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Article

Copper-Catalyzed sp^2 C−H Arylation and Alkynylation of Allenes via Hydrogen Atom Abstraction

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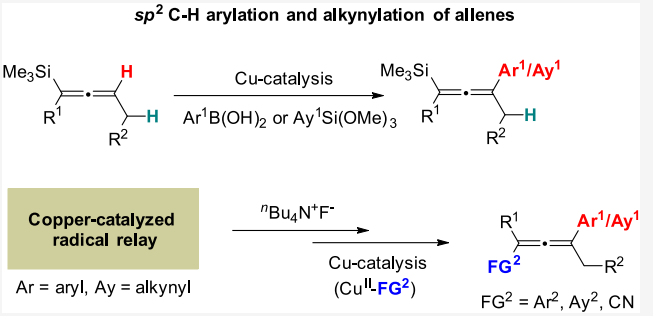
ABSTRACT: Development of methods for the sp^2 C−H transformations of allenes has received much attention, and it presents a powerful tool for the synthesis of complicated allene-containing bioactive molecules. With a copper-catalyzed radical relay, sp^2 allenic C−H arylation and alkynylation were established herein, using various aryl boronic acids and trimethoxysilyl-substituted alkynes as carbon nucleophiles and using electrophilic N−F reagents as nitrogen-centered radical precursors. These methods featured excellent site selectivity to deliver fully substituted allenes efficiently. Moreover, with silyl-substituted allenes as substrates, a subsequent dual sp^2 C−H functionalization process was established as well, which allowed for the divergent synthesis of multifunctionalized allenes, significantly expanding their chemical spaces.



INTRODUCTION

With a unique mutually perpendicular diene topology, rigid allene scaffolds are also found in natural products and pharmaceuticals, showcasing their significance in biological systems.[1] As shown in Scheme 1A, marasin, isolated from the culture medium of *Maresmius ramealis*, contains a conjugated allene structure, which serves as a potent active antibiotic component against *Staphylococcus aureus*.[2] In addition, phomallenic acids, which are new inhibitors of FabF, exhibited target selectivity in the gel elongation assay and in the whole-cell-based two-plate assay, and phomallenic acid C showed good antibacterial activity.[3] Moreover, allene-based bioactive compounds (e.g., prostaglandins) often act as reactive acceptors to inhibit the catalytic reactivity of enzymes and cytotoxic or antiviral agents.[4] However, the presence of natural products and pharmaceuticals containing allenes is relatively limited, and this scarcity underscores an urgent need to expand their chemical space, which is very important for the discovery of new therapeutic agents.[1c,d] Therefore, the exploration of robust synthetic methods for the direct functionalization of allenes will lay a solid foundation for this target.

Given the powerful strategy for the direct C−H transformations in organic synthesis,[5] transition metal-catalyzed direct C−H functionalization of the sp^2 C−H bonds of allenes presents a streamlined and powerful method for the synthesis of substituted allenes. Carreira and co-workers reported the first Pd(II)-catalyzed sp^2 C−H activation, which was promoted by a picolinamide directing group (Scheme 1B-*i*), thereby achieving the directing vinylation reactions.[6] Ma and co-workers communicated a Pd- or Rh-catalyzed Heck-type reaction of allenes via an addition/elimination process (Scheme 1B-*ii*).[7] In addition, Wang and co-workers developed an elegant iron-catalyzed allenic C−H addition to imines and aldehydes.[8] Despite these advancements, progress in this field is quite limited, and the development of such general and practical methods still remains a formidable challenge. Distinct from the aforementioned allenic C−H functionalizations, herein, we report the copper-catalyzed arylation and alkynylation of allenes, where sp^2 C−H bonds are site-selectively cleaved via hydrogen atom abstraction (HAA). This method allows us to convert simple allenes to aryl- or alkynyl-(Ay)-substituted allenes directly. More importantly, for the silyl-substituted allenes, two different functional groups can be readily introduced into allene molecules via sequential dual C−H functionalization, which enables the dramatic expansion of the chemical space of allene compounds, particularly for the bioactive molecules (Scheme 1C).

In recent years, we and another group independently disclosed a copper-catalyzed radical relay process for the site-selective sp^2 C−H cyanation of allenes, where the HAA process occurring at sp^2 C−H bonds was achieved by Cu-bound nitrogen-centered radicals (NCRs).[9,10] More importantly, existing hydrogen bonding between allenylic hydrogen and fluoride at a Cu(II) center is essential for the site-selective

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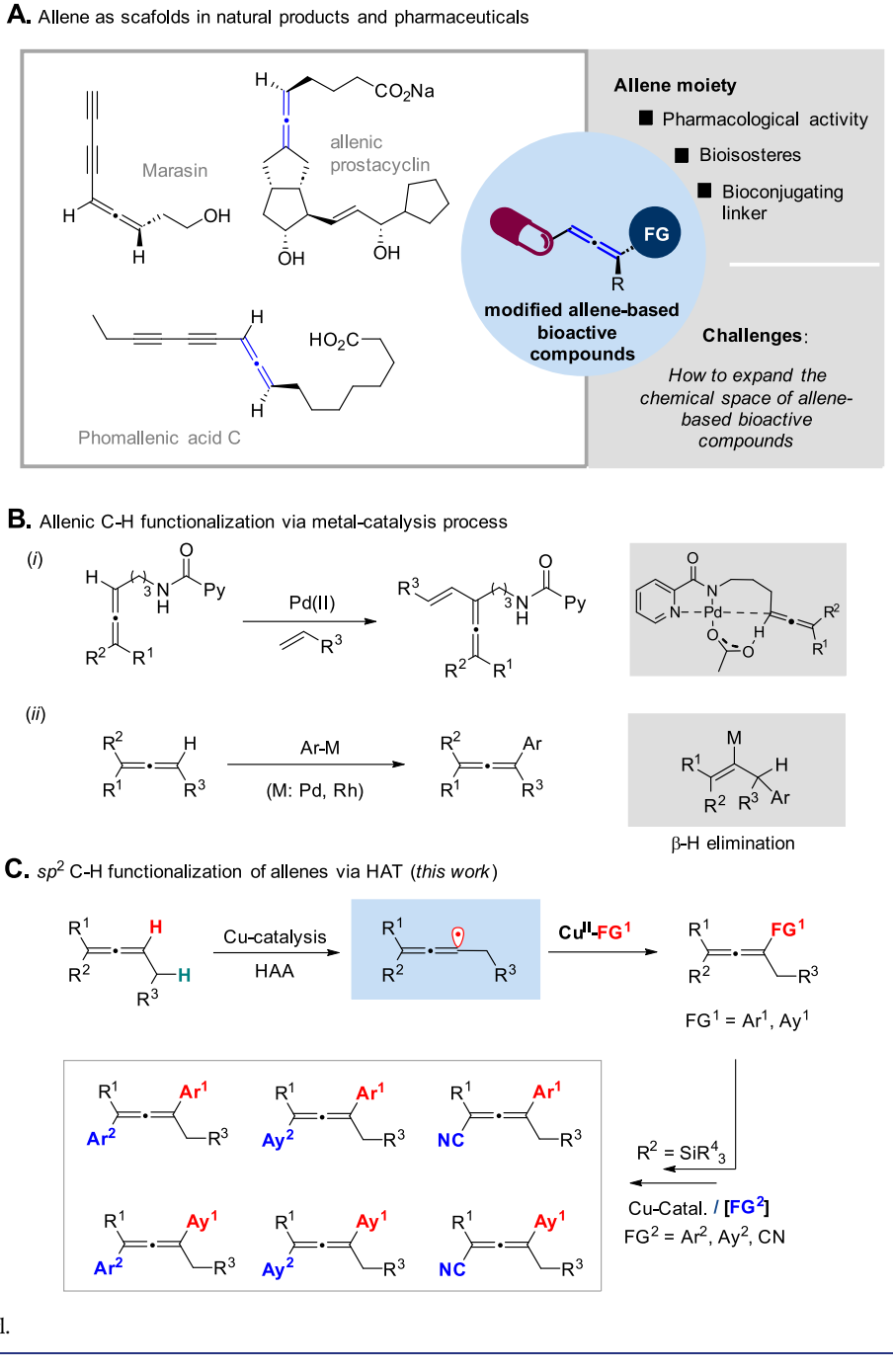
Scheme 1. Direct Carbonation of sp^2 C−H Bonds of Allenes[a]



[a]Ar = aryl, Ay = alkynyl.

