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Copper-catalyzed three-component oxycyanation of alkenes†

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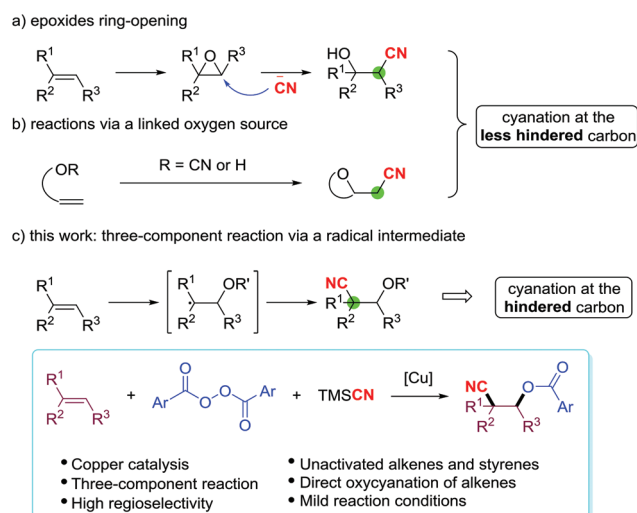
A copper-catalyzed, three-component reaction for the direct oxycyanation of various alkenes with aryl diacyl peroxides and trimethylsilyl cyanide has been developed. Both unactivated alkenes and styrenes are reliable substrates and produce β -cyanohydrin derivatives. An asymmetric version of this reaction has been conducted and proceeds well.

Nitriles are important molecules that are structural motifs in natural products and pharmaceuticals.¹ They are also one of the most versatile types of compounds in organic synthesis because the cyano group can be easily transformed into other different functional groups to afford valuable organic compounds.² In view of the abundant supply of alkenes, direct vicinal cyanofunctionalization of C=C double bonds is a straightforward strategy for the construction of nitriles. The cyanofunctionalization of the C=C double bond has drawn much attention and significant advances have been achieved in the hydrocyanation³ and carbocyanation⁴ of alkenes through either an intramolecular or an intermolecular process.⁵

The direct vicinal oxycyanation of alkenes is a remarkable strategy which simultaneously incorporates a cyano group and an oxygen-containing group into the C=C double bond, forming versatile β -cyanohydrins or their derivatives. A common and versatile approach to β -cyanohydrins is the nucleophilic ring-opening of strained triangular epoxides with a cyanide anion source (Scheme 1a).⁶ The cyanide anion prefers to regioselectively attack the less substituted carbon center in the epoxide. In recent years, successful oxycyanation of alkenes has also been developed. Nakao *et al.*⁷ and Shi's group⁸ independently disclosed a palladium-catalyzed intramolecular oxycyanation of C=C double bonds (Scheme 1b). Both the methods are proposed to involve the cleavage of the O-CN bond by an electron-rich Pd(0) catalyst, as depicted in

their mechanisms. On the other hand, two-component oxycyanation of alkenes with a linked oxygen source has been reported by Alexanian,⁹ Han,^{5g} and Zhu¹⁰ (Scheme 1b). However, these oxycyanation reactions are limited by their tendency to generate β -cyanohydrin derivatives with the cyano group attached to the less substituted carbon center.

An attraction of three-component oxycyanation of alkenes is that it uses a one-step process to assemble multifunctional structures from various compounds, and this can greatly broaden the utility of the method. Recently, Liu *et al.* described an electron donor-acceptor (EDA) complex enabled three-component oxycyanation of C=C double bonds.¹¹ Electron-rich vinyl ethers are the key substrates in this reaction, but the direct oxycyanation of alkenes in a three-component model with generic unactivated alkenes is a valuable process. Herein, we report the three-component, copper-catalyzed oxycyanation of unactivated alkenes and styrenes with



Scheme 1 Oxycyanation of alkenes.

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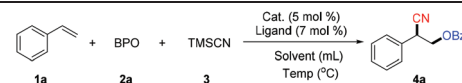
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aryl diacyl peroxides as the oxygen source and trimethylsilyl cyanide (TMSCN) as the cyano source (Scheme 1c). Mechanistic studies suggest that the O-radical attacks the double bond first and the reaction produces the β -cyanohydrin derivatives with the cyano group at the more substituted carbon center.

We began by examining the scope of copper catalysts, ligands, solvents and temperature, using the model reaction of styrene with benzoyl peroxide¹² (BPO, **2a**) and TMSCN (**3**). The details of the optimization of the conditions are provided in Table 1. Copper catalysts were screened with 1,10-phenanthroline (**L1**) as the ligand and CH₃CN as the solvent at 50 °C. Cu(CH₃CN)₄PF₆ was the most effective catalyst tested with which the reaction provided the desired oxycyanation product (**4a**) in 47% yield (entries 1–3). Solvents such as HFIP (hexafluoroisopropanol) and 1,4-dioxane were less efficient than CH₃CN, but TFEA (2,2,2-trifluoroethanol) provided the highest yield (entries 4–6). The yield of **4a** was increased to 77% by using higher concentrations of the substrates (entries 7–9). Other ligands were evaluated, and it was found that 1,10-phenanthroline is the most effective ligand (entries 10–14 vs. entry 9). The yield of the desired product (**4a**) was further improved to 83% by using two equivalents of TMSCN (entry 15). In the absence of any ligand, the catalytic efficiency drops dramatically (entry 16).

