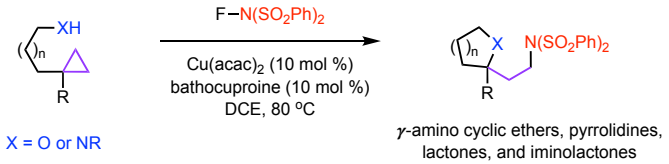
Copper-Catalyzed 1,3-Aminocyclization of Cyclopropanes as A Rapid Entry to γ-Amino Heterocycles

Andrew L. Nguyen, Justin Zhang, Sheng-Hao Huang, and Qiu Wang

Department of Chemistry, Duke University, Durham, North Carolina 27708, United States

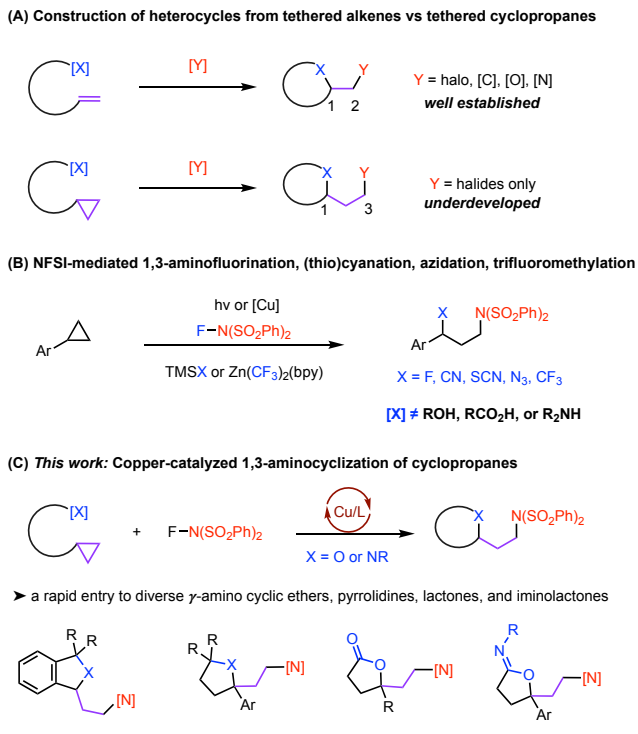
Supporting Information Placeholder

ABSTRACT: We herein report a copper-catalyzed 1,3-aminocyclization of cyclopropanes as a direct and versatile entry to important heterocycles. This reaction was initiated by a copper-catalyzed, NFSI-promoted ring opening of cyclopropanes followed by nucleophilic cyclization. A variety of nucleophiles successfully participate in this transformation, including alcohols, carboxylic acids, sulfonamides, and amides, for the construction of diverse cyclic ethers, pyrrolidines, lactones, and iminolactones.



Heterocycles constitute important structures and have an essential role in pharmaceuticals, agrochemicals, and functional materials.[1] Efficient construction of diversely functionalized heterocycles is a significant topic in organic chemistry. Catalytic difunctionalization of heteroatom-tethered alkenes with another functionality has been extensively explored for the synthesis of β-functionalized heterocycles (**Scheme 1A**).[2] Building upon different activation strategies, these difunctionalization methods of alkenes provide a powerful, rapid access to a wide range of valuable heterocycles. In comparison, construction of γ-functionalized heterocycles by 1,3-difunctionalization of heteroatom-tethered cyclopropanes remains underexplored, though it presents great potential as a facile entry to these important motifs. Cyclopropanes are known as highly strained systems and show intriguing reactivity that resembles the character of a carbon-carbon double bond.[3] The ring opening transformations of cyclopropanes driven by their high strain offer promising opportunities to develop new synthetic capability for rapidly increasing structural complexity and diversity.[4] However, most advances using this approach have been focused on activated donor-acceptor cyclopropanes that bear electron-withdrawing groups and electron-donating groups.[5] Only a few examples of non-activated cyclopropanes have been reported for the construction of heterocycles (**Scheme 1A**). The halocyclization of cyclopropanes using highly electrophilic halides have been developed for the construction of γ-bromo and γ-iodo-oxycycles.[6] Furthermore, the creation of 4-substituted fluoropiperidines has been realized by a BF_3-mediated fluorocyclization of cyclopropane-bearing sulfonamide using monofluoroiodane(III) reagents.[7] Recently, electrochemical formation of oxazolines has also been achieved by 1,3-oxyfluorination of cyclopropanes.[8] Despite these advances for the construction of γ-halo heterocycles, new strategies to construct diversely γ-functionalized heterocycles are still in great demand.

