Copper-catalyzed enantioselective Sonogashira-type oxidative cross-coupling of unactivated C(sp³)–H bonds with alkynes

Zhen-Hua Zhang¹,²,₄, Xiao-Yang Dong²,₄, Xuan-Yi Du²,₄, Qiang-Shuai Gu⁴, Zhong-Liang Li³ & Xin-Yuan Liu²*

Transition metal-catalyzed enantioselective Sonogashira-type oxidative C(sp³)–C(sp) coupling of unactivated C(sp³)–H bonds with terminal alkynes has remained a prominent challenge. The difficulties mainly stem from the regiocontrol in unactivated C(sp³)–H bond functionalization and the inhibition of readily occurring Glaser homocoupling of terminal alkynes. Here, we report a copper/chiral cinchona alkaloid-based N,N,P-ligand catalyst for asymmetric oxidative cross-coupling of unactivated C(sp³)–H bonds with terminal alkynes in a highly regio-, chemo-, and enantioselective manner. The use of N-fluoroamide as a mild oxidant is essential to site-selectively generate alkyl radical species while efficiently avoiding Glaser homocoupling. This reaction accommodates a range of (hetero)aryl and alkyl alkynes; (hetero)benzylic and propargylic C(sp³)–H bonds are all applicable. This process allows expedient access to chiral alkynyl amides/aldehydes. More importantly, it also provides a versatile tool for the construction of chiral C(sp³)–C(sp), C(sp³)–C(sp²), and C(sp³)–C(sp³) bonds when allied with follow-up transformations.

¹Shandong Provincial Key Laboratory of Detection Technology for Tumor Markers, School of Chemistry and Chemical Engineering, Linyi University, Linyi 276005, China. ²Shenzhen Grubbs Institute and Department of Chemistry, Southern University of Science and Technology, Shenzhen 518055, China. ³Academy for Advanced Interdisciplinary Studies and Department of Chemistry, Southern University of Science and Technology, Shenzhen 518055, China. ⁴These authors contributed equally: Zhen-Hua Zhang, Xiao-Yang Dong, Xuan-Yi Du. *email: liuxy3@sustech.edu.cn
As one of the most fundamental motifs in organic chemistry, chiral alkenes play an essential role in biology, medicinal chemistry, and material science\(^1,2\). They also serve as vital synthetic precursors for many functionalities such as alkanes, alkenes, aldehydes, carboxylic acids, and heterocycles on both laboratory and industrial scales\(^1,2\). Accordingly, a variety of catalytic methods have been developed to enantioselectively deliver chiral C(sp\(^3\))—C(sp\(^3\)) bonds\(^3\)−13. From the viewpoint of step- and atom-economy, a direct enantioselective alkylation of a C(sp\(^3\))—H bond would be highly appealing\(^14\)−16. Thus, directed palladium-catalyzed C–H activation has been shown to be an effective strategy for C(sp\(^3\))—H alkylation\(^17\)−19. However, only a few enantioselective examples have been disclosed with the expensive alkynyl bromide/iodine as the alkylation reagents\(^20\)−22. In comparison, an enantioselective Sonogashira-type cross-dehydrogenative coupling (CDC) of C(sp\(^3\))—H bonds with low-cost terminal alkynes would be more ideal due to the ready availability of both coupling partners. In this respect, Li and others have pioneered in establishing enantioselective alkynylation for realization of asymmetric alkene difunctionalization\(^23\)−32. The stereochemical control was elegantly implemented via chiral Lewis acid-catalyzed nucleophilic addition to the in situ generated iminium ions (Fig. 1a)\(^23\)−32. However, the enantioselective oxidative cross-coupling of common unactivated C(sp\(^3\))—H bonds poses a significant challenge to this strategy. Two major difficulties have to be overcome: (1) The site-selective generation of carbocation species from such unactivated C(sp\(^3\))—H bonds is relatively difficult compared with that adjacent to nitrogen. (2) The chemo- and enantiocontrol of the non-heteroatom-stabilized carbocations are also more challenging due to their inherently high reactivity. Clearly, a conceptually different approach is highly desirable to achieve the enantioselective oxidative cross-coupling of unactivated C(sp\(^3\))—H bonds and terminal alkynes.

