

# **Copper-Catalyzed Trifluoromethylation of Terminal Alkenes through** Allylic C–H Bond Activation

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Supporting Information

ABSTRACT: An unprecedented type of reaction for Cucatalyzed trifluoromethylation of terminal alkenes is reported. This reaction represents a rare instance of catalytic trifluoromethylation through  $C(sp^3)$ -H activation. It also provides a mechanistically unique example of Cu-catalyzed allylic C-H activation/functionalization. Both experimental and theoretical analyses indicate that the trifluoromethylation may occur via a Heck-like four-membered-ring transition state.

The trifluoromethyl group is an important structural motif in I many biologically active compounds because this substituent can often enhance their chemical and metabolic stability, lipophilicity, and binding selectivity.<sup>1</sup> Accordingly, it has been of great synthetic interest to develop efficient methods for incorporation of CF<sub>3</sub> into diverse organic structures.<sup>2</sup> The earlier studies in this area focused on various noncatalytic trifluoromethylation reactions, mostly generating  $C(sp^3)-CF_3$  bonds. Some examples include the nucleophilic addition of TMSCF<sub>3</sub> to carbonyl compounds<sup>3</sup> and the  $\alpha$ -trifluoromethylation of ketones using Togni and Umemoto's reagents.<sup>4</sup> Unfortunately, these methods usually suffer from relatively harsh reaction conditions and limited functional group tolerance. To overcome the problems, recent research on trifluoromethylation has paid more attention to transition-metal-catalyzed methods.<sup>5</sup> For instance, Pd-catalyzed methods for trifluoromethylation of  $C(sp^2)$ -H and  $C(sp^2)$ -halide bonds have been developed,<sup>6-9</sup> and Cu-mediated<sup>10</sup> or Cu-catalyzed<sup>11</sup> trifluoromethylation of aryl/vinyl halides and boronic acids and of terminal alkynes<sup>12</sup> have been described. In comparison with the earlier trifluoromethylation methods, the newly developed catalytic reactions employ milder conditions and afford the desired products in higher yields with improved functional group tolerance.

Most of the above transition-metal-catalyzed trifluoromethylation reactions generate  $C(sp^2)-CF_3$  or  $C(sp)-CF_3$  bonds. This creates the interesting challenge of developing new transition-metal-catalyzed trifluoromethylation processes to make  $C(sp^3)$ -CF<sub>3</sub> bonds. Herein we describe an unprecedented reaction for Cu-catalyzed trifluoromethylation of terminal alkenes via allylic  $C(sp^3)$ -H bond activation (Scheme 1). The significance of this reaction is threefold: (1) The reaction provides one of the first examples of catalytic trifluoromethylation to produce  $C(sp^3)-CF_3$  bonds via  $C(sp^3)-H$  activation. (2) Although a number of examples of Pd-catalyzed allylic C-H activation and functionalization have been reported,<sup>13</sup> the use of Cu in such reactions has been much less examined.<sup>14</sup> (3)Compounds carrying CF<sub>3</sub> at their allylic positions are versatile

Scheme 1. Trifluoromethylation at Allylic Positions



precursors for the synthesis of other types of CF<sub>3</sub>-containing molecules,<sup>15</sup> but only a few methods to prepare such intermediates have been developed. Matsubara et al.<sup>16</sup> once described Pdcatalyzed coupling of allyl and alkenylstannanes with perfluoroalkyl iodides, whereas Chen and co-workers<sup>17a-c</sup> and Kim and Shreeve<sup>17d</sup> reported Cu-mediated nucleophilic trifluoromethylation of allyl halides. In comparison with the previous methods, our new reaction starts from simpler substrates and shows better functional group tolerance. The new reaction also exhibits a good tolerance to moisture and can be conducted under mild conditions.

