DOI: 10.1002/anie.201210250

Trifluoromethylation

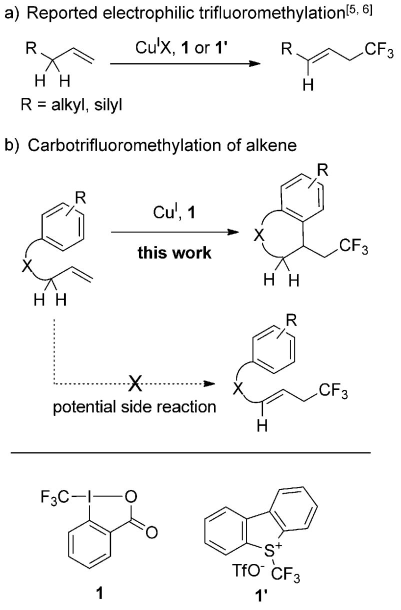
Alkene Trifluoromethylation Coupled with C–C Bond Formation: Construction of Trifluoromethylated Carbocycles and Heterocycles[**]

*Hiromichi Egami, Ryo Shimizu, Shintaro Kawamura, and Mikiko Sodeoka**

The trifluoromethyl group is of great interest in pharmaceutical chemistry, agrochemistry, and materials science because of its unique properties,[1] and great efforts have been made to develop reactions for its introduction into organic molecules.[2] Indeed, many methods for formation of not only C_{sp^2}–CF_3, but also C_{sp^3}–CF_3 bonds have been developed.[3,4] Nevertheless, new synthetic methods to form C–CF_3 bonds, especially C_{sp^3}–CF_3 bonds, in a wider range of molecular contexts are still needed.

Regarding trifluoromethylation of the C=C bond,[5] a notable development has been the deprotonative trifluoromethylation of simple alkenes, a method reported in 2011 (Scheme 1 a).[5a–c] In contrast, we recently reported[6] the trifluoromethylation of allylsilanes using the CuI/Togni's reagent (**1**)[7] system. Based on the resulting mechanistic insight, oxytrifluoromethylation of styrene derivatives was achieved under mild reaction conditions and direct synthesis of β-trifluoromethylstyrene derivatives from styrenes was demonstrated.[8] Szabó and co-workers also independently studied the oxytrifluoromethylation of multiple bonds with the CuI/**1** system,[9a] and Zhu and Buchwald developed an intramolecular reaction of simple alkenes[9b] in the wake of their deprotonative trifluoromethylation.[5a]

Following from our previous studies, we investigated difunctionalization-type trifluoromethylation of the C=C bond,[10] thus focusing on the use of carbon nucleophiles. In 2012, Liu and co-workers reported the palladium/ytterbium-catalyzed oxidative aryl trifluoromethylation of activated alkenes using a combination of $TMSCF_3/CsF/PhI(OAc)_2$.[11] Although Liu's method provided structures bearing a trifluoromethyl group, only oxindole synthesis from α,β-unsaturated amide derivatives was demonstrated. Other types of carbocycles and heterocycles, such as indane, tetralin, indoline, and tetrahydroquinoline, are also found in many bioactive compounds, and their trifluoromethylated derivatives may exhibit altered potency. It is well known that treatment of an alkene bearing allylic protons under trifluoromethylation conditions provides the deprotonative trifluoromethylation product (Scheme 1 a).[5,6] Difunctionalization-type trifluoromethylation of unactivated alkenes, especially those having allylic protons, is still challenging (Scheme 1 b). Based on our previous mechanistic insights,[6,8] we considered that the acceleration of the reaction by orbital interactions between the alkene and aryl group would favor the desired trifluoromethylation reaction coupled with intramolecular C–C bond formation. Herein we report the copper-catalyzed carbotrifluoromethylation of simple C=C bonds, using the Cu^I/**1** system, as well as a unique 1,6-oxytrifluoromethylation reaction.



Scheme 1. a) Reported electrophilic trifluoromethylation.[5,6] b) Trifluoromethylation coupled with construction of carbocycles and heterocycles.

