JACS
JOURNAL OF THE AMERICAN CHEMICAL SOCIETY

COMMUNICATION

pubs.acs.org/JACS

Copper-Catalyzed Trifluoromethylation of Terminal Alkenes through Allylic C−H Bond Activation

Jun Xu,[†,‡] Yao Fu,[*,†] Dong-Fen Luo,[†] Yuan-Ye Jiang,[†] Bin Xiao,[‡] Zhao-Jing Liu,[‡] Tian-Jun Gong,[†] and Lei Liu[*,†,‡]

[†]Department of Chemistry, Joint Laboratory of Green Synthetic Chemistry, University of Science and Technology of China, Hefei 230026, China
[‡]Department of Chemistry, Tsinghua University, Beijing 100084, China

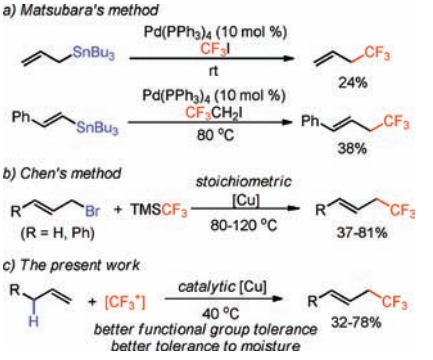
Supporting Information

ABSTRACT: An unprecedented type of reaction for Cu-catalyzed 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 many biologically active compounds because this substituent can often enhance their chemical and metabolic stability, lipophilicity, and binding selectivity.[1] Accordingly, it has been of great synthetic interest to develop efficient methods for incorporation of CF_3 into diverse organic structures.[2] 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 $TMSCF_3$ to carbonyl compounds[3] and the α-trifluoromethylation of ketones using Togni and Umemoto's reagents.[4] 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.[5] For instance, Pd-catalyzed methods for trifluoromethylation of C(sp^2)−H and C(sp^2)−halide bonds have been developed,[6−9] and Cu-mediated[10] or Cu-catalyzed[11] trifluoromethylation of aryl/vinyl halides and boronic acids and of terminal alkynes[12] 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_3 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,[13] the use of Cu in such reactions has been much less examined.[14] (3) Compounds carrying CF_3 at their allylic positions are versatile precursors for the synthesis of other types of CF_3-containing molecules,[15] but only a few methods to prepare such intermediates have been developed. Matsubara et al.[16] once described Pd-catalyzed coupling of allyl and alkenylstannanes with perfluoroalkyl iodides, whereas Chen and co-workers[17a−c] and Kim and Shreeve[17d] 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.

Scheme 1. Trifluoromethylation at Allylic Positions



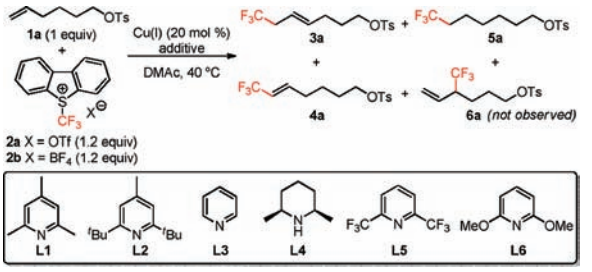
Our study began with an inadvertent discovery of the reaction between compound **1a** and Umemoto's reagent **2a**. In a very recent work,[11b] we showed that CuOAc can catalyze the trifluoromethylation of aryl, heteroaryl, and vinyl boronic acids in the presence of 2,4,6-trimethylpyridine (**L1**). 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

Received: July 8, 2011
Published: September 13, 2011

 © 2011 American Chemical Society

Table 1. Optimization of the Reaction Conditions[a]