Enantioselective C(sp\(^3\))—H bond functionalization by merging a site-selective hydrogen atom abstraction (HAA) process with asymmetric copper-catalyzed cross-coupling has received much attention over the past several years\(^33\)−44. At the same time, we have recently developed a copper/cinchona alkaloid-based N,N-ligand catalyst, which could intimately associate with alkyl radical species (Fig. 1b). However, common oxidants for HAA readily lead to site-selective HAA on unactivated C(sp\(^3\))—H bonds and enantioselective coupling with terminal alkynes (Fig. 1b). However, common oxidants for HAA readily lead to copper-catalyzed Glaser homocoupling of terminal alkynes\(^47\)\(^48\). To this end, we have been encouraged by the mild oxidation power of N-halogenated amides employed in recent remote C(sp\(^3\))—H

---

**Fig. 1** Sonogashira-type enantioselective oxidative cross-coupling of C(sp\(^3\))—H bonds with terminal alkynes. **a** Previous ionic-type dehydrogenative coupling of C(sp\(^3\))—H bonds adjacent to nitrogen. **b** Our proposal: tandem HAA and copper-catalyzed Sonogashira-type coupling. **c** Amide-directed enantioselective coupling of C(sp\(^3\))—H bonds with terminal alkynes. HAA: hydroatom abstraction, [ox] oxidant, SET single-electron transfer.
functionalization transformations based on the classic Hofmann–Löffler–Freytag and Barton reactions. More importantly, the corresponding amidyl radicals commonly exhibit robust HAA reactivity and site-selectivity. Thus, we questioned if a removable directing amide group would be viable for sequential N-oxidation and asymmetric copper-catalyzed Sonogashira-type coupling of unactivated C–H bonds with terminal alkynes.

Herein, we describe our efforts toward the development of radical asymmetric oxidative cross-coupling of unactivated C(sp3)–H bonds with terminal alkynes enabled by copper(I)/cinchona alkaloid-based N,N,P-ligand catalysis. Notably, this protocol not only provides a range of chiral alkynyl amides and alkynyl aldehydes (Fig. 1c) but also, together with further transformations, offers a general way for chiral C(sp3)–C(sp3), C(sp3)–C(sp2), and C(sp3)–C(sp2) bond construction.

**Table 1 Screening of reaction conditions**

| Entry | 1    | [Cu] | Base   | L* | Solvent       | Yield (%) | Ee (%) |
|-------|------|------|--------|----|---------------|-----------|--------|
| 1     | 1aa  | Cul  | Cs2CO3 | L1 | DCM           | <5, 0, 0  | 6      |
| 2     | 1aa  | Cul  | Cs2CO3 | L2 | DCM           | 8, 0, 0   | 74     |
| 3     | 1aa  | Cul  | Cs2CO3 | L3 | DCM           | <5, 0, 0  | 68     |
| 4     | 1aa  | Cul  | Cs2CO3 | L4 | DCM           | 15, 0, 0  | 51     |
| 5     | 1aa  | Cul  | Cs2CO3 | L5 | DCM           | 0, 0, 0   | -      |
| 6     | 1aa  | Cul  | Cs2CO3 | L6 | DCM           | 0, 0, 0   | 76     |
| 7     | 1aa  | Cul  | Cs2CO3 | L7 | 1,2-Dichloroethane | 0, 0, 0   | -      |
| 8     | 1aa  | Cul  | Cs2CO3 | L8 | Benzene       | 92, 0, 0  | 64     |
| 9     | 1aa  | Cul  | Cs2CO3 | L9 | EtOAc         | 92, 0, 0  | 91     |
| 10    | 1aa  | Cul  | Cs2CO3 | L10| THF           | 88, 0, 0  | 94     |
| 11    | 1aa  | Cul  | Cs2CO3 | L11| THF           | 64, 0, 0  | 93     |
| 12    | 1aa  | CuBr | Cs2CO3 | L12| THF           | 91, 0, 0  | 92     |
| 13    | 1aa  | CuTc | Cs2CO3 | L13| THF           | 80, 0, 0  | 94     |
| 14    | 1aa  | CuOAc| Cs2CO3 | L14| THF           | <5, 0, 81 | 85     |
| 15    | 1aa  | Cu   | Na2CO3 | L15| THF           | 27, 0, 62 | 93     |
| 16    | 1aa  | Cu   | K2CO3  | L16| THF           | 71, 0, 26 | 93     |
| 17    | 1aa  | Cu   | KOH   | L17| THF           | 66, 0, 0  | 94     |
| 18    | 1aa  | Cu   | KOBu  | L18| THF           | 31, 0, 0  | 92     |
| 19    | 1aa  | Cu   | Cs2CO3 | L19| THF           | 0, 0, 0   | -      |
| 20    | 1aa  | Cu   | Cs2CO3 | L20| THF           | 0, 0, 0   | 92     |
| 21    | 1aa  | Cu   | Cs2CO3 | L21| THF           | 0, 0, 0   | -      |
| 22    | 1aa  | Cu   | Cs2CO3 | L22| THF           | 0, 0, 0   | 92     |
| 23    | 1aa  | Cu   | Cs2CO3 | L23| THF           | 0, 0, 0   | -      |