Table 1 Optimization of the reaction conditions^a



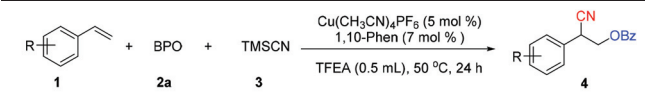
Entry	Cat.	Ligand	Solvent (mL)	Yield ^b (%)
1	Cu(CH ₃ CN) ₄ PF ₆	L1	CH ₃ CN (2)	47
2	CuTc	L1	CH ₃ CN (2)	17
3	CuOAc	L1	CH ₃ CN (2)	2
4	Cu(CH ₃ CN) ₄ PF ₆	L1	HFIP (2)	33
5	Cu(CH ₃ CN) ₄ PF ₆	L1	Dioxane (2)	23
6	Cu(CH ₃ CN) ₄ PF ₆	L1	TFEA (2)	54
7	Cu(CH ₃ CN) ₄ PF ₆	L1	TFEA (1.5)	60
8	Cu(CH ₃ CN) ₄ PF ₆	L1	TFEA (1)	67
9	Cu(CH ₃ CN) ₄ PF ₆	L1	TFEA (0.5)	77
10	Cu(CH ₃ CN) ₄ PF ₆	L2	TFEA (0.5)	38
11	Cu(CH ₃ CN) ₄ PF ₆	L3	TFEA (0.5)	35
12	Cu(CH ₃ CN) ₄ PF ₆	L4	TFEA (0.5)	66
13	Cu(CH ₃ CN) ₄ PF ₆	L5	TFEA (0.5)	69
14	Cu(CH ₃ CN) ₄ PF ₆	L6	TFEA (0.5)	71
15 ^c	Cu(CH ₃ CN) ₄ PF ₆	L1	TFEA (0.5)	83(81)
16	Cu(CH ₃ CN) ₄ PF ₆	—	TFEA (0.5)	13

^a Reaction conditions: **1a** (0.50 mmol, 1 equiv.), **2a** (1.5 equiv.), **3** (1.5 equiv.), cat., ligand, and solvent, at 50 °C for 24 h. ^b Yield was determined by ¹H NMR analysis. ^c 2 equiv. of **3** were used; an isolated yield in parentheses.

With the optimized reaction conditions in hand, the substrate scope of the reaction with respect to vinylarenes was investigated (Table 2). The reactions of *o*-, *m*- or *p*-alkyl-substituted vinylarenes with BPO afforded the corresponding oxycyanation products (**4b–4e**) in moderate yields. Vinylarenes bearing an ester substituent also underwent this reaction, affording the product (**4f**) in 66% yield. When a halogen, such as fluorine, chlorine, or bromine, was attached to the phenyl ring, the reaction afforded the desired products (**4g–4k**) in moderate yields. A 1,1-disubstituted vinylarene was also examined and it was found to be a suitable substrate in the reaction, producing the product (**4l**) in 53% yield. Acyclic or cyclic 1,2-disubstituted vinylarenes were also compatible under the reaction conditions, giving the corresponding oxycyanation products (**4m–4p**) in moderate yields. This reaction can proceed with more complex substrates. For example, the oxycyanation product (**4q**) can be produced in 46% yield with the substrate that is a derivative from the natural product estrone.¹³

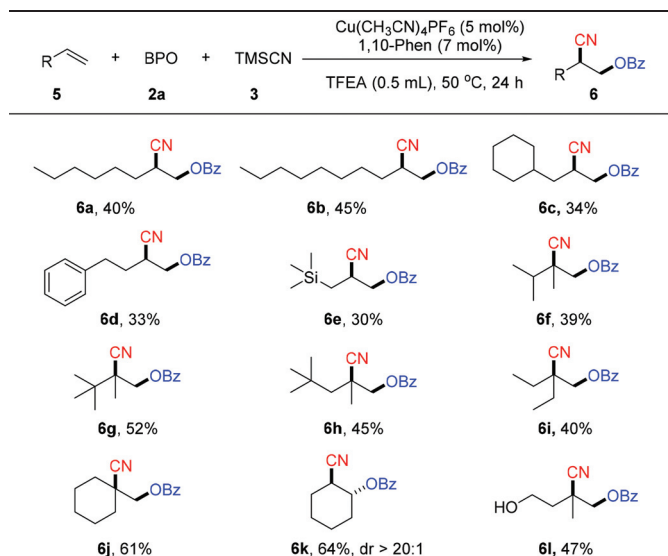
We next examined unactivated alkenes, a class of challenging but useful substrates (Table 3). In general, the reactions of a variety of unactivated alkenes afford the corresponding products with less efficiency than the reactions of styrenes. Unactivated alkenes with an alkyl chain could afford the desired oxycyanation in moderate yield (**6a–6c**). 1,1-Disubstituted unactivated alkenes were suitable substrates for this reaction, producing the oxycyanation products (**6f–6j**) in yields of 39–61%. Notably, this reaction can use not only terminal alkenes as the substrates, but also internal alkenes. For example, cyclohexene is a good substrate for the reaction, affording the desired product (**6h**) in 61% yield. Substrates

Table 2 Scope for oxycyanation of styrenes^a



4b , 53%	4c , 55%	4d , 43%	4e , 66%
4f , 66%	4g , 67%	4h , 62%	4i , 53%
4j , 64%	4k , 56%	4l , 53%	4m , 53%, dr = 1:1
4n , 51%, dr > 20:1	4o , 43%, dr = 5:1	4p , 30%, dr = 2:1	4q , ^b 46%, dr = 1:1

^a Reaction conditions: **1** (0.50 mmol, 1 equiv.), **2a** (1.5 equiv.), and **3** (2 equiv.) in TFEA (0.5 mL) at 50 °C for 24 h. ^b Addition of 5 mol % of Hantzsch ester.

