Fluorine

Deutsche Ausgabe: DOI: 10.1002/ange.201604127
Internationale Ausgabe: DOI: 10.1002/anie.201604127

Perfluoroalkylation of Unactivated Alkenes with Acid Anhydrides as the Perfluoroalkyl Source

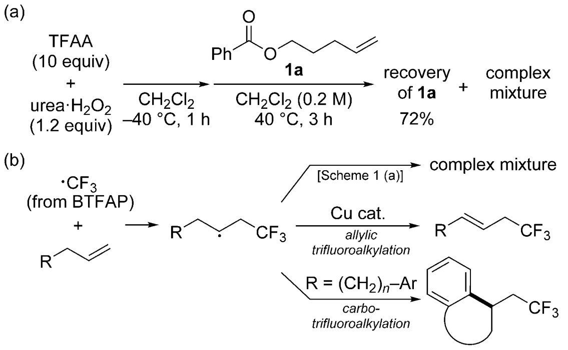
*Shintaro Kawamura and Mikiko Sodeoka**

Abstract: *An efficient perfluoroalkylation of unactivated alkenes with perfluoro acid anhydrides was developed. Copper salts play a crucial role as a catalyst to achieve allylic perfluoroalkylation with the in situ generated bis(perfluoroacyl) peroxides. Furthermore, carboperfluoroalkylation of alkene bearing an aromatic ring at an appropriate position on the carbon side chain was found to proceed under metal-free conditions to afford carbocycles or heterocycles bearing a perfluoroalkyl group. This method, which makes use of readily available perfluoroalkyl sources, offers a convenient and powerful tool for introducing a perfluoroalkyl group onto an sp*^{3} *carbon to construct synthetically useful skeletons.*

Perfluoroalkyl compounds, in particular trifluoromethyl compounds, are of considerable interest as drugs, agrochemicals, and functional materials because of the unique properties of the fluorine atom.[1,2] Therefore, there is great demand for convenient and practical synthetic methods.

Recently, alkene trifluoromethylation has been realized through the development of excellent electrophilic trifluoromethylating reagents such as the Togni reagent and the Umemoto reagent, which enable the direct construction of synthetically important organic frameworks bearing a trifluoromethyl group on an sp^3 carbon.[3–7] We have developed various difunctionalization-type trifluoromethylation reactions using the Togni reagent,[4e,5a,6a,7] and a diverse array of trifluoromethylated compounds can now be accessed. The high cost and multistep preparation of these sophisticated reagents, however, might hinder industrial application. Therefore, a convenient and practical alternative trifluoromethyl source is still needed.

Trifluoroacetic anhydride (TFAA) is inexpensively produced on a large scale and is commonly used as a reagent in organic syntheses; it could thus be a suitable alternative trifluoromethyl source.[8] Indeed, oxidized TFAAs such as bis(trifluoroacetyl) peroxide (BTFAP)[9–11] and a pyridine *N*-oxide/TFAA adduct[12] have been used as trifluoromethyl radical sources for the trifluoromethylation of aromatic compounds and limited types of alkenes.[11–14] However, trifluoromethylation of alkenes, in particular those that are unactivated, with TFAA as a trifluoromethyl source remains an important challenge. Indeed, our preliminary examination of the reaction of an unactivated alkene **1a** with BTFAP generated in situ from TFAA and urea·H_2O_2[10,15] was unsuccessful, and a large amount of starting material was recovered along with a complex mixture of trifluoromethylated products (Scheme 1a).[16]



Scheme 1. a) Preliminary result of trifluoromethylation of unactivated alkene **1a** with TFAA/urea·H_2O_2. b) Reactivity control of the alkyl radical.

The reaction at higher temperature accelerated the consumption of **1a**, but many products were formed (Table S1 and Figure S1 in the Supporting Information). The observed low product selectivity suggests that an acceleration of CF_3 radical generation as attempted in the aromatic trifluoromethylations[9–14] is not sufficient to achieve trifluoromethylation of unactivated alkenes.[9b] Instead, selective transformation of a highly reactive alkyl radical, resulting from the reaction of an alkene with a CF_3 radical, into the product would be the key to success for efficient trifluoromethylation of alkenes. We found two principles for controlling the reactivity of the radical intermediate: rapid oxidation to the cation and intramolecular trapping (Scheme 1b). Herein, we disclose a high-yielding copper-catalyzed allylic trifluoromethylation of alkenes with TFAA as the trifluoromethyl source, and its extension to allylic perfluoroalkylation. In addition, we report carboperfluoroalkylation of alkenes under metal-free conditions, which is useful for the construction of various carbocycles.

