



Cite this: *Chem. Sci.*, 2019, 10, 9265

All publication charges for this article have been paid for by the Royal Society of Chemistry

Saturated oxygen and nitrogen heterocycles via oxidative coupling of alkyltrifluoroborates with alkenols, alkenoic acids and protected alkenylamines†

Jonathan M. Shikora, Chanchamnan Um, Zainab M. Khoder and Sherry R. Chemler *

Saturated heterocycles are important components of many bioactive compounds. The method disclosed herein enables a general route to a range of 5-, 6- and 7-membered oxygen and nitrogen heterocycles by coupling potassium alkyltrifluoroborates with heteroatom-tethered alkenes, predominantly styrenes, under copper-catalyzed conditions, in the presence of MnO₂. The method was applied to the synthesis of the core of the anti-depressant drug citalopram. The reaction scope and observed reactivity is consistent with a polar/radical mechanism involving intermolecular addition of the alkyl radical to the alkene followed by [Cu(III)]-facilitated C–O (or C–N) bond forming reductive elimination.

Received 11th June 2019
Accepted 17th August 2019

DOI: 10.1039/c9sc02835h

rsc.li/chemical-science

Introduction

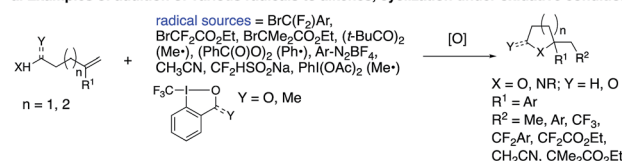
The flexible, convergent synthesis of saturated oxygen and nitrogen heterocycles can be accomplished by the addition of a carbon radical to readily available alkenoic acids, alkenols and alkenyl amines under oxidative conditions (Scheme 1a).^{1–10}

The carbon radical source is an important variable in these alkene addition processes. Alkylhalides have been applied, in particular when their metal-catalyzed reduction forms stabilized or semi-stabilized carbon radicals, such as those conjugated with carbonyl groups¹¹ or that are perhalogenated.¹⁰ Halosulfonate salts that form radicals by oxidative desulfonation have also been used.^{4,5} Hypervalent iodine reagents that decompose in the presence of metal catalysts to generate alkyl radicals have been used in such alkene coupling reactions.^{2,3,6–8} Nitriles, whose alpha positions can be deprotonated and oxidized, have been applied as the stabilized alkyl radical component.⁹ Less stable alkyl radicals, generated by decomposition of peroxides¹ and from aryldiazonium salts, have also been used.³ Benzyl and other simple alkyl radicals are generally lacking in these radical addition/cyclization methodologies.

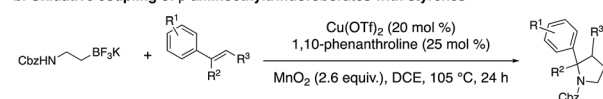
We and others have been exploring the use of alkyltrifluoroborates as radical precursors in oxidative coupling reactions.¹² Oxidation of the alkyltrifluoroborates by metal catalysts under either thermal or photochemical activation enables the

generation of a range of alkyl radicals that can undergo direct addition or metal-catalyzed coupling with appropriate coupling partners including alkenes. Primary, secondary and benzylic radicals are among the alkyl radicals formed under such oxidative conditions from alkyltrifluoroborates.

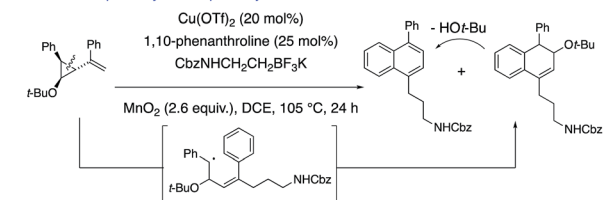
a. Examples of addition of various radicals to alkenes, cyclization under oxidative conditions



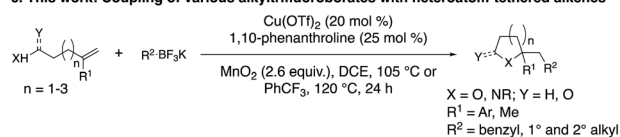
b. Oxidative coupling of β-aminoethyltrifluoroborates with styrenes



