JACS
JOURNAL OF THE AMERICAN CHEMICAL SOCIETY
pubs.acs.org/JACS
Perspective

Metal-Bound Heteroatom Radicals: Advancing Site-Selective C−H Functionalization

Jiayuan Li, Tobias Blockhaus, and Guosheng Liu*

Cite This: https://doi.org/10.1021/jacs.5c07456
Read Online
ACCESS | Metrics & More | Article Recommendations

ABSTRACT: Selective transformation of C−H bonds represents a frontier research area in synthetic chemistry. While the high reactivity of radicals provides an alternative and efficient pathway for C−H bond functionalization, controlling their selectivity—particularly in processes such as site-selective hydrogen atom abstraction (HAA)—remains a long-standing and unresolved challenge in radical chemistry, largely due to the lack of effective regulation strategies. This review deliberately avoids a comprehensive discussion of the field's current state or landmark discoveries in C−H functionalization. Instead, by focusing on recent advances in metal-catalyzed, highly site-selective C−H bond transformations, this Perspective elucidates how metal-bound radicals enable precise hydrogen abstraction for targeted functionalization. This emerging paradigm offers innovative strategies for regulating radical behavior, potentially unlocking novel radical-mediated selective transformations—including but not limited to the precise functionalization of C−H bonds.

INTRODUCTION

Direct C−H functionalization has emerged as a transformative strategy in organic synthesis, offering a streamlined alternative to traditional methods that rely on prefunctionalized substrates. By targeting inert C−H bonds—ubiquitous in hydrocarbons, pharmaceuticals, and materials—this approach minimizes synthetic steps, enhances atom economy, and provides efficient access to structurally complex molecules.[1] Over the past decades, methodologies such as metal-catalyzed C−H activation,[2] metal-carbene insertions,[3] organocatalysis,[4] and enzyme catalysis[5] have revolutionized molecular editing, leading to significant advancements in drug discovery and materials science.[6] Among these strategies, radical-mediated C−H functionalization stands out for its ability to cleave inert C−H bonds under mild conditions, offering complementary site-selectivity and enabling straightforward, cost-effective transformations.[7] Recent advances in photocatalysis[8] and electrocatalysis[9] have further expanded the scope of radical C−H functionalization, positioning it as an indispensable tool for molecular synthesis.

A key challenge in radical C−H functionalization is achieving selective control, particularly in determining site-selectivity for substrates containing multiple C−H bonds with comparable reactivity.[10] This transformation generally proceeds through two critical steps: (1) hydrogen atom abstraction (HAA) to generate a carbon radical, and (2) radical functionalization via addition or atom transfer (Figure 1A). Site-selectivity is thus governed by two distinct stages: the thermodynamic/kinetic preferences of HAA and the subsequent reactivity of the carbon radical. In typical radical sp^3 C−H functionalization reactions, HAA often performs as rate-determining step, and this irreversible step makes it the primary determinant of site selectivity. However, if HAA becomes reversible by fine-tuning energy barrier, selectivity could instead be controlled by the second radical bond-forming step.[11] Reversible hydrogen atom abstraction (HAA) is rare in radical chemistry but offers a promising avenue for enhancing site-selectivity in C−H functionalization. Xu and co-workers introduced a C−H sampling strategy, where arylthiol enables reversible HAA, allowing a 1,4-cyano shift to achieve positional exchange between a cyano (CN) group and an unactivated C−H bond via radical translocation.[12] Building on this concept, Hu and co-workers developed a site-selective terminal C(sp^3)−H borylation of unbranched alkanes using $FeCl_3$ photocatalysis.[13] Wherein, light-activated $[FeCl_4]^-$ generates a chlorine radical for unselective HAA, but the presence of diphenyl sulfoxide directs site-selectivity—terminal radicals undergo borylation, while secondary radicals engage in reversible HAA, regenerating the alkane. Recent advances in stereochemical editing via reversible hydrogen atom abstraction (HAA)—including developments involving nonmetal-bound hydrogen atom transfer (HAT) species,[14] as well as formal reversible HAT processes enabling deracemization[15,16] and epimerization[17]—further highlight the potential of radical-based strategies for addressing selectivity challenges in C−H functionalization. Although a comprehensive discussion of these emerging methodologies is beyond the scope of this Perspective, these examples collectively underscore the expanding utility of reversible HAA in achieving precise control over radical-mediated transformations.

Received: May 3, 2025
Revised: June 9, 2025
Accepted: June 10, 2025
Published: June 14, 2025

https://doi.org/10.1021/jacs.5c07456
J. Am. Chem. Soc. XXXX, XXX, XXX−XXX

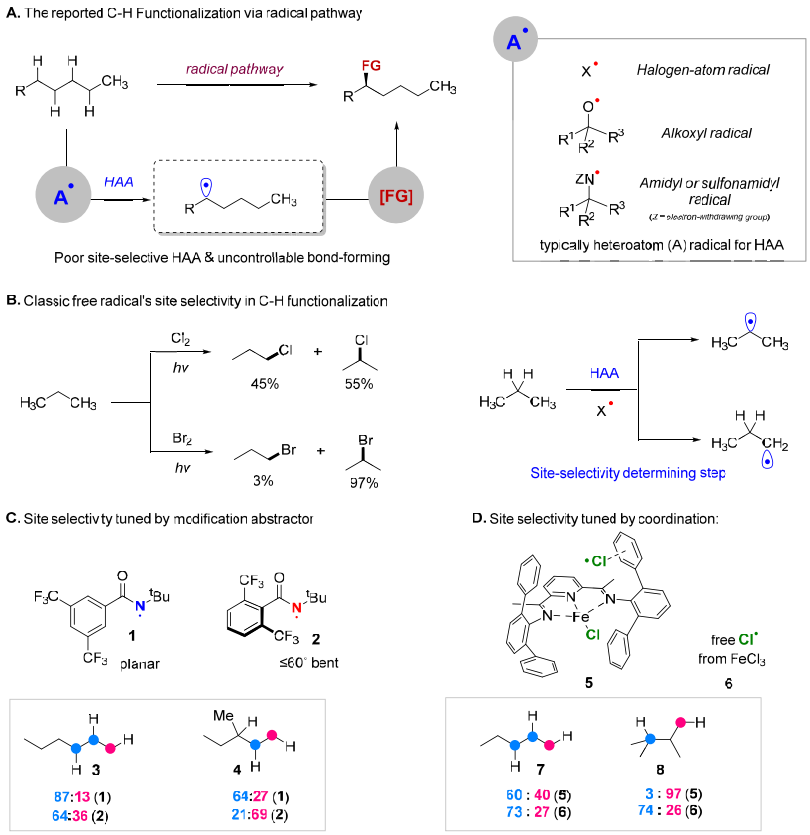

Figure 1. Site-selective radical C−H functionalization.

For the hydrogen atom abstraction (HAA) process, site-selectivity is governed by two competing factors: (1) Enthalpic effects, favoring cleavage of weaker C−H bonds (tertiary < secondary < primary BDE), and (2) Polarity effects, where electronic interactions stabilize transition states. Commonly used HAA abstractors—alkoxyl,[18] amidyl,[19] and halogen radicals[20]—are typically electrophilic, following a predictable tertiary > secondary > primary selectivity trend toward C−H bonds as the BDE increases and the electron-richness of the C−H bond decreases.[21] This trend aligns with the Hammond−Leffler postulate:[22] highly reactive radicals (e.g., Cl·) favor early transition states (TS) driven by exothermic H−X bond formation, enabling cleavage of strong Csp^3-H bonds but sacrificing selectivity (Figure 1B). Conversely, less reactive radicals (e.g., Br·) adopt later TS that better discriminate C−H bond stability, yet struggle to abstract inert bonds.[23] This reactivity-selectivity trade-off is particularly acute for inert Csp^3-H bonds, which resist polarization and demand high-energy abstractors prone to indiscriminate reactivity.

Intramolecular HAA circumvents these limitations through geometric constraints (e.g., 1,5- or 1,6-HAT) that direct radicals to specific sites, but such strategies require prefunctionalized substrates. Traditional intermolecular abstractors—alkoxyl, amidyl, halogen atom radicals,—often exhibit poor site-selectivity due to unmodulated reactivity. Recent modifications, such as steric shielding or electronic tuning, have improved selectivity, yet precise control remains elusive.

For example, Alexanian and colleagues demonstrated in 2018 that the site-selectivity of HAA could be tuned through steric modulation of the HAA mediators (for **3**, Figure 1C), and the chlorination of primary C−H bonds is predominated over secondary/tertiary sites with nitrogen centered radical (NCR) **2** in the case of **4** (Figure 1C).[23,24] The remarkably increased site-selectivity arose from the kinetic control, in which NCR **2** with *ortho*-CF_3 features a steric bulkier than NCR **1** with *meta*-CF_3, hindered access to sterically congested tertiary/secondary C−H bonds. However, this strategy requires substrate-specific mediator design, limiting its broader applicability. As an exciting discovery, a complementary approach involves taming inherently reactive chlorine radical by arenes via weak interaction.[25] Very recently, the Nocera group achieved sterically controlled enantioenriched photochlorination using (DPI)FeCl complexes to confine chlorine radicals within a secondary coordination sphere (Figure 1D).[26] This spatial constraint redirected the innate preference of free Cl· radicals to favor primary/secondary C−H bonds over tertiary sites. Transient absorption spectroscopy confirmed that Cl· radicals formed (Cl·larene) complexes with aromatic groups on the pyridine diimine ligand, attenuating their reactivity and enabling site-selective abstraction.[27] These examples highlight the potential of catalyst-controlled strategies to override intrinsic radical preferences, offering a more generalizable platform for selective C−H functionalization.

This Perspective introduces a new catalytic strategy for site-selective hydrogen atom abstraction (HAA) of C−H bonds, wherein commonly employed heteroatom radicals are modulated by metal species through coordination interactions. Distinct from classical enzyme-mimetic catalysis involving high-valent metal−oxo species[28] or metalloradical catalysis (MRC)[29] based on covalently metal-bound radicals, our focus is on **metal-bound heteroatom radicals via noncovalent coordination** as HAA acceptors. In this context, site-selective

https://doi.org/10.1021/jacs.5c07456
J. Am. Chem. Soc. XXXX, XXX, XXX−XXX

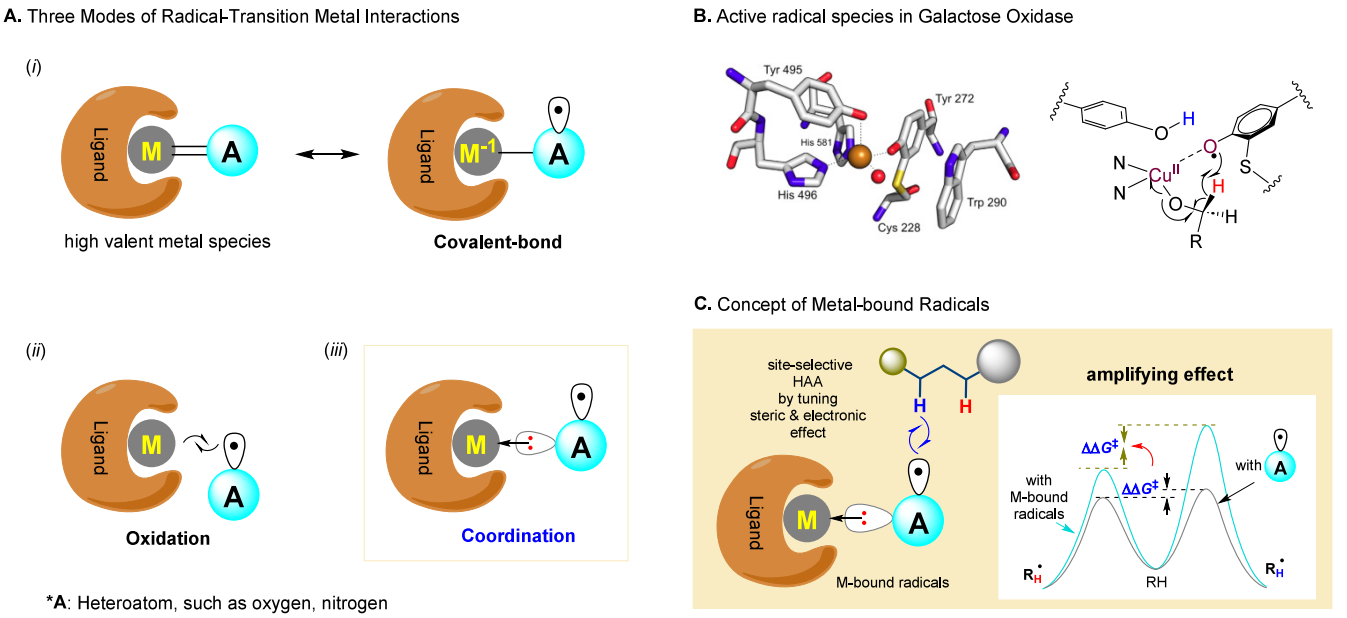

Figure 2. Enzymatic and metal-bound radical strategies for selective HAA.

HAA is achieved by tuning the ligands on the metal center. This Perspective explores the fundamental interactions between heteroatom radicals and transition-metal species, emphasizing how such coordination modulates site-specific C−H bond functionalization. We conclude by identifying key challenges and offering an outlook on future directions in this emerging field.

