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Copper-catalyzed synthesis of trifluoromethyl-substituted isoxazolines†

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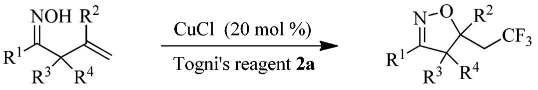
A mild and efficient copper-catalyzed trifluoromethylation reaction which involves the cyclization of oximes has been developed. This method provides a convenient access to a variety of useful CF_3-containing 4,5-dihydroisoxazoles by constructing a C–CF_3 bond and a C–O bond in one step.

The trifluoromethyl group is considered to be a useful structural motif in pharmaceuticals, agrochemicals and functional materials, mainly because of the excellent metabolic stability, elevated electronegativity, and high lipophilicity.[1,2] Therefore, the development of new methods for the synthesis of CF_3-containing compounds is a research hotspot in the field of organic synthesis. In recent years, a series of transition metal-mediated or -catalyzed and photoredox catalyzed construction of a C–CF_3 bond has been reported.[3–8] However, the synthesis of CF_3-containing heterocycles has been less explored,[9] and most of the construction methods in heterocycles are focused on direct C–H trifluoromethylation. Thus, synthesis of trifluoromethyl-substituted heterocycles through a pattern of cyclization is becoming a fascinating way for us to explore. Recently, Buchwald *et al.* and Liu *et al.*, independently, reported the oxytrifluoromethylation of unactivated alkenes based on a copper catalyst,[10] and intramolecular oxidative aryltrifluoromethylation of activated alkenes using $TMSCF_3$ (Ruppert–Prakash reagent)[11] in the presence of $Pd(OAc)_2$.[12]

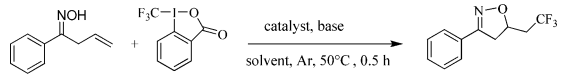
As we know, oximes are fascinating synthetic reagents since they have both nitrogen and oxygen atoms as nucleophiles.[13] In 2012, the intramolecular addition of the oxime radical to a carbon–carbon double bond to form isoxazolines was reported by Han *et al.*[14] Inspired by this intriguing work and in connection with our interest in the synthesis of heterocycles,[15] we report an efficient procedure for the preparation of a series of trifluoromethyl-substituted 4,5-dihydroisoxazoles by using Togni's reagent[16] (Scheme 1).



Scheme 1 Synthesis of trifluoromethyl-substituted isoxazolines.

To begin, substrate **1a** was chosen as a model substrate for our investigation. We used Togni's reagent **2a** as the trifluoromethylation reagent under a catalytic amount of CuCl and KF as the base in DMF. The reaction proceeded smoothly, which gave the desired product **3a** in 65% yield (Table 1, entry 1).

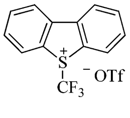
Table 1 Optimization of the reaction conditions[a]



1a + **2a** → **3a**

Entry	Catalyst	Base	Solvent	Yield[b] (%)
1	CuCl	KF	DMF	65
2[c]	CuCl	KF	DMF	0
3[d]	CuCl	KF	DMF	0
4[e]	—	KF	DMF	0
5	$Cu(OTf)_2$	KF	DMF	18
6	$Cu(OAc)_2$	KF	DMF	40
7	$[Cu(OTf)_2]\cdot C_6H_6$	KF	DMF	10
8	CuI	KF	DMF	62
9	CuBr	KF	DMF	61
10	CuCl	K_3PO_4	DMF	73
11	CuCl	K_2CO_3	DMF	70
12	CuCl	Cs_2CO_3	DMF	59
13	**CuCl**	**NaOAc**	**DMF**	**79**
14	CuCl	NaOAc	CH_3CN	42
15	CuCl	NaOAc	THF	30
16	CuCl	NaOAc	NMP	70
17	CuCl	NaOAc	DMSO	69
18	CuCl	NaOAc	DMAC	67

[a] Reaction conditions: **1a** (0.2 mmol), **2a** (0.3 mmol), copper catalyst (0.04 mmol), base (0.24 mmol), solvent (3 mL), 50 °C, 0.5 h, under argon. [b] Isolated yield. [c] $TMSCF_3$ was used. [d] Umemoto's reagent **2b** was used. [e] Without CuCl.