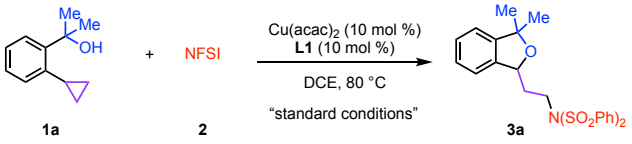
Scheme 1. Difunctionalization of alkenes and cyclopropanes toward rapid construction of heterocycles



In 2016, the Lectka group reported a novel 1,3-aminofluorination of aryl cyclopropanes using *N*-fluorobenzenesulfonimide (NFSI) by photolysis or copper catalysis (**Scheme 1B**).[9] Built on this copper-NFSI system, the Zhang group has developed an elegant series of 1,3-aminocyanation,[10] aminoazidation,[11] and aminothiocyanation[12] of aryl cyclopropanes using trimethylsilyl-based nucleophiles (i.e., TMSCN, $TMSN_3$, TMSSCN). The Li group also achieved 1,3-amino trifluoromethylation of cyclopropanes using $(bpy)Zn(CF_3)_2$.[13] However, the coupling with a common oxygen or nitrogen nucleophile has been yet to be realized in the NSFI-mediated ring-opening difunctionalization of cyclopropanes. In this paper, we report the development of ring-opening aminocyclization of *O*- or *N*-tethered cyclopropanes, using the copper catalysis and NFSI, as a direct entry to γ-amino heterocycles. This approach proves effective for the modular construction of diverse cyclic ethers, pyrrolidines, lactones, and iminolactones (**Scheme 1C**).

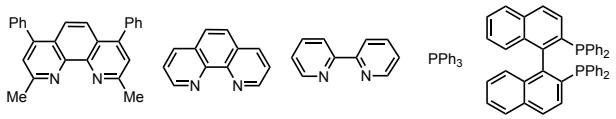
Our investigations began with the reaction using 2-(2-cyclopropylphenyl)propan-2-ol **1a** as the model substrate

Table 1. Condition optimization of 1,3-aminooxygenation of 1a toward the cyclic ether formation[a]



1a 2 3a

Entry	Variation from standard conditions	**3a** (%)[b]
1	none	56
2	No $Cu(acac)_2$	0
3	$Cu(OAc)_2$ instead of $Cu(acac)_2$	50
4	$Cu(OTf)_2$ instead of $Cu(acac)_2$	12
5	CuBr instead of $Cu(acac)_2$	48
6	$Cu(MeCN)_4BF_4$ instead of $Cu(acac)_2$	35
7	Cu_2O instead of $Cu(acac)_2$	35
8	No L1	trace
9	**L2** instead of L1	24
10	**L3** instead of L1	31
11	**L4** instead of L1	38
12	**L5** instead of L1	34



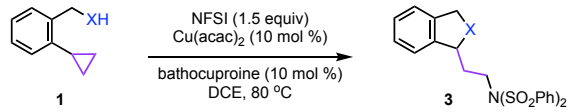
L1 L2 L3 L4 L5

[a]Reaction conditions: **1a** (0.2 mmol, 1.0 equiv), **2** (1.5 equiv), Solvent (1.0 mL). [b]Yields determined by ^{1}H-NMR analysis using dibromomethane as an internal standard.