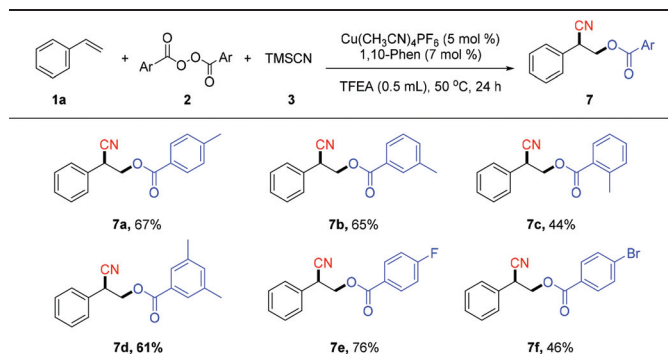
Table 3 Scope of the oxycyanation reaction with unactivated alkenes^a

^a Reaction conditions: 5 (0.50 mmol, 1 equiv.), 2a (1.5 equiv.), and 3 (2 equiv.) in TFEA (0.5 mL) at 50 °C for 24 h.

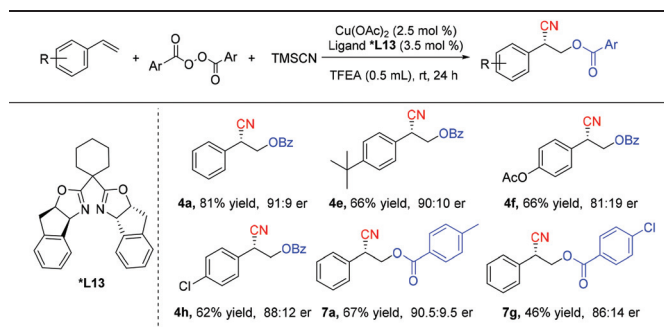
with a phenyl group (6d), a trimethylsilyl group (6e) or a free hydroxyl group (6l) are compatible with the reaction, making it a powerful method for the difunctionalization of alkenes.

The scope of diacyl peroxides in this oxycyanation reaction was also examined (Table 4). A variety of diacyl peroxides can afford the corresponding oxycyanation products (7a–7f) in moderate yields.^{12a}

The copper-catalyzed asymmetric oxycyanation of alkenes was also evaluated.^{12c,14} After considerable evaluation (for details, see the ESI†), a combination of a Cu(II) species and a bisoxazoline ligand (*L13) was found to be the most efficient catalyst system, and the results are summarized in Table 5. The copper-catalyzed asymmetric oxycyanation of alkenes could afford the desired products with an er value of 91:9. However, under the asymmetric conditions, almost no enantiomeric excess was obtained with an aliphatic alkene (5d).

Table 4 Scope of the oxycyanation reaction with diacyl peroxides^a

^a Reaction conditions: 1a (0.5 mmol), 2 (0.75 mmol), and 3 (1.0 mmol) in TFEA (0.5 mL) at 50 °C for 24 h.

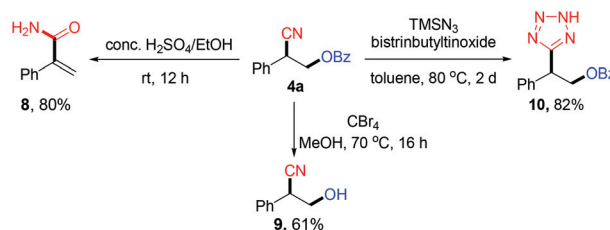
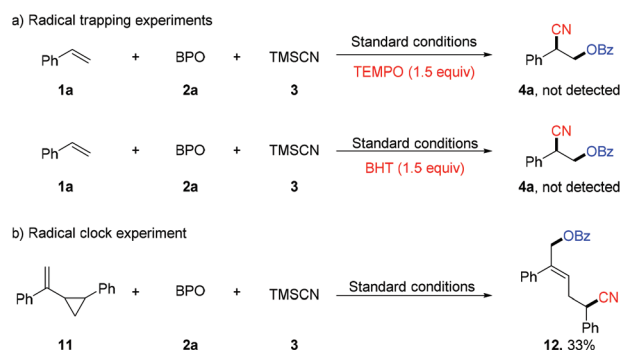
Table 5 Asymmetric oxycyanation of alkenes^a

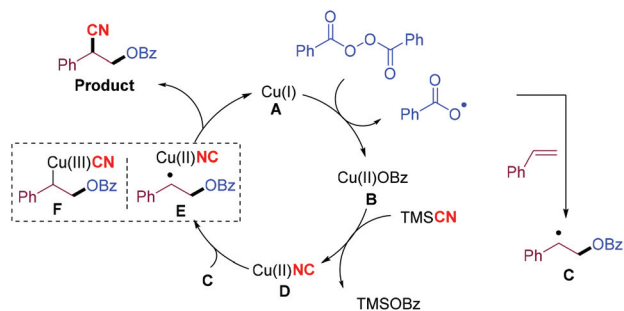
^a 1 (0.5 mmol), 2 (0.75 mmol), and 3 (1.0 mmol) in TFEA (0.5 mL) at rt for 24 h.

