



Cite this: *Org. Biomol. Chem.*, 2015, **13**, 8411  
 Received 11th June 2015,  
 Accepted 2nd July 2015  
 DOI: 10.1039/c5ob01196e  
[www.rsc.org/obc](http://www.rsc.org/obc)

## Copper-catalyzed trifluoromethylation of alkenes: synthesis of trifluoromethylated benzoxazines†

Sadhan Jana, Athira Ashokan, Shailesh Kumar, Ajay Verma and Sangit Kumar\*

A simple base and ligand free copper catalyzed method for the construction of trifluoromethylated benzoxazines has been developed by using Umemoto's reagent. It involves the oxidative difunctionalization of alkenes through tandem C–O and C–CF<sub>3</sub> bond formations. Furthermore, synthesized benzoxazines were selectively converted into trifluoromethylated allylic and (*E*)-vinylic benzamides by the treatment of KO<sup>t</sup>Bu and CH<sub>3</sub>Li, respectively.

Benzoxazines, *N,O*-containing six membered heterocycles, are present in many drug molecules and herbicides and are also widely used as building blocks for bioactive molecules. They show interesting biological and pharmaceutical properties such as progesterone receptor (PR) modulation, and anti-anxiety, anti-HIV, agonist, and antagonist activities (Fig. 1).<sup>1,2</sup>

Incorporation of the CF<sub>3</sub> group in the organic molecule enhances several biological properties such as solubility, lipophilicity, metabolic stability, binding selectivity *etc.*<sup>3</sup> As a result, several trifluoromethylated heterocycles such as efavirenz and celecoxib were used as potential drugs for the treatment of HIV infection, arthritis, and spondylitis.<sup>4</sup>

As a consequence, versatile methodologies are being established for the introduction of the CF<sub>3</sub> moiety into heterocycles and related organic molecules.<sup>5–12</sup> However, the synthesis of CF<sub>3</sub>-containing heterocycles through intramolecular cyclization has been less explored. In 2013, Buchwald *et al.* reported copper-catalyzed intramolecular oxytrifluoromethylation of unactivated alkenes using Togni's reagent for the synthesis of trifluoromethylated lactones.<sup>6</sup> Subsequently, intramolecular aminotrifluoromethylation<sup>7</sup> and carbotrifluoromethylation<sup>8</sup> of simple alkenes have been successfully established. The Fu group had developed transition metal-free synthesis of trifluoromethylated oxazolines exploiting CF<sub>3</sub>SO<sub>2</sub>Na as a CF<sub>3</sub> source.<sup>9</sup>

Construction of the benzoxazine ring has been achieved by the intramolecular cyclization of alkenes using electrophiles such as Br<sup>+</sup>, I<sup>+</sup>, and KSCN and K<sub>2</sub>S<sub>2</sub>O<sub>8</sub> combination.<sup>13,14</sup> Benzoxazines comprising the CF<sub>3</sub> group has remained an unexplored area. Recently, Xiao *et al.* has demonstrated photocatalytic oxytrifluoromethylation of *N*-allylamides for the synthesis of trifluoromethylated benzoxazines using the expensive Ru(bpy)<sub>3</sub>(PF<sub>6</sub>)<sub>2</sub> catalyst and a base by a radical pathway.<sup>15d</sup>

Copper-catalyzed trifluoromethylation of terminal alkenes through allylic C–H bond activation has been accomplished by Fu and Liu *et al.* exploiting the copper catalyst, Umemoto's reagent, and the 2,4,6-trimethyl pyridine reaction system (Scheme 1, eqn (1)).<sup>10a</sup> In view of the recent advances in

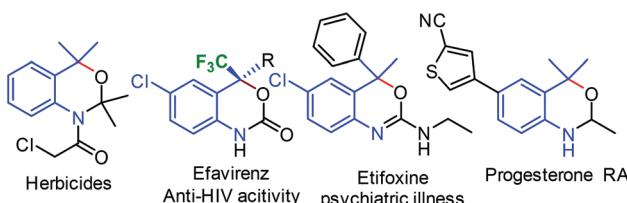
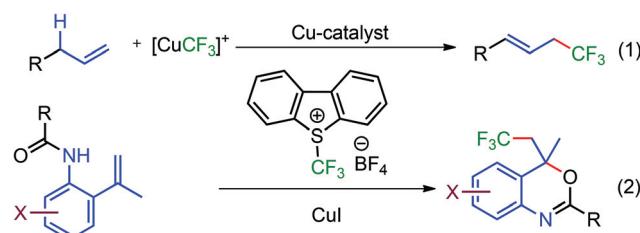


Fig. 1 Benzoxazine and related drugs.