2b

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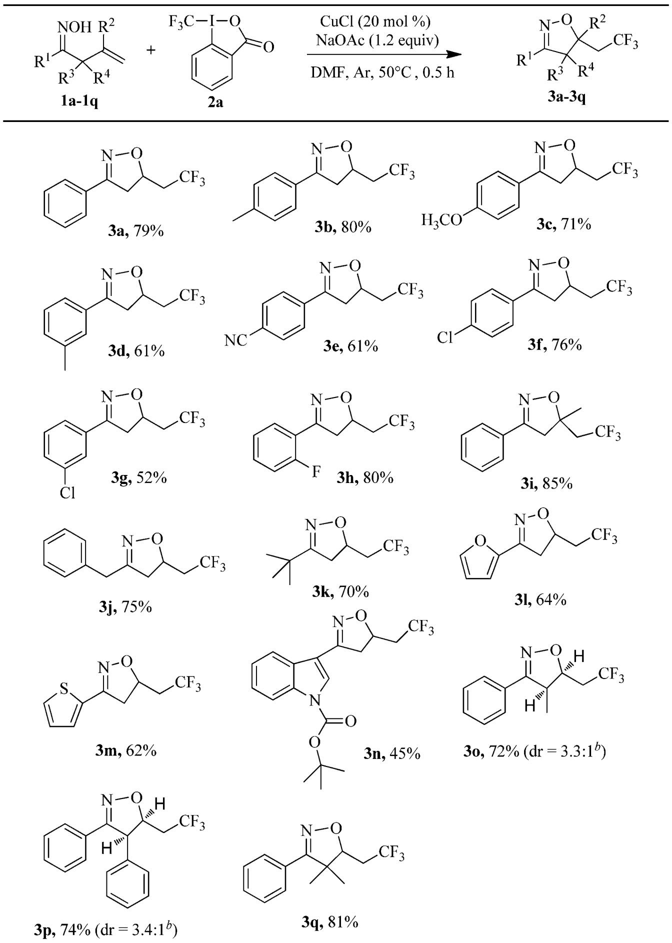
† Electronic supplementary information (ESI) available: Experimental procedures and analysis data for new compounds. CCDC 932707(**3a**). For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c3cc42588f

Subsequently, we tested $TMSCF_3$ and Umemoto's reagent **2b**[17] as the trifluoromethylation reagents. Unfortunately, no desired product was observed (Table 1, entries 2 and 3). The copper catalyst was found to be essential to the reaction, since no desired product was observed in the absence of the copper catalyst (Table 1, entry 4). For comparison, other copper catalysts were also studied, but using $Cu(OTf)_2$, $Cu(OAc)_2$, and $[Cu(OTf)_2]\cdot C_6H_6$ led to lower yields (Table 1, entries 5–7). The effect of inorganic bases was also examined (Table 1, entries 10–13). The yield of **3a** was increased to 79% when NaOAc was used (Table 1, entry 13). Other solvents, such as CH_3CN and THF, were found to be less effective for this reaction. Thus, 20 mol% CuCl, 1.2 equiv. NaOAc and 1.5 equiv. Togni's reagent **2a** in DMF at 50 °C under an argon atmosphere were considered as the optimal reaction conditions.[18]