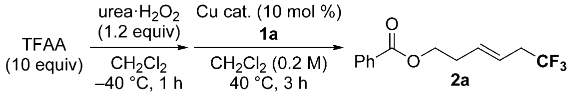
We speculated that a transition-metal catalyst could act as an electron acceptor and oxidize the alkyl radical to the cation through single electron transfer (SET). We thus examined the effects of transition-metal salts (Table 1 and Table S1).[17] First, $Cu(O_2CCF_3)_2$ was selected as the catalyst for this purpose. Fortunately, we found that it selectively gave allylic

---

[*] Dr. S. Kawamura, Prof. Dr. M. Sodeoka
Synthetic Organic Chemistry Laboratory, RIKEN
2-1 Hirosawa, Wako, Saitama 351-0198 (Japan)
and
RIKEN Center for Sustainable Resource Science
2-1 Hirosawa, Wako, Saitama 351-0198 (Japan)
E-mail: sodeoka@riken.jp

Supporting information for this article can be found under: http://dx.doi.org/10.1002/anie.201604127.

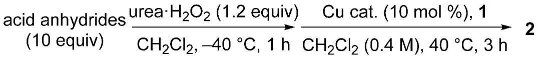
Table 1: Allylic trifluoromethylation of **1a** with TFAA.

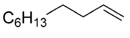
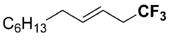
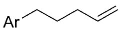
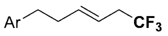
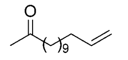
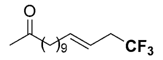
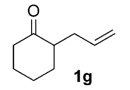
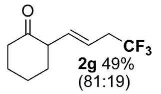
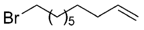
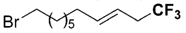
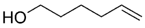
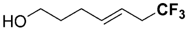
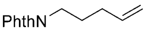
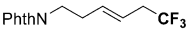
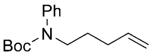
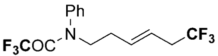
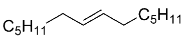
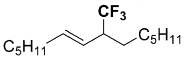
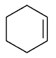
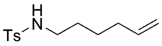
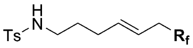


Entry	Catalyst	Yield of **2a** [%] (*E*/*Z*)[a]	Recov. of **1a** [%][a]
1	none	not detected	72
2	$Cu(O_2CCF_3)_2$	64 (76:24)	32
3	$[Cu(CH_3CN)_4]PF_6$	92 (78:22)	5
4[b]	$[Cu(CH_3CN)_4]PF_6$	95 (78:22)[c]	4

[a] Yields and *E*/*Z* ratios were determined by ^{1}H and ^{19}F NMR analysis. [b] The reaction was conducted in 0.4 M CH_2Cl_2. [c] Yield of isolated product.

Table 2: Substrate scope for the Cu-catalyzed perfluoroalkylation with perfluoro acid anhydride.



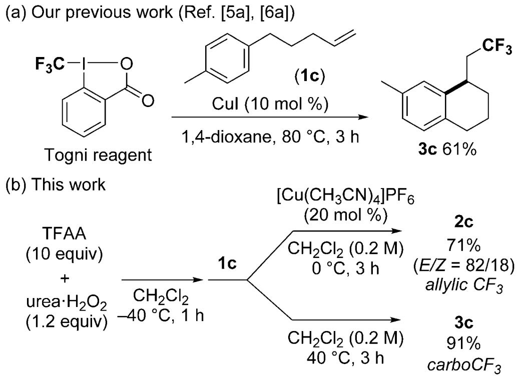
Entry	Starting material	Product / Isolated yield (*E*/*Z*)[a]
1	 **1b**	 **2b** 82% (80:20)
		
2[b,c]	**1c–e**	Ar = 4-MeC_6H_4 (**2c**) 71% (82:18)
3[b,c]		Ar = 4-FC_6H_4 (**2d**) 77% (79:21)
4[b,c,d]		Ar = 4-$MeOC_6H_4$ (**2e**) 73% (81:19)
5	 **1f**	 **2f** 83% (79:21)
6	 **1g**	 **2g** 49% (81:19)
7[c,e]	 **1h**	 **2h** 92% (80:20)
8[c]	 **1i**	 **2i** 80% (73:27)
9	 **1j**	 **2j** 93% (71:29)
10	 **1k**	 **2k'** 91% (76:24)
11	 **1l**	 **2l** 75% (96:4)
12	 **1m**	 **2m** 48% (NMR yield)
		
