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sp^3 C-H Oxidation by Remote H-Radical Shift with Oxygen- and Nitrogen-Radicals: A Recent Update

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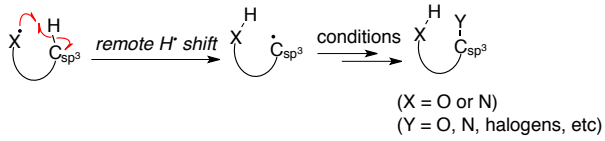
This review updates recent advances in aliphatic sp^3 C-H bond oxidation by remote H-radical abstraction with oxygen- and nitrogen-radicals classifying by types of the radical precursors.

1. Introduction

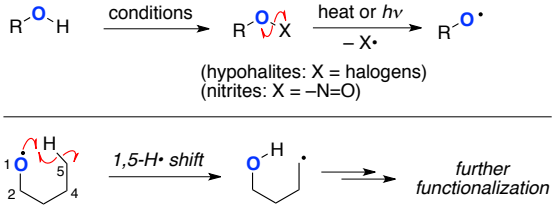
Aliphatic sp^3 C-H bonds are the most basic unit in organic molecules, while they are chemically very stable under various reaction conditions unless otherwise being activated by the adjacent functional groups such as carbonyl groups. Direct functionalization (oxidation) of such inert sp^3 C-H bonds could offer new trends of approaches to prepare valuable functional molecules in atom- and step-economical manners.[1] Therefore, various methods for the sp^3 C-H oxidation have been developed especially using transition metal catalysts, in which those via directed C-H metallation (via organometallic intermediates) and concerted C-H oxidation with metal-carbene or nitrene (singlet) species are the-state-of-the-art examples, enabling sp^3 C-H oxidation with chemo-, regio-, and stereoselective fashions. On the other hand, remote H-radical shift (typically, 1,5-H shift) is an alternative yet distinct way to oxidize the sp^3 C-H bonds, which could not be functionalized by the conventional transition-metal catalyzed manners. Recently, various novel chemical approaches for sp^3 C-H oxidation by the remote H-radical shift have been elegantly designed and practiced especially using readily available oxygen- and nitrogen-radical precursors (Scheme 1). Herein, we review and summarize the newly emerging generation of these sp^3 C-H oxidation strategies with oxygen- and nitrogen-radicals (O- and N-radicals) systematically classifying with the kinds of the radicals and their precursors utilized for the remote H-radical abstraction.[2,3]



Scheme 1 sp^3 C-H oxidation by H-radical abstraction by O- and N-radicals

2. With O-Radicals

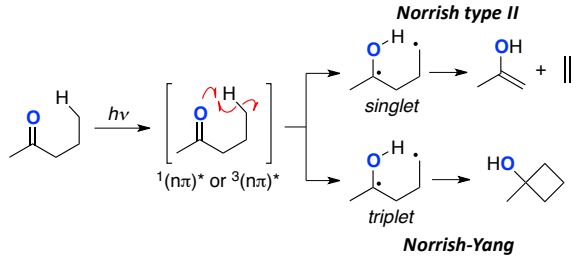
Alkoxy radicals (O-radicals) are considerably reactive (electrophilic) to undergo abstraction of a H-radical from the remote intramolecular sp^3 C-H bonds as one of the possible reaction pathways.[4] From the viewpoints of energy and structural factors (i.e. enthalpy control, entropy factor, and proximity effects) on the intramolecular H-radical abstraction, 1,5-H shift is the most favourable mode among these events, while functionalization of more remote C-H bonds might be possible by rational design of the substrates.[5] Due to the high bond-dissociation enthalpy (BDE) of the O-H bonds of aliphatic alcohols (about 93-105 kcal/mol), however, it is impossible to generate alkoxy radicals directly by homolysis of the O-H bonds. Therefore, various reactive precursors such as alkyl hypohalites and alkyl nitrites have been prepared from the corresponding alcohols and utilized for generation of the O-radicals for 1,5-H radical shift and subsequent oxidation of the resulting C-radicals (Scheme 2). These methods have recently been utilized mainly for oxidative manipulation of carbohydrates and steroids.[6]



Scheme 2 Generation of alkoxy radicals and their 1,5-H radical shift

Photo-excited ketones (with singlet or triplet nπ*-excited state) undergo H-radical abstraction from their γ-position to form the corresponding biradicals either in singlet or triplet state, that is analogous to the 1,5-H radical shift with alkoxy radicals (Scheme 3).[7] Radical fragmentation (*the Norrish type II reaction*) could take place from the singlet state biradicals, while cyclobutane formation via radical coupling could mainly proceed from the triplet ones (*the Norrish-Yang reaction*).

Rational design of the carbonyl substrates has enabled other types of ring-construction reactions or oxidation of the remote C-H bonds.

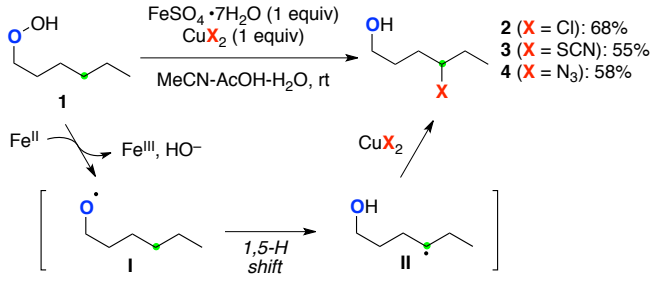


Scheme 3 the Norrish type II and Norrish-Yang reactions of carbonyl compounds

These reactions are outside of the scope of this review, while the interested readers are encouraged to peruse the sophisticated reviews and articles cited in the references. Emphasis in this section will be put on the recent advances of aliphatic C-H oxidation with O-radicals or their equivalents derived from the other classes of precursors.

