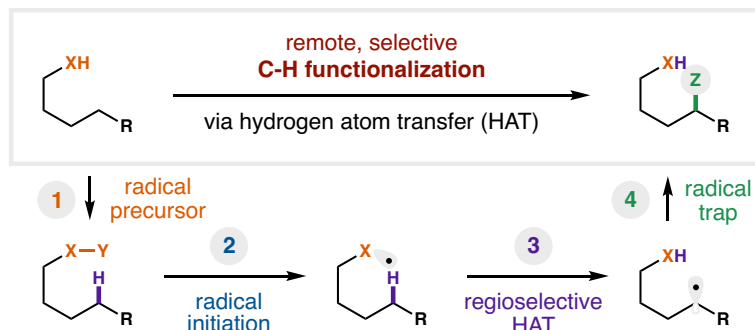


Remote C-H Functionalization via Selective Hydrogen Atom Transfer

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Abstract The selective functionalization of remote C-H bonds via intramolecular hydrogen atom transfer (HAT) is transformative for organic synthesis. This radical-mediated strategy provides access to novel reactivity that is complementary to closed-shell pathways. As modern methods for mild generation of radicals are continually developed, inherent selectivity paradigms of HAT mechanisms offer unparalleled opportunities for developing new strategies for C-H functionalization. This Review outlines the history, recent advances, and mechanistic underpinnings of intramolecular HAT as a guide to addressing ongoing challenges in this arena.

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Key words Hydrogen Atom Transfer, Remote C-H Functionalization, Radicals, Nitrogen-centered radicals, Oxygen-centered radicals

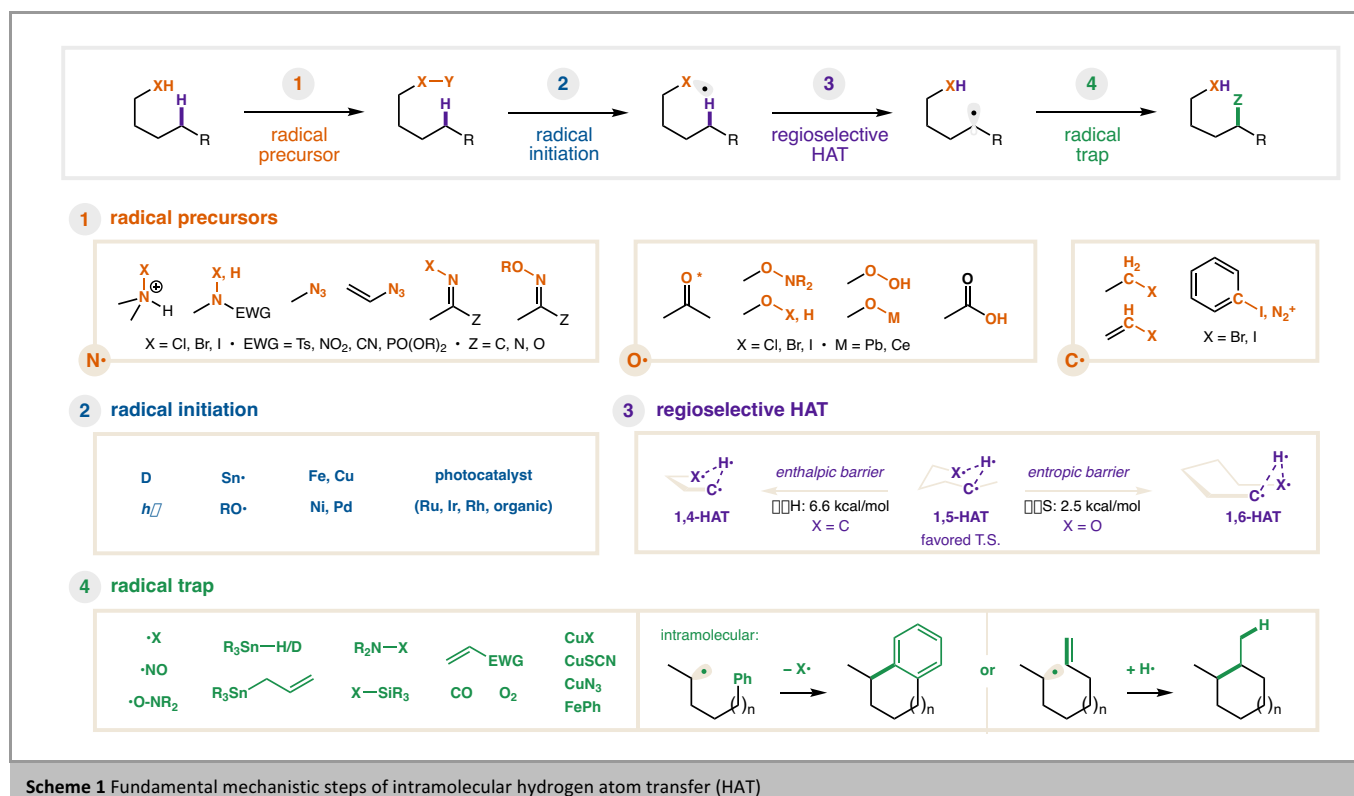
1 Introduction

In modern organic synthesis, C-H functionalization is the chemical equivalent of adding the final brush strokes to a painting. While it conveniently allows for blemishes to be swiftly corrected without restarting from a blank canvas, it also necessitates great care not to disrupt the overall beauty of a near-finished piece. Similarly, since the C-H bond is the most ubiquitous motif in organic chemistry, its modification within a complex molecule necessitates a high level of care and precision. Thus, the most important challenge of C-H functionalization is selectivity.^{1–4} In recent decades, metal-based C-H activation^{5–7} and insertion^{8,9} mechanisms have been employed with increasing frequency to address the challenges of chemo- regio- and stereo- selectivity.

In contrast, radical-mediated C-H functionalization,¹⁰ while discovered earlier,^{11–13} has played a much less significant role in advancing the frontiers of selective C-H functionalization. This is somewhat surprising given that intramolecular hydrogen atom transfer (HAT)¹⁴ of a C-H to a remote radical site¹⁵ is typically quite selective^{16–18} and exergonic.¹⁴ The latter feature suggests these processes may be promoted under milder reaction conditions than their metal-mediated counterparts. In our estimation, however, the traditionally harsh conditions employed for radical generation have precluded an objective evaluation of the full synthetic potential of open-shell pathways. For instance, radical initiation has historically been conducted with strong acid, refluxing peroxides, or high energy UV light. Fortunately, modern methods now allow mild access to radicals (e.g. iodonium reagents,^{19–21} photoredox catalysts^{22–24}), thereby enabling synthetic chemists to more fully explore the inherent selectivity of C-H functionalizations mediated by the diverse chemistry^{25–28} of single-electron transfer (SET) pathways.

This Review is intended to be more instructive than exhaustive. Therefore, its focus on intramolecular HAT will highlight the key discoveries in these areas, with emphasis on the development of new strategies to (i) generate unique radicals (ii) from tailored precursors and to (iii) trap these relayed radicals in novel ways. Our objective is to illustrate the innovations and general lessons from pioneering – and more recent – contributions in each of these areas, in order to inform the reader of the challenges and opportunities that lie ahead.

The general strategy of remote, directed C-H functionalization via HAT can be divided into four main components, as outlined above and detailed further in Scheme 1. Specifically, the mechanistic features that are common to all intramolecular HAT reactions include: (1) generation of a radical precursor; (2) initiation of the radical; (3) regioselective HAT; and (4) trapping of the relayed radical. A brief overview of the salient aspects of each elementary step is described below.



(1) Radical precursor. The first, and perhaps most important, step in promoting an intramolecular HAT is the two-electron construction of a precursor that will enable access to the key, single-electron intermediate. The most common form of HAT-initiation is from N- O- or C-centered radicals,²⁸ and this Review is organized into three parts, each describing the reactivity of one of these radicals. As shown in Scheme 1, there is a range of related methods for accessing each radical type. For example, N-centered radicals are typically accessed via SET reduction or homolysis of a weak N-X bond, where X is a halide or N₂ nucleofuge. Similarly, O-centered radicals are typically accessed via homolysis of a weak O-X bond (or via photoexcitation of a carbonyl). Historically, these weak heteroatom-halide bonds have been pre-formed, but they are now typically generated *in situ*.¹⁹ Finally, C-centered radicals (alkyl, aryl, and vinyl) can be accessed from weak C-X or C-N₂ precursors.

(2) Radical initiation. The next, key step in any HAT mechanism is the generation of the open-shell intermediate. Historically, this has been the most limiting aspect of HAT chemistry, as typical strategies employ strong acid, high temperatures, unstable peroxides, toxic organotin reagents, or high energy UV light. More recently, however, earth abundant metals (e.g. Fe, Cu, Ni), hypervalent iodine reagents, and visible-light-mediated photoredox catalysts enable mild access to radicals, harnessing inherent HAT selectivity pathways.

(3) Regioselective HAT. Despite the rapid, exergonic nature of many intramolecular H-atom transfer events, H• abstraction frequently occurs with complete δ regioselectivity. The 1,5-HAT pathway is most typical thanks to a pre-organized, six-membered, cyclic transition state, with nearly linear C-H-X geometry (153° for O•).¹⁶ For the C• mediated process, there is a

strong enthalpic preference for 1,5-HAT over 1,4-HAT ($\Delta\Delta H$: 6.6 kcal/mol).²⁹ In contrast, 1,5-HAT over 1,6-HAT selectivity stems from a lower entropic barrier ($\Delta\Delta S$: 8.3 eu, 2.5 kcal/mol) in the O• pathway.³⁰ As a consequence, the rate of 1,5-HAT is at least 10x faster ($2.7 \times 10^7 \text{ s}^{-1}$) vs the 1,4 or 1,6 variants.³¹ Rare exceptions¹⁷ to this rule are cases where C-5 lacks an H atom, or when adjacent C-H bonds are significantly weaker (e.g. benzylic, tertiary, α -oxy), or when geometry precludes 1,5-HAT. Otherwise, selective 1,5-HAT of an initiating radical typically offers access to a δ carbon radical, exclusively.

(4) Radical trap. Last, but certainly not least, the overall transformation – and the specific identity of the group that is incorporated via C-H functionalization – relies on the trap that is used. In this regard, radical-mediated processes offer a wide array of synthetic complementarity to other metal-mediated approaches. For example, unlike the strong reliance of the latter on aryl halide or organometallic coupling partners, radical traps can range from caged radicals (X•, NO•, ON•) to weakly bonded main group molecules (N-X, Si-X, Sn-H, Sn-allyl) to metal salts (CuX, CuSCN, CuN₃) to π -systems (alkenes, arenes). This diversity of methods suitable for terminating HAT mechanisms allows for the widest scope of reactivity that is available for C-H functionalization via any single approach.

The following is a selected collection, showcasing the range of intramolecular HAT-mediated reactions, classified by the identity of the radical that initiates H-atom transfer (e.g. N, O, C).

