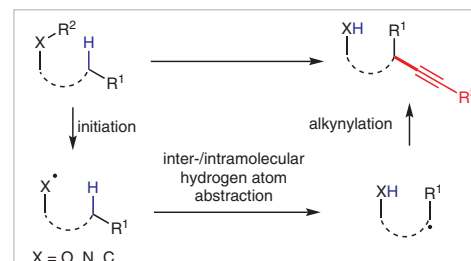


Recent Advances in Radical-Involved Alkynylation of Unactivated C(sp³)-H Bonds by Hydrogen Atom Abstraction

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Abstract The direct C(sp³)-H functionalization is one of the major research topics in synthetic chemistry since C(sp³)-H bonds are ubiquitous in every aspect of chemistry. Despite impressive advances in transition-metal-catalyzed C(sp³)-H activation, the radical-initiated process via hydrogen atom abstraction (HAA) of C(sp³)-H bonds represents a more appealing strategy owing to the mild reaction conditions and good regioselectivity. Given the importance of alkynes as versatile synthons in organic synthesis and key structural motifs in drug discovery, great efforts have been made toward their synthesis via the combination of HAA and alkynylation process in recent years. This review summarizes the recent progress in radical-initiated C(sp³)-H alkynylation reactions with emphasis on the alkynylating reagents and mechanistic discussion.

- 1 Introduction
- 2 Alkynylation of C(sp³)-H via Intermolecular Hydrogen Atom Abstraction
- 3 Alkynylation of C(sp³)-H via Intramolecular Hydrogen Atom Abstraction
- 4 Conclusion

Key words alkynes, radical reaction, hydrogen atom abstraction, radical translocation, C(sp³)-H functionalization

1 Introduction

As one of the most important functional groups in organic chemistry, alkynes play an important role in synthetic chemistry, material science, chemical biology, and medicinal chemistry.^{1,2} Therefore, great efforts have been devoted to the development of novel synthetic methods to generate substituted alkynes in the past decades.^{3,4} In this context, transition-metal-catalyzed Sonogashira coupling of termi-

nal alkynes and aryl/vinyl (pseudo)halides has been proved to be one of the most effective methods for constructing the C(sp²)-C(sp) bonds.² In recent years, more and more attention has been paid to the formation of C(sp³)-C(sp) bonds, including cross-coupling of terminal alkynes with alkyl halides,^{5,6} decarboxylative C(sp³)-C(sp) coupling reactions^{7,8} and so on. Notably, these methods require the utilization of prefunctionalized alkyl halides or carboxylic acid derivatives. Despite these impressive advances, the development efficient and practical alkynylation reactions from more easily available feedstocks is in great demand.

C(sp³)-H bonds are ubiquitous in every aspect of chemistry and are one of the most prevalent building blocks in organic synthesis. Thus, the direct alkynylation of C(sp³)-H bonds is a highly attractive approach due to the high atom and step economy.^{9,10} However, it is a challenging task to realize the C(sp³)-H functionalization in a regioselective and chemoselective manner because the C(sp³)-H bonds are generally inert and there are usually many C(sp³)-H bonds in one molecule. Over the past decades, the direct C(sp³)-H functionalization have been a hot topic in organic synthesis. In particular, the transition-metal-catalyzed C(sp³)-H activation has been developed into a powerful tool in this area.¹¹ In recent years, radical reactions have attracted much attention from organic chemists due to their high reactivity and chemoselectivity as well as mild reaction conditions.¹² In this context, the radical-initiated alkynylation of C(sp³)-H bonds has evolved into a conceptually distinct approach for synthesis alkynes from alkane feedstocks and important breakthrough has been made in the past several years. Mechanistically, the driving force for the reaction is the intra-/intermolecular hydrogen atom abstraction (HAA) process of C(sp³)-H bonds by a highly reactive radical spe-