Department of Chemistry, Indian Institute of Science Education and Research (IISER) Bhopal, Bhopal By-Pass Road, Bhauri, Bhopal, Madhya Pradesh 462066, India.  
 E-mail: sangitkumar@iiserb.ac.in

† Electronic supplementary information (ESI) available: Experimental procedure, spectra, crystal data. CCDC 1063690 (3f), 1402832 (5d) and 1402833 (3z). For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c5ob01196e



Scheme 1 Synthesis of trifluoromethylated alkenes and benzoxazines.



Cu-catalyzed functionalization of alkenes,<sup>16,17</sup> we envisioned, trifluoromethylation of the terminal alkene followed by intramolecular addition of oxygen for the synthesis of trifluoromethylated benzoxazines keeping the allylic C–H bond intact (eqn (2)). Herein, we present a simple base and ligand-free Cu-catalyzed synthesis of trifluoromethylated benzoxazine heterocycles from *N*-(2-(prop-1-en-2-yl)benzamide substrates **1** using Umemoto's reagent **2** (Scheme 1, eqn (2)). Synthesized trifluoromethylated benzoxazines were also selectively converted into trifluoromethylated allylic and (*E*)-vinyllic benzamides.

We initially examined the reaction of *N*-(2-(prop-1-en-2-yl)benzamide **1a** with CuI (20 mol%) and various trifluoromethylating reagents in DCE (Table 1, entries 1–4). TMSCF<sub>3</sub> was observed to be sluggish and the formation of the desired product was not realized. Togni's reagent gave a mixture of the desired trifluoromethylated product **3a** in low yield (30%) along with 45% allylic trifluoromethylated product **4a** (entry 1, Table 1). Shreeve's reagent, a triflate analogue of **2** provided 37% yield of **3a**. The use of Umemoto's reagent **2**, led to further increase in the yield by 15% of the desired product **3a**. The presence of copper is crucial for trifluoromethylation as the reaction failed to provide even traces of **3a** in the absence of copper (entry 5, Table 1). Although, various Cu sources (Table 1, entries 6–9, 14), ligands, and bases were screened (see ESI, Table S1, pp. S5–S6† for detailed optimization study), CuI alone was observed to be effective. The change in solvent from DCE to DMF, DMAc, NMP, and DMSO (Table 1, entries

Table 1 Optimization of the reaction conditions<sup>a</sup>

Entry	Catalyst + CF <sub>3</sub> source	Solvent	Yield of <b>3a</b> <sup>b</sup>
1	CuI + Togni's reagent	DCE	30 <sup>b</sup> , 45 <sup>c</sup>
2	CuI + TMSCF <sub>3</sub>	DCE	ND
3	CuI + Shreeve's reagent	DCE	37
4	CuI + <b>2</b>	DCE	52
5	– + <b>2</b>	DCE	ND
6	CuTc + <b>2</b>	DCE	17
7	CuCN + <b>2</b>	DCE	26
8	[Cu(CH <sub>3</sub> CN) <sub>4</sub> ]BF <sub>4</sub> + <b>2</b>	DCE	5
9	[Cu(CH <sub>3</sub> CN) <sub>4</sub> ]PF <sub>6</sub> + <b>2</b>	DCE	6
10	CuI + <b>2</b>	DMF	52
11	CuI + <b>2</b>	DMAc	58
12	CuI + <b>2</b>	NMP	39
13	CuI + <b>2</b>	DMSO	68
14	Cu	DMSO	18

