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Oxidative 1,2-carboamination of alkenes with alkyl nitriles and amines toward γ -amino alkyl nitriles

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Difunctionalization of alkenes has become a powerful tool for quickly increasing molecular complexity in synthesis. Despite significant progress in the area of alkene difunctionalization involving the incorporation of a nitrogen atom across the C–C double bonds, approaches for the direct 1,2-carboamination of alkenes to produce linear *N*-containing molecules are scarce and remain a formidable challenge. Here we describe a radical-mediated oxidative intermolecular 1,2-alkylation of alkenes with alkyl nitriles and amines involving C(sp³)-H oxidative functionalization catalysed by a combination of Ag₂CO₃ with iron Lewis acids. This three-component alkene 1,2-alkylation method is initiated by the C(sp³)-H oxidative radical functionalization, which enables one-step formation of two new chemical bonds, a C–C bond and a C–N bond, to selectively produce γ -amino alkyl nitriles.

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Difunctionalization of alkenes represents one of the most powerful and straightforward tools to build complex molecules via one-step construction of two chemical bonds that possess significantly synthetic utility in chemical synthesis^{1–6}. One of the major synthetic targets for such transformations, including diamination^{7–15}, aminoxygenation^{16–24}, aminohalogenation^{25–30} and carboamination^{31–36}, is the incorporation of a nitrogen atom (amino, amide or azide groups) across the C–C double bonds to build useful *N*-containing molecules through the formation of a C–N bond. Despite significant progress in the field, approaches of the alkene carboamination for producing linear *N*-containing molecules are scarce and remain a great challenge (Fig. 1a): available intermolecular transformations for producing linear *N*-containing molecules are restricted to the special amination reagents^{33–36}. Further, to our knowledge, three-component carboamination reactions of the alkenes via C–H functionalization have never been reported.

In recent years, the C–H oxidative functionalization reaction has attracted much attention due to its inherent features, such as high step economy and atom economy^{1–6,37–41}. Typical transformations include the difunctionalization of alkenes with alkyl C(sp³)-H bonds^{42–55} and the majority of which rely on the formation of a sp³-hybridized carbon-centred radical from the oxidative cleavage of the corresponding alkyl C(sp³)-H bond followed by addition across the C–C double bond^{43–59}. However, such approaches are restricted to the 1,2-aryllalkylation^{52–63}, 1,2-dialkylation⁵⁴ and 1,2-oxyalkylation^{55–59} of the alkenes, and the available three-component transformations are scarce^{53,55}. In light of these literature results^{43–59} and our continuous interest in oxidative radical reactions^{60–63}, we envisioned that this C–H oxidative radical functionalization strategy might be viable to achieve 1,2-carboamination of alkenes with new-conceptual, general and straightforward features.

Herein, we report an iron-catalysed oxidative three-component 1,2-carboamination of alkenes with alkyl nitriles and amines through C(sp³)-H oxidative radical functionalization to assemble γ -amino alkyl nitriles using Ag₂CO₃ as oxidant (Fig. 1b). The reaction enables the simultaneous formation of two new chemical bonds, a C–C bond and a C–N bond, by a sequence of C–H oxidative cleavage, radical addition across the alkenes and amination in a highly atom-economic and selective manner^{64–68}.

Results

Reaction optimization. We initiated the study by investigating various reaction parameters for the three-component reaction of *p*-methoxystyrene (**1a**) with acetonitrile (**2a**) and dibenzylamine