*Reaction conditions: 1a (0.1 mmol), 2a (0.2 mmol), [Cu] (10 mol%), L* (10 mol%), and base (0.1 mmol) in dry solvent (1.2 mL) at room temperature (rt) for 16 h

**Notes:**

- Yield based on 1H NMR analysis of the crude product using CH2Br2 as an internal standard
- Ee values based on HPLC analysis
- A trace amount of product
- CuI (5 mol%), L* (5 mol%) for 24 h
- CuI (2 mol%), L* (2 mol%) for 36 h
- Without 2a
Results

Reaction optimization. To verify our hypothesis, N-halo-amides 1aa and 1ab as well as O-acylhydroxylamide 1ac were prepared, which all can generate the amidyl radical via single-electron reduction by a Cu(I) catalyst. Initial treatment of N-fluoroamide 1aa with phenylacetylene 2a and Cs₂CO₃ in the presence of CuI and our designed bidentate quinine-derived sulfonamide ligands L₁ and L₂ did not provide any products (entries 1 and 2, Table 1). We tentatively ascribed the results to the insufficient reducing capability of Cu(I) catalysts. Thus, we speculated that an additional coordinative amine or phosphine moieties on the ligands might help increase the electron-density on copper and enhance its reducing power. As such, cinchona alkaloid-derived Nakamura’s tridentate N,N,N-ligand L₃ and Dixon’s N,N,P-ligand L₅ as well as their analogs L₄ and L₆, respectively, were examined. And most of them led to the desired product 3a with promising enantioselectivity (entries 3–6, Table 1). In contrast, N-chloroamide 1ab and O-acylhydroxylamide 1ac only afforded Glaser homocoupling product 3a′ (entries 7 and 8, Table 1) under such reaction conditions, indicating the importance of the chosen amidyl radical precursor. Further screening of Cu(I) catalysts and solvents (entries 9–15, Table 1) proved that CuI in Tetrahydrofuran (THF) was the best (88% yield and 94% ee; entry 12, Table 1). An evaluation of base indicated significant impacts on the efficiency and selectivity (entries 16–18, Table 1) and Cs₂CO₃ was found to be particularly effective to inhibit the formation of side product 3a″. Lowering the catalyst loading affected the yield but not the enantioselectivity (entries 19 and 20, Table 1). Control experiments showed that both the N,N,P-ligand and the alkyne were necessary for efficient amide consumption (entries 21–23, Table 1). Thus, both of them are required for the copper center to efficiently reduce the mild N–F oxidant.