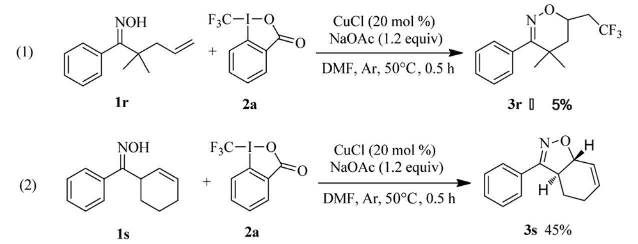
With the optimized reaction conditions in hand, we further explored the scope of trifluoromethylation with a variety of β,γ-unsaturated oximes (Table 2). In most cases, oximes **1a–q** proceeded smoothly to give the corresponding trifluoromethylated products **3a–q** in moderate to good yields under the optimal conditions. The structures of the products were deduced from their IR, ^1H NMR, ^{13}C NMR, ^{19}F NMR and HRMS spectroscopic data. In addition, the NMR-based structures were further confirmed by the X-ray crystal structure analysis of **3a** (see ESI†). Both electron-donating and electron-withdrawing groups at the aromatic rings were found to be tolerated in this reaction. Heterocycle-containing oximes were also transformed into the desired product **3l–3n** in 45–64% yield. Reaction of substrates **1o** and **1p** gave a mixture of diastereoisomers **3o** (d.r. = 3.3 : 1) and **3p** (d.r. = 3.4 : 1), respectively. However, it is difficult to obtain the 6-*exo*-trig cyclization products in this reaction and only a trace amount of the trifluoromethylated product was detected using GC-MS when **1r** was used as the substrate (Scheme 2, eqn (1)). We found that 1,2-disubstituted olefin **1s** was not suitable for the reaction and only dihydroisoxazole **3s** was obtained in 45% yield (Scheme 2, eqn (2)).

Table 2 Scope of copper-catalyzed trifluoromethylation of β,γ-unsaturated oximes with a hypervalent iodine(III) reagent **2a**[a]



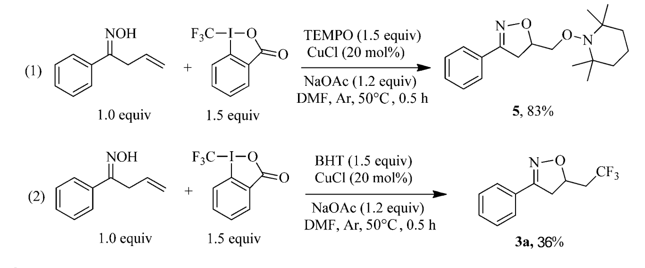
1a-1q
2a
3a-3q
3a, 79%
3b, 80%
3c, 71%
3d, 61%
3e, 61%
3f, 76%
3g, 52%
3h, 80%
3i, 85%
3j, 75%
3k, 70%
3l, 64%
3m, 62%
3n, 45%
3o, 72% (dr = 3.3:1[b])
3p, 74% (dr = 3.4:1[b])
3q, 81%

[a] Reaction conditions: **1** (0.2 mmol), **2a** (0.3 mmol), CuCl (0.04 mmol), NaOAc (0.24 mmol), DMF (3 mL), 50 °C, 0.5 h, under argon, isolated yield. [b] The ratio of diastereomers was determined by crude ^1H NMR and ^{19}F NMR. Structures of the major diastereomers are shown.

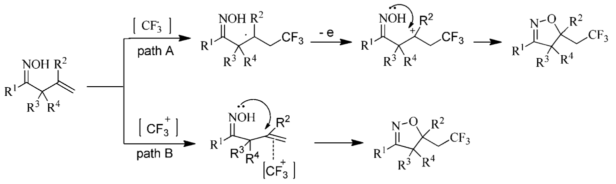


Scheme 2 Copper-catalyzed trifluoromethylation of γ,δ-unsaturated oxime and cyclohex-2-en-1-yl(phenyl)methanone oxime.

To gain some mechanistic insights into the current trifluoromethylation reaction, inhibition experiments were conducted. We added TEMPO (2,2,6,6-tetramethyl-1-piperidinyloxy) to the reaction mixture, and the trifluoromethylation reaction was found to be completely inhibited. Instead, the TEMPO-trapped 4,5-dihydroisoxazole **5** was obtained in 83% yield (Scheme 3, eqn (1)). This result did not aid our understanding of the reaction mechanism, which may be initiated by the oxime radical.[14] But, when BHT (2,6-di-*tert*-butyl-4-methyl-phenol) was added to the optimal conditions, to our surprise, the desired product was obtained with a low yield (36%) (Scheme 3, eqn (2)), and a BHT–CF_3 adduct was detected using GC-MS. These experimental results provided evidence that the reaction mechanism might involve the CF_3 radical and the CF_3 cation. Thus, two plausible mechanisms[19–21] for this transformation are proposed in Scheme 4. In path A, in the presence of copper catalyst and Togni's reagent, a single-electron oxidation occurs resulting in the formation of a radical intermediate, which could be further trapped by the oxygen atom to generate the cyclization product. In path B, first, reaction of Cu(I) with Togni's reagent would



Scheme 3 Trapping experiments.