To achieve carbotrifluoromethylation of a simple alkene bearing allylic protons, it is important to prevent competitive deprotonative trifluoromethylation of the alkene.[5,6] Compound **2a** was used as a test substrate for the screening of reaction conditions (Table 1). Use of $[(MeCN)_4Cu]PF_6$ in CH_2Cl_2 at room temperature selectively afforded the deprotonative trifluoromethylation product **4a** in low yield (entry 1). The carbotrifluoromethylation product **3a** was obtained in 18% yield in 1,2-dichloroethane (DCE) at 80 °C, but **4a** was again the major product (entry 2). Surpris-

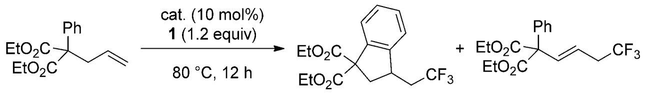
---

[*] Dr. H. Egami, R. Shimizu, S. Kawamura, Prof. Dr. M. Sodeoka
Synthetic Organic Chemistry Laboratory, RIKEN
2-1 Hirosawa, Wako, Saitama 351-0198 (Japan)
E-mail: sodeoka@riken.jp
Dr. H. Egami, S. Kawamura, Prof. Dr. M. Sodeoka
Sodeoka Live Cell Chemistry Project, ERATO
Japan Science and Technology Agency
2-1 Hirosawa, Wako, Saitama 351-0198 (Japan)
R. Shimizu, Prof. Dr. M. Sodeoka
Graduate School of Science and Engineering
Saitama University
255 Shimo-okubo, Sakura-ku, Saitama 338-8570 (Japan)

[**] This work was supported in part by a Grant-in-aid for Young Scientists (B) from the MEXT (No. 23750116) and by Project Funding for Basic Science from RIKEN.

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201210250.

Table 1: Screening of reaction conditions.[a]

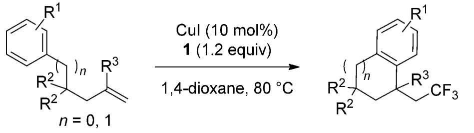


2a **3a** **4a**

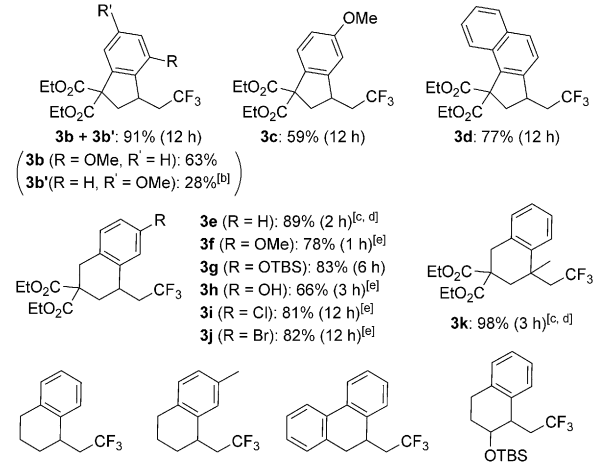
Entry	Cat.	Solvent	Yield [%][b]	
			3a	**4a**
1[c]	$[Cu(MeCN)_4]PF_6$	CH_2Cl_2	2	19
2	$[Cu(MeCN)_4]PF_6$	DCE	18	43
3	CuI	DCE	58	12
4	CuI	$CHCl_3$	57	22
5	CuI	EtOH	26	4
6	CuI	DMF	50	22
7	CuI	1,4-dioxane	64[e]	trace
8	CuI	1,4-dioxane[f]	78[e]	trace
9	CuOAc	1,4-dioxane	59	10
10	$Cu(OAc)_2$	1,4-dioxane	0	0

[a] The reactions were carried out with copper salt (10 mol%) and **1** (1.2 equiv) at 80 °C on a 0.2 mmol scale, unless otherwise mentioned. [b] Determined by ^{19}F NMR analysis of the reaction mixture using trifluorotoluene as an internal standard. [c] Run at 23 °C. [d] Not detected. [e] Yield of isolated product. [f] Degassed solvent was used. DMF = *N*,*N*-dimethylformamide.