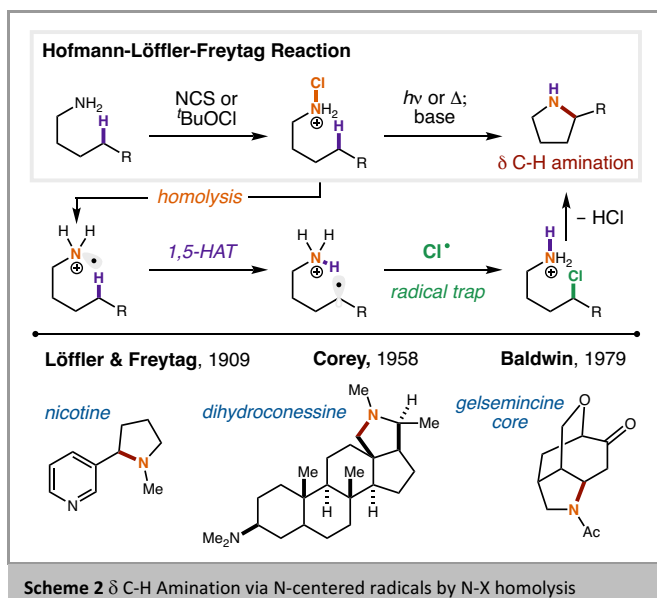
2 Nitrogen-centered radicals

In the field of intramolecular HAT chemistry, N-centered radicals enjoy a prominent role.¹⁸ Historically, these radicals

were the first used to initiate remote H-atom transfer. Additionally, they are the most tunable (via N-substitution), enabling fine modulation of their polarity,³² which is known to highly influence HAT reactivity. And thanks to their versatility, N-centered radicals are now accessible via the widest range of mild, radical-initiation methods.^{33,34}

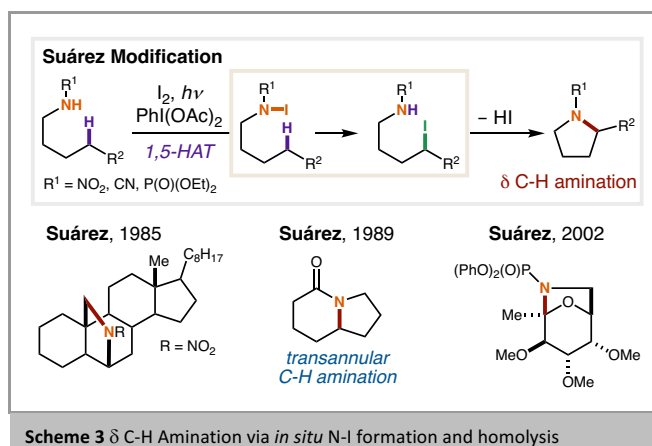
2.1 sp^3 N radical initiation

The earliest example of selective C-H functionalization via HAT was reported by Hofmann in the late 1800's (Scheme 2).³⁵ This N-centered radical reaction, now known as the Hofmann-Löffler-Freytag (HLF) reaction, arises from photolytic homolysis of a cationic N-haloamine.^{36,37} The resulting aminium radical cation is sufficiently polarized³² to enable the abstraction of a hydrogen atom from the δ carbon, producing a new C-centered radical. The selectivity of this 1,5-HAT is governed by a chair-like transition state. The ensuing δ C-radical is then trapped by recombination with a caged X^\bullet (or N-X) to generate a δ halide, which is then displaced via base-induced, intramolecular cyclization. This strategy for accessing pyrrolidines directly from amines via δ C-H amination has enabled the streamlined synthesis of several natural products and their derivatives. For instance, Löffler and Freytag employed this reaction in the synthesis of nicotine from the corresponding N-halo amine,³⁸ and later, Corey and Hertler employed this approach in the synthesis of a series of cyclo-aminated steroid derivatives.³⁹ Baldwin and Doll extended this method to the use of amides in the total synthesis of gelsemicine.⁴⁰ Overall, the HLF reaction has played a vital role in demonstrating HAT as a robust and selective radical-mediated C-H functionalization method.

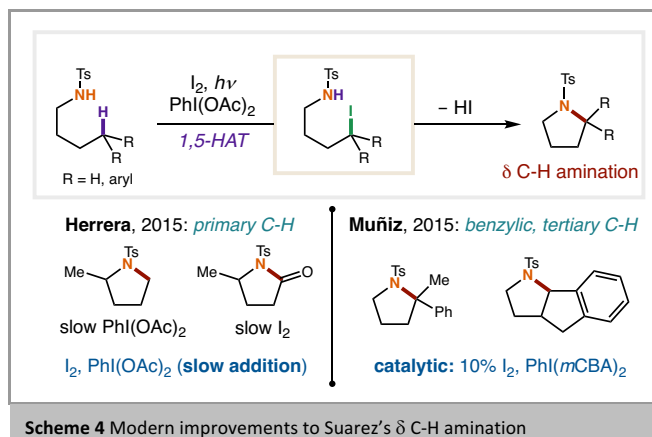


Hofmann's seminal report inspired continued development of intramolecular HAT strategies for selective C-H functionalization, especially via N-centered radicals. In the original reports of the HLF reaction, the use of strong acid and high temperatures were required to generate the polarized N-radical, thereby prohibiting the use of acid-sensitive functional groups. Additionally, the need for N-X pre-formation limited the scope and efficiency of this method. In 1985, nearly a century later,

Suárez and co-workers circumvented the need to pre-form the N-haloamine by generating N-I *in situ* (Scheme 3).⁴¹ By employing molecular iodine and a hypervalent iodine oxidant, $\text{PhI}(\text{OAc})_2$, N-I is generated from transiently formed AcO-I ,⁴² and the ensuing weak N-I bond is homolyzed by light to generate the analogous electrophilic nitrogen-centered radical. Furthermore, the need for strongly acidic media is circumvented by the use of electron-deficient protecting groups (e.g. NO_2 , CN) to polarize the N-radical. Through this modified HLF reaction mechanism, a series of pyrrolidines were generated, including steroid derivatives. Suárez and co-workers applied these milder reaction conditions to the synthesis of bicyclic lactams via transannular C-H lactamization,⁴³ as well as to the δ C-H amination of carbohydrates at the anomeric carbon.^{44,45}



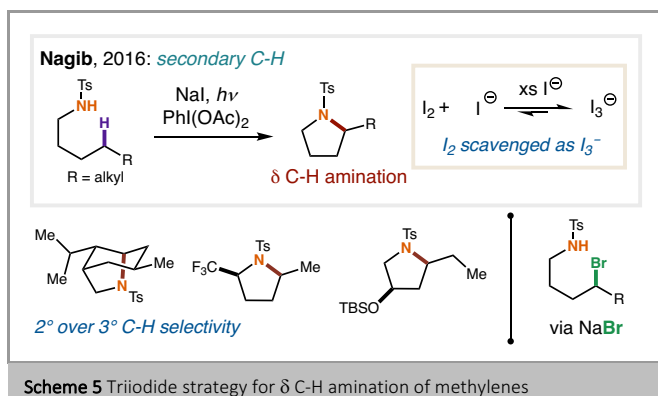
In 2015, the groups of Herrera⁴⁶ and Muñiz⁴⁷ separately explored further modifications of the HLF reaction (Scheme 4). Whereas the Suárez HLF reaction efficiently aminates weak C-H bonds (benzylic, tertiary, α -oxy), Herrera and co-workers investigated 1,5-HAT from primary C-H bonds. The challenge of this transformation arises from the high BDE of primary C-H bonds (>100 kcal vs 90 kcal, benzylic).⁴⁸ Their solution involves adding $\text{PhI}(\text{OAc})_2$ oxidant to the reaction portion-wise to prevent over-oxidized side-products, in favor of desired reactivity. Alternatively, divergent reactivity to access lactams was accomplished using slow addition of I_2 , providing a wide scope of 2-pyrrolidinones instead.



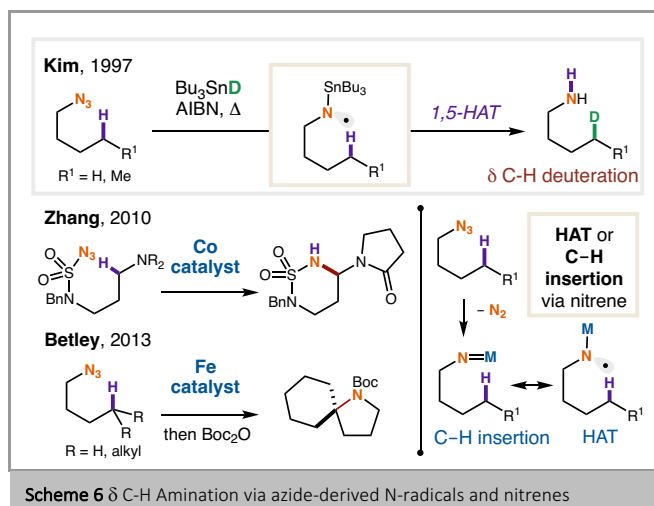
In the same year, Martínez and Muñiz reported a catalytic variant of the Suárez reaction, using 10 mol% of I_2 and a tailored

hypervalent iodine oxidant.⁴⁷ This represents the first, catalytic HLF reaction. Its utility is best for weaker benzylic and tertiary C-H bonds. In 2017, the labs of Muñiz and Reiher reported a dual-catalytic method for δ C-H amination in which an organic photoredox catalyst allows for catalytic re-oxidation of the I^- to the I_2 co-catalyst. In this pathway, air serves as the terminal oxidant to reform I_2 from the HI byproduct.⁴⁹

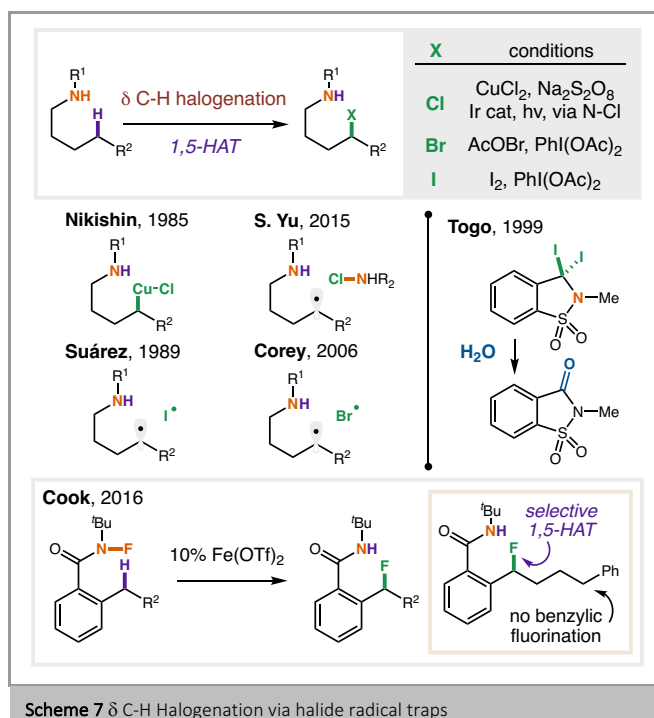
Although many HLF modifications are iodine-mediated, excess I_2 can generate undesired oxidized side-products, leading to poor product formation in cases such as the amination of secondary C-H bonds. Our group recently introduced a solution to this challenge that circumvents the build-up of excess I_2 by generating it *in situ* via slow oxidation of NaI (Scheme 5).⁵⁰ In this approach, triiodide (I_3^-) is generated in equilibrium upon combination of I_2 and NaI, whereby I^- scavenges I_2 and limits side-products derived from I_2 oxidation. This triiodide-mediated approach is the first to enable δ C-H amination of amines with secondary C-H bonds, and serves to complement methods that are better suited for stronger C-H bonds. Notably, this reaction is selective for δ secondary C-H functionalization – even in the presence of weaker tertiary C-H bonds – and provides a broad scope of substituted pyrrolidines from these ubiquitous precursors. Interestingly, the use of NaCl or NaBr facilitates interception of two key intermediates in the proposed mechanism: the N-Cl amine, as well as the δ -Br amine.