Scheme 4 Proposed mechanism.

provide CF_3^+, then the alkene is activated by the electrophilic CF_3^+, and the oxygen atom of oxime attacks the activated alkene to give 4,5-dihydroisoxazole.

In summary, we have developed an efficient copper-catalyzed trifluoromethylation reaction which involves the cyclization of oximes to construct a C–CF_3 bond and a C–O bond in one step. This reaction provides a convenient and straightforward method to prepare a variety of useful trifluoromethyl-substituted isoxazolines. Further studies and application of this reaction are in progress.

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Notes and references

1 (*a*) P. Kirsch, *Modern Fluoroorganic Chemistry*, Wiley-VCH, Weinheim, Germany, 2004; (*b*) K. Uneyama, *Organofluorine Chemistry*, Blackwell, Oxford, U.K., 2006; (*c*) I. Ojima, *Fluorine in Medicinal Chemistry and Chemical Biology*, Wiley-Blackwell, Chichester, U.K., 2009; (*d*) B. E. Smart, *Chem. Rev.*, 1996, **96**, 1555; (*e*) M. Schlosser, *Angew. Chem., Int. Ed.*, 2006, **45**, 5432; (*f*) K. Muller, C. Faeh and F. Diederich, *Science*, 2007, **317**, 1881; (*g*) D. O'Hagan, *Chem. Soc. Rev.*, 2008, **37**, 308; (*h*) S. Purser, P. R. Moore, S. Swallow and V. Gouverneur, *Chem. Soc. Rev.*, 2008, **37**, 320.

2 (*a*) M. Shimizu and T. Hiyama, *Angew. Chem., Int. Ed.*, 2005, **44**, 214; (*b*) M. Hird, *Chem. Soc. Rev.*, 2007, **36**, 2070; (*c*) J.-A. Ma and D. Cahard, *Chem. Rev.*, 2008, **108**, PR1; (*d*) K. L. Kirk, *Org. Process Res. Dev.*, 2008, **12**, 305.

3 (*a*) L. Zhao and C.-J. Li, *Angew. Chem., Int. Ed.*, 2008, **47**, 7075; (*b*) X. Wang, L. Truesdale and J.-Q. Yu, *J. Am. Chem. Soc.*, 2010, **132**, 3648; (*c*) R. J. Lundgren and M. Stradiotto, *Angew. Chem., Int. Ed.*, 2010, **49**, 9322; (*d*) J. Xie and Z.-Z. Huang, *Angew. Chem., Int. Ed.*, 2010, **49**, 10181; (*e*) Y. Ji, T. Brueckl, R. D. Baxter, Y. Fujiwara, I. B. Seiple, S. Su, D. G. Blackmond and P. S. Baran, *Proc. Natl. Acad. Sci. U. S. A.*, 2011, **108**, 14411; (*f*) A. T. Parsons, T. D. Senecal and S. L. Buchwald, *Angew. Chem., Int. Ed.*, 2012, **51**, 2947; (*g*) T. Liu, X. Shao, Y. Wu and Q. Shen, *Angew. Chem., Int. Ed.*, 2012, **51**, 540.

4 (*a*) E. J. Cho and S. L. Buchwald, *Org. Lett.*, 2011, **13**, 6552; (*b*) N. D. Ball, J. B. Gary, Y. Ye and M. S. Sanford, *J. Am. Chem. Soc.*, 2011, **133**, 7577; (*c*) Y. Ye, S. H. Lee and M. S. Sanford, *Org. Lett.*, 2011, **13**, 5464; (*d*) I. Popov, S. Lindeman and O. Daugulis, *J. Am. Chem. Soc.*, 2011, **133**, 9286; (*e*) R. N. Loy and M. S. Sanford, *Org. Lett.*, 2011, **13**, 2548; (*f*) J. Xu, D.-F. Luo, B. Xiao, Z.-J. Liu, T.-J. Gong, Y. Fu and L. Liu, *Chem. Commun.*, 2011, **47**, 4300; (*g*) N. D. Litvinas, P. S. Fier and J. F. Hartwig, *Angew. Chem., Int. Ed.*, 2012, **51**, 536.