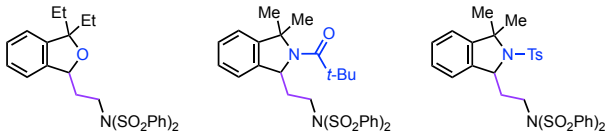
(**Table 1**). The standard reaction conditions were established, with $Cu(acac)_2$ (10 mol%) and bathocuproine **L1** (10 mol%) at 80 °C in DCE, which gave the desired cyclic ether product **3a** in 56% yield (entry 1). Control experiment shows that a copper catalyst is required for the formation of **3a** (entry 2). Other copper catalysts also promoted the reaction yet were slightly inferior to $Cu(acac)_2$ (entries 3–7). Furthermore, the use of bathocuproine **L1** was critical (entry 8) and other ligands were less effective such as **L2**, **L3**, **L4** and **L5** (entries 9–12). Among different solvents, DCE performed best in this reaction. Variation of other parameters such as equivalent, temperatures, and concentrations decreased the reaction efficacy.[14]

With standard conditions established, we studied the capability of different tethered nucleophiles in the copper-catalyzed 1,3-ring opening reaction of 2-cyclopropylphenyl substrates **1** (**Scheme 2**). In addition to model substrate **1a**, the reaction of diethyl substituted alcohol **1b** afforded cyclic ether **3b** in 45% yield. Next, we examined amide **1c** and sulfonamide **1d**, both of which gave desired five-membered azaheterocyclic products **3c** and **3d** in 62% and 55% yields, respectively. The reaction of carboxylic acid **1e** performed well to produce γ-sulfonimide lactone **3e** in 63% yield. Interestingly, the reactions of amides **1f–1g** delivered iminolactones **3f–3g**, while the lactams products were not observed, favoring *O*-attack over *N*-attack for these amide substrates.[15]

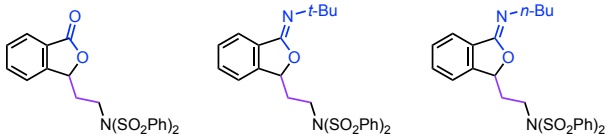
Scheme 2. Formation of different heterocycles from 1,3-aminocyclization of 2-cyclopropylphenyl substrates 1.



1 3



3b: 45% **3c:** 62% **3d:** 55%



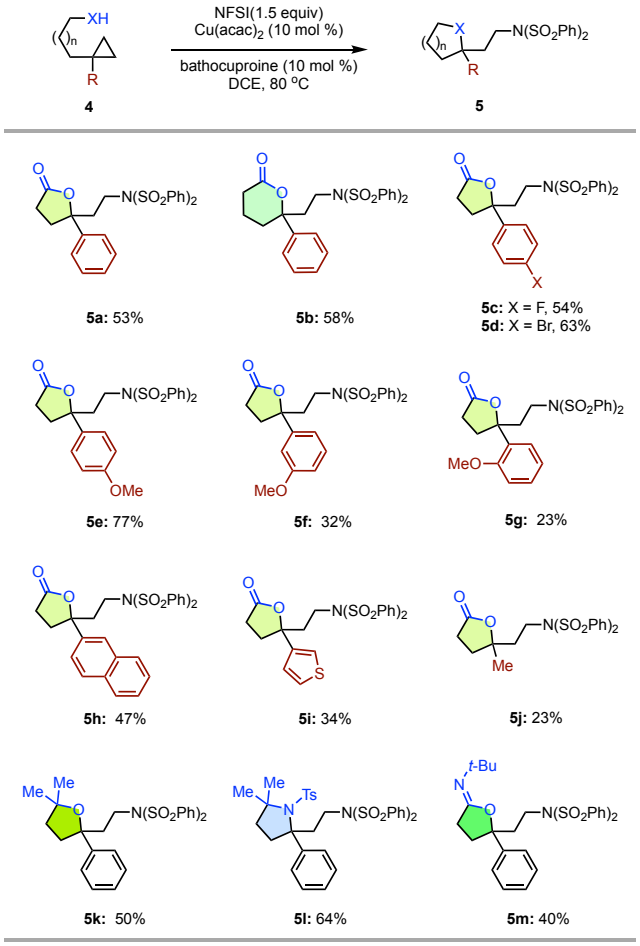
3e: 63% **3f:** 58% **3g:** 47%

Reaction conditions: **1** (0.2 mmol, 1.0 equiv), NFSI (1.5 equiv), DCE (1.0 mL). Isolated yields shown.