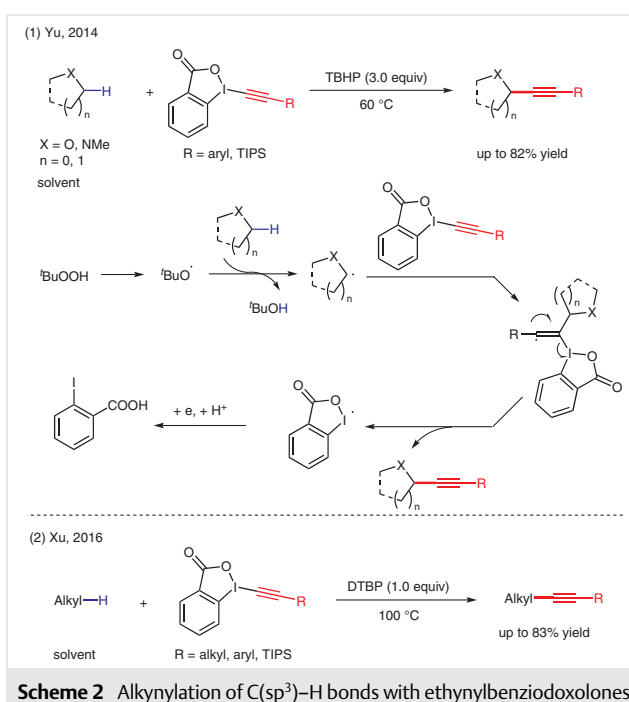
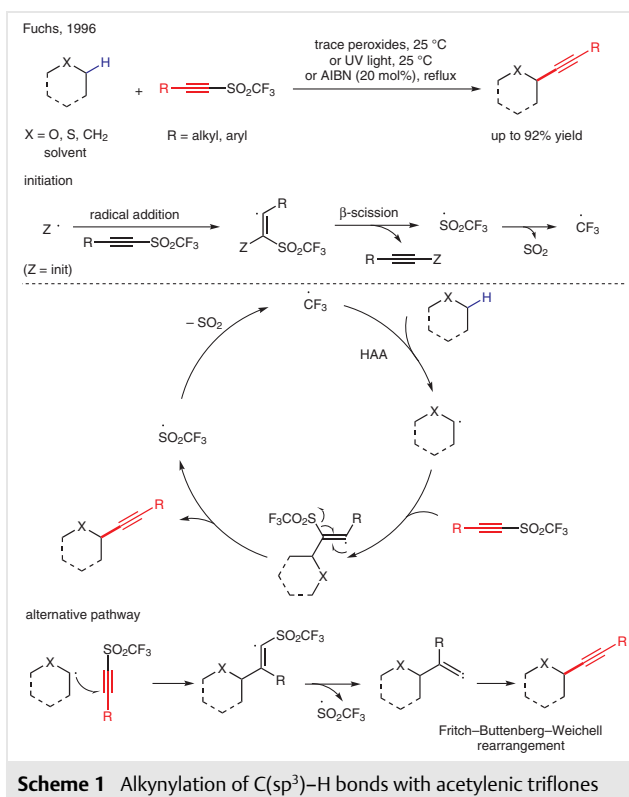
cies (N-, O-centered radical or aryl/vinyl radical) to generate a lower-energy alkyl radical intermediate owing to the difference in bond-dissociation energies (BDE).¹³

This review mainly focuses on the recent progress in the alkylation of the C(sp³)-H bonds via a radical process. The reactions are classified into two categories according to the initiation step: the intermolecular and intramolecular HAA process followed by subsequent alkylation. We regret that we cannot include other protocols for radical alkylation process, such as the radical C-C bond cleavage¹⁴ or C(sp³)-C(sp) cross-coupling¹⁵ due to the limited space.

