sp³ C–H oxidation by remote H-radical shift with oxygen- and nitrogen-radicals: a recent update

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This review updates on recent advances in aliphatic sp³ C–H bond oxidation by remote H-radical abstraction with oxygen- and nitrogen-radicals classifying by the type of the radical precursors.

1. Introduction

Aliphatic sp³ C–H bonds are the most basic units in organic molecules, while they are chemically very stable under various reaction conditions unless otherwise activated by adjacent functional groups such as carbonyl groups. Direct functionalization (oxidation) of such inert sp³ C–H bonds could offer new trends in approaches to prepare valuable functional molecules in atom- and step-economical manners. Therefore, various methods for sp³ C–H oxidation have been developed, especially using transition metal catalysts, of 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 sp³ C–H oxidation in chemo-, regio-, and stereoselective fashions. On the other hand, remote H-radical shift (typically, a 1,5-H shift) is an alternative yet distinct way of oxidizing the sp³ C–H bonds, which could not be functionalized in conventional transition-metal catalyzed manners. Recently, various novel chemical approaches for sp³ 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 a newly emerging generation of these sp³ C–H oxidation strategies with oxygen- and nitrogen-radicals (O- and N-radicals) systematically classifying by the type of the radicals and their precursors utilized for the remote H-radical abstraction.2,3

2. With O-radicals

Alkoxy radicals (O-radicals) are considerably reactive (electrophilic) to undergo abstraction of a H-radical from the remote C–H oxidation in experiments.

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intramolecular sp³ C–H bonds as one of the possible reaction pathways. From the viewpoints of energy and structural factors (i.e. enthalpy control, entropy factor, and proximity effects) in 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. Due to the high bond-dissociation enthalpy (BDE) of the O–H bonds of aliphatic alcohols (about 93–105 kcal mol⁻¹), 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.

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 the singlet or triplet state, which is analogous to the 1,5-H radical shift with alkoxy radicals (Scheme 3). 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.

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

2.1. 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 sp³ C–H functionalization of alkyl hydroperoxides with a (semi-)stoichiometric Fe(II)–Cu(II) bimetallic system (Scheme 4). 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.

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''-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). Reductive generation of O-radical I by the reaction of hydroperoxide 5 with Cu(I) species and oxidative chlorine-atom transfer functionalization of the C-radical 6 would then proceed through the use of an oxidant such as Fe(III) salts or PBN for the formation of alkyl chloride 6.

Scheme 1 sp³ C–H oxidation by H-radical abstraction by O- and N-radicals.

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

Scheme 3 The Norrish type II and Norrish–Yang reactions of carbonyl compounds.

Scheme 4 sp³ C–H functionalization with alkyl hydroperoxides by Fe(II)–Cu(II).

Scheme 5 Cu-catalyzed sp³ C–H chlorination with hydroperoxides.
zation of the resulting C-radical II by Cu(II)–Cl species enabled the redox-neutral catalytic turnover with the single metallic system.

If reductive generation of the O-radicals from hydroperoxides could be achieved under an O2 atmosphere, the C-radicals generated via a 1,5-H radical shift could be trapped by O2 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, which could be catalyzed by the Cu(OAc)2·1,10-phenanthroline system in the presence of Et3N (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, which was reduced by LiAlH4 to obtain 1,4-diol 9 as a single product.

The role of Et3N should be as the terminal reductant of CuII species, enabling us to keep lower valent CuI species for the reductive generation of O-radical I even under an O2 atmosphere. The resulting O-radical I induces a 1,5-H radical shift to generate C-radical II, which 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-hydroxypythalimide (NHPI) as a co-reagent for the C–H bond oxygenation (Scheme 7). The aerobic reaction of alkane 10 bearing a dibenzylc 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, the phthalimide N-oxyl radical generated oxidatively from NHPI might undergo H-radical abstraction from 10 to generate the C-radical I,11 which is trapped by molecular oxygen to form peroxy radical II. The peroxy radical could be taken over to the next remote C–H oxygenation.

Taniguchi very recently developed direct conversion of aliphatic alkenes such as 13 and 15 to the corresponding 1,4-diols under iron(II) phthalocyanine [Fe(Pc)]-catalyzed aerobic reaction conditions in the presence of NaBH4 (Scheme 8).12 The reaction is initiated by hydroirorination 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 \( \text{I} \). The organo-iron(III) intermediate \( \text{I} \) was reacted with molecular oxygen and converted into iron(III)-peroxide complex \( \text{II} \), which undergoes Fenton-type fragmentation to give alkoxy radical \( \text{III} \). The subsequent 1,5-H radical shift forms the C-radical \( \text{IV} \), which is similarly trapped with molecular oxygen to give peroxy radical \( \text{V} \). Finally, reduction of \( \text{V} \) under the present reaction conditions could terminate the process to form 1,4-diol \( \text{14} \).