(**3a**) (Table 1). A combination of 10 mol% Fe(OTf)₃, 2 equiv Ag₂CO₃, 120 °C and 24 h were found as the optimal reaction conditions for the conversion of alkene **1a**, nitrile **2a** and amine **3a** to the desired product **4** in 82% yield (entry 1). The results suggest that Ag₂CO₃ is the real catalysts and Fe(OTf)₃ only serves as a Lewis acid to promote the reaction (entries 2 and 3): although in the absence of Fe(OTf)₃, transformation of alkene **2a** to **4** took place albeit giving a lower yield (entry 2), no desired reaction was observed without Ag salts (entry 3). Other Ag salts, including Ag₂O, AgOAc and AgNO₃, had the catalytic activity for the reaction, but they were less effective than Ag₂CO₃ (entries 4–6). Among the amount of Ag₂CO₃ examined, the use of 2 equiv was turned out to be preferred (entries 1, 7 and 8). Encouraged by these, a series of other Lewis acids, such as FeCl₃, Yb(OTf)₃, Cu(OTf)₂ and In(OTf)₃, were tested (entries 9–12): they could improve the reaction, but were less effective than Fe(OTf)₃. Notably, the use of other bases, Na₂CO₃ or Cs₂CO₃, instead of Ag₂CO₃, resulted in no formation of product **4** (entries 13 and 14), suggesting that Ag₂CO₃ may act as an oxidant and a catalyst, not a base. Notably, the reported efficient oxidative systems, *t*BuOO*t*Bu di-*tert*-butyl peroxide (DTBP)^{42–55} or Ag₂CO₃/K₂S₂O₈ (refs 60–67) displayed rather lower activity for the reaction (entries 15 and 16). We found that the reaction was sensitive to the temperatures (entries 17 and 18): a lower temperature (100 °C) had a negative effect on the reaction, whereas a higher temperature (130 °C) did not improve the yield compared with the results at 120 °C. Gratifyingly, the reaction could be successfully performed in PhCF₃ medium (entry 19).

Substrate scope with amines and amides. We next explored the scope of this Ag₂CO₃-mediated 1,2-carboamination protocol under the optimal reaction conditions with regard to alkenes **1**, nitriles **2** and amines **3** (Tables 2 and 3). We first turned our attention to investigate the applicability of the optimal conditions in the reaction with various amines **3b–m** in the presence of alkene **1a** and acetonitrile **2a** (Table 2). The results indicated that a wide range of secondary and primary amines **3b–j** were smoothly converted to the desired products **5–13** in moderate to good yields. *N*-Methyl-1-phenylmethanamine (**3b**) was viable to furnish **5** with 89% yield in the presence of Fe(OTf)₃ and Ag₂CO₃. For other amines **3c–j**, however, Fe(OTf)₃ displayed less efficient than FeCl₃ (products **6–13**): although treatment of alkene **1a** with nitrile **2a**, diisopropylamine (**3c**), Fe(OTf)₃ and Ag₂CO₃ afforded **6** in 56% yield, the use of FeCl₃ instead of Fe(OTf)₃ enhanced the yield to 66%. Similarly, the yield of **10** from the reaction with morpholine (**3g**) increased from 74 to 83% when using FeCl₃ instead of Fe(OTf)₃. To our delight, the optimal

Figure 1 | 1,2-Carboamination of alkenes. (a) Previous work for 1,2-carboamination of alkenes^{33–36}. (b) Our radical-mediated three-component, oxidative carboamination between alkenes, alkyl nitriles and amines using a C–H oxidative functionalization.

Table 1 | Screening of optimal reaction conditions.

Entry	Variation from the optimal conditions	Yield (%) [*]
1	None	82
2	Without Fe(OTf) ₃	33
3	Without Ag ₂ CO ₃	0
4	Ag ₂ O instead of Ag ₂ CO ₃	34
5	AgOAc instead of Ag ₂ CO ₃	15
6	AgNO ₃ instead of Ag ₂ CO ₃	6
7	Ag ₂ CO ₃ (1 equiv)	53
8	Ag ₂ CO ₃ (3 equiv)	80
9	FeCl ₃ instead of Fe(OTf) ₃	68
10	Yb(OTf) ₃ instead of Fe(OTf) ₃	68
11	Cu(OTf) ₂ instead of Fe(OTf) ₃	41
12	In(OTf) ₃ instead of Fe(OTf) ₃	63
13	Na ₂ CO ₃ instead of Ag ₂ CO ₃	0
14	Cs ₂ CO ₃ instead of Ag ₂ CO ₃	0
15	(tBuO) ₂ instead of Ag ₂ CO ₃	trace
16 [†]	Ag ₂ CO ₃ /K ₂ S ₂ O ₈ instead of Ag ₂ CO ₃	trace
17	At 100 °C	52
18	At 130 °C	80
19 [‡]	MeCN (0.2 ml; 3.85 mmol)	78

Experiments were performed with **1a** (0.3 mmol), MeCN **2a** (2 ml), Bn₂NH **3a** (2 equiv), Fe(OTf)₃ (10 mol%), Ag₂CO₃ (2 equiv), 120 °C and 24 h.