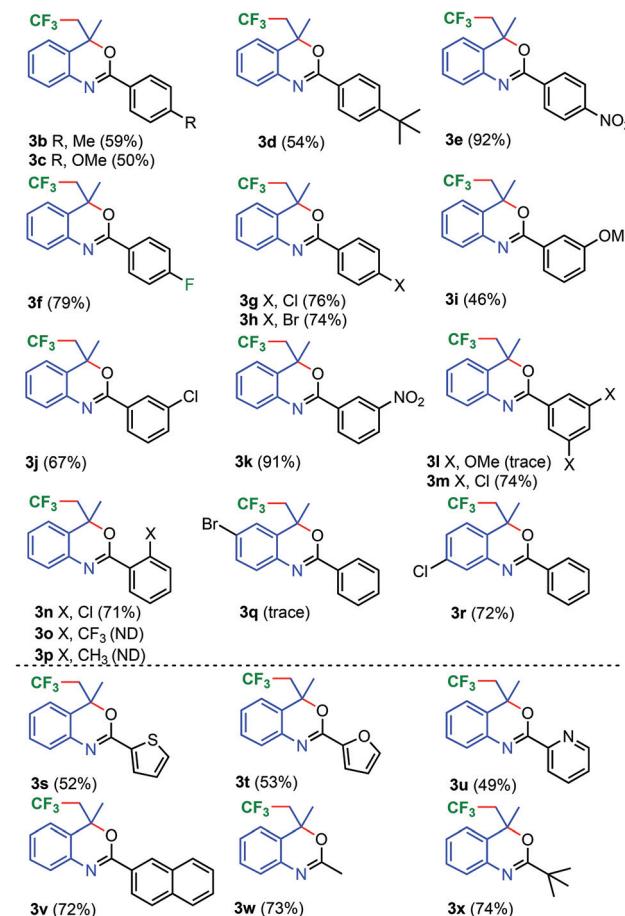
<sup>a</sup> All reactions were carried out using 0.2 mmol of **1a**, 0.35 mmol of **2** in 1 mL solvent at 80 °C in a Schlenk tube under nitrogen and the progress of the reaction was monitored by TLC up to 35 h.

<sup>b</sup> Percentage yield was determined by <sup>19</sup>F-NMR using fluorobenzene as an internal standard. <sup>c</sup> Yield of **4a**. ND = not detected, CuTc = thiophene-2-carbonyloxylate copper(I).

10–13) led to further improvement in the yield and the best yield (68%) was obtained in DMSO (entry 13, Table 1).

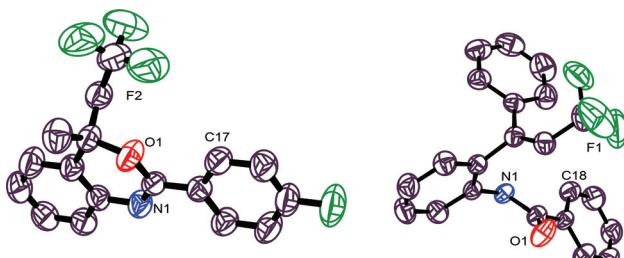
Next, the substrate scope of trifluoromethylation of the alkenes using 20 mol% of CuI at 80 °C in DMSO was studied. The substitution in the amide ring of **1a** was explored (Scheme 2). Alkenes with electron donating substituents such as CH<sub>3</sub>, OCH<sub>3</sub>, and 'Bu at the *para*-position of the benzamide ring, gave trifluoromethylated benzoxazines **3b**–**3d** in moderate yields (50–59%) whereas the electron withdrawing groups such as NO<sub>2</sub>, F, Cl, and Br favoured the trifluoromethylation which indeed led to good yields (74–92%) of **3e**–**3h**.

Structures of CF<sub>3</sub>-benzoxazines **3f** and **3z** are also established by the single crystal structure study (Fig. 2, for **3z** and crystallographic details, please see the ESI, pp. S202–S232†). *meta*-Methoxy substituted benzoxazine **3i** was obtained in moderate yield (46%) whereas Cl and NO<sub>2</sub> substituted benzoxazines **3j** and **3k** were obtained in 67 and 91% yields, respectively. The reaction of the *meta*-di-OCH<sub>3</sub>-substituted substrate was observed to be sluggish and only trace amounts of the respective trifluoromethylated benzoxazine **3l** were isolated. On the other hand, *meta*-di-chloro-substituted benzoxazine **3m** was obtained in 74% yield.