2.2. Oxaziridines

Oxaziridines are easily prepared by oxygenation of the corresponding imine and are stable to handle. The reactivity of oxaziridines could be controlled and tuned by modification of their substituents. Recently, the Du Bois group developed intermolecular sp\(^3\) C–H hydroxylation mediated by oxaziridine derivatives \( \text{in situ} \) from benzoxathiazine catalysts with \( \text{H}_2\text{O}_2 \) 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 \( N \)-sulfonoyl oxaziridine derivatives (Scheme 9 for the reaction of oxaziridine \( \text{17} \)).\(^{14}\) The reaction is likely initiated by formation of Cu(II)-oxaziridine complex \( \text{I} \) that induces remote H-radical abstraction along with N–O bond homolysis to give C-radical intermediate \( \text{II} \) having a Cu(III) sulfonamide moiety. Subsequent C–N bond forming cyclization (radical recombination) provides hemiaminal product \( \text{18} \), which could serve as a versatile intermediate for further molecular transformations for the synthesis of azaheterocycles \( \text{via} \) reduction (for \( \text{19} \)) and oxidation (for \( \text{20} \)) as well as Lewis acid-mediated C–C bond formation (for \( \text{21} \)). In this C–H oxidation process, the putative Cu(II)-oxaziridine complex \( \text{I} \) formally serves as an equivalent of the O-radical for remote H-radical abstraction, in which \( \delta \)-C–H oxidation \( \text{via} \) 1,6-H shift is interestingly more favoured than \( \gamma \)-C–H oxidation \( \text{via} \) 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.

2.3. Peroxy nitrites

Taniguchi recently disclosed multi-functionalization of aliphatic alkenes using tert-butyl nitrite under an \( \text{O}_2 \) atmosphere, which resulted in the formation of lactols \( \text{via} \) aliphatic sp\(^3\) C–H oxygenation induced by \( \text{in situ} \) generated peroxy nitrite (Scheme 10 for the reaction of alkene \( \text{22} \)).\(^{15}\) The process is initiated by aerobic oxynitration of alkenes \( \text{22} \) \( \text{via} \) radical addition of \( \text{in situ} \) formed \( \text{NO}_2 \) onto the C=C bond followed by trapping of the resulting C-radical \( \text{I} \) with \( \text{O}_2 \), affording peroxy radical intermediate \( \text{II} \). Further reaction of peroxy radical \( \text{II} \) with tert-butyl nitrite gives peroxy nitrite \( \text{III} \), homolysis of which generates O-radical \( \text{IV} \). Subsequently, 1,5-H shift

![Scheme 9](image-url)  
Cu-catalyzed C–H amination with oxaziridines.

![Scheme 10](image-url)  
Aerobic multi-functionalization of alkenes mediated by tert-BuONO.
is induced by O-radical IV to form C-radical V that is finally oxygenated to afford lactol 23.16

2.4. 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 electrons through the N–O bond (BDE = 83 kcal mol⁻¹).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 generates 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).

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 K₂CO₃ in DMF at 140 °C delivered dihydroisoxazoles 25 via β-C–H oxygenation. The reaction is initiated by a 1,5-H radical shift of the iminoxyl radical to generate the C-radical I, which is trapped by another molecule of TEMPO to give III. Elimination of TEMPO-H forms α,β-unsaturated oximes III, which is followed by intramolecular cyclization to give dihydroisoxazoles 25. The methodology is capable of oxidizing non-benzylic tertiary C–H bonds (for 25c), while the yield was moderate.

We also found that aerobic treatment of N-benzyl amidoximes such as 26 in the presence of K₃PO₄ generates the corresponding iminoxyl radical I (Scheme 13).20 Subsequent 1,5-H radical shift gives the C-radical II, which might be further oxidized to the corresponding imine III. Cyclization of imine III gives 4,5-dihydro-1,2,4-oxadiazole IV, which undergoes aromatization to afford 1,2,4-oxadiazole like 27.

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 a 1,5-H radical shift to form C-radicals. Further chlorination of the C-radicals followed by base-mediated intramolecular substitution reactions results in the C–N bond. As such, being similar to the generation methods of O-radicals from aliphatic alcohols (Scheme 2), methods of generation 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.