5 (*a*) V. V. Grushin and W. J. Marshall, *J. Am. Chem. Soc.*, 2006, **128**, 12644; (*b*) E. J. Cho, T. D. Senecal, T. Kinzel, Y. Zhang, D. A. Watson and S. L. Buchwald, *Science*, 2010, **328**, 1679; (*c*) N. D. Ball, J. W. Kampf and M. S. Sanford, *J. Am. Chem. Soc.*, 2010, **132**, 2878; (*d*) L.-L. Chu and F.-L. Qing, *Org. Lett.*, 2010, **12**, 5060; (*e*) T. Liu and Q. Shen, *Org. Lett.*, 2011, **13**, 2342; (*f*) O. A. Tomashenko, E. C. Escudero-Adan, M. M. Belmonte and V. V. Grushin, *Angew. Chem., Int. Ed.*, 2011, **50**, 7655; (*g*) A. Hafner and S. Bräse, *Adv. Synth. Catal.*, 2011, **353**, 3044.

6 (*a*) J. Wedemann, T. Heiner, G. Mloston, G. K. S. Prakash and G. A. Olah, *Angew. Chem., Int. Ed.*, 1998, **37**, 820; (*b*) G. K. S. Prakash, M. Mandal and G. A. Olah, *Org. Lett.*, 2011, **3**, 2847; (*c*) E. Mejia and A. Togni, *ACS Catal.*, 2012, **2**, 521; (*d*) P. Novak, A. Lishchynskyi and V. V. Grushin, *Angew. Chem., Int. Ed.*, 2012, **51**, 7767; (*e*) P. Novak, A. Lishchynskyi and V. V. Grushin, *J. Am. Chem. Soc.*, 2012, **134**, 16167.

7 (*a*) D. A. Nagib, M. E. Scott and D. W. C. MacMillan, *J. Am. Chem. Soc.*, 2009, **131**, 10875; (*b*) D. A. Nagib and D. W. C. MacMillan, *Nature*, 2011, **480**, 224; (*c*) J. D. Nguyen, J. W. Tucker, M. D. Konieczynska and C. R. J. Stephenson, *J. Am. Chem. Soc.*, 2011, **133**, 4160; (*d*) C.-J. Wallentin, J. D. Nguyen, P. Finkbeiner and C. R. J. Stephenson, *J. Am. Chem. Soc.*, 2012, **134**, 8875; (*e*) N. Iqbal, S. Choi, E. Ko and E. J. Cho, *Tetrahedron Lett.*, 2012, **53**, 2005; (*f*) Y. Ye and M. S. Sanford, *J. Am. Chem. Soc.*, 2012, **134**, 9034.

8 (*a*) H. Morimoto, T. Tsubogo, N. D. Litvinas and J. F. Hartwig, *Angew. Chem., Int. Ed.*, 2011, **50**, 3793; (*b*) X. Jiang, L. Chu and F.-L. Qing, *J. Org. Chem.*, 2012, **77**, 1251; (*c*) Y. Miyake, S. Ota and Y. Nishibayashi, *Chem.–Eur. J.*, 2012, **18**, 13255; (*d*) Y. Yasu, T. Koike and M. Akita, *Angew. Chem., Int. Ed.*, 2012, **51**, 9567; (*e*) Q. Qi, Q. Shen and L. Lu, *J. Am. Chem. Soc.*, 2012, **134**, 6548.