Table 2: Trifluoromethylation of simple alkenes coupled with construction of carbocycles.[a]



n = 0, 1
2 **3**



3b + 3b': 91% (12 h)
(**3b** (R = OMe, R' = H): 63%
3b'(R = H, R' = OMe): 28%[b])

3c: 59% (12 h)

3d: 77% (12 h)

3e (R = H): 89% (2 h)[c, d]
3f (R = OMe): 78% (1 h)[e]
3g (R = OTBS): 83% (6 h)
3h (R = OH): 66% (3 h)[e]
3i (R = Cl): 81% (12 h)[e]
3j (R = Br): 82% (12 h)[e]

3k: 98% (3 h)[c, d]

3l: 76% (3 h)

3m: 61% (3 h)

3n: 95% (1 h)[e]

3o: 71% (12 h)[c, d, f]
(d.r. = 1:0.8)

[a] The reactions were carried out with CuI (10 mol%) and **1** (1.2 equiv) in degassed 1,4-dioxane at 80 °C, unless otherwise mentioned. [b] Yield determined by ^1H NMR analysis of a mixture with **2b**. [c] Run in CH_2Cl_2. [d] Run at 40 °C. [e] Run in DCE. [f] Yield of diastereomeric mixture.

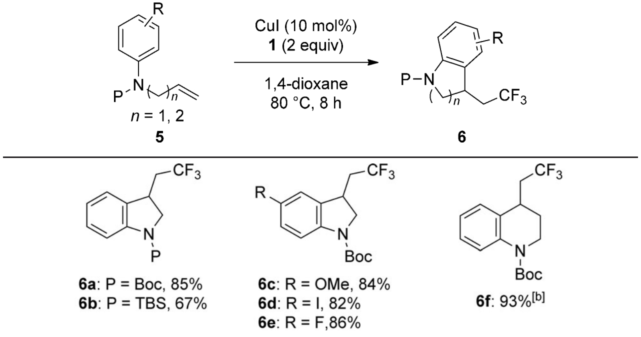
ingly, CuI provided **3a** in 58% yield, together with **4a** in 12% yield (entry 3). It was found that the solvent affected the product selectivity (entries 3–7). The reaction of **2a** in 1,4-dioxane afforded the desired product **3a** with high selectivity (entry 7). Dissolved oxygen in the solvent interfered with the desired reaction and **1** was partly decomposed when solvent, which was not degassed, was used. A higher yield was observed in degassed solvent (entry 8). Copper(II) species did not work for this reaction. For example, no reaction was observed with $Cu(OAc)_2$ (entry 10).

Having established optimized reaction conditions, we next examined the scope of this reaction (Table 2). Other five-membered-ring products (**3b–d**) were obtained in good yields. The reaction of **2b** bearing a methoxy group at the *m*-position proceeded smoothly to give the cyclized product in 91% yield. Cyclization proceeded predominantly at the position *ortho* to the methoxy group (regioisomers **3b** = 63%; **3b'** = 28%). The substrate bearing a naphthyl group, **2d**, which could potentially provide both five- and six-membered-ring products, gave only the five-membered-ring product **3d** in 77% yield. In contrast to this, it was found that formation of six-membered rings (**3e–j**) was much faster than that of five-membered rings, and no deprotonative trifluoromethylation product was observed, even in chlorinated solvents. The substrate **2e** afforded the corresponding product **3e** in 89% yield even at 40 °C in CH_2Cl_2. Although electronic effects at the phenyl ring affected the reaction rate, good to high yields of the carbotrifluoromethylation products were obtained. The TBS group remained intact under the reaction conditions used, and the nonprotected phenol derivative was successfully converted into the corresponding product **3h** in 66% yield.[12] Bromine and chlorine on the phenyl ring were tolerant of the reaction conditions (**3i**, **3j**). A methyl group on the terminal olefin (R^3 = Me) did not affect the desired reaction, and the reaction of compound **2k** proceeded at 40 °C without difficulty to provide the carbocyclic product **3k** having a quaternary carbon center, bearing a trifluoroethyl group, in 98% yield. To our delight, **2l** and **2m** bearing no quaternary carbon atom selectively afforded the desired corresponding carbocyclic products **3l** and **3m** in 76% and 61% yields, respectively. The reaction of the biaryl compound **2n** bearing methylene protons positioned between a phenyl group and a vinyl group also proceeded without difficulty. The corresponding carbocycle **3n** was obtained in 95% yield and no deprotonative trifluoromethylation product was observed. Reaction of the substrate having an oxygen substituent, **2o**, also proceeded smoothly at 40 °C in CH_2Cl_2 to give **3o** in good yield (diastereomeric mixture, d.r. = 1:0.8).