We next examined the scope of this 1,3-aminofunctionalization reaction as a modular approach for the construction of diverse γ-amino-heterocycles (**Scheme 3**). We first examined the 1,3-aminooxygenation reactions of

carboxylic acid-tethered 1,1-disubstituted cyclopropanes **4** for the construction of lactones. Under the standard conditions, the reaction of simple 3-(1-phenylcyclopropyl)propanoic acid **4a** successfully afforded five-membered lactone **5a** in 53% yield. The reaction also effectively furnished six-membered lactone **5b** in 58% yield. Different substituents on the aryl ring (**5c–5g**) were also examined to probe their influences on this transformation. The method is applicable to aryl substrates with electron-deficient groups such as fluoride (**5c**) and bromide (**5d**), as well as aryl substrates bearing an electron-rich methoxy group at the *para, meta*, or *ortho*-position (**5e–5g**). Besides simple aryl-substituted cyclopropanes, 1-naphthyl- and 3-thiophenyl-cyclopropane carboxylic acids also successfully delivered lactones **5h** and **5i**, in 47% and 34% yields, respectively. Excitingly, the reaction of alkyl-substituted cyclopropane **4j** also formed desired product **5j** in 23% yield, even though this substrate lacks the stabilizing effect of an aryl group in the ring-opened intermediate. Besides carboxylic acids, cyclopropane-tethered alcohols also furnished tetrahydrofuran

Scheme 3. Construction of diverse oxo- and azaheterocycles from 1,1-disubstituted cyclopropanes.

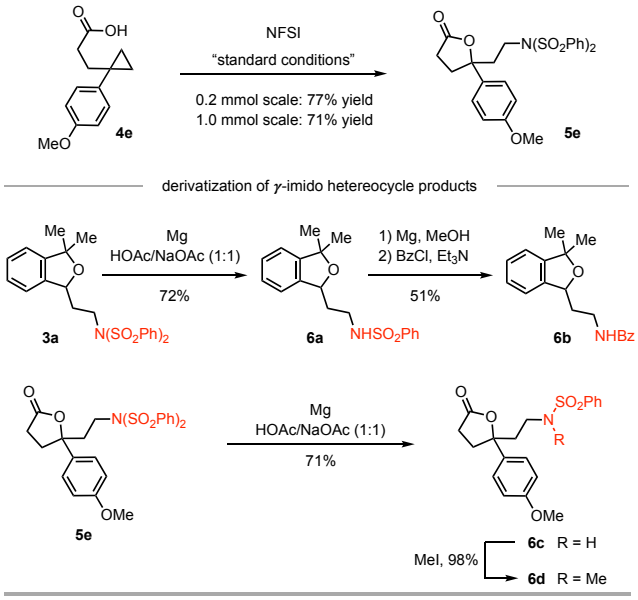


Reaction conditions: **4** (0.2 mmol, 1.0 equiv), NFSI (1.5 equiv), DCE (1.0 mL). Isolated yields shown.

product **5k** in 50% yield. We next studied the competency of nitrogen nucleophiles to participate in a 1,3-diamination reaction for the construction of azaheterocycles The reaction of cyclopropane-containing sulfonamide **4l** successfully provided the 1,3-diamination pyrrolidine product **5l** in 64% yield. The reaction of *N*-(*tert*-butyl)-amide-tethered cyclopropane **4m** delivered *O*-trapped 1,3-amino oxygenated iminolactone **5m**, while *N*-trapped 1,3-diamination lactam product was not formed, similar to the outcomes of the reactions using benzamides (**3e–3f**, Scheme 2). Collectively, these examples showcased that this cyclopropane 1,3-aminofunctionalization transformation offers a rapid, effective entry to diverse oxo- and aza-heterocycles.