2 Alkylation of C(sp³)-H via Intermolecular Hydrogen Atom Abstraction

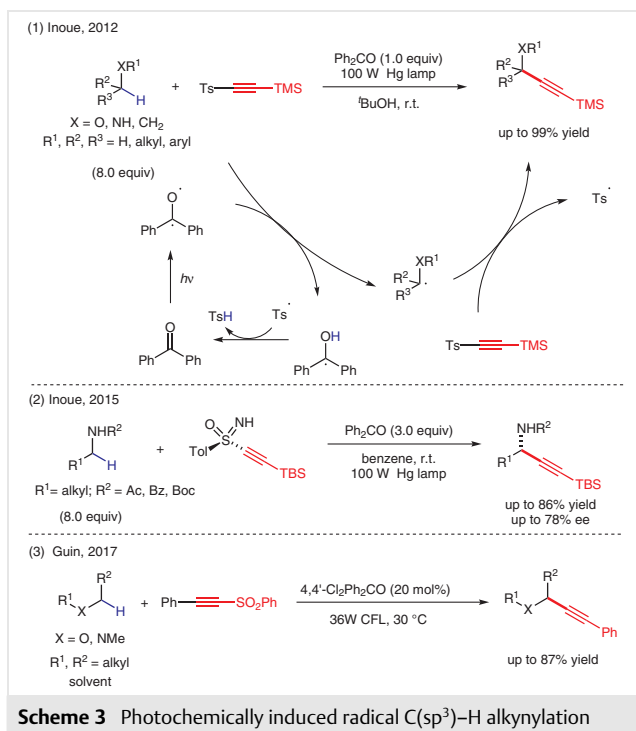
In 1996, Fuchs and co-workers reported a metal-free alkylation reaction of C(sp³)-H bonds with prefunctionalized acetylenic triflones utilizing proper radical initiators (peroxides, AIBN, or UV irradiation, Scheme 1).¹⁶ This type of alkylation reaction exhibited a broad substrate scope to furnish α -alkynylated alkanes, heterocycloalkanes, ethers, and sulfides in up to 92% yield. Based on their mechanistic study, the authors assumed that a trifluoromethyl (CF₃) radical was first generated from the reaction of radical initiator and acetylenic triflones via the domino radical addition- β -scission-sulfur dioxide releasing process. The electrophilic CF₃ radical could abstract C(sp³)-H to deliver an alkyl radical intermediate, which underwent a sequential radical addition to acetylenic triflones and β -scission process to afford the desired C-H alkylation products. An alternative process via the addition of alkyl radical to the β -carbon of acetylenic triflones followed by fragmentation to generate vinylidene carbenes, which underwent the Fritch-Buttenberg-Weichell rearrangement to afford the desired products, is also possible (Scheme 1).¹⁷

In 2014, Chen and Yu described an alkylation of α -C(sp³)-H bonds of ethers and amides with ethynylbenziodoxolones (EBX) using *tert*-butylhydroperoxide (TBHP) as the oxidant (Scheme 2, eq. 1).¹⁸ They found that in the presence of TBHP, saturated heterocycles, and EBX reacted smoothly to deliver the α -alkynylated heterocycloalkanes in good yields. In this process, an alkyl radical adjacent to the heteroatom could be generated via intermolecular HAA by a *tert*-butoxy radical in the presence of TBHP. The alkyl radical then added to the triple bond of EBX to provide a new radical intermediate, followed by subsequent β -elimination to afford the alkynylated product with the formation of a benziodoxolonyl radical. Finally, 2-iodobenzoic acid was afforded via reduction-protonation of the benziodoxolonyl radical. In 2016, Feng and Xu realized a similar alkylation of unactivated C(sp³)-H bonds employing di-*tert*-butylperoxide (DTBP) as the oxidant (Scheme 2, eq. 2).¹⁹ In this work, unactivated secondary and tertiary C(sp³)-H of saturated hydrocarbons are both smoothly alkylation.



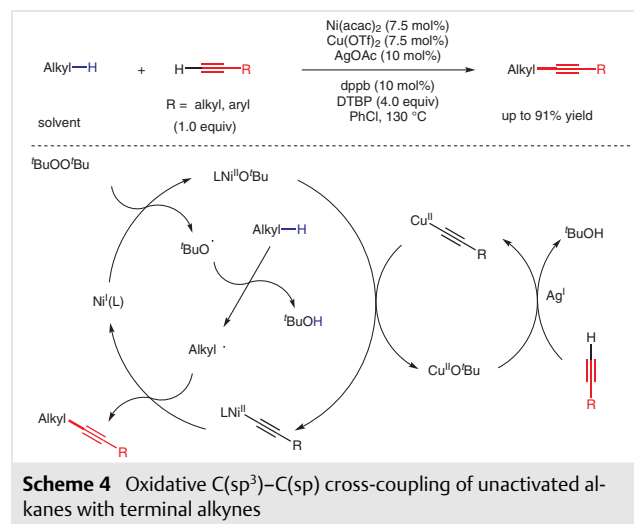
In 2012, Inoue and co-workers described a photoinduced C(sp³)-H alkylation of ethers, amides, and alkanes with 1-tosyl-2-(trimethylsilyl)acetylene using a stoichiometric amount of benzophenone as the oxygen radical pre-