This reaction system was successfully applied to N-protected allylaniline and homoallylaniline derivatives, thus affording trifluoromethylated heterocycles (Table 3). The reaction of *N*-Boc-allylaniline **5a** gave **6a** in 85% yield. This reaction could be also applied to TBS-protected allylaniline, that is, **5b** afforded the corresponding heterocyclic product **6b** in good yield. Substituents on the phenyl ring had a negligible impact on these reactions, and high yields of the corresponding indoline derivatives **6c–e** were obtained.[13] Six-membered-ring formation was faster than that of five-membered-ring formation, as in the case of carbocycles, and **6f** was produced in 93% yield within 1 hour.

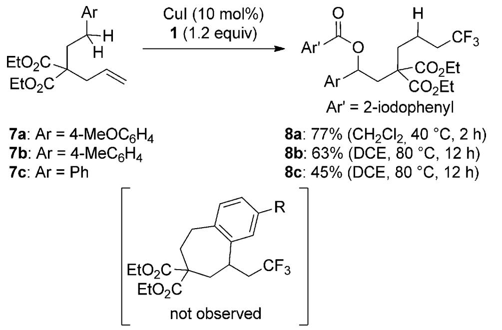
In anticipation of seven-membered ring forming carbotrifluoromethylation of alkenes, the substrate **7a** was exposed to the described reaction conditions. To our surprise, the 1,6-oxytrifluoromethylation product **8a** was obtained in 77%

Table 3: Carbotrifluoromethylation of N-protected allylanilines and homoallylaniline.[a]



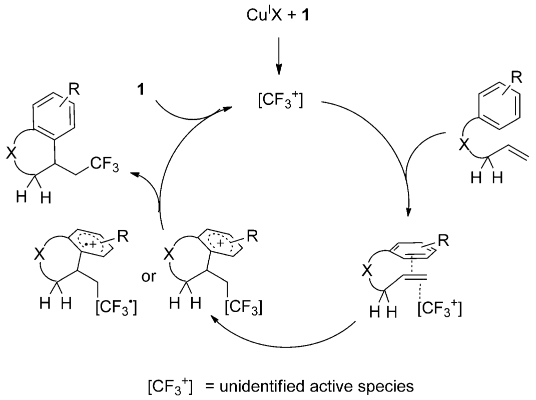
[a] The reactions were carried out with CuI (10 mol%) and **1** (2 equiv) in degassed 1,4-dioxane at 80 °C, unless otherwise mentioned. [b] Run for 1 h.

yield, and no carbocyclic product was observed (Scheme 2). Similar results were obtained in the reactions of **7b** and **7c**. In these reactions, deprotonative trifluoromethylation products were isolated in 7%, 8%, and 25% yield from **7a**, **7b**, and **7c**, respectively. We suppose that this reaction proceeds by a 1,5-hydride shift and trapping of an intermediate by 2-iodobenzoate generated from **1**.



Scheme 2. 1,6-Oxytrifluoromethylation of alkenes.

The proposed mechanism is illustrated in Scheme 3. Although the true active species is not clear, we speculate that an electrophilic active species would be generated by the reaction of copper iodide with **1**. The alkene moiety is first activated by an electrophilic active species, then electron transfer from the aryl ring through the C=C bond and C–C bond formation would occur. Based on the fact that the reaction of the six-membered ring was faster than that of the five-membered ring, we believe that acceleration by orbital interaction of aryl ring and alkene is crucial for this carbotrifluoromethylation.



Scheme 3. Proposed mechanism.

In summary, we have achieved copper-catalyzed trifluoromethylation of simple alkenes bearing allylic protons, coupled with C_{sp^3}–C_{Ar} bond formation. These reactions provide trifluoromethylated carbocycles and heterocycles in good to high yields. We propose that orbital interactions between the alkene and aryl ring promotes the desired reaction. In addition, our finding of 1,6-oxytrifluoromethylation through a 1,5-hydride shift raises the interesting possibility of trifluoromethylation-initiated remote functionalization. Further investigations of this reaction system and mechanistic studies are under way in our laboratory.