Substrate scope. With the optimized conditions in hand, the scope of alkynes was next explored (Fig. 2). A series of aryl and heteroaryl alkynes was reacted under standard conditions (Fig. 2). The results are summarized in Table 2. A representative series of products is given in Fig. 2. The full data set is provided in Table 2.

![Fig. 2 Substrate scope of alkynes. Standard conditions: 1aa (0.2 mmol), alkyne (0.4 mmol), CuI (10 mol%), L5 (10 mol%), and Cs₂CO₃ (1.0 equiv.) in THF (2.4 mL) at rt for 16 h. Isolated yield based on 1aa is given. Ee values are based on HPLC analysis. CuTc (15 mol%), L5 (10 mol%), and Cs₂CO₃ (2.0 equiv.) in THF at rt for 24 h. Bpin pinacolborato, TMS trimethylsilyl.](https://doi.org/10.1038/s41467-019-13705-1)
alkynes, including those having electron-donating or -withdrawing groups at different positions (ortho, meta, or para) of phenyl rings, reacted smoothly to afford 3a–3p in 62–98% yield with 87–94% ee. Many functional groups, such as methoxyl (3b), halo (3d–3i), trifluoromethyl (3j), cyano (3k), formyl (3l and 3m), methoxycarbonyl (3n), pinacolborato (3o), and terminal alkylnyl (3p), were all compatible with the reaction conditions. Furthermore, a range of heteroaryl alkynes, such as 3-pyridinyl,
2-thiophenyl, and 3-thiophenyl, all worked well to deliver $3q$–$3s$ in good yields with excellent enantioselectivity. We were especially pleased to find that alkyl alkynes were also competent coupling partners. For example, the aliphatic alkynes underwent the reaction to give $3t$ and $3u$ with good results in the presence of 2 equivalents of Cs$_2$CO$_3$. A wide range of functional groups, such as conjugating alkenyl ($3v$ and $3w$), cyclopropanyl ($3x$), acetal ($3y$), carbazole ($3z$), cyano ($3za$), primary chloride ($3zb$), ester ($3zd$), and even hydroxy ($3ze$), and even hydroxy ($3zf$) groups, at different positions of the backbone phenyl rings were well accommodated in the direct alkynylation of the α-C–H bond. It also proceeded smoothly to give $3zo$ in excellent enantioselectivity. In addition, a silyl alkyne was easily converted to terminal alkyne, thus providing valuable chiral building blocks.

The scope of N-fluorocarboxamides bearing secondary benzylic C(sp$^3$)–H bonds was next evaluated (Fig. 3a). Simple alkyl-substituted substrates worked well to give alkynylation products $3zf$–$3zh$ with excellent regio- and enantioselectivity. Noteworthy is that the reaction is not restricted to benzylic or heterobenzylic C(sp$^3$)–H bond functionalization. For example, various propargylic C(sp$^3$)–H bonds were amenable to this transformation, therefore providing $3zs$–$3zu$ in moderate to high enantioselectivity. Interestingly, a substrate containing only simple alkyl δ-C–H bonds also underwent the reaction to deliver $3zu$ in excellent regioselectivity, albeit with no enantioselectivity. The reaction is currently under further optimization for potential enaniotrope control in our laboratory.

**Fig. 4** Straightforward transformation. a The directing amide group was readily removed by sequential amide reduction to aldehyde and decarbonylation. b The essential alkyne moiety in the product was straightforwardly transformed into Z-alkene and alkane featuring chiral C(sp$^3$)–C(sp$^3$) and C(sp$^3$)–C(sp$^3$) bonds. c Silyl alkyne was easily converted to terminal alkyne, thus providing valuable chiral building blocks.
comparing its HPLC spectrum and optical rotation with those reported in literature. Another feature of this protocol is the reactive alkyne moieties in products, which could be readily converted to a Z-alkene group in 6 and a saturated alkyl group in 7 upon hydrogenation to different extents (Fig. 4b), respectively. Therefore, it provides a versatile and complementary tool to other direct methods for the construction of chiral C(sp^3)–C(sp^2) and C(sp^3)–C(sp^3) bonds. In addition, the TMS group in 3ze could be straightforwardly unmasked to provide the chiral terminal alkyne 8 in 86% yield without any loss of enantioselectivity (Fig. 4c). Such enantioenriched terminal alkynes are valuable chiral building blocks for a range of transformations.