To demonstrate synthetic utility of this ring-opening difunctionalization reaction of cyclopropanes, we performed the 1-mmol-scale reaction of cyclopropane **4d**, which delivered lactone product **5e** in 71% yield (**Scheme 4**). We also investigated the derivatization of γ-sulfonimide heterocyclic products. The treatment of imide **3a** with magnesium in HOAc/NaOAc buffered solution[10] afforded sulfonamide **6a** in 72% yield. Further reduction of **6a** with magnesium in MeOH followed by benzylation provided benzamide **6b**. Similarly, the sulfonamide **5e** was readily transformed into sulfonamide **6c,** as well as *N*-methyl sulfonamide **6d** by subsequent methylation.

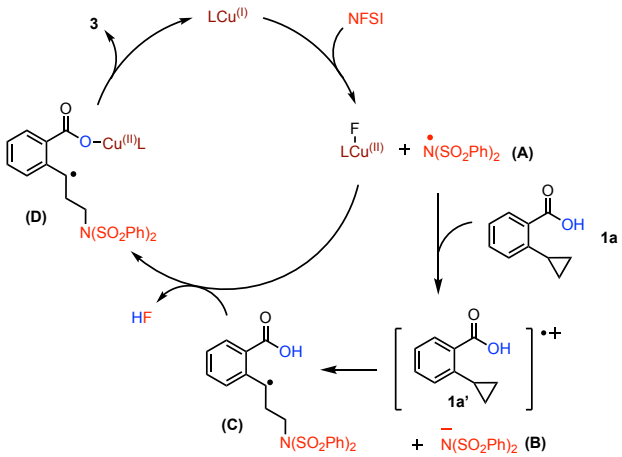
Scheme 4. Applications for the synthesis of diverse γ-amino lactones



In the control experiments with a stoichiometric amount of a radical scavenger (TEMPO or BHT), the formation of **5a** in the reaction of **4a** was completely inhibited. These observations support the possible involvement of the radical intermediates under our reaction conditions. Based on our results and the previous work related to NFSI-induced arylcyclopropane ring opening reactions,[9-13] we propose the

reaction mechanism for the 1,3-aminocyclization reaction in our work (**Scheme 5**). The copper (I) catalyst, generated *in situ* from a copper (II) precursor, would cleave the N–F bond of NFSI to form the *N*-centered radical (**A**), which would mediate the activation of the cyclopropane **1a** by a single electron transfer (SET) process. The subsequent nucleophilic addition from sulfonamide anion (**B**) induced the carbon-carbon bond cleavage of cyclopropylarene radical cation **1a'**, generating the ring-opened carbon radical (**C**). Finally, the formation of carbon-heteroatom bonds (i.e., **3**) was furnished along with the regeneration of the copper (I) catalyst, by either a radical pathway via a copper complex intermediate (**D**) or a radical-polar crossover process.[16] Future studies will be undertaken toward a better understanding of the carbon-heteroatom bonding formation.

Scheme 5. Proposed mechanism



In summary, we have developed a copper-catalyzed cyclopropane ring-opened 1,3-aminocyclization using NFSI for a rapid entry to γ-amino oxo- and aza-heterocycles. Furthermore, this method features simple catalytic systems and mild conditions. It is expected to find useful applications for the synthesis of biologically important heterocycles.

ASSOCIATED CONTENT

Data Availability Statement

The data underlying this study are available in the published article and its Supporting Information .

Supporting Information Statement

Condition optimizations; experimental procedures; compound characterization; and NMR spectra (PDF)

AUTHOR INFORMATION

Corresponding Author

⁎qiu.wang@duke.edu

Notes

The authors declare no conflict of interest.