cursor upon light irradiation (Scheme 3, eq. 1).²⁰ After the hydrogen atom abstraction by the photoexcited benzophenone, the generated alkyl radical could be captured by the electron-deficient alkyne to afford the alkynylated products. Afterwards, the same group realized the enantioselective alkynylation of C(sp³)-H bonds adjacent to a nitrogen atom using the chiral sulfoximine as a traceless chiral auxiliary under photoirradiation conditions (Scheme 3, eq. 2).²¹ However, after extensive screening of reaction conditions, the alkynylated product was obtained only in 86% yield and 78% ee with a stoichiometric amount of chiral sulfoximine reagent. In 2017, a catalytic alkynylation of C(sp³)-H bonds was achieved by Guin and co-workers with 20 mol% of a diarylketone derivative in the presence of a household fluorescent light bulb (Scheme 3, eq. 3).²² This process allows easy access to alkynyl-substituted ethers/amides in good yields with broad functional group tolerance under mild reaction conditions.



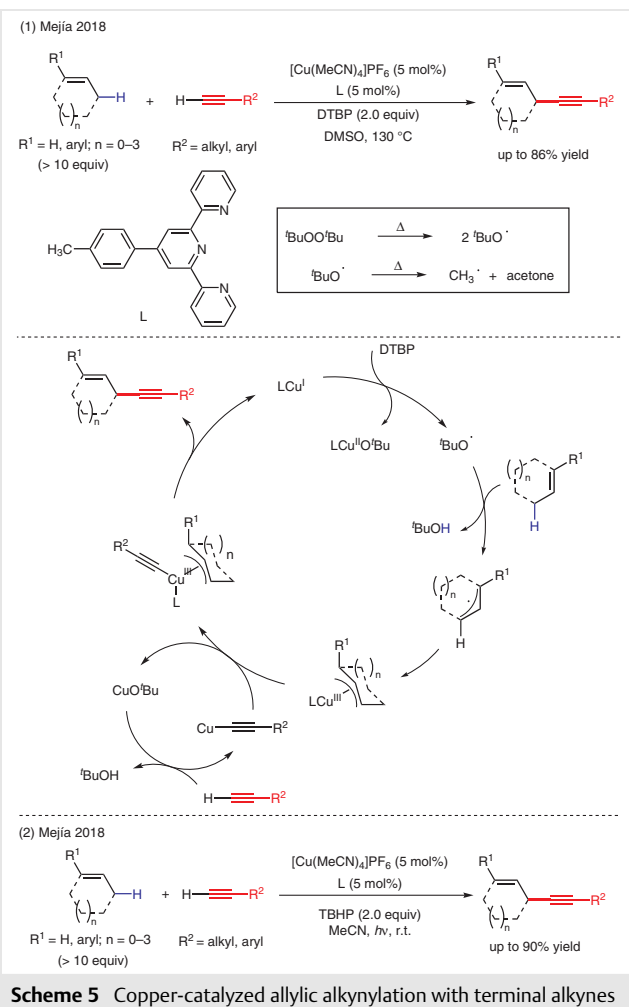
It is found that the alkynylation of carbon-centered radicals generated by HAA mostly employ alkynyl sulfones or hypervalent EBX reagents as alkynylating reagents via a sequential α -addition- β -scission sequence. In addition, most reported intermolecular reactions deal with the activated C(sp³)-H bonds adjacent to a heteroatom. In this scenario, the direct use of terminal alkynes for alkynylation of unactivated C(sp³)-H bonds should be more atom-economical than the electrophilic alkynylating reagents from a practical perspective.

In 2016, Lei and co-workers developed a Ni/Cu/Ag multimetallic catalytic system for C(sp³)-C(sp) cross-coupling of alkanes with terminal alkynes in the presence of DTBP (Scheme 4).²³ A wide array of alkanes and terminal alkynes were well accommodated to the strategy and gave the corresponding products in good yields. However, the alkanes were used as co-solvent to ensure good yields. A significant kinetic isotopic effect was observed, demonstrating that the C-H cleavage contributed to the rate-determining step. Consequently, the authors proposed a plausible mechanism: the LNi^I species acted as the active catalyst, which underwent a SET process with DTBP to generate *tert*-butoxyl radical and LNi^{II}O^tBu species. The *tert*-butoxyl radical then abstracted the hydrogen atom of alkane to provide an alkyl radical intermediate. At same time, the alkynyl Cu^{II} species, which was generated by synergistically activation of copper and silver with terminal alkyne, underwent a transmetalation with the LNi^{II}O^tBu species to afford the alkynyl Ni^{II} complex. Finally, the alkyl radical could be trapped by the alkynyl Ni^{II} complex to deliver the C(sp³)-H alkynylation products and regenerate the LNi^I species either through radical homolytic substitution or reductive elimination.