Evidence for a primarily radical pathway



c. This work: Coupling of various alkyltrifluoroborates with heteroatom-tethered alkenes



Department of Chemistry, State University of New York at Buffalo, Natural Science Complex, Buffalo, New York, 14260, USA. E-mail: schemler@buffalo.edu

† Electronic supplementary information (ESI) available: Experimental procedures, NMR spectra of all new intermediates and products. See DOI: 10.1039/c9sc02835h

Scheme 1 Radical additions to alkenes and oxidative cyclizations thereof.

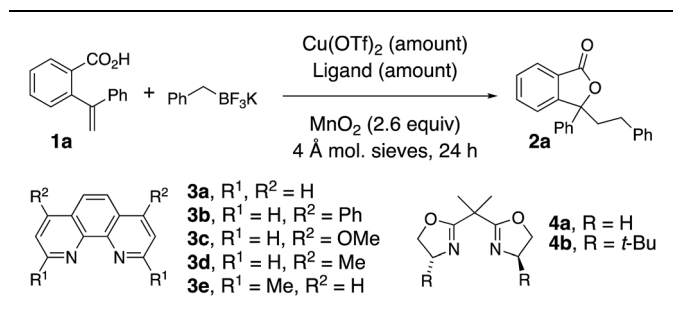


We recently reported on the synthesis of 2-arylpiperidines *via* copper-catalyzed oxidative coupling of styrenes with potassium *N*-carbamoyl- β -aminoethyl trifluoroborates (Scheme 1b).¹³ In these reactions, the [Cu] salt oxidizes the alkyltrifluoroborate to a primary carbon radical. Addition of the radical to the styrene, followed by cyclization *via* addition of the pendant carbamate under the oxidative conditions generates the 2-arylpiperidine. A radical clock experiment supported a mechanism involving primarily carbon radical intermediates (as opposed to carbocation).¹³ Herein we present a new approach to the synthesis of a broad range of saturated heterocycles by addition of various potassium alkyltrifluoroborates to heteroatom-functionalized alkenes, primarily styrenes.

Results and discussion

The oxidative coupling/cyclization of 2-(1-phenylvinyl)benzoic acid **1a** with potassium benzyltrifluoroborate (limiting reagent) was investigated as illustrated in Table 1. Reaction variables such as substrate and copper loading, solvent, temperature, ligand and oxidant were explored. Coupling **1a** (1 equiv.) with

Table 1 Reaction optimization^a



Entry	Mol% Cu(OTf) ₂	Ligand (mol%)	Solvent	Temp (°C)	Yield (%)
1 ^b	20	3a (25)	DCE	105	78
2	20	3a (25)	DCE	105	84
3	5	3a (6)	DCE	105	71
4	10	3a (12)	DCE	105	71
5	—	—	DCE	105	51
6	20	3a (25)	PhCH ₃	120	48
7	20	3a (25)	PhCF ₃	120	82
8	20	3a (25)	Dioxane	120	71
9	20	3b (25)	DCE	105	62
10	20	3c (25)	DCE	105	84
11	20	3d (25)	DCE	105	77
12	20	3e (25)	DCE	105	66
13	20	4a (25)	DCE	105	71
14	20	—	DCE	105	54
15 ^c	20	3a (25)	DCE	105	67
16 ^d	20	3a (25)	DCE	105	35
17 ^e	20	3a (25)	DCE	105	73