Our study began with an inadvertent discovery of the reaction between compound 1a and Umemoto's reagent 2a. In a very recent work,<sup>11b</sup> we showed that CuOAc can catalyze the trifluoromethylation of aryl, heteroaryl, and vinyl boronic acids in the presence of 2,4,6-trimethylpyridine (L1). Thus, we were very surprised to find that a simple olefin such as 1a can also react with **2a** (1.2 equiv) when treated with CuOAc and L1 (Table 1, entry 1). The major product turned out to be compound **3a**, although the yield was only modest. To improve the yield, we examined different Cu(I) salts (entries 2-4) until we found that (thiophene-2-carbonyloxy)copper (CuTc) increased the yield to 84%. In this case, we also isolated the byproducts of the reaction. Compounds 4a and 5a were identified (3a:4a:5a > 20:1:2), but it was surprising that compound 6a was never observed. Thus, this trifluoromethylation reaction is regiospecific to the terminal carbon atom of the substrate.

To optimize the reaction, we changed L1 to other bases but observed only poorer performance (entries 5-9). We also



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Ta	ble	1.	Opti	mization	of th	e R	eaction	Conditions	и
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1a ( 2a X = 0 2b X = 1	1 equiv) $\downarrow^+$ $\bigcirc$ $X^{\Theta}$ CF <sub>3</sub> $X^{\Theta}$ DTf (1.2 equilibrium BF <sub>4</sub> (1.2 equilibrium 1.2	s Cu(l) (20 ) <u>additi</u> DMAc, 4 liv)	F mol%) <u>ve</u> ⊮0°C F <sub>3</sub>	3C 3a + 9C 4a	∽ots + <sup>F</sup>	5a CF3 + 6a (no	OTs OTs t observed)
	L <sub>'Bu</sub>	L2	L3		F <sub>3</sub> C N L5	CF <sub>3 MeO</sub>	N OMe L6
entry	CuX	(20 mol	%)	additive	(equiv)	GC yield	l of <b>3a</b> (%)
1	C 01			T 1 (2		26	

1	CuOAc	L1 (2.0)	36
2	CuI	L1 (2.0)	trace
3	$[Cu(OTf)]_2 \cdot C_6H_6$	L1 (2.0)	22
4	CuTc	L1 (2.0)	84 $(76)^b$
5	CuTc	L2 (2.0)	29
6	CuTc	L3 (2.0)	8
7	CuTc	L4 (2.0)	46
8	CuTc	L5 (2.0)	trace
9	CuTc	L6 (2.0)	5
10 <sup>c</sup>	CuTc	L1 (2.0)	68
$11^d$	CuTc	L1 (2.0)	32
$12^e$	CuTc	L1 (2.0)	86
13 <sup>f</sup>	CuTc	L1 (2.0)	78
$14^g$	CuTc	L1 (2.0)	84
15	-	L1 (2.0)	0
$16^h$	CuTc	L1 (2.0)	trace
17	$Pd(OAc)_2^i$	L1 (2.0)	0
18	CuTc <sup>i</sup>	L1 (2.0)	10
19	$CuTc^{i} + Pd(OAc)_{2}^{i}$	L1 (2.0)	10

<sup>*a*</sup> CuTc = (thiophene-2-carbonyloxy)copper, DMAc = *N*,*N*-dimethylacetamide. <sup>*b*</sup> The isolated yield is shown in parentheses; **3a:4a:5a** > 20:1:2. <sup>*c*</sup> The reaction was conducted at 60 °C. <sup>*d*</sup> The reaction was conducted at 25 °C. <sup>*e*</sup> **2a** was increased to 1.6 equiv. <sup>*f*</sup> 1.2 equiv of **2b** was used. <sup>*g*</sup> 2 equiv of H<sub>2</sub>O was added. <sup>*h*</sup> The reaction was conducted under an air atmosphere. <sup>*i*</sup> 5 mol %.

optimized the solvent and found N,N-dimethylacetamide (DMAc) to be optimal (see the Supporting Information). Furthermore, the best reaction temperature was 40 °C, as the yield decreased at both higher and lower temperatures (entries 10 and 11). Use of more 2a (1.6 equiv) improved the yield only slightly (entry 12), whereas the use of a different trifluoromethylating reagent, 2b, led to a similar yield (entry 13).<sup>18</sup> It is important to note that the reaction is not sensitive to moisture, as addition of 2 equiv of water did not decrease the yield (entry 14). Nonetheless, the Cu catalyst is necessary in the reaction (entry 15), and the reaction must be conducted under an inert atmosphere (entry 16). Finally, it was found that Pd(OAc)<sub>2</sub> cannot trigger this trifluoromethylation reaction (entry 17). We also tested the reactions with 5 mol % CuTc alone and with 5 mol % CuTc and 5 mol % Pd(OAc)<sub>2</sub> together (entries 18 and 19). The yields under both conditions were 10%, ruling out the possible involvement of Pd contamination in the catalysis.