13	**1n**	$R_f = CF_3$ (**2n**) 95% (72:28)
14		$R_f = C_2F_5$ (**2n'**) 80% (72:28)
15		$R_f = C_3F_7$ (**2n''**) 72% (75:25)

[a] *E*/*Z* ratios were determined by ^{19}F NMR analysis. [b] The reaction was conducted in 0.2 M CH_2Cl_2 at 0 °C. [c] 20 mol% of the catalyst was used. [d] $Cu(O_2CCF_3)_2$ was used instead of $[Cu(CH_3CN)_4]PF_6$. [e] The crude product was hydrolyzed with Et_3N/SiO_2.

trifluoromethylation product **2a**,[4] which was not detected in the reaction without the catalyst (entry 1), as the major product in 64% yield (entry 2). After further screening of catalysts and optimization of the reaction conditions,[17] $[Cu(CH_3CN)_4]PF_6$ was found to give the best result (entries 3 and 4), affording **2a** in 95% yield when using 0.4 M CH_2Cl_2 (entry 4). Cu^I species probably accelerate the initial CF_3 radical generation through SET with BTFAP,[18] and the resulting Cu^{II} species would then play a role in controlling the product selectivity. It is noteworthy that this reaction could be conducted on a gram scale without problems.[17]

We next examined the substrate scope of the reaction under the optimal conditions (Table 2). When 1-decene **1b**, which is without any influential functional groups, was subjected to the reaction, the desired trifluoromethyl product **2b** was obtained in 82% yield (entry 1). The reaction of an alkene bearing aromatic rings proceeded selectively at the double bond, affording the desired products in 71–77% yield (entries 2–4). $Cu(O_2CCF_3)_2$ gave better results (73% yield) than $[Cu(CH_3CN)_4]PF_6$ (36% yield) in the reaction of the anisyl substrate **1e** (entry 4). Ketone (**1f** and **1g**) and bromo (**1h**) substituents were tolerated under these conditions (entries 5–7, 83%, 49%, and 92% yield, respectively). An alkene bearing a free hydroxy group (**1i**) afforded **2i** in 80% yield after hydrolysis of the trifluoroacetylated hydroxyl group with Et_3N-pretreated silica gel[19] (entry 8). The phthalimide substrate **1j** gave the product **2j** in excellent yield (entry 9, 93%). Allylic trifluoromethylation of **1k** also proceeded efficiently, and removal of the Boc group, probably by TFA generated during the reaction, and subsequent trifluoroacetylation afforded **2k′** in excellent yield (entry 7, 91%). Acyclic (**1l**) and cyclic (**1m**) internal alkenes were also amenable to the reaction (entries 11 and 12, 75% and 48% yield, respectively). Notably, tetradecene **1l** gave the product **2l** with a higher *E*/*Z* ratio than terminal alkenes ($E/Z = 96{:}4$).[20] In addition, this method was applicable to perfluoroalkylation with perfluoro acid anhydrides possessing a longer perfluoroalkyl group, as well as trifluoromethylation (entries 13–15). The desired pentafluoroethyl and heptafluoropropyl compounds were obtained from Ts-protected alkenyl amine **1n** in 80% and 72% yield, respectively.

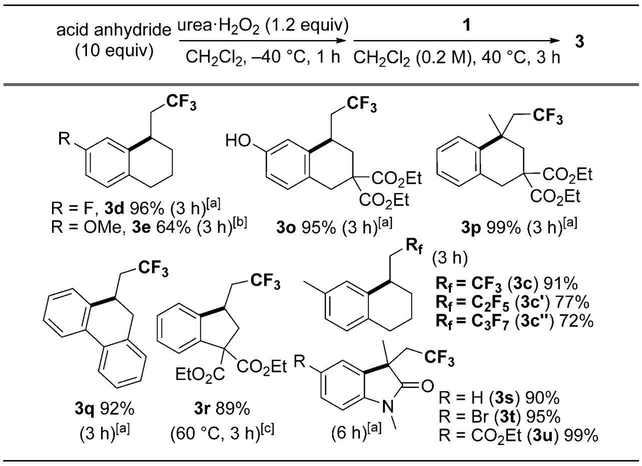
Based on our original work (Scheme 2a),[5a,6a] we next considered carbotrifluoromethylation using TFAA. In the reaction of **1c** shown in Table 2 (entry 2), the carbotrifluoromethylation product **3c** was formed as a byproduct (21% yield). After examination of the reaction conditions, the reaction of **1c** with TFAA/urea·H_2O_2 was found to proceed selectively under metal-free conditions, affording the carbocyclic product **3c** in 91% yield (Scheme 2b). The current