HAA,[9] and the resultant allenic radical could be efficiently trapped by Cu(II) cyanide.[9−11] By combining copper-catalyzed radical arylation[12] and alkynylation,[13] the direct sp^2 C−H functionalization of allenes might be expected via the cross-coupling of allenic radicals to Ar−Cu(II) or alkynyl-Cu(II) species. In this scenario, this approach offers practical alternatives for constructing multifunctionalized allenes directly from simple allenes, providing easy access to highly versatile allene-based products with high efficiency. However, how to match the HAA process and the crossover of the highly reactive allenic radicals and Cu(II) species is essential for the target of the allene-to-allene direct transformations.

RESULTS AND DISCUSSION

Based on the previously reported sp^3 C−H functionalizations,[14] the sp^2 C−H arylation reaction of allene **1a** was investigated by using $CF_3C_6H_4B(OH)_2$ **2a** as an arylation reagent, Li_2CO_3 as a base, and **NF-1** as a nitrogen-centered radical (NCR) precursor. After careful screening, we found that the reaction indeed occurred to give the sp^2 C−H arylation product **3a** with excellent site selectivity (C_{sp^2}/C_{sp^3} > 20:1), and the best result (81% yield) was obtained with 5 mol % CuOAc/**L1** in a mixed solvent of CH_2Cl_2/DMAc (Scheme 2A-i, entry 1). When the ratio of **L1**:Cu(I) was increased from 1.2:1 to 2.4:1, the in situ-formed $(\mathbf{L1})_2$Cu exhibited poor catalytic reactivity, and the arylation reaction was inhibited completely (entry 2, 2A-*i*). Although the complex of Box-type ligand **L2** with Cu(I)

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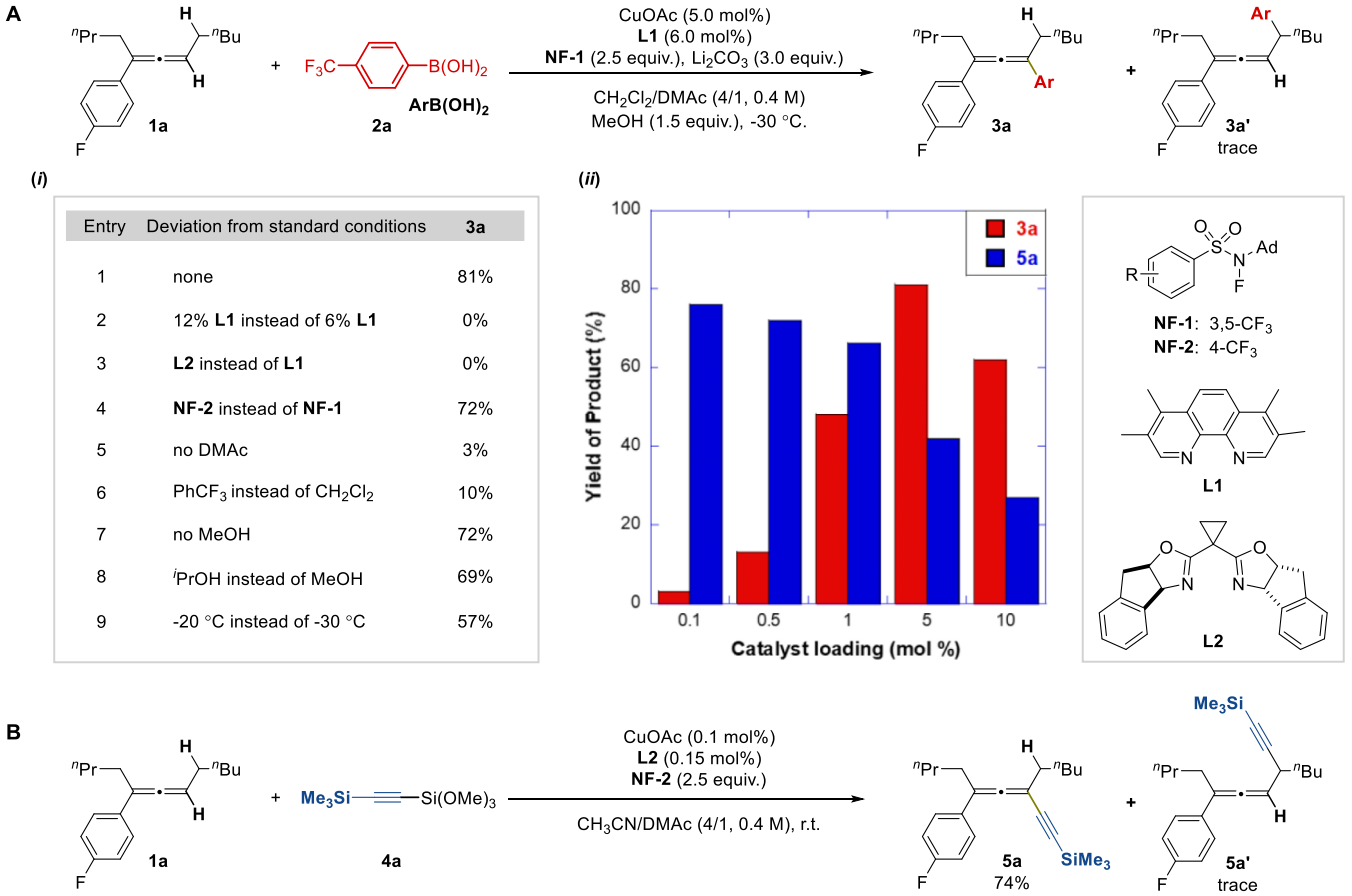
Scheme 2. Optimization of the Reaction Conditions[a]



Entry	Deviation from standard conditions	3a
1	none	81%
2	12% **L1** instead of 6% **L1**	0%
3	**L2** instead of **L1**	0%
4	**NF-2** instead of **NF-1**	72%
5	no DMAc	3%
6	$PhCF_3$ instead of CH_2Cl_2	10%
7	no MeOH	72%
8	^{i}PrOH instead of MeOH	69%
9	-20 °C instead of -30 °C	57%

[a](A) sp^2 C−H arylation of allenes. Reaction conditions on a 0.2 mmol scale: CuOAc (5.0 mol %), **L1** (6.0 mol %), **1a** (0.2 mmol), **NF-1** (0.5 mmol), aryl boronic acid **2a** (0.8 mmol), Li_2CO_3 (0.6 mmol), CH_2Cl_2/DMAc (4/1, 0.4 M), MeOH (1.5 equiv), under Ar at −30 °C. (B) sp^2 C−H alkynylation of allenes. Reaction conditions on a 0.2 mmol scale: CuOAc (0.1 mol %), **L2** (0.15 mol %), **1a** (0.2 mmol), **NF-2** (0.5 mmol), **4a** (1.2 mmol), CH_3CN/DMAc (4/1, 0.4 M), under Ar at r.t. The yields were determined by the crude ^{19}F NMR with CF_3-DMAc as an internal standard.

exhibited a higher reductive activation compared to **L1**, product **3a** completely disappeared (entry 3; for details, see the Supporting Information). In addition, compared to **NF-1**, the reaction with **NF-2** reagent gave product **3a** in a slightly lower yield (72%, entry 4). The cosolvents DMAc and CH_2Cl_2 played an essential role in the desired arylation reaction. When DMAc was absent, the reaction gave product **3a** in a less than 5% yield, along with a mess of side reactions (entry 5).[15] Changing the cosolvent CH_2Cl_2 by $PhCF_3$ also diminished the yield of product **3a** dramatically (entry 6). In addition, using MeOH as an additive was beneficial to accelerate the transmetalation of aryl boronic acids to Cu(II) species, which is beneficial for the arylation reaction. When MeOH was removed or replaced with isopropyl alcohol, the yield was slightly diminished (entries 7−8). Finally, increasing the reaction temperature could decrease the yield of the arylation product **3a** (entry 9).