Azides have been implemented as an alternative to haloamines as precursors to N-centered radicals, enabling similar reactivity (Scheme 6). Kim *et al* generated N-radicals by combination of alkyl azides and Bu_3Sn^\bullet , followed by loss of N_2 .⁵¹ The resultant, Sn-stabilized N-radical effectively performs a 1,5-HAT to yield the δ C-radical, which is then trapped by Bu_3Sn-D affording selective δ -deuteration. In later years, metal-catalyzed variants were also developed for conversion of azides to nitrenoids. Zhang and co-workers first employed this strategy using a Co(II) metalloporphyrin catalyst.⁵² Mechanistic studies suggest the reaction proceeds through H-atom abstraction.⁵³ Similarly, the Betley group reported a nitrene-mediated C-H amination of both activated and unactivated C-H bonds δ to azides, using high-spin Fe(II) catalysts.⁵⁴ The mechanism was proposed to occur either via intramolecular HAT from the imido radical, or via a closed-shell C-H insertion pathway.

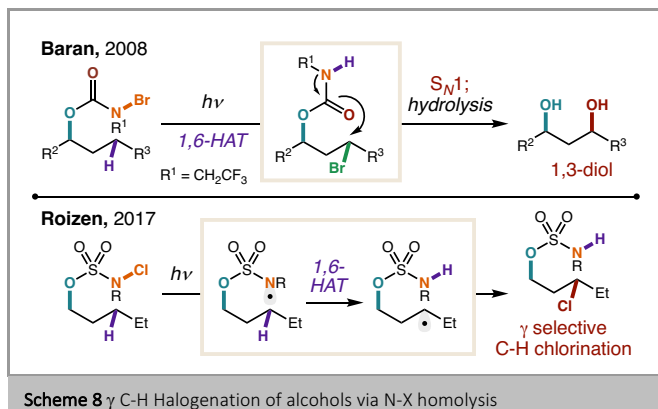


In addition to selective C-H aminations, N-centered radicals have also been employed to generate other functional groups from inert, distal C-H bonds. For example, intercepting the δ -halo intermediate of the HLF mechanism has been developed as an important method for installing a versatile halide group at the δ position via remote C-H functionalization (Scheme 7). Nikishin and co-workers reported the first δ chlorination in 1985 using stoichiometric $CuCl_2$ and sodium persulfate.⁵⁵ More recently, S. Yu and co-workers reported a modern variant to access δ chlorination using photoredox catalysis from the pre-formed N-Cl amine.⁵⁶ While the I_2 -mediated HLF reaction typically results in rapid cyclization of the δ iodide, early reports by Suárez included the observation of a small amount of δ iodide remaining, as well as trace δ di-iodide byproduct.⁴³ Togo and co-workers demonstrated that these multi-iodination products could be harnessed in the synthesis of saccharides via a triple C-H iodination of *o*-tosylamides at the benzylic position, followed by ring-closure and hydrolysis.⁵⁷

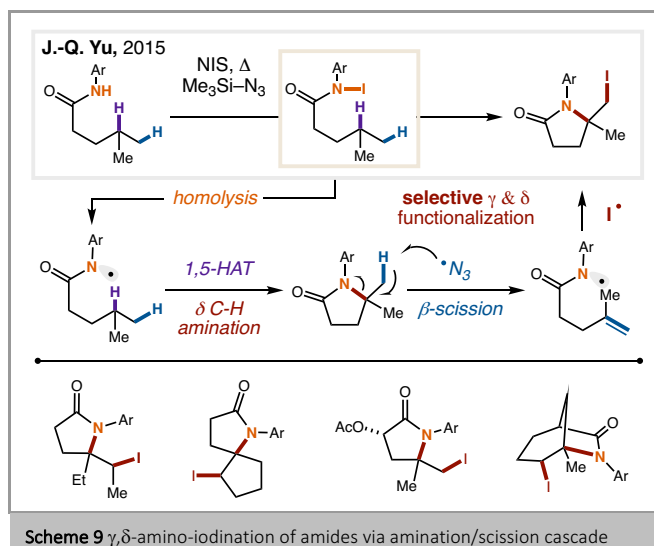


Selective C-H bromination was obtained by Corey and co-workers using *in situ* generation of a trifluoroacetamide N-Br via direct amide combination with acetyl hypobromite (AcO-Br).⁵⁸ Under these reaction conditions, HLF amination does not occur on the δ bromide. Recently, J.-Q. Yu and co-workers introduced a Cu-catalyzed approach to the δ bromination using Me₃Si-N₃ and NBS to generate transient amidyl radicals and intercept their δ -C radicals.⁵⁹ Completing the halogen series, Cook and co-workers reported the first δ C-H fluorination, enabled by Fe-catalyzed transposition of an N-F to a benzylic C-F with complete selectivity, derived from 1,5-HAT of an amidyl radical, even in the presence of other benzylic C-H bonds.⁶⁰

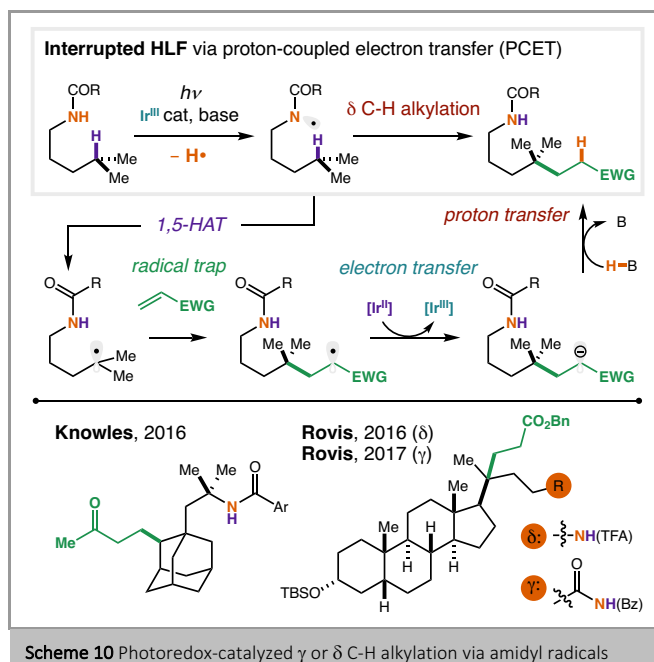
In 2008, Baran and co-workers developed an HAT-based C-H halogenation strategy to access 1,3-diols from N-bromo carbamates (Scheme 8).⁶¹ Following photo-initiated homolysis of N-Br, 1,6-HAT occurs along with Br• trapping, affording the alkyl bromide. Although the HLF reaction typically undergoes 1,5-HAT, this carbamate tether promotes a seven-membered, cyclic transition state, affording the γ halide. The caveat is H• abstraction must be from a benzylic or tertiary C-H bond. The resulting alkyl bromide is then displaced, generating an imino-carbamate. This intermediate is hydrolyzed to unmask the 1,3-diol, providing access to a synthetically valuable motif in a one-pot synthesis from the N-bromo carbamate. Notably, this strategy enabled the total synthesis of several natural products, including rengyol and isorengyol. In 2017, Roizen and co-workers reported N-chloro sulfamates facilitate highly selective γ halogenation of secondary C-H bonds.⁶² This photo-initiated chlorination remains γ -selective even in the presence of weaker C-H bonds that are tertiary or α to heteroatoms. It is expected this robust γ -selectivity – dictated by sulfamate geometry – is extendable to other γ C-H functionalizations.



Recently, J.-Q. Yu and co-workers utilized amidyl radicals to simultaneously functionalize both γ and δ C-H bonds in a single cascade reaction to generate iodolactams from alkyl amides (Scheme 9).⁶³ This transformation begins with *in situ* conversion of an amide to its corresponding N-I intermediate by treatment with NIS. Following 1,5-HAT, iodination, and lactam formation, the mechanism then proceeds via an azido radical-mediated β -scission of the C-N to form a terminal olefin. Subsequent 5-*exo*-trig cyclization and I• trapping yields the δ -iodo- γ -lactam. This selective dual-functionalization method converts two remote C-H bonds into vicinal functionalities in a single step.



The common feature in all of the previously described mechanisms is the SET reduction or homolysis of a weak N-X to generate an N• intermediate. Even the modern Suárez variant employs *in situ* N-X formation. In all these cases, there must be an X• or weak N-X present; and these are great traps for the δ radical. Thus, while there are several methods of accessing δ C-H functionalization with halides and heteroatoms, there is no possibility for accessing C-C formation via this mechanism.



In 2016, the labs of Knowles⁶⁴ and Rovis⁶⁵ independently reported methods to construct distal C-C bonds via amidyl radicals and circumvented the need for pre-installation, or *in situ* generation, of an N-X bond (Scheme 10). This mechanism proceeds via a neutral amidyl radical, which is generated from oxidative proton-coupled electron transfer (PCET) by an excited iridium photocatalyst. As in the HLF reaction, the resulting amidyl radical undergoes a 1,5-HAT to form a carbon-centered radical. However, instead of undergoing typical X• trapping (since there is no halogen), the C-radical is trapped via 1,4-addition into a Michael acceptor, producing a new C-C bond

from a tertiary δ C-H bond. Reduction of the newly formed α -EWG C-radical provides a stabilized anion and regenerates the Ir(III) catalyst. Upon protonation of the anion, the remote functionalized product is isolated. This first, interrupted HLF reaction represents the only method for δ C-H alkylation by HAT from an N-radical. Its success stems from avoiding the need for halogens (X_2 or *in situ* N-X) to generate the N-radical, and thus non-halide based trapping mechanisms may now be accessed.

In 2017, Rovis and co-workers reported a related method, wherein C-H alkylation occurs on the carbonyl side chain of the amide (rather than the N-substituent).⁶⁶ Since regioselectivity is again dictated by a 1,5-HAT mechanism from an amidyl radical, C-H alkylation is γ selective in this case.

2.2 sp^2 N radical initiation

An iminyl (sp^2) N-centered radical exhibits complementary reactivity to aminyl (sp^3) N-radicals. Extensive kinetic studies by Newcomb and co-workers⁶⁷ have shown that iminyl radicals undergo faster addition to olefins and slower reduction by an intermolecular H-atom relative to neutral aminyl radicals. This distinct kinetic profile of the $N(sp^2)$ -centered radical allows access to different synthetic avenues. While pioneering work from Forrester⁶⁸, Zard⁶⁹, Narasaka⁷⁰, and Weinreb⁷¹ have shown the synthetic utility of iminyl radicals by their addition into π -systems, there are few reports on $N(sp^2)$ radical-based HAT. The harsh conditions typically employed to generate iminyl radicals (strong oxidants, elevated temperatures) have likely limited an extensive exploration of this reactivity.

