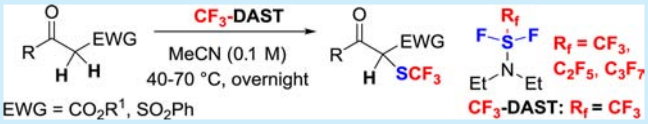
Organic LETTERS
Letter
pubs.acs.org/OrgLett

Perfluoroalkyl Analogues of Diethylaminosulfur Trifluoride: Reagents for Perfluoroalkylthiolation of Active Methylene Compounds under Mild Conditions

Ibrayim Saidalimu,[†] Shugo Suzuki,[†] Takuya Yoshioka,[†] Etsuko Tokunaga,[†] and Norio Shibata*[,†]

[†]Department of Nanopharmaceutical Sciences & Department of Frontier Materials, Nagoya Institute of Technology, Gokiso, Showa-ku, Nagoya 466-8555, Japan

Supporting Information



ABSTRACT: Trifluoromethyl diethylaminosulfur difluoride (CF_3-DAST) was found to be an efficient reagent for the trifluoromethylthiolation of α-methylene-β-keto esters providing α-trifluoromethylthio-β-keto esters in good to high yields. α-Methylene-β-keto sulfones were also accepted as substrates by CF_3-DAST to furnish the corresponding α-trifluoromethylthio compounds. This strategy can be extended to perfluoroalkylthiolation reactions using perfluoroethyl-DAST (C_2F_5-DAST) and perfluoropropyl-DAST (C_3F_7-DAST).

Organofluorine compounds have drawn considerable attention in the last few decades owing to their successful histories in the pharmaceutical and agrochemical industries.[1] Since it is almost impossible to obtain organofluorine compounds from natural resources, medicinal research has devised efficient synthetic methodologies to produce them.[2] While the classical synthesis of organofluorine compounds requires toxic and explosive reagents, the development of shelf-stable reagents for fluorination and trifluoromethylation has dramatically changed the dynamics of medicinal chemistry research.[3] Diethylaminosulfur trifluoride (DAST), one of the pioneering reagents for this purpose, was reported in the 1970s.[4] It was developed as a shelf-stable alternative of gaseous sulfur tetrafluoride (SF_4). Hydroxyl and carbonyl moieties are efficiently converted into corresponding fluorides by DAST via nucleophilic fluorination, either by an S_N1 or S_N2 pathway, but this depends on the substrate. DAST is now a very popular reagent for nucleophilic fluorination, and several DAST derivatives such as Morph-DAST,[5] DeoxoFluor,[6] XtalFluor,[7] and more[8] were also devised with improved reactivity and properties (Figure 1a). In this context, we are interested in the trifluoromethyl derivative of DAST, trifluoromethyldiethylaminosulfur difluoride (CF_3-DAST).[9a] CF_3-DAST was prepared by Langlois and Billard et al., who used it to prepare trifluoromethylthioanilines.[9b,c] During our fluorination research using DAST,[10] we recently came across a unique reaction of CF_3-DAST with β-keto esters providing acyl fluorides with α-trifluoromethylthio (SCF_3) esters via a C−C bond cleavage (Figure 1b).[10a] The uniqueness of this unexpected reaction and the importance of SCF_3 compounds[11] for biologically active molecules encouraged us to further extend their application by using CF_3-DAST. We noticed that CF_3-DAST initiates unprecedented reaction pathways depending on the α-methine or α-methylene of the β-keto ester structures. While the reaction of CF_3-DAST with β-keto esters having α-methine moiety furnishes α-SCF_3 esters via C−C bond cleavage[10a] (mentioned above, previous work), β-keto esters with an α-methylene moiety directly provide α-SCF_3 β-keto esters without cleavage of the C−C bond of the original β-keto esters structures in good to high yields (Figure 1c).