Scheme 2 Synthesis of CF<sub>3</sub>-benzoxazines: scope with respect to amide and aniline rings.



Fig. 2 ORTEP diagrams of **3f** and **5d**.

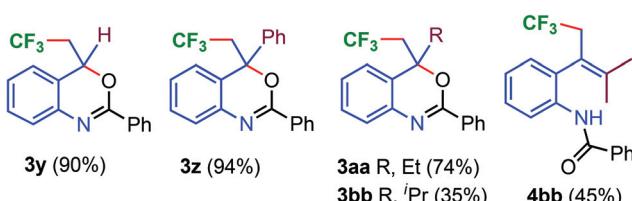
Similarly, the substrate with *ortho*-chloro substitution in the amide ring, gave the desired trifluoromethylated benzoxazine **3n** in good yield (71%). *ortho*-Methyl and trifluoromethyl substituted substrates failed to yield trifluoromethylated benzoxazines **3o** and **3p** and recovered quantitatively and this could be due to the steric effect of  $\text{CH}_3$  and  $\text{CF}_3$  which may prevent the coordination of the  $-\text{CONHPh}$  group (*vide infra*).

On the other hand, bromo-substitution in the aniline ring *para* to NH has a negative effect on the trifluoromethylation reaction as only trace amounts of **3q** were obtained. The substrate with a chloro substituent in the aniline ring, *para* to the alkene, underwent trifluoromethylation smoothly and yielded chloro benzoxazines **3r** in 72% yield.

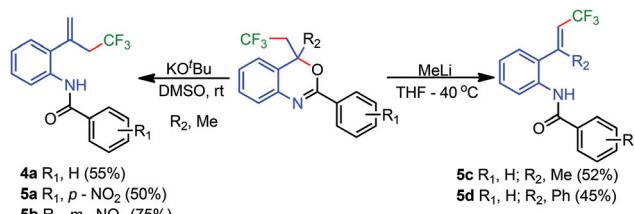
Next, the substrates with various *N*-aromatics such as naphthyl heteroaromatics; thiophenyl, furanyl, and pyridinyl were subjected to trifluoromethylation reaction. Indeed, the reaction also showed compatibility with naphthyl and hetero-aryl containing substrates and respective trifluoromethyl benzoxazines **3s**–**3v** were obtained in 49–72% yields.

Substrates not only with various aryl benzamides but also with alkyl amides such as methyl and *tert*-butyl substituents were tolerated and yielded trifluoromethylated benzoxazines **3w** and **3x** in 73 and 74% yields, respectively.

After studying various *N*-aryl, alkyl and benzamide substrates, *C*-2 substituted alkenes were explored in the copper-catalyzed *C*– $\text{CF}_3$  and *C*– $\text{O}$  bond formation reaction (Scheme 3). Alkenes with H and Ph substituents at the *C*-2 position provided excellent yields (90 and 94%) of trifluoromethylated benzoxazines **3y** and **3z**. *C*-2 substituted methyl, ethyl, and isopropyl benzoxazines (**3a**, *vide supra*), **3aa**, and **3bb** were obtained in 68, 74, and 35% yields, respectively. In the case of **3bb**, formation of trifluoromethylated, the uncyclized product **4bb** in 45% yield was also observed.



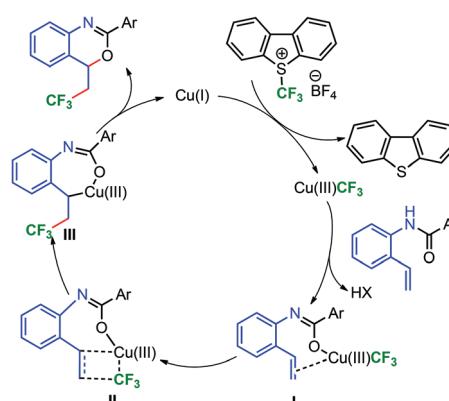
Scheme 3 Substrate scope with regard to olefins.