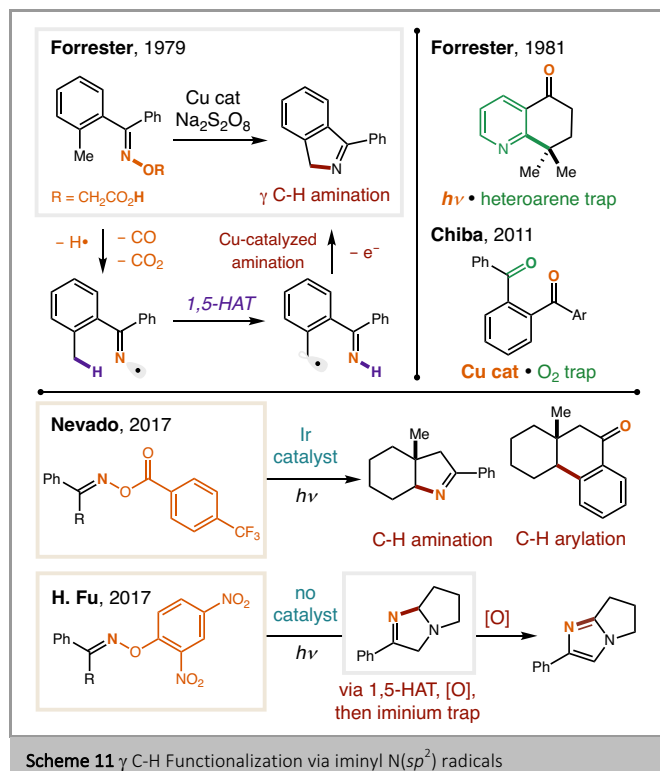
acid.⁷³ Upon Cu-catalyzed, persulfate-mediated $1e^-$ oxidation, and subsequent loss of CO_2 and CO, the iminyl radical engages in several reactive pathways, including HAT. The resulting benzylic radical is oxidized under these conditions and trapped by the imine via intramolecular cyclization. Various tetralone derivatives were synthesized via this new iminyl-radical based approach, including pyridyl analogs.^{74,75}

In 2011, Chiba and co-workers reported a Cu-catalyzed benzylic oxygenation via iminyl radicals.⁷⁶ The radical precursors were generated by *in situ* Grignard addition into nitriles to form aryl imines. Next, direct Cu-catalyzed oxidation under O_2 atmosphere facilitated 1,5-HAT of the iminyl radical to form a benzylic radical, which is subsequently trapped by O_2 to provide a 1,4-keto-imine, which upon hydrolysis affords the di-keto product.

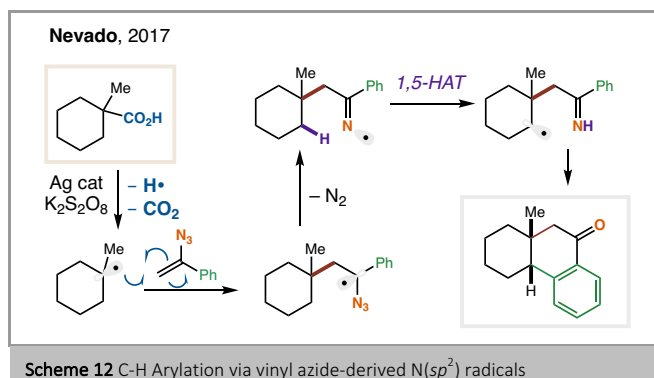
In 2017, Shu and Nevado reported a mild, photoredox catalyzed method to access and harness iminyl radicals (Scheme 11).⁷⁷ Employing acyl oximes as radical precursors, it was found that Ir photocatalysts could reduce the weak N-O bond of the oxime to generate an iminyl radical. Upon HAT, the δ C-radical could either result in C-N or C-C formation, depending on reaction conditions. In the former case, an oxidation event turns over the photocatalyst and allows for C-H amination via ring-closure in the presence of DBU. On the other hand, C-H arylation is observed in a CH_3CN/H_2O mixture when the radical first adds into an arene before oxidation by the catalyst.

H. Fu and colleagues⁷⁸ have similarly employed an oxime for photoinduced iminyl radical formation.⁷⁹ However, by designing a more easily reduced (2,4-dinitrophenyl) nucleofuge, it was found that a metal catalyst is not needed. Instead, tertiary amines are able to form an excited state complex with the dinitrophenyl group to promote photo-induced fragmentation. In their system, the resultant iminyl radical undergoes 1,5-HAT to generate an α -amino radical. Oxidation of this species affords transient formation of an iminium, which is then trapped by the pendant imine. An additional oxidation under the reaction conditions provides the heterocyclic product.

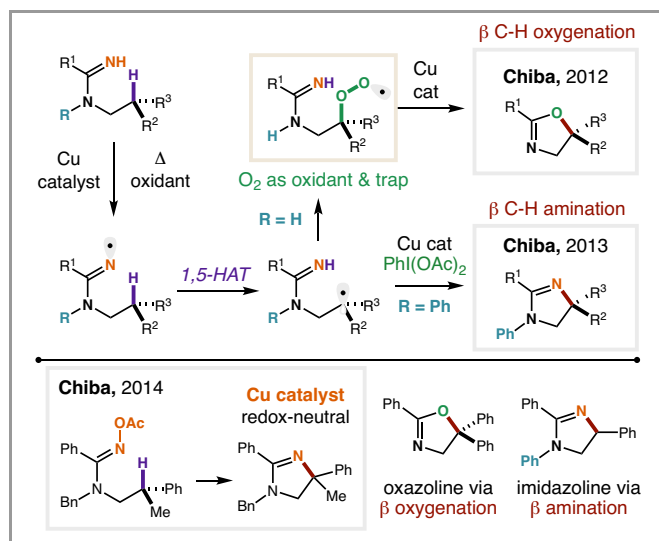
Typically, $N(sp^2)$ radical precursors are generated by either condensation of hydroxylamine onto a ketone, or acylation of an oxime. However, Nevado's lab recently employed a synthetically distinct route to generate an iminyl radical (Scheme 12)⁸⁰ – via Suzuki's method of C• addition into vinyl azides.⁸¹ Upon decarboxylative radical formation and addition into vinyl azide, the intermediary α -azido radical rapidly expels N_2 to form an iminyl radical that promotes HAT and subsequent γ -arylation.



An initial report by Forrester *et al* in 1979 demonstrated iminyl radicals are capable of performing 1,5-HAT to form a radical δ to N – and γ to an imine (Scheme 11).⁷² These radicals were generated by decomposition of oximes bearing a pendant



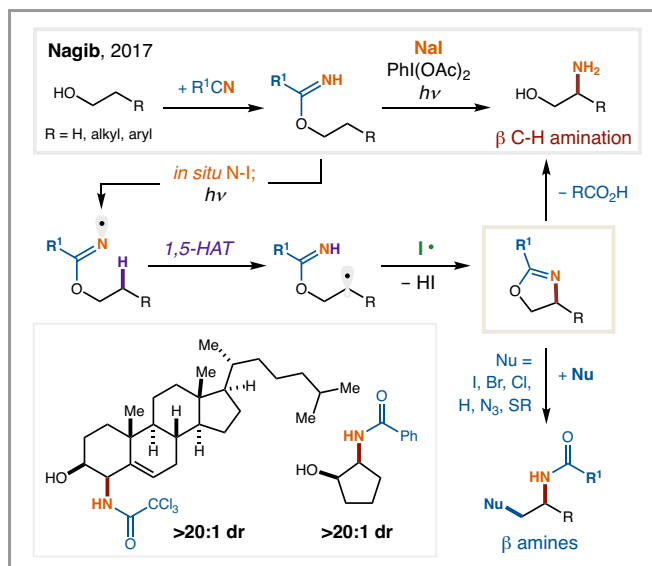
In 2012, Chiba's lab reported the first use of an amidinyl radical in HAT (Scheme 13).⁸² These amidine radical precursors are readily derived from amines, and can be oxidized directly using a Cu catalyst and O₂ as the oxidant. Upon HAT from tertiary or benzylic C-H bonds, the resulting radical (δ to the N, or β to the amidine) can be trapped in divergent ways to access either β -oxygenation or β -amination. In the former case, O₂ serves as the trap, and an ensuing Cu-mediated fragmentation and cyclization affords oxazolines via β -oxygenation. Shortly after, Chiba and co-workers reported N-Ph amidines are converted to imidazolines via an alternate β -amination pathway that employs PhI(OAc)₂ as the oxidant instead of O₂.⁸³ This powerful method of converting an amine to a vicinal diamine via β C-H amination was further extended by Chiba's group in 2014 through the development of a redox-neutral variant.⁸⁴ The use of amidoximes, or the oxime variant of an amidine, as a radical precursor allows for an oxidant-free approach. In this case, the Cu serves as a radical initiator by reducing the weak N-O of the oxime, and the oxidized Cu later serves as a trap of the relayed radical, wherein oxidation allows for redox turnover of the Cu catalyst along with formation of the imidazoline.



Scheme 13 β C-H Functionalization of amines via amidine radicals

Recently, our group reported a complementary strategy to convert alcohols to β -amino alcohols by C-H amination via *in situ* generated imidate radicals (Scheme 14).⁸⁵ To achieve the goal of simplified access to an N(*sp*²) radical from an abundant functional group (e.g. an alcohol), we envisioned imidates as radical precursors. They are easily prepared *in situ* via nitrile condensation with alcohols,⁸⁶ and their closed-shell reactivity is well understood (e.g. the Overman rearrangement).⁸⁷ However, imidate radicals were previously only employed in π -addition cyclizations.⁸⁸ Fortunately, under our triiodide-mediated δ C-H amination conditions (i.e. NaI, PhI(OAc)₂), it was observed that the β C-H amination of a range of alcohols was possible via this imidate-based strategy. In the mechanism, the imidate forms an N-I bond *in situ*, which is homolytically cleaved by visible light to generate an N(*sp*²) radical. Ensuing 1,5-HAT translocates the radical to the β carbon, which is subsequently trapped by I• and displaced intramolecularly to afford an oxazoline product. Notably, benzylic, allylic, secondary and even primary C-H bonds are aminated in this approach. The identity of the imidate

enables the amination of these bonds of varying strength. For example, trichloroacetimidate promotes benzylic and allylic amination, quantitatively, while benzimidates enable C-H amination of stronger, primary and secondary C-H bonds. As an illustration of its synthetic utility, the oxazoline intermediate can be hydrolyzed to a free β -amino alcohol, or substituted by nucleophilic addition to access a family of β amines.