After the studies of sp^2 C−H arylation, we turned our attention to the alkynylation reaction (Scheme 2B). Under the standard arylation condition A, the desired sp^2 C−H alkynylation of allene **1a** occurred along with Glaser-type self-coupling diyne as a side product. With further optimized conditions, the best yield (74%) was obtained under the standard reaction condition B, where 0.1 mol % CuOAc/**L2** and **NF-2** reagent were applied at room temperature. Most importantly, we first disclosed that the catalyst loading is essential for both reactions but with an opposite effect. Decreasing the copper catalyst could remarkably diminish the yield of C−H arylation product **3a** (red column) but significantly increase the yield of alkylation product **5a** (blue column) (Scheme 2A-ii). In addition, all of the above reactions exhibited excellent site selectivity, where this alkynylation exclusively occurred at the allenic C−H position (C_{sp^2}−H/C_{sp^3}−H > 20:1). Although we are currently unable to give a detailed explanation, these outcomes might be attributed to the stability of Cu(II) species. We assumed that the Aryl-Cu(II) species is likely less stable than the alkynyl-Cu(II) species; thus, a high concentration of Aryl-Cu(II) species is required to trap allenic radicals efficiently.

With the optimized reaction conditions A in hand, the scope of the sp^2 C−H arylation of allenes was first evaluated. As shown in Figure 1A, for the aryl-substituted allenes, various aryl boronic acids were suitable for the sp^2 C−H arylation reactions to provide the corresponding products **3a**−**3k** in good yields (typically 46−83%) with excellent site selectivities (from 11:1 to >20:1). A wide array of functional groups, such as CF_3 (**3a** and **3j**), sulfone (**3b**), nitrile (**3c** and **3g**−**3i**), OCF_3 (**3d**), and carboxylic ester (**3e**−**3f** and **3k**), could be well tolerated under our current reaction conditions. In addition, alkyl-substituted allenes were also suitable to give sp^2 C−H arylation products **3L**−**3q** in good yields (64−73%) with good site selectivities (the ratios of C_{sp^2}−H/C_{sp^3}−H ranged from 6:1 to 12:1), which are slightly lower than those of aryl-substituted allenes (e.g., **3a**). For

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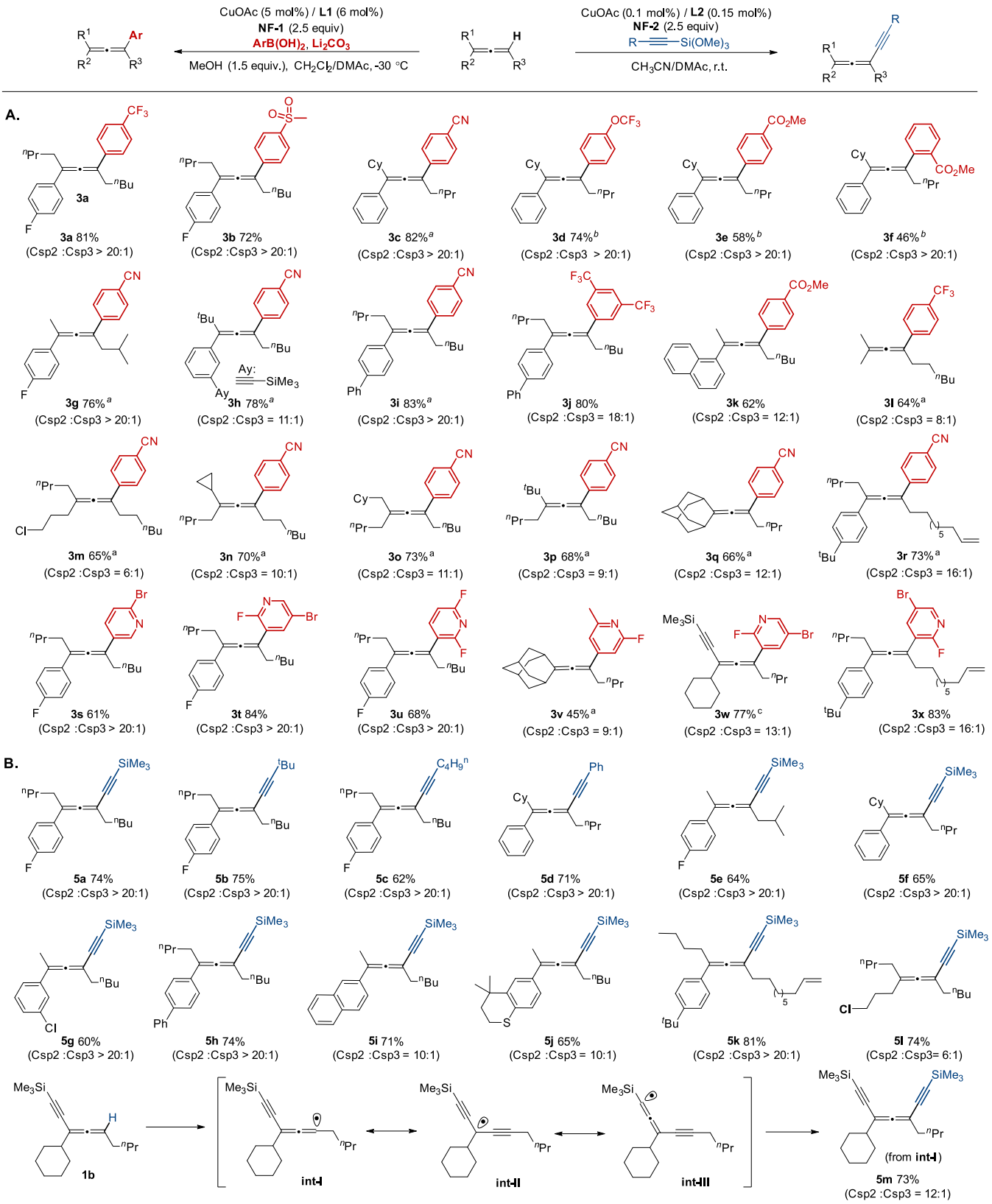

Figure 1. Substrate scope for sp^2 C−H functionalization. The reaction was performed on a 0.2 mmol scale. Arylation (conditions **A**): CuOAc (5.0 mol %), **L1** (6.0 mol %), allene (0.2 mmol), **NF-1** (0.5 mmol), aryl boronic acid (0.8 mmol), Li_2CO_3 (0.6 mmol), CH_2Cl_2/DMAc (4/1, 0.4 M), MeOH (1.5 equiv), under Ar at −30 °C. [a]The reaction was conducted at −20 °C and monitored by thin-layer chromatography. [b]The reaction was conducted at r.t. [c]The reaction was conducted at −10 °C. Alkynylation (conditions **B**): CuOAc (0.1 mol %), **L2** (0.15 mol %), allene (0.2 mmol), **NF-2** (0.6 mmol), alkynylation reagent (1.2 mmol), and CH_3CN/DMAc (4/1, 0.4 M) under Ar at r.t. The isolated yields of the target products are given.