COORDINATION OF METAL AND RADICALS

A foundational concept in organometallic chemistry is the coordination between transition metals and lone-pair-bearing heteroatoms, a principle extensively applied in catalyst design. The interplay between metals and radical species can manifest in three distinct interaction modes, each imparting unique reactivity characteristics. First, in classical enzyme-mimetic catalysis, high-valent metal−oxo species are recognized as oxo-radicals covalently bound to metals (e.g., Fe or Mn).[28,30] These species play a central role in enzymatic and biomimetic oxidation processes, mediating site-selective C−H bond activation through precise electronic control (Figure 2A-*i*). Similarly, in metalloradical catalysis, metal−nitrene and metal−carbene complexes exhibit covalent metal−heteroatom bonding, with spin density delocalized over both the metal and the heteroatom.[29,31] Second, for free radicals (e.g., O- or N-centered radicals), interactions with metal species often proceed via a single-electron oxidation process (Figure 2A-*ii*).[32] In some cases, a radical species pairs its unpaired electron with a metal-centered electron to form a covalent bond, simultaneously oxidizing the metal to access higher-valent metal intermediates that participate in downstream transformations such as reductive elimination.[33] Third, inspired by the above coordination modes, radical coordination can occur when a heteroatom-centered radical (e.g., N· or O·) donates a lone pair to an empty orbital of a metal center (e.g., Cu(II)), forming a dative interaction that retains substantial radical character and spin density on the heteroatom without full covalent bond formation (Figure 2A-*iii*). These interaction modes are distinguished by retention of spin density, covalent bonding, or changes in the metal oxidation state. As the classical metal−oxo systems and metalloradical catalysis have been extensively reviewed,[28,29] they fall beyond the scope of this discussion. Instead, this Perspective focuses on metal−radical coordination via dative interactions, a concept supported by enzymatic systems such as galactose oxidase, where a Cu(II)-bound phenoxy radical mediates alcohol oxidation (Figure 2B).[34] In this system, the protein scaffold preorganizes the substrate and stabilizes the transition state, enabling selective cleavage of weak C−H bonds. Beyond enzymology, the metal−radical coordination strategy has also been employed in molecular magnetism. For example, stable organic radicals coordinated to transition-metal centers exhibit strong metal−ligand magnetic exchange interactions, promoting cooperative magnetic behavior in molecular frameworks.[35] Similarly, the coordination of a stable aminyl radical to a Rh(I) complex has been isolated and structurally characterized.[36] Early studies showed that the generation of metal-complexed aminyl radicals under neutral conditions could modulate radical addition reactivity, preventing undesired side reactions.[37] Instead, the potential metal-coordinated transient heteroatom radicals, such as *tert*-butoxy and amidyl species, offers a promising avenue to control the reactivity and selectivity of heteroatom radicals in HAA of aliphatic C(sp^3)−H bonds—marking a paradigm shift in radical abstractor design (Figure 2C). These systems integrate the intrinsic reactivity of free radicals with the tunability of metal−ligand coordination, enabling precise control over the steric and electronic environment of the radical. This approach enhances site-selective HAA of inert C(sp^3)−H bonds and mirrors the cooperative mechanisms seen in enzymatic C−H activation, where metal−radical interplay enables both high reactivity and exceptional site discrimination.

The integration of metal-heteroatom radical systems offers a versatile platform for addressing the reactivity-selectivity dichotomy in radical C−H functionalization. Tailoring ligand architectures fine-tunes these systems to target specific C−H bonds, enabling predictable, substrate-agnostic site-selective control. Mechanistic insights into metal-radical synergy will drive the next generation of catalyst design for inert C(sp^3)−H

https://doi.org/10.1021/jacs.5c07456
J. Am. Chem. Soc. XXXX, XXX, XXX−XXX

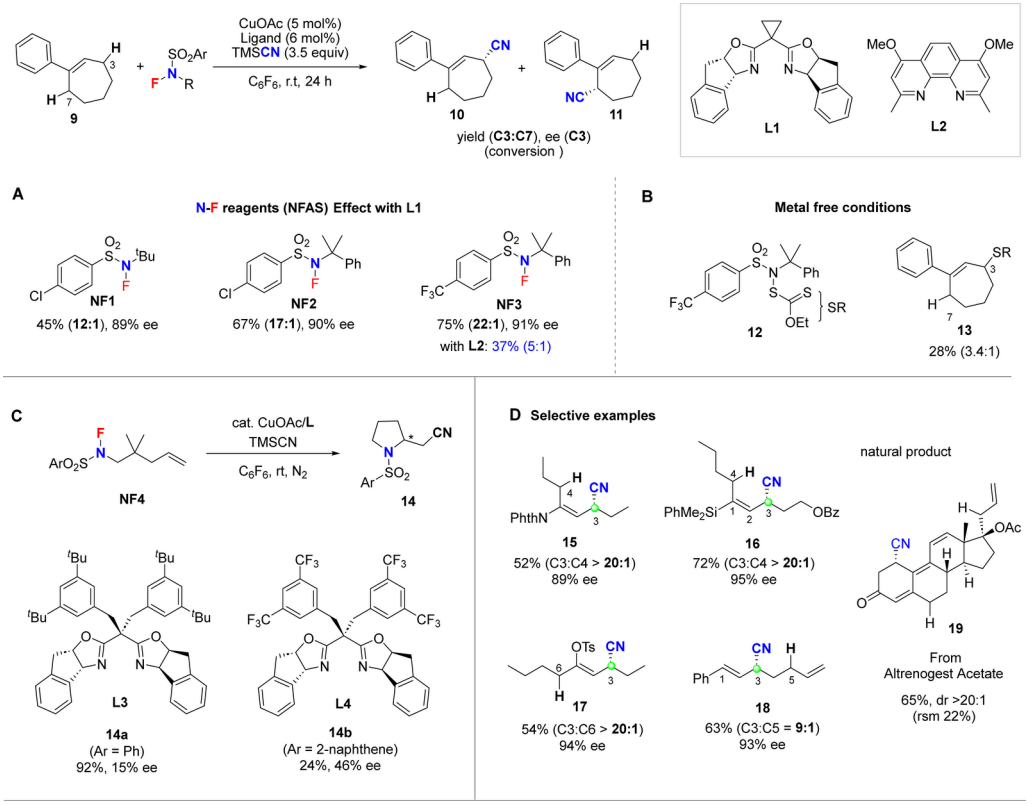

Figure 3. Site- and enantioselective allylic C−H cyanation via HAA by Cu(II)-bound nitrogen radical.

functionalization, bridging biological precision with synthetic flexibility.

Copper(II)-Bound NCRs. While enantioselective radical reactions have been extensively explored via a copper-catalyzed radical relay process,[38] controlling site-selectivity during intermolecular HAA remains a formidable and underaddressed challenge, particularly in substrates with multiple C−H bonds of comparable reactivity.[39] Addressing this gap, Liu, Lin, and co-workers demonstrated that Cu(II)-bound nitrogen-centered radicals (NCRs) override innate radical preferences to achieve site-selective allylic C−H cyanation (Figure 3).[40] By modulating N-fluoroalkylsulfonamide (NFAS) precursors and chiral ligands, this strategy delivers exceptional site-, and enantiocontrol. Key to this advance was the discovery that Cu(II) coordination to the NCR stabilizes the radical and amplifies its selectivity. Steric and electronic tuning of NFAS precursors in the presence of the copper catalyst proved pivotal (Figure 3A): bulkier alkyl substituents (e.g., **NF1** → **NF2**) increased yield (45% → 67%) and C3:C7 selectivity (12:1 → 17:1), while electron-withdrawing aryl groups (**NF3**) further enhanced both yield (75%) and selectivity (22:1). Enantioselectivity remained uniformly high (89−91% ee) across NFAS variants, confirming that stereochemical outcomes are governed by the chiral ligand rather than the NCR precursor. Strikingly, replacing the chiral ligand with a smaller nonchiral ligand (**L2**) drastically reduced both selectivity (22:1 → 5:1) and efficiency (75% → 37%). Under metal-free conditions, the same NCR achieved only modest site-selectivity (3.4:1 for **13**), underscoring the indispensability of Cu(II) coordination (Figure 3B). Mechanistic validation via intramolecular cyclization revealed enantioselectivity induced transfer by chiral ligands, implicating the Cu(II)-bound NCR formation and participation in radical addition toward alkene (Figure 3C). These findings highlight the important role of the copper complex in tuning the reactivity and selectivity of the NCR for site-specific HAA, delivering site- and enantioselective C−H cyanation products. It is worth noting that the site-selectivity is not only governed by steric effect, but also by electronic effect. The reaction is kinetically favorable to occur at less steric position (**15**−**17**), and weaker C−H bonds (**18**). The strategy's robustness was further demonstrated in complex substrates, such as Altrenogest derivatives (**19**), where multiple allylic C−H bonds with near-identical steric/electronic environments were selectively differentiated (Figure 3D).

Computational studies provided more insight of the mechanism (Figure 4A): the interaction of Cu(II) species with free NCR is preferred to coordinate to oxygen atom of NCR, which is more stable than free NCR by 9.4 kcal/mol. In contrast, the alternative Cu(III) species exhibits a much higher energy barrier. In addition, compared to the HAA of free NCR, Cu(II)-bound NCR remarkably increase the $\Delta\Delta G^{\ddagger}$ for HAA at competing sites (C3 vs. C7) from 1.5 to 2.6 kcal/mol, translating to a dramatic selectivity leap (C3:C7 = 22:1 vs. 3.4:1 for free NCR, Figure 4B). This metal-radical cooperativity effectively decouples reaction selectivity from the marginal difference in inherent reactivity of the C−H sites, establishing a blueprint for predictable, catalyst-controlled site-selectivity in radical-mediated C−H functionalization.

Building on these mechanistic insights, the Cu(II)-bound nitrogen-centered radical strategy was extended to benzylic C−H cyanation (Figure 5),[41] further demonstrating its generality. For the case of ethylfluorene (**20**), asymmetric cyanation occurs exclusively at the less steric benzylic position of the ethyl group with ligand **L5**, despite the doubly benzylic methylene group in fluorene having a lower bond dissociation energy (BDE) (calculated: methylenic C−H = 80.1 kcal/mol

https://doi.org/10.1021/jacs.5c07456
J. Am. Chem. Soc. XXXX, XXX, XXX−XXX

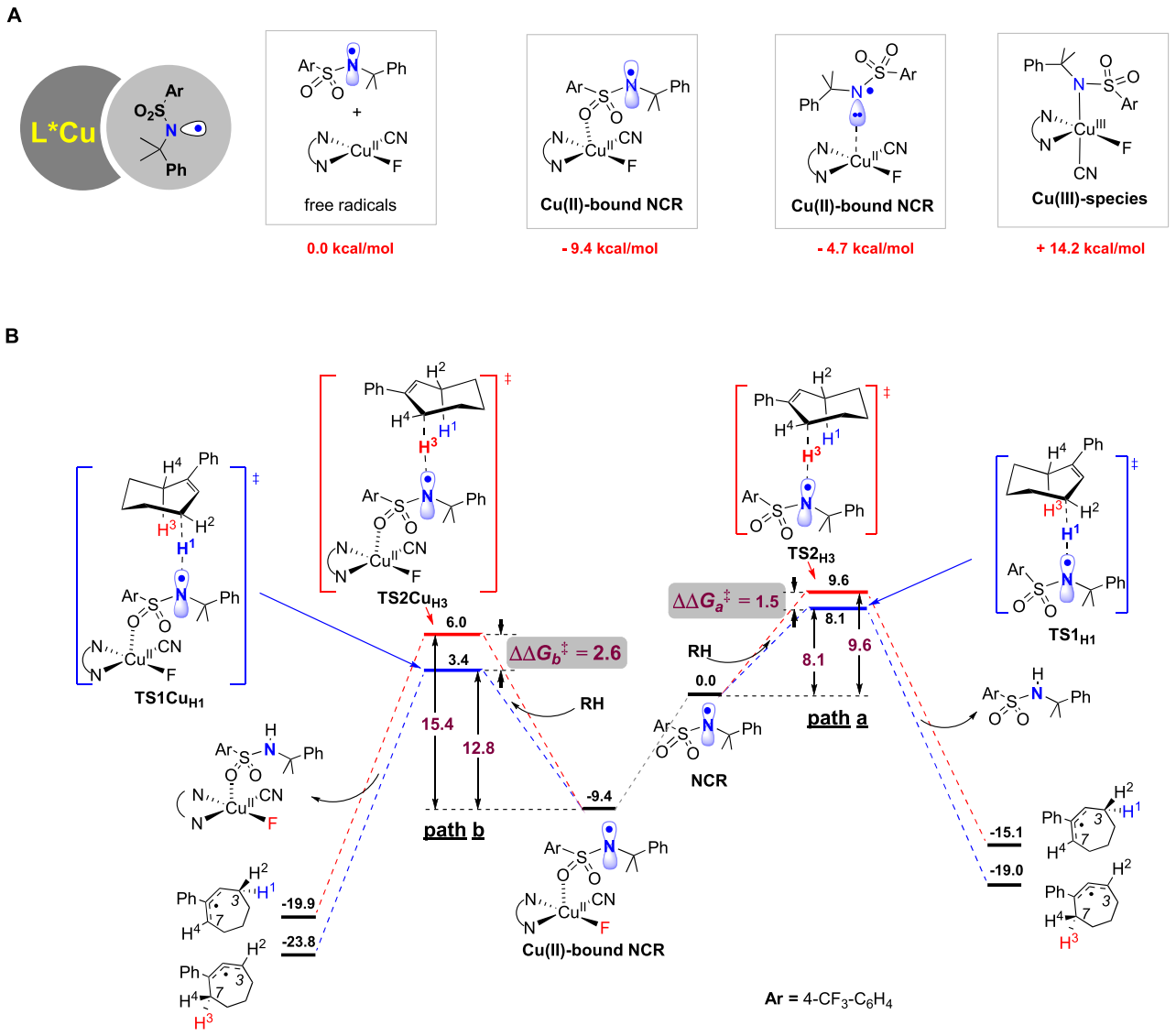

Figure 4. DFT for site- and enantioselective allylic C−H cyanation.

vs benzylic C−H = 83.1 kcal/mol). This inversion of thermodynamic expectations highlights how steric and electronic modulation by the Cu(II)-ligand framework overrides innate BDE trends. Similarly, in substrates with two benzylic positions—one adjacent to a naphthalene ring and the other to a phenyl group—HAA favors the naphthalene-adjacent site. Altering *para* substituents (**21**−**23**) from electron-donating to electron-withdrawing groups amplifies selectivity from 12:1 to 29:1, highlighting electronic effects as a critical lever. Most strikingly, ligand engineering enables even reversal of site preference: for the case of **24**, selectivity favors the naphthalene-adjacent C−H bond (19:1) with **L5**, whereas **L6** reduces this preference (4:1), and the bulky **L9** (*tert*-butyl-substituted) reverses it entirely, favoring the phenyl-adjacent site (1:10).[42] This ligand-dependent tunability, spanning steric shielding to electronic polarization, conclusively ties site-selectivity to the Cu(II)-NCR coordination environment rather than substrate-driven biases.

