Trifluoromethylation of α-Haloketones

DATASET · SEPTEMBER 2012

JACS
JOURNAL OF THE AMERICAN CHEMICAL SOCIETY
Communication
pubs.acs.org/JACS

Trifluoromethylation of α-Haloketones

Petr Novák, Anton Lishchynskyi, and Vladimir V. Grushin*

Institute of Chemical Research of Catalonia (ICIQ), Tarragona 43007, Spain

Supporting Information

ABSTRACT: The C−X bond (X = Br, Cl) of α-haloketones is smoothly trifluoromethylated with the fluoroform-derived $CuCF_3$ reagent recently developed in our laboratories. This is the first nucleophilic α-trifluoromethylation reaction of carbonyl compounds and a rare example of CF_3−$C(sp^3)$ coupling. The transformation employs only low-cost chemicals and cleanly occurs in up to 99% yield at room temperature, thereby providing an unprecedentedly easy entry to valuable 2,2,2-trifluoroethylketones.

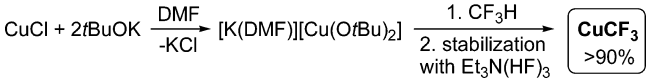
Organic compounds bearing a CF_3 group play an important role in the production of agrochemicals, pharmaceuticals, and specialty materials.[1] The high demand for new trifluoromethylation methods has led to considerable progress in the area, especially in recent years.[2] Nonetheless, no large-scale industrial processes have emerged from this research effort, mainly because of the prohibitively high cost of the CF_3-transferring reagents developed to date.

Trifluoromethane (CHF_3, fluoroform, HFC-23), a side product of Teflon manufacturing, is generated in the amount of ca. 20 000−25 000 t per annum. While being nontoxic and ozone-friendly, fluoroform (bp = −82 °C) has a tremendous global warming potential, 11 700 times that of CO_2 when compared over a 100-year period.[3] The long, 264-year atmospheric lifetime of HFC-23 and a steady 5% annual growth of its concentration in the atmosphere over the decades pose a serious ecological danger. To address this threat, the side-produced CHF_3 should be either destroyed or used as a feedstock for manufacturing fluorochemicals. The second of these two options is vastly preferable, especially taking into account the fact that HFC-23 is difficult and expensive to incinerate.

Considering the above, fluoroform is the most attractive CF_3 source for trifluoromethylation reactions. Efficient use of CHF_3 in synthesis would allow production of useful materials from this inevitably side-generated waste chemical that otherwise must be destroyed in a costly process. Therefore, the development of industrially feasible routes to valuable organofluorine compounds from poorly reactive CHF_3 is a critical task of modern chemical research. However, only very limited progress toward this goal has been made, thus far.[3−5]

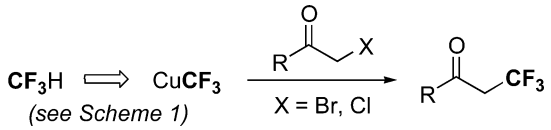
We have recently discovered a new reaction of direct cupration of fluoroform (Scheme 1).[2m,6] This reaction employs only low-cost materials and readily occurs at room temperature and atmospheric pressure to furnish $CuCF_3$ in nearly quantitative yield. The thus produced $CuCF_3$, stabilized with $Et_3N{\cdot}3HF$ (TREAT HF), has been used for efficient

Scheme 1. Direct Cupration of Fluoroform[6]



trifluoromethylation of aryl halides[6] and boronic acids.[7] Herein we report a new reaction, nucleophilic trifluoromethylation of α-haloketones with fluoroform-derived $CuCF_3$. This transformation (Scheme 2) is regiospecific for the substrate C−X (X = Br, Cl) bond, readily occurring at room temperature and affording 2,2,2-trifluoroethylketones in high yield.