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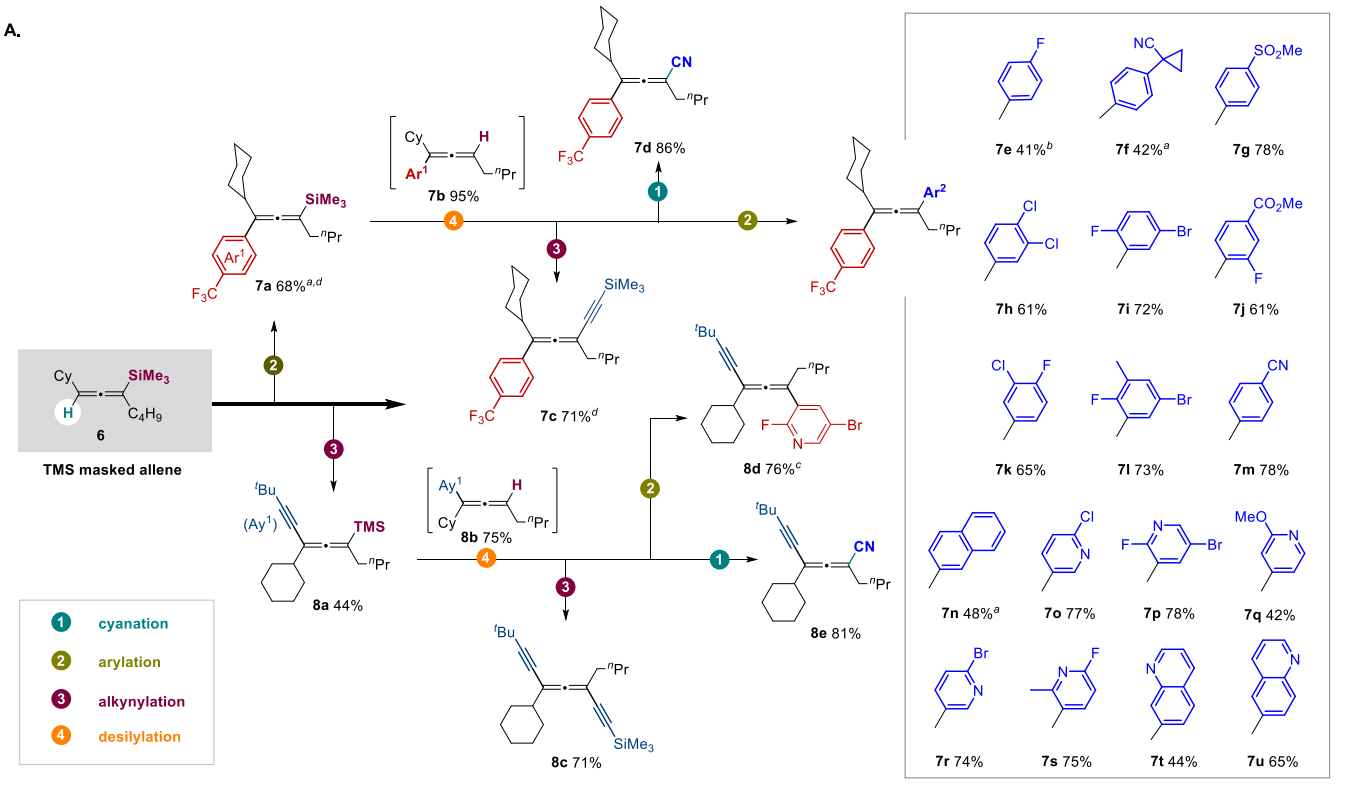

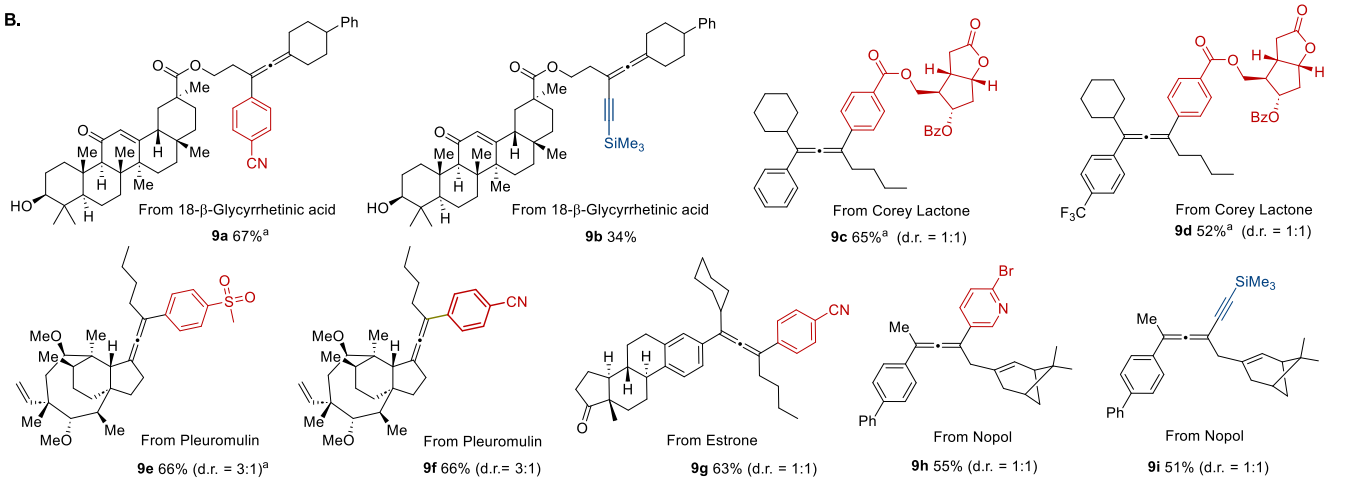

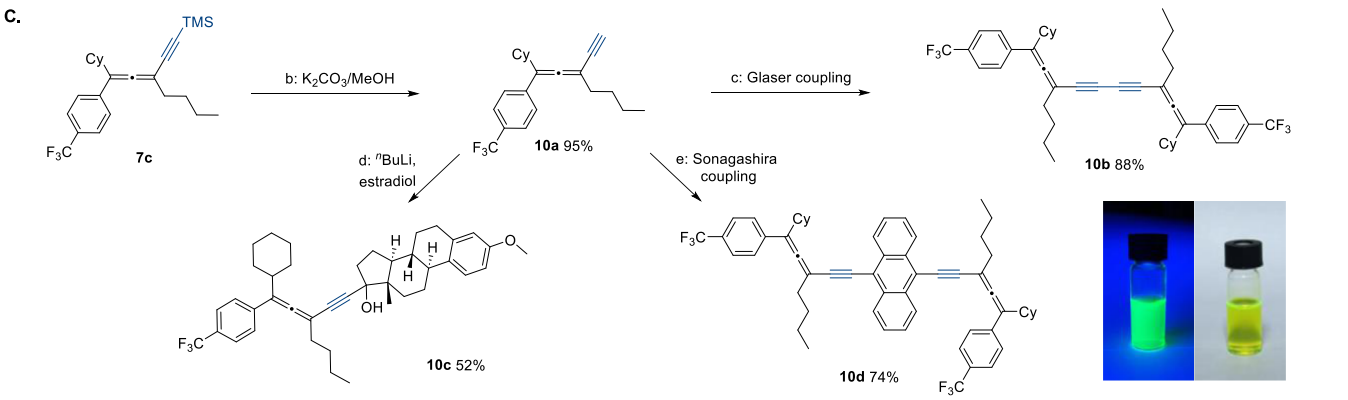

Figure 2. Direct functionalization of allenes and product transformations. (A) Sequential dual sp^2 C−H functionalizations of simple allenes. The reaction conditions for procedures 1−4 are mentioned in the Supporting Information. (B) Late-stage functionalization of complex allene-based compounds. (C) Product transformations. [a]The reaction was conducted at r.t.; [b]the reaction was conducted at 60 °C. [c]The reaction was conducted at −10 °C. [d]The reaction was conducted on a 2.0 mmol scale. The isolated yield of the target product is given.

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the substrate bearing an extra sp^3 allylic C−H bond, the HAA process still exclusively occurred at the sp^2 allenic position to give **3r** in a good yield (73%), while the allylic C−H bond was intact, indicating the exquisite site-selective HAA ability of the current catalytic system. More importantly, various pyridine-type aryl boronic acids were proven to be good candidates, and the reaction proceeded smoothly to yield pyridinyl-substituted allene products **3s**−**3x** in satisfied results. It should be noted that the standard conditions exhibited excellent compatibility with several unsaturated C−C bonds, such as alkene (**3r** and **3x**) and alkyne (**3h** and **3w**), and these sensitive functional groups survived to allow further functionalization reactions. Distinct from sp^2 C−H cyanation,[9] the reaction of disubstituted allenes exhibited poor chemoselectivity to give a mixture of mono- and diarylation products, where the arylated allene could further undergo a sequential sp^2 C−H arylation to give diarylation product (for details, see the Supporting Information).

