14[d]	**2e**	$LiBH_4$	(4-MeO)PhOH	< 5 / n.d.
15[e]	**2e**	$LiBH_4$	(4-MeO)PhOH	< 5 / n.d.



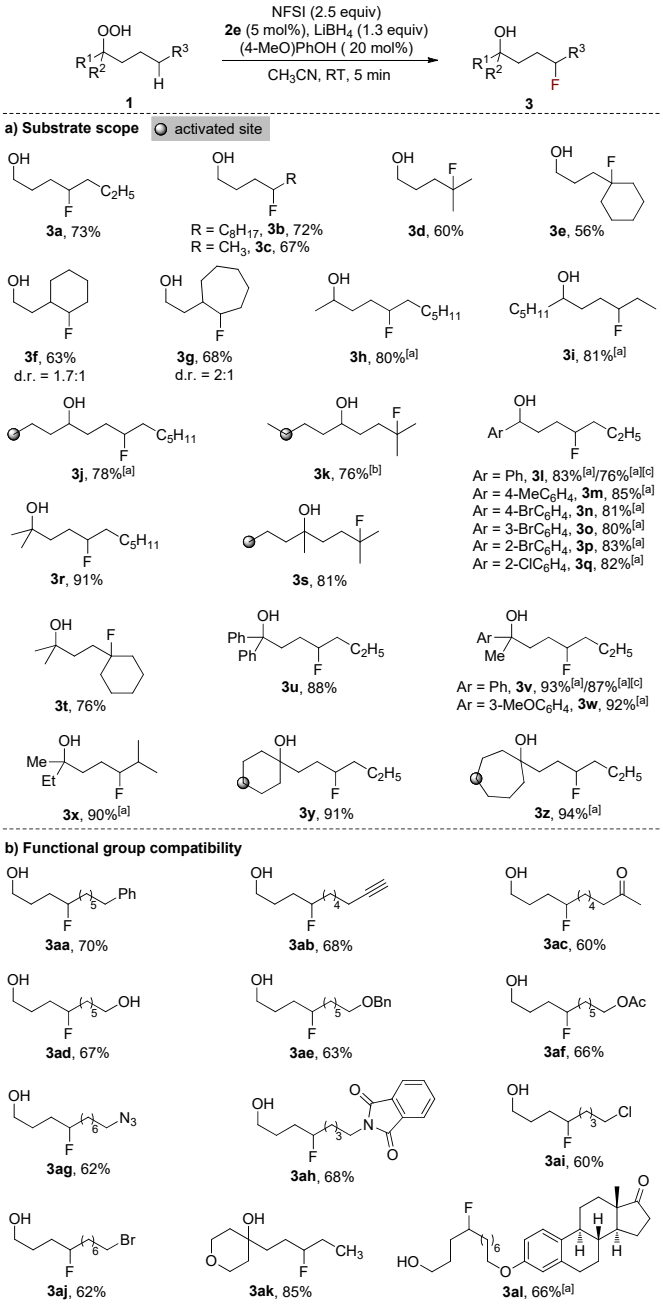


[a] Conditions: **1a** (0.1 mmol), NFSI (0.25 mmol), catalyst (0.005 mmol), reductant (0.13 mmol), and additive (0.02 mmol) in CH_3CN (1.0 mL) at rt for 10 min, unless otherwise specified. [b] Yield of isolated product. [c] Selectfluor instead of NFSI. [d] FP instead of NFSI. [e] **1a'** or **1a''** as substrate. n.d. = not determined.

with common functionalities including aryl (**3l-3q** and **3aa**), alkynyl (**3ab**), carbonyl (**3ac**), hydroxy (**3ad**), benzyl ether (**3ae**), acetate (**3af**), azide (**3ag**), amide (**3ah**), halide (**3ai** and **3aj**), and tetrahydropyran (**3ak**) moieties well tolerated for further manipulation (Scheme 1b). Importantly, only δ-fluorinated products were always obtained even when more reactive C–H bonds, such as tertiary (**3f**, **3g**, and **3x**), benzylic (**3l-3q**, **3aa**, and **3ae**), propargyl (**3ab**), α-carbonyl (**3ac**), α-oxy (**3ad-3af**), and α-amino (**3ag** and **3ah**) ones, were present. Moreover, when multiple electronically and sterically differentiated δ-C−H bonds exist in a substrate, the preferences for linear secondary C−H bond over primary one (**3j** and **3s**) or secondary one of carbocycles (**3y** and **3z**) and for linear tertiary C−H bond over secondary one (**3k**) were observed. The fluorination of estrone derivative **1al** bearing multiple reactive tertiary, benzylic, α-oxy, and α-carbonyl C–H bonds exclusively yielded **3al**, further demonstrating the unique site-selectivity of the guided protocol. Comparable efficiency was observed when the reaction was performed in a larger scale (**3l** and **3v**).