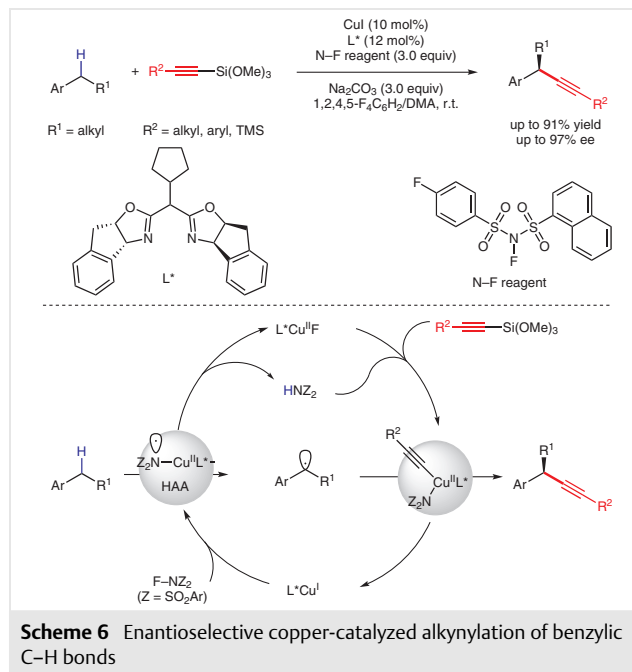
In 2018, Mejía and co-workers described a copper-catalyzed allylic C(sp³)-H alkynylation reaction with terminal alkynes using DTBP as the oxidant at 130 °C (Scheme 5, eq. 1).²⁴ It is essential to use a tridentate pyridine ligand to control the desired product selectivity over the other byproducts and regioisomers. Based on experimental observations, the authors proposed a preliminary mechanism involved an intermolecular hydrogen atom abstraction process. In this process, two *tert*-butoxyl radicals were generated by the homolytic cleavage of DTBP. The formed *tert*-butoxyl radical could selectively abstract a hydrogen atom from the allylic position of alkenes to generate an allyl radical. Recently, the same group reported an allylic alkynyla-

tion of cyclic alkenes at room temperature using a copper(I) terpyridyl complex as the photocatalyst/initiator in the presence of TBHP (Scheme 5, eq. 2).²⁵ Under irradiation, the excited copper(I) species underwent a SET process with TBHP to produce an oxygen-centered radical, followed by an intermolecular hydrogen abstraction of cyclic alkenes to generate the corresponding allylic radicals.



Recently, Liu and co-workers developed an enantioselective copper-catalyzed alkylation of benzylic C–H bonds with terminal alkynes in the presence of a chiral Box ligand to prepare enantioenriched benzylic alkynes in good yields under mild conditions (Scheme 6).²⁶ Notably, the authors used only a stoichiometric amount of alkanes as the substrates rather than as co-solvent in this reaction. Moreover, the kinetic isotope effect (KIE) experiment suggested that hydrogen atom abstraction was likely involved in the rate-limiting step. Mechanistically, the L^*Cu^I complex underwent a SET process with the oxidant (N–F reagent) to generate a transient Cu^{II} -bound N-centered radical, which could abstract a benzylic hydrogen atom, affording the ben-

zylic radical. The chiral Cu^{II} -alkynyl-(bisarenesulfonimide) complex was then able to capture the benzylic radical to deliver the chiral alkylation products.