Second, the sp^2 C−H alkynylation of allenes was further investigated with 0.1 mol % Cu(I)/**L2** in the cosolvent CH_3CN/DMAc. As shown in Figure 1B, various alkynylation reagents, including silyl-, alkyl-, and phenyl-substituted alkynyl reagents (**4a**−**4d**), were tested, and the reactions proceeded very well to give the corresponding sp^2 C−H alkynylation products **5a**−**5d** in good yields with excellent site selectivity (>20:1). Similar to arylation, the reactions of various aryl-substituted allenes (**5e**−**5i**) proceeded smoothly as well, and the substrate containing a sulfur atom (**5j**) also exhibited good reactivity. Again, for the substrate with an extra active allylic C−H bond, the HAA reaction still occurred at the allenic position to give **5k** in a good yield (81%) with excellent site selectivity. Moreover, the reaction of trialkyl-substituted allene also proceeded steadily to give product **5l** in a 74% yield with a slightly lower site selectivity (6:1). Finally, the conjugated allenyne substrate was also investigated, and it was found that the reaction of **1b** still occurred at the allenic position to provide allene-diyne product **5m** in a 73% yield with a 12:1 site selectivity. Notably, the involved allenic radical **int-I** might have resonated to other radical species **int-II** and **int-III**; however, only intermediate **int-I** could react with Cu(II) species to yield the desired alkynylation product **5m** selectively, probably owing to the steric effect.

Encouraged by the sp^2 C−H arylation and alkynylation reactions, we assumed that these methods provided a good opportunity to carry out the target of expanding the chemical space of allene-based bioactive compounds. First, we surveyed the possible sequential sp^2 C−H functionalization of allenes. As shown in Figure 2A, the TMS-substituted allene **6** was selected as a substrate for the first sp^2 C−H arylation to provide allene product **7a** in a 68% yield. After removal of TMS by tetrabutylammonium fluoride, the sequential allenic C−H functionalization of **7b**, such as alkynylation and cyanation, proceeded smoothly to give difunctionalized allenes **7c** and **7d** in good yields and selectivity.

More importantly, with this sequential dual sp^2 C−H arylation of **6**, diaryl-substituted allenes **7e**−**7u** could be readily obtained with high efficiency, where a series of aryl and heteroaryl groups were compatible. In addition, with a similar process initiated by sp^2 C−H alkynylation, substrate **6** could be converted to dialkynylated allene **8c**, alkynyl-arylated allene **8d**, and alkynyl-allenyl nitrile **8e** with high efficiency. These outcomes demonstrated that direct allenic C−H functionalization via the HAA process presented a powerful tool for the synthesis of versatile allenic compounds from simple allenes.

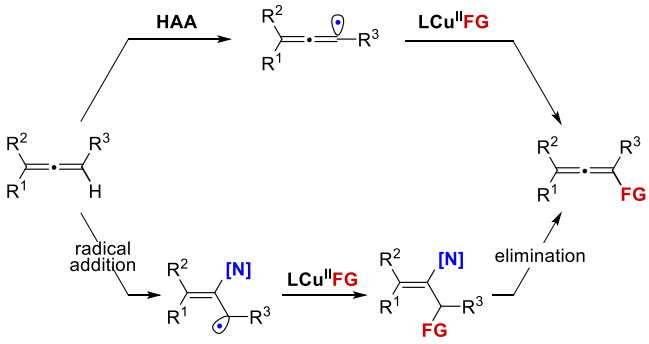
Second, the excellent functional group compatibility and high site selectivity of the method prompted us to test its potential for the late-stage modification of complex allene compounds derived from drug molecules and natural products. As shown in Figure 2B, a series of complex substrates derived from glycyrrhetinic acid (**9a**−**9b**), Corey lactone (**9c**−**9d**), pleuromulin (**9e**−**9f**), estrone (**9g**), and nopol (**9h**−**9i**) were suitable for this sp^2 C−H arylation and alkynylation with excellent site selectivity (typically sp^2/sp^3 > 20:1), where an array of functional groups, including esters, ethers, and ketones, are compatible with the standard conditions. Again, other active C−H bonds at the benzylic and allylic positions, or adjacent to an oxygen atom, were retained.

Functionalized allenylic alkynes have been recognized as important building blocks for organic synthesis. As shown in Figure 2C, after the removal of the TMS group, terminal alkynye **10a** could be further transferred to some complex structures. For instance, the Glaser coupling product **10b** features a diyne structure which frequently exposes high application in medicinal chemistry and functional materials.[2c,16] The addition of carbonyl groups yielded estradiol derivative **10c** in a 52% yield. Under Sonogashira coupling conditions with 9,10-dibromoanthracene, compound **10d** was prepared in a 74% yield, which exhibited a strong fluorescence effect.

MECHANISM

For the sp^2 C−H functionalization of allenes, there are two mechanistic pathways (Scheme 3): (1) a sequential HAA process and radical coupling with Cu(II) species (top); (2) radical difunctionalization of the C═C bond in allenes and sequential elimination of amides (bottom). To provide insight into the plausible HAA pathway, some control experiments were conducted, which are shown in Scheme 4. First, radical clock substrate **11** was synthesized and treated under standard conditions. The ring-opened product **12** was obtained in a 57% yield, indicating that the reaction possibly undergoes the radical abstraction of a hydrogen atom at the sp^2 allenic position. Furthermore, the generated sp^2 allenic C-radical and its resonant sp^3 propargylic C-radical proceed to a radical ring opening, and the benzylic radical is sequentially trapped by Cu(II)-Ar species to yield product **12** (Scheme 4a). Second, when TEMPO (0.5 equiv) was added into the reaction mixture of **1a** under the standard conditions, the yield of arylation product **3a** was significantly diminished, and product **13** generated from the radical trapping process of sp^2 allenic radical by TEMPO was detected by high-resolution mass spectrometry (HRMS) (Scheme 4b). Third, the kinetic isotopic effect was significantly

Scheme 3. Proposed Pathway



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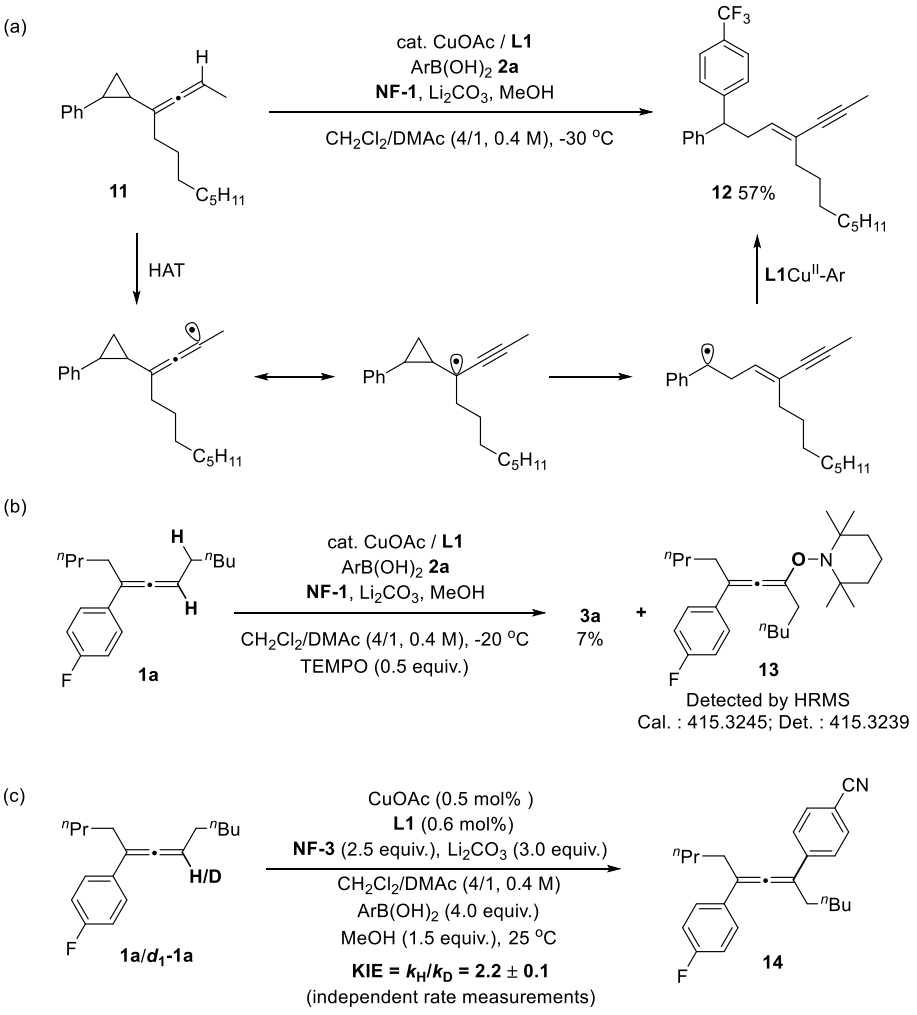
Scheme 4. Mechanism Studies on the HAA Pathway



observed in independent rate measurements of **1a** and $\mathbf{d}_1$-1a, where an average value of KIE = 2.2 ± 0.1 was obtained after three times (Scheme 4c). These outcomes indicated that the reaction should be initiated by a rate-determining HAA of sp^2 C−H bonds and that the allenic radical is involved as a key intermediate for the desired C−H functionalization.