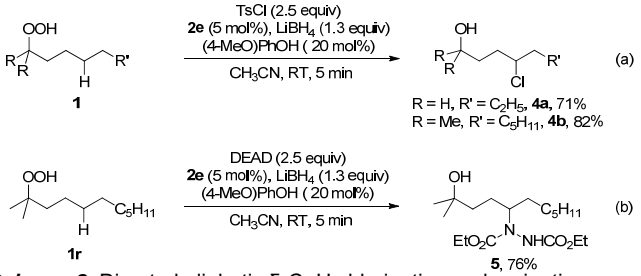
The modularity of the protocol demonstrated by effective δ-C−H chlorination (Scheme 2a) and amination (Scheme 2b) through changing NFSI to *p*-toluenesulfonyl chloride (TsCl)[18] and diethyl azodicarboxylate (DEAD), respectively. Although the scope of these transformations was not exclusively investigated, these results provide a proof of concept for the modularity of the protocol.

1,5-HAT initiated intermolecular C–H alkylation has recently been disclosed.[5,19] However, efficient functionalization has been



Scheme 1. Scope of directed δ-C−H fluorination. [a] d.r. = 1:1. [b] 4:1 regioselectivity is observed. [c] Reaction in 3.0 mmol scale.

demonstrated principally for activated C−H bonds adjacent to a heteroatom and unactivated tertiary ones. An efficient substitution of unactivated methylene C(sp^3)–H bonds remains elusive.[7] In addition, 1,5-HAT initiated intermolecular C–H alkynylation has never been reported to date. Therefore, we further explore the generality of our protocol in remote aliphatic alkynylation. Alkoxyl



Scheme 2. Directed aliphatic δ-C−H chlorination and amination.

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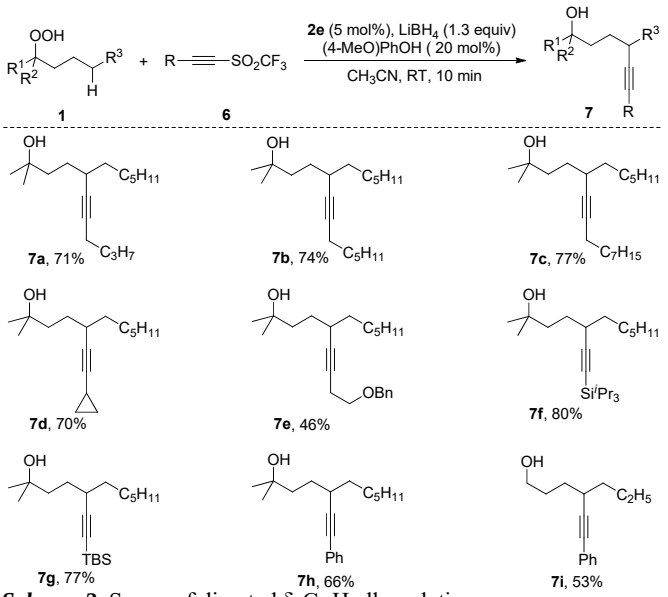
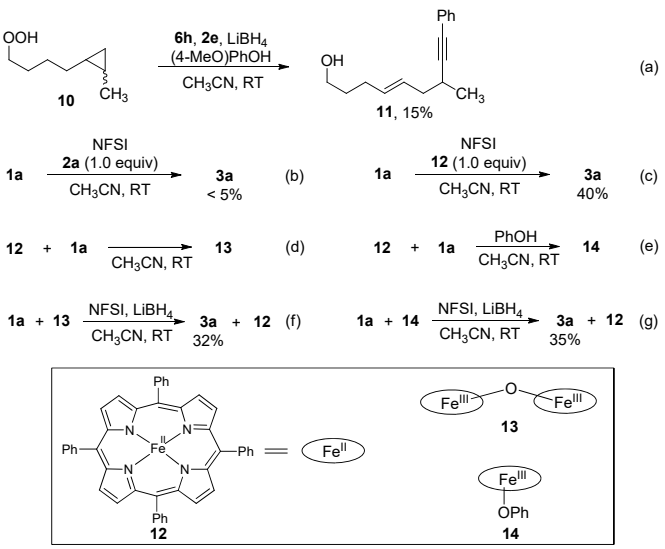