**Mechanism investigation.** To gain some insight into the reaction mechanism, control experiments with radical inhibitors 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) and butylated hydroxytoluene (BHT) were conducted, respectively, indicating reaction inhibition (Supplementary Fig. 1a). Moreover, a radical clock experiment showed that substrate 9 underwent a tandem cyclopropane ring-opening/alkyne trapping process to provide 10 in 72% yield with 74% ee (Fig. 5a). These observations support the possible formation of alkyl radical species from in situ-generated amidyl radical species via 1,5(6)-HAA processes. Deuterium-labeling experiments indicated an intramolecular kinetic isotope effect (KIE) value of 1.94 and an intermolecular KIE value of 1.16. Thus, the 1,5-HAA process might be not involved in the rate-determining step(s) (Supplementary Fig. 1b and 1c). In addition, only in the presence of L5 could copper phenylacetylide initiate the reaction (Fig. 5b). This result, together with the aforementioned effects of ligand and phenylacetylene for efficient amide consumption (entries 21–23, Table 1), demonstrates that the complex of copper phenylacetylide with the chiral ligand might be the initial complex to start this reaction.

**Fig. 5 Mechanistic investigations.** a The radical-clock substrate (±)-9 underwent ring opening before the C–C bond formation, thus indicating the initial generation of a benzylic radical. b The reaction of 1aa with copper acetylide did not occur in the absence of L5, indicating that both chiral ligand and terminal alkyne are indispensable for reaction initiation. c The reaction was proposed to proceed through sequential single-electron reduction of substrate 1, 1,5(6)-HAA, and copper-catalyzed C(sp^3)–C(sp) coupling.
On the basis of abovementioned observations and previous reports, a plausible mechanism was tentatively proposed, as shown in Fig. 5c. Initially, CuX reacts with chiral ligand and terminal alkyne in the presence of base, giving chiral Cu(I) acetylide complex B. Subsequent single-electron transfer (SET) of B with N-fluorocarboxamide I results in the formation of Cu(II) acetylide complex C and the amidal radical D. The amidal radical then undergoes intramolecular 1,5(6)-HAA to generate alkyl radical species E. Next, C(sp²)–C(sp³) coupling via reductive elimination of a Cu(III) intermediate F gives rise to enantioenriched product 3 and chiral Cu(I) complex A.

Discussion
We have discovered copper/cinchona alkaloid-based N,N,P-ligand catalysts to accomplish a radical asymmetric oxidative C(sp³)–C(sp) cross-coupling of unactivated C(sp³)–H bonds and terminal alkynes. The utilization of a removable amide group to direct the site-selective formation of alkyl radical species via a HAA is crucial to the success of the transformation. In addition, the use of N-fluorocarboxamides as mild amidyl radical precursors is critical for inhibiting the Glaser homocoupling. Further, the strategic utilization of chiral cinchona alkaloid-derived N,N,P-ligands proved to be essential for eliciting the initial SET between copper and the mild N-fluorocarboxamides oxidant while imparting excellentenantidiscrimination in the final C–C coupling step. This strategy allows for the facile assembly of chiral alkyln amides/aldheydes and also provides a generally robust tool for the construction of chiral C(sp³)–C(sp), C(sp³)–C(sp²), and C(sp³)–C(sp) bonds. Further studies toward the development of direct enantioselective oxidative Sonogashira-type coupling of unactivated C(sp³)–H bonds with terminal alkynes are ongoing in our laboratory.