In contrast, an alternative pathway involving a radical addition/elimination process was also examined. First, the standard reaction of **1a** was carefully analyzed by HRMS and ^{1}H NMR spectroscopy, and the radical addition product **15** was not observed (Scheme 5a). Second, during the study of the cyanation of allenes,[9] the reaction of terminal allene **16** afforded a desired cyanation product **17** in a 20% yield, along with a side radical addition product **18** in a 32% yield (Scheme 5b). To test the possible elimination pathway, compound **18** was added to the standard conditions of cyanation and arylation of compound **1b**. However, the related elimination product **17** was not observed, and compound **18** was recovered in a near quantitative yield (Scheme 5b,c). Considering that the acidity of the proton at the benzylic position in arylation product **15** is weaker than that of the proton at **C1** in cyanation product **18**, the elimination of **15** should be more difficult. Therefore, the elimination pathway should be unlikely. We reasoned that, due to the steric effect, the bulkier Cu(II)-bound NCRs involved in the reaction prefer HAA rather than radical addition of the C═C bond of allenes.

Based on these outcomes, a plausible mechanism is described in Scheme 6. The reaction started with an electron transfer process between L*Cu(I) and the NF reagent. Subsequently, the generated Cu(II)-bound N-centered radical abstracted the hydrogen atom from allenic sp^2 C−H bonds. After the ligand exchange at a Cu(II) center, the resulting allenic radical was then chemoselectively trapped by Cu(II)-Ar or Cu(II)-alkynyl species to deliver the allenic sp^2 C−H functionalization products. Again, the site-selective HAA is attributed to the unique pocket created by the Cu-bound NCR, where the fluoride in the Cu(II) center bonds to the hydrogen atom at the allylic position, which was reported in our previous allenic C−H cyanation.[9]

■ CONCLUSIONS

With an established HAA process by Cu(II)-bound NCRs, the sp^2 C−H arylation and alkynylation of allenes were achieved with good to excellent site selectivity. The reaction featured good functional group tolerance and broad substrate scope and even complex substrates derived from natural products and drugs. Moreover, a sequential dual sp^2 C−H functionalization of allenes was also disclosed as well, which could be used to synthesize various allenes efficiently from simple allenes, enabling the expansion of the chemical space of allene-based compounds.

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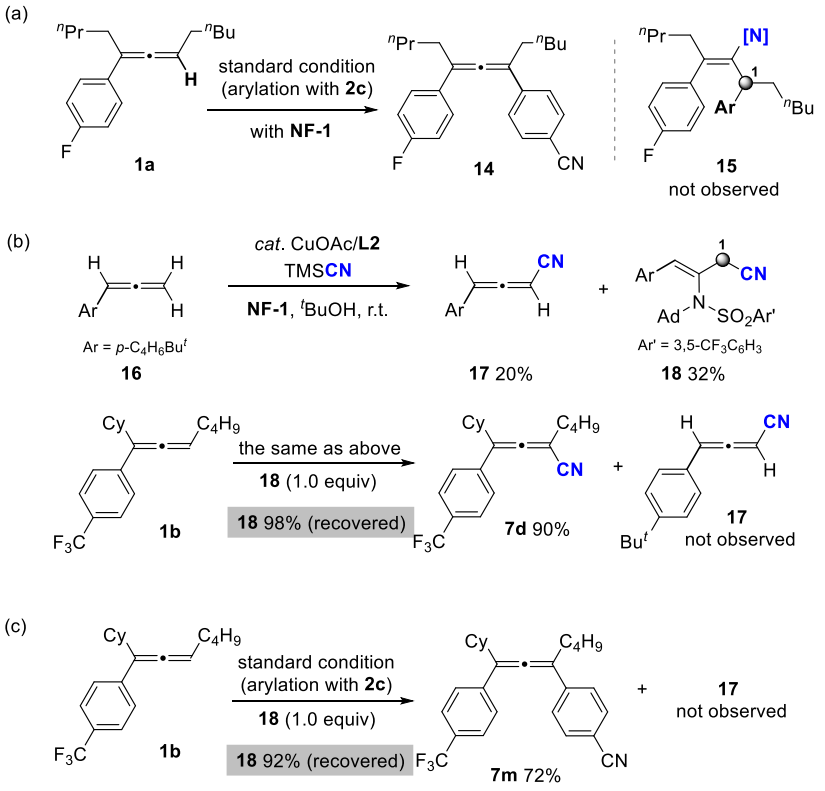
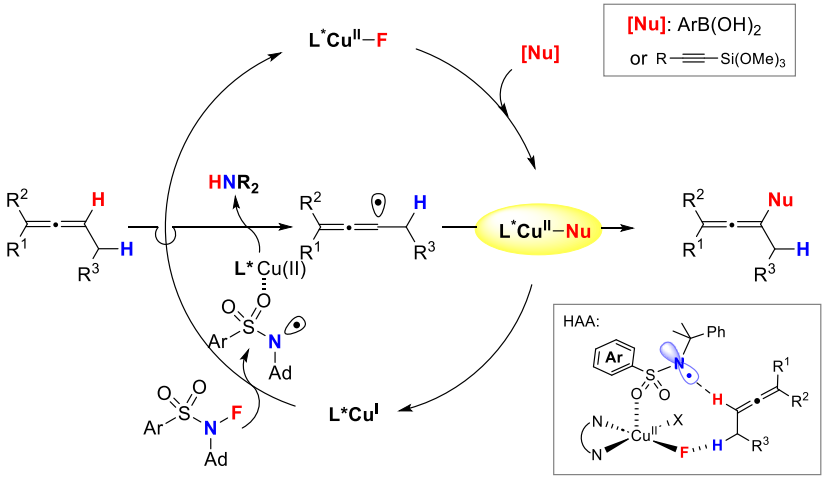
Scheme 5. Alternative Pathway on Radical Addition/Elimination



Scheme 6. Proposed Catalytic Cycle



■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/jacs.4c09324.

Experimental procedures and characterization data (PDF)

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) (a) Ban, H. S.; Onagi, S.; Uno, M.; Nabeyama, W.; Nakamura, H. Allene as an Alternative Functional Group for Drug Design: Effect of C-C Multiple Bonds Conjugated with Quinazolines on the Inhibition of EGFR Tyrosine Kinase. *ChemMedChem* **2008**, *3*, 1094−1103. (b) Hoffmann-Röder, A.; Krause, N. Synthesis and Properties of Allenic Natural Products and Pharmaceuticals. *Angew. Chem., Int. Ed.* **2004**, *43*, 1196−1216. (c) Brummond, K. M.; Chen, H. Allenes in Natural Product Synthesis. In *Modern allene chemistry*; Krause, N., Hashmi, S. K., Eds.; Wiley VCH, 2004; pp 1041−1089. (d) Krause, N.; Hoffmann-Röder, A. Allenic Natural Products and Pharmaceuticals in. In *Modern allene chemistry*; Krause, N., Hashmi, S. K., Eds.; Wiley VCH, 2004; pp 997−1039.

(2) (a) Bendz, G. *Ark. Kemi* **1959**, *14*, 305. (b) Cambie, R. C.; Hirschberg, A.; Jones, E. R. H.; Lowe, G. 783. Chemistry of the higher fungi. Part XVI. Polyacetylenic metabolites from Aleurodiscus roseus. *J. Chem. Soc. C* **1963**, 4120. (c) Davies, D. G.; Hodge, P. Biosynthesis of the allene (−)-marasin in Marasmius ramealis. *Org. Biomol. Chem.* **2005**, *3*, 1690−1693.