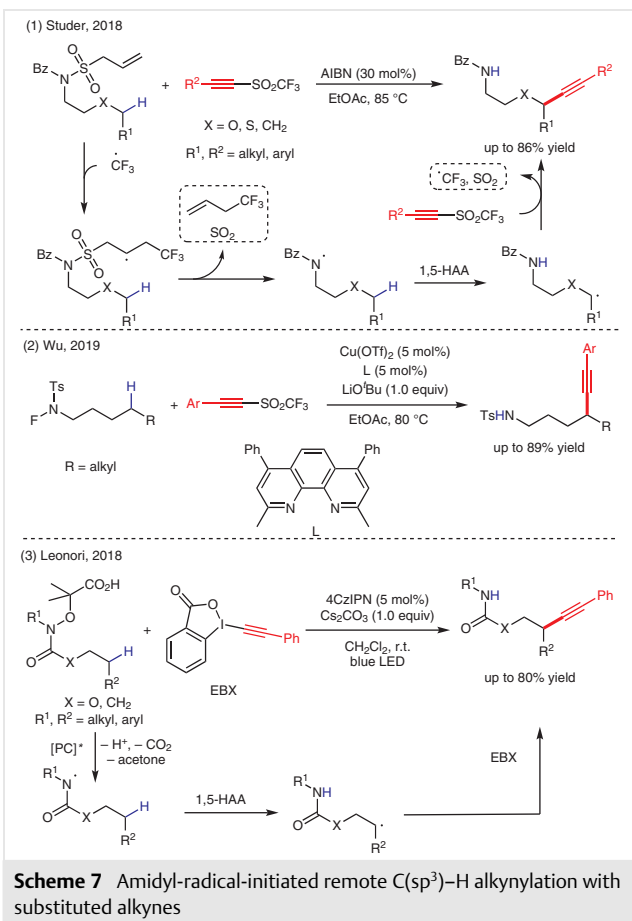


3 Alkylation of $C(sp^3)$ –H via Intramolecular Hydrogen Atom Transfer

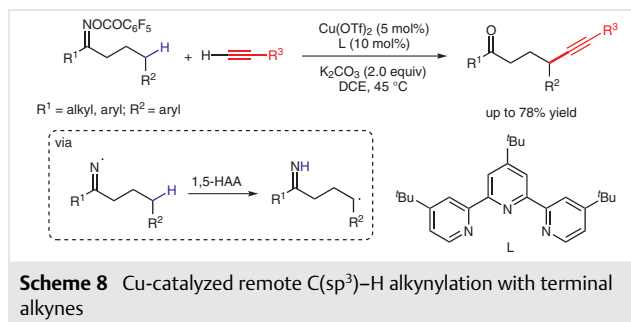
The radical $C(sp^3)$ –H functionalization via the intermolecular hydrogen atom abstraction generally has the problem of regioselectivity owing to the multiple $C(sp^3)$ –H bonds. In contrast, the intramolecular hydrogen atom abstraction process triggered by reactive radical can render a regioselective δ - $C(sp^3)$ –H functionalization owing to the favorable 1,5-HAA process, found in Hofmann–Löffler–Freitag (HLF) reaction.²⁷ Recently, the alkylation of remote $C(sp^3)$ –H bonds, mainly triggered by reactive heteroatom radicals, such as nitrogen- and oxygen-centered radicals, has emerged as an efficient strategy for the construction of $C(sp^3)$ – $C(sp)$ bonds.

In 2018, Studer and co-workers developed a remote $C(sp^3)$ –H alkylation with excellent regioselectivity at unactivated site using AIBN as the radical initiator and allylsulfonamides as the N-radical precursors (Scheme 7, eq. 1).²⁸ With this strategy, unactivated secondary and tertiary as well as primary $C(sp^3)$ –H bonds could be alkylated in up to 86% yield. In this work, the reliable intramolecular 1,5-HAA of amidyl radical led to the translocated alkyl radical, which was alkylated by acetylenic triflones via a sequential α -addition/ β -scission sequence. In 2019, Wu and co-workers successfully developed a copper-catalyzed remote $C(sp^3)$ –H alkylation of *N*-fluoro-sulfonamides with acetylene sulfones (Scheme 7, eq. 2).²⁹ The amidyl radical

was generated through a single electron reduction of the N-F bond by copper catalyst, and then underwent an intramolecular 1,5-HAA process to afford an alkyl radical, which was alkynylated by acetylene sulfone derivatives. In 2018, Leonori and co-workers realized a selective alkynylation of amides and protected amines at distal positions under photoredox catalysis (Scheme 7, eq. 3).³⁰ The process was based on the photoinduced SET oxidative generation of an electrophilic amidyl radical and its subsequent translocation by a 1,5-HAA process, resulting in the remote C(sp³)-H alkylation using the EBX reagent.