The strategy's versatility is further exemplified by its expansion to diverse benzylic C−H functionalizations (Figure 6). For instance, using *N*-fluorobenzenesulfonimide (NFSI) as the abstractor precursor and nonchiral ligand **L10**, site-selective benzylic C−H arylation (**26**−**27**) was achieved with >20:1 selectivity.[43] Remarkably, employing chiral ligand **L6** enabled site- and enantioselective benzylic alkylation (94% ee, >20:1 site-selectivity for **29**), demonstrating dual control over reactivity and stereochemistry.[44] Collectively, these examples illustrate an unified design principle: by tailoring ligand architecture and radical precursors, the Cu(II)-bound NCR system achieves precise, programmable control over HAA site-selectivity. This paradigm bridges the reactivity-selectivity divide, offering a versatile platform for site-selective functionalization of allylic and benzylic C−H bonds—even in electronically and sterically congested settings.

Expanding beyond C(sp^3)−H activation, the copper-bound NCR strategy addresses persistent challenges in radical C(sp^2)−H functionalization, particularly in allenes. Despite extensive research into allene transformations, selective hydrogen atom abstraction (HAA) at the C(sp^2)−H site remains elusive. This challenge arises because radicals preferentially undergo radical addition to the allene π-system rather than direct HAA. Radical addition generates a resonance-stabilized allylic radical, whereas direct HAA at a C(sp^2)−H bond typically yields a localized allenic radical (or

https://doi.org/10.1021/jacs.5c07456
J. Am. Chem. Soc. XXXX, XXX, XXX−XXX

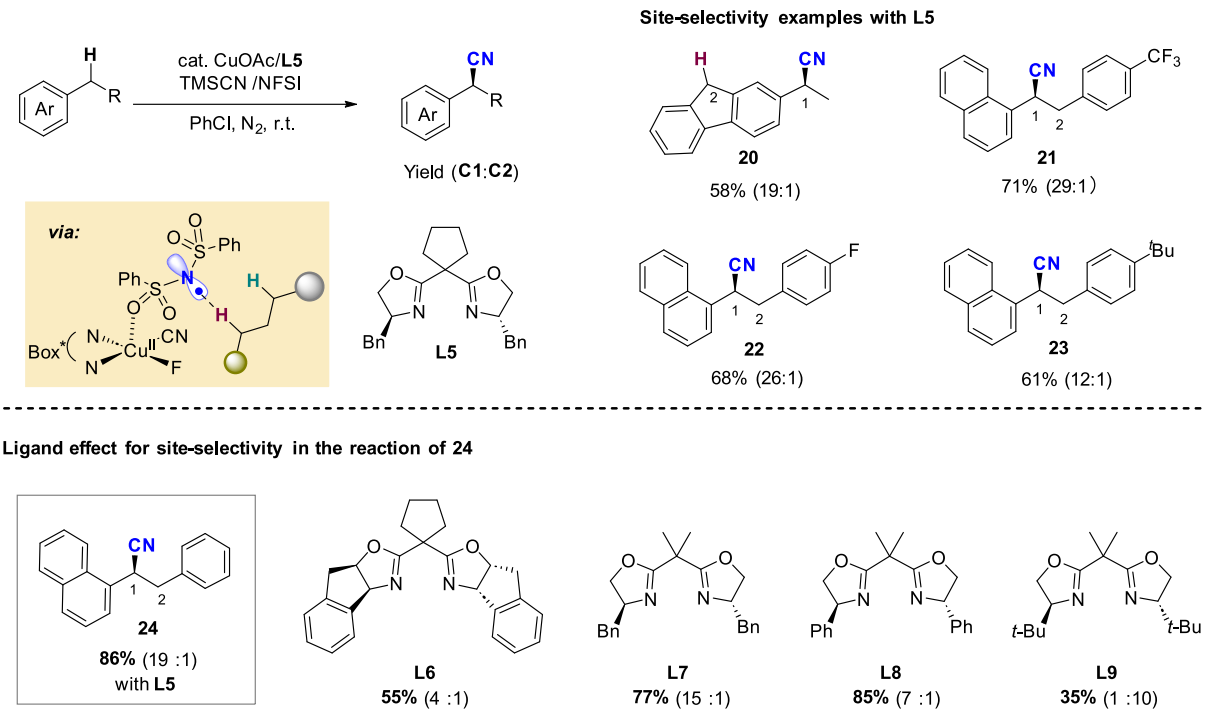

Figure 5. Site- and enantioselective benzylic C−H cyanation.

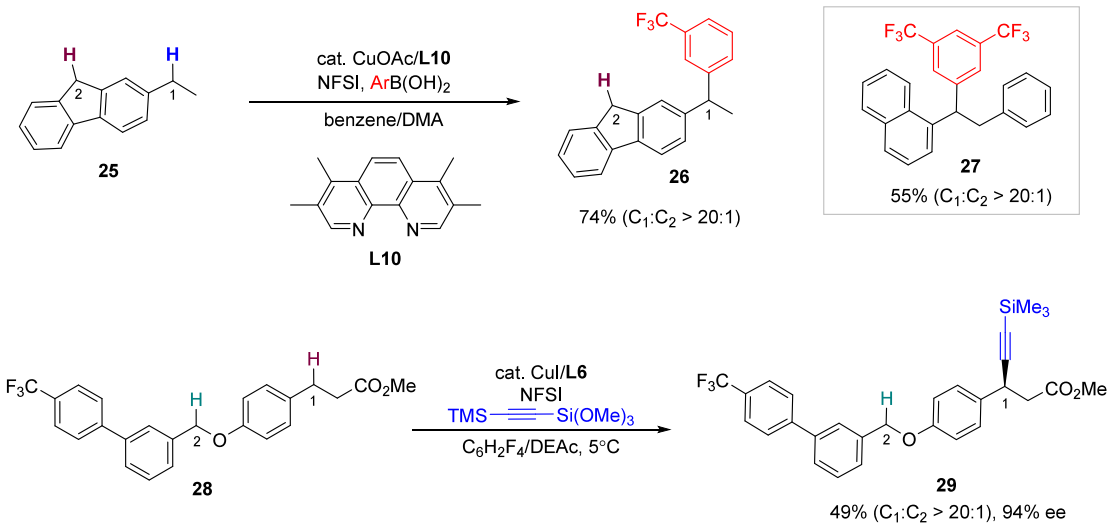

Figure 6. Site- and enantioselective benzylic C−H arylation and alkylation.

vinyl from alkene and aryl radicals from arenes), which is less stabilized unless specific resonance effects are operative (Figure 7A).[45]

Notably, the Cu(II)-NCR system enables good to excellent site-selective C(sp^2)−H abstraction in allenes, overcoming both chemo- and site-selectivity challenges. A key factor in this transformation is the fluoride ligand in the copper complex, which engages in hydrogen bonding with the acidic allylic hydrogen of substrate, facilitating precise HAA via an exquisite transition state (Figure 7B). This interaction lowers the activation energy (ΔG) for selective C(sp^2)−H abstraction, effectively distinguishing between allenic C(sp^2)−H and allenylic C(sp^3)−H bonds despite their nearly identical bond dissociation energies.

The utility of this Cu(II)-NCR system is exemplified by its application in direct allenic C−H functionalization using NFAS in conjunction with a tailored ligand system. The reaction delivers allenyl nitriles with high site-selectivity, achieving C(sp^2):C(sp^3) ratios ranging from 2.4:1 to 5.4:1. Further optimization, employing *t*-BuOH as the solvent and (**L1**)CuOAc as the catalyst, enhanced the selectivity to an impressive 12:1 (Figure 7B).[45a] In contrast, replacing N−F reagents with oxygen-based radical precursors, such as TBHP, resulted in a complete loss of site-selectivity (Csp^2:Csp^3 = 1:1), highlighting the critical role of FCu(II)-NCR interactions in directing HAA, distinct from simple steric-based site recognition. More important, the explored catalytic system exhibits broad substrate scope with excellent site-selectivity, even with various out competing sp^3 C−H bonds (e.g., benzylic, allylic, or those adjacent to heteroatoms). Beyond C(sp^2)−H cyanation, this mechanistic advantage extends to site-selective arylation and alkynylation of allenes.[45b] By

https://doi.org/10.1021/jacs.5c07456
J. Am. Chem. Soc. XXXX, XXX, XXX−XXX

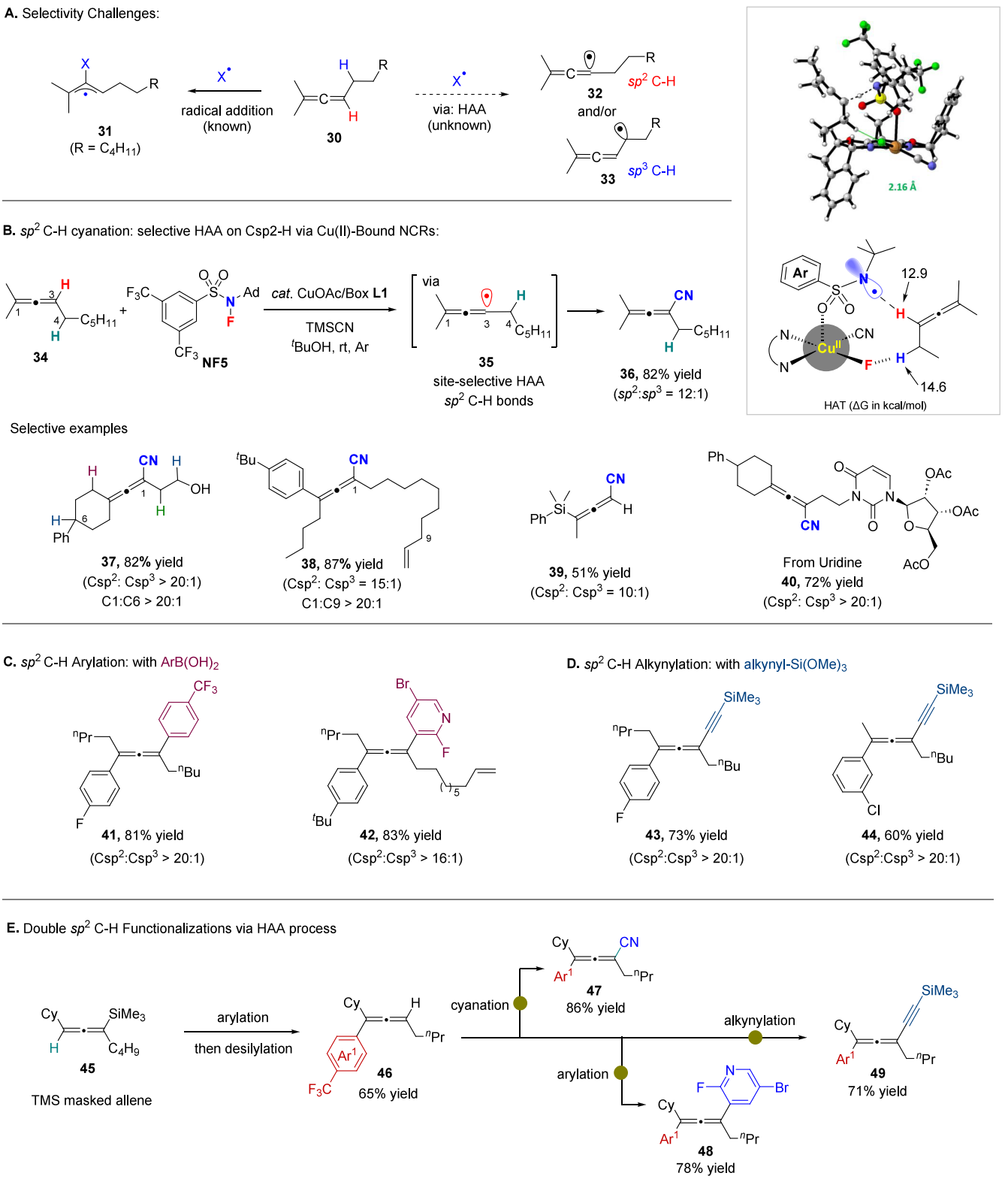

Figure 7. Site- and enantioselective allenylic C−H functionalization. Note: NCR with ^{t}Bu group was used as a simplified model in the DFT calculation.