Scheme 2. Trifluoromethylation of α-Haloketones with Fluoroform-Derived $CuCF_3$



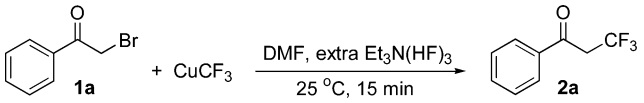
α-Trifluoromethylation of carbonyl compounds, "one of the most important reactions not only in organofluorine chemistry but also in medicinal chemistry"[8] and "a central objective in the field of chemical synthesis,"[9] has been achieved by the radical and electrophilic CF_3 addition to enolates and silyl enol ethers.[2a,d−i,s,8−12] The highly sought-after, yet previously unreported nucleophilic α-trifluoromethylation (Scheme 2) cannot be performed with conventional CF_3^- synthons such as CF_3SiR_3 because they bring about facile CF_3-addition across the C=O bond.[13]

We were pleased to find that 2-bromoacetophenone (**1a**) readily reacted with CHF_3-derived $CuCF_3$[6] at room temperature to give 2-trifluoromethylacetophenone (**2a**) in 75−80% yield within 15 min. No CF_3 addition to the carbonyl group[13] was observed (^{19}F NMR). It was noticed, however, that the just produced **2a** was unstable in the reaction medium, decaying at a rate slower than, yet comparable with, that of its formation. Attempts were made to avoid the decomposition by quenching the mixture with H_2O immediately after full conversion of **1a** was reached. This, however, did not solve the problem, as the newly formed ketone continued to decompose even after the addition of water. We reasoned that the lack of stability of **2a** in the reaction medium was likely due to HF elimination,[10h] induced by the Et_3N base present in the stabilized $CuCF_3$ reagent.[14] Indeed, buffering the reaction solution with nearly pH-neutral TREAT HF[15] provided stabilization to **2a**, while

Received: August 6, 2012
Published: September 21, 2012

   dx.doi.org/10.1021/ja307783w | J. Am. Chem. Soc. 2012, 134, 16167−16170

Table 1. Optimization of Trifluoromethylation of 1a



entry	$CuCF_3$ (equiv)	extra $Et_3N{\cdot}3HF$ (mol per mol $CuCF_3$)	method[a]	^{19}F NMR yield of **2a** (%)
1	1.3	0		79
2	1.3	0.10	A	85
3	1.3	0.13	A	77
4[b]	1.3	0.20	A	87
5	1.3	0.20	B	96
6	1.2	0.20	B	90
7	1.0	0.20	B	85

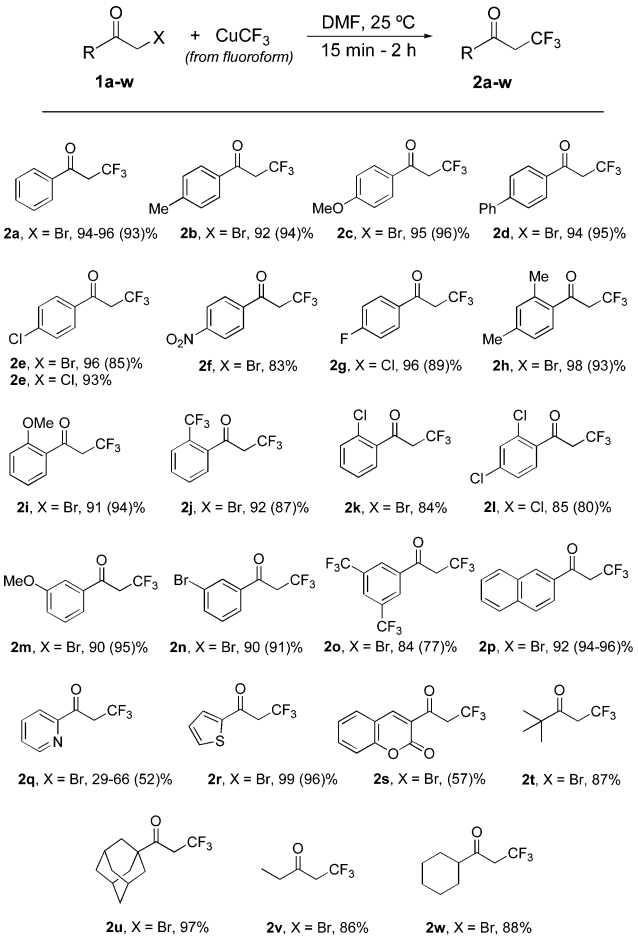
[a]Method A: extra $Et_3N{\cdot}3HF$ was added immediately after mixing **1a** with stabilized $CuCF_3$; Method B: extra $Et_3N{\cdot}3HF$ was added to stabilized $CuCF_3$ prior to reaction with **1a**. See the Supporting Information for more details. [b]1 h at 0 °C.