With an optimized set of reaction conditions, we examined the scope of the trifluoromethylation process (Table 2) and found that a variety of terminal alkenes can be transformed into the Table 2. Scope of Cu-Catalyzed Trifluoromethylation<sup>a</sup>



<sup>*a*</sup> The reactions were conducted under the optimized conditions on a 0.2 mmol scale. Isolated yields are reported. The **3:4:5** ratios were determined by <sup>19</sup>F NMR analysis and are shown in the parentheses.

desired products in modest to good yields (up to 78%). Many synthetically important functional groups, including sulfonate, ester, amine, ketal, nitro, ether, amide, ketone, hydroxyl, and even epoxide, are well-tolerated in the reaction. Moreover, arene rings carrying iodo, bromo, and chloro substituents are compatible with the reaction, enabling additional modifications at the halogenated positions. In most of the reactions, we observed that compound 3 (i.e., 3a-z) constitutes the major product, whereas compounds 4 and 5 are produced as byproducts. An exceptional substrate is **1aa**, which generates similar quantities of **3aa** (32%) and 4aa (38%). Finally, we found that the reaction is sensitive to the steric hindrance of the olefin substrate. Terminal alkenes without any substituent at the 2-position are viable substrates, whereas 2-substituted terminal alkenes or internal (including cyclic) alkenes cannot be converted using the present protocol even when the reaction temperature is increased to 80 °C. We also attempted to optimize the reactions with internal alkenes by increasing the amounts of the catalyst and 2a but still could not obtain any desired products.

Further optimization of the catalyst/ligand systems may expand the substrate scope to 2-substituted terminal alkenes and internal alkenes, but we decided to leave this challenge for our ensuing research. Here we want to comment on the synthetic utility of this trifluoromethylation reaction. As shown in Scheme 2, the products in Table 1 can readily be converted to trifluoromethylated expoxides,<sup>19</sup> 1,2-diols,<sup>20</sup> 2-amino alcohols,<sup>21</sup> and cyclopropanes<sup>22</sup> through well-established methods. These functionalized trifluoromethylated compounds are otherwise difficult to make using previous methods, and the availability of these  $CF_3$ -containing compounds may facilitate studies in many areas.

In regard to the reaction mechanism, we first excluded the involvement of an allylic radical intermediate. This mechanism was proposed for Cu-catalyzed allylic oxidation or alkylation,<sup>14</sup>





Scheme 3. Reactions in CD<sub>3</sub>OD



but it cannot explain why **6a** was never observed in the reaction. The formation of 5a-z is also difficult to explain using an allylic radical mechanism. Furthermore, the radical allylic H-abstraction mechanism cannot explain why the reaction does not favor internal alkenes.

We next tested the Cu–allyl mechanism (Scheme 3). First, **1a** was treated with CuTc and **L1** in the absence of **2a**. Through <sup>1</sup>H NMR analysis of the recovered materials, we found no incorporation of deuterium at position *i* of **1a**. We did not observe the isomerization of **1a** to **11** either. We subsequently performed trifluoromethylation in CD<sub>3</sub>OD. We were surprised to find that although **3a** was produced, the major product became **4a**. Nonetheless, we did not observe any incorporation of deuterium at positions *iii* or *iv* in the products or at position *i* of the recovered reactant **1a**. Finally, a trace amount of **5a** was also detected. These results argue against a Cu–allyl mechanism.