leveraging a copper-catalyzed radical relay with aryl boronic acids or trimethoxysilyl-substituted alkynes as carbon nucleophiles and electrophilic N−F reagents as NCR precursors, exceptional site-selectivity was achieved. Functionalization occurred predominantly at the allenic C(sp^2)−H site, with selectivity ratios exceeding 20:1 (Figure 7C-7D). Even in substrates containing multiple allylic C(sp^3)−H bonds, the C(sp^2):C(sp^3) selectivity remained high (6:1 to 12:1) in sterically demanding systems. Moreover, with TMS-protected allenes, highly site-selective double C(sp^2)−H functionalization was achieved, providing a robust route to tetra-substituted allene synthesis (Figure 7E).

https://doi.org/10.1021/jacs.5c07456
J. Am. Chem. Soc. XXXX, XXX, XXX−XXX

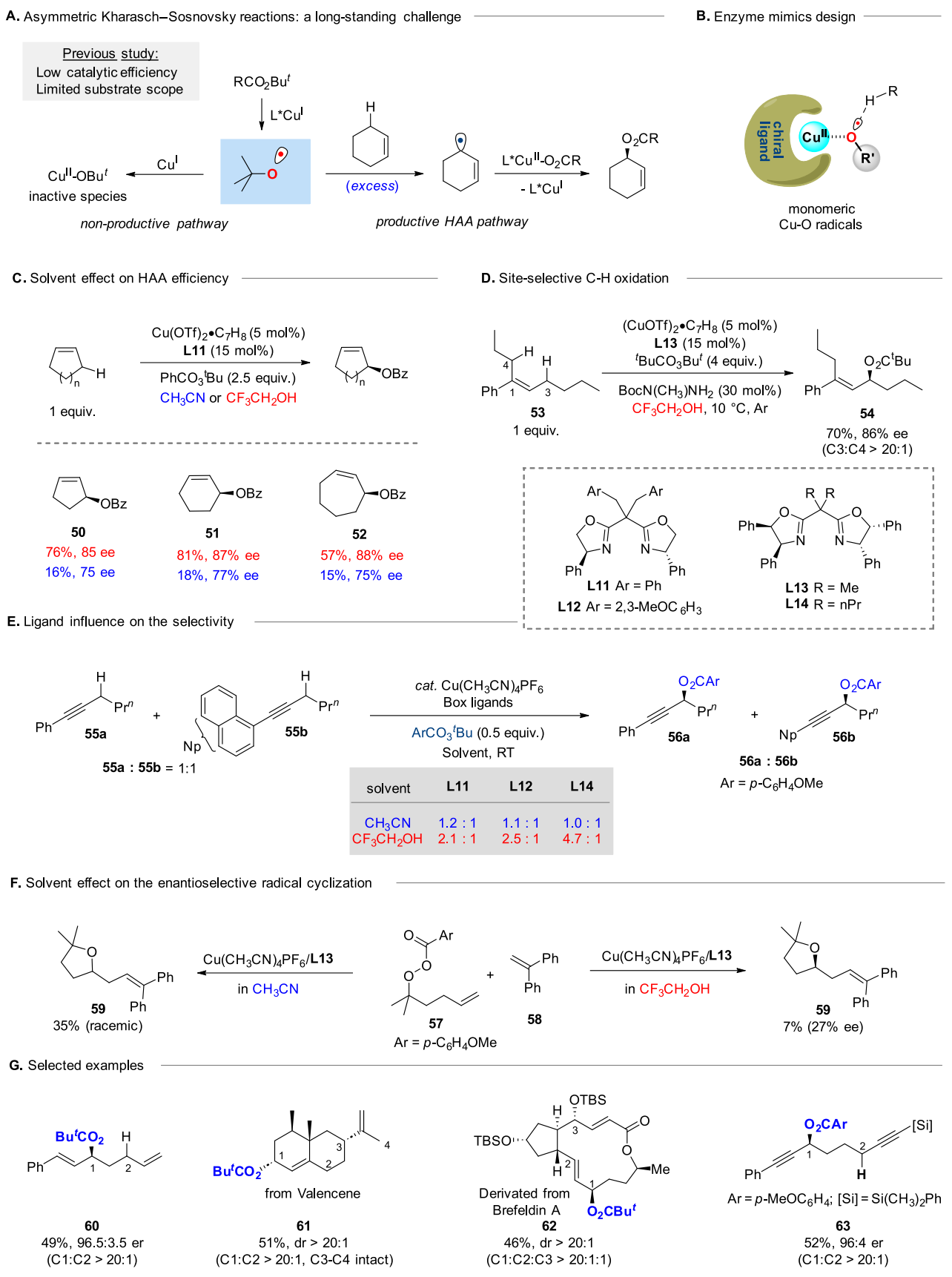

Figure 8. Site- and enantioselective allylic and propargylic C−H oxidation via a Cu(II)-bound *tert*-butoxy radical.

https://doi.org/10.1021/jacs.5c07456
J. Am. Chem. Soc. XXXX, XXX, XXX−XXX

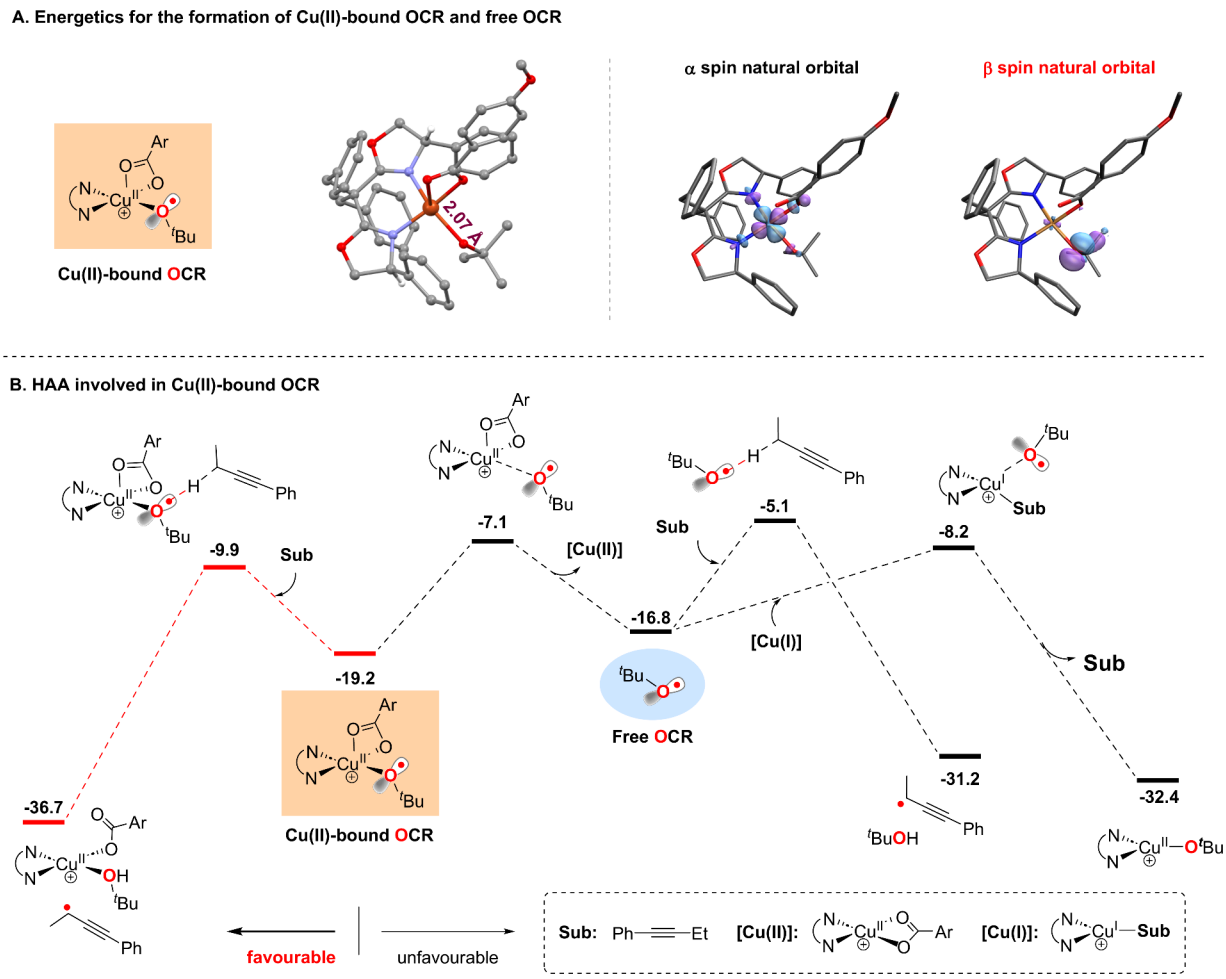

Figure 9. DFT calculation on the structures and reactivities of Cu(II)-bound *tert*-butoxy radical in CF_3CH_2OH.

Copper(II)-Bound OCRs. The Kharasch−Sosnovsky (K−S) reaction, a cornerstone copper-catalyzed allylic oxidation, represents a powerful tool for sp^3 C−H functionalization in organic synthesis.[46] Despite its broad utility, asymmetric variants of this reaction have historically faced significant challenges, including limited substrate scope, modest enantioselectivity, and inefficiencies necessitating excess substrates (Figure 8A).[47] Recent advancements in photoinduced strategies have reinvigorated efforts to address these limitations.[48−52] In 2023, Kramer and co-workers demonstrated an intermolecular enantioselective benzylic C−H amination using dual copper and photocatalysis, achieving high yields and enantioselectivity with alkylarenes as limiting reagents.[48] Concurrently, Zhou and co-workers developed a cationic copper catalyst system, where the BArF anion proved critical for enhancing both catalytic efficiency and stereocontrol.[49] These innovations were extended to asymmetric allylic and propargylic C−H oxidations by the Kramer,[50] Yu,[51] and Zhou[52] groups, leveraging aryl-substituted alkenes to achieve high efficiency and enantioselectivity. Central to these methodologies is a photoexcited Cu(I) mechanism, where visible-light activation facilitates single-electron transfer (SET) to *tert*-butyl peroxybenzoate (TBPB), generating *tert*-butoxy radicals for HAA. The resulting allylic radicals are trapped by chiral bis(oxazoline)-Cu(II) complexes, forming π-allyl Cu(III) intermediates that undergo stereocontrolled reductive elimination—a marked departure from traditional radical quenching pathways.

A longstanding challenge in asymmetric K−S reactions has been the competitive quenching of *tert*-butoxy radicals by Cu(I), which deactivates the catalyst via Cu(II) byproduct formation (Figure 8A).[32a] Photoinduced strategies circumvent this by promoting O−O bond cleavage in peroxides, effectively lowering Cu(I) concentrations and suppressing undesired side reactions.[53] Nevertheless, controlling site-selectivity in substrates with multiple analogous C−H bonds remains a persistent hurdle. Addressing this, Liu and Lin introduced an enzyme-mimetic system employing Cu(II)-bound *tert*-butoxy radicals as HAA acceptors (Figure 8B).[54] By stabilizing these radicals through direct coordination to Cu(II), nonproductive Cu(I) oxidation is eliminated, enabling efficient HAA even with stoichiometric substrates. Fluorinated alcohols, such as CF_3CH_2OH, play a pivotal role by stabilizing Cu(II)-oxidizing species through hydrogen-bonding networks, as evidenced by stark solvent-dependent reactivity: cyclic alkenes in CF_3CH_2OH afforded products in 57−81% yield with high e.e., whereas reactions in CH_3CN yielded <20% conversion and poor stereocontrol (Figure 8C). Remarkably, this system was extended to acyclic alkenes, achieving unprecedented site-selectivity (Figure 8D), thus bridging a critical gap in the field.

Besides these results, additional experimental and computational studies validate this mechanism on the Cu(II)-bound OCRs. Ligand design further modulates the competitive

https://doi.org/10.1021/jacs.5c07456
J. Am. Chem. Soc. XXXX, XXX, XXX−XXX

propargylic C−H oxidation of **55a** and **55b**; in CF_3CH_2OH, steric tuning of Box ligands shifts propargylic C−H selectivity from 2.1:1 (**L11**) to 4.7:1 (**L14**) (Figure 8E), contrasting with the unselective ∼1:1 ratio in CH_3CN. A tandem radical cyclization confirms Cu(II)-OCR involvement, delivering a cyclized product with 27% ee in CF_3CH_2OH versus racemic mixtures in CH_3CN (Figure 8F). This system features broad substrate scope, which includes aryl- and alkyl-substituted, di- and trisubstituted, cyclic and acyclic alkenes, aryl- and alkyl-substituted alkynes. More important, excellent site-selectivity (>20:1) is achieved, even for the complex substrates, exemplified by late-stage Brefeldin A derivative oxidation (Figure 8G).