Experimental Section

General procedure for trifluoromethylation of simple alkenes coupled with construction of carbocycles: CuI (3.8 mg, 10 mol%) and Togni's reagent (**1**; 76 mg, 1.2 equiv) were weighed and added to a Schlenk flask, which was flame-dried under vacuum. The flask was evacuated and back filled with nitrogen. Degassed 1,4-dioxane (1 mL) and **2a** (55.3 mg, 0.2 mmol) were then added. The reaction mixture was stirred for 12 h at 80 °C and diluted with ethyl acetate (5 mL). The solution was washed with aqueous $NaHCO_3$ and brine. The organic layer was dried over $MgSO_4$. After filtration, the organic solvent was evaporated and the residue was subjected to column chromatography on silica gel (*n*-hexane/ethyl acetate 20:1) to give the trifluoromethylated product **3a** (53.9 mg, 78%) as a colorless oil.

Received: December 23, 2012

Keywords: alkene · copper · fluorine · heterocycles · homogeneous catalysis

---

[1] a) P. Kirsch, *Modern Fluoroorganic Chemistry: Synthesis Reactivity, Applications*, Wiley-VCH, Weinheim, **2004**; b) J.-P. Bégué, D. Bonnet-Delpon, *Bioorganic and Medicinal Chemistry of Fluorine*, Wiley-VCH, Hoboken, **2008**; c) I. Ojima, *Fluorine in Medicinal Chemistry and Chemical Biology*, Wiley-Blackwell, Chichester, **2009**; d) P. Jeschke, *ChemBioChem* **2004**, *5*, 570; e) M. Shimizu, T. Hiyama, *Angew. Chem.* **2005**, *117*, 218; *Angew. Chem. Int. Ed.* **2005**, *44*, 214; f) M. Schlosser, *Angew. Chem.* **2006**, *118*, 5558; *Angew. Chem. Int. Ed.* **2006**, *45*, 5432; g) C. Isanbor, D. O'Hangan, *J. Fluorine Chem.* **2006**, *127*, 303; h) K. Müller, C. Faeh, F. Diederich, *Science* **2007**, *317*, 1881; i) W. K. Hagmann, *J. Med. Chem.* **2008**, *51*, 4359.

[2] For recent reviews on trifluoromethylation reactions, see: a) Y. Zheng, J.-A. Ma, *Adv. Synth. Catal.* **2010**, *352*, 2745; b) S. Roy, B. T. Gregg, G. W. Gribble, V.-D. Le, S. Roy, *Tetrahedron* **2011**, *67*, 2161; c) O. A. Tomashenko, V. V. Grushin, *Chem. Rev.* **2011**, *111*, 4475; d) T. Furuya, A. S. Kamlet, T. Ritter, *Nature* **2011**, *473*, 470; e) H. Amii, *J. Synth. Org. Chem. Jpn.* **2011**, *69*, 752; f) X.-F. Wu, H. Neumann, M. Beller, *Chem. Asian J.* **2012**, *7*, 1744; g) A. Studer, *Angew. Chem.* **2012**, *124*, 9082; *Angew. Chem. Int. Ed.* **2012**, *51*, 8950; h) Y. Ye, M. S. Sanford, *Synlett* **2012**, 2005.