^{*}Average isolated yield twice.

[†]Ag₂CO₃ (20 mol%) and K₂S₂O₈ (2 equiv).

[‡]PhCF₃ (1.8 ml).

Table 3 | Variation of the alkenes (1).

Experiments were performed with **1** (0.3 mmol), nitrile **2a** (2 ml), amine **3g** (2 equiv), FeCl₃ (10 mol%), Ag₂CO₃ (2 equiv), 120 °C, 24 h. The dr value is given in parentheses as determined by ¹H NMR analysis of the crude product.

^{*}Using (E)-1-methoxy-4-(prop-1-en-1-yl)benzene (**1o**).

[†]Using (Z)-1-methoxy-4-(prop-1-en-1-yl)benzene (**1p**).

Table 2 | Variation of the alkyl nitriles (2) and amines (3).

Experiments were performed with **1a** (0.3 mmol), nitrile **2** (2 ml), amine **3** (2 equiv), [Fe] (10 mol%), Ag₂CO₃ (2 equiv), 120 °C, 24 h. The dr value is given in parentheses as determined by ¹H NMR analysis of the crude product.

^{*}Using Fe(OTf)₃.

[†]Using FeCl₃.

conditions were compatible with sulfonamides **3e**, **3k** and **3l**, giving products **8**, **14** and **15** in high yields. Unfortunately, attempt to difunctionalization with acetamide **3m** failed to build 1,2-carboamination product **16**.

Subsequently, the scope of alkyl nitriles **2** was exploited in the presence of alkene **1a**, morpholine **3g**, FeCl₃ and Ag₂CO₃ (Table 2). In the case of butyronitrile **2b**, the reaction afforded **17** in 66% yield. Gratifyingly, the reaction was well tolerated of various acetonitriles **2c–e** bearing a Ph group, a MeO group or a CO₂Et group at the α position, generating **18–20** in 50–70% yields. An interesting observation was that secondary alkyl nitrile **2f** containing a cyclohexyl ring also proceeded the reaction and resulted in the formation of **21** in 58% yield.

Substrate scope with alkenes. The optimal conditions were applicable to an array of alkenes **1b–f**, **1h–i** and **1k–s** (products **22–26**, **28–29** and **31–38**), but electron-withdrawing aryl alkene **1g** and simple aliphatic alkene, namely oct-1-ene (**1j**), had no reactivity (products **27** and **30**; Table 3). Initially, the substitution effect of the aryl ring at the terminal alkenes were examined: several substituted aryl rings, such as *m*-MeOC₆H₄, *o*-MeOC₆H₄, C₆H₅, *p*-MeC₆H₄, *m*-MeC₆H₄, naphthalen-2-yl and 3-methylthiophen-2-yl, were perfectly tolerated, and both the electronic nature of the aryl group and the substituent position on the aryl group had an impact on the reactivity (products **22–29**). Using *m*-methoxystyrene (**1b**), for example, afforded **22** in 55% yield, whereas bulky *o*-methoxystyrene (**1c**) furnished **23** in 76% yield. Alkene **1f** having a weak electron-deficient 4-ClC₆H₄ group successfully underwent the 1,2-alkylamination reaction to offer **26**, albeit in a diminished yield. However, alkene **1g** having a strong electron-deficient 4-CNC₆H₄ group had no reactivity (product **27**). Gratifyingly, the optimal conditions were consistent with 1,1-disubstituted alkenes, including 1,1-diphenylethylene (**1k**), prop-1-en-2-ylbenzene (**1l**), 1-methoxy-4-(3-methylbut-3-en-1-yn-1-yl)benzene (**1m**) and 1-methylene-1,2,3,4-tetrahydronaphthalene (**1n**), generating **31–34** with concomitant formation of a quaternary carbon centre. A particularly attractive feature of this 1,2-alkylamination is the ability to enable the conversion of

Figure 2 | Control experiments and utilizations of product 4. (a) Radical testing experiment based on the selectivity. (b) Trapping experiments with a stoichiometric amount of radical inhibitors. (c) Kinetic isotopic effect (KIE) study. (d) Synthetic utilizations.