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

3.1. Amides and carbamates

Corey developed site-selective bromination of N-trifluoroacetyl-isoleucine 28 using a stepwise HLF type strategy as shown in
Scheme 15. C–H bromination of N-trifluoroacetylisoleucine by the HLF strategy.

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

Scheme 17. Synthesis of dihydroxyeudesmane.


3.2. Oxaziridines

Aubé recently reported Cu(i)-catalyzed allylic sp3 C–H oxygenation with N-alkyl oxaziridines (Scheme 18 for the reaction of oxaziridine 36). In sharp contrast to the Cu(II)-catalyzed Yoon’s C–Hamination with N-sulfonyloxaziridines (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.
3.3. 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). 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 the use of the N-radicals derived from organic azides for remote sp<sup>3</sup> C–H oxidation have been quite rare.

Recently, Zhang reported Co(II)-catalyzed sp<sup>3</sup>C–H amination of sulfamoyl azides (Scheme 20). 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 on the aminated carbon (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 the putative N- and C-radical species I and II should be short-lived.

Betley reported that the iron(II) dipyrrinato complex could catalyze intramolecular C–H amination of organic azides for the construction of azaheterocycles (Scheme 21 for the conversion of azide 45 to pyrrolidine 46). The reaction might include iron(III) imido radical intermediate I that could induce a 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.

3.4. N–H ketimines, amidines, and amidoximes

As shown 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<sup>2</sup>-hybridized N-radicals (iminyl radicals) under Cu-catalyzed aerobic reaction conditions (Scheme 22). N–H ketimines were prepared in situ by the reaction of benzonitriles and Grignard reagents followed by quenching with MeOH, and were utilized directly for the next oxidative generation of iminyl radicals.

As shown in Scheme 23, we found that the resulting iminyl radicals I undergo a 1,5-H radical shift to form the C-radicals II, which could be trapped by molecular oxygen to form peroxy radicals III. For example, the reaction of ortho-benzylaryl nitrites R-MgBr with Cu(I) or Cu(II) salts under O<sub>2</sub> led to the formation of iminyl radicals.
ketimine 47 underwent methylene C–H oxygenation to afford 1,2-dibenzoyle benzene 48, which are very versatile precursors for the synthesis of various azaheterocycles such as phthalazine 49 and isoindoline 50. On the other hand, the reactions of ortho-cyclohexylphenyl ketimine 51 having a tertiary C–H bond delivered a very unique amino-endoperoxide 52 via C–H oxygenation and subsequent intramolecular cyclization of the peroxide moiety with the N–H ketimine part.

The Cu-catalyzed aerobic reaction of N-alkylamidines such as 53 afforded amidinyl radicals I (N-radicals) via single-electron-oxidation and deprotonation of the amidine moiety, which was followed by a 1,5-H-radical shift to generate the corresponding C-radicals II (Scheme 24). The successive trapping of the resulting C-radicals with molecular O₂ forms peroxide radicals III (the C–O bond formation). Reduction of peroxide radicals III generates alkoxides, cyclization of which with the amidine moiety finally affords dihydrooxazoles like 54. This strategy could also be applied for the synthesis of 1,3-benzoxazines such as 56 from N-(2-isopropylphenyl)amidines like 55 via a 1,6-H shift.

Instead of molecular oxygen as an oxidant, the use of a 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 25a for the reaction of amidine 57). 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 a 6-membered-ring via a 1,6-H-radical shift was enabled by blocking the 5-position as the quaternary carbon of amidine 59, delivering tetrahydropyrimidine 60 (Scheme 25b).

The disadvantage of this reaction is that it requires 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. Employing a stoichiometric oxidant such as PhI(OAc)₂ enabled the Cu-catalyzed aerobic C–H oxygenation with N–H ketimines.

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\text{Cu(OAc)}_2 + \text{O}_2 + \text{PhI(OAc)}_2 \rightarrow \text{PhI(OAc)}_3 + \text{Cu(OAc)}_2
\]
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 studies 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, many 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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Notes and references


2 This review does not include remote sp\(^3\) C–H oxidation using C-radicals. For reviews on sp\(^3\) C–H functionalization with C-radicals, see: (a) P. Dauban, Acc. Chem. Res., 2012, 45, 911; (b) J. Robertson, J. Pillai and R. K. Lush, Chem. Soc. Rev., 2001, 30, 94.

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16 The same group reported that the reactions in the presence of water afforded 4-hydroxy-5-nitropentyl nitrate, see: D. Hihore and T. Taniguchi, Beilstein J. Org. Chem., 2013, 9, 1713.