Scheme 2. Carbotrifluoromethylation throughintramolecular carbocycle formation.

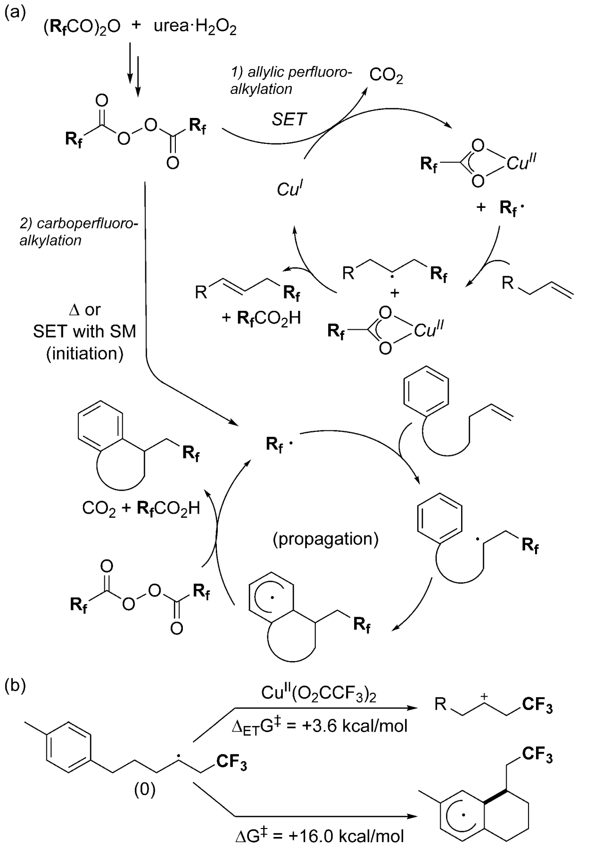
method gave the product in higher yield and under milder conditions than our previous reaction using the Togni reagent, and catalyst-controlled switching of the allylic and carbotrifluoromethylation reaction was achieved.

Table 3: Substrate scope for the carboperfluoroalkylation.



[a] The reaction was conducted in 0.4 M CH_2Cl_2. [b] The reaction was conducted in 0.02 M CH_2Cl_2. [c] 1,2-Dichloroethane was used instead of CH_2Cl_2.

We then examined the scope of the reaction (Table 3). We found that 4-fluorophenylpentene **1d** furnished the desired product **3d** in excellent yield (96 %). A substrate with an electron-rich methoxyphenyl group also gave the desired product **3e** in 64 % yield under dilute conditions. A phenol substituent was tolerated in the reaction (**3o**; 95 %), and the *gem*-disubstituted alkene **1p** afforded the desired product **3p** in 99 % yield. Allylated biphenyl **1q** provided the desired carbocyclic product **3q** in 92 % yield without formation of the allylic trifluoromethylation product. A five-membered ring was also successfully constructed in 1,2-dichloroethane at 60 °C (**3r**; 89 % yield). In addition, this method was applicable to reaction with perfluoro acid anhydrides possessing longer perfluoroalkyl groups, affording the desired products **3c′** and **3c″** in 77 % and 72 % yield, respectively. Furthermore, trifluoromethyloxindoles were synthesized from acrylamides under the current reaction conditions.[6] When *N*-methyl-*N*-phenylmethacrylamide **1s** was employed in the reaction, oxindole **3s** was obtained in 90 % yield. Bromo and ethyl ester substituents on the phenyl group were well tolerated and oxindoles **3t** and **3u** were obtained in 95 % and 99 % yields, respectively.



Scheme 3. a) Proposed mechanism of the present reactions. b) Comparison of the activation energies of SET and intramolecular carbocyclization.