Finally, we considered another mechanism<sup>23</sup> that was recently proposed for Cu-catalyzed C–H functionalization<sup>24</sup> in which the Cu–C bond is generated via a Heck-like four-membered-ring transition state. As shown in Figure 1,<sup>25</sup> in the proposed catalytic cycle, the reaction starts with complex IN0, which reacts with 2a to produce the Cu(III) complex IN1. The olefin substrate replaces OTf<sup>-</sup> in IN1 to generate IN2 and IN3. From IN3, the critical Heck-like four-membered-ring transition state (TS1a) is identified. Through TS1a the CF<sub>3</sub> group is transferred to the terminal carbon atom, whereas the formation of its isomer requires TS1a-iso, which is much less stable. This theoretical prediction explains why 6a is not observed and also indicates that the functionalization of internal alkenes is more difficult than for terminal alkenes.

The immediate product of **TS1a** is **IN4**. After OTf<sup>-</sup> coordinates to Cu, an elimination reaction takes place at **IN5**. Our calculations indicate that the generation of **3a** is more favorable than that of **4a**. This prediction is consistent with the regioselectivity observed in DMAc.<sup>25</sup> It is also expected that **IN5** may be directly protonated at the Cu–C bond, generating compound



Reaction coordinate (B3P86/CPCM, basis set = SDD for Cu and 6-311+G(2d,p) for ther other atoms)

Figure 1. Proposed mechanism for Cu-catalyzed trifluoromethylation and corresponding theoretical calculations.

**5a**. It is noteworthy that the energy barrier from **IN5** to **TS2** is only +5.6 kcal/mol, indicating a very fast elimination. This may explain why only a trace amount of **5a** is produced. In the catalytic cycle, the rate-limiting step corresponds to the Heck-like four-membered-ring transition state **TS1a**. The overall barrier is +27.2 kcal/mol, which is a reasonable value as judged by the reaction temperature (40 °C). Thus the Heck-like mechanism is consistent with most of the observations in our experiments.<sup>26</sup> Importantly, this Heck-like mechanism distinguishes the present reaction from the previous Cu-catalyzed allylic C–H activation/ functionalization reactions.<sup>14</sup>

In summary, we have reported an unprecedented type of Cucatalyzed trifluoromethylation reaction involving allylic C–H bond activation. This reaction provides a rare instance of catalytic trifluoromethylation through  $C(sp^3)$ –H activation. It also presents a mechanistically uncommon example of Cu-catalyzed allylic C–H activation/functionalization. Both experimental tests and theoretical analysis indicate that the reaction may proceed through a Heck-like four-membered-ring transition state. The reaction can be conducted under mild conditions without the need for anhydrous solvents and shows good functional group tolerance. The presence of an olefin moiety in the product also promises the subsequent conversion to more functionalized trifluoromethylated compounds.

#### ASSOCIATED CONTENT

**Supporting Information.** Experimental details and compound characterizations. This material is available free of charge via the Internet at http://pubs.acs.org.

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#### REFERENCES

(1) (a) Schlosser, M. Angew. Chem., Int. Ed. 2006, 45, 5432.
(b) Muller, K.; Faeh, C.; Diederich, F. Science 2007, 317, 1881.

(2) (a) Shimizu, M.; Hiyama, T. *Angew. Chem., Int. Ed.* 2005, 44, 214.
(b) Koller, R.; Stanek, K.; Stolz, D.; Aardoom, R.; Niedermann, K.; Togni, A. *Angew. Chem., Int. Ed.* 2009, 48, 4332.

(3) Gawronski, J.; Wascinska, N.; Gajewy, J. Chem. Rev. 2008, 108, 5227.

(4) (a) Umemoto, T.; Ishihara, S. *Tetrahedron Lett.* **1990**, *31*, 3579. (b) Umemoto, T.; Ishihara, S. *J. Am. Chem. Soc.* **1993**, *115*, 2156. (c) Umemoto, T.; Adachi, K.; Ishihara, S. *J. Org. Chem.* **2007**, *72*, 6905. (d) Kieltsch, I.; Eisenberger, P.; Togni, A. Angew. Chem., Int. Ed. **2007**, *46*, 754.