The absolute configuration of the products (R-form of 4e, CCDC 2040065†) was confirmed by X-ray single crystal diffraction.

In order to demonstrate the potential synthetic value of the oxycyanation reactions, we investigated the subsequent transformations of compound 4a. As shown in Scheme 2, the oxycyanation product (4a) efficiently engaged in selective olefination, deprotection or cyano functionalization to afford an α,β -unsaturated primary amide (8), a β -cyanohydrin (9), or a tetrazole (10).¹⁵ These results demonstrate the potential of this method to provide valuable synthetic compounds.

Preliminary experiments were performed to probe the mechanism of the oxycyanation reaction (Scheme 3). First,

**Scheme 2** Synthetic applications of the oxycyanation products.**Scheme 3** Preliminary mechanistic studies.



Scheme 4 Plausible catalytic cycle for the oxycyanation of alkenes.

radical trapping experiments were conducted and found that TEMPO (2,2,6,6-tetramethyl-1-piperidinyloxy) and BHT (2,6-di-*tert*-butyl-4-methylphenol) inhibit the formation of the oxycyanation product¹⁶ (Scheme 3a). The results are consistent with the involvement of radical species. To further support this hypothesis, compound **11** bearing a cyclopropylmethyl moiety was tested as a radical clock (Scheme 3b).¹⁷ The reaction of compound **11** with BPO and TMS-CN afforded the ring-opening product (**12**) in 33% yield, further supporting the involvement of radical species in the reaction.

Based on these mechanistic studies, a catalytic mechanism† for the oxycyanation reaction is proposed (Scheme 4). Initially, a copper(I) species (**A**) undergoes single-electron transfer with BPO to afford the copper(II) species (**B**) and a benzoyl radical,^{12a,18} which can be trapped by an alkene to produce a more stable carbon-centered radical (**C**). Upon ligand exchange with TMS-CN, the copper(II) species (**B**) is converted into a copper(II) species (**D**),^{12c,19} which then undergoes cyano group transfer with the stabilized carbon-centered radical (**C**) through an intermediate (**E**) to afford the oxycyanation product, and regenerate the copper catalyst. The oxycyanation product can also be formed through the reductive elimination of the copper(III) species (**F**).²⁰

Conclusions

In conclusion, we have developed a copper-catalyzed three-component reaction which leads to direct oxycyanation of various alkenes with aryl diacyl peroxides and TMS-CN. Both unactivated alkenes and styrenes are reliable substrates under the mild reaction conditions, affording β-cyanoalcohol derivatives in moderate to good yields. The utility of these direct oxycyanation products has been demonstrated with further synthetic applications. The copper-catalyzed asymmetric oxycyanation of alkenes has been conducted and proceeds well.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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Notes and references

- (a) F. F. Fleming, Nitrile-containing natural products, *Nat. Prod. Rep.*, 1999, **16**, 597; (b) F. F. Fleming, L. Yao, P. C. Ravikumar, L. Funk and B. C. Shook, Nitrile-containing pharmaceuticals: efficacious roles of the nitrile pharmacophore, *J. Med. Chem.*, 2010, **53**, 7902.
- (a) Z. Rappoport and S. Patai, *The Chemistry of the Cyano Group*, Wiley, London, 1970; (b) G. Yan, Y. Zhang and J. Wang, Recent Advances in the Synthesis of Aryl Nitrile Compounds, *Adv. Synth. Catal.*, 2017, **359**, 4068.
- (a) A. Falk, A. L. Goderz and H. G. Schmalz, Enantioselective nickel-catalyzed hydrocyanation of vinylarenes using chiral phosphine-phosphite ligands and TMS-CN as a source of HCN, *Angew. Chem., Int. Ed.*, 2013, **52**, 1576; (b) Y. Liu, S. Shirakawa and K. Maruoka, Phase-transfer-catalyzed asymmetric conjugate cyanation of alkylidenemalonates with KCN in the presence of a Bronsted acid additive, *Org. Lett.*, 2013, **15**, 1230; (c) C. Lu, X. Su and P. E. Floreancig, Stereocontrolled cyanohydrin ether synthesis through chiral Bronsted acid-mediated vinyl ether hydrocyanation, *J. Org. Chem.*, 2013, **78**, 9366; (d) Y. Sakaguchi, N. Kurono, K. Yamauchi and T. Ohkuma, Asymmetric conjugate hydrocyanation of α,β-unsaturated N-acylpyrroles with the Ru(phgly)₂(binap)-CH₃OLi catalyst system, *Org. Lett.*, 2014, **16**, 808; (e) J. Zhang, X. Liu and R. Wang, Magnesium complexes as highly effective catalysts for conjugate cyanation of α,β-unsaturated amides and ketones, *Chem. – Eur. J.*, 2014, **20**, 4911; (f) Y.-J. Zhang, Q.-L. Hou, H.-J. Wang and W.-W. Liao, Lewis base-promoted rearrangement of allylic cyanohydrins: construction of functionalized nitriles bearing 1,3-diketone moieties, *J. Org. Chem.*, 2014, **79**, 10890; (g) S. Arai, H. Hori, Y. Amako and A. Nishida, A new protocol for nickel-catalysed regio- and stereoselective hydrocyanation of allenes, *Chem. Commun.*, 2015, **51**, 7493; (h) A. Falk, A. Cavalieri, G. S. Nichol, D. Vogt and H.-G. Schmalz, Enantioselective Nickel-Catalyzed Hydrocyanation using Chiral Phosphine-Phosphite Ligands: Recent Improvements and Insights, *Adv. Synth. Catal.*, 2015, **357**, 3317; (i) K. Kiyokawa, T. Nagata, J. Hayakawa and S. Minakata, Straightforward synthesis of 1,2-dicyanoalkanes from nitroalkenes and silyl cyanide mediated by tetrabutylammonium fluoride, *Chem. – Eur. J.*, 2015, **21**, 1280; (j) X. Fang, P. Yu and B. Morandi, Catalytic reversible alkene-nitrile interconversion through controllable transfer hydrocyanation, *Science*, 2016, **351**, 832; (k) A. Jakhar, P. Kumari, M. Nazish, N.-u. H. Khan,