Scheme 4 Further modification of  $\text{CF}_3$ -benzoxazines.

Next, the synthetic utility of trifluoromethylated benzoxazines was explored (Scheme 4). An addition of  $\text{KO}'\text{Bu}$  to benzoxazines **3a**, **3e**, and **3k** provided trifluoromethylated allylic benzamides **4a**, **5a**, and **5b**, respectively. Interestingly, treatment of **3a** and **3y** with  $\text{CH}_3\text{Li}$  provided trifluoromethylated (*E*)-vinyl benzamides **5c** and **5d**, respectively. The structure of **5d** is also established by the X-ray single crystal study (Fig. 2). It seems that  $\text{KO}'\text{Bu}$  removes the less hindered methyl proton whereas  $\text{CH}_3\text{Li}$  prefers abstraction of the highly acidic proton adjacent to the  $\text{CF}_3$  group.

In the mechanistic consideration, copper(i) can form the  $\text{Cu}(\text{III})\text{CF}_3$  intermediate by the reaction of Umemoto's reagent 2 (Scheme 5).<sup>10a</sup> The formation of the  $\text{Cu}(\text{i})\text{CF}_3$  intermediate is also possible by the disproportionation of  $\text{Cu}(\text{i})$  into  $\text{Cu}(\text{ii})$  and  $\text{Cu}(\text{0})$  followed by the reaction of  $\text{Cu}(\text{0})$  with Umemoto's reagent (please see the ESI, pp. S8–S13† for details).<sup>12e,18</sup> Nevertheless, both  $\text{Cu}(\text{i})\text{CF}_3$  and  $\text{Cu}(\text{III})\text{CF}_3$  could act as a trifluoromethylating reagent.<sup>12e</sup> Ligand exchange with the alkenamide substrate would lead to the substrate–copper intermediate **I**.<sup>19</sup>

Intramolecular coordination of an alkene followed by the formation of the Heck-type four-membered ring would generate the transition state **II**. This could allow the formation of the  $\text{C}-\text{CF}_3$  bond leading to **III**, subsequent reductive elimination may give benzoxazine, by concomitant release of the catalyst. It seems unlikely that the reaction proceeds *via* a radical pathway because the reaction mixture failed to give any signal in the EPR spectrum.



Scheme 5 Mechanism for Cu-catalyzed trifluoromethylation.



The non-reactive nature of *ortho*-methyl and trifluoromethyl substituted substrates (*vide supra*, **3o** and **3p**) and formation of the trifluoromethylated allylic product **4bb** could be rationalized based on the proposed intermediates **I-III**. It seems that allylic trifluoromethylation of the alkene through the allylic C–H bond activation process<sup>10a</sup> also occurred along with the formation of new C–CF<sub>3</sub> and C–O bonds. This may be due to the steric effect of the iso-propyl substituent, therefore, giving a mixture of the C–CF<sub>3</sub> and C–O bond forming product **3bb** and the trifluoromethylated allylic product **4bb**.

In conclusion, we have developed a simple, ligand and base free copper catalyzed method for the construction of trifluoromethylated benzoxazines by using Umemoto's reagent. As the reaction involves mild conditions, trifluoromethylated benzoxazines with functionalities such as nitro and bromo could be constructed which are useful for the later stage modifications. The synthetic utility of trifluoromethylation reaction has also been demonstrated by converting CF<sub>3</sub>-containing benzoxazines into allylic and (*E*) vinylic benzamides. The stereoselective synthesis utilizing a chiral ligand and copper catalytic system as well as the biological study of trifluoromethylated benzoxazines are under investigation in our laboratory.

S.K. thanks DRDO, New Delhi and IISER, Bhopal for generous funding. S.J., S.K. and A.V. acknowledge IISER, Bhopal and UGC, New Delhi, respectively, for the fellowship. S.K. also thanks Ch. Durga Prasad for proofreading the manuscript.