Figure 3 | Possible mechanism. The alkyl radical **C** is generated from decomposition of the AgCH_2CN intermediate **B** via single-electron transfer. Subsequently, addition of the alkyl radical **C** across the C–C double and oxidative amination afford product **4**.

di- and trisubstituted internal alkenes **1o–s** to diverse complex products **35–38** in moderate to good yields. It was noted that the reaction of (*E*)-1-methoxy-4-(prop-1-en-1-yl)benzene (**1o**) or (*Z*)-1-methoxy-4-(prop-1-en-1-yl)benzene (**1p**) had no retention of geometrical selectivity in the double bond (product **35**), which supported a radical process.

Control experiments and mechanistic studies. Using (1-cyclopropylvinyl)benzene (**1t**) to react with nitrile **2a** and amine **3g**, the 1,2-alkylation product **39** along with the mono alkylation/ring-opening/cyclization product **40** was observed (Fig. 2a)⁵⁵. Notably, the reaction of alkene **1a** with nitrile **2a** and amine **3a** could not take place in the presence of a stoichiometric amount of radical

inhibitors, such as 2,2,6,6-Tetramethyl-1-piperidinyloxy (TEMPO), 2,6-di-*tert*-butyl-4-methylphenol and hydroquinone (Fig. 2b).

In addition, under the optimal conditions nitrile **2a** reacted with TEMPO afforded product **41**. These results suggested that the current reaction is triggered by a free-radical process. The kinetic isotope effect experiment gave a large kinetic isotope effect value ($k_{\text{H}}/k_{\text{D}} = 2.7$), implying that the cleavage of the $\text{C}(sp^3)\text{–H}$ bond may be rate-limiting (Fig. 2c and for the detailed information, see Supplementary Fig. 39)^{37–55}. Gratifyingly, product **4** were easily converted to 1,4-diamine **42**, γ -amino acid **43** and γ -amino amide **44** in good yields (Fig. 2d)^{69,70}.

Consequently, the mechanisms for the Ag_2CO_3 -mediated 1,2-alkylation reaction was proposed (Fig. 3)^{31–68}.

Coordination of the nitrogen atom in MeCN **2a** with AgCO₃ gives the intermediate **A**, which sequentially reacts with AgCO₃ to afford the AgCH₂CN intermediate **B** and AgHCO₃. The decomposition of the AgCH₂CN intermediate **B** readily takes place under heating to form the alkyl radical **C** (supported by the results of Fig. 2b), AgHCO₃ and the Ag⁰ species [Ag(s)] through single electron transfer^{42–65}. Subsequently, addition of the alkyl radical **C** across the C–C double bond in alkene **1a** produces the alkyl radical intermediate **D** (supported by the reaction of alkene **1t**; Fig. 2a). Intermediate **D** is converted into the carbon-centered cation **E**, followed by reaction with amine **3a** affords the product **4**, AgHCO₃ and the Ag⁰ species through a sequence of oxidation and nucleophilic addition^{64–68}. Notably, the radical intermediates **C** and **D** can be stabilized by Lewis acids, thus improving the yields.

In summary, we have developed a silver-mediated intermolecular 1,2-alkylation of alkenes with alkyl nitriles and amines involving C(sp³)–H oxidative radical functionalization for producing γ -amino alkyl nitriles. The generality of such an intermolecular 1,2-alkylation reaction is demonstrated by a wide scope with respect to alkenes, alkyl nitriles and amines. The radical mechanism was also discussed according to the control experiments. Importantly, applications of the products, γ -amino alkyl nitriles, to prepare other valuable synthons have been examined. Currently, our laboratory is working to apply this C–H oxidative radical functionalization strategy in synthesis.

Methods

General procedure for 1,2-carboamination of alkenes. To a Schlenk tube were added Fe(OTf)₃ or FeCl₃ (10 mol%), Ag₂CO₃ (0.6 mmol), alkene **1** (0.3 mmol), amine **2** (0.6 mmol) and MeCN (2 ml). Then the tube was recharged with argon and the mixture was stirred at 120 °C for 24 h. After cooling to room temperature, the mixture was filtered through a small plug of silica gel to remove the precipitate and washed with EtOAc (3 × 10 ml). The solvent was then removed in vacuo and the residue was further purified by silica gel flash column chromatography (10–40% ethyl acetate/hexane + 0.1% Et₃N) to afford the desired product.