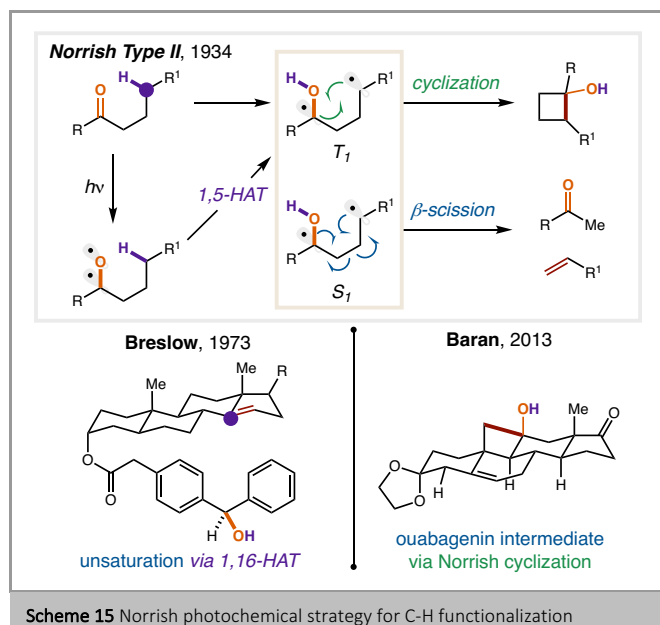
Scheme 14 β C-H Amination of alcohols via imidate radicals

3 Oxygen-centered radicals

Another common initiator of intramolecular HAT is the oxygen-centered radical. The more electronegative oxygen atom ($\chi = 3.4$, O vs 3.0, N or 2.5, C) provides a greater driving force for HAT due to the following two, related factors: (1) an open-shell is highly disfavored for this atom, whose electronegativity is second only to fluorine, thereby promoting HAT; and (2) the O-H that forms upon HAT is rather strong (BDE = 110 kcal, O-H vs N-H, C-H, <100 kcal). Thanks to these favorable driving forces, the remote radicals generated via HAT from O-centered radicals have become the most synthetically versatile, allowing for halogen, heteroatom, and even alkyl trapping of the intermediate carbon radical. The challenge for this mechanism ultimately lies in the generation of radicals on such an electronegative atom. The three most common pathways (carbonyl photo-excitation, and alkoxy or non-alkoxy radical initiation) are described below.

3.1 Carbonyl diradical initiation

In the earliest example of HAT mediated by an O-centered radical, Norrish reported the photo-initiated generation of 1,4-diradicals from alkyl or aryl ketones bearing γ C-H bonds (Scheme 15).⁸⁹ Upon photo-excitation of the ketone, the more reactive O-radical undergoes 1,5-HAT to generate a 1,4-diradical intermediate – with both C-radicals remaining. Depending on the nature of the photo-excited state, the diradical species will then either recombine to yield cyclobutanol (via triplet state, *T*₁) or fragment via β -scission to form an enol and alkene (via singlet state, *S*₁).⁹⁰

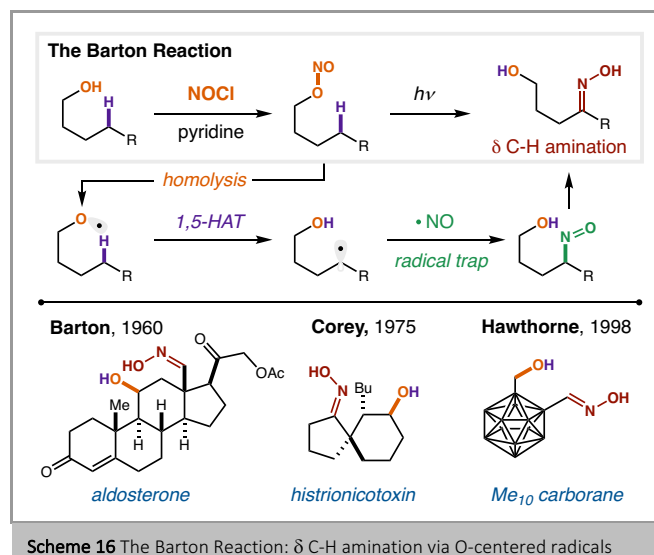


Scheme 15 Norrish photochemical strategy for C-H functionalization

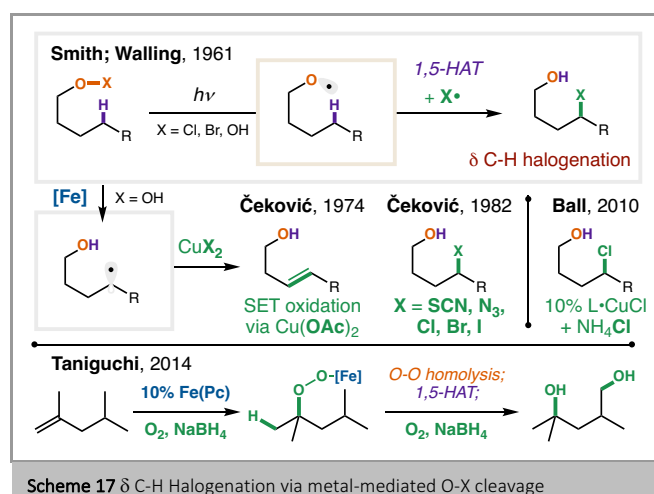
Taking advantage of this mode of carbonyl reactivity in a landmark discovery, Breslow and co-workers achieved selective abstraction of the C14 hydrogen atom within a steroid via the diradical of a benzophenone carbonyl, which was tethered to the C3 alcohol via esterification.⁹¹ In this case, a subsequent, oxidative HAT adjacent to the resulting C-radical furnishes a remote olefin. More recently, in the synthesis of *ouabagenin*, Baran and co-workers utilized the C-C bond-forming, Norrish reaction to construct the key C19 oxidation en route to the natural product from an acyclic, β -methyl ketone precursor.⁹²

3.2 Alkoxy radical initiation

Since alcohols are one of the most common and versatile functional groups in synthesis, the formation of O-centered radicals from alcohols has enabled the development of a family of important C-H functionalization methods. The first example of HAT from an alcohol-derived alkoxy radical was discovered by Sir Derek Barton in 1960, and was eventually recognized with a Nobel Prize in 1969 (Scheme 16).^{93–95} Barton's solution for generating the reactive O-radical was to first synthesize a precursor containing a weak N-O bond. This nitrite can be conveniently prepared via combination of an alcohol with nitrosyl chloride in dry pyridine. Photolytic homolysis forms both $\bullet\text{NO}$ and an alkoxy radical. Upon 1,5-HAT, the δ C-radical of the alcohol recombines with the $\bullet\text{NO}$ to form a δ -nitroso alcohol, which tautomerizes to form the δ -aminated oxime product. Barton and co-workers demonstrated the synthetic utility of this new C-H functionalization reaction within a variety of steroid cores, including aldosterone.⁹⁶ There have been many important applications of this method for the remote C-H amination of hydrocarbon cores, such as Corey and co-workers' synthesis of histrionicotoxin.⁹⁷ As an added example of the broad utility of this strategy for the incorporation of functionality at remote C-H bonds, the δ -amination of Me_{10} -carborane was accomplished by Hawthorne and co-workers.⁹⁸

Scheme 16 The Barton Reaction: δ C-H amination via O-centered radicals

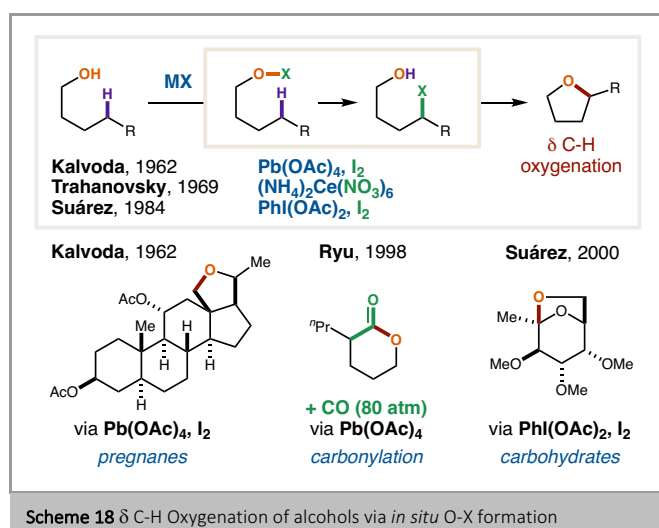
Within a year of Barton's discovery of an O-centered radical synthetic route via nitrite homolysis, the labs of Smith⁹⁹ and Walling¹⁰⁰ developed alternate pathways to access alkoxy radical-mediated HAT via homolysis of O-X bonds (Scheme 17). In analogy to the N-Cl precursor of the HLF reaction, the O-Cl of hypochlorite precursors are readily homolyzed by photolysis to give alkoxy radicals. Upon HAT, the δ C-radical recombines with the $\bullet\text{Cl}$ to form a δ -chloro alcohol, which is readily cyclized with base to form tetrahydrofurans.¹⁰¹

Scheme 17 δ C-H Halogenation via metal-mediated O-X cleavage

In the following decades, a tour de force of applications of this approach was developed by Čeković and co-workers.¹⁶ Among them, the use of hydroperoxides enables the isolation of these relatively more stable, radical precursors. Iron-mediated cleavage of the peroxide O-O bond affords the δ C-radical intermediate, which can be trapped by cupric salts in rapid, radical-combination mechanisms reminiscent of those pioneered by Kochi.^{102,103} For example, the use of $\text{Cu}(\text{OAc})_2$ facilitates the subsequent, single-electron transfer (SET) oxidation and elimination to form the δ -unsaturated alcohol.^{104,105} Alternatively, when other copper salts (CuX_2 , where $\text{X} = \text{SCN}, \text{N}_3, \text{Cl}, \text{Br}, \text{I}$) are employed, substitution of the δ C with the X ligand of CuX_2 is achieved, offering access to a range of δ -functionalized alcohols.¹⁰⁶ A modern variant of this family of Čeković reactions includes the catalytic version reported by

Ball and co-workers in 2010.¹⁰⁷ In this protocol, the conversion of hydroperoxides to δ -chloro alcohols is achieved via the use of a sub-stoichiometric amount of a Cu catalyst for the first time, also in the presence of a terminal chloride source, NH_4Cl , in excess. The use of a tridentate amine ligand appears vital for promoting catalytic peroxide reduction, likely due to the more reducing nature of this ATRP catalyst.