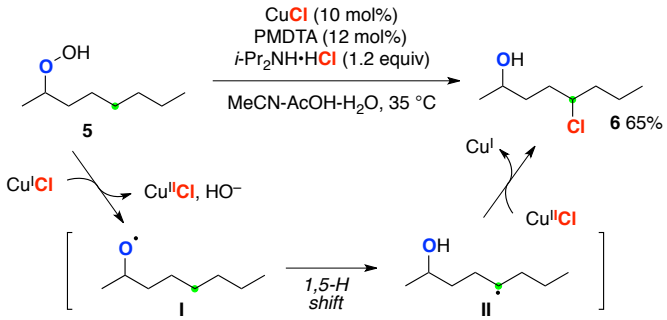
Hydroperoxides

Single-electron-reduction of hydroperoxides with lower valent metal salts can produce the O-radicals with elimination of a hydroxy ion. For a pioneering example, Čeković developed remote sp^3 C-H functionalization of alkyl hydroperoxides with a (semi-)stoichiometric Fe(II)-Cu(II) bimetallic system (Scheme 4).[8] For example, single-electron-reduction of hydroperoxide **1** by Fe(II) species proceeds to generate the O-radical **I**, subsequent 1,5-H radical shift of which generates the corresponding C-radical **II**. The resulting C-radical is further oxidized by the present Cu(II) salts to form alkyl chloride **2**, thiocyanate **3**, and azide **4**, subject to the counter ions of the Cu(II) salts.



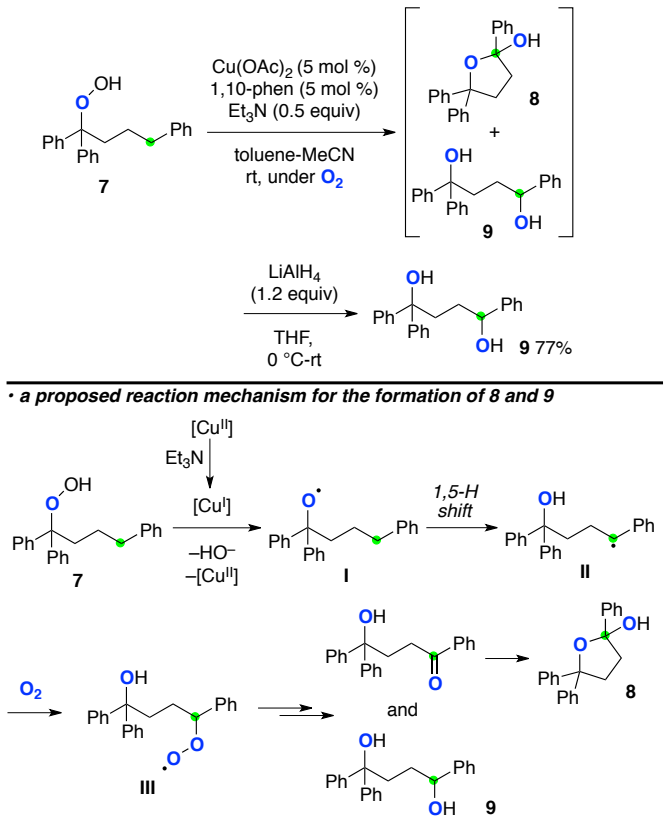
Scheme 4 sp^3 C-H functionalization with alkyl hydroperoxides by Fe(II)-Cu(II)

Ball recently reported the first catalytic aliphatic C-H chlorination of alkyl hydroperoxides using CuCl as a single catalyst in the presence of *N,N,N',N'',N''*-pentamethyldiethylenetriamine (PMDTA) as a ligand and readily available ammonium chloride salts as the chlorine atom source (Scheme 5 for the reaction of hydroperoxide **5** to chloride **6**).[9] Reductive generation of O-radical **I** by the reaction of hydroperoxide **5** with Cu(I) species and oxidative chlorine-atom transfer functionalization of the resulting C-radical **II** by Cu(II)-Cl species enabled the redox-neutral catalytic turnover with the single metallic system.



Scheme 5 Cu-catalyzed sp^3 C-H chlorination with hydroperoxides

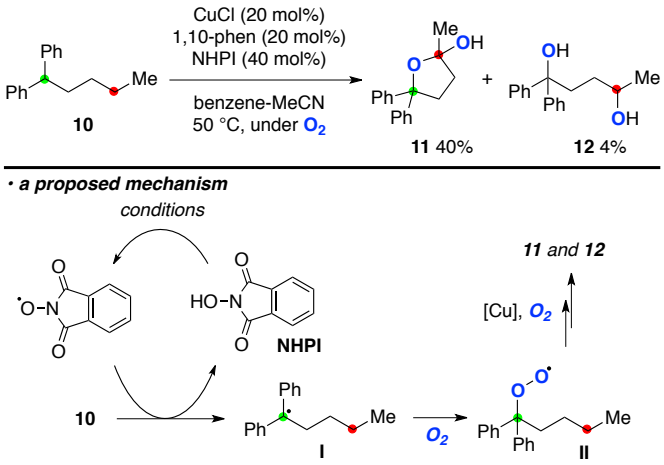
If reductive generation of the O-radicals from hydroperoxides could be achieved under an O_2 atmosphere, the C-radicals generated via 1,5-H radical shift could be trapped by O_2 to form the new C-O bonds. Our group has recently realized this concept for the aerobic synthesis of 1,4-diols from alkyl hydroperoxides, that could be catalyzed by $Cu(OAc)_2$-1,10-phenanthroline system in the presence of Et_3N (Scheme 6).[10] For example, the reaction of hydroperoxide **7** provided methylene C-H oxygenation products, hemiacetal **8** and 1,4-diol **9** as a mixture, that was reduced by $LiAlH_4$ to obtain 1,4-diol **9** as a single product.



Scheme 6 Cu-catalyzed aerobic sp^3 C-H oxygenation with hydroperoxides

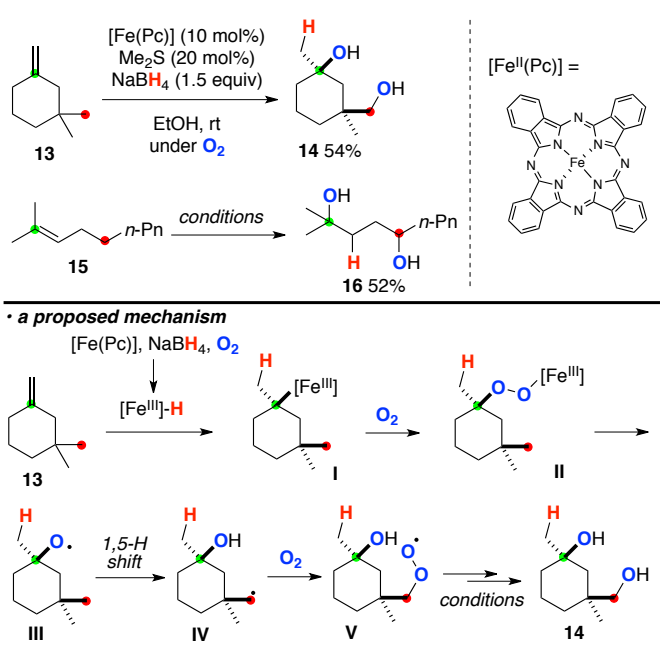
The role of Et_3N should be the terminal reductant of Cu^{II} species, enabling to keep lower valent Cu^{I} species for the reductive generation of O-radical **I** even under an O_2 atmosphere. The resulting O-radical **I** induces 1,5-H radical shift to generate C-radical **II**, that is trapped with molecular O2 to form peroxy radical **III**. Further conversion of **III** into hemiacetal **8** and 1,4-diol **9** is carried out under the present reaction conditions.