Although details of the reaction mechanism are still unclear, a possible mechanism is shown in Scheme 3a. First, the diacyl peroxide is generated from the acid anhydride and urea·H_2O_2. In the case of allylic perfluoroalkylation (path 1), SET between the diacyl peroxide and the Cu^I catalyst triggers the generation of a perfluoroalkyl radical through decarboxylation.[18] The perfluoroalkyl radical reacts with the alkene, affording an alkyl radical intermediate.[21] At the final step of the catalytic cycle, the product is formed through oxidation of the radical by the Cu^{II} species, followed by deprotonation. In the absence of a copper catalyst, the reaction would proceed through a radical chain reaction (path 2). Initial formation of the perfluoroalkyl radical should occur through thermal decomposition of the peroxide and/or SET between the substrate and the peroxide.[9b] The perfluoroalkyl radical reacts with the double bond and the resulting alkyl radical undergoes intramolecular reaction with the aromatic ring. Then an aromatization through SET to the diacyl peroxide and subsequent deprotonation affords the desired product and regenerates the perfluoroalkyl radical. In addition, DFT studies suggested that SET from the alkyl radical to the Cu^{II} catalyst should be faster than cyclization in the reaction of **1c**, which is in agreement with the experimental result regarding catalyst-controlled switching of the product generated (Scheme 3b).[17,22]

In conclusion, we have developed a highly practical and efficient method for allylic and carboperfluoroalkylation of unactivated alkenes, with perfluoro acid anhydrides as an expedient perfluoroalkyl source. We believe that this convenient and straightforward method will facilitate the discovery of new drugs, agrochemicals, and functional materials bearing perfluoroalkyl groups, which are often incorporated into candidate molecules to improve characteristics such as lipophilicity, metabolic stability, and pharmacokinetics. Further investigation of the substrate scope and mechanistic studies are ongoing.

Acknowledgements

This work was supported by JSPS KAKENHI (No. 15K17860) and Project Funding from RIKEN. The computational study was conducted on the HOKUSAI-GW (RIKEN).

Keywords: alkenes · copper · homogeneous catalysis · perfluoroalkylation · peroxide

How to cite: *Angew. Chem. Int. Ed.* **2016**, *55*, 8740–8743
Angew. Chem. **2016**, *128*, 8882–8885

---

[1] Selected reviews: a) S. Purser, P. R. Moore, S. Swallowb, V. Gouverneur, *Chem. Soc. Rev.* **2008**, *37*, 320; b) W. K. Hagmann, *J. Med. Chem.* **2008**, *51*, 4359; c) D. O'Hagan, *J. Fluorine Chem.* **2010**, *131*, 1071.

[2] Selected books: a) I. Ojima, *Fluorine in Medicinal Chemistry and Chemical Biology*, Wiley-Blackwell, Chichester, **2009**; b) V. Gouverneur, K. Müller, *Fluorine in Pharmaceutical and Medicinal Chemistry: From Biophysical Aspects to Clinical Applications*, Imperial College Press, London, **2012**.

[3] Recent reviews on trifluoromethylation: a) H. Egami, M. Sodeoka, *Angew. Chem. Int. Ed.* **2014**, *53*, 8294; *Angew. Chem.* **2014**, *126*, 8434; b) J. Charpentier, N. Früh, A. Togni, *Chem. Rev.* **2015**, *115*, 650; c) E. Merino, C. Nevado, *Chem. Soc. Rev.* **2014**, *43*, 6598; d) L. Chu, F.-L. Qing, *Acc. Chem. Res.* **2014**, *47*, 1513; e) J. Xu, X. Liu, Y. Fu, *Tetrahedron Lett.* **2014**, *55*, 585; f) C. Zhang, *Adv. Synth. Catal.* **2014**, *356*, 2895; g) X. Liu, C. Xu, M. Wang, Q. Liu, *Chem. Rev.* **2015**, *115*, 683.

[4] Selected papers on allylic trifluoromethylation of alkenes: a) A. T. Parsons, S. L. Buchwald, *Angew. Chem. Int. Ed.* **2011**, *50*, 9120; *Angew. Chem.* **2011**, *123*, 9286; b) J. Xu, Y. Fu, D. Luo, Y. Jiang, B. Xiao, Z. Liu, T. Gong, L. Liu, *J. Am. Chem. Soc.* **2011**, *133*, 15300; c) X. Wang, Y. Ye, S. Zhang, J. Feng, Y. Xu, Y. Zhang, J. Wang, *J. Am. Chem. Soc.* **2011**, *133*, 16410; d) L. Chu, F.-Q. Qing, *Org. Lett.* **2012**, *14*, 2106; e) R. Shimizu, H. Egami, Y. Hamashima, M. Sodeoka, *Angew. Chem. Int. Ed.* **2012**, *51*, 4577; *Angew. Chem.* **2012**, *124*, 4655.