(3) Young, K.; Jayasuriya, H.; Ondeyka, J. G.; Herath, K.; Zhang, C.; Kodali, S.; Galgoci, A.; Painter, R.; Brown-Driver, V.; Yamamoto, R.; Silver, L. L.; Zheng, Y.; Ventura, J. I.; Sigmund, J.; Ha, S.; Basilio, A.; Vicente, F.; Tormo, J. R.; Pelaez, F.; Youngman, P.; Cully, D.; Barrett, J. F.; Schmatz, D.; Singh, S. B.; Wang, J. Discovery of FabH/FabF Inhibitors from Natural Products. *Antimicrob. Agents Chemother.* **2006**, *50*, 519−526.

(4) (a) Carpio, H.; Cooper, G. F.; Edwards, J. A.; Fried, J. H.; Garay, G. L.; Guzman, A.; Mendez, J. A.; Muchowski, J. M.; Roszkowski, A. P.; Van Horn, A. R.; Wren, D. Synthesis and gastric antisecretory properties of allenic 16-phenoxy-omega-tetranor prostaglandin E analogs. *Prostaglandins* **1987**, *33*, 169−180. (b) Walsh, C. Suicide substrates: mechanism-based enzyme inactivators. *Tetrahedron* **1982**, *38*, 871−909.

(5) (a) Davies, H. M. L.; Morton, D. Guiding principles for site-selective and stereoselective intermolecular C−H functionalization by donor/acceptor rhodium carbenes. *Chem. Soc. Rev.* **2011**, *40*, 1857−1869. (b) Zhang, F.-L.; Hong, K.; Li, T.-J.; Park, H.; Yu, J.-Q. Functionalization of C(sp^3)-H bonds using a transient directing group. *Science* **2016**, *351*, 252−256. (c) Che, C.-M.; Lo, V. K.-Y.; Zhou, C.-Y.; Huang, J.-S. Selective functionalisation of saturated C−H bonds with metalloporphyrin catalysts. *Chem. Soc. Rev.* **2011**, *40*, 1950−1975. (d) Woźniak, Ł.; Tan, J.-F.; Nguyen, Q.-H.; Madron du Vigné, A.; Smal, V.; Cao, Y.-X.; Cramer, N. Catalytic Enantioselective Functionalizations of C−H Bonds by Chiral Iridium Complexes. *Chem. Rev.* **2020**, *120* (18), 10516−10543. (e) White, M. C.; Zhao, J. Aliphatic C−H Oxidations for Late-Stage Functionalization. *J. Am. Chem. Soc.* **2018**, *140*, 13988−14009. (f) Che, C.-M.; Lo, V. K.-Y.; Zhou, C.-Y.; Huang, J.-S. Selective functionalisation of saturated C−H bonds with metalloporphyrin catalysts. *Chem. Soc. Rev.* **2011**, *40*, 1950−1975. (g) Golden, D. L.; Suh, S.-E.; Stahl, S. S. Radical C(sp^3)−H functionalization and cross-coupling reactions. *Nat. Rev. Chem* **2022**, *6*, 405−427.

(6) Schreib, B. S.; Son, M.; Aouane, F. A.; Baik, M.-H.; Carreira, E. M. Allene C(sp^2)−H Activation and Alkenylation Catalyzed by Palladium. *J. Am. Chem. Soc.* **2021**, *143* (51), 21705−21712.

(7) (a) Zeng, R.; Wu, S.; Fu, C.; Ma, S. Room-Temperature Synthesis of Trisubstituted Allenylsilanes via Regioselective C−H Functionalization. *J. Am. Chem. Soc.* **2013**, *135* (49), 18284−18287. (b) Fu, C.; Ma, S. Observation of the First Heck-Type Cross-Coupling Reaction of Allenes with Aryl Halides. Synthesis of Polysubstituted 1,2-Allenyl Sulfones. *Org. Lett.* **2005**, *7* (8), 1605−1607.

(8) Wang, Y.; Scrivener, S. G.; Zuo, X.-D.; Wang, R.; Palermo, P. N.; Murphy, E.; Durham, A. C.; Wang, Y.-M. Iron-Catalyzed Contrasteric Functionalization of Allenic C(sp^2)−H Bonds: Synthesis of α-Aminoalkyl 1,1-Disubstituted Allenes. *J. Am. Chem. Soc.* **2021**, *143*, 14998−15004.

(9) Cheng, Z.; Yang, T.; Li, C.; Deng, Y.; Zhang, F.; Chen, P.; Lin, Z.; Ma, S.; Liu, G. Site-Selective sp^2 C−H Cyanation of Allenes via Copper-Catalyzed Radical Relay. *J. Am. Chem. Soc.* **2023**, *145*, 25995−26002.

(10) Wei, Y.; Wang, Z.; Wang, K.; Qiu, J.-K.; Wang, Z.; Li, H.; Duan, X.; Guo, K.; Bao, X.; Wu, X. Copper-Catalyzed Radical Allene C(sp^2)-H Cyanation. *Angew. Chem., Int. Ed.* **2024**, *63*, No. e2023171.

(11) (a) Wang, F.; Wang, D.; Zhou, Y.; Liang, L.; Lu, R.; Chen, P.; Lin, Z.; Liu, G. Divergent Synthesis of CF_3-Substituted Allenyl Nitriles by Ligand-Controlled Radical 1,2- and 1,4-Addition to 1,3-Enynes. *Angew. Chem., Int. Ed.* **2018**, *57*, 7140−7145. (b) Ye, C.; Li, Y.; Zhu, X.; Hu, S.; Yuan, D.; Bao, H. Copper-catalyzed 1,4-alkylarylation of 1,3-enynes with masked alkyl electrophiles. *Chem. Sci.* **2019**, *10*, 3632−3636. (c) Zhang, K.-F.; Bian, K.-J.; Li, C.; Sheng, J.; Li, Y.; Wang, X.-S. Nickel-Catalyzed Carbofluoroalkylation of 1,3-Enynes to Access Structurally Diverse Fluoroalkylated Allenes. *Angew. Chem., Int. Ed.* **2019**, *58*, 5069−5074. (d) Zeng, Y.; Chiou, M.-F.; Zhu, X.; Cao, J.; Lv, D.; Jian, W.; Li, Y.; Zhang, X.; Bao, H. Copper-Catalyzed Enantioselective Radical 1,4-Difunctionalizationof 1,3-Enynes. *J. Am. Chem. Soc.* **2020**, *142*, 18014−18021. (e) Dong, X.-Y.; Zhan, T.-Y.; Jiang, S.-P.; Liu, X.-D.; Ye, L.; Li, Z.-L.; Gu, Q.-S.; Liu, X.-Y. Copper-Catalyzed Asymmetric Coupling of Allenyl Radicals with Terminal Alkynes to Access Tetrasubstituted Allenes. *Angew. Chem., Int. Ed.* **2021**, *60*, 2160−2164. (f) Lu, R.; Yang, T.; Chen, X.; Fan, W.; Chen, P.; Lin, Z.; Liu, G. Enantioselective Copper-Catalyzed Radical Cyanation of Propargylic C−H Bonds: Easy Access to Chiral Allenyl Nitriles. *J. Am. Chem. Soc.* **2021**, *143*, 14451−14457.