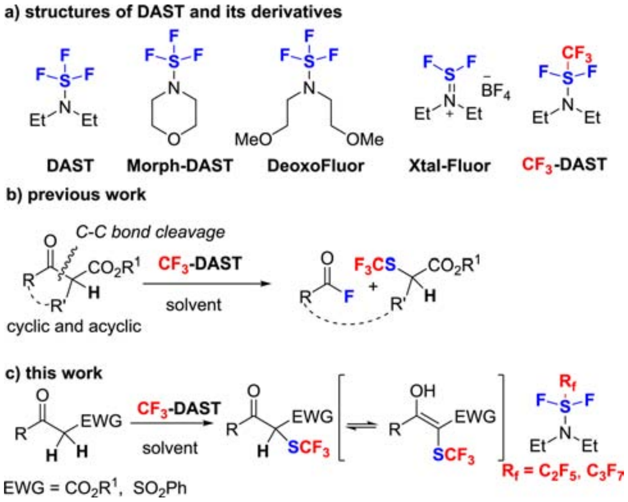


Figure 1. (a) Structures of DAST and its derivatives; (b) previous work; (c) this work.

The preparation of acyclic nono-α-SCF_3 β-keto esters by electrophilic trifluoromethylthiolation reagents is challenging,[12−14] due to the lower reactivity of acyclic β-keto esters rather than cyclic β-keto esters. This unique trifluoromethylthiolation by CF_3-DAST was found to be general not only for a variety of α-methylene-β-keto esters but also for β-keto sulfones with an α-methylene moiety. The CF_3-DAST strategy can be extended as an attractive alternative to further perfluoroalkylth-

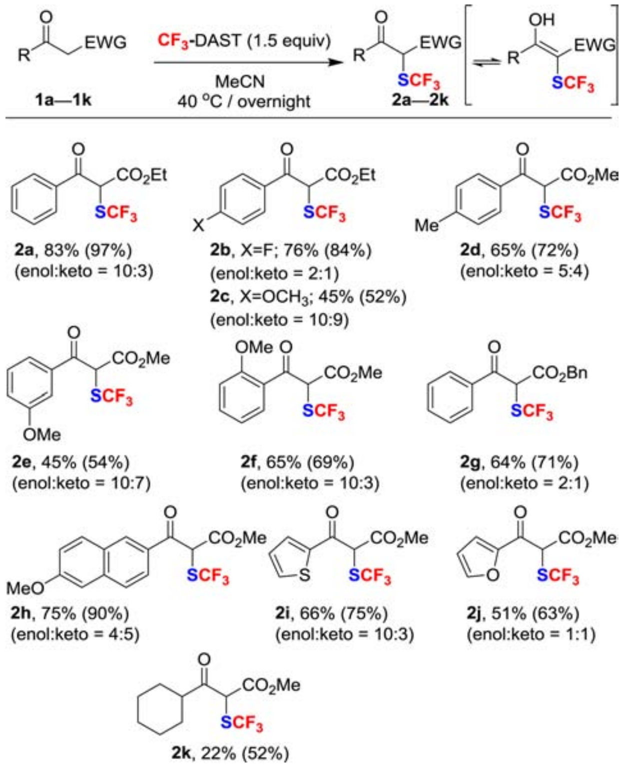
Received: November 3, 2016
Published: November 22, 2016

DOI: 10.1021/acs.orglett.6b03301
Org. Lett. 2016, 18, 6404−6407

iolation by using DAST perfluoroalkyl analogues such as perfluoroethyl-DAST and perfluoropropyl-DAST (C_2F_5-DAST, C_3F_7-DAST) to furnish the corresponding perfluoroalkylthiolated products in good to high yields. Perfluoroalkyl-DAST can be easily prepared in situ from commercially available reagents, DAST and $Me_3SiC_xF_y$; thus, this strategy should be a useful choice for the synthesis of a wide variety of acyclic α-perfluoroalkylthiolated compounds (Figure 1c).