[3] For selected reports on catalytic $C_{sp^2}{-}CF_3$ bond-forming reactions, see: a) M. Oishi, H. Kondo, H. Amii, *Chem. Commun.* **2009**, 1909; b) X. Wang, L. Truesdale, J.-Q. Yu, *J. Am. Chem. Soc.* **2010**, *132*, 3648; c) E. J. Cho, T. D. Cenecal, T. Kinzel, Y. Zhang, D. A. Watson, S. L. Buchwald, *Science* **2010**, *328*, 1679; d) R. Shimizu, H. Egami, T. Nagi, J. Chae, Y. Hamashima, M. Sodeoka, *Tetrahedron Lett.* **2010**, *51*, 5947; e) M. S. Wiehn, E. V. Vinogradova, A. Togni, *J. Fluorine Chem.* **2010**, *131*, 951; f) T. Knauber, F. Arikan, G.-V. Röschenthaler, L. J. Gooßen, *Chem. Eur. J.* **2011**, *17*, 2689; g) J. Xu, D.-F. Luo, B. Xiao, Z.-J. Liu, T.-J. Gong, Y. Fu, L. Liu, *Chem. Commun.* **2011**, *47*, 4300; h) T. Liu, Q. Shen, *Org. Lett.* **2011**, *13*, 2342; i) X. Mu, S. Chen, X. Zhen, G. Liu, *Chem. Eur. J.* **2011**, *17*, 6039; j) D. A. Nagib, D. W. C. MacMillan, *Nature* **2011**, *480*, 224; k) Z. Weng, R. Lee, W. Jia, Y. Yuan, W. Wang, X. Feng, K.-W. Huang, *Organometallics* **2011**, *30*, 3229; l) A. T. Parsons, T. D. Senecal, S. L. Buchwald, *Angew. Chem.* **2012**, *124*, 3001; *Angew. Chem. Int. Ed.* **2012**, *51*, 2947; m) Z. He, T. Luo, M. Hu, Y. Cao, J. Hu, *Angew. Chem.* **2012**, *124*, 4010; *Angew. Chem. Int. Ed.* **2012**, *51*, 3944; n) L. Chu, F.-L. Qing, *J. Am. Chem. Soc.* **2012**, *134*, 1298; o) Y. Ye, M. S. Sanford, *J. Am. Chem. Soc.* **2012**, *134*, 9034; p) X.-G. Zhang, H.-X. Dai, M. Wasa, J.-Q. Yu, *J. Am. Chem. Soc.* **2012**, *134*, 11948; q) Y. Fujiwara, J. A. Dixon, F. O'Hara, E. D. Funder, D. D. Dixon, R. A. Rodriguez, R. D. Baxter, B. Herlé, N. Sach, M. R. Collins, Y. Ishihara, P. S. Baran, *Nature* **2012**, *492*, 95.

[4] For selected reports on $C_{sp^3}{-}CF_3$ bond-forming reactions, see: a) T. Umemoto, K. Adachi, *J. Org. Chem.* **1994**, *59*, 5692; b) Y. Itoh, K. Mikami, *Tetrahedron* **2006**, *62*, 7199; c) H. Nagao, Y. Yamane, T. Mukaiyama, *Chem. Lett.* **2007**, *36*, 666; d) S. Mizuta, N. Shibata, S. Akiti, H. Fujimoto, S. Nakamura, T. Toru, *Org. Lett.* **2007**, *9*, 3707; e) D. A. Nagib, M. E. Scott, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2009**, *131*, 10875; f) A. E. Allen, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2010**, *132*, 4986; g) P. V. Pham, D. A. Nagib, D. W. C. MacMillan, *Angew. Chem.* **2011**, *123*, 6243; *Angew. Chem. Int. Ed.* **2011**, *50*, 6119; h) Q.-H. Deng, H. Wadepohl, L. H. Gade, *J. Am. Chem. Soc.* **2012**, *134*, 10769; i) M. Hu, C. Ni, J. Hu, *J. Am. Chem. Soc.* **2012**, *134*, 15257; j) P. Novák, A. Lishchynskyi, V. V. Grushin, *J. Am. Chem. Soc.* **2012**, *134*, 16167; k) C. Feng, T.-P. Loh, *Chem. Sci.* **2012**, *3*, 3458; l) G. K. S. Prakash, P. V. Jog, P. T. D. Batamack, G. A. Olah, *Science* **2012**, *338*, 1324.

[5] a) A. T. Parsons, S. L. Buchwald, *Angew. Chem.* **2011**, *123*, 9286–9289; *Angew. Chem. Int. Ed.* **2011**, *50*, 9120–9123; b) J. Xu, Y. Fu, D.-F. Luo, Y.-Y. Jiang, B. Xiao, Z.-J. Liu, T.-J. 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.-L. Qing, *Org. Lett.* **2012**, *14*, 2106.

[6] R. Shimizu, H. Egami, Y. Hamashima, M. Sodeoka, *Angew. Chem.* **2012**, *124*, 4655; *Angew. Chem. Int. Ed.* **2012**, *51*, 4577. Recently, the same type of reaction was reported, see: S. Mizuta, O. Galicia-López, K. M. Engle, S. Verhoog, K. Wheelhouse, G. Rassias, V. Gouverneur, *Chem. Eur. J.* **2012**, *18*, 8583.