This Cu-catalyzed aerobic C-H oxygenation could be further applied for direct conversion of alkane **10** to the corresponding 1,4-dioxygenated products **11** and **12** using *N*-hydroxyphthalimide (NHPI) as a co-reagent for the C-H bond oxygenation (Scheme 7). The aerobic reaction of alkane **10** bearing a dibenzylic tertiary C-H bond (marked in green) with the catalytic system of CuCl-1,10-phen (20 mol%) with NHPI (40 mol%) at 50 °C delivered lactol **11** and 1,4-diol **12** in 40% and 4% yields, respectively. In this process, phthalimide *N*-oxyl radical generated oxidatively from NHPI might undergo H-radical abstraction from **10** to generate the C-radical **I**,[11] that is trapped by molecular oxygen to form peroxy radical **II**. The peroxy radical could be taken over to the next remote C-H oxygenation.



Scheme 7 Cu-catalyzed aerobic 1,4-dioxygenation of alkane

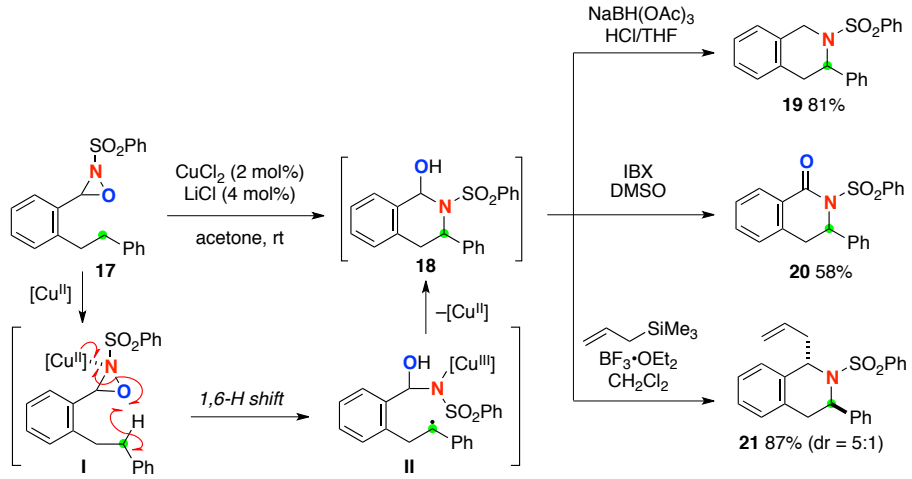
Taniguchi very recently developed direct conversion of aliphatic alkenes such as **13** and **15** to the corresponding 1,4-diols under an iron(II) phthalocyanine [Fe(Pc)]-catalyzed aerobic reaction conditions in the presence of $NaBH_4$ (Scheme 8).[12] The reaction is initiated by hydroironation onto the alkene (the reaction of **13** as example) by in-situ generated iron(III) hydride species under the present reaction conditions, affording organo-iron(III) intermediate **I**. The organo-iron(III) intermediate **I** was reacted with molecular oxygen and converted into iron(III)-peroxide complex **II**, that undergoes Fenton-type fragmentation to give alkoxy radical **III**. Subsequent 1,5-H radical shift forms the C-radical **IV**, that is similarly trapped with molecular oxygen to give peroxy radical **V**. Finally, reduction of **V** under the present reaction conditions could terminate the process to form 1,4-diol **14**.



Scheme 8 Fe(II)-catalyzed aerobic 1,4-diol synthesis from aliphatic alkenes in the presence of $NaBH_4$

Oxaziridines

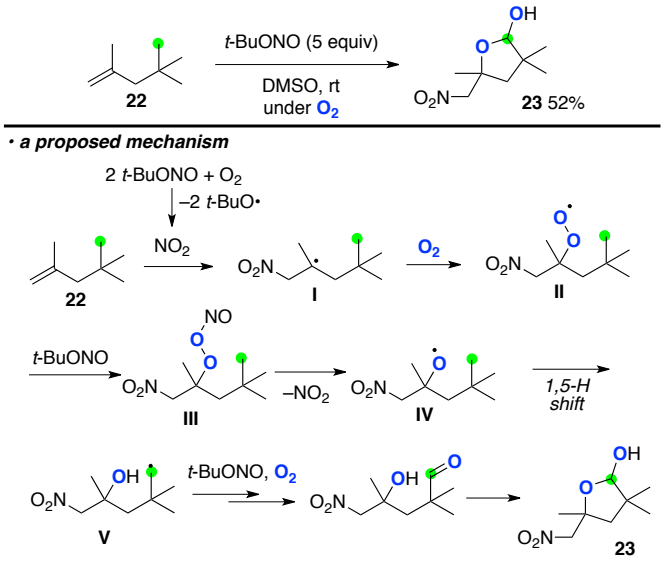
Oxaziridines are easily prepared by oxygenation of the corresponding imine and stable to handle. The reactivity of oxaziridines could be controlled and tuned by modification of their substituents. Recently, Du Bois group developed intermolecular sp^3 C-H hydroxylation mediated by oxaziridines generated *in situ* from benzoxathiazine catalysts with H_2O_2 or oxone.[13] The reaction mechanism of this hydroxylation was characterized as a concerted asynchronous process, thus being stereospecific. On the other hand, Yoon reported Cu(II)-catalyzed intramolecular sp^3-C-H amination with *N*-sulfonyl oxaziridine derivatives (Scheme 9 for the reaction of oxaziridine **17**).[14] The reaction is likely initiated by formation of Cu(II)-oxaziridine complex **I** that induces remote H-radical abstraction along with N-O bond homolysis to give C-radical intermediate **II** having a Cu(III) sulfonamide moiety. Subsequent C-N bond forming cyclization (radical recombination) provides hemiaminal product **18**, that could be served as a versatile intermediate for further molecular transformations for synthesis of azaheterocycles via reduction (for **19**) and oxidation (for **20**) as well as Lewis acid-mediated C-C bond formation (for **21**). In this C-H oxidation process, the putative Cu(II)-oxaziridine complex **I** formally plays as an equivalent of the O-radical for remote H-radical abstraction, in which δ-C-H oxidation via 1,6-H shift is interestingly more favoured than γ-C-H oxidation via 1,5-H shift. There is an interesting comparison of the reactivity of oxaziridines for radical-mediated C-H oxidation strategies with Cu-catalysts between this Yoon's C-H amination and Aube's C-H oxygenation (see Scheme 18), both of which are indeed mediated by oxaziridine derivatives with Cu-catalysts.