DFT calculations reveal that Cu(II)-bound *tert*-butoxy radical formation proceeds via a lower energy barrier in CF_3CH_2OH than in CH_3CN (Figure 9A), while this single-electron transfer (SET) were contributes as rate-determining in both cases. Most important, the Cu(II)-OCR is thermodynamically favored in CF_3CH_2OH ($\Delta G = -2.4$ kcal·mol^{-1} vs free OCR), whereas CH_3CN shifts equilibrium toward free OCRs. Structurally, the Cu(II)-OCR adopts a square pyramidal geometry with a 2.07 Å Cu−OCR bond and a singlet biradical configuration (α spin on Cu, β on OCR), stabilized by antiferromagnetic coupling. Kinetic studies show that HAA ($\Delta G^{\ddagger}$ = 9.3 kcal·mol^{-1}) outcompetes OCR dissociation ($\Delta G^{\ddagger}$ = 12.1 kcal·mol^{-1}), driving selective oxidation (Figure 9B). In contrast, free *tert*-butoxy radicals favor Cu(I) trapping ($\Delta G^{\ddagger}$ = 8.7 kcal·mol^{-1}) over HAA ($\Delta G^{\ddagger}$ = 11.8 kcal·mol^{-1}), aligning with unselective CH_3CN outcomes. Steric hindrance prevents direct Cu(II)-OCR quenching by Cu(I), ensuring catalytic efficiency. Moreover, remarkably distinct from the Cu(II)-bound NCRs, the direct coordination of oxygen of ^{t}BuO radical to the Cu(II) center enhances its HAA ability, where the energy barrier of HAA ($\Delta G^{\ddagger}$ = 9.3 kcal·mol^{-1}) is smaller than that of free *tert*-butoxy radical ($\Delta G^{\ddagger}$ = 11.7 kcal·mol^{-1}). The integration of Cu(II)-bound *tert*-butoxy radicals, stabilized through fluorinated alcohol-enabled hydrogen-bonding networks and ligand-driven steric modulation, resolves long-standing selectivity and efficiency barriers in asymmetric K−S reactions, establishing an enzyme-inspired paradigm for precise, site-selective C−H functionalization across diverse substrates, a transformative advance validated by synergistic experimental and computational mechanistic elucidation.

Iron(III)-Bound Aminyl Radicals. Notably, the strategy of using metal coordination to control site selectivity extends beyond Cu-bound heteroatom radicals. In 2024, Wang and Dang's group reported an elegant study on the highly site-selective arene C−H amination mediated by an iron-bound aminyl radical, demonstrating the potential of Fe-supported radicals in controlling regioselectivity (Figure 10A).[55] Unlike free aminyl radicals, which typically exhibit indiscriminate reactivity, the iron-bound aminyl radical engages in non-covalent interactions with electronically distinct arenes, facilitating precise site-selectivity through substrate chelation. This strategy overcomes the inherent electronic and steric biases governing classical homolytic aromatic substitution, allowing for selective C−H functionalization. Further exploration of iron-bound aminyl radicals in C−H amination revealed their ability to engage a diverse set of nitrogen-containing substrates, including 2-phenylethanols, benzamides, Weinreb amides, and 2-phenylacetamides, yielding *ortho*-selective amination products with high efficiency. The method exhibited

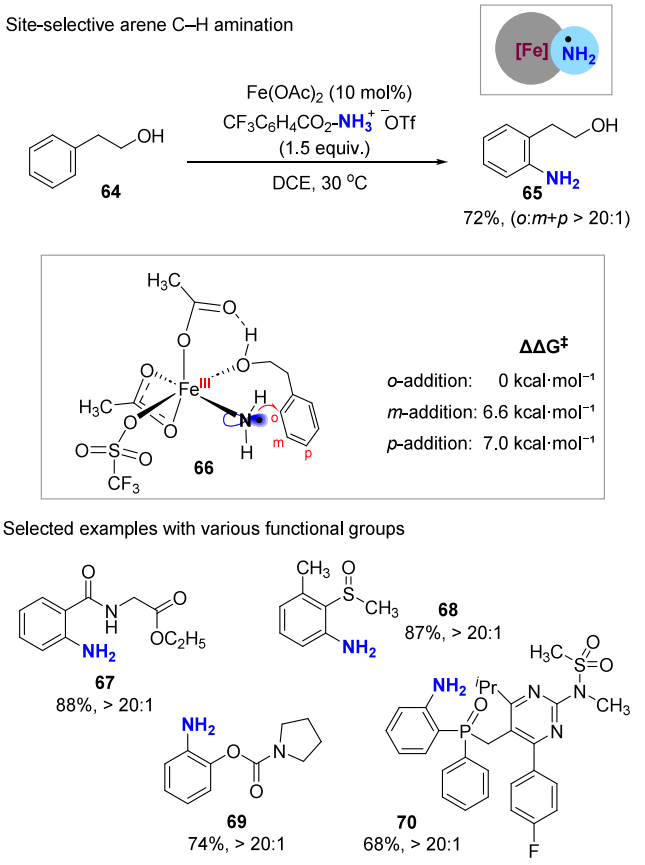

Figure 10. Fe(III)-bound NCRs in site-selective aryl C−H aminations.

broad functional-group tolerance, accommodating halides, boronic esters, and carboxylic acids, thereby facilitating downstream derivatization. Notably, iron-catalyzed amination proved effective even at sterically hindered sites, as demonstrated by the regioselective functionalization of substrates such as 3-phenylpropenamide and carbamates. Beyond simple arenes, the strategy extended to heterocycles and complex drug-like molecules, including sulfonamides and pyrimidines, maintaining consistent site selectivity. The persistence of iron-bound radicals in challenging substrates, such as pyridines and pyrazoles, underscores their unique reactivity profile, distinct from conventional transition-metal-catalyzed amination. The mild reaction conditions and high regioselectivity position iron-bound aminyl radicals as a valuable platform for late-stage functionalization and complex molecule synthesis. Beyond direct C−H amination, Wang and co-workers recently developed an iron-catalyzed NH transfer strategy that enables dynamic kinetic resolution (DKR) of sulfoxides, yielding enantioenriched NH-sulfoximines through a dual catalytic approach.[56] This work firmly establishes iron-bound N-centered radicals as key intermediates in asymmetric catalysis and highlights the potential of metal coordination in tuning heteroatom-centered radical reactivity beyond copper systems.

■ OUTLOOK AND PERSPECTIVE

Metal-bound heteroatom radicals have emerged as powerful yet underexplored intermediates in C−H functionalization, offering unique opportunities for precise reactivity control. While Cu(II)-bound radicals have been demonstrated in only a

https://doi.org/10.1021/jacs.5c07456
J. Am. Chem. Soc. XXXX, XXX, XXX−XXX

handful of C−H functionalization reactions, their full synthetic potential remains largely untapped. Expanding their utility could revolutionize site- and enantioselective functionalization strategies, unlocking new reaction manifolds that extend beyond current methodologies.

Conceptually, metal-bound radicals present a versatile platform for diverse radical transformations, including selective halogen atom abstraction, radical scission, and radical-mediated cross-coupling. Beyond C−H functionalization, their controlled reactivity could be harnessed in radical additions to carbon−carbon double bonds,[57,58] ring-opening reactions, and even complex molecular editing strategies. The ability to fine-tune reactivity through ligand design and metal coordination enables unprecedented control over selectivity, efficiency, and reaction outcomes. By tailoring steric and electronic environments, chemists can develop strategies to stabilize previously elusive intermediates and dictate radical behavior with precision.

It is important to clarify that the C(sp^3)−H bonds targeted in the current systems refer broadly to bonds with similar structural and electronic characteristics—those that are relatively more reactive within a molecule. While our work primarily focuses on relatively activated C(sp^3)−H bonds, we have demonstrated that in substrates containing multiple similar C−H bonds, selective functionalization can still be achieved. Truly inert C(sp^3)−H bonds, however, remain beyond the reach of the current catalytic systems, largely due to the challenges in efficient hydrogen atom abstraction. Addressing this limitation is a critical goal for future development, and active research efforts in our laboratory are directed toward designing more potent metal−radical catalysts capable of engaging these less reactive bonds. We hope that this Perspective will inspire further interest and collective effort from the broader community to tackle this outstanding challenge.

Nevertheless, significant hurdles remain. Advancing this field requires in-depth mechanistic studies to elucidate the structure, dynamics, and reactivity of metal-bound radicals. Fundamental investigations, including kinetic isotope effect (KIE) studies, spectroscopic in situ characterization, and computational DFT calculations, are essential to map out their mechanistic intricacies. The isolation of key intermediates will provide critical insights into their stability and reactivity profiles, guiding the design of new catalytic systems. Furthermore, beyond the well-studied Cu(II)-bound nitrogen- and oxygen-centered radicals, other coordination modes remain largely unexplored, presenting untapped opportunities for reactivity modulation.

Looking ahead, metal-bound radicals hold transformative potential in synthetic chemistry. By leveraging their unique properties, chemists can address long-standing challenges in reactivity and selectivity, paving the way for innovative and more sustainable synthetic methodologies. With continued exploration, this emerging paradigm has the power to reshape modern organic synthesis, offering new solutions for constructing complex molecules with unprecedented precision and efficiency.

AUTHOR INFORMATION

Corresponding Author

Guosheng Liu − *New Cornerstone Science Laboratory, State Key Laboratory of Organometallic Chemistry, and Shanghai Hongkong Joint Laboratory in Chemical Synthesis, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, University of Chinese Academy of Sciences, Shanghai 200032, China*; orcid.org/0000-0003-0572-9370; Email: gliu@mail.sioc.ac.cn

Authors

Jiayuan Li − *New Cornerstone Science Laboratory, State Key Laboratory of Organometallic Chemistry, and Shanghai Hongkong Joint Laboratory in Chemical Synthesis, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, University of Chinese Academy of Sciences, Shanghai 200032, China*

Tobias Blockhaus − *New Cornerstone Science Laboratory, State Key Laboratory of Organometallic Chemistry, and Shanghai Hongkong Joint Laboratory in Chemical Synthesis, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, University of Chinese Academy of Sciences, Shanghai 200032, China*

Complete contact information is available at: https://pubs.acs.org/10.1021/jacs.5c07456

Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

We thank all our group members at SIOC, particularly those involved in the studies of copper-bound radicals in C−H functionalizations, for their invaluable intellectual and experimental contributions. We are grateful for financial support provided by the National Key R&D Program of China (2021YFA1500100), the National Nature Science Foundation of China (Nos. 22331012, 92256301, 21821002, and 22171279), and the Strategic Priority Research Program of the Chinese Academy of Sciences (No. XDB0610000). G.L. acknowledges support from the Tencent Foundation through the New Cornerstone Science Foundation. G.L. thanks Dr. Tilong Yang and Prof. Zhenyang Lin at Hong Kong University of Science and Technology for their beneficial collaborations on this topic.

REFERENCES

(1) (a) Bergman, R. G. C−H Activation. *Nature* **2007**, *446*, 391−393. (b) Curran, D. P.; Porter, N.; Giese, B. Stereochemistry of Radical Reactions: Concepts, Guidelines, and Synthetic Applications. John Wiley & Sons: Weinheim; New York, 2008. (c) Giri, R.; Shi, B. F.; Engle, K. M.; Maugel, N.; Yu, J.-Q. Transition Metal-Catalyzed C-H Activation Reactions: Diastereoselectivity and Enantioselectivity. *Chem. Soc. Rev.* **2009**, *38*, 3242−3272. (d) Colby, D. A.; Bergman, R. G.; Ellman, J. A. Rhodium-Catalyzed C−C Bond Formation Via Heteroatom-Directed C−H Bond Activation. *Chem. Rev.* **2010**, *110*, 624−655. (e) Lyons, T. W.; Sanford, M. S. Palladium-Catalyzed Ligand-Directed C−H Functionalization Reactions. *Chem. Rev.* **2010**, *110*, 1147−1169. (f) Newhouse, T.; Baran, P. S. If C-H Bonds Could Talk: Selective C-H Bond Oxidation. *Angew. Chem., Int. Ed.* **2011**, *50*, 3362−3374. (g) Sun, C.-L.; Li, B.-J.; Shi, Z.-J. Direct C-H Transformation Via Iron Catalysis. *Chem. Rev.* **2011**, *111*, 1293−1314. (h) Wang, T.; Jiao, N. Direct Approaches to Nitriles Via Highly Efficient Nitrogenation Strategy through C-H or C-C Bond Cleavage. *Acc. Chem. Res.* **2014**, *47*, 1137−1145. (i) 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. (j) Parasram, M.; Gevorgyan, V. Silicon-Tethered Strategies for C-H Functionalization Reactions. *Acc. Chem. Res.* **2017**, *50*, 2038−2053.