## Notes and references

- (a) S. J. Hays, B. W. Caprathe, J. L. Gilmore, N. Amin, M. R. Emmerling, W. Michael, R. Nadimpalli, R. Nath, K. J. Raser, D. Stafford, D. Watson, K. Wang and J. C. Jaen, *J. Med. Chem.*, 1998, **41**, 1060; (b) N. Dias, J.-F. Goossens, B. Baldeyrou, A. Lansiaux, P. Colson, A. Di Salvo, J. Bernal, A. Turnbull, D. J. Mincher and C. Bailly, *Bioconjugate Chem.*, 2005, **16**, 949.
- P. Zhang, E. A. Terefenko, A. Fensome, Z. Zhang, Y. Zhu, J. Cohen, R. Winnerker, J. Wrobel and J. Yardley, *Bioorg. Med. Chem. Lett.*, 2002, **12**, 787.
- S. Purser, P. R. Moore, S. Swallow and V. Gouverneur, *Chem. Soc. Rev.*, 2008, **37**, 320.
- (a) J. W. Kobzina, *Canadian Patent* 1059125, 1979; (b) S. D. Young, S. F. Britcher, L. O. Tran, L. S. Payne, W. C. Lumma, T. A. Lyle, J. R. Huff, P. S. Anderson, D. B. Olsen, S. S. Carroll, D. J. Pettibone, J. A. O'Brien, R. G. Ball, S. K. Balani, J. H. Lin, I.-W. Chen, W. A. Schleif, V. V. Sardana, W. J. Long, V. W. Byres and E. A. Emini, *Antimicrob. Agents Chemother.*, 1995, **39**, 2602; (c) D. Putman, D. Hongenkamp, O. Dasse, E. R. Whittemore and M. S. Jansen, *US Patent* 20080039453A1, 2008.
- Recent reviews on trifluoromethylation: (a) H. Egami and M. Sodeoka, *Angew. Chem., Int. Ed.*, 2014, **53**, 8294; (b) S. Barata-Vallejo, B. Lantaño and A. Postigo, *Chem. – Eur. J.*, 2014, **20**, 16806; (c) J. Xu, X. Lui and Y. Fu, *Tetrahedron Lett.*, 2014, **55**, 585; (d) E. Merino and C. Nevado, *Chem. Soc. Rev.*, 2014, **43**, 6598; (e) T. Koike and M. Akita, *J. Fluorine Chem.*, 2014, **167**, 30; (f) C. Alonso, E. M. D. Marigorta, G. Rubiales and F. Palacios, *Chem. Rev.*, 2015, **115**, 1847; (g) J. Charpentier, N. Früh and A. Togni, *Chem. Rev.*, 2015, **115**, 650.
- Oxytrifluoromethylation: (a) R. Zhu and S. L. Buchwald, *J. Am. Chem. Soc.*, 2012, **134**, 12462; (b) R. Zhu and S. L. Buchwald, *Angew. Chem., Int. Ed.*, 2013, **52**, 12655; (c) Y.-T. He, H.-L. Li, Y.-F. Yang, Y.-Q. Wang, J.-Y. Luo, X.-Y. Liu and Y.-M. Liang, *Chem. Commun.*, 2013, **49**, 5687; (d) Q. Yu and S. Ma, *Chem. – Eur. J.*, 2013, **19**, 13304; (e) Photoredox-catalyzed: Y. Yasu, Y. Arai, R. Tomita, T. Koike and M. Akita, *Org. Lett.*, 2014, **16**, 780.