Scheme 9 *Cu-catalyzed C-H amination with oxaziridines*

Peroxy Nitrites

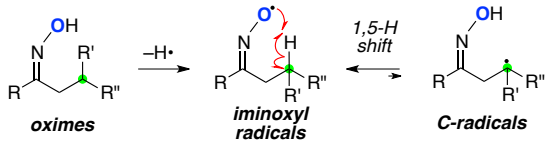
Taniguchi recently disclosed multi-functionalization of aliphatic alkenes using *tert*-butyl nitrite under an O_2 atmosphere, that resulted in formation of lactols via aliphatic sp^3 C-H oxygenation induced by *in-situ* generated peroxy nitrite (Scheme 10 for the reaction of alkene **22**).[15] The process is initiated by aerobic oxynitration of alkenes **22** via radical addition of *in-situ* formed NO_2 onto the C=C bond followed by trapping the resulting C-radical **I** with O_2, affording peroxy radical intermediate **II**. Further reaction of peroxy radical **II** with *tert*-butyl nitrite gives peroxy nitrite **III**, homolysis of which generates O-radical **IV**. Subsequently, 1,5-H shift is induced by O-radical **IV** to form C-radical **V** that is finally oxygenated to afford lactol **23**.[16]



Scheme 10 Aerobic multi-functionalization of alkenes mediated by *t*-BuONO

Oximes

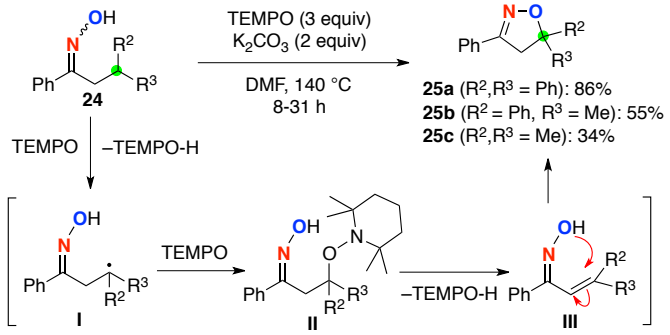
Due to the inherent high reactivity, the O-radicals often induce various side reactions (such as fragmentation, intermolecular C-H abstraction, etc). On the other hand, iminoxyl radicals derived from oximes are stabilized mainly by delocalization of unpaired electron through the N-O bond (BDE = 83 kcal/mol).[17,18] Our group has designed remote C-H oxidation using the stabilized iminoxyl radicals.[19] It could be envisioned that remote H-radical abstraction of the iminoxyl radicals generate the C-radicals in a reversible manner, in which the concentration of the C-radicals could be kept lower due to the weaker reactivity of the iminoxyl radicals. This can potentially result in highly selective oxidative transformation of the C-radicals (Scheme 11).



Scheme 11 *Stabilized oxime radicals for remote C-H oxidation*

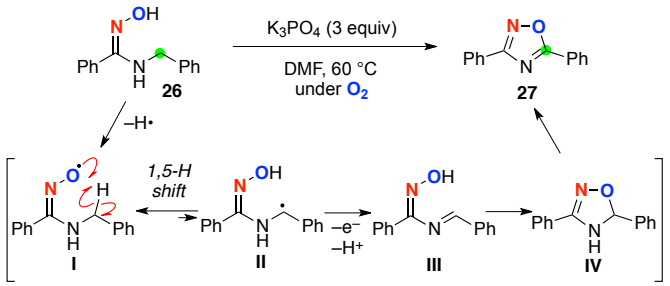
Based on this hypothesis, we have recently developed C-H oxygenation of ketoximes **24** using 2,2,6,6-tetramethylpiperidin-1-oxyl (TEMPO) as a radical initiator as well as an oxidant of the resulting C-radicals generated via 1,5-H shift (Scheme 12). Treatment of ketoximes **24** having a β-tertiary carbon with 3 equiv of TEMPO in the presence of K_2CO_3 in DMF at 140 °C delivered dihydroisoxazoles **25** via β-C-H oxygenation. The reaction is initiated by 1,5-H radical shift of the iminoxyl radical to generate the C-radical **I**, that is trapped by another molecule of TEMPO to give **II**. Elimination of TEMPO-H forms α,β-unsaturated oximes **III**, that is followed by intramolecular cyclization to give dihydroisoxazoles **25**. The methodology is capable of

oxidizing non-benzylic tertiary C-H bond (for **25c**), while the yield was moderate.



Scheme 12 *TEMPO-mediated C-H oxygenation*

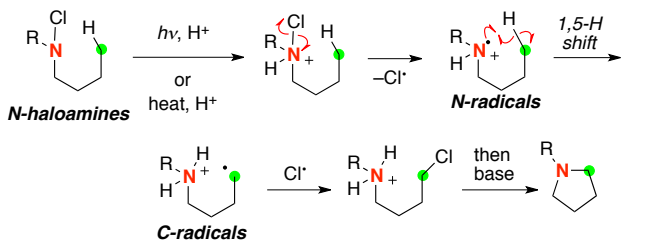
We also found that aerobic treatment of *N*-benzyl amidoximes such as **26** in the presence of K_3PO_4 generates the corresponding iminoxyl radical **I** (Scheme 13).[20] Subsequent 1,5-H radical shift to give the C-radical **II**, that might be further oxidized to the corresponding imine **III**. Cyclization of imine **III** gives 4,5-dihydro-1,2,4-oxadiazole **IV**, that undergoes aromatization to afford 1,2,4-oxadiazole like **27**.