(5) (a) Furuya, T.; Kamlet, A. S.; Ritter, T. *Nature* 2011, 473, 470.
(b) Tomashenko, O. A.; Grushin, V. V. *Chem. Rev.* 2011, 111, 4475.

(6) (a) Ball, N. D.; Kampf, J. W.; Sanford, M. S. J. Am. Chem. Soc.
2010, 132, 2878. (b) Ye, Y.; Ball, N. D.; Kampf, J. W.; Sanford, M. S. J. Am. Chem. Soc. 2010, 132, 14682. (c) Ball, N. D.; Gary, J. B.; Ye, Y.; Sanford, M. S. J. Am. Chem. Soc. 2011, 133, 7577.

(7) Wang, X.; Truesdale, L.; Yu, J.-Q. J. Am. Chem. Soc. 2010, 132, 3648.

(8) Cho, E. J.; Senecal, T. D.; Kinzel, T.; Zhang, Y.; Watson, D. A.; Buchwald, S. L. *Science* **2010**, 328, 1679.

(9) (a) Grushin, V. V.; Marshall, W. J. J. Am. Chem. Soc. 2006, 128, 4632.
(b) Grushin, V. V.; Marshall, W. J. J. Am. Chem. Soc. 2006, 128, 12644. (c) Mu, X.; Chen, S.-J.; Zhen, X.-L.; Liu, G.-S. Chem.—Eur. J. 2011, 17, 6039.

(10) (a) Chu, L.-L.; Qing, F.-L. Org. Lett. 2010, 12, 5060. (b) Senecal, T. D.; Parsons, A. T.; Buchwald, S. L. J. Org. Chem. 2011, 76, 1174.
(c) Zhang, C.-P.; Wang, Z.-L.; Chen, Q.-Y.; Zhang, C.-T.; Gu, Y.-C.; Xiao, J.-C. Angew. Chem., Int. Ed. 2011, 50, 1896. (d) Morimoto, H.; Tsubogo, T.; Litvinas, N. D.; Hartwig, J. F. Angew. Chem., Int. Ed. 2011, 50, 3793. (e) Tomashenko, O. A.; Escudero-Adan, E. C.; Belmonte, M. M.; Grushin, V. V. Angew. Chem., Int. Ed. 2011, 50, 7655. For earlier studies of Cu-mediated trifluoromethylation, see: (f) Kobayashi, Y.; Kumadaki, I. Tetrahedron Lett. 1969, 10, 4095. (g) Konderatenko, N. V.; Vechirko, E. P.; Yagupolskii, L. M. Synthesis 1980, 932. (h) Wiemers, D. M.; Burton, D. J. J. Am. Chem. Soc. 1986, 108, 832. (i) Cottet, F.; Schlosser, M. Eur. J. Org. Chem. 2002, 327. (j) Dubinina, G. G.; Furutachi, H.; Vicic, D. A. J. Am. Chem. Soc. 2008, 130, 8600. (k) Dubinina, G. G.; Ogikubo, J.; Vicic, D. A. Organometallics 2008, 27, 6233.

(11) (a) Oishi, M.; Kondo, H.; Amii, H. Chem. Commun. 2009, 1909.
(b) Xu, J.; Luo, D.-F.; Xiao, B.; Liu, Z.-J.; Gong, T.-J.; Fu, Y.; Liu, L. Chem.
Commun. 2011, 47, 4300. (c) Liu, T.; Shen, Q.-L. Org. Lett. 2011, 13, 2342.
(12) Chu, L.-L.; Qing, F.-L. J. Am. Chem. Soc. 2010, 132, 7262.

(12) Cha, E.-E., Olig, F.-E. J. Am. Chem. Soc. 2010, 132, 7202.
(13) (a) Chen, M. S.; White, M. C. J. Am. Chem. Soc. 2004, 126, 1346.