[5] Earlier reports on carbotrifluoromethylations: a) H. Egami, R. Shimizu, S. Kawamura, M. Sodeoka, *Angew. Chem. Int. Ed.* **2013**, *52*, 4000; *Angew. Chem.* **2013**, *125*, 4092; b) X. Dong, R. Sang, Q. Wang, X.-Y. Tang, M. Shi, *Chem. Eur. J.* **2013**, *19*, 16910; c) X. Liu, F. Xiong, X. Huang, L. Xu, P. Li, X. Wu, *Angew. Chem. Int. Ed.* **2013**, *52*, 6962; *Angew. Chem.* **2013**, *125*, 7100; d) Z.-M. Chen, W. Bai, S.-H. Wang, B.-M. Yang, Y.-Q. Tu, F.-M. Zhang, *Angew. Chem. Int. Ed.* **2013**, *52*, 9781; *Angew. Chem.* **2013**, *125*, 9963; e) N. O. Ilchenko, P. G. Janson, K. J. Szabó, *J. Org. Chem.* **2013**, *78*, 11087; f) P. Gao, X.-B. Yan, T. Tao, F. Yang, T. He, X.-R. Song, X.-Y. Liu, Y.-M. Liang, *Chem. Eur. J.* **2013**, *19*, 14420; g) Y.-T. He, L.-H. Li, Y.-F. Yang, Z.-Z. Zhou, H.-L. Hua, X.-Y. Liu, Y.-M. Liang, *Org. Lett.* **2014**, *16*, 270; h) F. Wang, D. Wang, X. Mu, P. Chen, G. Liu, *J. Am. Chem. Soc.* **2014**, *136*, 10202.

[6] Earlier reports on trifluoromethyl oxindole syntheses through carbotrifluoromethylation: a) H. Egami, R. Shimizu, M. Sodeoka, *J. Fluorine Chem.* **2013**, *152*, 51; b) W. Kong, M. Casimiro, N. Fuentes, E. Merino, C. Nevado, *Angew. Chem. Int. Ed.* **2013**, *52*, 13086; *Angew. Chem.* **2013**, *125*, 13324; c) P. Xu, J. Xie, Q. Xue, C. Pan, Y. Cheng, C. Zhu, *Chem. Eur. J.* **2013**, *19*, 14039; d) W. Kong, M. Casimiro, E. Merino, C. Nevado, *J. Am. Chem. Soc.* **2013**, *135*, 14480; e) J. Liu, S. Zhuang, Q. Gui, X. Chen, Z. Yang, Z. Tan, *Eur. J. Org. Chem.* **2014**, *2014*, 3196; f) L. Shi, X. Yang, Y. Wang, H. Yang, H. Fu, *Adv. Synth. Catal.* **2014**, *356*, 1021; g) L. Li, M. Deng, S.-C. Zheng, Y.-P. Xiong, B. Tan, X.-Y. Liu, *Org. Lett.* **2014**, *16*, 504; h) F. Yang, P. Klumphu, Y.-M. Liang, B. H. Lipshutz, *Chem. Commun.* **2014**, *50*, 936.

[7] a) R. Shimizu, H. Egami, T. Nagi, J. Chae, Y. Hamashima, M. Sodeoka, *Tetrahedron Lett.* **2010**, *51*, 5947; b) A. Miyazaki, R. Shimizu, H. Egami, M. Sodeoka, *Heterocycles* **2012**, *86*, 979; c) H. Egami, R. Shimizu, M. Sodeoka, *Tetrahedron Lett.* **2012**, *53*, 5503; d) H. Egami, S. Kawamura, A. Miyazaki, M. Sodeoka, *Angew. Chem. Int. Ed.* **2013**, *52*, 7841; *Angew. Chem.* **2013**, *125*, 7995; e) H. Egami, R. Shimizu, Y. Usui, M. Sodeoka, *Chem. Commun.* **2013**, *49*, 7346; f) H. Egami, R. Shimizu, Y. Usui, M. Sodeoka, *J. Fluorine Chem.* **2014**, *167*, 172; g) H. Egami, T. Ide, M. Fujita, T. Tojo, Y. Hamashima, M. Sodeoka, *Chem. Eur. J.* **2014**, *20*, 12061; h) S. Kawamura, H. Egami, M. Sodeoka, *J. Am. Chem. Soc.* **2015**, *137*, 4865; i) H. Egami, Y. Usui, S. Kawamura, S. Nagashima, M. Sodeoka, *Chem. Asian J.* **2015**, *10*, 2190.