Methods
General procedure A. This procedure applies to compounds 3a–p, 3r, 3s, 3v, 3y, 3z, 3zr, 3zs, 3zu, 3v, 3zt, 3ct, and 3v. Under argon atmosphere, an oven-dried reusable Schlenk tube equipped with a magnetic stir bar was charged with CuI (3.8 mg, 0.020 mmol, 10 mol%), Cs₂CO₃ (130.4 mg, 0.40 mmol, 2.0 equiv.), and anhydrous THF (2.4 mL). Then, N-fluorocarboxamide (0.20 mmol, 1.0 equiv.) and alkyne (0.40 mmol, 2.0 equiv.) were sequentially added into the mixture and the reaction mixture was stirred for rt for 24 h. Upon completion (monitored by TLC), the precipitate was filtered off and washed by DCM. The filtrate was evaporated and the residue was purified by column chromatography on silica gel to afford the desired product.

Received: 1 October 2019; Accepted: 20 November 2019
Published online: 12 December 2019

References
1. Diederich, F., Stang, P. J. & Tykwinski, R. R. (eds) Acetylene Chemistry: Chemistry, Biology, and Material Science (Wiley-VCH, Weinheim, 2005).
2. Frost, B. M. & Li, C.-J. (eds) Modern Alkylene Chemistry: Catalytic and Atom-Economic Transformations (Wiley-VCH, 2015).
3. Chen, Q. et al. Copper/guanidine-catalyzed asymmetric alykylation of isatins. Angew. Chem. Int. Ed. 55, 5286–5289 (2016).
4. Wang, Z.-X., Bai, X.-Y. & Li, B.-J. Recent progress of transition-metal-catalyzed enantioselective hydroalkynylation of alkynes. Synlett 28, 509–514 (2017).
5. Vaillant, F. L. & Waser, J. Alkylation of radicals: spotlight on the “third way” to transfer triple bonds. Chem. Sci. 10, 8909–8923 (2019).
6. Dabrowski, J. A., Gao, F. & Hoveyda, A. H. Enantioselective synthesis of alkynyl-substituted quaternary carbon stereogenic centers through NH–C– catalyzed acyllyl substitution reactions with (i–Bu)₂[alkynyl]aluminum reagents. J. Am. Chem. Soc. 133, 4778–4781 (2011).
7. Harada, A., Makida, Y., Sato, T., Ohmiya, H. & Sawamura, M. Copper-catalyzed enantioselective alkyl alykylation of terminal alkyne pronucleophiles. J. Am. Chem. Soc. 136, 13932–13939 (2014).
8. Cui, X.-Y. et al. (Guanidine)copper complex-catalyzed enantioselective dynamic kinetic alkyl alykylation under biphasic condition. J. Am. Chem. Soc. 140, 8448–8455 (2018).
9. Fu, L., Zhou, S., Wan, X., Chen, P. & Liu, G. Enantioselective trifluoromethyalkylation of alkynes via copper-catalyzed radical relay. J. Am. Chem. Soc. 140, 10965–10969 (2018).
10. Bai, X.-Y., Wang, Z.-X. & Li, B.-J. Iridium-catalyzed enantioselective hydroalkynylation of alkynes for the synthesis of homopropargyl amides. J. Org. Chem. 82, 9011–9016 (2016).
11. Wang, Z.-X., Bai, X.-Y., Yao, H.-C. & Li, B.-J. Synthesis of amides with remote stereocenters by catalytic asymmetric y-alkylation of α,β-unsatuated amides. J. Am. Chem. Soc. 138, 14872–14875 (2016).
12. Bai, X.-Y., Zhang, W.-W., Li, Q. & Li, B.-J. Highly enantioselective synthesis of propargyl amides through Rh-catalyzed asymmetric hydroalkynylation of enamides: scope, mechanism, and origin of selectivity. J. Am. Chem. Soc. 140, 506–514 (2018).
13. Wang, Z.-X. & Li, B.-J. Construction of acyclic quaternary carbon stereocenters by catalytic asymmetric hydroalkynylation of unactivated alkynes. J. Am. Chem. Soc. 141, 9312–9320 (2019).
14. Davies, H. M. L. & Beckwith, R. E. J. Catalytic enantioselective C–H activation by means of metal–carbonoid-induced C–H insertion. Chem. Rev. 10, 2861–2903 (2003).
15. Newton, C. G., Wang, S.-G., Oliveira, C. C. & Cramer, N. Catalytic enantioselective transformations involving C–H bond cleavage by transition-metal complexes. Chem. Rev. 117, 8908–8978 (2017).
16. Saint-Denis, T. G., Zhu, R.-Y., Chen, G., Wu, Q.-F. & Yu, J.-Q. Enantioselective C(sp³)–H bond activation by chiral transition metal catalysts. Science 359, eaao4798 (2018).
17. Ano, Y., Tobisu, M. & Chatani, N. Palladium-catalysed direct ethynylation of C(sp³)–H bonds in aliphatic carboxylic acid derivatives. J. Am. Chem. Soc. 133, 12984–12986 (2011).
18. He, J., Waa, M., Chan, K. S. L. & Yu, J.-Q. Palladium(0)-catalyzed alykylation of alkenes. J. Am. Chem. Soc. 135, 3387–3390 (2013).
19. Wang, B. et al. Palladium-catalyzed stereoretentive olefinification of unactivated C(sp³)–H bonds with vinyl iodides at room temperature: synthesis of β-vinyl α-amino acids. Org. Lett. 16, 6260–6263 (2014).
20. Wu, Q.-F. et al. Formation of α-chiral centers by asymmetric β-C(sp³)–H arylation, alykylation, and alkylation. Science 355, 499–503 (2017).
22. Han, Y.-Q. et al. Pd(II)-catalyzed enantioselective alkynylation of unbiased alkynes and tetrahydroisoquinolines with alkynes. Angew. Chem. Int. Ed. 57, 12388–12392 (2018).