- R. I. Kureshy, S. H. R. Abdi and E. Suresh, Catalytic asymmetric synthesis of enantioenriched β -nitronitrile bearing a C-CF₃ stereogenic center, *RSC Adv.*, 2016, **6**, 29977; (l) K. Kiyokawa, T. Nagata and S. Minakata, Electrophilic Cyanation of Boron Enolates: Efficient Access to Various beta-Ketonitrile Derivatives, *Angew. Chem., Int. Ed.*, 2016, **55**, 10458; (m) K. Nemoto, T. Nagafuchi, K.-i. Tominaga and K. Sato, Efficient nickel-catalyzed hydrocyanation of alkenes using acetone cyanohydrin as a safer cyano source, *Tetrahedron Lett.*, 2016, **57**, 3199; (n) G. Strappaveccia, T. Angelini, L. Bianchi, S. Santoro, O. Piermatti, D. Lanari and L. Vaccaro, Synthesis of β -Cyano Ketones Promoted by a Heterogeneous Fluoride Catalyst, *Adv. Synth. Catal.*, 2016, **358**, 2134; (o) Y. Amako, S. Arai and A. Nishida, Transfer of axial chirality through the nickel-catalysed hydrocyanation of chiral allenes, *Org. Biomol. Chem.*, 2017, **15**, 1612; (p) M. Hatano, K. Yamakawa and K. Ishihara, Enantioselective Conjugate Hydrocyanation of α,β -Unsaturated N-Acylpyrroles Catalyzed by Chiral Lithium (I) Phosphoryl Phenoxide, *ACS Catal.*, 2017, **7**, 6686; (q) Z. Li and J. Yin, Conjugate Hydrocyanation of Chalcone Derivatives Using Ethyl Cyanoacetate as an Organic Cyanide Source, *Chin. J. Chem.*, 2017, **35**, 1179; (r) A. Jakhar, M. Nazish, N. Gupta, N.-u. H. Khan and R. I. Kureshy, Enantioselective Addition of Cyanide to CF₃-Substituted Alkylidenemalonates: Construction of Trifluoromethylated All-Carbon Quaternary Stereocenters, *ChemistrySelect*, 2018, **3**, 4838; (s) A. Bhunia, K. Bergander and A. Studer, Cooperative Palladium/Lewis Acid-Catalyzed Transfer Hydrocyanation of Alkenes and Alkynes Using 1-Methylcyclohexa-2,5-diene-1-carbonitrile, *J. Am. Chem. Soc.*, 2018, **140**, 16353; (t) X. Li, C. You, J. Yang, S. Li, D. Zhang, H. Lv and X. Zhang, Asymmetric Hydrocyanation of Alkenes without HCN, *Angew. Chem., Int. Ed.*, 2019, **58**, 10928; (u) A. W. Schuppe, G. M. Borrajo-Calleja and S. L. Buchwald, Enantioselective Olefin Hydrocyanation without Cyanide, *J. Am. Chem. Soc.*, 2019, **141**, 18668; (v) L. Song, N. Fu, B. G. Ernst, W. H. Lee, M. O. Frederick, R. A. DiStasio Jr. and S. Lin, Dual electrocatalysis enables enantioselective hydrocyanation of conjugated alkenes, *Nat. Chem.*, 2020, **12**, 747; (w) R. Yu, S. Rajasekar and X. Fang, Enantioselective Nickel-Catalyzed Migratory Hydrocyanation of Nonconjugated Dienes, *Angew. Chem., Int. Ed.*, 2020, **59**, 21436.
- 4 (a) A. Pinto, Y. Jia, L. Neuville and J. Zhu, Palladium-catalyzed enantioselective domino heck-cyanation sequence: development and application to the total synthesis of eser-methole and physostigmine, *Chem. – Eur. J.*, 2007, **13**, 961; (b) M. P. Watson and E. N. Jacobsen, Asymmetric intramolecular arylcyanation of unactivated olefins via C-CN bond activation, *J. Am. Chem. Soc.*, 2008, **130**, 12594; (c) Y. Nakao, S. Ebata, A. Yada, T. Hiyama, M. Ikawa and S. Ogoshi, Intramolecular arylcyanation of alkenes catalyzed by nickel/AlMe₂Cl, *J. Am. Chem. Soc.*, 2008, **130**, 12874; (d) J. Chen, G. Zou and W. Liao, Metal-free intramolecular carbocyanation of activated alkenes: functionalized nitriles bearing beta-quaternary carbon centers, *Angew. Chem., Int. Ed.*, 2013, **52**, 9296; (e) N. O. Ilchenko, P. G. Janson and K. J. Szabo, Copper-mediated cyanotrifluoromethylation of styrenes using the Togni reagent, *J. Org. Chem.*, 2013, **78**, 11087; (f) Y.-T. He, L.-H. Li, Y.-F. Yang, Z.-Z. Zhou, H.-L. Hua, X.-Y. Liu and Y.-M. Liang, Copper-catalyzed intermolecular cyanotrifluoromethylation of alkenes, *Org. Lett.*, 2014, **16**, 270; (g) N. R. Rondla, J. M. Ogilvie, Z. Pan and C. J. Douglas, Palladium catalyzed intramolecular acylcyanation of alkenes using alpha-iminonitriles, *Chem. Commun.*, 2014, **50**, 8974; (h) D. A. Petrone, A. Yen, N. Zeidan and M. Lautens, Dearomative Indole Bisfunctionalization via a Diastereoselective Palladium-Catalyzed Arylcyanation, *Org. Lett.*, 2015, **17**, 4838; (i) N. S. Dange, F. Robert and Y. Landais, Free-Radical Carbocyanation of Cyclopropenes: Stereocontrolled Access to All-Carbon Quaternary Stereocenters in Acyclic Systems, *Org. Lett.*, 2016, **18**, 6156; (j) F. Wang, D. Wang, X. Wan, L. Wu, P. Chen and G. Liu, Enantioselective Copper-Catalyzed Intermolecular Cyanotrifluoromethylation of Alkenes via Radical Process, *J. Am. Chem. Soc.*, 2016, **138**, 15547; (k) N. Wang, L. Li, Z.-L. Li, N.-Y. Yang, Z. Guo, H.-X. Zhang and X.-Y. Liu, Catalytic Diverse Radical-Mediated 1,2-Cyanofunctionalization of Unactivated Alkenes via Synergistic Remote Cyano Migration and Protected Strategies, *Org. Lett.*, 2016, **18**, 6026; (l) Q. Guo, M. Wang, Y. Wang, Z. Xu and R. Wang, Photoinduced, copper-catalyzed three components cyanofluoroalkylation of alkenes with fluoroalkyl iodides as fluoroalkylation reagents, *Chem. Commun.*, 2017, **53**, 12317; (m) H. Hassan, V. Pirenne, M. Wissing, C. Khair, A. Hussain, F. Robert and Y. Landais, Free-Radical Carbocyanation of Olefins, *Chem. – Eur. J.*, 2017, **23**, 4651; (n) R. Ren, Z. Wu, L. Huan and C. Zhu, Synergistic Strategies of Cyano Migration and Photocatalysis for Difunctionalization of Unactivated Alkenes: Synthesis of Di- and Mono-Fluorinated Alkyl Nitriles, *Adv. Synth. Catal.*, 2017, **359**, 3052; (o) W. Sha, L. Deng, S. Ni, H. Mei, J. Han and Y. Pan, Merging Photoredox and Copper Catalysis: Enantioselective Radical Cyanoalkylation of Styrenes, *ACS Catal.*, 2018, **8**, 7489; (p) F. Wang, D. Wang, Y. Zhou, L. Liang, R. Lu, P. Chen, Z. Lin and G. Liu, Divergent Synthesis of CF₃-Substituted Allenyl Nitriles by Ligand-Controlled Radical 1,2- and 1,4-Addition to 1,3-Enynes, *Angew. Chem., Int. Ed.*, 2018, **57**, 7140; (q) Q. Guo, M. Wang, Q. Peng, Y. Huo, Q. Liu, R. Wang and Z. Xu, Dual-Functional Chiral Cu-Catalyst-Induced Photoredox Asymmetric Cyanofluoroalkylation of Alkenes, *ACS Catal.*, 2019, **9**, 4470; (r) M. Ji, Z. Wu and C. Zhu, Visible-light-induced consecutive C-C bond fragmentation and formation for the synthesis of elusive unsymmetric 1,8-dicarbonyl compounds, *Chem. Commun.*, 2019, **55**, 2368; (s) Y. Jiao, M.-F. Chiou, Y. Li and H. Bao, Copper-Catalyzed Radical Acyl-Cyanation of Alkenes with Mechanistic Studies on the tert-Butoxy Radical, *ACS Catal.*, 2019, **9**, 5191; (t) C. Wang, Q. Shang, R. Qi, H. Chai,