not decomposing the $CuCF_3$ reagent itself. Optimization of the quantity of the stabilizer (Table 1) showed that the highest yield of 96% (entry 5) could be obtained by adding 0.2 mol of extra $Et_3N{\cdot}3HF$ per mol of the stabilized $CuCF_3$ reagent prior to its use in the reaction.[16] Under such conditions, full conversion of **1a** was achieved with only 1.3 equiv of the copper reagent. Further lowering the amount of $CuCF_3$ to 1.2 and 1.0 equiv (entries 6 and 7) resulted in lower yields of 90% and 85%, respectively.

Having optimized the reaction conditions, we investigated the scope of the method (Scheme 3). The reactions were performed in the presence of 0.2−0.3 mol of extra TREAT HF per mol of $CuCF_3$. The previously optimized amount of $CuCF_3$ (1.3 equiv, see above) was used in all of the reactions of the α-bromo ketones bearing aromatic and heterocyclic rings, except for **1q**·HBr (see below). Nonaromatic substrates and α-chloroketones were trifluoromethylated with 1.5 equiv of $CuCF_3$. As can be seen from Scheme 3, the method has a broad scope and exhibits high functional group tolerance. The reaction affords $RCOCH_2CF_3$ for R = aryl (**2a**−**p**), heteroaryl (**2q**−**s**), and alkyl (**2t**−**w**). Both electron-donating (**2b**, **2c**, **2h**, **2i**, **2p**) and -withdrawing (**2e**−**g**, **2j**−**l**, **2m**−**o**) substituents on the aromatic ring are easily tolerated. Ortho-substituted substrates react as smoothly to give the desired products **2h**−**l** in 84−98% yield. Remarkably, not only α-bromo but also α-chloro derivatives could be trifluoromethylated in excellent yield (**2e**, **2g**, **2l**), despite the fact that organocopper compounds usually exhibit low reactivity toward Cl-electrophiles. The starting material for the preparation of **2q** was hydrobromide **1q**·HBr that, unlike **1q**, is stable and commercially available. The reaction of **1q**·HBr with $CuCF_3$ in amounts of 1.3, 2.0, and 3.0 equiv produced **2q** in 29%, 62%, and 66% ^{19}F NMR yield, respectively. These results suggested that the enhanced acidity of **1q**·HBr prompted partial decomposition of the $CuCF_3$ reagent. The larger scale trifluoromethylation of **1q**·HBr with 2.5 equiv of $CuCF_3$ furnished **2q** in 52% isolated yield (Scheme 3).

The α-trifluoromethylation reactions shown in Scheme 3 were performed on a 0.25 mmol scale for yield determination by ^{19}F NMR and on a 1−2 mmol scale for isolation of the products **2a**−**e**, **2g**−**j**, and **2l**−**s**. All isolated trifluoroethyl ketones were spectroscopically (^1H, ^{19}F NMR) and analytically pure (≥98%; often >99%), with the exception of **2h** (96−97% pure), **2m** (95% pure), and **2s** (95% pure). Both isolated **2m**