Data availability. The X-ray crystallographic coordinates for structures reported in this study have been deposited at the Cambridge Crystallographic Data Centre under deposition number 1453224 (4). These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif. All other data supporting the findings of this study are available within the article and its Supplementary Information file or from the authors upon reasonable request. For NMR spectra of the compounds in this article, see Supplementary Figs 1–39.

References

- Patai, S. *The Chemistry of Alkenes* (Wiley Interscience, 1964).
- Li, G., Chang, T.-T. & Sharpless, B. K. Catalytic asymmetric aminohydroxylation (AA) of olefins. *Angew. Chem. Int. Ed. Engl.* **35**, 451–454 (1996).
- Wolfe, J. P. Stereoselective synthesis of saturated heterocycles via palladium-catalyzed alkene carboetherification and carboamination reactions. *Synlett* **2008**, 2913–2937 (2008).
- Wolfe, J. P. Intramolecular alkoxyacylation and alkoxyacylation reactions: new types of alkene difunctionalizations for the construction of oxygen heterocycles. *Angew. Chem. Int. Ed.* **51**, 10224–10225 (2012).
- Romero, R. M., Woste, T. H. & Muniz, K. Vicinal difunctionalization of alkenes with iodine(III) reagents and catalysts. *Chem. Res.* **47**, 972–983 (2014).
- Francesca, C. & Goti, A. Metal-catalysed 1,2-diamination reactions. *Nat. Chem.* **1**, 269–275 (2009).
- Lucet, D., Gall, T. L. & Mioskowski, C. The chemistry of vicinal diamines. *Angew. Chem. Int. Ed.* **37**, 2580–2627 (1998).
- de Figueiredo, R. M. Transition-metal-catalyzed diamination of olefins. *Angew. Chem. Int. Ed.* **48**, 1190–1193 (2009).
- Zhu, Y., Cornwall, R. G., Du, H., Zhao, B. & Shi, Y. Catalytic diamination of olefins via N–N bond activation. *Acc. Chem. Res.* **47**, 3665–3678 (2014).
- Streuff, J., Höelmann, C. H., Nieger, M. & Muñoz, K. Palladium(II)-catalyzed intramolecular diamination of unfunctionalized alkenes. *J. Am. Chem. Soc.* **127**, 14586–14587 (2005).
- Iglesias, A., Pérez, E. & Muñoz, K. An Intermolecular palladium-catalyzed diamination of unactivated alkenes. *Angew. Chem. Int. Ed.* **49**, 8109–8111 (2010).
- Röben, C., Souto, J. A., González, Y., Lishchynskyi, A. & Muñoz, K. Enantioselective metal-free diamination of styrenes. *Angew. Chem. Int. Ed.* **50**, 9478–9482 (2011).
- Martínez, C. & Muñoz, K. Palladium-catalyzed vicinal difunctionalization of internal alkenes: diastereoselective synthesis of diamines. *Angew. Chem. Int. Ed.* **51**, 7031–7034 (2012).
- Zhang, B. & Studer, A. Copper-catalyzed intermolecular aminoazidation of alkenes. *Org. Lett.* **16**, 1790–1793 (2014).
- Yuan, Y.-A., Lu, D.-F., Chen, Y.-R. & Xu, H. Iron-catalyzed direct diazidation for a broad range of olefins. *Angew. Chem. Int. Ed.* **55**, 534–538 (2016).
- Alexanian, E. J., Lee, C. & Sorensen, E. J. Palladium-catalyzed ring-forming aminoacetoxylation of alkenes. *J. Am. Chem. Soc.* **127**, 7690–7691 (2005).
- Liu, G. & Stahl, S. S. Highly regioselective Pd-catalyzed intermolecular aminoacetoxylation of alkenes and evidence for cis-aminopalladation and SN₂ C–O bond formation. *J. Am. Chem. Soc.* **128**, 7179–7181 (2006).
- Desai, L. V. & Sanford, M. S. Construction of tetrahydrofurans by Pd^{II}/Pd^{IV}-catalyzed aminoxylation of alkenes. *Angew. Chem. Int. Ed.* **46**, 5737–5740 (2007).
- Zhu, H., Chen, P. & Liu, G. Pd-catalyzed intramolecular aminohydroxylation of alkenes with hydrogen peroxide as oxidant and water as nucleophile. *J. Am. Chem. Soc.* **136**, 1766–1769 (2014).