- H. Wang, M. Guo and Z. Xu, Cu-Catalyzed cyanoalkylation of electron-deficient alkenes with unactivated alkyl bromides, *Chem. Commun.*, 2019, **55**, 9991; (u) W. Bao, Z.-P. Gao, D.-P. Jin, C.-G. Xue, H. Liang, L.-S. Lei, X.-T. Xu, K. Zhang and S.-H. Wang, Direct synthesis of 2-substituted benzonitriles via alkylcyanation of arynes with N,N-disubstituted aminomalononitriles, *Chem. Commun.*, 2020, **56**, 7641; (v) X.-J. Chen, Q.-W. Gui, R. Yi, X. Yu, Z.-L. Wu, Y. Huang, Z. Cao and W.-M. He, Copper(I)-catalyzed intermolecular cyanoarylation of alkenes: convenient access to α -alkylated arylacetonitriles, *Org. Biomol. Chem.*, 2020, **18**, 5234; (w) M. Israr, H. Xiong, Y. Li and H. Bao, Copper-Catalyzed Enantioselective Cyano(Fluoro)Alkylation of Alkenes, *Adv. Synth. Catal.*, 2020, **362**, 2211; (x) T. Zhang, Y.-X. Luan, S.-J. Zheng, Q. Peng and M. Ye, Chiral Aluminum Complex Controls Enantioselective Nickel-Catalyzed Synthesis of Indenes: C-CN Bond Activation, *Angew. Chem.*, 2020, **59**, 7439.
- 5 (a) H. Zhang, W. Pu, T. Xiong, Y. Li, X. Zhou, K. Sun, Q. Liu and Q. Zhang, Copper-catalyzed intermolecular aminocyanation and diamination of alkenes, *Angew. Chem., Int. Ed.*, 2013, **52**, 2529; (b) H. Gao, B. Liu, W. Wu and H. Jiang, Palladium-catalyzed selective aminoamidation and aminocyanation of alkenes using isonitrile as amide and cyanide sources, *Chem. Commun.*, 2014, **50**, 15348; (c) Y. Miyazaki, N. Ohta, K. Semba and Y. Nakao, Intramolecular aminocyanation of alkenes by cooperative palladium/boron catalysis, *J. Am. Chem. Soc.*, 2014, **136**, 3732; (d) Z. Pan, S. M. Pound, N. R. Rondla and C. J. Douglas, Intramolecular aminocyanation of alkenes by N-CN bond cleavage, *Angew. Chem., Int. Ed.*, 2014, **53**, 5170; (e) L. Xu, X.-Q. Mou, Z.-M. Chen and S.-H. Wang, Copper-catalyzed intermolecular azidocyanation of aryl alkenes, *Chem. Commun.*, 2014, **50**, 10676; (f) Z. Wu, R. Ren and C. Zhu, Combination of a Cyano Migration Strategy and Alkene Difunctionalization: The Elusive Selective Azidocyanation of Unactivated Olefins, *Angew. Chem., Int. Ed.*, 2016, **55**, 10821; (g) F. Chen, F.-F. Zhu, M. Zhang, R.-H. Liu, W. Yu and B. Han, Iminoxyl Radical-Promoted Oxycyanation and Aminocyanation of Unactivated Alkenes: Synthesis of Cyano-Featured Isoxazolines and Cyclic Nitrones, *Org. Lett.*, 2017, **19**, 3255; (h) H. Shen, Q. Deng, R. Liu, Y. Feng, C. Zheng and Y. Xiong, Intramolecular aminocyanation of alkenes promoted by hypervalent iodine, *Org. Chem. Front.*, 2017, **4**, 1806; (i) D. Wang, F. Wang, P. Chen, Z. Lin and G. Liu, Enantioselective Copper-Catalyzed Intermolecular Amino- and Azidocyanation of Alkenes in a Radical Process, *Angew. Chem., Int. Ed.*, 2017, **56**, 2054; (j) Z. Pan, S. Wang, J. T. Brethorst and C. J. Douglas, Palladium and Lewis-Acid-Catalyzed Intramolecular Aminocyanation of Alkenes: Scope, Mechanism, and Stereoselective Alkene Difunctionalizations, *J. Am. Chem. Soc.*, 2018, **140**, 3331.
- 6 S. Yamasaki, M. Kanai and M. Shibasaki, Novel Multi-action of Zr Catalyst: One-Pot Synthesis of β -Cyanohydrins from Olefins, *J. Am. Chem. Soc.*, 2001, **123**, 1256.