23. Li, Z., Bohle, D. S. & Li, C.-J. CuBr-catalyzed efficient alkynylation of sp³ C–H bonds adjacent to a nitrogen atom. J. Am. Chem. Soc. 126, 11810–11811 (2004).

24. Li, Z. & Li, C.-J. Exploring copper catalysis: the cross-dehydrogenative coupling of alkynes and tetrahydroisoquinolines. Angew. Chem. Int. Ed. 53, 74–100 (2014).

25. Girard, S. A., Knauber, T. & Li, C.-J. The cross-dehydrogenative coupling of N-arylamides/dialkylzinc catalyzed enantioselective desymmetrization of aziridines with phenoxides. J. Am. Chem. Soc. 134, 19566–19569 (2012).

26. Glaser, C. Beiträge zur Kenntnifs des acetylenzolens. Ber. Dtsch. Chem. Ges. 2, 422–424 (1869).

27. Glaser, C. Beiträge zur Kenntnifs des acetylenzolens. Ber. Dtsch. Chem. Ges. 2, 422–424 (1869).

28. Kamata, K., Yamaguchi, S., Kotani, M., Yamaguchi, K. & Mizuno, N. Efficient oxidative alkene homocoupling catalyzed by a monomeric dicopper(CCu)-iminoguanidinate. Angew. Chem. Int. Ed. 47, 2407–2410 (2008).

29. Xiong, T. & Zhang, Q. New annihilation strategies based on nitrogen-centered radical chemistry. Chem. Soc. Rev. 45, 3069–3087 (2016).

30. Káráš, M. D. Photochemical generation of nitrogen-centered amidy, hydrazonyl, and imidyl radicals: methodology developments and catalytic applications. ACS Catal. 7, 4999–5022 (2017).

31. State, M. L., Nakafuku, K. M. & Nagib, D. A. Remote C–H functionalization via selective hydrogen atom transfer. Synthesis 50, 1569–1586 (2018).

32. Jiang, H. & Studer, A. Chemistry with N-centered radicals generated by single-electron transfer–oxidation using photoredox catalysis. CCS Chem. 1, 38–49 (2019).

33. Groendyke, B. J., Aboul-Samim, D. I. & Cook, S. P. Iron-catalyzed, fluoroamide-directed C–H fluorination. J. Am. Chem. Soc. 138, 12771–12774 (2016).