Scheme 3. Trifluoromethylation of α-Haloketones with Fluoroform-Derived $CuCF_3$ (^{19}F NMR Yields; Isolated Yields in Parentheses)



and **2s** were contaminated with ca. 5% of the corresponding hydrodebromination side-product $RCOCH_3$, whereas **2h** contained ca. 3−4% of unreacted **1h**. In some instances (**2b**−**d**, **2i**, **2m**, **2n**, and **2p**), the isolated yields slightly exceeded those determined by ^{19}F NMR in the parallel, lower-scale runs. The difference, however, is within the ca. 5% error in the yield determination by NMR. To demonstrate further scalability of the method, 2-bromoacetylnaphthalene **1p** was trifluoromethylated on an 8 mmol scale. In this experiment, the desired product **2p** was isolated analytically pure as a white crystalline solid in an amount of 1.83 g (96% yield).

Of the 23 trifluoromethylated compounds prepared in this work (Scheme 3), 12 have not been previously reported. In addition to full characterization of the new products by conventional analytical and spectroscopic techniques, **2d**, **2e**, and **2p** were studied by single-crystal X-ray diffraction (Figure 1, Table 2). Interestingly, the geometry parameters within the $C(O)CH_2CX_3$ moiety are virtually indistinguishable for X = F (**2e**, this work) and for X = H[17] (Table 2), even though the F-atoms certainly play a role in the crystal packing. This structural similarity might be yet another indication that the CF_3 group does not impose a positive charge on an adjacent atom.[2m,18]

Like any other synthetic protocol, our method is not without limitations. For instance, while the thienyl ketone **2r** was formed quantitatively and isolated in 93% yield, the pyridine (**2q**) and coumarin (**2s**) derivatives were obtained in noticeably

dx.doi.org/10.1021/ja307783w | J. Am. Chem. Soc. 2012, 134, 16167−16170

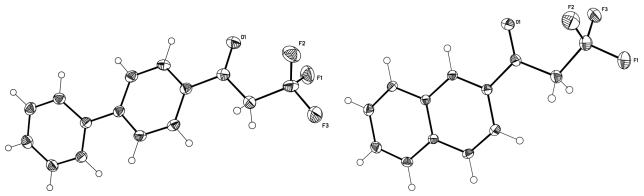
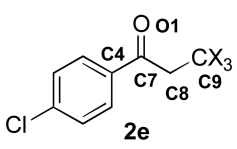
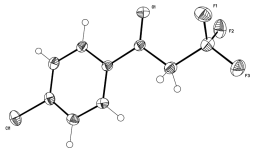


Figure 1. ORTEP drawings of **2d** (left) and **2p** (right) with thermal ellipsoids drawn to the 50% probability level.

Table 2. Selected Bond Distances (Å) and Bond Angles (deg) of 2e and Its Fluorine-Free Analogue[17]





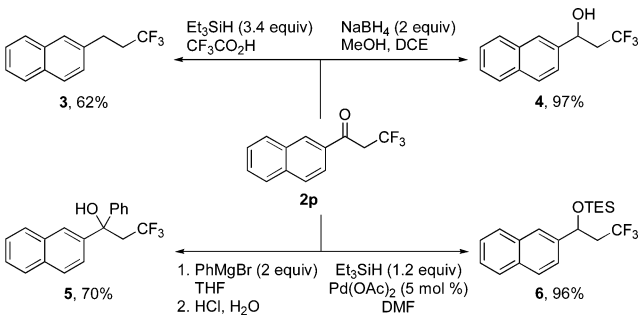
X	C9−C8	C8−C7	C7−C4	C7−O1	C7−C8−C9
F	1.512(2)	1.517(2)	1.488(2)	1.214(1)	113.7(1)
H	1.516(4)	1.511(4)	1.500(4)	1.215(3)	114.0(2)

lower isolated yields (52−57%). Secondary halides of the type RCOCH(R′)X (R′ = Me, X = Br; R′ = Ph, X = Cl) and α-haloesters appeared poorly reactive toward $CuCF_3$ under the conditions used for the trifluoromethylation of **1a−w**.