[7] For selected reports on trifluoromethylation using Togni's reagent, see: a) P. Eisenberger, S. Gischig, A. Togni, *Chem. Eur. J.* **2006**, *12*, 2579; b) I. Kieltsch, P. Eisenberger, A. Togni, *Angew. Chem.* **2007**, *119*, 768; *Angew. Chem. Int. Ed.* **2007**, *46*, 754; c) R. Koller, K. Stanek, D. Stolz, R. Aardoom, K. Niedermann, A. Togni, *Angew. Chem.* **2009**, *121*, 4396; *Angew. Chem. Int. Ed.* **2009**, *48*, 4332; d) K. Niedermann, N. Früh, E. Vinogradova, M. S. Wiehn, A. Moreno, A. Togni, *Angew. Chem.* **2011**, *123*, 1091; *Angew. Chem. Int. Ed.* **2011**, *50*, 1059.

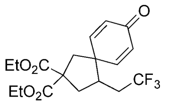
[8] H. Egami, R. Shimizu, M. Sodeoka, *Tetrahedron Lett.* **2012**, *53*, 5503.

[9] a) P. G. Janson, I. Ghoneim, N. O. Ilchenko, K. J. Szabó, *Org. Lett.* **2012**, *14*, 2882; b) R. Zhu, S. L. Buchwald, *J. Am. Chem. Soc.* **2012**, *134*, 12462. Other types of oxytrifluoromethylations of C=C bond have been reported. See: c) T. Fuchikami, Y. Shibata, H. Urata, *Chem. Lett.* **1987**, 521; d) K. Uneyama, *Tetrahedron* **1991**, *47*, 555; e) Y. Sato, S. Watanabe, K. Uneyama, *Bull. Chem. Soc. Jpn.* **1993**, *66*, 1840; f) T. Yajima, H. Nagano, C. Saito, *Tetrahedron Lett.* **2003**, *44*, 7027; g) C.-P. Zhang, Z.-L. Wang, Q.-Y. Chen, C.-T. Zhang, Y.-C. Gu, J.-C. Xiao, *Chem. Commun.* **2011**, *47*, 6632; h) Y. Li, A. Studer, *Angew. Chem.* **2012**, *124*, 8345; *Angew. Chem. Int. Ed.* **2012**, *51*, 8221; i) Y. Yasu, T. Koike, M. Akita, *Angew. Chem.* **2012**, *124*, 9705; *Angew. Chem. Int. Ed.* **2012**, *51*, 9567.

[10] For selected reviews on difunctionalization of olefins, see: a) B. Jacques, K. Muñiz in *Catalyzed Carbon-Heteroatom Bond Formation* (Ed.: A. K. Yudin), Wiley-VCH, Weinheim, **2011**, pp. 119–135; b) V. Kotov, C. C. Scarborough, S. S. Stahl, *Inorg. Chem.* **2007**, *46*, 1910; c) K. H. Jensen, M. S. Sigman, *Org. Biomol. Chem.* **2008**, *6*, 4083; d) S. R. Chemler, *Org. Biomol. Chem.* **2009**, *7*, 3009; e) S. E. Denmark, W. E. Kuester, M. T. Burk, *Angew. Chem.* **2012**, *124*, 11098–11113; *Angew. Chem. Int. Ed.* **2012**, *51*, 10938–10953.

[11] X. Mu, T. Wu, H.-Y. Wang, Y.-L. Guo, G. Liu, *J. Am. Chem. Soc.* **2012**, *134*, 878.

[12] Interestingly, the spiro compound **3p** was obtained in the reactions of **2f**, **2g**, and **2h** in yields of 8%, 10%, and 21%, respectively. For the mechanism, we hypothesize that C−C bond formation directly occurs simultaneously with electron transfer. However, because of the generation of **3p**, the possibility of the mechanism to proceed via a spirointermediate with subsequent 1,2-migration cannot be excluded.



3p

[13] *N*-Mesyl-3-(2,2,2-trifluoroethyl)-5-fluoroindoline was synthesized using a multistep procedure. See: F. Bertrand, V. Pevere, B. Quiclet-Sire, S. Z. Zard, *Org. Lett.* **2001**, *3*, 1069.