9 (*a*) 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; (*b*) H. Kawai, k. Tachi, E. Tokunaga, M. Shiro and N. Shibata, *Angew. Chem., Int. Ed.*, 2011, **50**, 7803; (*c*) X. Mu, S. Chen, X. Zhen and D. Liu, *Chem.–Eur. J.*, 2011, **17**, 6039; (*d*) L. Chu and F.-L. Qing, *J. Am. Chem. Soc.*, 2012, **134**, 1298; (*e*) X.-G. Zhang, H.-X. Dai, M. Wasa and J.-Q. Yu, *J. Am. Chem. Soc.*, 2012, **134**, 11948.

10 R. Zhu and S. L. Buchwald, *J. Am. Chem. Soc.*, 2012, **134**, 12462.

11 (*a*) G. K. S. Prakash and A. K. Yudin, *Chem. Rev.*, 1997, **97**, 757; (*b*) R. P. Sing and J. M. Shreeve, *Tetrahedron*, 2000, **56**, 7613.

12 X. Mu, T. Wu, H. Wang, Y. Guo and G. Liu, *J. Am. Chem. Soc.*, 2012, **134**, 878.

13 (*a*) S. Zaman, K. Mitsuru and A. D. Abell, *Org. Lett.*, 2005, **7**, 609; (*b*) H. Miyabe, K. Yoshida, V. K. Reddy, A. Matsumura and Y. Takemoto, *J. Org. Chem.*, 2005, **70**, 5630; (*c*) J. Kassa, K. Kuca, L. Bartosova and G. Kunesova, *Curr. Org. Chem.*, 2007, **11**, 267; (*d*) M.-K. Zhu, J.-F. Zhao and T.-P. Loh, *J. Am. Chem. Soc.*, 2010, **132**, 6284.

14 B. Han, X.-L. Yang, R. Fang, W. Yu, C. Wang, X.-Y. Duan and S. Liu, *Angew. Chem., Int. Ed.*, 2012, **51**, 8816.

15 K.-G. Ji, H.-T. Zhu, F. Yang, A. Shoukat, X.-F. Xia, Y.-F. Yang, X.-Y. Liu and Y.-M. Liang, *J. Org. Chem.*, 2010, **75**, 5670.

16 (*a*) P. Eisenberger, S. Gischig and A. Togni, *Chem.–Eur. J.*, 2006, **12**, 2579; (*b*) K. Niedermann, N. Fruh, E. Vinogradova, M. S. Wiehn, A. Moreno and A. Togni, *Angew. Chem., Int. Ed.*, 2011, **50**, 1059; (*c*) V. Matoušek, A. Togni, V. Bizet and D. Cahard, *Org. Lett.*, 2011, **13**, 5762.

17 T. Umemoto and S. Ishihara, *Tetrahedron Lett.*, 1990, **31**, 3579.

18 See ESI† for detailed data.

19 (*a*) T. Okano, T. Uekawa and S. Eguchi, *Bull. Chem. Soc. Jpn.*, 1989, **62**, 2575; (*b*) N. Kamigata, T. Fukushima and M. Yoshida, *Chem. Lett.*, 1990, 649; (*c*) N. Kamigata, T. Ohtsuka, T. Fukushima, M. Yoshida and T. Shimizu, *J. Chem. Soc., Perkin Trans. 1*, 1994, 1339.

20 (*a*) X. Wang, Y. Ye, S. Zhang, J. Feng, Y. Xu, Y. Zhang and J. Wang, *J. Am. Chem. Soc.*, 2011, **133**, 16410; (*b*) A. T. Parsons and S. L. Buchwald, *Angew. Chem., Int. Ed.*, 2011, **50**, 9120; (*c*) 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; (*d*) Y. Yasu, T. Koike and M. Akita, *Chem. Commun.*, 2013, **49**, 2037.

21 (*a*) R. Shimizu, H. Egami, T. Nagi, J. Chae, Y. Hamashima and M. Sodeoka, *Tetrahedron Lett.*, 2010, **51**, 5947; (*b*) R. Shimizu, H. Egami, Y. Hamashima and M. Sodeoka, *Angew. Chem., Int. Ed.*, 2012, **51**, 4577; (*c*) H. Egami, R. Shintaro, S. Kawamura and M. Sodeoka, *Angew. Chem., Int. Ed.*, 2013, **52**, 4000.