The detailed mechanism of the trifluoromethylation of α-haloketones with $CuCF_3$ remains to be elucidated. For that, however, a better understanding of the structure of the $CuCF_3$ species in solution is needed. These studies are currently in progress in our laboratories. In the meantime, we propose that coordination of the Cu-atom to the carbonyl and halide facilitates substitution with the CF_3 group, possibly as in the reported[19] Cu-catalyzed cross-coupling of alkylzinc reagents with α-chloroketones.

The utility of our method was further demonstrated by performing a series of chemical modifications of a new ketone **2p**. As shown in Scheme 4, the carbonyl group of **2p** can be

Scheme 4. Examples of Synthetic Utility of 2p



reduced exhaustively via ionic hydrogenation to give **3**, or partially with $NaBH_4$, to produce alcohol **4**. On treatment of **2p** with PhMgBr, tertiary alcohol **5** was obtained. Hydrosylilation of **2p** afforded **6** in nearly quantitative yield.

The previously developed electrophilic and radical α-trifluoromethylation methodologies[2a,d−i,s,8−11] offer good synthetic opportunities for medicinal chemistry and agrochemical discovery research. Our method, however, while exhibiting higher functional group tolerance and yields in general, might also provide a number of advantages for potential larger scale operations. In particular:

- Our reaction employs $CuCF_3$ that is produced directly from fluoroform, by far the cheapest and most readily available and atom-economical CF_3 source.
- In most instances, enolates and silyl enol ethers, the substrates employed in the radical and electrophilic α-trifluoromethylation reactions, should be premade using a strong base, such as LDA.[20] This adds to the cost and puts additional limitations on functional groups that can be present in the system. In contrast, our method utilizes readily available, easily accessible, and inexpensive α-haloketones that are used without any premodification.
- Although styrenes can be used directly in the recently reported[11] radical trifluoromethylation with costly $[Ph_2SCF_3]^+$ OTf^-, the yields of the α-trifluoromethylacetophenone products are only 20−40%.

In conclusion, we have developed the first nucleophilic trifluoromethylation of the C−X (X = Br, Cl) bond of α-haloketones. The method employs only low-cost, readily available chemicals, including fluoroform, by far the best and cheapest CF_3 source. The reaction is high-yielding, rapidly and smoothly occurring at ambient temperature and exhibiting unprecedented functional group tolerance. It is hoped that the new method will find applications in the synthesis of biologically active compounds and specialty materials.

■ ASSOCIATED CONTENT

Supporting Information

Full details of synthetic (PDF) and crystallographic studies (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

vgrushin@iciq.es

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We thank Drs. Jordi Benet-Buchholz, Eduardo C. Escudero-Adán, Eddy Martin, and Marta Martínez Belmonte for single-crystal X-ray diffraction studies. The ICIQ Foundation, Consolider Ingenio 2010 (Grant CSD2006-0003), and The Spanish Government (Grant CTQ2011-25418) are thankfully acknowledged for support of this work.

■ REFERENCES

(1) For selected monographs, see: (a) Hudlicky, M. *Chemistry of Organic Fluorine Compounds*; Ellis Horwood: New York, 1976. (b) Banks, R. E. *Organofluorine Chemicals and Their Industrial Applications*; Ellis Horwood: West Sussex, U.K., 1979. (c) Filler, R.; Kobayashi, Y. *Biomedicinal Aspects of Fluorine Chemistry*; Kodansha-Elsevier: New York, 1982. (d) Kirsch, P. *Modern Fluoroorganic Chemistry*; Wiley-VCH: Weinheim, 2004. (e) Uneyama, K. *Organofluorine Chemistry*; Blackwell: Oxford, U.K., 2006. (f) Ojima, I. *Fluorine in Medicinal Chemistry and Chemical Biology*; Wiley-Blackwell: Chichester, U.K., 2009. (g) Petrov, V. A. *Fluorinated Heterocyclic Compounds. Synthesis, Chemistry and Applications*; Wiley: Hoboken, NJ, 2009.