(b) Chen, M. S.; Prabagaran, N.; Labenz, N. A.; White, M. C. J. Am. Chen.
(b) Chen, M. S.; Prabagaran, N.; Labenz, N. A.; White, M. C. J. Am. Chen.
Soc. 2005, 127, 6970. (c) Fraunhoffer, K. J.; White, M. C. J. Am. Chem. Soc.
2007, 129, 7274. (d) Reed, S. A.; White, M. C. J. Am. Chem. Soc.
2009, 131, 11701. (f) Vermeulen, N. A.; Delcamp, J. H.; White, M. C. J. Am.
Chem. Soc. 2010, 132, 11323. (g) Campbell, A. N.; White, P. B.; Guzei, I. A.;
Stahl, S. S. J. Am. Chem. Soc. 2010, 132, 15116. (h) Yin, G.-Y.; Wu, Y.-C.; Liu,
G.-S. J. Am. Chem. Soc. 2010, 132, 11978.

(14) Previous Cu-catalyzed allylic C-H functionalization mostly proceeds through a radical-type mechanism involving allylic H abstraction. See: (a) Andrus, M. B.; Lashley, J. C. *Tetrahedron* 2002, *58*, 845.
(b) Clark, J. S.; Roche, C. *Chem. Commun.* 2005, 5175. (c) Li, Z.-P.; Li, C.-J. *J. Am. Chem. Soc.* 2006, *128*, 56.

(15) Isanbor, C.; O'Hagan, D. J. Fluorine Chem. 2006, 127, 303.

(16) Matsubara, S.; Mitani, M.; Utimoto, K. *Tetrahedron Lett.* **1987**, 28, 5857.

(17) (a) Su, D.-B.; Duan, J.-X.; Chen, Q.-Y. Tetrahedron Lett. 1991,
32, 7689. (b) Chen, Q.-Y.; Duan, J.-X. J. Chem. Soc., Chem. Commun.
1993, 1389. (c) Duan, J.-X.; Su, D.-B.; Chen, Q.-Y. J. Fluorine Chem. 1993,
61, 279. (d) Kim, J.; Shreeve, J. M. Org. Biomol. Chem. 2004, 2, 2728.

(18) We tested only Umemoto's reagents **2a** and **2b** because other  $CF_3^+$  reagents were either not commercially available or too expensive and less stable (such as Tongi's reagent).

(19) Mitchell, J. M.; Finney, N. S. J. Am. Chem. Soc. 2001, 123, 862.

(20) Kolb, H. C.; VanNieuwenhze, M. S.; Sharpless, K. B. *Chem. Rev.* **1994**, *94*, 2483.

(21) Rudolph, J.; Sennhenn, P. C.; Vlaar, C. P.; Sharpless, K. B. Angew. Chem., Int. Ed. Engl. **1996**, 35, 2810.

(22) Guastavino, J. F.; Rossi, R. A. Organometallics 2009, 28, 2646.

(23) For related studies, see: (a) Phipps, R. J.; Gaunt, M. J. Science 2009, 323, 1593. (b) Duong, H. A.; Gilligan, R. E.; Cooke, M. L.; Phipps, R. J.; Gaunt, M. J. Angew. Chem., Int. Ed. 2011, 50, 463.

(24) Chen, B.; Hou, X.-L.; Li, Y.-X.; Wu, Y.-D. J. Am. Chem. Soc. 2011, 133, 7668.

(25) Similar computational methods have been used to study related Cu-catalyzed reactions. For recent examples, see: (a) Zhang, S.-L.; Liu, L.; Fu, Y.; Guo, Q.-X. Organometallics **2007**, *26*, 4546. (b) Dang, L.; Lin, Z.; Marder, T. B. Organometallics **2008**, *27*, 4443. (c) Ozen, C.; Tuzun, N. S. Organometallics **2008**, *27*, 4600. (d) Wang, M.; Lin, Z. Organometallics **2010**, *29*, 3077. (e) Yu, H.-Z.; Jiang, Y.-Y.; Fu, Y.; Liu, L. J. Am. Chem. Soc. **2010**, *132*, 18078. (f) Zhang, S.; Ding, Y. Organometallics **2011**, *30*, 633.

(26) Coordination of solvent molecules to the Cu center in the intermediates and transition states remains challenging to describe by computational methods. Therefore, more detailed theoretical analysis is needed to accurately explain the experimental regioselectivity (in particular, the strange regioselectivity observed in  $CD_3OD$ ).