Scheme 13 *Aerobic C-H oxygenation with N-Benzyl amidoximes*

3. With N-Radicals

The most famous classical example of aliphatic C-H oxidation with N-radicals is the Hofmann-Löffler-Freytag (HLF) reaction. The HLF reaction is probably the very first example of the "*C-H functionalization*" chemistry (Scheme 14).[21] The process is initiated by thermal or photochemical decomposition of protonated N-haloamines for generation of N-radicals, which immediately induce 1,5-H radical shift to form C-radicals. Further chlorination of the C-radicals followed by base-mediated intramolecular substitution reaction results in the C-N bond. As such, being similar with the generation methods of O-radicals from aliphatic alcohols (Scheme 2), those of N-radicals from aliphatic amines have relied on the *in-situ* generation of highly reactive N-haloamine derivatives and their homolytic N-X bond cleavage.

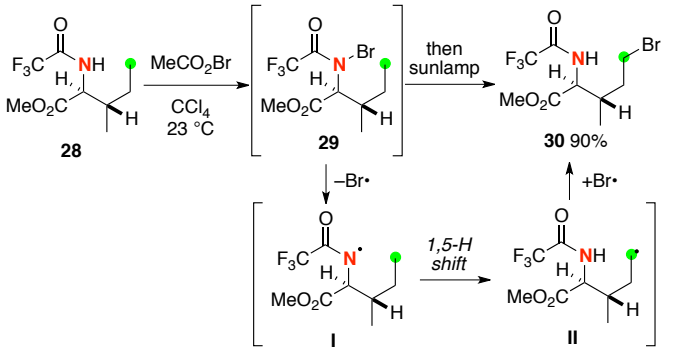


Scheme 14 *The Hofmann-Löffler-Freytag reaction with aminyl radicals*

However, due to the instability of N-haloamines and inherent high chemical reactivity of the resulting N-radicals, the reactions with these N-radicals result in poor product yields with difficulty of the reaction control. Recently, various rational designs of new N-radical sources have delivered robust and predictable site-selective aliphatic C-H oxidation strategies, that are highlighted in this section.

Amides and Carbamates

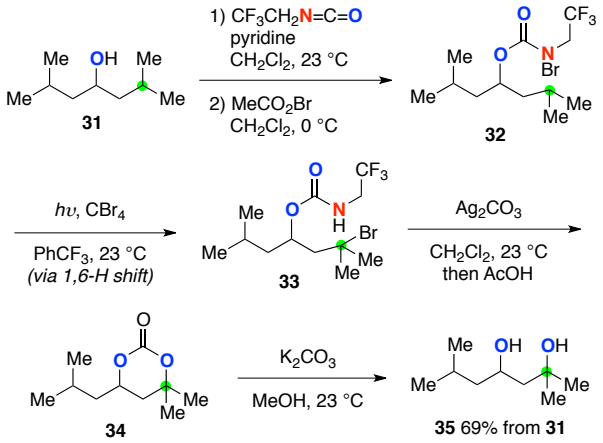
Corey developed site-selective bromination of N-trifluoroacetylisoleucine **28** using a stepwise HLF type strategy as shown in Scheme 15.[22] Treatment of trifluoroacetamide **28** with acetyl hypobromide gives N-bromo derivative **29**, that was subsequently reacted under irradiation by sunlamp to give C-H bromination product **30** via 1,5-H shift of the resulting N-radical **I** followed by bromine atom transfer to the resulting C-radical **II**. The electron-withdrawing trifluoroacetyl group on the N-radical **I** could enhance efficiency of the processes.[23]



Scheme 15 *C-H bromination of N-trifluoroacetylisoleucine by the HLF strategy*

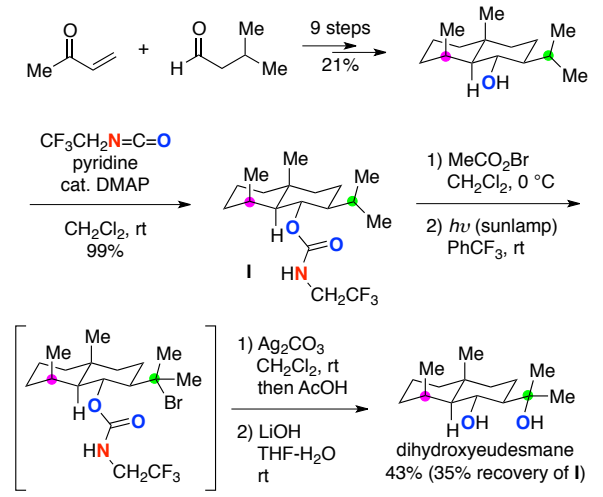
Baran recently devised trifluoroethyl carbamates for the stepwise (the HLF type), yet strikingly efficient aliphatic C-H hydroxylation (Scheme 16 for the conversion of alcohol **31**).[24] Starting from aliphatic alcohols, the corresponding 1,3-diols could be prepared via multi-step sequence including 1) installation of trifluoroethyl carbamate onto alcohol **31**; 2) formation of N-bromocarbamate **32**; 3) generation of the N-radicals by photolysis and successive remote C-H bromination to form **33** (the HLF type); 4) Ag_2CO_3-mediated cyclization followed by hydrolysis to afford cyclic carbonate **34**; 5) basic solvolysis to deliver 1,3-diol **35**. Of worthy to note in this method is preferential 1,6-H radical shift of **32** via the amidoyl

radicals as well as exclusive O-cyclization of **33** with Ag_2CO_3, enabling selective synthesis of 1,3-diol **35**.



Scheme 16 Synthesis of 1,3-diols from aliphatic alcohols

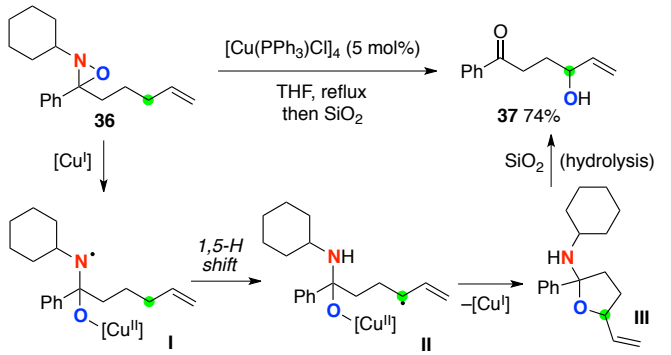
While this strategy is applicable for hydroxylation of only tertiary or benzylic C-H bonds in general, its robustness was indeed proved by concise synthesis of several eudesmane terpenes.[25] For example, in the synthesis of dihydroxyeudesmane (Scheme 17), site-selective C-H hydroxylation of the isopropyl C-H bond (marked in green) over another tertiary C-H bond (marked in purple) was achieved based on the trifluoroethyl carbamate-mediated radical C-H bond oxidation.