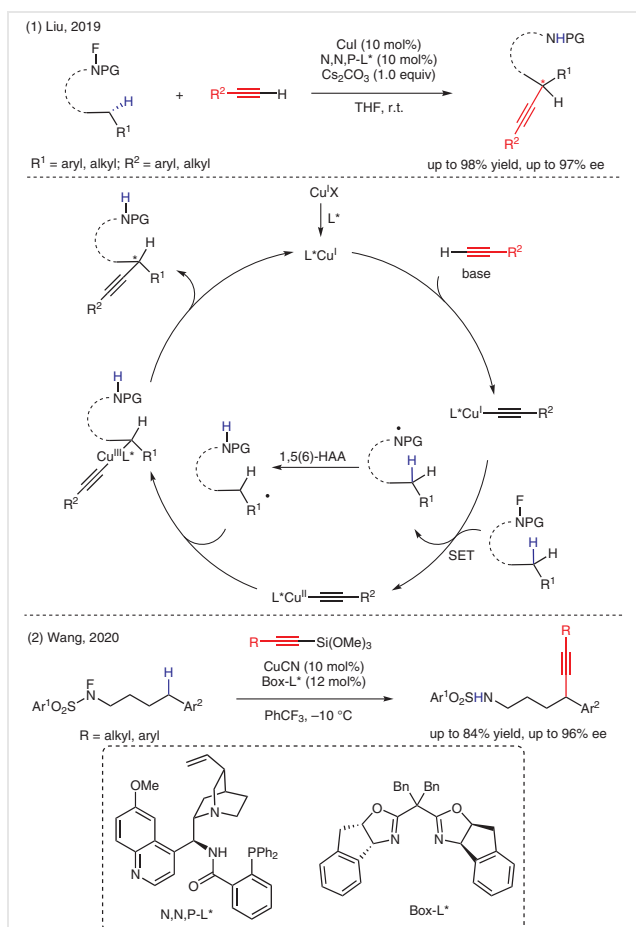


Similar to amidyl radicals, the iminyl radicals are also reactive enough to undergo a 1,5-HAA process to achieve remote C(sp³)-H bond functionalization (Scheme 8).³¹ In 2019, Zhu and co-workers disclosed a remote alkylation of C(sp³)-H bonds with terminal alkynes in the presence of a catalytic copper salt and a tridentate ligand, affording γ -alkynyl ketones with a broad substrate scope. The reaction proceeded through a domino sequence, including copper-catalyzed N-O reduction to generate the iminyl radical, followed by a radical translocation via 1,5-HAA and copper-catalyzed alkylation of the resulting alkyl radical species.

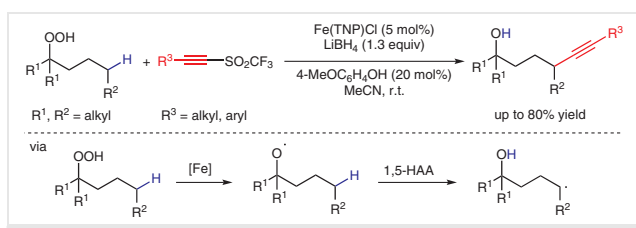


Our group has been focusing on the design of novel chiral anionic ligands to realize the radical-involved asymmetric transformations and recently discovered that a copper/cinchona alkaloid based multidentate N,N,P-ligand catalyst could be utilized to achieve the asymmetric Sonogashira cross-coupling reactions.^{6,8} Almost at the same time, we found that this catalytic system could also accomplish the radical asymmetric oxidative C(sp³)-C(sp) cross-coupling of unactivated C(sp³)-H bonds and terminal alkynes in a highly regio-, chemo-, and enantioselective manner (Scheme 9, eq. 1).³² The use of N-fluorocarboxamides as mild amidyl radical precursors was critical for inhibiting the Glaser homocoupling. Mechanistically, Cu^I firstly reacted with the chiral ligand and terminal alkyne in the presence of base, giving the chiral Cu^I acetylide complex. Subsequent SET of the chiral Cu^I acetylide complex with N-fluorocarboxamide resulted in the formation of Cu^{II} acetylide complex and the amidyl radical. The amidyl radical then underwent an intramolecular 1,5(6)-HAA to generate an alkyl radical species. Finally, C(sp³)-C(sp) coupling via reductive elimination of a Cu^{III} intermediate gave rise to the enantioenriched alkynes and regenerated the chiral Cu^I complex. Afterwards, using the similar strategy, Wang and co-workers described a copper-catalyzed enantioselective remote C(sp³)-H alkylation of linear sulfonamides with silyl-substituted acetylenes in the presence of a chiral Box ligand (Scheme 9, eq. 2).³³