CF_3-DAST was prepared by the treatment of DAST and the Ruppert−Prakash reagent (CF_3SiMe_3) in the presence of diisopropyethyllamine ($^i Pr_2NEt$) in dichloromethane at −10 °C for 2 h according to a previous report,[10a] and it was used directly without purification. After the reaction conditions were surveyed (see Table S1 in the Supporting Information), α-methylene-β-keto esters **1a** reacted overnight with CF_3-DAST (1.5 equiv, 0.5 M mixture in DCM) in acetonitrile at 40 °C under an argon atmosphere to furnish α-SCF_3-β-keto esters **2a** in 97% yield (83% isolated yield) (Scheme 1). A functional group on the benzene ring (Me, F, OMe), its position (*o*-, *m*- and *p*-), and the size of the ester group (CO_2Me, CO_2Et, CO_2Bn) of **1** were well accepted under the same conditions with CF_3-DAST to provide the corresponding α-CF_3S-β-keto esters **2b−g**. Electron-rich 2-naphthalene **1h** and heterocyclic substrates **1i,j** also underwent the same transformation to give the corresponding α-SCF_3 products **2h−j** in 51−75% yield. Nonaromatic substrate **2k** was also nicely converted to desired product **2k** in an acceptable yield. In all cases, the isolation yields were lower than those of ^{19}F NMR yields. The highly enolizable character of **2** makes their purification by silica gel column chromatography difficult. Due to the strong advantages of the SCF_3 group in pharmacy and agrochemistry, several electrophilic shelf-stable reagents have been reported by us and others for the trifluoromethylthiolation of β-keto esters.[12,13] Transformation of acyclic β-keto esters to the corresponding mono-α-SCF_3-products is challenging by our previous reagent.[13a] Shen and co-workers overcame this issue with their *N*-(trifluoromethyl)thiosaccharin reagent.[13c] *N*-(Trifluoromethyl)thiosulfonamide reagent, prepared by Billard et al., followed next.[13d] Therefore, the CF_3-DAST reagent is another choice of this transformation.

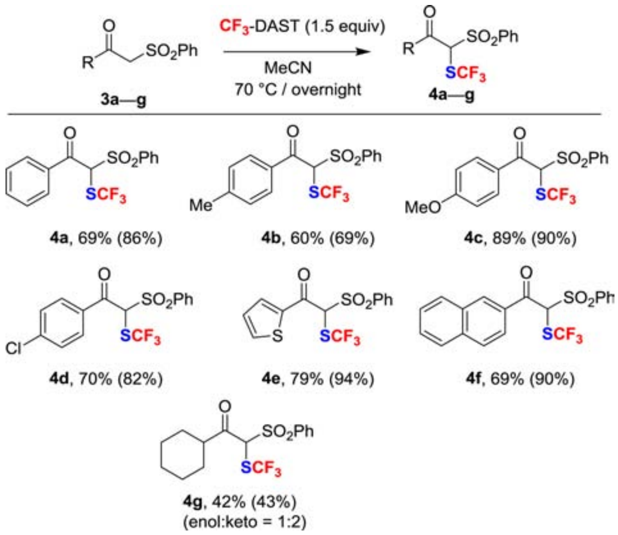
Scheme 1. Scope of Acyclic β-Keto Ester Substrates[a]



[a]The reaction of **1a—k** with 1.5 equiv of CF_3-DAST (0.5 M mixture in DCM) was carried out in acetonitrile at 40 °C overnight. For detailed reaction conditions, see the SI. Yields are isolated yields. ^{19}F NMR yields with an internal standard, $C_6H_5CF_3$, are also shown in parentheses.

We next examined the trifluoromethylthiolation of α-methylene-β-keto sulfones **3** (Scheme 2). Under a slightly higher reaction temperature (70 °C), sulfones **3** were efficiently trifluoromethylthiolated by CF_3-DAST to give corresponding α-SCF_3-β-keto sulfones **4**. The functional acceptability of **3** was almost the same as for α-methylene-β-keto esters **1** and desired α-SCF_3-β-keto sulfones **4a−g** were obtained in good yields, as high as 89% (as much as 94% of ^{19}F NMR yields), independent of the nature of the aryl group **3a−d**, heterocycle **3e**, and nonaromatic substrate **3g**.