Scheme 17 Synthesis of dihydroxyeudesmane

Oxaziridines

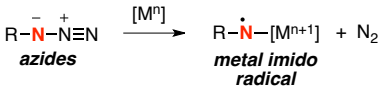
Aubé recently reported Cu(I)-catalyzed allylic sp^3 C-H oxygenation with N-alkyl oxaziridines (Scheme 18 for the reaction of oxaziridine **36**).[26] In sharp contrast to the Cu(II)-catalyzed Yoon's C-H amination with N-sulfonyl oxaziridines (see Scheme 9), this method could transfer an oxygen atom into the targeted C-H bonds during the radical reaction sequence, including 1) reductive homolysis of the N-O bond of N-alkyl oxaziridines with the Cu(I) catalyst to form aminyl radical **I** with the Cu(II)-alkoxide moiety; 2) 1,5-H radical shift to form the corresponding C-radical **II**; 3) reductive C-O bond formation (radical recombination) to form cyclic hemiaminal **III** with regeneration of Cu(I) species; 4) hydrolysis to form γ-hydroxy ketone **37**.



Scheme 18 Cu-catalyzed C-H oxygenation of oxaziridines

Azides

Single-electron-reduction of azides with lower valent metal species can potentially generate the corresponding N-radical having a N-metal bond (metal imido radicals) along with elimination of dinitrogen (Scheme 19).[27] The resulting N-radicals have been utilized mainly for amino-cyclization onto the alkene tethers for construction of azaheterocyclic frameworks. On the other hand, reports on use of the N-radicals derived from organic azides for remote sp^3 C-H oxidation have been quite rare.[28]

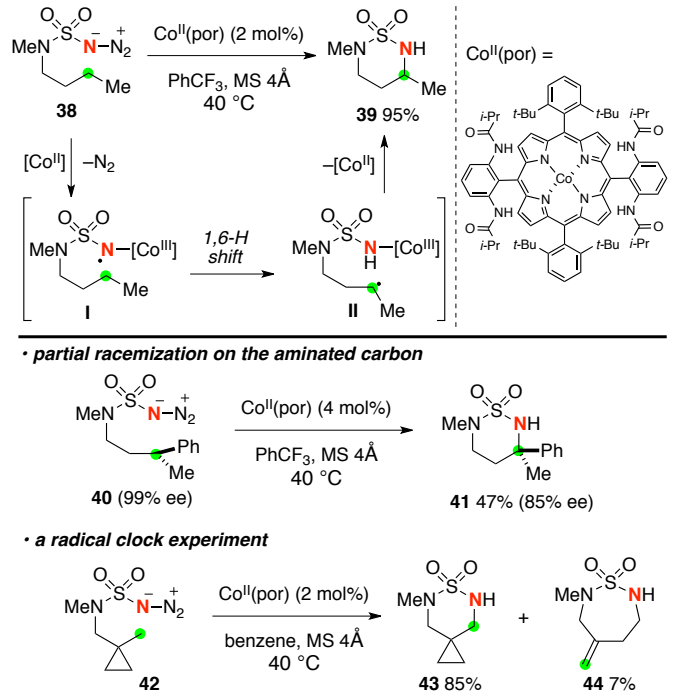


Scheme 19 Single-electron-reduction of azides

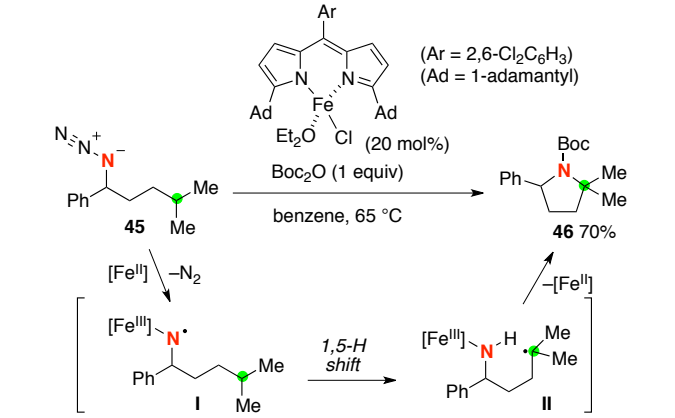
Recently, Zhang reported Co(II)-porphyrin-catalyzed sp^3 C-H amination with sulfamoyl azides to construct 6-membered ring sulfamides (Scheme 20).[29] The proposed reaction mechanism includes 1) selective 1,6 H-radical shift of the Co(III) imido radical intermediate **I** and 2) C-N bond formation by radical recombination of the resulting C-radical **II** with elimination of Co(II) species. The presence of the radical species **I** and **II** was proved by partial racemization of the aminated carbon having pre-installed chirality (the reaction of **40** to **41**) as well as the radical clock experiment with cyclopropyl substrate **42** to form 7-membered-ring *exo*-methylene sulfamide **44**, while both of the putative N- and C-radical species **I** and **II** should be short-lived.