ACKNOWLEDGMENT

We acknowledge financial support provided by the National Science Foundation (2154501) and Duke University. The authors acknowledge the assistance of Dr. Peter Silinski (Duke University) and Noah H. Watkins (Duke University) for the analysis of high-resolution mass spectrometry and NMR spectra.

REFERENCES

(1) (a) Vitaku, E.; Smith, D. T.; Njardarson, J. T. Analysis of the Structural Diversity, Substitution Patterns, and Frequency of Nitrogen Heterocycles among U.S. FDA Approved Pharmaceuticals. *J. Med. Chem.* **2014**, *57* (24), 10257–10274. (b) Lamberth, C. Heterocyclic chemistry in crop protection. *Pest Management Science* **2013**, *69* (10), 1106–1114. (c) Kerru, N.; Gummidi, L.; Maddila, S.; Gangu, K. K.; Jonnalagadda, S. B. A Review on Recent Advances in Nitrogen-Containing Molecules and Their Biological Applications. *Molecules* **2020**, *25* (8), 1909.

(2) Selected example, see: (a) McDonald, R. I.; Liu, G.; Stahl, S. S. Palladium(II)-Catalyzed Alkene Functionalization via Nucleopalladation: Stereochemical Pathways and Enantioselective Catalytic Applications. *Chem. Rev.* **2011**, *111* (4), 2981-3019. (b) Race, N. J.; Hazelden, I. R.; Faulkner, A.; Bower, J. F. Recent developments in the use of aza-Heck cyclizations for the synthesis of chiral N-heterocycles. *Chem. Sci.* **2017**, *8* (8), 5248–5260. (c) Choury, M.; Basilio Lopes, A.; Blond, G.; Gulea, M. Synthesis of Medium-Sized Heterocycles by Transition-Metal-Catalyzed Intramolecular Cyclization. *Molecules* **2020**, *25* (14), 3147. (d) Sonawane, A. D.; Sonawane, R. A.; Ninomiya, M.; Koketsu, M. Synthesis of Seleno-Heterocycles via Electrophilic/Radical Cyclization of Alkyne Containing Heteroatoms. *Adv. Synth. Catal.* **2020**, *362* (17), 3485–3515. (e) Liao, J.; Yang, X.; Ouyang, L.; Lai, Y.; Huang, J.; Luo, R. Recent advances in cascade radical cyclization of radical acceptors for the synthesis of carbo- and heterocycles. *Org. Chem. Front.* **2021**, *8* (6), 1345–1363.

(3) de Meijere, A. Bonding Properties of Cyclopropane and Their Chemical Consequences. *Angew. Chem. Int. Ed.* **1979**, *18* (11), 809–826.

(4) (a) Danishefsky, S. Electrophilic cyclopropanes in organic synthesis. *Acc. Chem. Res.* **1979**, *12* (2), 66–72. (b) Wong, H. N. C.; Hon, M. Y.; Tse, C. W.; Yip, Y. C.; Tanko, J.; Hudlicky, T. Use of cyclopropanes and their derivatives in organic synthesis. *Chem. Rev.* **1989**, *89* (1), 165–198.

(5) Selected example, see: (a) Schneider, T. F.; Kaschel, J.; Werz, D. B. A New Golden Age for Donor–Acceptor Cyclopropanes. *Angew. Chem. Int. Ed.* **2014**, *53* (22), 5504–5523. (b) Grover, H. K.; Emmett, M. R.; Kerr, M. A. Carbocycles from donor–acceptor cyclopropanes. *Org. Biomol. Chem.* **2015**, *13* (3), 655–671. (c) Ghosh, K.; Das, S. Recent advances in ring-opening of donor acceptor cyclopropanes using C-nucleophiles. *Org. Biomol. Chem.* **2021**, *19* (5), 965–982. (d) Singh, P.; Varshnaya, R. K.; Dey, R.; Banerjee, P. Donor–Acceptor Cyclopropanes as an Expedient Building Block Towards the Construction of Nitrogen-Containing Molecules: An Update. *Adv. Synth. Catal.* **2020**, *362* (7), 1447–1484. (e) Pirenne, V.; Muriel, B.; Waser, J. Catalytic Enantioselective Ring-Opening Reactions of Cyclopropanes. *Chem. Rev.* **2021**, *121* (1),