- Zhu, H., Chen, P. & Liu, G. Palladium-catalyzed intramolecular aminoacetoxylation of unactivated alkenes with hydrogen peroxide as oxidant. *Org. Lett.* **17**, 1485–1488 (2015).
- Chen, C., Chen, P. & Liu, G. Palladium-catalyzed intramolecular aminotrioxymethoxylation of alkenes. *J. Am. Chem. Soc.* **137**, 15648–15651 (2015).
- Sun, X. *et al.* Mn-catalyzed highly efficient aerobic oxidative hydroxyazidation of olefins: a direct approach to β -azido alcohols. *J. Am. Chem. Soc.* **137**, 6059–6066 (2015).
- Rao, W.-H., Yin, X.-S. & Shi, B.-F. Catalyst-controlled amino-versus oxy-acetoxylation of urea-tethered alkenes: efficient synthesis of cyclic ureas and isoureas. *Org. Lett.* **17**, 3758–3761 (2015).
- Legnani, L. & Morandi, B. Direct catalytic synthesis of unprotected 2-amino-1-phenylethanol from alkenes by using iron(II) phthalocyanine. *Angew. Chem. Int. Ed.* **55**, 2248–2251 (2016).
- Wu, T., Yin, G. & Liu, G. Palladium-catalyzed intramolecular aminofluorination of unactivated alkenes. *J. Am. Chem. Soc.* **131**, 16354–16355 (2009).
- Qiu, S., Xu, T., Zhou, J., Guo, Y. & Liu, G. Palladium-catalyzed intermolecular aminofluorination of styrene. *J. Am. Chem. Soc.* **132**, 2856–2857 (2010).
- Yin, G., Wu, T. & Liu, G. Highly selective palladium-catalyzed intramolecular chloroamination of unactivated alkenes by using hydrogen peroxide as an oxidant. *Chem. Eur. J.* **18**, 451–455 (2012).
- Bovino, M. T. & Chemler, S. R. Catalytic enantioselective alkene aminohalogenation/cyclization involving atom transfer. *Angew. Chem. Int. Ed.* **51**, 3923–3927 (2012).
- Kong, W., Feige, P., de Haro, T. & Nevado, C. Regio- and enantioselective aminofluorination of alkenes. *Angew. Chem. Int. Ed.* **52**, 2469–2473 (2013).
- Zhang, H., Song, Y., Zhao, J., Zhang, J. & Zhang, Q. Regioselective radical aminofluorination of styrenes. *Angew. Chem. Int. Ed.* **53**, 11079–11083 (2014).
- Mai, D. N. & Wolfe, J. P. Asymmetric palladium-catalyzed carboamination reactions for the synthesis of enantiomerically enriched 2-(arylmethyl)- and 2-(alkenylmethyl)pyrrolidines. *J. Am. Chem. Soc.* **132**, 12157–12159 (2010).
- Faulkner, A., Scott, J. S. & Bower, J. F. An umpolung approach to alkene carboamination: palladium catalyzed 1,2-amino-acylation, -carboxylation, -arylation, -vinylation, and -alkynylation. *J. Am. Chem. Soc.* **137**, 7224–7230 (2015).
- Piou, T. & Rovis, T. Rhodium-catalysed syn-carboamination of alkenes via a transient directing group. *Nature* **527**, 86–90 (2015).
- Cheng, J., Qi, X., Li, M., Chen, P. & Liu, G. Palladium-catalyzed intermolecular aminocarbonylation of alkenes: efficient access of β -amino acid derivatives. *J. Am. Chem. Soc.* **137**, 2480–2483 (2015).
- Weidner, K., Girault, A., Panchaud, P. & Renaud, P. Efficient carboazidation of alkenes using a radical desulfonylative azide transfer process. *J. Am. Chem. Soc.* **132**, 17511–17515 (2010).
- Zhang, H. *et al.* Copper-catalyzed intermolecular aminocyanation and diamination of alkenes. *Angew. Chem. Int. Ed.* **52**, 2529–2533 (2013).
- Liu, C., Zhang, H., Shi, W. & Lei, A. Bond formations between two nucleophiles: transition metal catalyzed oxidative cross-coupling reactions. *Chem. Rev.* **111**, 1780–1824 (2011).
- Xie, Y.-X., Song, R.-J., Xiang, J.-N. & Li, J.-H. Transition metal-catalyzed C–H oxidation reactions. *Chin. J. Org. Chem.* **32**, 1555–1567 (2012).
- Zhang, C., Tang, C. & Jiao, N. Recent advances in copper-catalyzed dehydrogenative functionalization via a single electron transfer (SET) process. *Chem. Soc. Rev.* **41**, 3464–3484 (2012).