Scheme 2. Scope of Acyclic β-Keto Sulfone Substrates[a]

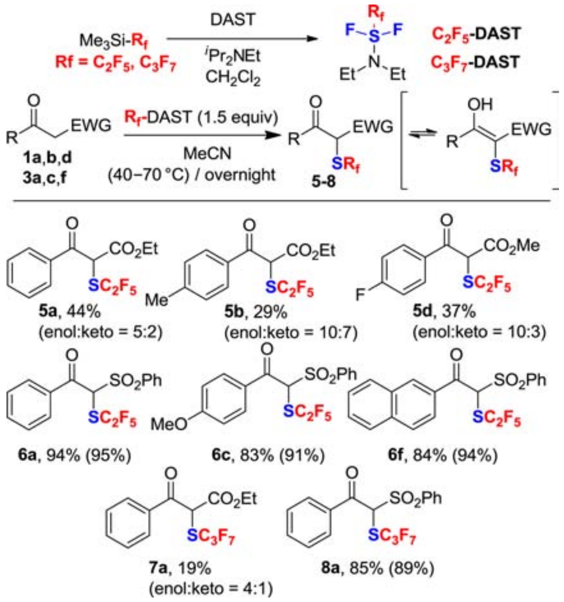


[a]The reaction of **3a−g** with 1.5 equiv of CF_3-DAST (0.5 M mixture in DCM) was carried out overnight in acetonitrile at 70 °C for. For detailed reaction conditions, see the SI. Yields are isolated yields. ^{19}F NMR yields with an internal standard, $C_6H_5CF_3$, are also shown in parentheses.

The idea of using CF_3-DAST was expanded to previously unknown perfluoroethyl-DAST (C_2F_5-DAST) and perfluoropropyl-DAST (C_3F_7-DAST). Both C_2F_5-DAST and C_3F_7-DAST were readily prepared in situ from DAST and C_2F_5-$SiMe_3$ or C_3F_7-$SiMe_3$ in the presence of $^i Pr_2NEt$ (Scheme 3). β-Keto esters **1** and sulfones **3** reacted efficiently with C_2F_5-DAST and C_3F_7-DAST to provide SC_2F_5-keto esters **5**, SC_2F_5-keto sulfones **6**, and their SC_3F_7-analogues **7** and **8** in moderate to good yields, respectively.

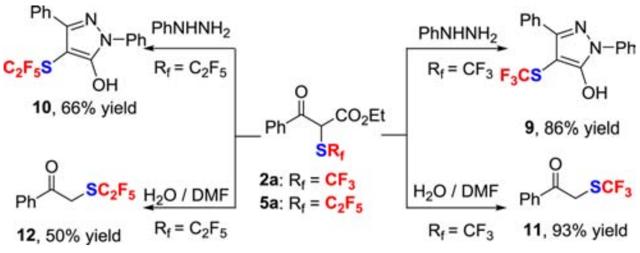
The synthetic utility of SCF_3 and SC_2F_5 products are shown in Scheme 4. The reaction of **2a** and **5a** with phenyl hydrazine provided the pyrazole derivatives **9** and **10**, respectively. The same substrates **2a** and **5a** were also converted to the

Scheme 3. Perfluoroalkylthiolation Using C_2F_5-DAST and C_3F_7-DAST[a]



[a] The reaction of **1** or **3** with 1.5 equiv of C_2F_5-DAST or C_3F_7-DAST (0.5 M mixture in DCM) was carried out overnight in acetonitrile at 40 or 70 °C. For detailed reaction conditions, see the SI. Yields are isolated yields. ^{19}F NMR yields with an internal standard, $C_6H_5CF_3$, are also shown in parentheses.

Scheme 4. Application of Products 2a and 5a



acetophenone derivatives **11** and **12** very easily after the treatment of water in DMF (93% and 50%, respectively).