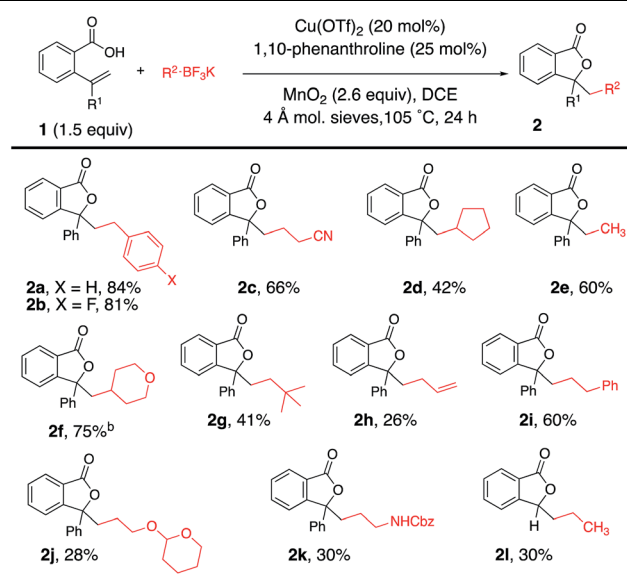
^a All reactions were run in a sealed tube under argon with 0.125 mmol BnBF₃K and 1.5 equiv. of acid **1a** in DCE (0.125 mM) unless otherwise noted. ^b Reaction run with 1 equiv. of acid **1a**. ^c Reaction run with Ag₂CO₃ (1.3 equiv.) instead of MnO₂. ^d Reaction run with K₂S₂O₈ (2.6 equiv.) instead of MnO₂. ^e Reaction run with 1 mmol BnBF₃K.

BnBF₃K in the presence of 20 mol% Cu(OTf)₂, 25 mol% 1,10-phenanthroline (**3a**) and MnO₂ (2.6 equiv.) in 1,2-dichloroethane (DCE) at 105 °C gave 78% of lactone **2a** (Table 1, entries 1). An increase of **1a** loading to 1.5 equiv. resulted in a higher isolated yield of **2a** (84%, Table 1, entry 2). A decrease in Cu(OTf)₂ loading to 5 and 10 mol% both gave 71% isolated yield of lactone **2a** (Table 1, entries 3 and 4). In the absence of [Cu], lactone **2a** is still formed, albeit in diminished yield (51%, Table 1, entry 5 and see below Scheme 4 and associated discussion). The reactions in toluene and dioxane were less productive while the reaction in PhCF₃ gave a comparable yield to DCE (Table 1, entries 6–8). The use of other ligands, **3b–e** and **4a**, or no ligand, gave reactions with equivalent or lower yields (Table 1, entries 9–14). When Ag₂CO₃ or K₂S₂O₈ were used instead of MnO₂, lower yields were obtained (Table 1, entries 15 and 16). The reaction scale with respect to limiting BnBF₃K could be run on 1 mmol scale (73% isolated **2a**, Table 1, entry 17).

Using the optimal reaction conditions (Table 1, entry 2), the alkyltrifluoroborate scope was next explored in the coupling/cyclization reaction with alkenoic acids **1** (Table 2). Alkyltrifluoroborates such as benzylic, primary, methyl, ethyl, neopentyl, allylic and secondary, and alkyls functionalized with a nitrile, an acetal and a carbamate all underwent the coupling reaction with varying levels of efficiency. A *tert*-butyl ester-functionalized alkyltrifluoroborate was also a viable coupling partner [see Table 4 (**8g**) and Table 5 (**12j**)]. Neither CF₃BF₃K nor *t*-BuOCH₂BF₃K gave the desired coupling product with **1a**.

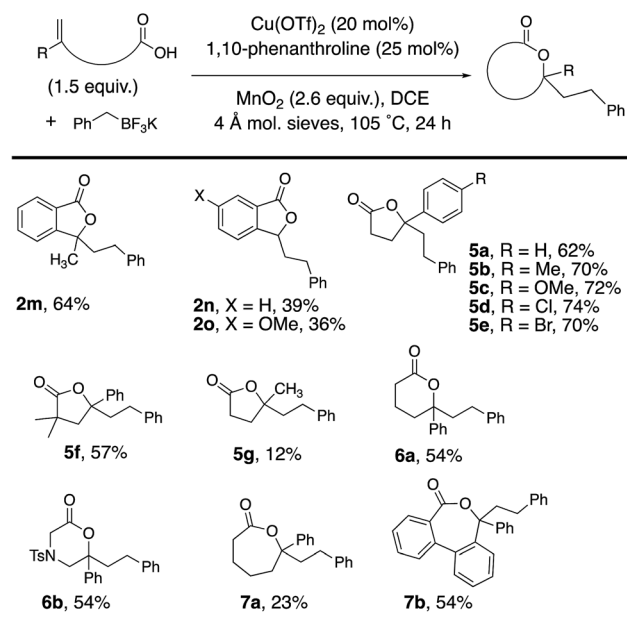
Alkenoic acid substituent effects were further explored (Tables 2 and 3). Diaryl alkenes, such as **1a**, reacted most efficiently to give phthalide **2a** in 84% (Table 2). Replacing the phenyl with methyl (Table 3, **2m**, 64%) or H (Table 3, **2n**, 39%) gave lower phthalide yields. Substitution on the arene