(2) For selected recent reviews, see: (a) Cahard, D.; Ma, J.-A. *Chem. Rev.* **2004**, *104*, 6119. (b) Schlosser, M. *Angew. Chem., Int. Ed.* **2006**, *45*, 5432. (c) Prakash, G. K. S.; Hu, J. *Acc. Chem. Res.* **2007**, *40*, 921.

(d) Cahard, D.; Ma, J.-A. *J. Fluorine. Chem.* **2007**, *128*, 975. (e) Kieltsch, I.; Eisenberger, P.; Stanek, K.; Togni, A. *Chimia* **2008**, *62*, 260. (f) Uneyama, K.; Katagiri, T.; Amii, H. *Acc. Chem. Res.* **2008**, *41*, 817. (g) Ma, J.-A.; Cahard, D. *Chem. Rev.* **2008**, *108*, PR1. (h) Shibata, N.; Matsnev, A.; Cahard, D. *Beilstein J. Org. Chem* **2010**, *6*, 65. (i) Sato, K.; Tarui, A.; Omote, M.; Ando, A.; Kumadaki, I. *Synthesis* **2010**, 1865. (j) Dhara, M. G.; Banerjee, S. *Prog. Polym. Sci.* **2010**, *35*, 1022. (k) Koller, R.; Togni, A. *Chim. Oggi* **2010**, *28*, 33. (l) Roy, S.; Gregg, B. T.; Gribble, G. W.; Le, V.-D.; Roy, S. *Tetrahedron* **2011**, *67*, 2161. (m) Tomashenko, O. A.; Grushin, V. V. *Chem. Rev.* **2011**, *111*, 4475. (n) Qing, F.-L.; Zheng, F. *Synlett* **2011**, 1052. (o) Dilman, A. D.; Levin, V. V. *Eur. J. Org. Chem.* **2011**, 831. (p) Nie, J.; Guo, H.-C.; Cahard, D.; Ma, J.-A. *Chem. Rev.* **2011**, *111*, 455. (q) Grygorenko, O. O.; Artamonov, O. S.; Komarov, I. V.; Mykhailiuk, P. K. *Tetrahedron* **2011**, *67*, 803. (r) Acena, J. L.; Sorochinsky, A. E.; Soloshonok, V. A. *Synthesis* **2012**, *44*, 1591. (s) Macé, Y.; Magnier, E. *Eur. J. Org. Chem.* **2012**, 2479.

(3) Han, W.; Li, Y; Tang, H.; Liu, H. *J. Fluorine Chem.* **2012**, *140*, 7.

(4) Langlois, B. R.; Billard, T. *ACS Symp. Ser.* **2005**, *911*, 57.

(5) (a) A high-temperature (550 °C) gas-phase catalytic process has been recently developed[5b] to produce CF_3I from CHF_3 and I_2 at up to ca. 80% conversion and ca. 60% selectivity. The high cost of iodine puts limitations on many applications of CF_3I.[3] (b) Nagasaki, N.; Morikuni, Y.; Kawada, K.; Arai, S. *Catal. Today* **2004**, *88*, 121.

(6) (a) Zanardi, A.; Novikov, M. A.; Martin, E.; Benet-Buchholz, J.; Grushin., V. V. *J. Am. Chem. Soc.* **2011**, *133*, 20901. (b) Patent pending.

(7) Novák, P.; Lishchynskyi, A.; Grushin, V. V. *Angew. Chem., Int. Ed.* **2012**, *51*, 7767.

(8) Sato, K.; Yuki, T.; Yamaguchi, R.; Hamano, T.; Tarui, A.; Omote, M.; Kumadaki, I.; Ando, A. *J. Org. Chem.* **2009**, *74*, 3815.

(9) Pham, P. V.; Nagib, D. A.; MacMillan, D. W. C. *Angew. Chem., Int. Ed.* **2011**, *50*, 6119.