Betley reported that iron(II) dipyrrinato complex could catalyze intramolecular C-H amination of organic azides for construction of azaheterocycles (Scheme 21 for the conversion of azide **45** to pyrrolidine **46**).[30] The reaction might include iron(III) imido radical intermediate **I** that could induce remote H-radical shift (mainly 1,5-H shift). In contrast to Zhang's C-H

amination (Scheme 20), no racemization at the aminated carbon having pre-installed chirality was observed. Moreover, a cyclopropyl moiety was kept intact in the radical clock experiment. Therefore, a concerted C-H amination pathway may not be ruled out as the amination mechanism.[31]



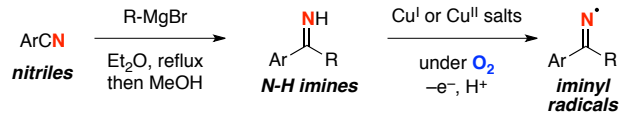
Scheme 20 Co(II)-catalyzed C-H amination of sulfamoyl azides



Scheme 21 Fe-catalyzed C-H amination with organic azides

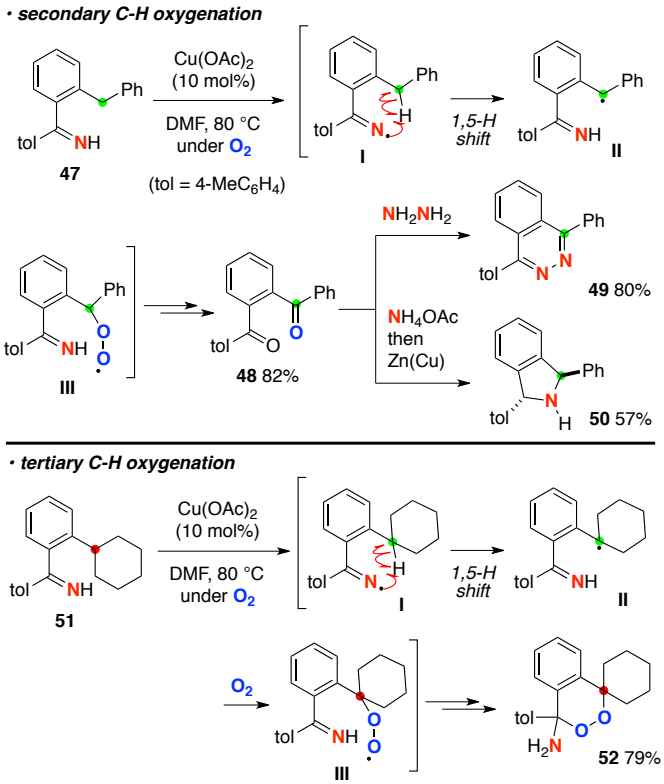
N-H Ketimines, Amidines, and Amidoximes

As representated by the HLF reaction, the typical aliphatic C-H oxidation actually requires several steps (i.e. preparation of *N*-haloamines, radical C-H halogenation, and base-mediated substitution reaction for the C-N bond construction) to obtain the target products. From the step- and atom-economical points of views, it would be rather ideal if N-H bonds could directly be converted into the N-radicals for subsequent remote C-H oxidation. In this aspect, we have recently utilized N-H ketimine for direct generation of the corresponding sp^2-hybridized *N*-radicals (iminyl radicals) under Cu-catalyzed aerobic reaction conditions (Scheme 22).[32] *N*-H ketimines were prepared *in situ* by the reactions of benzonitriles and Grignard reagents followed by quenching with MeOH, and utilized directly for the next oxidative generation of iminyl radicals.



Scheme 22 Oxidative generation of iminyl radicals from *N*-H ketimines

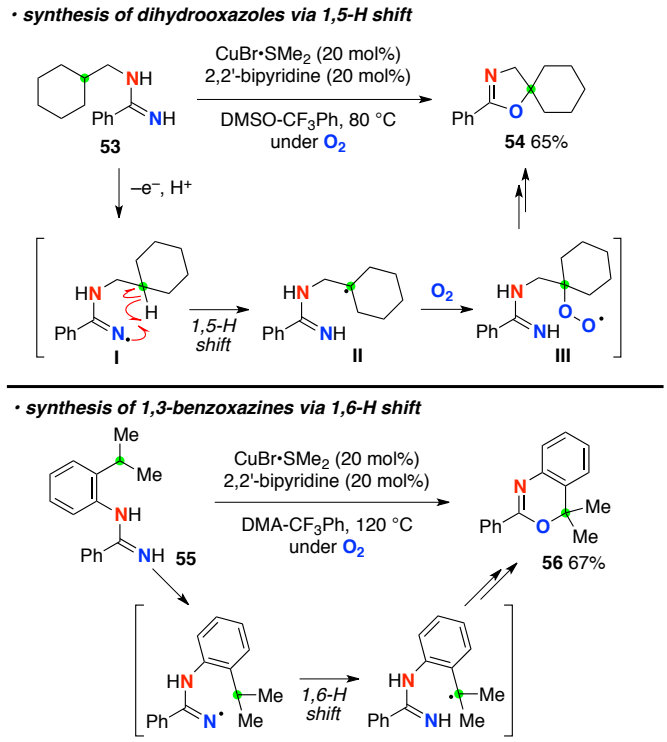
As shown in Scheme 23, we found that the resulting iminyl radicals **I** undergo 1,5-H radical shift to form the C-radicals **II**, that could be trapped by molecular oxygen to form peroxy radicals **III**. For example, the reaction of *ortho*-benzylaryl ketimine **47** underwent methylene C-H oxygenation to afford 1,2-dibenzoyl benzene **48**, which are very versatile precursors for synthesis of various azaheterocycles such as phthalazine **49** and isoindoline **50**.[33] On the other hand, the reactions of *ortho*-cyclohexylphenyl ketimine **51** having a tertiary C-H bond delivered very unique amino-endoperoxide **52** via C-H oxygenation and subsequent intramolecular cyclization of the peroxy moiety with the *N*-H ketimine part.



Scheme 23 Cu-catalyzed aerobic C-H oxygenation with *N*-H ketimines

The Cu-catalyzed aerobic reaction of *N*-alkylamidines such as **53** afforded aminidyl radicals **I** (N-radicals) via single-electron-oxidation and deprotonation of the amidine moiety,

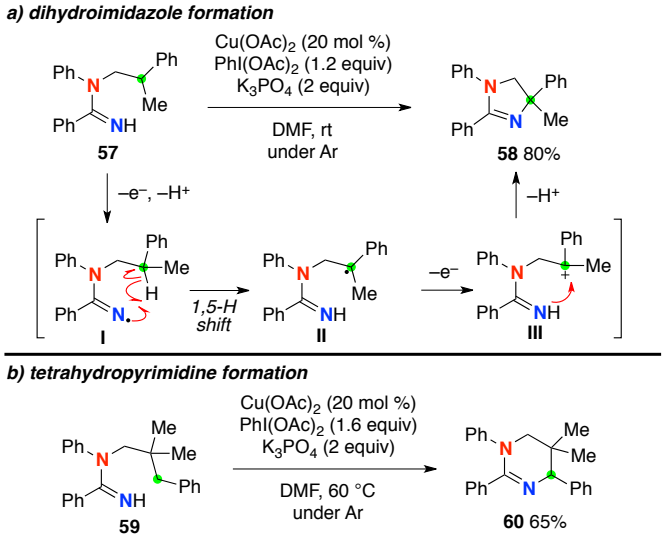
that is followed by 1,5-H-radical shift to generate the corresponding C-radicals **II** (Scheme 24).[34] The successive trapping of the resulting C-radicals with molecular O_2 forms peroxy radicals **III** (the C-O bond formation). Reduction of peroxy radicals **III** generates alkoxides, cyclization of which with the amidine moiety finally affords dihydrooxazoles like **54**. This strategy could also be applied for synthesis of 1,3-benzoxazines such as **56** from *N*-(2-isopropylphenyl)amidines like **55** via 1,6-H shift.