Oxygen-centered radicals are also highly reactive to trigger the 1,5-HAA process to achieve distal C(sp³)-H bond functionalization. They are more electrophilic and reactive than nitrogen-centered radicals because of the higher electronegativity of the oxygen atom. In 2018, Liu and co-workers described an iron(II)-catalyzed site-selective alkylation of unactivated C(sp³)-H bonds of alkyl hydroperoxides with acetylenic triflones (Scheme 10).³⁴ The reaction was initiated by Fe(II)-mediated SET reduction of alkyl hydroperoxide, affording the oxygen-centered radical, which underwent an intramolecular 1,5-HAA process to afford the alkyl radical. This radical intermediate could be captured by acetylenic triflones via a sequential α -addition/ β -scission process.



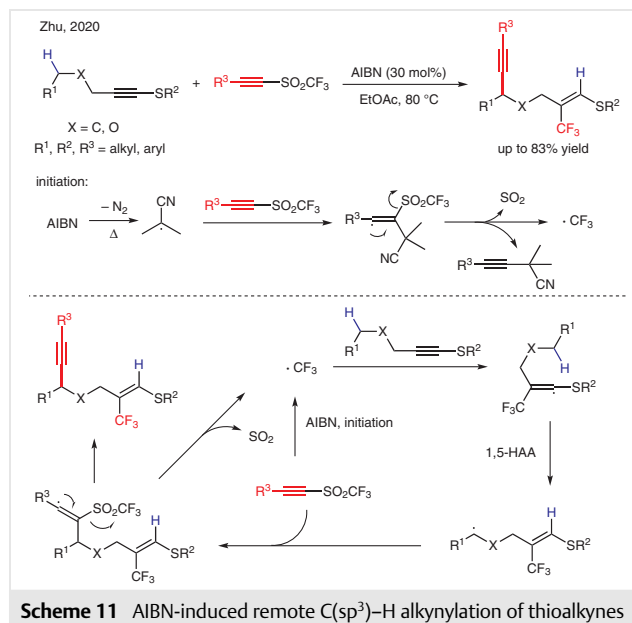
Scheme 9 Copper-catalyzed enantioselective oxidative cross-coupling of unactivated $C(\text{sp}^3)\text{-H}$ bonds with alkynes



Scheme 10 Iron-catalyzed remote $C(\text{sp}^3)\text{-H}$ alkylation of peroxides

Aryl/vinyl radicals are also considered as reactive radicals and can abstract a hydrogen atom from the remote unactivated $C(\text{sp}^3)\text{-H}$ bonds. Zhu and co-workers have very recently reported an AIBN-catalyzed trifluoromethyl alkylation of thioalkynes of thioalkynes with alkynyl triflones as both the CF_3 and alkyne donors (Scheme 11).³⁵ AIBN was used as the radical initiator, and the generated vinyl radical favored an intramolecular 1,5-HAA process to release a nucleophilic alkyl radical, which could finally be

alkynylated using acetylenic triflones. The intramolecular 1,5-HAA could not only control the site selectivity of remote $C\text{-H}$ functionalization but also lead to a stereospecific *trans*-hydrotrifluoromethylation of triple bonds.



Scheme 11 AIBN-induced remote $C(\text{sp}^3)\text{-H}$ alkylation of thioalkynes

4 Conclusion

In summary, we have witnessed a rapid development of the formation of $C(\text{sp}^3)\text{-C}(\text{sp})$ bonds through alkylation of unactivated $C(\text{sp}^3)\text{-H}$ bonds via the alkyl radical intermediate generated by hydrogen atom abstraction. This strategy has become a powerful method for the expedited access to synthetically valuable alkynes. Despite the great achievements in the past few years, many challenges remain to be addressed in the future: (1) The development of more asymmetric transformations for $C(\text{sp}^3)\text{-H}$ alkylation. (2) Using the terminal alkynes as ideal alkynylating reagents. (3) Identifying suitable HAA reagents in intermolecular $C(\text{sp}^3)\text{-H}$ alkylation to achieve the reaction in a stoichiometric number of substrates instead of the utilization of substrates as a solvent.

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