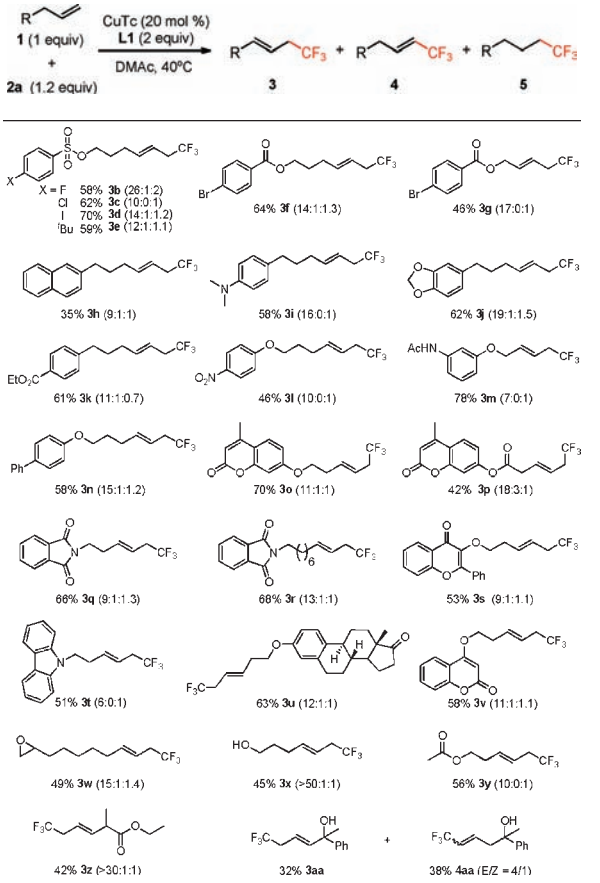
entry	CuX (20 mol %)	additive (equiv)	GC yield of **3a** (%)
1	CuOAc	**L1** (2.0)	36
2	CuI	**L1** (2.0)	trace
3	$[Cu(OTf)]_2 \cdot C_6H_6$	**L1** (2.0)	22
4	**CuTc**	**L1** (**2.0**)	**84** (**76**)[b]
5	CuTc	**L2** (2.0)	29
6	CuTc	**L3** (2.0)	8
7	CuTc	**L4** (2.0)	46
8	CuTc	**L5** (2.0)	trace
9	CuTc	**L6** (2.0)	5
10[c]	CuTc	**L1** (2.0)	68
11[d]	CuTc	**L1** (2.0)	32
12[e]	CuTc	**L1** (2.0)	86
13[f]	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[i]	**L1** (2.0)	10
19	CuTc[i] + $Pd(OAc)_2$[i]	**L1** (2.0)	10

[a] CuTc = (thiophene-2-carbonyloxy)copper, DMAc = *N*,*N*-dimethylacetamide. [b] The isolated yield is shown in parentheses; **3a**:**4a**:**5a** > 20:1:2. [c] The reaction was conducted at 60 °C. [d] The reaction was conducted at 25 °C. [e] **2a** was increased to 1.6 equiv. [f] 1.2 equiv of **2b** was used. [g] 2 equiv of H_2O was added. [h] The reaction was conducted under an air atmosphere. [i] 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).[18] 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 $Pd(OAc)_2$ 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 % $Pd(OAc)_2$ 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[a]



[a] 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 ^{19}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

dx.doi.org/10.1021/ja206330m |*J. Am. Chem. Soc.* 2011, 133, 15300–15303

expoxides,[19] 1,2-diols,[20] 2-amino alcohols,[21] and cyclopropanes[22] 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.

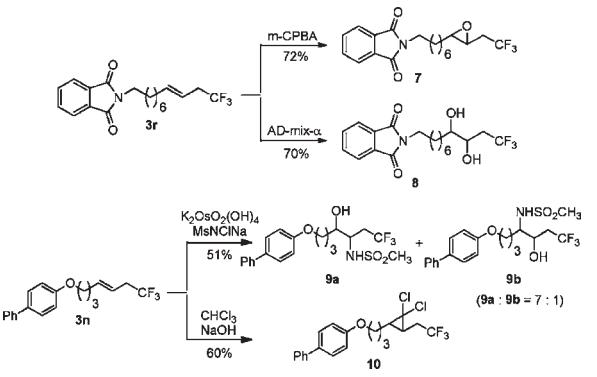
In regard to the reaction mechanism, we first excluded the involvement of an allylic radical intermediate. This mechanism was proposed for Cu-catalyzed allylic oxidation or alkylation,[14] but it cannot explain why **6a** was never observed in the reaction. The formation of **5a**−**z** is also difficult 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 ^{1}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_3OD. 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.