(2) (a) Ackermann, L. Carboxylate-Assisted Ruthenium-Catalyzed Alkyne Annulations by C-H/Het-H Bond Functionalizations. *Acc.*

https://doi.org/10.1021/jacs.5c07456
J. Am. Chem. Soc. XXXX, XXX, XXX−XXX

Chem. Res. **2014**, *47*, 281−295. (b) Tang, S.; Liu, K.; Liu, C.; Lei, A. Olefinic C-H Functionalization through Radical Alkenylation. *Chem. Soc. Rev.* **2015**, *44*, 1070−1082. (c) Hartwig, J. F.; Larsen, M. A. Undirected, Homogeneous C-H Bond Functionalization: Challenges and Opportunities. *ACS Cent. Sci.* **2016**, *2*, 281−292. (d) Yang, Y.-F.; Hong, X.; Yu, J.-Q.; Houk, K. N. Experimental-Computational Synergy for Selective Pd(II)-Catalyzed C-H Activation of Aryl and Alkyl Groups. *Acc. Chem. Res.* **2017**, *50*, 2853−2860. (e) Karimov, R. R.; Hartwig, J. F. Transition-Metal-Catalyzed Selective Functionalization of C(sp^3)-H Bonds in Natural Products. *Angew. Chem., Int. Ed.* **2018**, *57*, 4234−4241. (f) Meng, G.; Lam, N. Y. S.; Lucas, E. L.; Saint-Denis, T. G.; Verma, P.; Chekshin, N.; Yu, J.-Q. Achieving Site-Selectivity for C-H Activation Processes Based on Distance and Geometry: A Carpenter's Approach. *J. Am. Chem. Soc.* **2020**, *142*, 10571−10591. (g) Liu, C.-X.; Yin, S.-Y.; Zhao, F.; Yang, H.; Feng, Z.; Gu, Q.; You, S.-L. Rhodium-Catalyzed Asymmetric C-H Functionalization Reactions. *Chem. Rev.* **2023**, *123*, 10079−10134.

(3) (a) Davies, H. M. Recent Advances in Catalytic Enantioselective Intermolecular C-H Functionalization. *Angew. Chem., Int. Ed.* **2006**, *45*, 6422−6425. (b) Davies, H. M.; 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. (c) Davies, H. M. L.; Liao, K. Dirhodium Tetracarboxylates as Catalysts for Selective Intermolecular C-H Functionalization. *Nat. Rev. Chem.* **2019**, *3*, 347−360.

(4) (a) Borie, C.; Ackermann, L.; Nechab, M. Enantioselective Syntheses of Indanes: From Organocatalysis to C-H Functionalization. *Chem. Soc. Rev.* **2016**, *45*, 1368−1386. (b) Qin, Y.; Zhu, L.; Luo, S. Organocatalysis in Inert C-H Bond Functionalization. *Chem. Rev.* **2017**, *117*, 9433−9520. (c) Lasso, J. D.; Castillo-Pazos, D. J.; Li, C.-J. Green Chemistry Meets Medicinal Chemistry: A Perspective on Modern Metal-Free Late-Stage Functionalization Reactions. *Chem. Soc. Rev.* **2021**, *50*, 10955−10982.

(5) (a) Lewis, J. C.; Coelho, P. S.; Arnold, F. H. Enzymatic Functionalization of Carbon-Hydrogen Bonds. *Chem. Soc. Rev.* **2011**, *40*, 2003−2021. (b) Yang, Y.; Arnold, F. H. Navigating the Unnatural Reaction Space: Directed Evolution of Heme Proteins for Selective Carbene and Nitrene Transfer. *Acc. Chem. Res.* **2021**, *54*, 1209−1225. (c) Mondal, D.; Snodgrass, H. M.; Gomez, C. A.; Lewis, J. C. Non-Native Site-Selective Enzyme Catalysis. *Chem. Rev.* **2023**, *123*, 10381−10431.

(6) (a) Wencel-Delord, J.; Glorius, F. C-H Bond Activation Enables the Rapid Construction and Late-Stage Diversification of Functional Molecules. *Nat. Chem.* **2013**, *5*, 369−375. (b) Brustad, E. M. C-H Activation: New Recipes for Biocatalysis. *Nat. Chem. Biol.* **2014**, *10*, 170−171.

(7) (a) Campos, K. R. Direct sp^3 C-H Bond Activation Adjacent to Nitrogen in Heterocycles. *Chem. Soc. Rev.* **2007**, *36*, 1069−1084. (b) Lu, Q.; Glorius, F. Radical Enantioselective C(sp^3)-H Functionalization. *Angew. Chem., Int. Ed.* **2017**, *56*, 49−51. (c) Wang, X.; Studer, A. Iodine(III) Reagents in Radical Chemistry. *Acc. Chem. Res.* **2017**, *50*, 1712−1724. (d) Szpera, R.; Moseley, D. F. J.; Smith, L. B.; Sterling, A. J.; Gouverneur, V. The Fluorination of C-H Bonds: Developments and Perspectives. *Angew. Chem., Int. Ed.* **2019**, *58*, 14824−14848. (e) Nobile, E.; Castanheiro, T.; Besset, T. Radical-Promoted Distal C-H Functionalization of C(sp^3) Centers with Fluorinated Moieties. *Angew. Chem., Int. Ed.* **2021**, *60*, 12170−12191. (f) Ju, M.; Lu, Z.; Novaes, L. F. T.; Martinez Alvarado, J. I.; Lin, S. Frustrated Radical Pairs in Organic Synthesis. *J. Am. Chem. Soc.* **2023**, *145*, 19478−19489.

(8) (a) Chen, B.; Wu, L.-Z.; Tung, C.-H. Photocatalytic Activation of Less Reactive Bonds and Their Functionalization Via Hydrogen-Evolution Cross-Couplings. *Acc. Chem. Res.* **2018**, *51*, 2512−2523. (b) Yan, D.-M.; Chen, J.-R.; Xiao, W.-J. New Roles for Photoexcited Eosin Y in Photochemical Reactions. *Angew. Chem., Int. Ed.* **2019**, *58*, 378−380. (c) Kariofillis, S. K.; Doyle, A. G. Synthetic and Mechanistic Implications of Chlorine Photoelimination in Nickel/Photoredox C(sp^3)-H Cross-Coupling. *Acc. Chem. Res.* **2021**, *54*, 988−1000. (d) Bellotti, P.; Huang, H.-M.; Faber, T.; Glorius, F. Photocatalytic Late-Stage C-H Functionalization. *Chem. Rev.* **2023**, *123*, 4237−4352. (e) Zhang, J.; Rueping, M. Metallaphotoredox Catalysis for sp^3 C-H Functionalizations through Hydrogen Atom Transfer (HAT). *Chem. Soc. Rev.* **2023**, *52*, 4099−4120. (f) An, Q.; Chang, L.; Pan, H.; Zuo, Z. Ligand-to-Metal Charge Transfer (LMCT) Catalysis: Harnessing Simple Cerium Catalysts for Selective Functionalization of Inert C-H and C-C Bonds. *Acc. Chem. Res.* **2024**, *57*, 2915−2927. (g) Wang, P.-Z.; Zhang, B.; Xiao, W.-J.; Chen, J.-R. Photocatalysis Meets Copper Catalysis: A New Opportunity for Asymmetric Multicomponent Radical Cross-Coupling Reactions. *Acc. Chem. Res.* **2024**, *57*, 3433−3448. (h) Xu, G.-Q.; Wang, W.-D.; Xu, P.-F. Photocatalyzed Enantioselective Functionalization of C(sp^3)-H Bonds. *J. Am. Chem. Soc.* **2024**, *146*, 1209−1223.

(9) (a) Yi, H.; Zhang, G.; Wang, H.; Huang, Z.; Wang, J.; Singh, A. K.; Lei, A. Recent Advances in Radical C-H Activation/Radical Cross-Coupling. *Chem. Rev.* **2017**, *117*, 9016−9085. (b) Xiong, P.; Xu, H.-C. Chemistry with Electrochemically Generated N-Centered Radicals. *Acc. Chem. Res.* **2019**, *52*, 3339−3350. (c) Wang, F.; Stahl, S. S. Electrochemical Oxidation of Organic Molecules at Lower Overpotential: Accessing Broader Functional Group Compatibility with Electron-Proton Transfer Mediators. *Acc. Chem. Res.* **2020**, *53*, 561−574. (d) Novaes, L. F. T.; Liu, J.; Shen, Y.; Lu, L.; Meinhardt, J. M.; Lin, S. Electrocatalysis as an Enabling Technology for Organic Synthesis. *Chem. Soc. Rev.* **2021**, *50*, 7941−8002. (e) Yuan, Y.; Yang, J.; Lei, A. Recent Advances in Electrochemical Oxidative Cross-Coupling with Hydrogen Evolution Involving Radicals. *Chem. Soc. Rev.* **2021**, *50*, 10058−10086. (f) Murray, P. R. D.; Cox, J. H.; Chiappini, N. D.; Roos, C. B.; McLoughlin, E. A.; Hejna, B. G.; Nguyen, S. T.; Ripberger, H. H.; Ganley, J. M.; Tsui, E.; Shin, N. Y.; Koronkiewicz, B.; Qiu, G.; Knowles, R. R. Photochemical and Electrochemical Applications of Proton-Coupled Electron Transfer in Organic Synthesis. *Chem. Rev.* **2022**, *122*, 2017−2291. (g) Zhang, W.; Guan, W.; Martinez Alvarado, J. I.; Novaes, L. F. T.; Lin, S. Deep Electroreductive Chemistry: Harnessing Carbon- and Silicon-Based Reactive Intermediates in Organic Synthesis. *ACS Catal.* **2023**, *13*, 8038−8048.

(10) (a) Romero, N. A.; Margrey, K. A.; Tay, N. E.; Nicewicz, D. A. Site-Selective Arene C-H Amination Via Photoredox Catalysis. *Science* **2015**, *349*, 1326−1330. (b) Guan, H.; Sun, S.; Mao, Y.; Chen, L.; Lu, R.; Huang, J.; Liu, L. Iron(II)-Catalyzed Site-Selective Functionalization of Unactivated C(sp^3)-H Bonds Guided by Alkoxyl Radicals. *Angew. Chem., Int. Ed.* **2018**, *57*, 11413−11417. (c) Xu, J.; Li, R.; Ma, Y.; Zhu, J.; Shen, C.; Jiang, H. Site-Selective α-C(sp^3)-H Arylation of Dialkylamines Via Hydrogen Atom Transfer Catalysis-Enabled Radical Aryl Migration. *Nat. Commun.* **2024**, *15*, 6791.

(11) Shen, Y.; Funez-Ardoiz, I.; Schoenebeck, F.; Rovis, T. Site-Selective A-C-H Functionalization of Trialkylamines Via Reversible Hydrogen Atom Transfer Catalysis. *J. Am. Chem. Soc.* **2021**, *143*, 18952−18959.

(12) Chen, K.; Zeng, Q.; Xie, L.; Xue, Z.; Wang, J.; Xu, Y. Functional-Group Translocation of Cyano Groups by Reversible C-H Sampling. *Nature* **2023**, *620*, 1007−1012.

(13) Wang, M.; Huang, Y.; Hu, P. Terminal C(sp^3)-H Borylation through Intermolecular Radical Sampling. *Science* **2024**, *383*, 537−544.

(14) (a) Wang, Y.; Carder, H. M.; Wendlandt, A. E. Synthesis of Rare Sugar Isomers through Site-Selective Epimerization. *Nature* **2020**, *578*, 403−408. (b) Zhang, Y.-A.; Palani, V.; Seim, A. E.; Wang, Y.; Wang, K. J.; Wendlandt, A. E. Stereochemical Editing Logic Powered by the Epimerization of Unactivated Tertiary Stereocenters. *Science* **2022**, *378*, 383−390. (c) Carder, H. M.; Occhialini, G.; Bistoni, G.; Riplinger, C.; Kwan, E. E.; Wendlandt, A. E. The Sugar Cube: Network Control and Emergence in Stereoediting Reactions. *Science* **2024**, *385*, 456−463. (d) Wang, Y.; Hu, X.; Morales-Rivera, C. A.; Li, G.-X.; Huang, X.; He, G.; Liu, P.; Chen, G. Epimerization of Tertiary Carbon Centers via Reversible Radical Cleavage of Unactivated C(sp3)−H Bonds. *J. Am. Chem. Soc.* **2018**, *140*, 9678−9684.