Table 2 Trifluoroborate scope^a



^a Reaction conditions from Table 1, entry 2 were used unless otherwise noted. ^b 10 mol% Cu(OTf)₂ and 12 mol% 1,10-phenanthroline was used.



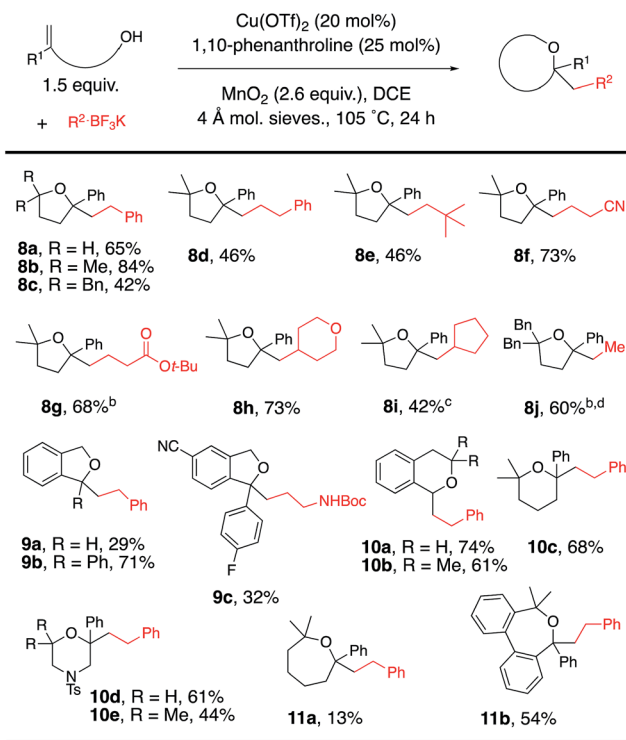
Table 3 Alkenoic acid scope^a

^a Reaction conditions from Table 1, entry 2 were used unless otherwise noted.

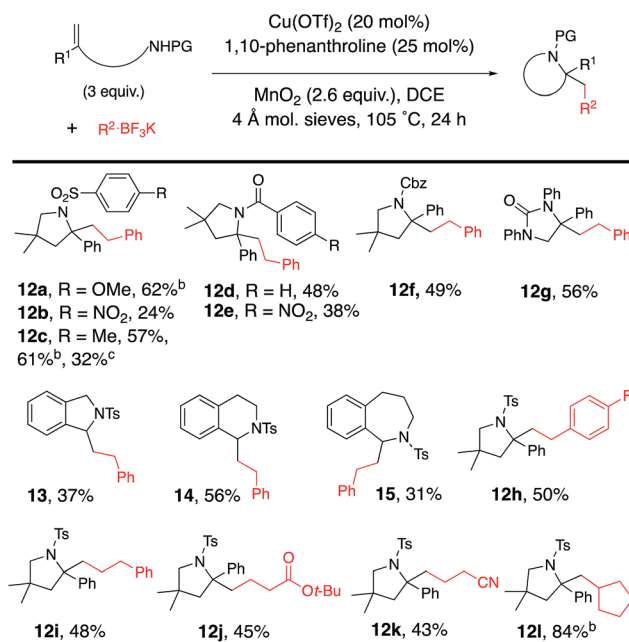
conjugated to the alkene was tolerated, and lactones **5a–f** were formed in good yields. A 1,1-dialkyl substituted alkene did undergo addition and cyclization but the desired product was generated in much lower yield (**5g**, 12%). The remainder of the mass in the lower yielding reactions included unreacted alkenoic acid, (PhCH₂)₂ (benzyl radical dimerization)¹⁴ and benzyl alcohol. Both 6-membered (**6a** and **6b**) and 7-membered ring lactones (**7a** and **7b**) could also be formed. The 2,2'-disubstituted biaryl-backed alkenoic acid provided **7b** more efficiently than the largely aliphatic-backed heptenoic acid gave **7a**.