(12) (a) Wu, L.; Wang, F.; Wan, X.; Wang, D.; Chen, P.; Liu, G. Asymmetric Cu-Catalyzed Intermolecular Trifluoromethylarylation of Styrenes: Enantioselective Arylation of Benzylic Radicals. *J. Am. Chem.*

Soc. **2017**, *139*, 2904−2907. (b) Wang, D.; Wu, L.; Wang, F.; Wan, X.; Chen, P.; Lin, Z.; Liu, G. Asymmetric Copper-Catalyzed Intermolecular Aminoarylation of Styrenes: Efficient Access to Optical 2,2-Diarylethylamines. *J. Am. Chem. Soc.* **2017**, *139*, 6811−6814. (c) Jia, Y.; Zhang, Z.; Yu, G.; Jiang, X.; Lu, L.; Xiao, W.-J. Visible Light Induced Copper-Catalyzed Enantioselective Deaminative Arylation of Amino Acid Derivatives Assisted by Phenol. *Angew. Chem., Int. Ed.* **2023**, *62*, No. e2023121. (d) Yu, X.-Y.; Zhao, Q.-Q.; Chen, J.; Chen, J.-R.; Xiao, W.-J. Copper-Catalyzed Radical Cross-Coupling of Redox-Active Oxime Esters, Styrenes, and Boronic Acids. *Angew. Chem., Int. Ed.* **2018**, *57*, 15505−15509. (e) Zhang, Z.; Górski, B.; Leonori, D. Merging Halogen-Atom Transfer (XAT) and Copper Catalysis for the Modular Suzuki−Miyaura-Type Cross-Coupling of Alkyl Iodides and Organoborons. *J. Am. Chem. Soc.* **2022**, *144* (4), 1986−1992. (f) Zhang, Z.; Stateman, L. M.; Nagib, D. A. δ C−H (hetero)arylation *via* Cu-catalyzed radical relay. *Chem. Sci.* **2019**, *10*, 1207−1211. (g) Li, Z.; Wang, Q.; Zhu, J. Copper-Catalyzed Arylation of Remote C(sp^3)−H Bonds in Carboxamides and Sulfonamides. *Angew. Chem., Int. Ed.* **2018**, *57*, 13288−13292. (h) Wang, F.-L.; Liu, L.; Yang, C.-J.; Luan, C.; Yang, J.; Chen, J.-J.; Gu, Q.-S.; Li, Z.-L.; Liu, X.-Y. Synthesis of α-Quaternary β-Lactams via Copper-Catalyzed Enantioconvergent Radical C(sp^3)−C(sp^2) Cross-Coupling with Organoboronate Esters. *Angew. Chem., Int. Ed.* **2023**, *62*, No. e20221470. (i) Sakurai, S.; Matsumoto, A.; Kano, T.; Maruoka, K. Cu-Catalyzed Enantioselective Alkylarylation of Vinylarenes Enabled by Chiral Binaphthyl−BOX Hybrid Ligands. *J. Am. Chem. Soc.* **2020**, *142* (45), 19017−19022. (j) Hu, D.-D.; Nie, T.-M.; Xiao, X.; Li, K.; Li, Y.-B.; Gao, Q.; Bi, Y.-X.; Wang, X.-S. Enantioselective Construction of C-SCF_3 Stereocenters via Nickel Catalyzed Asymmetric Negishi Coupling Reaction. *Angew. Chem., Int. Ed.* **2024**, *63*, No. e202400308. (k) Shen, Y.; Gu, Y.; Martin, R. sp^3 C−H Arylation and Alkylation Enabled by the Synergy of Triplet Excited Ketones and Nickel Catalysts. *J. Am. Chem. Soc.* **2018**, *140*, 12200−12209. (l) Huang, H.; Bellotti, P.; Erchinger, J. E.; Paulisch, T. O.; Glorius, F. Radical Carbonyl Umpolung Arylation via Dual Nickel Catalysis. *J. Am. Chem. Soc.* **2022**, *144*, 1899−1909. (m) Liu, K.; Studer, A. Formal β-C−H Arylation of Aldehydes and Ketones by Cooperative Nickel and Photoredox Catalysis. *Angew. Chem., Int. Ed.* **2022**, *61*, No. e2022065. (n) Guo, L.; Yuan, M.; Zhang, Y.; Wang, F.; Zhu, S.; Gutierrez, O.; Chu, L. General Method for Enantioselective Three-Component Carboarylation of Alkenes Enabled by Visible-Light Dual Photoredox/Nickel Catalysis. *J. Am. Chem. Soc.* **2020**, *142* (48), 20390−20399.

(13) (a) Fu, L.; Zhang, Z.; Chen, P.; Lin, Z.; Liu, G. Enantioselective Copper-Catalyzed Alkynylation of Benzylic C-H Bonds via Radical Relay. *J. Am. Chem. Soc.* **2020**, *142*, 12493−12500. (b) Wang, C.-Y.; Qin, Z.-Y.; Huang, Y.-L.; Hou, Y.-M.; Jin, R.-X.; Li, C.; Wang, X. Enantioselective Copper-Catalyzed Remote C(sp^3)−H Alkynylation of Linear Primary Sulfonamides. *Org. Lett.* **2020**, *22*, 4006−4009. (c) Wang, F.-L.; Yang, C.-J.; Liu, J.-R.; Yang, N.-Y.; Dong, X.-Y.; Jiang, R.-Q.; Chang, X.-Y.; Li, Z.-L.; Xu, G.-X.; Yuan, D.-L.; Zhang, Y.-S.; Gu, Q.-S.; Hong, X.; Liu, X.-Y. Mechanism-based ligand design for copper-catalysed enantioconvergent C(sp^3)−C(sp) cross-coupling of tertiary electrophiles with alkynes. *Nat. Chem.* **2022**, *14*, 949−957. (d) Liu, L.; Guo, K.-X.; Tian, Y.; Yang, C.-J.; Gu, Q.-S.; Li, Z.-L.; Ye, L.; Liu, X.-Y. Copper-Catalyzed Intermolecular Enantioselective Radical Oxidative C(sp^3)-H/C(sp)-H Cross-Coupling with Rationally Designed Oxazoline-Derived N, N, P(O)-Ligands. *Angew. Chem., Int. Ed.* **2021**, *60*, 26710−26717. (e) Xia, L.; Jin, M.; Jiao, Y.; Yu, S. Synthesis of C-Alkynyl Glycosides by Photoredox-Catalyzed Reductive Coupling of Alkynyl Bromides with Glycosyl Bromides. *Org. Lett.* **2022**, *24* (1), 364−368.

(14) For some reviews, see: (a) Zhang, Z.; Chen, P.; Liu, G. Copper-catalyzed radical relay in C(sp^3)−H functionalization. *Chem. Soc. Rev.* **2022**, *51*, 1640−1658. (b) Wang, F.; Chen, P.; Liu, G. Copper-Catalyzed Radical Relay for Asymmetric Radical Transformations. *Acc. Chem. Res.* **2018**, *51*, 2036−2046. (c) For some examples, see Chen, S.-J.; Krska, S. W.; Stahl, S. S. Copper-Catalyzed Benzylic C−H Cross-Coupling Enabled by Redox Buffers: Expanding Synthetic Access to Three-Dimensional Chemical Space. *Acc. Chem. Res.* **2023**, *56*, 3604−3615. (d) Zhang, W.; Chen, P.; Liu, G. Copper-Catalyzed Arylation of Benzylic C−H bonds with Alkylarenes as the Limiting Reagents. *J. Am. Chem. Soc.* **2017**, *139*, 7709−7712. (e) Vasilopoulos, A.; Zultanski, S. L.; Stahl, S. S. Feedstocks to Pharmacophores: Cu-Catalyzed Oxidative Arylation of Inexpensive Alkylarenes Enabling Direct Access to Diarylalkanes. *J. Am. Chem. Soc.* **2017**, *139*, 7705−7708. (f) Zhang, W.; Wu, L.; Chen, P.; Liu, G. Enantioselective Arylation of Benzylic C−H Bonds by Copper-Catalyzed Radical Relay. *Angew. Chem., Int. Ed.* **2019**, *58*, 6425−6429. (g) Cheng, X.; Lu, H.; Lu, Z. Enantioselective benzylic C−H arylation via photoredox and nickel dual catalysis. *Nat. Commun.* **2019**, *10*, 3549−3556.

(15) Addition of DMAc is beneficial for the desired C−H functionalization, which was observed in the previous studies, see refs 13a and[14f]. We assumed that, as a polar coordinating solvent, DMAc possibly acts as an L-type ligand to stabilize Cu(II)-Ar and Cu(II)-Ay intermediate, which is very important for the subsequent radical coupling with allenic radicals.

(16) Lahoz, I. R.; Navarro-Vázquez, A.; Alonso-Gómez, J. L.; Cid, M. M. Acetylenic Homocoupling Methodology Towards the Synthesis of 1,3-Butadiynyl Macrocycles: [14_2]-Alleno-Acetylenic Cyclophanes. *Eur. J. Org Chem.* **2014**, *2014*, 1915−1924.

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