https://doi.org/10.1021/jacs.5c07456
J. Am. Chem. Soc. XXXX, XXX, XXX−XXX

(15) Shin, N. Y.; Ryss, J. M.; Zhang, X.; Miller, S. J.; Knowles, R. R. Light-Driven Deracemization Enabled by Excited-State Electron Transfer. *Science* **2019**, *366*, 364−369.
(16) (a) Iglhaut, M.; Bach, T. Stereochemical Editing at sp^3-Hybridized Carbon Centers by Reversible, Photochemically Triggered Hydrogen Atom Transfer. *Acc. Chem. Res.* **2025**, *58*, 777−786. (b) Holzl-Hobmeier, A.; Bauer, A.; Silva, A. V.; Huber, S. M.; Bannwarth, C.; Bach, T. Catalytic Deracemization of Chiral Allenes by Sensitized Excitation with Visible Light. *Nature* **2018**, *564*, 240−243.
(17) (a) Shen, Z.; Walker, M. M.; Chen, S.; Parada, G. A.; Chu, D. M.; Dongbang, S.; Mayer, J. M.; Houk, K. N.; Ellman, J. A. General Light-Mediated, Highly Diastereoselective Piperidine Epimerization: From Most Accessible to Most Stable Stereoisomer. *J. Am. Chem. Soc.* **2021**, *143*, 126−131. (b) Lewis, J. C.; Bergman, R. G.; Ellman, J. A. Direct Functionalization of Nitrogen Heterocycles Via Rh-Catalyzed C-H Bond Activation. *Acc. Chem. Res.* **2008**, *41*, 1013−1025.
(18) (a) Herron, A. N.; Liu, D.; Xia, G.; Yu, J.-Q. δ-C-H Mono- and Dihalogenation of Alcohols. *J. Am. Chem. Soc.* **2020**, *142*, 2766−2770. (b) Salamone, M.; Bietti, M. Tuning Reactivity and Selectivity in Hydrogen Atom Transfer from Aliphatic C-H Bonds to Alkoxyl Radicals: Role of Structural and Medium Effects. *Acc. Chem. Res.* **2015**, *48*, 2895−2903. (c) Wu, X.; Wang, M.; Huan, L.; Wang, D.; Wang, J.; Zhu, C. Tertiary-Alcohol-Directed Functionalization of Remote C(sp^3)-H Bonds by Sequential Hydrogen Atom and Heteroaryl Migrations. *Angew. Chem., Int. Ed.* **2018**, *57*, 1640−1644. (d) An, Q.; Xing, Y.-Y.; Pu, R.; Jia, M.; Chen, Y.; Hu, A.; Zhang, S.-Q.; Yu, N.; Du, J.; Zhang, Y.; Chen, J.; Liu, W.; Hong, X.; Zuo, Z. Identification of Alkoxy Radicals as Hydrogen Atom Transfer Agents in Ce-Catalyzed C-H Functionalization. *J. Am. Chem. Soc.* **2023**, *145*, 359−376. (e) Zhang, J.; Li, Y.; Zhang, F.; Hu, C.; Chen, Y. Generation of Alkoxyl Radicals by Photoredox Catalysis Enables Selective C(sp^3)-H Functionalization under Mild Reaction Conditions. *Angew. Chem., Int. Ed.* **2016**, *55*, 1872−1875. (f) Bao, X.; Wang, Q.; Zhu, J. Dual Photoredox/Copper Catalysis for the Remote C(sp^3)-H Functionalization of Alcohols and Alkyl Halides by N-Alkoxypyridinium Salts. *Angew. Chem., Int. Ed.* **2019**, *58*, 2139−2143. (g) An, Q.; Wang, Z.; Chen, Y.; Wang, X.; Zhang, K.; Pan, H.; Liu, W.; Zuo, Z. Cerium-Catalyzed C-H Functionalizations of Alkanes Utilizing Alcohols as Hydrogen Atom Transfer Agents. *J. Am. Chem. Soc.* **2020**, *142*, 6216−6226. (h) Finis, D. S.; Nicewicz, D. A. Alkoxy Radical Generation Mediated by Sulfoxide Cation Radicals for Alcohol-Directed Aliphatic C-H Functionalization. *J. Am. Chem. Soc.* **2024**, *146*, 16830−16837.
(19) (a) Entgelmeier, L. M.; Mori, S.; Sendo, S.; Yamaguchi, R.; Suzuki, R.; Yanai, T.; Garcia Mancheno, O.; Ohmatsu, K.; Ooi, T. Zwitterionic Acridinium Amidate: A Nitrogen-Centered Radical Catalyst for Photoinduced Direct Hydrogen Atom Transfer. *Angew. Chem., Int. Ed.* **2024**, *63*, No. e202404890. (b) Jiang, Y.; Li, H.; Tang, H.; Zhang, Q.; Yang, H.; Pan, Y.; Zou, C.; Zhang, H.; Walsh, P. J.; Yang, X. Visible-Light-Driven Net-1,2-Hydrogen Atom Transfer of Amidyl Radicals to Access Beta-Amido Ketone Derivatives. *Chem. Sci.* **2025**, *16*, 962−969. (c) Lee, W.; Jung, S.; Kim, M.; Hong, S. Site-Selective Direct C-H Pyridylation of Unactivated Alkanes by Triplet Excited Anthraquinone. *J. Am. Chem. Soc.* **2021**, *143*, 3003−3012. (d) Wang, L.; Xia, Y.; Bergander, K.; Studer, A. Remote Site-specific Radical Alkynylation of Unactivated C-H Bonds. *Org. Lett.* **2018**, *20*, 5817−5820. (e) 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. (f) Choi, G. J.; Zhu, Q.; Miller, D. C.; Gu, C. J.; Knowles, R. R. Catalytic Alkylation of Remote C-H Bonds Enabled by Proton-Coupled Electron Transfer. *Nature* **2016**, *539*, 268−271.
(20) (a) Bonciolini, S.; Noël, T.; Capaldo, L. Synthetic Applications of Photocatalyzed Halogen-Radical Mediated Hydrogen Atom Transfer for C-H Bond Functionalization. *Eur. J. Org. Chem.* **2022**, *34*, No. e202200417. (b) Wang, Q.-L.; Sun, Z.; Huang, H.; Mao, G.; Deng, G.-J. Stoichiometric Couplings of Methylarenes through Visible-Light-Induced Bromo Radical Formation from Aryl Halides. *Green Chem.* **2022**, *24*, 3293−3299. (c) Qu, C.-H.; Li, S.-T.; Liu, J.-B.; Chen, Z.-Z.; Tang, D.-Y.; Li, J.-H.; Song, G.-T. Site-Selective Access to Functionalized Pyrroloquinoxalinones Via H-Atom Transfer from N Horizontal Linec(sp^2)-H Bonds of Quinoxalinones. *Org. Lett.* **2024**, *26*, 9244−9250. (d) Cusumano, A. Q.; Chaffin, B. C.; Doyle, A. G. Mechanism of Ni-Catalyzed Photochemical Halogen Atom-Mediated C(sp^3)-H Arylation. *J. Am. Chem. Soc.* **2024**, *146*, 15331−15344. (e) Shaikh, M.; Rubalcaba, K.; Yan, Y. Halide Perovskite Induces Halogen/Hydrogen Atom Transfer (XAT/HAT) for Allylic C-H Amination. *Angew. Chem., Int. Ed.* **2025**, *64*, No. e202413012. (f) Ackerman, L. K. G.; Martinez Alvarado, J. I.; Doyle, A. G. Direct C-C Bond Formation from Alkanes Using Ni-Photoredox Catalysis. *J. Am. Chem. Soc.* **2018**, *140*, 14059−14063. (g) Itabashi, Y.; Asahara, H.; Ohkubo, K. Chlorine-Radical-Mediated C-H Oxygenation Reaction under Light Irradiation. *Chem. Commun.* **2023**, *59*, 7506−7517.
(21) (a) Feng, Y.; Liu, L.; Wang, J.-T.; Zhao, S.-W.; Guo, Q.-X. Homolytic C-H and N-H Bond Dissociation Energies of Strained Organic Compounds. *J. Org. Chem.* **2004**, *69*, 3129−3138. (b) Lucarini, M.; Pedrielli, P.; Pedulli, G. F.; Valgimigli, L.; Gigmes, D.; Tordo, P. Bond Dissociation Energies of the N-H Bond and Rate Constants for the Reaction with Alkyl, Alkoxyl, and Peroxyl Radicals of Phenothiazines and Related Compounds. *J. Am. Chem. Soc.* **1999**, *121*, 11546−11553.
(22) (a) Solà, M.; Toro-Labbé, A. The Hammond Postulate and the Principle of Maximum Hardness in Some Intramolecular Rearrangement Reactions. *J. Phys. Chem. A* **1999**, *103*, 8847−8852. (b) Manz, T. A.; Sholl, D. S. A Dimensionless Reaction Coordinate for Quantifying the Lateness of Transition States. *J. Comput. Chem.* **2010**, *31*, 1528−1541. (c) Politzer, P.; Reimers, J. R.; Murray, J. S.; Toro-Labbé, A. Reaction Force and Its Link to Diabatic Analysis: A Unifying Approach to Analyzing Chemical Reactions. *J. Phys. Chem. Lett.* **2010**, *1*, 2858−2862.
(23) Carestia, A. M.; Ravelli, D.; Alexanian, E. J. Reagent-Dictated Site Selectivity in Intermolecular Aliphatic C-H Functionalizations Using Nitrogen-Centered Radicals. *Chem. Sci.* **2018**, *9*, 5360−5365.
(24) (a) Na, C. G.; Alexanian, E. J. A General Approach to Site-Specific, Intramolecular C-H Functionalization Using Dithiocarbamates. *Angew. Chem., Int. Ed.* **2018**, *57*, 13106−13109. (b) Quinn, R. K.; Konst, Z. A.; Michalak, S. E.; Schmidt, Y.; Szklarski, A. R.; Flores, A. R.; Nam, S.; Horne, D. A.; Vanderwal, C. D.; Alexanian, E. J. Site-Selective Aliphatic C-H Chlorination Using N-Chloroamides Enables a Synthesis of Chlorolissoclimide. *J. Am. Chem. Soc.* **2016**, *138*, 696−702. (c) Zhang, B.; Erb, F. R.; Vasilopoulos, A.; Voight, E. A.; Alexanian, E. J. General Synthesis of N-Alkylindoles from N,N-Dialkylanilines Via [4 + 1] Annulative Double C-H Functionalization. *J. Am. Chem. Soc.* **2023**, *145*, 26540−26544.
(25) (a) Russell, G. A.; Brown, H. C. The Liquid Phase Photochlorination and Sulfuryl Chloride Chlorination of Branched-chain Hydrocarbons - the Effect of Structure on the Relative Reactivities of Tertiary Hydrogen in Free Radical Chlorinations. *J. Am. Chem. Soc.* **1955**, *77*, 4031−4035. (b) Bunce, N. J.; Ingold, K. U.; Landers, J. P.; Lusztyk, J.; Scaiano, J. C. Kinetic-Study of the Photochlorination of 2,3-Dimethylbutane and Other Alkanes in Solution in the Presence of Benzene - First Measurements of the Absolute Rate Constants for Hydrogen Abstraction by the "Free" Chlorine Atom and the Chlorine Atom Benzene Π-Complex. Identification of These 2 Species as the Only Hydrogen Abstractors in These Systems. *J. Am. Chem. Soc.* **1985**, *107*, 5464−5472.
(26) Gonzalez, M. I.; Gygi, D.; Qin, Y.; Zhu, Q.; Johnson, E. J.; Chen, Y. S.; Nocera, D. G. Taming the Chlorine Radical: Enforcing Steric Control over Chlorine-Radical-Mediated C-H Activation. *J. Am. Chem. Soc.* **2022**, *144*, 1464−1472.
(27) Gygi, D.; Gonzalez, M. I.; Hwang, S. J.; Xia, K. T.; Qin, Y.; Johnson, E. J.; Gygi, F.; Chen, Y.-S.; Nocera, D. G. Capturing the Complete Reaction Profile of a C-H Bond Activation. *J. Am. Chem. Soc.* **2021**, *143*, 6060−6064.
(28) (a) Meunier, B.; de Visser, S. P.; Shaik, S. Mechanism of Oxidation Reactions Catalyzed by Cytochrome P450 Enzymes. *Chem.*

https://doi.org/10.1021/jacs.5c07456
J. Am. Chem. Soc. XXXX, XXX, XXX−XXX

Rev. **2004**, *104*, 3947−3980. (b) Gunay, A.; Theopold, K. H. C-H Bond Activations by Metal Oxo Compounds. *Chem. Rev.* **2010**, *110*, 1060−1081. (c) Baglia, R. A.; Zaragoza, J. P. T.; Goldberg, D. P. Biomimetic Reactivity of Oxygen-Derived Manganese and Iron Porphyrinoid Complexes. *Chem. Rev.* **2017**, *117*, 13320−13352. (d) Costas, M. Selective C-H Oxidation Catalyzed by Metalloporphyrins. *Coordin. Chem. Rev.* **2011**, *255*, 2912−2932. (e) Fukuzumi, S. Electron-Transfer Properties of High-Valent Metal-Oxo Complexes. *Coordin. Chem. Rev.* **2013**, *257*, 1564−1575. (f) Oloo, W. N.; Que, L. Bioinspired nonheme iron catalysts for C-H and C = C bond oxidation: insights into the nature of the metal-based oxidants. *Acc. Chem. Res.* **2015**, *48*, 2612−2621. (g) Huang, X.; Groves, J. T. Oxygen Activation and Radical Transformations in Heme Proteins and Metalloporphyrins. *Chem. Rev.* **2018**, *118*, 2491−2553.

(29) Lee, W.-C. C.; Zhang, X. P. Metalloradical Catalysis: General Approach for Controlling Reactivity and Selectivity of Homolytic Radical Reactions. *Angew. Chem., Int. Ed.* **2024**, *63*, No. e202320243.

(30) (a) Milan, M.; Salamone, M.; Costas, M.; Bietti, M. The Quest for Selectivity in Hydrogen Atom Transfer Based Aliphatic C-H Bond Oxygenation. *Acc. Chem. Res.* **2018**, *51*, 1984−1995. (b) Nam, W.; Lee, Y. M.; Fukuzumi, S. Hydrogen Atom Transfer Reactions of Mononuclear Nonheme Metal-Oxygen Intermediates. *Acc. Chem. Res.* **2018**, *51*, 2014−2022. (c) Sacramento, J. J. D.; Goldberg, D. P. Factors Affecting Hydrogen Atom Transfer Reactivity of Metal-Oxo Porphyrinoid Complexes. *Acc. Chem. Res.* **2018**, *51*, 2641−2652. (d) Boaz, N. C.; Bell, S. R.; Groves, J. T. Ferryl Protonation in Oxoiron(IV) Porphyrins and Its Role in Oxygen Transfer. *J. Am. Chem. Soc.* **2015**, *137*, 2875−2885. (e) Palone, A.; Casadevall, G.; Ruiz-Barragan, S.; Call, A.; Osuna, S.; Bietti, M.; Costas, M. C-H Bonds as Functional Groups: Simultaneous Generation of Multiple Stereocenters by Enantioselective Hydroxylation at Unactivated Tertiary C-H Bonds. *J. Am. Chem. Soc.* **2023**, *145*, 15742−15753. (f) Zhang, L.; Seo, M. S.; Choi, Y.; Ezhov, R.; Maximova, O.; Malik, D. D.; Ng, M.; Lee, Y. M.; Sarangi, R.; Pushkar, Y. N.; Cho, K. B.; Nam, W. A Manganese Compound I Model with a High Reactivity in the Oxidation of Organic Substrates and Water. *J. Am. Chem. Soc.* **2023**, *145*, 8319−8325. (g) Rittle, J.; Green, M. T. Cytochrome P450 Compound I: Capture, Characterization, and C-H Bond Activation Kinetics. *Science* **2010**, *330*, 933−937.