The scope was next expanded to alkenol coupling/cyclization for the synthesis of saturated oxygen heterocycles (Table 4). The synthesis of tetrahydrofurans (**8a–j**), phthalans (**9a–c**), isochromans (**10a**, **10b**), a pyran (**10c**), morpholines (**10d**, **10e**) and oxepans (**11a**, **11b**) is enabled by this oxidative coupling reaction. Phthalan **9c**, product of coupling of potassium *N*-Cbz-β-aminoethyltrifluoroborate with the respective 4-cyanophenyl-functionalized alkenol, is a reasonable intermediate for the synthesis of citalopram,^{9,15} a drug used for the treatment of depression.

The reaction was expanded to protected alkenyl amine coupling/cyclization for the synthesis of saturated nitrogen heterocycles (Table 5). In this reaction higher alkenylamine loading (3 equiv., 57% of **12c**) gave notably higher isolated yield (32% of **12c** was obtained when 2 equiv. of alkenyl amide was used). Various *N*-substituted alkenylamines produced pyrrolidines (**12a–f**, **12h–l**), a cyclic urea (**12g**), an isoindoline (**13**), a tetrahydroisoquinoline (**14**) and a tetrahydrobenzazepine (**15**).

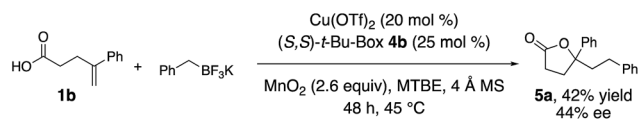
Table 4 Alkenol scope^a

^a Reaction conditions from Table 1, entry 2 were used unless otherwise noted. ^b Reaction run in PhCF₃ at 120 °C. ^c Reaction run with 10 mol% Cu(OTf)₂, 12 mol% 1,10-phenanthroline. ^d Reaction run for 48 h.

Table 5 Alkenyl amide scope^a

^a Reaction conditions from Table 1, entry 2 were used except 3 equiv. of alkenylamide was used. ^b Reaction run in PhCF₃ at 120 °C. ^c Reaction run with 2 equiv. alkenylamide. PG = protecting group.





Scheme 2 Ligand-induced enantioselectivity.

Enantioselective conditions

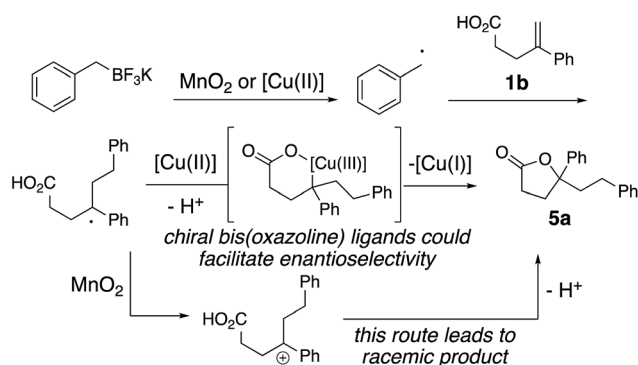
We explored the potential for a chiral ligand to control absolute stereochemistry in our oxidative coupling. A brief substrate and ligand screen revealed that 4-phenylpent-4-enoic acid (**1b**) can undergo enantioselective coupling/cyclization under minimally modified (lower temperature, *t*-BuOMe as solvent) reaction conditions using the (*S,S*)-*t*-Bu-Box **4b** (Scheme 2, 42% yield, 44% ee).^{2,3} In the absence of [Cu], 15% of lactone **5a** was formed as a racemate, indicating some background reaction can occur. In the absence of MnO₂, using 50 mol% copper loading and 55 mol% of **4b**, **5a** was obtained in 22% yield and 44% ee, indicating the potential MnO₂ promoted background reaction is unlikely to be affecting the reaction's enantioselectivity.