- Aminotrifluoromethylation: (a) J.-S. Lin, Y.-P. Xiong, C.-L. Ma, L.-J. Zhao, B. Tan and X.-Y. Liu, *Chem. – Eur. J.*, 2014, **20**, 1332; (b) J.-S. Lin, X.-G. Liu, X.-L. Zhu, B. Tan and X.-Y. Liu, *J. Org. Chem.*, 2014, **79**, 7084; (c) S. Kawamura, H. Egami and M. Sodeoka, *J. Am. Chem. Soc.*, 2015, **137**, 4865; (d) P. Yu, S.-C. Zheng, N.-Y. Yang, B. Tan and X.-Y. Liu, *Angew. Chem., Int. Ed.*, 2015, **54**, 4041.
- Carbotrifluoromethylation: (a) H. Egami, R. Shimizu, S. Kawamura and M. Sodeoka, *Angew. Chem., Int. Ed.*, 2013, **52**, 4000; (b) P. Gao, X.-B. Yan, T. Tao, F. Yang, T. He, X.-R. Song, X.-Y. Liu and Y.-M. Liang, *Chem. – Eur. J.*, 2013, **19**, 14420; (c) P. Xu, J. Xie, Q. Xue, C. Pan, Y. Change and C. Zhu, *Chem. – Eur. J.*, 2013, **19**, 14039; (d) H. Egami, R. Shimizu and M. Sodeoka, *J. Fluorine Chem.*, 2013, **152**, 51; (e) L. Li, M. Deng, S.-C. Zheng, Y.-P. Xiong, B. Tan and X.-Y. Yuan, *Org. Lett.*, 2014, **16**, 504; (f) G. Han, Y. Liu and Q. Wang, *Org. Lett.*, 2014, **16**, 3188; (g) G. Hang, Q. Wang, Y. Liu and Q. Wang, *Org. Lett.*, 2014, **16**, 5914; (h) Y.-T. He, L.-H. Li, Z.-Z. Zhou, H.-L. Hua, Y.-F. Qiu, X.-Y. Liu and Y.-M. Liang, *Org. Lett.*, 2014, **16**, 3896; (i) J. Xu, Y.-L. Wang, T.-J. Gong, B. Xio and Y. Fu, *Chem. Commun.*, 2014, **50**, 12915; (j) Y. Wang, M. Jiang and J.-T. Liu, *Chem. – Eur. J.*, 2014, **20**, 15315; (k) L. Hung, J.-S. Lin, B. Tan and X.-Y. Liu, *ACS Catal.*, 2015, **5**, 2826; (l) H.-L. Hua, Y.-T. He, Y.-F. Qiu, Y.-X. Li, B. Song, P. Gao, X.-R. Song, D.-H. Guo, X.-Y. Liu and Y.-M. Liang, *Chem. – Eur. J.*, 2015, **21**, 1468; (m) L. Huang, S.-C. Zheng, B. Tan and X.-Y. Liu, *Chem. – Eur. J.*, 2015, **21**, 6718.
- J. Yu, H. Yang and H. Fu, *Adv. Synth. Catal.*, 2014, **356**, 3669.
- (a) J. Xu, Y. Fu, D.-F. Luo, Y.-Y. Jiang, B. Xiao, Z.-J. Liu, T.-J. Gong and L. Liu, *J. Am. Chem. Soc.*, 2011, **133**, 15300; (b) D.-F. Luo, J. Xu, Y. Fu and Q.-X. Guo, *Tetrahedron Lett.*, 2012, **53**, 2769; (c) C.-T. Yang, Z.-Q. Zhang, H. Tajuddin, C.-C. Wu, J. Liang, J.-H. Liu, Y. Fu, M. Czyzewska, P. G. Steel, T. B. Marder and L. Liu, *Angew. Chem., Int. Ed.*, 2012, **51**, 528; (d) J. Xu, B. Xiao, C.-Q. Xie, D.-F. Luo, L. Liu and Y. Fu, *Angew. Chem., Int. Ed.*, 2012, **51**, 12551; (e) J.-J. Dai, C. Fang, B. Xiao, J. Yi, J. Xu, Z.-J. Liu, X. Lu, L. Liu and Y. Fu, *J. Am. Chem. Soc.*, 2013, **135**, 8436; (f) Q. Lu, H. Yu and Y. Fu, *Chem. Commun.*, 2013, **49**, 10847.
- (a) G. G. Dubinina, H. Furutachi and D. A. Vicic, *J. Am. Chem. Soc.*, 2008, **130**, 8600; (b) C.-P. Zhang, Z.-L. Wang,