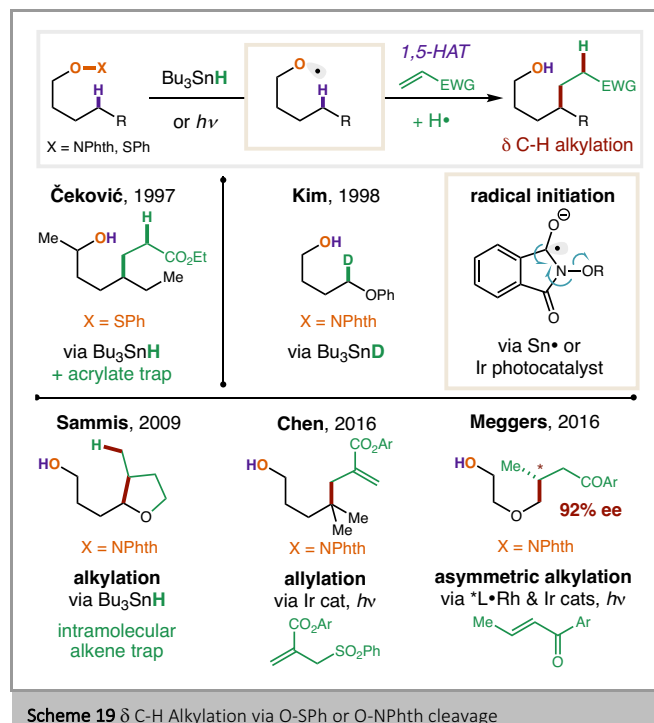
Taniguchi and co-workers have recently disclosed another interesting peroxide-based HAT, which is promoted by a sub-stoichiometric iron phthalocyanine catalyst.¹⁰⁸ In their cascade mechanism, alkenes are converted to hydroperoxides by combination of $\text{Fe}(\text{Pc})$, O_2 and NaBH_4 . The ensuing O-O reduction is mediated by the Fe catalyst, whose turnover is again mediated by O_2 and NaBH_4 , resulting in formation of a 1,4-diol from the parent alkene.



In 1962, on the heels of Barton, Smith, and Walling's discoveries of HAT reactions mediated by O-centered radicals, Kalvoda and co-workers reported the first example of the *direct* generation of an alkoxy radical from an alcohol.¹⁰⁹ The key to this solution is *in situ* formation of an O-X bond by the reagent combination of $\text{Pb}(\text{OAc})_4$ and I_2 . A hypoiodite, AcO-I , is likely formed, which can combine with the alcohol to generate the weak O-I bond of the alcohol hypoiodite.⁴² Upon homolysis, HAT, and halide radical trap, the δ -iodo alcohol is formed *in situ*, which readily cyclizes to form the δ -oxygenated tetrahydrofuran product. Kalvoda and co-workers employed this approach to the synthesis of the pregnane steroids. In 1998, Ryu demonstrated the δ -carbon radical could be intercepted by CO to provide the carbonylated radical, which is oxidatively combined with the alcohol to provide a cyclic ester.¹¹⁰ This approach offers a valuable synthetic approach to access lactones directly from alcohols via δ C-H oxygenation.¹¹¹

In 1969, Trahanovsky and co-workers demonstrated that ceric ammonium nitrate (CAN) could also be employed as an alternative to the Pb-based pathway.¹¹² The intermediate radical may be trapped by the single-electron, Ce oxidant via either inner or outer sphere SET oxidation. Notably, in 1984, Suárez and co-workers made perhaps the most significant advance in this area by employing hypervalent iodine, $\text{PhI}(\text{OAc})_2$, to generate the alkoxy radical, in lieu of a Pb or Ce oxidant.¹¹³ This lead-free alternative offers a complementary pathway to access

the weak O-I bond of the alcohol hypoiodite, and the ensuing etherification cascade pathway. Suárez and co-workers demonstrated the broad utility of this mild, photolytic method in the synthesis of a range of δ -oxygenated steroid and carbohydrate analogs.^{44,114}



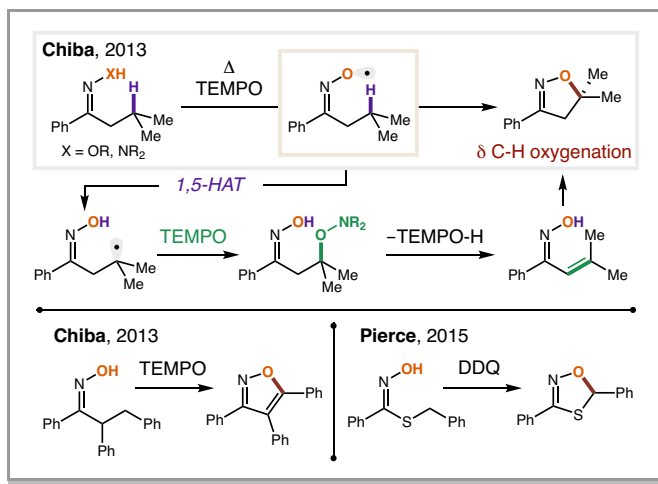
In addition to homolysis of O-X and O-O bonds, O-centered radicals may be accessed via scission of weak O-S or O-N bonds. For example, in 1997, Čeković reported that the O-SPh bond of benzenesulfonates is cleaved by photolytic generation of a thiophilic tin radical (Scheme 19).^{115–117} In this alternate approach to the typical homolysis pathway, the alkoxy radicals that are formed no longer have a radical counterpart and are available to interact with a range of traps following 1,5-HAT. Notably, these δ -carbon radicals combine rapidly with electron-deficient olefins ($k_{\text{add}} = 3 \times 10^5 \text{ M}^{-1}\text{s}^{-1}$), even in the presence of Sn-H, which provides the terminal H-atom for this alkylation cascade. This strategy for multi-component δ C-H alkylation, pioneered by Čeković and co-workers, has been the only known approach for HAT-mediated δ C-C bond formation, until the recent PCET-based method for N-centered radicals.^{64,65}

As a bench-stable, isolable alternative to sulfonates, Kim and co-workers introduced N-alkoxy-phthalimides, whose weak O-N bond can also be cleaved by Sn radicals.¹¹⁸ In this case, Sn^\bullet combines with the imide carbonyl to form a captodatively stabilized C-radical, whose β -scission forms an alkoxy radical. When Sn-D is employed, δ -deuteration is observed, indicating the presence of an alkoxy-radical-mediated HAT mechanism. Sammis and co-workers employed these N-alkoxy-phthalimide precursors to enable intramolecular trapping of electronically neutral alkenes.^{119,120} Recently, a Sn-free alternative has been developed via the use of photoredox catalysis. In this case, a photo-excited Ir catalyst serves as a SET reductant capable of reducing the N-O bond generating a spectator phthalimide anion along with the alkoxy radical. In 2016, Chen and co-workers were able to trap the δ radical with allyl sulfones to enable δ C-H

allylation.¹²¹ In the same year, Meggers and co-workers demonstrated that the Ir photoredox catalyzed SET reduction of the N-O could be coupled with a second catalytic cycle, wherein a chiral Rh complex could exhibit stereocontrol over the δ radical addition into enones.¹²² Indeed, this alkylation is the first and only method for enabling asymmetric termination of a radical resulting from an intramolecular HAT.

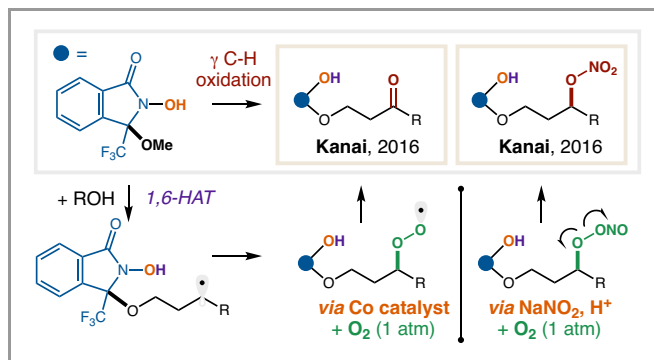
3.3 Non-alkoxy radical initiation

Alongside alkoxy radicals, the O-centered radicals that are substituted with adjacent heteroatoms (e.g. N-O•), are also synthetically useful, since they (1) are typically easier to access via oxidation, and (2) afford distinct classes of products. For example, Chiba and co-workers have shown that both oximes and hydrazones, which are each readily accessible by carbonyl condensation, are prone to facile oxidation when heated in the presence of TEMPO (Scheme 20).¹²³ The heteroatom-substituted O• is stabilized by resonance, which facilitates its generation by mild oxidants, especially compared to alcohols, which are not as easily oxidized. Furthermore, the α -N influences the reactivity of the O• mediated HAT, as well as the ensuing cyclization to generate the isoxazoline product. With further aryl substitution, Chiba and co-workers found that isoxazoles are also accessible. In a mechanistically similar vein, Pierce and co-workers have demonstrated that thiohydroxamic acids can be oxidized by DDQ to form an N-O• that effects HAT and subsequent oxidative cyclization to access oxathiazoles.¹²⁴



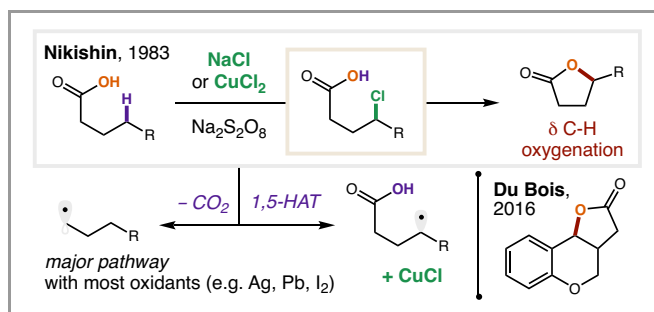
Scheme 20 δ C-H Oxidation via *in situ* oxime-derived radicals

In a complementary pathway to SET reduction of the N-O in N-alkoxy-phthalimides, Kanai and co-workers have shown that oxidative conditions can leave the N-O intact and form an O-centered radical instead (Scheme 21). When this hydroxylamine radical is reversibly appended onto an alcohol, it can facilitate 1,6-HAT due to conformational constraints of the directing activator group. In 2016, the Kanai lab showed that Co catalysts under aerobic conditions can initiate radical generation and terminate the ensuing radical to afford γ -ketones on hydroxylamine-radical-appended alcohols.¹²⁵ In the same year, the Kanai lab also showed that these radical precursor scaffolds can be combined with *in situ* generated NO_x species to form γ -nitrated alcohols.¹²⁶



Scheme 21 δ C-H Oxidation via *in situ* hydroxylamine radicals

A final class of O-centered radicals employed in HAT is generated from carboxylates (Scheme 22). Although it is easier to access O• from a carboxylate (1.4 V vs >2 V for alcohol)¹²⁷ via SET oxidation using Ag, Pb, or I, the overriding challenge of this approach is that decarboxylation is quite facile (*cf.* Kolbe, Hunsdiecker reactions). In 1983, Nikishin and co-workers discovered a method of bypassing this major byproduct-forming pathway by using a CuCl/Na₂S₂O₈ oxidant.¹²⁸ The ensuing HAT, Cl• trap, and chloride displacement affords γ -lactones via γ C-H oxygenation of acids. Interestingly, a NaCl/Na₂S₂O₈ combination is also effective in promoting this transformation, thus the role of the copper remains unclear. Most recently, Du Bois and co-workers have shown that phenylbutyric acid derivatives bearing a benzylic γ C-H bond are also mediated by a Cu-catalyzed process.¹²⁹ However, mechanistic experiments indicate that in contrast to non-benzyl carboxylates, intermolecular HAT of a benzyl C-H by sulfate radicals is more likely in this case.