(10) (a) Miura, K.; Taniguchi, M.; Nozaki, K.; Oshima, K.; Utimoto, K. *Tetrahedron Lett.* **1990**, *31*, 6391. (b) Langlois, B. R.; Laurent, E.; Roidot, N. *Tetrahedron Lett.* **1992**, *33*, 1291. (c) Umemoto, T.; Ishihara, S. *J. Am. Chem. Soc.* **1993**, *115*, 2156. (d) Umemoto, T.; Adachi, K *J. Org. Chem.* **1994**, *59*, 5692. (e) Kamigata, N.; Udodaira, K.; Shimizu, T. *Phosphorus, Sulfur Silicon Relat. Elem.* **1997**, *129*, 155. (f) Ma, J.-A.; Cahard, D. *J. Org. Chem.* **2003**, *68*, 8726. (g) Blazejewski, J.-C.; Wilmshurst, M. P.; Popkin, M. D.; Wakselman, C.; Laurent, G.; Nonclercq, D.; Cleeren, A.; Ma, Y.; Seoc, H.-S.; Leclercq, G. *Bioorg. Med. Chem.* **2003**, *11*, 335. (h) Itoh, Y.; Mikami, K. *Org. Lett.* **2005**, *7*, 649. (i) Itoh, Y.; Mikami, K. *Org. Lett.* **2005**, *7*, 4883. (j) Itoh, Y.; Mikami, K. *J. Fluorine Chem.* **2006**, *127*, 539. (k) Mikami, K.; Tomita, Y.; Ichikawa, Y.; Amikura, K.; Itoh, Y. *Org. Lett.* **2006**, *8*, 4671. (l) Itoh, Y.; Mikami, K. *Tetrahedron* **2006**, *62*, 7141. (m) Itoh, Y.; Houk, K. N.; Mikami, K. *J. Org. Chem.* **2006**, *71*, 8918. (n) Yomita, Y.; Ichikawa, Y.; Itoh, Y.; Kawada, K.; Mikami, K. *Tetrahedron Lett.* **2007**, *48*, 8922. (o) Petrik, V.; Cahard, D. *Tetrahedron Lett.* **2007**, *48*, 3327. (p) Kieltsch, I.; Eisenberger, P.; Togni, A. *Angew. Chem., Int. Ed.* **2007**, *46*, 754. (q) Tomita, Y.; Itoh, Y.; Mikami, K. *Chem. Lett.* **2008**, *37*, 1080. (r) Noritake, S.; Shibata, N.; Nakamura, S.; Toru, T.; Shiro, M. *Eur. J. Org. Chem.* **2008**, 3465. (s) Sato, K.; Yuki, T.; Tarui, A.; Omote, M.; Kumadaki, I.; Ando, A. *Tetrahedron Lett.* **2008**, *49*, 3558. (t) Sato, K.; Yuki, T.; Yamaguchi, R.; Hamano, T.; Tarui, A.; Omote, M.; Kumadaki, I.; Ando, A. *J. Fluorine Chem.* **2008**, *129*, 51. (u) Noritake, S.; Shibata, N.; Nomura, Y.; Huang, Y.; Matsnev, A.; Nakamura, S.; Toru, T.; Cahard, D. *Org. Biomol. Chem.* **2009**, *7*, 3599. (v) Nagib, D. A.; Scott, M. E.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2009**, *131*, 10875. (w) Allen, A. E.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2010**, *132*, 4986. (x) Matoušek, V.; Togni, A.; Bizet, V.; Cahard, D. *Org. Lett.* **2011**, *13*, 5762. (y) Herrmann, A. T.; Smith, L. L.; Zakarian, A. *J. Am. Chem. Soc.* **2012**, *134*, 6976. (z) Deng, Q.-H.; Wadepohl, H.; Gade, L. H. *J. Am. Chem. Soc.* **2012**, *134*, 10769. (aa) Ohtsuka, Y.; Uraguchi, D.; Yamamoto, K.; Tokuhisa, K.; Yamakawa, T. *Tetrahedron* **2012**, *68*, 2636.