Proposed mechanism

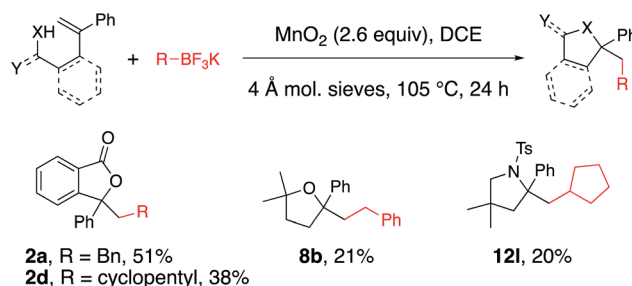
The proposed mechanism is illustrated in Scheme 3. Either copper(II) or MnO₂, or a mixture of both, oxidizes the alkyltrifluoroborate to the corresponding radical.¹⁴ Addition of the resulting alkyl radical to **1b** provides a benzylic radical intermediate. The enantioselective result in Scheme 2 supports the involvement of a chiral ligand-bound copper complex in the C–O bond formation. Thus, formation of an alkyl copper(III) intermediate *via* addition of the alkyl radical to the [Cu(II)] complex and subsequent C–O bond formation *via* reductive elimination generates lactone **5a** (Scheme 3).^{3,16} The [Cu(II)] is regenerated by oxidation of [Cu(I)] to [Cu(II)] by MnO₂ to continue the catalytic cycle (not shown). The background reaction observed under MnO₂-only conditions likely occurs *via* the alternative benzylic carbocation intermediate, which would be expected to give racemic **5a** (Scheme 3).

MnO₂-promoted reactions

The possibility of an oxidative coupling involving only MnO₂ as oxidant was further investigated (Scheme 4). Manganese



Scheme 3 Proposed mechanism.

Scheme 4 MnO₂-only oxidative cyclization.

salts have previously demonstrated the ability to oxidize alkyltrifluoroborates and boronic acids to radicals, that then undergo oxidative coupling with alkenoic acids¹⁷ or heteroarenes (Minisci reaction).¹⁸ Under reaction conditions analogous to our alkyltrifluoroborate couplings, but in the absence of any [Cu] salt, we found that alkenoic acids, alkenyl alcohols and alkenyl amines do undergo the oxidative cyclizations, albeit with generally lower efficiency. The secondary cyclopentyl trifluoroborate reacted similarly with alkenoic acid **1a** in the presence of MnO₂, both with and without [Cu] catalyst (42% vs. 38% of **2d**, compare Table 2 to Scheme 4), while benzyltrifluoroborate gave notably higher yield with the catalytic [Cu] conditions (84% vs. 51% of **2a**, compare Table 1, entry 3 to Scheme 4). In the absence of [Cu] catalyst, alkenol and alkenyl amide substrates gave considerably lower yields of their corresponding heterocycles **8b** (84% with [Cu] vs. 21% without, Table 4 and Scheme 4) and **12l** (84% with [Cu] vs. 20% without, Table 5 and Scheme 4). In the MnO₂ promoted reactions it is likely the C–O and C–N bond formations involve addition of the heteroatom to a carbocationic intermediate (Scheme 3).¹⁷

Conclusions

The copper-catalyzed addition of alkyltrifluoroborates to heteroatom-tethered vinyl arenes under oxidative conditions has been demonstrated to be a general route to saturated oxygen and nitrogen heterocycles. The possibility of asymmetric catalysis has been demonstrated. The observed reactivity is largely consistent with alkyl radical addition to the vinyl arene and [Cu(III)]-facilitated C–O and C–N bond formation. A good range of alkyltrifluoroborates serve as alkyl radical source; these reagents are complementary to radical precursors that generally involve generation of more stabilized radicals.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

We thank the National Institutes of Health (GM078383) and the Arthur C. Cope Fund for support of this research.