- 7 D. C. Koester, M. Kobayashi, D. B. Werz and Y. Nakao, Intramolecular oxycyanation of alkenes by cooperative Pd/BPh₃ catalysis, *J. Am. Chem. Soc.*, 2012, **134**, 6544.
- 8 Y. C. Yuan, H. B. Yang, X. Y. Tang, Y. Wei and M. Shi, Unprecedented Oxycyanation of Methylenecyclopropanes for the Facile Synthesis of Benzoxazine Compounds Containing a Cyano Group, *Chem. – Eur. J.*, 2016, **22**, 5146.
- 9 R. K. Quinn, V. A. Schmidt and E. J. Alexanian, Radical carboxygenations of alkenes using hydroxamic acids, *Chem. Sci.*, 2013, **4**, 4030.
- 10 F. Meng, H. Zhang, K. Guo, J. Dong, A. M. Lu and Y. Zhu, Access to Cyano-Containing Isoxazolines via Copper-Catalyzed Domino Cyclization/Cyanation of Alkenyl Oximes, *J. Org. Chem.*, 2017, **82**, 10742.
- 11 J.-L. Liu, Z.-F. Zhu and F. Liu, Oxycyanation of Vinyl Ethers with 2,2,6,6-Tetramethyl-N-oxopiperidinium Enabled by Electron Donor-Acceptor Complex, *Org. Lett.*, 2018, **20**, 720.
- 12 (a) N. Zhu, B. Qian, H. Xiong and H. Bao, Copper-catalyzed regioselective allylic oxidation of olefins via C-H activation, *Tetrahedron Lett.*, 2017, **58**, 4125; (b) B. Qian, H. Xiong, N. Zhu, C. Ye, W. Jian and H. Bao, Copper-catalyzed diesterification of 1,3-diene for the synthesis of allylic diester compounds, *Tetrahedron Lett.*, 2016, **57**, 3400; (c) Y. Zeng, M. F. Chiou, X. Zhu, J. Cao, D. Lv, W. Jian, Y. Li, X. Zhang and H. Bao, Copper-Catalyzed Enantioselective Radical 1,4-Difunctionalization of 1,3-Enynes, *J. Am. Chem. Soc.*, 2020, **142**, 18014.
- 13 (a) F. Wang, D. Wang, X. Mu, P. Chen and G. Liu, Copper-catalyzed intermolecular trifluoromethylarylation of alkenes: Mutual activation of arylboronic acid and CF₃⁺ reagent, *J. Am. Chem. Soc.*, 2014, **136**, 10202; (b) X. Sun, X. Li, S. Song, Y. Zhu, Y.-F. Liang and N. Jiao, Mn-Catalyzed Highly Efficient Aerobic Oxidative Hydroxyazidation of Olefins: A Direct Approach to β -Azido Alcohols, *J. Am. Chem. Soc.*, 2015, **137**, 6059.
- 14 (a) W. Zhang, F. Wang, S. D. McCann, D. Wang, P. Chen, S. S. Stahl and G. Liu, Enantioselective cyanation of benzylic C-H bonds via copper-catalyzed radical relay, *Science*, 2016, **353**, 1014; (b) F. Wang, P. Chen and G. Liu, Copper-Catalyzed Radical Relay for Asymmetric Radical Transformations, *Acc. Chem. Res.*, 2018, **51**, 2036; (c) F. D. Lu, D. Liu, L. Zhu, L. Q. Lu, Q. Yang, Q. Q. Zhou, Y. Wei, Y. Lan and W. J. Xiao, Asymmetric Propargylic Radical Cyanation Enabled by Dual Organophotoredox and Copper Catalysis, *J. Am. Chem. Soc.*, 2019, **141**, 6167; (d) M. Israr, H. Xiong, Y. Li and H. Bao, Copper-Catalyzed Enantioselective Cyano(Fluoro)Alkylation of Alkenes, *Adv. Synth. Catal.*, 2020, **362**, 2211.
- 15 A. L. Fuentes de Arriba, E. Lenci, M. Sonawane, O. Formery and D. J. Dixon, Iridium-Catalyzed Reductive Strecker Reaction for Late-Stage Amide and Lactam Cyanation, *Angew. Chem., Int. Ed.*, 2017, **56**, 3655.
- 16 (a) G. Moad, E. Rizzardo and D. H. Solomon, On the regioselectivity of free radical processes; reactions of benzoyloxy, phenyl and t-butoxy radicals with some α,β -unsaturated esters, *Aust. J. Chem.*, 1983, **36**, 1573; (b) X. Zhu, C. Ye, Y. Li