40. Girard, S. A., Knauber, T. & Li, C.-J. The cross-dehydrogenative coupling of Csp³-bonds: a versatile strategy for C-C bond formations. *Angew. Chem. Int. Ed.* **53**, 74–100 (2014).
41. Song, R.-J., Liu, Y., Xie, Y.-X. & Li, J.-H. Difunctionalization of acrylamides through C-H oxidative radical coupling: new approaches to oxindoles. *Synthesis* **47**, 1195–1209 (2015).
42. Wu, T., Mu, X. & Liu, G.-S. Palladium-catalyzed oxidative arylalkylation of activated alkenes: dual C-H bond cleavage of an arene and acetonitrile. *Angew. Chem. Int. Ed.* **50**, 12578–12581 (2011).
43. Wei, W.-T. *et al.* Synthesis of oxindoles by iron-catalyzed oxidative 1,2-alkylarylation of activated alkenes with an aryl C(sp²)-H bond and a C(sp³)-H bond adjacent to a heteroatom. *Angew. Chem. Int. Ed.* **52**, 3638–3641 (2013).
44. Zhou, M.-B. *et al.* Oxidative 1,2-difunctionalization of activated alkenes with benzylic C(sp³)-H bonds and aryl C(sp²)-H bonds. *Chem. Commun.* **49**, 10817–10819 (2013).
45. Zhou, S.-L., Guo, L.-N., Wang, H. & Duan, X.-H. Copper-catalyzed oxidative benzylarylation of acrylamides by benzylic C-H bond functionalization for the synthesis of oxindoles. *Chem. Eur. J.* **19**, 12970–12973 (2013).
46. Wang, H., Guo, L.-N. & Duan, X.-H. Silver-catalyzed oxidative coupling/cyclization of acrylamides with 1,3-dicarbonyl compounds. *Chem. Commun.* **49**, 10370–10373 (2013).
47. Li, Z.-J., Zhang, Y., Zhang, L.-Z. & Liu, Z.-Q. Free-radical cascade alkylarylation of alkenes with simple alkanes: highly efficient access to oxindoles via selective (sp³)C-H and (sp²)C-H bond functionalization. *Org. Lett.* **16**, 382–385 (2014).
48. Li, J., Wang, Z., Wu, N., Gao, G. & You, J. Radical cascade cyanomethylation of activated alkenes to construct cyano substituted oxindoles. *Chem. Commun.* **50**, 15049–15051 (2014).
49. Chu, X.-Q., Xing, Z.-H., Meng, H., Xu, X.-P. & Ji, S.-J. Copper-mediated radical alkylarylation of unactivated alkenes with acetonitrile leading to fluorenes and pyrroloindoles. *Org. Chem. Front.* **3**, 165–169 (2016).
50. Li, Y., Liu, B., Li, H.-B., Wang, Q. & Li, J.-H. Oxidative radical 1,2-alkylarylation of alkenes with α -C(sp³)-H bonds of acetonitriles involving 1,2-aryl migration. *Chem. Commun.* **51**, 1024–1026 (2015).
51. Chu, X.-Q., Meng, H., Zi, Y., Xu, X.-P. & Ji, S.-J. Oxidative C(sp³)-H functionalization of acetonitrile and alkanes with allylic alcohols under metal-free conditions. *Org. Chem. Front.* **2**, 216–220 (2015).
52. Bunescu, A., Wang, Q. & Zhu, J. Copper-catalyzed cyanomethylation of allylic alcohols with concomitant 1,2-aryl migration: efficient synthesis of functionalized ketones containing an α -quaternary center. *Angew. Chem. Int. Ed.* **54**, 3132–3135 (2015).
53. Bunescu, A., Wang, Q. & Zhu, J. Synthesis of functionalized epoxides by copper-catalyzed alkylative epoxidation of allylic alcohols with alkyl nitriles. *Org. Lett.* **17**, 1890–1893 (2015).
54. Liang, W., Chen, P. & Liu, G. AgF-mediated dialkylation of activate alkenes: an efficient access to nitrile-containing spirooxindoles. *Chin. J. Chem.* **32**, 681–684 (2014).