34. Wang, F., Chen, P. & Liu, G. Copper-catalyzed arylation of remote C(sp³)–H bonds in carboxamides and sulfonamides. Angew. Chem. Int. Ed. 57, 12388–12392 (2018).

35. Jiang, H. & Studer, A. Amidyl radicals by oxidation of a-amido-oxo acids: transition metal-free amidofluorination of unactivated Alkenes. Angew. Chem. Int. Ed. 57, 10707–10711 (2018).

36. Barton, D. H. R., Beaton, J. M., Geller, L. E. & Pechet, M. M. A new family of benzylic free radicals. J. Am. Chem. Soc. 83, 4076–4083 (1961).

37. Grady, S. A., Knauber, T. & Li, C.-J. The cross-dehydrogenative coupling of N-arylamides/dialkylzinc catalyzed enantioselective desymmetrization of aziridines with phenoxides. J. Am. Chem. Soc. 134, 19566–19569 (2012).

38. Short, M. A., Blackburn, J. M. & Roizen, J. L. Sulfamate esters guide selective Cu-catalyzed radical relay. Chem. Soc. Rev. 45, 39–58 (2016).

39. Priepichka, I., Kundra, S., Hearne, Z. & Li, C.-J. Efficient merging of copper and photoredox catalysis for the asymmetric cross-dehydrogenative-coupling of alkynes and tetrahydroisoquinolines. Org. Biomol. Chem. 13, 447–451 (2015).

40. Jiang, H., Seidler, G. & Studer, A. Carboamination of unactivated alkenes via three-component radical conjugate addition. Angew. Chem. Int. Ed. 58, 2510–2513 (2019).

41. Liu, Z. & Li, C.-J. Copper-catalyzed remote C(sp³)–H trifluoromethylation of carboxamides and sulfonamides. Angew. Chem. Int. Ed. 58, 10744–10747 (2019).

42. Glaser, C. Beiträge zur Kenntnifs des acetylenzolens. Ber. Dtsch. Chem. Ges. 2, 422–424 (1869).

43. Glaser, C. Beiträge zur Kenntnifs des acetylenzolens. Ber. Dtsch. Chem. Ges. 2, 422–424 (1869).

44. Kamata, K., Yamaguchi, S., Kotani, M., Yamaguchi, K. & Mizuno, N. Efficient oxidative alkene homocoupling catalyzed by a monomeric dicopper(CCu)-iminoguanidinate. Angew. Chem. Int. Ed. 47, 2407–2410 (2008).

45. Xiong, T. & Zhang, Q. New annihilation strategies based on nitrogen-centered radical chemistry. Chem. Soc. Rev. 45, 3069–3087 (2016).

46. Kharasch, M. S. & Sosnovsky, G. The reactions of substituted silicotungstate. J. Org. Chem. 17, 766–768 (1952).

47. Glaser, C. Beiträge zur Kenntnifs des acetylenzolens. Ber. Dtsch. Chem. Ges. 2, 422–424 (1869).

48. Kamata, K., Yamaguchi, S., Kotani, M., Yamaguchi, K. & Mizuno, N. Efficient oxidative alkene homocoupling catalyzed by a monomeric dicopper(CCu)-iminoguanidinate. Angew. Chem. Int. Ed. 47, 2407–2410 (2008).
Additional information
Supplementary information is available for this paper at https://doi.org/10.1038/s41467-019-13705-1.

Correspondence and requests for materials should be addressed to X.-Y.L.

Peer review information Nature Communications thanks Andrew Parsons and the other, anonymous, reviewer(s) for their contribution to the peer review of this work. Peer reviewer reports are available.

Reprints and permission information is available at http://www.nature.com/reprints

Publisher’s note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Open Access This article is licensed under a Creative Commons Attribution 4.0 International License, which permits use, sharing, adaptation, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons license, and indicate if changes were made. The images or other third party material in this article are included in the article’s Creative Commons license, unless indicated otherwise in a credit line to the material. If material is not included in the article’s Creative Commons license and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this license, visit http://creativecommons.org/licenses/by/4.0/.

© The Author(s) 2019