(11) Radical trifluoromethylation of styrenes has recently been reported: Zhang, C.-P.; Wang, Z.-L.; Chen, Q.-Y.; Zhang, C.-T.; Gu, Y.-C.; Xiao, J.-C. *Chem. Commun.* **2011**, *47*, 6632.

(12) Other methods to synthesize carbonyl compounds bearing a CF_3 group in the α-position include the addition of acid fluorides RC(O)F to $CH_2{=}CF_2$,[12a] hydrolysis of CF_3-substituted alkenyldiazenes[12b] and 1-morpholino-2-trifluoromethylcycloalkenes,[12c] and homologation with 2-diazo-1,1,1-trifluoroethane.[12d−g] (a) Belen'kii, G. G.; German, L. S. *Izv. Akad. Nauk SSSR, Ser. Khim* **1974**, 942. (b) Kamitori, Y.; Hojo, M.; Masuda, R.; Ohara, S.; Kawamura, Y.; Ebisu, T. *Synthesis* **1989**, 43. (c) Kirij, N. V.; Pasenok, S. V.; Yagupolskii, Yu. L.; Tyrra, W.; Naumann, D. *J. Fluorine Chem.* **2000**, *106*, 217. (d) Fields, R.; Tomlinson, P. *J. Fluorine Chem.* **1979**, *14*, 19. (e) Tordeux, M.; Wakselman, C. *J. Fluorine Chem.* **1981**, *17*, 299. (f) Tordeux, M.; Wakselman, C. *J. Fluorine Chem.* **1982**, *21*, 99. (g) Morandi, B.; Carreira, E. M. *Angew. Chem., Int. Ed.* **2011**, *50*, 9085.

(13) Prakash, G. K. S.; Yudin, A. K. *Chem. Rev.* **1997**, *97*, 757.

(14) Et_3N is released in the amount of 0.33 equiv per Cu upon the stabilization of fluoroform-derived $CuCF_3$ with $Et_3N{\cdot}3HF$.[6]

(15) McClinton, M. A. *Aldrichimica Acta* **1995**, *28*, 31.

(16) A safety concern regarding the use of TREAT HF has been previously raised and addressed.[7] It is worth re-emphasizing that although TREAT HF should be handled with care, this reagent distills without decomposition, does not corrode borosilicate glass, has a pH close to neutral, and is not nearly as dangerous as other HF sources such as liquid HF, aqueous HF, and Py·HF (70% HF).[15]

(17) Cox, P. J. *Acta Crystallogr., Sect. E* **2002**, *E58*, o661.

(18) For example, see: (a) Pople, J. A.; Gordon, M. *J. Am. Chem. Soc.* **1967**, *89*, 4253. (b) Holmes, S. A.; Thomas, T. D. *J. Am. Chem. Soc.* **1975**, *97*, 2337. (c) Palmer, M. H. *J. Mol. Struct.* **2000**, *500*, 225. (d) Goodman, J.; Grushin, V. V.; Larichev, R. B.; Macgregor, S. A.; Marshall, W. J.; Roe, D. C. *J. Am. Chem. Soc.* **2009**, *131*, 4236. (e) Goodman, J.; Grushin, V. V.; Larichev, R. B.; Macgregor, S. A.; Marshall, W. J.; Roe, D. C. *J. Am. Chem. Soc.* **2010**, *132*, 12013. (f) Algarra, A. G.; Grushin, V. V.; Macgregor, S. A. *Organometallics* **2012**, *31*, 1467.

(19) Malosh, C. F.; Ready, J. M. *J. Am. Chem. Soc.* **2004**, *126*, 10240.

(20) Most recently, a few methods were reported[9,10y−aa] for one-pot radical/electrophilic α-trifluoromethylation of some carbonyl compounds in the absence of a strong alkali metal base such as LDA. The only example of such trifluoromethylation of ketones is the formation of **2a** in 76% yield in the photochemical reaction of acetophenone with CF_3I in the presence of *i*-Pr_2NEt and *t*-$Bu(Me)_2SiOTf$.[9]