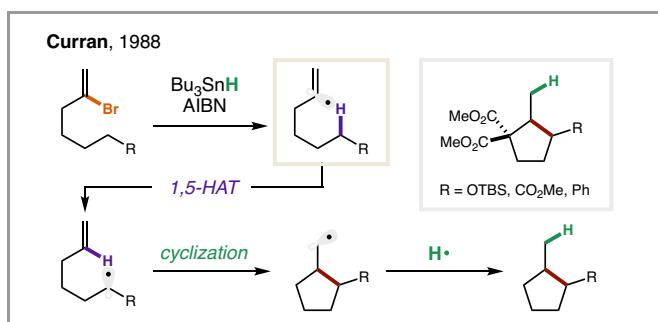
Scheme 22 δ C-H Lactonization via *in situ* carboxylate O-H oxidation

4 Carbon-centered radicals

HAT mediated by C-centered radicals are more rare than their heteroatom counterparts. Unlike the N• and O• initiated mechanisms, in which C-H is exchanged for a stronger N-H or O-H bond,¹⁸ the C• pathway suffers from the challenge that both the HAT precursor and product similarly contain a C-H bond. Therefore, a necessary driving force is required in these transformations, such as the exchange of an C(sp²)-centered radical for a lower energy C(sp³) radical via HAT of an alkyl C-H to form a stronger aryl C-H bond. Although bond strength is not the only determinant of HAT-based chemical reactivity (since HAT reactions are often irreversible, exothermic processes with early transition states),¹⁴ BDE of reactants often serve as a useful guide for predicting HAT reactivity.

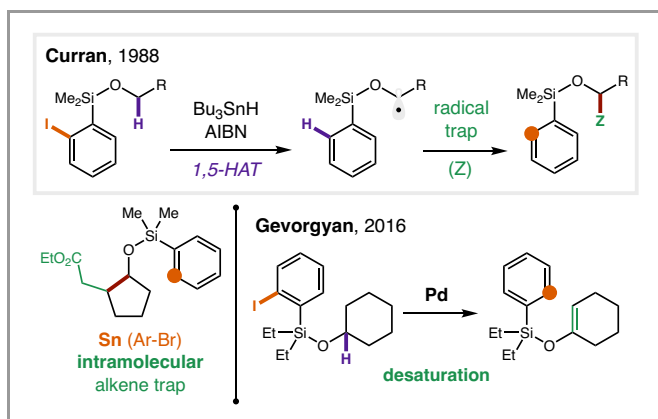
4.1 sp^2 C radical initiation

The translocation of C^\bullet sites by intramolecular HAT between C-H bonds was first reported by Curran *et al* in 1988.¹³⁰ This pioneering work made use of the energy difference between $C(sp^2)$ and $C(sp^3)$ radicals to promote HAT from an alkyl C-H to a vinyl radical (Scheme 23). In their early reports, Curran *et al* demonstrated that vinyl bromides are capable of serving as both radical precursor and intramolecular trap, to afford substituted cyclopentanes. In this mechanism, Bu_3Sn-H also plays a dual role in chain propagation, via vinyl radical initiation as well as alkyl radical termination.¹³¹ A recent synthesis by Vellucci and Beaudry of the aspidosperma alkaloid, goniomitine, via a vinyl-bromide initiated HAT cascade.¹³² An excellent review by D  n  s, Beaufile, and Renaud describes major developments in the synthesis of five-membered rings by this approach of translocation and cyclization of vinyl radicals.¹³³



Scheme 23   Alkylation via vinyl bromide-derived $C(sp^2)$ radicals

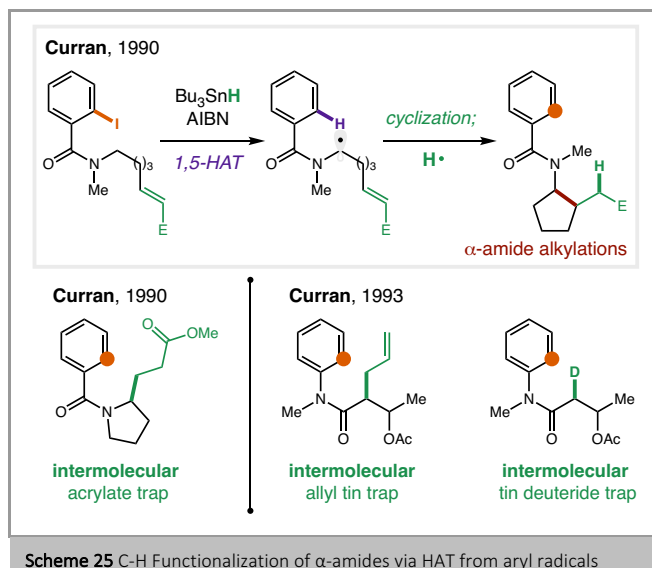
An important application of this mechanism is the incorporation of aryl radical precursors as protecting groups on alcohols, as either benzyl or silyl ethers. An example of the latter includes use of *o*-iodo-phenyl silyl ether as a radical precursor, which enables selective 1,5-HAT from an α -oxy C-H (Scheme 24).^{134,135} This stabilized radical was trapped by electrophilic olefins in an intramolecular fashion. Inspired by this radical translocation reaction, Gevorgyan and co-workers recently developed a method to introduce an olefin functionality via Pd catalysis.¹³⁶ In this mechanism, radical initiation and post-HAT elimination are both mediated by Pd in a mechanism that combines metal-catalysis and intramolecular HAT.



Scheme 24 α -Ether C-H functionalization via HAT from aryl radicals

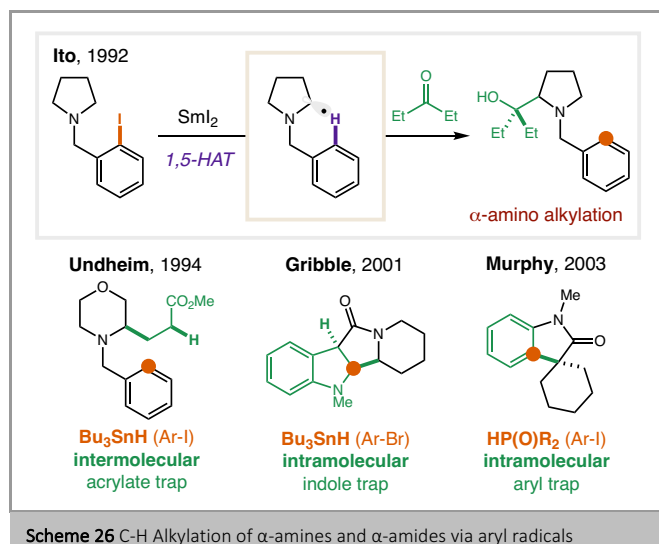
Like alcohols, amines are also readily converted to radical precursors that can facilitate intramolecular HAT. The

collaborating labs of Snieckus and Curran demonstrated that *o*-iodo-benzamides are suitable radical precursors that provide streamlined access to α -amino radicals via HAT (Scheme 25).¹³⁷ Upon tin-mediated abstraction of $C(sp^2)$ -I to form an aryl radical, HAT enables distal functionalizations via both intra- and inter-molecular trapping of the α -amino radical. Applications of this α -amino C-H functionalization include cyclization, allylation, and deuteration.^{137–140} The mechanism of formation of the aryl radical by Bu_3Sn-H has been studied extensively.¹⁴¹

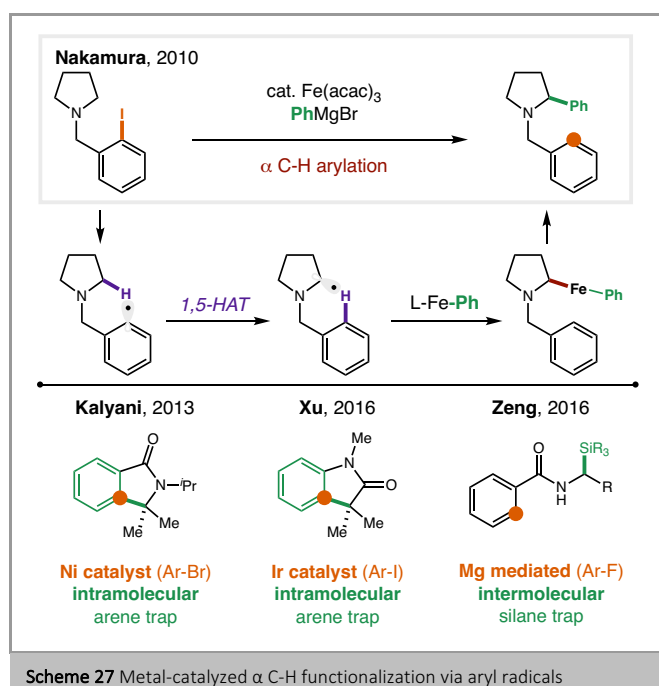


Scheme 25 C-H Functionalization of α -amides via HAT from aryl radicals

Ito and co-workers demonstrated amines (vs amides) also undergo HAT via an *o*-iodo-benzyl precursor (Scheme 26).¹⁴² Employing SmI_2 as a radical initiator, α -amino C-H abstraction is followed by ketone trapping to afford α -C-H alkylated amines. The postulated, penultimate intermediate is an α -amino Sm species that readily combines with carbonyls.¹⁴³ Undheim and co-workers extended this radical translocation of amine substrates to intermolecular α -amino C-H alkylation with alkene traps, such as acrylate.^{144,145} Using a 2-Br indole as a precursor, Gribble *et al* employed a C2-indole radical to effect HAT. Ensuing α -amido radical addition back into the indole trap forms indolines.¹⁴⁶ As a Sn-free alternative, Murphy and co-workers developed a strategy that employs dialkylphosphine oxide as a radical initiator for iodide abstraction of *o*-anilides. Following HAT, the α -acyl radical combines with the anilide to form indolone heterocycles via C-H arylation.¹⁴⁷

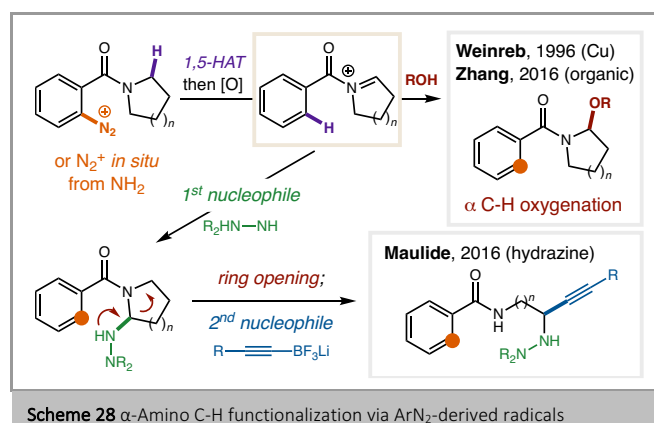


Modern adaptations of these aryl radical-mediated HAT reactions employ metal catalysts to serve the dual roles of radical initiation and termination. In 2010, Nakamura reported an iron-catalyzed α -amino arylation reaction, in which aryl Grignards are cross-coupled with the α -amino radical (Scheme 27).¹⁴⁸ Similarly, Ni and Ir-catalyzed variants of this class of reactions have been developed by the labs of Kalyani¹⁴⁹ and Xu,¹⁵⁰ respectively. In these mechanistically, related reactions, pendant arenes serve as radical traps. A Mg-mediated version was also recently reported by the Zeng group.¹⁵¹ Here, either 1e-reduction, or fluoride abstraction, generates the aryl radical species, which effects 1,5-HAT to yield a Mg-stabilized α -amido radical that is trapped by chlorosilanes to construct C-Si bonds, expanding the radical translocation method beyond the introduction of C-X, C-O, C-C, and C-N bonds.