55. Bunescu, A., Wang, Q. & Zhu, J. Copper-mediated/catalyzed oxyalkylation of alkenes with alkyl nitriles. *Chem. Eur. J.* **20**, 14633–14636 (2014).
56. Chatalova-Sazepin, C., Wang, Q., Sammis, G. M. & Zhu, J. Copper-catalyzed intermolecular carboetherification of unactivated alkenes by alkyl nitriles and alcohols. *Angew. Chem. Int. Ed.* **54**, 5443–5446 (2015).
57. Liao, Z. *et al.* Copper-catalyzed radical carboxygeneration: alkylation and alkoxylation of styrenes. *Chem. Asian J.* **10**, 96–99 (2015).
58. Ha, T. M., Chatalova-Sazepin, C., Wang, Q. & Zhu, J. Copper-catalyzed formal [2 + 2 + 1] heteroannulation of alkenes, alkyl nitriles, and water: method development and application to a total synthesis of (±)-Sacidumlignan D. *Angew. Chem. Int. Ed.* **55**, 9249–9252 (2016).
59. Ha, T. M., Wang, Q. & Zhu, J. Copper-catalysed cyanoalkylative cycloetherification of alkenes to 1,3-dihydroisobenzofurans: development and application to the synthesis of citalopram. *Chem. Commun.* **52**, 11100–11103 (2016).
60. Zhou, M.-B. *et al.* Metal-free oxidative tandem coupling of activated alkenes with carbonyl C(sp²)-H bonds and aryl C(sp²)-H bonds using TBHP. *Chem. Sci.* **4**, 2690–2694 (2013).
61. Fan, J.-H. *et al.* Iron-catalyzed oxidative arylmethylation of activated alkenes using a peroxide as the methyl source. *Synlett* **25**, 657–660 (2014).
62. Hu, M. *et al.* Metal-free radical [2 + 2 + 1] carbocyclization of benzene-linked 1,n-enynes: dual C(sp³)-H functionalization adjacent to a heteroatom. *Angew. Chem. Int. Ed.* **54**, 9577–9580 (2015).
63. Ouyang, X.-H., Song, R.-J., Hu, M., Yang, Y. & Li, J.-H. Silver-mediated intermolecular 1,2-alkylarylation of styrenes with α -carbonyl alkyl bromides and indoles. *Angew. Chem. Int. Ed.* **55**, 3187–3191 (2016).
64. Harmata, M. *Silver in Organic Chemistry* (John Wiley & Sons Inc., 2010).
65. He, C. *et al.* Silver-mediated oxidative C-H/C-H functionalization: a strategy to construct polysubstituted furans. *J. Am. Chem. Soc.* **134**, 5766–5769 (2012).
66. Li, Z., Song, L. & Li, C. Silver-catalyzed radical aminofluorination of unactivated alkenes in aqueous media. *J. Am. Chem. Soc.* **135**, 4640–4643 (2013).
67. Wei, X.-H., Li, Y.-M., Zhou, A.-X., Yang, T.-T. & Yang, S.-D. Silver-catalyzed carboazidation of arylacrylamides. *Org. Lett.* **15**, 4158–4161 (2013).
68. Liu, J. *et al.* Silver-catalyzed cross-coupling of isocyanides and active methylene compounds by a radical process. *Angew. Chem. Int. Ed.* **54**, 10618–10622 (2015).
69. Rappoport, Z. *The Chemistry of the Cyano Group* (Wiley, 1970).
70. Maffioli, S. I., Marzorati, E. & Marazzi, A. Mild and reversible dehydration of primary amides with PdCl₂ in aqueous acetonitrile. *Org. Lett.* **7**, 5237–5239 (2005).

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Author contributions

Y.-Y.L. and X.-H.Y. contributed equally to this work. Y.-Y.L., X.-H.Y., S.L. and J.-H.L. conceived the project and wrote the manuscript. Y.-Y.L. and X.-H.Y. performed the experiments. Y.-Y.L., X.-H.Y. and R.-J.S. analysed the data.

Additional information

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