The reaction mechanism for the formation of **2a** from **1a** is suggested as follows (Figure 2). Initially, CF_3-DAST reacts with the OH moiety of the enol form **1a′** to furnish enol ether **A** with the elimination of HF. HF is presumably trapped by the $^iPr_2NEt$. **A** spontaneously rearranges to **B** with the formation of a carbon−sulfur (C−S) bond. **B** changes smoothly to its enol form **B′** due to the higher acidity of methine H in **B** induced by the high electron negativity of sulfur. The elimination of imine as a HF salt from a transition state **TS**, in which the hydrogen bond between F and H should be a trigger for this elimination, gives **2a** as an equilibrium mixture with **2a′**.

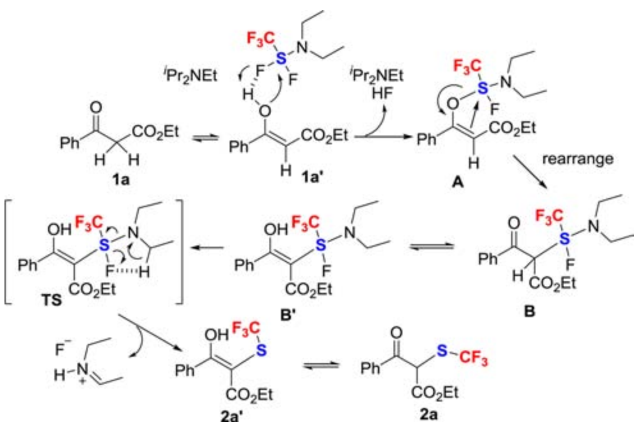


Figure 2. Proposed reaction mechanism.

In conclusion, a novel trifluoromethylthiolation of α-methylene-β-keto esters by the use of CF_3-DAST providing acyclic α-trifluoromethythio-β-keto esters was reported. β-Keto sulfones were also acceptable under the same conditions. The method can be extended to perfluoroalkylthiolations using perfluoro analogues of DAST, such as C_2F_5-DAST and C_3H_7-DAST, which are easily prepared in situ from DAST with corresponding perfluoroalkylsilanes. Since both DAST and perfluoroalkylsilanes are readily available, our strategy would be a useful choice for the synthesis of a wide variety of acyclic α-perfluoroalkylthiolated compounds. A potential for the reaction of CF_3-DAST with alcohols and aldehydes are under investigation.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b03301.

Experimental procedures and NMR spectra (PDF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: nozshiba@nitech.ac.jp.

ORCID

Norio Shibata: 0000-0002-3742-4064

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This research is partially supported by the Platform Project for Supporting in Drug Discovery and Life Science Research (Platform for Drug Discovery, Informatics, and Structural Life Science) from the Japan Agency for Medical Research and Development (AMED), the Advanced Catalytic Transformation (ACT-C) from the JST Agency, and the Kobayashi International Foundation.

■ REFERENCES

(1) (a) Kirsch, P. *Modern Fluoroorganic Chemistry: Synthesis, Reactivity, Applications*; Wiley-VCH: Weinheim, 2013. (b) Ojima, I. *Front Matter: Fluorine in Medicinal Chemistry and Chemical Biology*; John Wiley & Sons, Ltd.: Chichester, 2009.

(2) (a) Campbell, M. G.; Ritter, T. *Chem. Rev.* **2015**, *115*, 612. (b) Yang, X.; Wu, T.; Phipps, R. J.; Toste, F. D. *Chem. Rev.* **2015**, *115*, 826. (c) Ma, J.-A.; Cahard, D. *Chem. Rev.* **2008**, *108*, PR1. (d) Huang, Y.-Y.; Yang, X.; Chen, Z.; Verpoort, F.; Shibata, N. *Chem. - Eur. J.* **2015**, *21*, 8664. (e) Champagne, A.; Desroches, J.; Hamel, J.-D.; Vandamme, M.; Paquin, J.-F. *Chem. Rev.* **2015**, *115*, 9073. (f) Charpentier, J.; Früh, N.; Togni, A. *Chem. Rev.* **2015**, *115*, 650. (g) Liu, X.; Xu, C.; Wang, M.; Liu, Q. *Chem. Rev.* **2015**, *115*, 683. (h) Fustero, S.; Simón-Fuentes, A.; Barrio, P.; Haufe, G. *Chem. Rev.* **2015**, *115*, 871. (i) Kawai, H.; Shibata, N. *Chem. Rec.* **2014**, *14*, 1024. (j) Purser, S.; Moore, P. R.; Swallow, S.; Gouverneur, V. *Chem. Soc.*