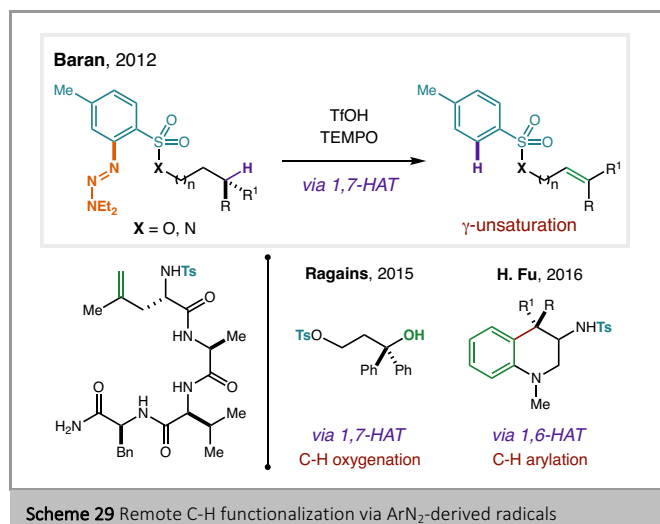


While aryl halides are most common, other substituted arenes can also be employed as radical precursors. For example,

aryl diazoniums, ArN_2^+ , are synthetically useful aryl radical precursors¹⁵² that facilitate efficient C-C formation, such as in the Meerwein arylation of olefins.¹⁵³ In 1954, Hey and Turpin demonstrated that *o*- N_2 -benzamides are de-methylated upon diazonium decomposition.¹⁵⁴ Building on this pioneering discovery, Weinreb and coworkers developed a general method for α -functionalization of benzamides (Scheme 28).¹⁵⁵ This method involves Cu-catalyzed decomposition of the diazonium to an aryl radical, followed by 1,5-HAT of the α -amino C-H. Rapid oxidation of this electron-rich radical leads to transient iminium cation formation that is trapped by alcohols. Recently, the labs of Zhang and Qi have developed metal-free versions of this transformation, using ascorbic acid as the radical initiator, or organic photocatalysts.^{156,157} Additionally, the hemiaminal products were treated with a Lewis acid and either allyl-SiMe₃ or Me₃Si-CN to afford a net C-H α -allylation or α -cyanation. Alternatively, Maulide and co-workers employed a hydrazine that serves two roles: reductant to generate the aryl radical, and nucleophile for addition into the transient iminium formed upon α -amino radical oxidation.¹⁵⁸ The resultant cyclic aminals open to form stable hydrazones, which can be treated with a second (alkyne) nucleophile to provide ring-opened addition products.



In 2012, Baran and co-workers employed an aryl triazene as a radical precursor, since it serves as an aryl diazonium-equivalent upon loss of an amine (Scheme 29).¹⁵⁹ In the presence of an acid or metal salt, the *in situ* generated diazonium is rapidly reduced and extrudes N_2 to form an aryl radical. After a rare, 1,7-HAT (likely dictated by the sulfonate geometry), subsequent oxidation and elimination is facilitated by TEMPO to form remote alkenes. This remote desaturation is accessible for both alcohols and amines by use of the triazene-based precursor/protecting groups. In a related method, Ragains and co-workers employed an Ir photocatalyst to promote the same triazene sulfonate-mediated 1,7-HAT.¹⁶⁰ However, the termination entails a catalyst-turnover oxidation, which affords a tertiary cation that is hydrolyzed with H_2O to yield a net γ -C-H hydroxylation.

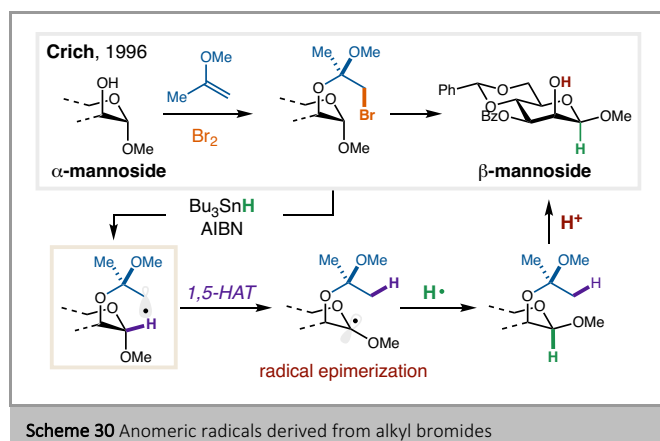


Scheme 29 Remote C-H functionalization via ArN₂-derived radicals

H. Fu and co-workers incorporated these triazenes within amides to promote 1,6-HAT (dictated by formation of a tertiary radical). This remote C(*sp*³) radical is trapped by a pendant aryl group to form heterocycles.¹⁶¹ The further development of new pathways based on such orthogonal radical precursors may enable access to iterative HAT-based C-H functionalizations with different traps and selectivities.

4.2 sp^3 C radical initiation

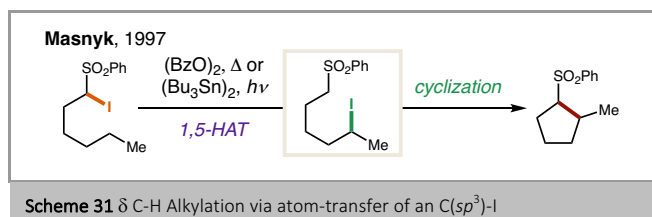
The challenge associated with HAT initiated by $C(sp^3)$ -centered radicals is the lack of energetic difference between the initial C^\bullet and the resultant C^\bullet after HAT. A solution to this problem was developed by Crich *et al*, wherein generation of a more stable α -oxy radical is the driving force (Scheme 30).¹⁶² In a pioneering example of $sp^3 C^\bullet$ initiated HAT, epimerization of α -mannoside to β -mannoside was accomplished – overcoming an anomeric stereo-preference, a challenge in its own right.



Scheme 30 Anomeric radicals derived from alkyl bromides

In this radical-mediated epimerization, Sn[•] initiated reduction of an alkyl bromide affords a primary, *sp*³ C[•] that undergoes 1,5-HAT to generate a more stable, secondary, α-oxy radical – with added anomeric stabilization. A terminal, chain-propagating Sn-H reduction from the less sterically encumbered bottom face affords a 2:1 ratio of α:β mannoside – favoring the isomer not stabilized by the anomeric effect. The Ueno-Stork method was employed to rapidly install the *sp*³ C-Br, radical

precursor via bromoetherification.^{163,164} After epimerization, this traceless ketal is hydrolyzed via acidic work-up.

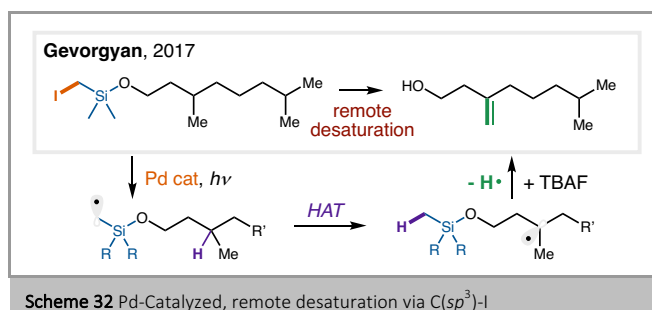


Scheme 31 δ C-H Alkylation via atom-transfer of an $C(sp^3)$ -

Another strategy for promoting HAT via an sp^3 C• is to employ an α -EWG halide, whose C-X bond strength is weaker than the translocated, secondary C-X. In 1997, Masnyk reported the use of an α -sulfonyl iodide as a radical precursor to effect an HAT-induced cyclization to form cyclopentanes from acyclic alkanes via δ C-H functionalization (Scheme 31).¹⁶⁵ In this case, radical initiation via thermal peroxide initiation or photolytic Sn-Sn cleavage precedes I• abstraction from a radical precursor that is easily prepared by α -iodination of the acidic alkyl sulfone. Upon 1,5-HAT, a secondary sp^3 C• abstracts an iodide via radical recombination, or chain propagation, to afford an atom-transfer adduct. The resulting δ -iodo sulfone undergoes base-mediated intramolecular cyclization to generate cyclopentanes – an all-carbon version of the HLF reaction.

Although these sp^3 C• induced HAT mechanisms are rare, and most challenging, there remains great opportunity to design new strategies that favor C• to C• translocation. For example, mechanistic studies by Wood *et al* have demonstrated that captodative stabilization can override a kinetic isotope effect in dictating the fate of 1,5-HAT.¹⁶⁶ In particular, it was observed that radical translocation favors formation of more stable, amino acid α -radicals over simply α -amino ones that lack the additional push-pull effects of captodative stabilization.¹⁶⁷

Most recently, Gevorgyan and co-workers introduced a Pd-photocatalyzed remote desaturation of aliphatic alcohols (Scheme 32).¹⁶⁸ Employing α -silyl-methyl-halides as precursors (developed by Nishiyama *et al* for radical addition to olefins),¹⁶⁹ they demonstrated a hybrid Pd-radical mechanism facilitates SET reduction, regioselective HAT, and Pd-catalyzed β -hydrogen elimination to afford selective, remote desaturation of aliphatic alcohols.



Scheme 32 Pd-Catalyzed, remote desaturation via C(sp³)-

5 Conclusions

Selective C-H functionalization via intramolecular HAT is a strategy that benefits from a mechanistically distinct pathway with complementary reactivity parameters to metal-based C-H activation routes. As new methods for mild radical-generation continually give way to new reaction development, there is also a sustained expansion of our understanding of the inherent chemo- regio- and stereo- selectivity rules for HAT mechanisms. While this mode of C-H functionalization is perhaps the oldest, its current revival of interest with new tools and methods offers ample opportunity for further, major contributions to the field of organic synthesis. For example, thanks to developments in the past year alone, δ C-C formation has been achieved for the first time (for N \cdot initiation), asymmetric δ C-C formation is now possible with chiral catalysis (via O \cdot initiation), and anilines offer orthogonal HAT initiation as diazonium surrogates (by C \cdot initiation). In pursuit of solving ongoing challenges, new radical precursors will likely need to be designed, allowing for more creative methods of trapping these relayed radicals. Needless to say, with continued development of disruptive new methods, the future of C-H functionalization by radical translocation will continue to be exciting.

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Biosketches



Left to right: Leah, Kohki, David

Leah Stateman (Orland Park, IL) earned a B.Sc. with honors at Illinois State University in 2015, where she studied the synthesis of carbaporphyrinoids with Prof. Timothy Lash. At OSU, she has pioneered our team's development of catalytic, remote C-H functionalizations via hydrogen atom transfer. Leah is a 2016 National Science Foundation Graduate Research Fellow.

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