- and H. Bao, Iron-Catalyzed Radical Decarboxylative Oxyalkylation of Terminal Alkynes with Alkyl Peroxides, *Chem. – Eur. J.*, 2017, **23**, 10254; (c) W. A. Pryor, J. T. Gu and D. F. Church, Trapping free radicals formed in the reaction of ozone with simple olefins using 2,6-di-tert-butyl-4-cresol (BHT), *J. Org. Chem.*, 1985, **50**, 185; (d) H. Zhou, W. Jian, B. Qian, C. Ye, D. Li, J. Zhou and H. Bao, Copper-Catalyzed Ligand-Free Diazidation of Olefins with TMSN₃ in CH₃CN or in H₂O, *Org. Lett.*, 2017, **19**, 6120.
- 17 (a) D. Griller and K. U. Ingold, Free-radical clocks, *Acc. Chem. Res.*, 2002, **13**, 317; (b) W. Deng, W. Feng, Y. Li and H. Bao, Merging Visible-Light Photocatalysis and Transition-Metal Catalysis in Three-Component Alkyl-Fluorination of Olefins with a Fluoride Ion, *Org. Lett.*, 2018, **20**, 4245.
- 18 (a) E. Vismara, A. Donna, F. Minisci, A. Naggi, N. Pastori and G. Torri, Reactivity of carbohydrate radicals derived from iodo sugars and dibenzoyl peroxide. Homolytic heteroaromatic and aromatic substitution, reduction, and oxidation, *J. Org. Chem.*, 1993, **58**, 959; (b) C. Qian, D. Lin, Y. Deng, X. Q. Zhang, H. Jiang, G. Miao, X. Tang and W. Zeng, Palladium-catalyzed ortho-functionalization of azoarenes with aryl acylperoxides, *Org. Biomol. Chem.*, 2014, **12**, 5866.
- 19 X. Zhu, W. Deng, M. F. Chiou, C. Ye, W. Jian, Y. Zeng, Y. Jiao, L. Ge, Y. Li, X. Zhang and H. Bao, Copper-Catalyzed Radical 1,4-Difunctionalization of 1,3-Enynes with Alkyl Diacyl Peroxides and N-Fluorobenzenesulfonimide, *J. Am. Chem. Soc.*, 2019, **141**, 548.
- 20 (a) Q. Zhang, Y. Liu, T. Wang, X. Zhang, C. Long, Y. D. Wu and M. X. Wang, Mechanistic Study on Cu(II)-Catalyzed Oxidative Cross-Coupling Reaction between Arenes and Boronic Acids under Aerobic Conditions, *J. Am. Chem. Soc.*, 2018, **140**, 5579; (b) S. D. McCann and S. S. Stahl, Copper-Catalyzed Aerobic Oxidations of Organic Molecules: Pathways for Two-Electron Oxidation with a Four-Electron Oxidant and a One-Electron Redox-Active Catalyst, *Acc. Chem. Res.*, 2015, **48**, 1756.