[8] H. Sawada, *Chem. Rev.* **1996**, *96*, 1779.

[9] a) M. Yoshida, T. Yoshida, M. Kobayashi, N. Kamigata, *J. Chem. Soc. Perkin Trans. 1* **1989**, 909; b) H. Sawada, M. Nakayama, M. Yoshida, T. Yoshida, N. Kamigata, *J. Fluorine Chem.* **1990**, *46*, 423; See also, c) V. L. Salenko, L. S. Kobrina, G. G. Yakobsen, *Zh. Org. Khim.* **1981**, *17*, 1296; d) Y. Hayakawa, N. Terasawa, H. Sawada, *Polymer* **2001**, *42*, 4081.

[10] a) S. Zhong, A. Hafner, C. Hussal, M. Nieger, S. Bräse, *RSC Adv.* **2015**, *5*, 6255; See also b) C. W. Jones, W. R. Sanderson, J. P. Sankey, U.S. Patent 5,557,008 September 6, **1995**.

[11] Sawada, Kobayashi, and Yoshida reported oxytrifluoromethylation of styrenes through the introduction of a trifluoroacetoxy group with isolated BTFAP (30% preparation yield) in Freon 113, though only a few examples were given. H. Sawada, M. Kobayashi, M. Yoshida, U.S. 4,956,123, September 14, **1988**.

[12] Stephenson and co-workers reported a reaction using a combination of a photoredox catalyst and a pyridine-*N*-oxide/TFAA adduct; a few examples of the reaction of activated alkenes were described, although the yields were modest. J. W. Beatty, J. J. Douglas, K. P. Cole, C. R. J. Stephenson, *Nat. Commun.* **2015**, *6*, 7919.

[13] Socolov and co-workers indirectly evaluated the reactivity of the CF$_3$ radical generated through thermal decomposition of BTFAP with fluorinated ethylenes: S. I. Servo, M. V. Zhuravlev, V. P. Sass, S. V. Socolov, *Zh. Org. Khim.* **1981**, *17*, 53.

[14] Alkene perfluoroalkylation with fluorinated diacyl peroxides such as (C$_2$F$_5$COO)$_2$ and (C$_3$F$_7$COO)$_2$ is also rare, and there is a significant limitation in the substrate scope: a) M. Sansotera, C. Gambarotti, A. Famulari, A. Baggioli, R. Soave, F. Venturini, S. V. Meille, I. Wlassics, W. Navarrini, *Tetrahedron* **2014**, *70*, 5298; b) M. Yoshida, K. Moriya, H. Sawada, M. Kobayashi, *Chem. Lett.* **1985**, 755.

[15] Kita's procedure for preparation of BTFAP was applied to our reaction. T. Dohi, Y. Minamitsuji, A. Maruyama, S. Hirose, Y. Kita, *Org. Lett.* **2008**, *10*, 3559.

[16] ^{1}H and ^{19}F NMR analyses of the crude product indicated the formation of hydrotrifluoromethylation and vinylic trifluoromethylation products in 10% and 6% yields, respectively, together with unidentified products.

[17] For further details, see the Supporting Information.

[18] C.-X. Zhao, G.-F. Chen, Y.-L. Qu, X.-K. Jiang, *J. Fluorine Chem.* **1987**, *37*, 215.

[19] L. Ou, D. Bai, *Org. Prep. Proced. Int.* **1999**, *31*, 333.

[20] The observed stereoselectivity was considered to be governed by steric repulsion of the substituents in the transition state of the deprotonation from the cationic intermediate.

[21] A. Bravo, H.-R. Bjørsvik, F. Fontana, L. Liguori, A. Mele, F. Minisci, *J. Org. Chem.* **1997**, *62*, 7128.

[22] Reaction pathways involving alkyl copper intermediates (see Ref. [4c]) cannot be ruled out from the presented results.

Received: April 28, 2016