227–263. (f) Taily, I. M.; Saha, D.; Banerjee, P. Arylcyclopropane yet in its infancy: the challenges and recent advances in its functionalization. *Org. Biomol. Chem.* **2021**, *19* (40), 8627–8645. (g) Cohen, Y.; Cohen, A.; Marek, I. Creating Stereocenters within Acyclic Systems by C–C Bond Cleavage of Cyclopropanes. *Chem. Rev.* **2021**, *121* (1), 140–161.

(6) (a) Rösner, C.; Hennecke, U. Homohalocyclization: Electrophilic Bromine-Induced Cyclizations of Cyclopropanes. *Org. Lett.* **2015**, *17* (13), 3226–3229. (b) Wong, Y.-C.; Ke, Z.; Yeung, Y.-Y. Lewis Basic Sulfide Catalyzed Electrophilic Bromocyclization of Cyclopropylmethyl Amide. *Org. Lett.* **2015**, *17* (20), 4944–4947. (c) Gieuw, M. H.; Leung, V. M.-Y.; Ke, Z.; Yeung, Y.-Y. Electrophilic Bromolactonization of Cyclopropyl Diesters Using Lewis Basic Chalcogenide Catalysts. *Adv. Synth. Catal.* **2018**, *360* (22), 4306–4311. (d) Leung, V. M.-Y.; Gieuw, M. H.; Ke, Z.; Yeung, Y.-Y. Intermolecular Electrophilic Bromoesterification and Bromoetherification of Unactivated Cyclopropanes. *Adv. Synth. Catal.* **2020**, *362* (10), 2039–2044.

(7) Ren, J.; Du, F.-H.; Jia, M.-C.; Hu, Z.-N.; Chen, Z.; Zhang, C. Ring Expansion Fluorination of Unactivated Cyclopropanes Mediated by a New Monofluoroiodane(III) Reagent. *Angew. Chem. Int. Ed.* **2021**, *60* (45), 24171–24178.

(8) Darzina, M.; Jirgensons, A. Electrochemical Formation of Oxazolines by 1,3-Oxyfluorination of Non-activated Cyclopropanes. *Org. Lett.* **2024**, *26* (11), 2158–2162.

(9) Pitts, C. R.; Ling, B.; Snyder, J. A.; Bragg, A. E.; Lectka, T. Aminofluorination of Cyclopropanes: A Multifold Approach through a Common, Catalytically Generated Intermediate. *J. Am. Chem. Soc.* **2016**, *138* (20), 6598–6609.

(10) Yang, S.; Wang, L.; Zhang, H.; Liu, C.; Zhang, L.; Wang, X.; Zhang, G.; Li, Y.; Zhang, Q. Copper-Catalyzed Asymmetric Aminocyanation of Arylcyclopropanes for Synthesis of γ-Amino Nitriles. *ACS Catal.* **2019**, *9* (1), 716–721.

(11) Wang, L.; Wang, X.; Zhang, G.; Yang, S.; Li, Y.; Zhang, Q. Copper-catalyzed 1,3-aminoazidation of arylcyclopropanes: a facile access to 1,3-diamine derivatives. *Org. Chem. Front.* **2019**, *6* (16), 2934–2938.

(12) Wang, X.; Wang, L.; Yang, S.; Zhang, L.; Li, Y.; Zhang, Q. Copper-catalyzed 1,3-aminothiocyanation of arylcyclopropanes. *Org. Biomol. Chem.* **2020**, *18* (26), 4932–4935.

(13) Zhang, H.; Xiao, H.; Jiang, F.; Fang, Y.; Zhu, L.; Li, C. Copper-Catalyzed Ring-Opening 1,3-Aminotrifluoromethylation of Arylcyclopropanes. *Org. Lett.* **2021**, *23* (6), 2268–2272.