Scheme 3. Scope of directed δ-C−H alkynylation.

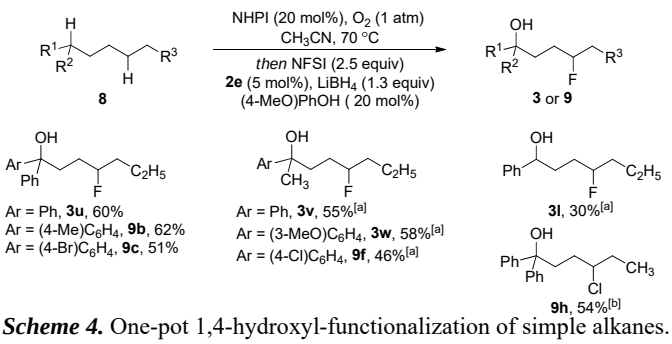


Scheme 5. Mechanistic studies.

radical directed δ-C−H alkynylation proved to be viable when alkynyl trifluoromethyl sulfone **6** was adopted as alkynylating agent (Scheme 3).[20] A variety of alkyl acetylenes (**7a**-**7c**) were installed at secondary methylene site in good yields. Alkyl acetylenes bearing functional groups, such as cyclopropane (**7d**) and benzyl ether (**7e**), together with silyl (**7f** and **7g**) and phenyl acetylenes (**7h** and **7i**) were also tolerated for further manipulation.

Perhaps the most striking advance of this modular protocol would be direct installation of hydroperoxide moiety into non-oxygenated alkanes through aerobic C−H oxygenation for subsequent remote functionalization.[21] Accordingly, a one-pot 1,4-difunctionalization of non-oxygenated alkanes was established (Scheme 4). Electronically varied diaryl substituted alkanes **8a**-**8c** underwent *N*-hydroxyphthalimide (NHPI) catalyzed aerobic C−H oxygenation followed by remote aliphatic fluorination, furnishing δ-hydroxyl fluorides **3u**, **9b**, and **9c** in good yields. Aryl methyl substituted **8d**-**8f** and mono-phenyl substituted **8g** were also suitable substrates when catalytic AIBN (azobisisobutyronitrile) was applied to aerobic C−H oxygenation, though a decreased yield was observed for the latter. This one-pot protocol was also applicable to 1,4-hydroxyl chlorination process (**9h**).

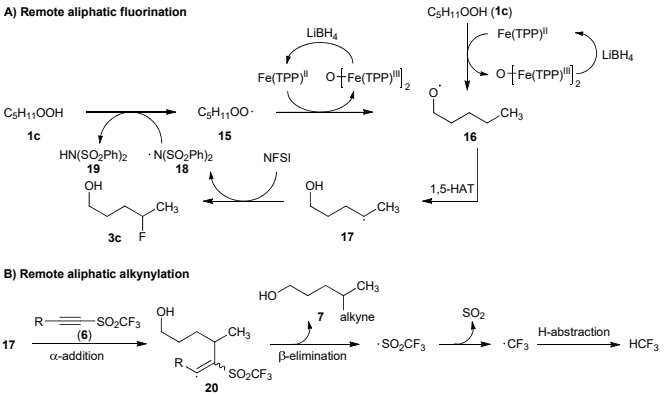
A series of experiments were conducted to gain mechanistic insights (Scheme 5). Firstly, alkynylation of cyclopropyl **10** yielded **11**, supporting the operation of an intramolecular 1,5-HAT process (Scheme 5a). Secondly, stoichiometric iron complex was applied to the reaction to understand the role of base metal catalyst in the redox cycle. Stoichiometric Fe(TPP)^{III}Cl (**2a**) failed to promote the fluorination reaction (Scheme 5b); stoichiometric Fe(TPP)^{II} (**12**) that was prepared through reduction of **2a** with $NaBH_4$,[22] effects the reaction in a comparable yield with that of catalytic variant (Scheme 5c). These observations suggested that **12** might be the species mediating one-electron reduction of **1a**. **12** reacted with **1a** furnishing oxo-bridged dimer (TPP)FeOFe(TPP) **13** (Scheme 5d);[23] the reaction of **12**, **1a**, and PhOH provided phenolate Fe(TPP)^{III}OPh **14** (Scheme 5e);[23] it is known that **13** reacts with PhOH giving **14**.[23b] Moreover, the combination of **13** or **14** with $LiBH_4$ gave **3a** together with **12** (Schemes 5f and 5g). These observations indicated the intermediacy of **13** and **14** as oxidized high-valent iron species, though the origin of phenol additive for improving the reaction efficiency remains unclear at present.