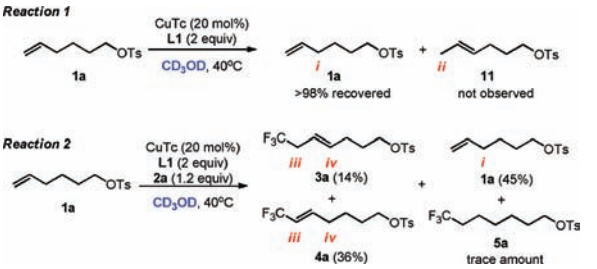
Finally, we considered another mechanism[23] that was recently proposed for Cu-catalyzed C−H functionalization[24] in which the Cu−C bond is generated via a Heck-like four-membered-ring transition state. As shown in Figure 1,[25] in the proposed catalytic cycle, the reaction starts with complex **IN0**, which reacts with **2a** to produce the Cu(III) complex **IN1**. The olefin substrate replaces OTf^- 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_3 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^- 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.[25] It is also expected that **IN5** may be directly protonated at the Cu−C bond, generating compound

Scheme 2. Further Conversion of the Products in Table 1



Scheme 3. Reactions in CD_3OD



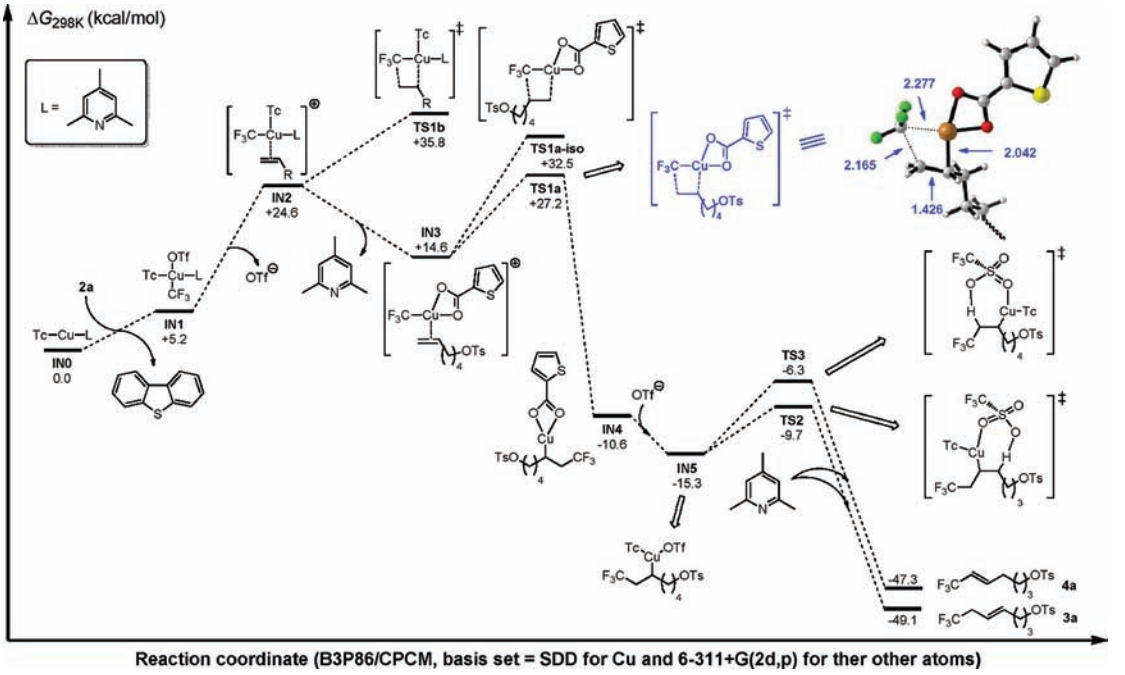


Figure 1. Proposed mechanism for Cu-catalyzed trifluoromethylation and corresponding theoretical calculations.

dx.doi.org/10.1021/ja206330m |*J. Am. Chem. Soc.* 2011, 133, 15300–15303

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.[26] Importantly, this Heck-like mechanism distinguishes the present reaction from the previous Cu-catalyzed allylic C−H activation/functionalization reactions.[14]

In summary, we have reported an unprecedented type of Cu-catalyzed 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.

■ AUTHOR INFORMATION

Corresponding Authors
fuyao@ustc.edu.cn; lliu@mail.tsinghua.edu.cn

■ ACKNOWLEDGMENT

This study was supported by NSFC (20832004 and 20972148), CAS, FRFCU (WK2060190003), and NCET (08-0519).

■ 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.

(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. Chem. 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.* **2008**, *130*, 3316. (e) Reed, S A.; Mazzotti, A. R.; 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).