(14) See the Supporting Information for more details on the reaction condition optimization.

(15) (a) Shen, K.; Wang, Q. Copper-catalyzed aminotrifluoromethylation of alkenes: a facile synthesis of CF3-containing lactams. *Org. Chem. Front.* **2016**, *3* (2), 222–226. (b) Maejima, S.; Yamaguchi, E.; Itoh, A. Three-Component Iminolactonization Reaction via Bifunctionalization of Olefins Using Molecular Iodine and Visible Light. *J. Org. Chem.* **2020**, *85* (16), 10709–10718.

(16) Examples that involve copper-catalyzed C–O bond formation, see: (a) Kochi, J. K.; Bemis, A. Carbonium ions from alkyl radicals by electron transfer. *J. Am. Chem. Soc.* **1968**, *90* (15), 4038–4051. (b) Kochi, J. K.; Bemis, A.; Jenkins, C. L. Mechanism of electron transfer oxidation of alkyl radicals by copper(II) complexes. *J. Am. Chem. Soc.* **1968**, *90* (17), 4616–4625. (c) King, A. E.; Ryland, B. L.; Brunold, T. C.; Stahl, S. S. Kinetic and Spectroscopic Studies of Aerobic Copper(II)-Catalyzed Methoxylation of Arylboronic Esters and Insights into Aryl Transmetalation to Copper(II). *Organomet.* **2012**, *31* (22), 7948–7957. (d) Suess, A. M.; Ertem, M. Z.; Cramer, C. J.; Stahl, S. S. Divergence between Organometallic and Single-Electron-Transfer Mechanisms in Copper(II)-Mediated Aerobic C–H Oxidation. *J. Am. Chem. Soc.* **2013**, *135* (26), 9797–9804. (e) Hemric, B. N.; Shen, K.; Wang, Q. Copper-Catalyzed Amino Lactonization and Amino Oxygenation of Alkenes Using *O*-Benzoylhydroxylamines. *J. Am. Chem. Soc.* **2016**, *138* (18), 5813–5816. (f) Elwell, C. E.; Gagnon, N. L.; Neisen, B. D.; Dhar, D.; Spaeth, A. D.; Yee, G. M.; Tolman, W. B. Copper–Oxygen Complexes Revisited: Structures, Spectroscopy, and Reactivity. *Chem. Rev.* **2017**, *117* (3), 2059–2107. (g) Hemric, B. N.; Chen, A. W.; Wang, Q. Copper-Catalyzed Modular Amino Oxygenation of Alkenes: Access to Diverse 1,2-Amino Oxygen-Containing Skeletons. *J. Org. Chem.* **2019**, *84* (3), 1468–1488. (h) Hemric, B. N.; Chen, A. W.; Wang, Q. Copper-Catalyzed 1,2-Amino Oxygenation of 1,3-Dienes: A Chemo-, Regio-, and Site-Selective Three-Component Reaction with O-Acylhydroxylamines and Carboxylic Acids. *ACS Catal.* **2019**, *9* (11), 10070–10076. (i) Reed, N. L.; Lutovsky, G. A.; Yoon, T. P. Copper-Mediated Radical–Polar Crossover Enables Photocatalytic Oxidative Functionalization of Sterically Bulky Alkenes. *J. Am. Chem. Soc.* **2021**, *143* (16), 6065-6070. (j) Xu, L.-P.; Haines, B. E.; Ajitha, M. J.; Yu, J.-Q.; Musaev, D. G. Unified Mechanistic Concept of the Copper-Catalyzed and Amide-Oxazoline-Directed C(sp2)–H Bond Functionalization. *ACS Catal.* **2021**, *11* (20), 12620-12631. (k) Wang, P.-Z.; Chen, J.-R.; Xiao, W.-J. Emerging Trends in Copper-Promoted Radical-Involved C–O Bond Formations. *J. Am. Chem. Soc.* **2023**, *145* (32), 17527–17550.