Scheme 4. One-pot 1,4-hydroxyl-functionalization of simple alkanes. [a] 0.5 mol% AIBN for C−H oxygenation. [b] TsCl instead of NFSI.

According to the preliminary studies, a plausible mechanism is proposed (Scheme 6). The reaction was initiated by Fe(TPP)^{II} mediated one-electron reduction of **1c** affording alkoxyl radical **16** together with oxo-bridged dimer (TPP)FeOFe(TPP) (Scheme 6A).[24] **16** underwent 1,5-HAT yielding **17**, which then reacted with NFSI providing fluoride **3c** and radical **18**. Given that the O−H bond in alkyl hydroperoxide **1c** possesses the lowest bond dissociation energy in the system,[25] we envisioned that **18** might abstract the hydrogen atom from **1c** generating **19** together with peroxide radical **15**. **15** was next reduced by Fe(TPP)^{II} furnishing **16** for the complete redox cycle. For the alkynylation, **17** reacted with **6** via an α-addition/β-elimination process yielding **7** and HCF_3 (Scheme 6B).[20]

In summary, by using an Fe(II)-catalyzed, orchestrated redox



Scheme 6. The proposed mechanism.

process, we have established a general and modular alkoxyl radical-guided strategy for site-selective functionalization of unactivated methylene and methine C–H bonds. The mild, expeditious, and operationally simple protocol allows for efficient remote aliphatic fluorination of structurally and electronically varied primary, secondary, and tertiary hydroperoxides with excellent functional group tolerance. The generality and modularity of the method is further demonstrated by directed aliphatic chlorination, amination, and alkynylation in high efficiency. The application in one-pot 1,4-hydroxyl-functionalization of non-oxygenated alkane substrates initiated by aerobic C−H oxygenation is further demonstrated. The generality and modularity of the directed C–H functionalization strategy, the predictable regioselective manner, and the omnipresence and versatility of hydroxy groups indicate that the approach outlined herein will have broad applications in late-stage diversity-oriented functionalization of complex molecules.

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Keywords: C−H functionalization · site-selectivity · fluorination · alkynylation · alkoxyl radical

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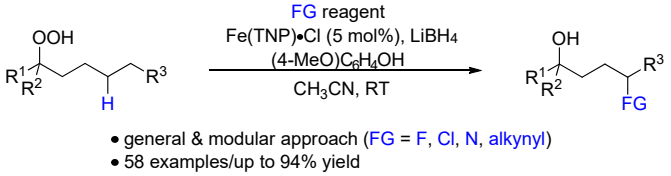
Fe(II)-Catalyzed Site-selective Functionalization of Unactivated C(sp^3)–H Bonds Guided by Alkoxyl Radical



Site-selective intermolecular aliphatic functionalization: An alkoxyl radical-guided strategy for site-selective functionalization of unactivated methylene and methine C–H bonds enabled by an Fe(II)-catalyzed orchestrated redox process is described. The mild, expeditious, and modular protocol allows for efficient remote aliphatic fluorination, chlorination, amination, and alkynylation of structurally and electronically varied primary, secondary, and tertiary hydroperoxides with excellent functional group tolerance. The application in one-pot 1,4-hydroxyl-functionalization of non-oxygenated alkanes initiated by aerobic C−H oxygenation is also demonstrated.