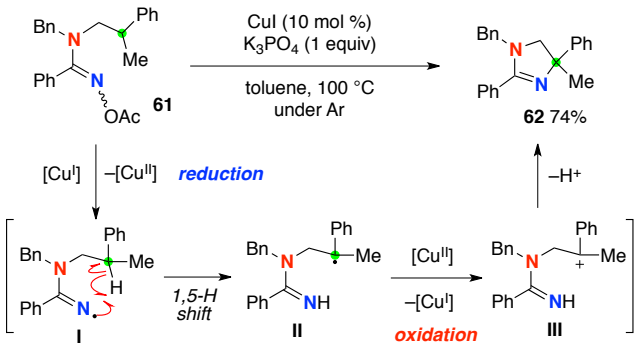
Scheme 24 Cu-catalyzed C-H oxygeanation with amidines

Instead of molecular oxygen as an oxidant, use of stoichiometric amount of $PhI(OAc)_2$ with $Cu(OAc)_2$ as a catalyst under an inert atmosphere enabled aliphatic C-H amination of N-alkylamidines (Scheme 25-a for the reaction of amidine **57**).[35] Under the reaction conditions, the resulting C-radicals **II** generated by the 1,5-H shift of amidinyl radical **I** could be further oxidized to the corresponding carbocations **III**, which are trapped by the amidine nitrogen to give dihydroimidazoles such as **58**. Formation of 6-membered-ring via 1,6-H-radical shift was enabled by blocking the 5-position as the quaternary carbon of amidine **59**, delivering tetrahydropyrimidine **60** (Scheme 25-b).

Disadvantage of this reaction is to require a stoichiometric use of $PhI(OAc)_2$ to maintain the catalytic turnover, obviously because of the redox nature of this strategy, needing two-electron oxidation (for generation of amidinyl radical **I** from the amidine and oxidation of transient C-radical **II** to carbocation **III**) to carry out the aliphatic C-H amination. Employment of amidoximes as a precursor of the amidinyl radical **I** enabled an entirely catalytic redox-neutral system only with a catalytic amount of CuI for the C-H amination (Scheme 26 for the reaction of amidoxime **61**).[36] The reaction is initiated by reduction of the N-O bond of amidoxime **61** with Cu(I), generating amidinyl radicals **I** along with Cu(II) species. After the 1,5-H shift, the resulting C-radical **II** is oxidized to the carbocation **III** by the Cu(II) to result in formation of dihydroimidazole **62** and re-generation of Cu(I) species.



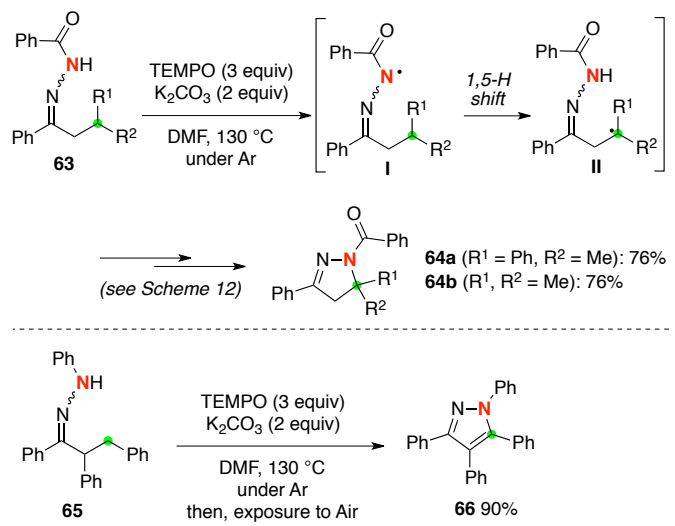
Scheme 25 Cu-catalyzed $PhI(OAc)_2$-mediated C-H amination with amidines



Scheme 26 Redox-neutral C-H amination with amidoximes

Hydrazones

Hydrazones have the structural analogy with oximes, and are thus expected to undergo sp^3 C-H amination with the corresponding N-radicals (hydrazone radicals) generated by H-radical abstraction (Scheme 27). Similarly with oxime chemistry (Scheme 12), we found that treatment of hydrazones **63** with TEMPO (3 equiv) delivered the corresponding β-C-H amination products, dihydropyrazoles **64** in good yields.[37] Amination of non-benzylic methine C-H bonds (for **64b**) also proceeded smoothly. 1,3,4,5-Tetraphenylpyrazole **66** was synthesized by methylene C-H amination of hydrazone **65** followed by further aerobic aromatization.



Scheme 27 TEMPO-mediated C-H amination with hydrazones

4. Conclusions

This review highlighted recent reports on aliphatic sp^3 C-H bond oxidation by remote H-radical abstraction with oxygen- and nitrogen-radicals. In terms of the oxidation processes of aliphatic sp^3 C-H bonds, nonetheless, these examples are conceptually incremental works of the Hofmann-Löffler-Freytag (HLF) reaction originally developed over 100 years ago. However, various readily available radical precursors have been devised and applied to execute predictable site-selective sp^3 C-H oxidation under milder and user-friendly reaction conditions. We anticipate that these free-radical strategies will provide new synthetic tactics for aliphatic sp^3 C-H oxidation to approach highly oxidized complex molecules. Thus, more challenges and opportunities still remain for further development of aliphatic sp^3 C-H oxidation with radicals in terms of the reaction efficiency and practicability; for example, by exploiting omnipotent and robust catalysts enabling rigorous control of the highly reactive radical species in a series of process events such as their generation (initiation), application (aliphatic sp^3 C-H oxidation), and termination.

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