Notes and references

- 1 (a) X. Bao, T. Yokoe, T. M. Ha, Q. Wang and J. Zhu, *Nat. Commun.*, 2018, **9**, 3725; (b) Intermolecular: W. Jian, L. Ge, Y. Jiao, B. Qian and H. Bao, *Angew. Chem., Int. Ed.*, 2017, **56**, 3650.
- 2 R. Zhu and S. L. Buchwald, *Angew. Chem., Int. Ed.*, 2013, **52**, 12655.
- 3 R. Zhu and S. L. Buchwald, *J. Am. Chem. Soc.*, 2015, **137**, 8069.
- 4 S. Zhang, L. Li, J. Zhang, J. Zhang, M. Xue and K. Xu, *Chem. Sci.*, 2019, **10**, 3181.
- 5 J.-S. Lin, F.-L. Wang, X.-Y. Dong, W.-W. He, Y. Yuan, S. Chen and X.-Y. Liu, *Nat. Commun.*, 2017, **8**, 14841.
- 6 Y.-F. Cheng, X.-Y. Dong, Q.-S. Gu, Z.-L. Yu and X.-Y. Liu, *Angew. Chem., Int. Ed.*, 2017, **56**, 8883.
- 7 K. Shen and Q. Wang, *Org. Chem. Front.*, 2016, **3**, 222.
- 8 J.-S. Lin, X.-Y. Dong, T.-T. Li, N.-C. Jiang, B. Tan and X.-Y. Liu, *J. Am. Chem. Soc.*, 2016, **138**, 9357.
- 9 T. M. Ha, Q. Wang and J. Zhu, *Chem. Commun.*, 2016, **52**, 11100.
- 10 Y. Da, S. Han, X. Du, S. Liu, L. Liu and J. Li, *Org. Lett.*, 2018, **20**, 5149.
- 11 S. N. Gockel, T. L. Buchanan and K. L. Hull, *J. Am. Chem. Soc.*, 2018, **140**, 58.
- 12 (a) K. Duan, X. Yan, Y. Liu and Z. Li, *Adv. Syn. Cat.*, 2018, **360**, 2781; (b) J. K. Matsui, S. B. Lang, D. R. Heitz and G. A. Molander, *ACS Catal.*, 2017, **7**, 2563; (c) D. R. Heitz, K. Rizwan and G. A. Molander, *J. Org. Chem.*, 2016, **81**, 7308; (d) For related [Cu(II)]-catalyzed reactions with alkyltin reagents, see: M. U. Luescher and J. W. Bode, *Synlett*, 2019, **30**, 464; (e) Electrochemically promoted intermolecular couplings with vinyl and alkynyltrifluoroborates: P. Xiong, H. Long, J. Song, Y. Wang, J. F. Li and H. C. Xu, *J. Am. Chem. Soc.*, 2018, **140**, 16387.
- 13 C. Um and S. R. Chemler, *Org. Lett.*, 2016, **18**, 2515.
- 14 T. W. Liwosz and S. R. Chemler, *Org. Lett.*, 2013, **15**, 3034.
- 15 (a) A. Carlsson, K. Fuxe, B. Hamberger and T. Malmfors, *Br. J. Pharmacol.*, 1969, **36**, 18; (b) J. F. M. Hewitt, L. Williams, P. Aggarwal, C. D. Smith and D. J. France, *Chem. Sci.*, 2013, **4**, 3538 and references therein (c) C. Alamillo-Ferrer, M. Karabourniotis-Sotti, A. R. Kennedy, M. Campbell and N. C. O. Tomkinson, *Org. Lett.*, 2016, **18**, 3102.
- 16 related enantioselective reactions involving Cu(III) intermediates: (a) M. B. Andrus and Z. Zhou, *J. Am. Chem. Soc.*, 2002, **124**, 8806; (b) F. Wang, P. Chen and G. Liu, *Acc. Chem. Res.*, 2018, **51**, 2036.
- 17 Y. Gao, J. Xu, P. Zhang, H. Fang, G. Tang and Y. Zhao, *RSC Adv.*, 2015, **5**, 36167.
- 18 G. A. Molander, V. Colombel and V. A. Braz, *Org. Lett.*, 2011, **13**, 1852.