(31) (a) Lang, K.; Torker, S.; Wojtas, L.; Zhang, X. P. Asymmetric Induction and Enantiodivergence in Catalytic Radical C-H Amination Via Enantiodifferentiative H-Atom Abstraction and Stereoretentive Radical Substitution. *J. Am. Chem. Soc.* **2019**, *141*, 12388−12396. (b) Dzik, W. I.; Xu, X.; Zhang, X. P.; Reek, J. N. H.; de Bruin, B. 'Carbene Radicals' in Co^{II}(Por)-Catalyzed Olefin Cyclopropanation. *J. Am. Chem. Soc.* **2010**, *132*, 10891−10902. (c) Xie, J.; Xu, P.; Zhu, Y. L.; Wang, J.; Lee, W.-C. C.; Zhang, X. P. New Catalytic Radical Process Involving 1,4-Hydrogen Atom Abstraction: Asymmetric Construction of Cyclobutanones. *J. Am. Chem. Soc.* **2021**, *143*, 11670−11678. (d) Lee, W.-C. C.; Wang, D.-S.; Zhu, Y.; Zhang, X. P. Iron(III)-Based Metalloradical Catalysis for Asymmetric Cyclopropanation Via a Stepwise Radical Mechanism. *Nat. Chem.* **2023**, *15*, 1569−1580. (e) Xu, P.; Xie, J.; Wang, D.-S.; Zhang, X. P. Metalloradical Approach for Concurrent Control in Intermolecular Radical Allylic C-H Amination. *Nat. Chem.* **2023**, *15*, 498−507.

(32) (a) Gephart, I. I. I.; R, T.; McMullin, C. L.; Sapiezynski, N. G.; Jang, E. S.; Aguila, M. J. B.; Cundari, T. R.; Warren, T. H. Reaction of Cu^{I} with Dialkyl Peroxides: Cu^{II}-Alkoxides, Alkoxy Radicals, and Catalytic C-H Etherification. *J. Am. Chem. Soc.* **2012**, *134*, 17350−17353. (b) Hu, H.; Chen, S. J.; Mandal, M.; Pratik, S. M.; Buss, J. A.; Krska, S. W.; Cramer, C. J.; Stahl, S. S. Copper-Catalysed Benzylic C-H Coupling with Alcohols Via Radical Relay Enabled by Redox Buffering. *Nat. Catal.* **2020**, *3*, 358−367. (c) Golden, D. L.; Zhang, C.; Chen, S. J.; Vasilopoulos, A.; Guzei, I. A.; Stahl, S. S. Benzylic C-H Esterification with Limiting C-H Substrate Enabled by Photochemical Redox Buffering of the Cu Catalyst. *J. Am. Chem. Soc.* **2023**, *145*, 9434−9440. (d) Mandal, M.; Buss, J. A.; Chen, S.-J.; Cramer, C. J.; Stahl, S. S. Mechanistic Insights into Radical Formation and Functionalization in Copper/N-Fluorobenzenesulfonimide Radical-Relay Reactions. *Chem. Sci.* **2024**, *15*, 1364−1373.

(33) (a) Bour, J. R.; Ferguson, D. M.; McClain, E. J.; Kampf, J. W.; Sanford, M. S. Connecting Organometallic Ni(III) and Ni(IV): Reactions of Carbon-Centered Radicals with High-Valent Organonickel Complexes. *J. Am. Chem. Soc.* **2019**, *141*, 8914−8920. (b) Bakhoda, A. G.; Wiese, S.; Greene, C.; Figula, B. C.; Bertke, J. A.; Warren, T. H. Radical Capture at Nickel(II) Complexes: C-C, C-N, and C-O Bond Formation. *Organometallics* **2020**, *39*, 1710−1718. (c) Lin, Q.; Spielvogel, E. H.; Diao, T. Carbon-centered radical capture at nickel(II) complexes: Spectroscopic evidence, rates, and selectivity. *Chem.* **2023**, *9*, 1295−1308.

(34) (a) Whittaker, J. W. Free Radical Catalysis by Galactose Oxidase. *Chem. Rev.* **2003**, *103*, 2347−2363. (b) Solomon, E. I.; Heppner, D. E.; Johnston, E. M.; Ginsbach, J. W.; Cirera, J.; Qayyum, M.; Kieber-Emmons, M. T.; Kjaergaard, C. H.; Hadt, R. G.; Tian, L. Copper Active Sites in Biology. *Chem. Rev.* **2014**, *114*, 3659−3853.

(35) Caneschi, A.; Gatteschi, D.; Sessoli, R.; Rey, P. Toward Molecular Magnets: The Metal-Radical Approach. *Acc. Chem. Res.* **1989**, *22*, 392−398.

(36) Büttner, T.; Geier, J.; Frison, G.; Harmer, J.; Calle, C.; Schweiger, A.; Schönberg, H.; Grützmacher, H. A Stable Aminyl Radical Metal Complex. *Science* **2005**, *307*, 235−238.

(37) (a) Minisci, F. Free-Radical Additions to Olefins in the Presence of Redox Systems. *Acc. Chem. Res.* **1975**, *8*, 165−171. (b) Stella, L. Homolytic Cyclizations of N-Chloroalkenylamines. *Angew. Chem., Int. Ed.* **1983**, *22*, 337−350.

(38) (a) Wang, F.; Chen, P.; Liu, G. Copper-Catalyzed Radical Relay for Asymmetric Radical Transformations. *Acc. Chem. Res.* **2018**, *51*, 2036−2046. (b) Wang, F.; Chen, P.; Liu, G. Copper-Catalysed Asymmetric Radical Cyanation. *Nat. Synth.* **2022**, *1*, 107−116.

(39) Zhang, Z.; Chen, P.; Liu, G. Copper-Catalyzed Radical Relay in $C(sp^3)$-H Functionalization. *Chem. Soc. Rev.* **2022**, *51*, 1640−1658.

(40) Li, J.; Zhang, Z.; Wu, L.; Zhang, W.; Chen, P.; Lin, Z.; Liu, G. Site-specific Allylic C-H Bond Functionalization with a Copper-Bound N-Centred Radical. *Nature* **2019**, *574*, 516−521.

(41) Zhang, W.; Wang, F.; McCann, S. D.; Wang, D.; Chen, P.; Stahl, S. S.; Liu, G. Enantioselective Cyanation of Benzylic C-H Bonds Via Copper-Catalyzed Radical Relay. *Science* **2016**, *353*, 1014−1018.

(42) Lu, R. Enantioselective Copper-Catalyzed Radical Cyanation of C-H Bonds; Ph.D. Dissertation, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, Shanghai, China, 2021.

(43) 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.

(44) 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.

(45) (a) 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. (b) Cheng, Z.; Zhang, J.; Li, C.; Li, X.; Chen, P.; Liu, G. Copper-Catalyzed sp^2 C-H Arylation and Alkynylation of Allenes Via Hydrogen Atom Abstraction. *J. Am. Chem. Soc.* **2024**, *146*, 24689−24698.

(46) Kharasch, M. S.; Sosnovsky, G. The Reactions of T-Butyl Perbenzoate and Olefins—a Stereospecific Reaction. *J. Am. Chem. Soc.* **1958**, *80*, 756.

(47) (a) Eames, J.; Watkinson, M. Catalytic Allylic Oxidation of Alkenes Using an Asymmetric Kharasch-Sosnovsky Reaction. *Angew. Chem., Int. Ed.* **2001**, *40*, 3567−3571. (b) Andrus, M. B.; Zhou, Z. Highly Enantioselective Copper-Bisoxazoline-Catalyzed Allylic Oxidation of Cyclic Olefins with Tert-Butyl *P*-Nitroperbenzoate. *J. Am. Chem. Soc.* **2002**, *124*, 8806−8807.

(48) Chen, X.; Lian, Z.; Kramer, S. Enantioselective Intermolecular Radical Amidation and Amination of Benzylic C-H Bonds Via Dual Copper and Photocatalysis. *Angew. Chem., Int. Ed.* **2023**, *62*, No. e202217638.

https://doi.org/10.1021/jacs.5c07456
J. Am. Chem. Soc. XXXX, XXX, XXX−XXX

(49) Dai, L.; Chen, Y.-Y.; Xiao, L.-J.; Zhou, Q.-L. Intermolecular Enantioselective Benzylic C(sp^3)−H Amination by Cationic Copper Catalysis. *Angew. Chem., Int. Ed.* **2023**, *62*, No. e202304427.
(50) Chen, X.; Li, H.-H.; Kramer, S. Photoinduced Copper-Catalyzed Enantioselective Allylic C(sp^3)−H Oxidation of Acyclic 1-Aryl-2-Alkyl Alkenes as Limiting Substrates. *Angew. Chem., Int. Ed.* **2024**, *63*, No. e202413190.
(51) Tang, S.; Xu, H.; Dang, Y.; Yu, S. Photoexcited Copper-Catalyzed Enantioselective Allylic C(sp^3)-H Acyloxylation of Acyclic Internal Alkenes. *J. Am. Chem. Soc.* **2024**, *146*, 27196−27203.
(52) Liu, X.-M.; Li, F.; Wang, T.; Dai, L.; Yang, Y.; Jiang, N.-Q.; Xue, L.-Y.; Liu, J.-Y.; Xue, X.-S.; Xiao, L.-J.; Zhou, Q.-L. Catalytic Asymmetric Oxidative Coupling between C(sp^3)−H Bonds and Carboxylic Acids. *J. Am. Chem. Soc.* **2025**, *147*, 627−635.
(53) (a) Golden, D. L.; Zhang, C.; Chen, S.-J.; Vasilopoulos, A.; Guzei, I. A.; Stahl, S. S. Benzylic C-H Esterification with Limiting C-H Substrate Enabled by Photochemical Redox Buffering of the Cu Catalyst. *J. Am. Chem. Soc.* **2023**, *145*, 9434−9440. (b) Hu, H.; Chen, S.-J.; Mandal, M.; Pratik, S. M.; Buss, J. A.; Krska, S. W.; Cramer, C. J.; Stahl, S. S. Copper-Catalysed Benzylic C-H Coupling with Alcohols Via Radical Relay Enabled by Redox Buffering. *Nat. Catal.* **2020**, *3*, 358−367.
(54) Zhang, H.; Zhou, Y.; Yang, T.; Wu, J.; Chen, P.; Lin, Z.; Liu, G. Site- and Enantioselective Allylic and Propargylic C−H Oxidation Enabled by Copper-Based Biomimetic Catalysis. *Nat. Catal.* **2025**, *8*, 58−66.
(55) Ma, C.-R.; Huang, G.-W.; Xu, H.; Wang, Z.-L.; Li, Z.-H.; Liu, J.; Yang, Y.; Li, G.-Y.; Dang, Y.-F.; Wang, F. Site-Selective Arene C-H Amination with Iron-Aminyl Radical. *Nat.Catal.* **2024**, *7*, 636−645.
(56) Fan, F.-X.; Xu, H.; Tang, S.-X.; Dang, Y.; Wang, F. Iron-Catalysed Stereoselective NH Transfer Enables Dynamic Kinetic Resolution of Sulfoxides. *Nat. Commun.* **2025**, *16*, 1471.
(57) A Cu(II)-bound amidyl radical was proposed in the difunctionalization of alkenes; see: Li, Y.; Liang, Y.; Dong, J.; Deng, Y.; Zhao, C.; Su, Z.; Guan; Bi, X.; Liu, Q.; Fu, J. Directed Copper-Catalyzed Intermolecular Aminative Difunctionalization of Unactivated Alkenes. *J. Am. Chem. Soc.* **2019**, *141*, 18475−18485.
(58) A Cu(I)-bound amidyl radical was proposed in the difunctionalization of alkenes; see: Liang, Y.-J.; Sun, M.-J.; Zhang, G.; Yin, J.-J.; Guan, W.; Xiong, T.; Zhang, Q. Copper-Catalyzed Hydroamination of Polyfluoroalkyl Substituted Alkenes Via Asymmetric Radical Cross-Coupling Access to α-Chiral Tertiary Alkylamines. *Chem. Catal.* **2022**, *2*, 2379−2390.

NOTE ADDED AFTER ASAP PUBLICATION

The version of this paper that was published ASAP June 14, 2025, contained an error in Figure 4A. The corrected version was posted June 16, 2025.

https://doi.org/10.1021/jacs.5c07456
J. Am. Chem. Soc. XXXX, XXX, XXX−XXX