Q.-Y. Chen, C.-T. Zhang, Y.-C. Gu and J.-C. Xiao, *Angew. Chem., Int. Ed.*, 2011, **50**, 1896.

12 (a) T. Umemoto and S. Ishihara, *Tetrahedron Lett.*, 1990, **31**, 3579; (b) T. Umemoto and S. Ishihara, *J. Am. Chem. Soc.*, 1993, **115**, 2156; (c) T. Umemoto, S. Ishihara and K. Adachi, *J. Fluorine Chem.*, 1995, **74**, 77; (d) T. Umemoto and S. Ishihara, *J. Fluorine Chem.*, 1999, **98**, 75; (e) C. Zhange, *Org. Biomol. Chem.*, 2014, **12**, 6580.

13 (a) Synthesis of an oxazoline moiety: L. Engman, *J. Org. Chem.*, 1991, **56**, 3425; (b) A. Jaganathan, A. Garzan, D. C. Whitehead, R. J. Staples and B. Borhan, *Angew. Chem., Int. Ed.*, 2011, **50**, 2593; (c) Y.-M. Wang, J. Wu, C. Hoong, V. Rauniyar and F. D. Toste, *J. Am. Chem. Soc.*, 2012, **134**, 12928; (d) J. Wu, Y.-M. Wang, A. Drljevic, V. Rauniyar, R. J. Phipps and F. D. Toste, *Proc. Natl. Acad. Sci. U. S. A.*, 2013, **110**, 13729; (e) A. Jaganathan, R. J. Staples and B. Borhan, *J. Am. Chem. Soc.*, 2013, **135**, 14806; (f) Q. Yin and S.-L. You, *Org. Lett.*, 2013, **15**, 4266.

14 H. Yang, X.-H. Duan, J.-F. Zhao and L.-N. Guo, *Org. Lett.*, 2015, **17**, 1998.

15 (a) F.-L. Liu, J.-R. Chen, B. Feng, X.-Q. Hu, L.-H. Ye, L.-Q. Lu and W.-J. Xiao, *Org. Biomol. Chem.*, 2014, **12**, 1057; (b) X.-Q. Hu, J.-R. Chen, Q. Wei, F.-L. Liu, Q.-H. Deng, A. M. Beauchemin and W.-J. Xiao, *Angew. Chem., Int. Ed.*, 2014, **53**, 12163; (c) X.-Q. Hu, G. Feng, J.-R. Chen, D.-M. Yan, Q.-Q. Zhao, Q. Wei and W.-J. Xiao, *Org. Biomol. Chem.*, 2015, **13**, 3457; (d) Q.-H. Deng, J.-R. Chen, Q. Wei, Q.-Q. Zhao, L.-Q. Lu and W.-J. Xiao, *Chem. Commun.*, 2015, **51**, 3537.

16 Recent review on Cu-catalyzed functionalization of C–C multiple bonds: Y. Shimizu and M. Kanai, *Tetrahedron Lett.*, 2014, **55**, 3727.

17 (a) J. Lu, Y. Jin, H. Liu, Y. Jaing and H. Fu, *Org. Lett.*, 2011, **13**, 3694; (b) S. Majima, Y. Shimizu and M. Kanai, *Tetrahedron Lett.*, 2012, **53**, 4381; (c) X. Wang, Y. Jin, Y. Zhao, L. Zhu and H. Fu, *Org. Lett.*, 2012, **14**, 452; (d) J. Kawai, P. K. Chikkade, Y. Shimizu and M. Kanai, *Angew. Chem., Int. Ed.*, 2013, **52**, 7177; (e) K. Kaneko, T. Yoshino, S. Matsunaga and M. Kanai, *Org. Lett.*, 2013, **15**, 2502; (f) T. Itoh, Y. Shimizu and M. Kanai, *Org. Lett.*, 2014, **16**, 2736.

18  $^{19}\text{F}$  NMR of the reaction mixture of **2** and CuI indicates a signal at  $-32.7$  ppm which is attributed to  $\text{Cu}(\text{i})\text{CF}_3$ . The reported value of  $\text{Cu}(\text{i})\text{CF}_3$  is  $\delta -33.9$  ppm; see ref. 11b.

19 For the coordination of Cu with oxygen over alkene in related substrates, please see: B. Chen, X.-L. Hou, Y.-X. Li and Y.-D. Wu, *J. Am. Chem. Soc.*, 2011, **133**, 7668.