Rev. **2008**, *37*, 320. (k) O'Hagan, D. *Chem. Soc. Rev.* **2008**, *37*, 308. (l) Prakash, G. K. S.; Yudin, A. K. *Chem. Rev.* **1997**, *97*, 757.

(3) (a) Shibata, N.; Matsnev, A.; Cahard, D. *Beilstein J. Org. Chem.* **2010**, *6*, 65. (b) Shibata, N. *Bull. Chem. Soc. Jpn.* **2016**, *89*, 1307. (c) Shibata, N.; Mizuta, S.; Kawai, H. *Tetrahedron: Asymmetry* **2008**, *19*, 2633. (d) Shibata, N.; Ishimaru, T.; Nakamura, S.; Toru, T. J. *J. Fluorine Chem.* **2007**, *128*, 469.

(4) (a) Markovskij, L. N.; Pashinnik, V. E.; Kirsanov, A. V. *Synthesis* **1973**, *1973*, 787. (b) Middleton, W. J. J. *J. Org. Chem.* **1975**, *40*, 574. (c) Singh, R. P.; Shreeve, J. M. *Synthesis* **2002**, *17*, 2561. (d) Kirk, K. L. *Org. Process Res. Dev.* **2008**, *12*, 305.

(5) Mykhailiuk, P. K.; Shishkina, S. V.; Shishkin, O. V.; Zaporozhets, O. A.; Komarov, I. V. *Tetrahedron* **2011**, *67*, 3091.

(6) (a) Lal, G. S.; Pez, G. P.; Pesaresi, R. J.; Prozonic, F. M.; Cheng, H. J. *J. Org. Chem.* **1999**, *64*, 7048. (b) Lal, G. S.; Pez, G. P.; Pesaresi, R. J.; Prozonic, F. M. *Chem. Commun.* **1999**, *2*, 215.

(7) (a) Beaulieu, F.; Beauregard, L.-P.; Courchesne, G.; Couturier, M.; LaFlamme, F.; L'Heureux, A. *Org. Lett.* **2009**, *11*, 5050. (b) L'Heureux, A.; Beaulieu, F.; Bennett, C.; Bill, D. R.; Clayton, S.; LaFlamme, F.; Mirmehrabi, M.; Tadayon, S.; Tovell, D.; Couturier, M. J. *J. Org. Chem.* **2010**, *75*, 3401. (c) Mahé, O.; L'Heureux, A.; Couturier, M.; Bennett, C.; Clayton, S.; Tovell, D.; Beaulieu, F.; Paquin, J.-F. J. *J. Fluorine Chem.* **2013**, *153*, 57.

(8) (a) Nielsen, M. K.; Ugaz, C. R.; Li, W.; Doyle, A. G. *J. Am. Chem. Soc.* **2015**, *137*, 9571. (b) Sheppard, W. A. *J. Am. Chem. Soc.* **1960**, *82*, 4751. (c) Umemoto, T.; Singh, R. P.; Xu, Y.; Saito, N. *J. Am. Chem. Soc.* **2010**, *132*, 18199. (d) Hayashi, H.; Sonoda, H.; Fukumura, K.; Nagata, T. *Chem. Commun.* **2002**, 1618. (e) Petrov, V. A.; Swearingen, S.; Hong, W.; Petersen, W. C. *J. Fluorine Chem.* **2001**, *109*, 25. (f) Tang, P.; Wang, W.; Ritter, T. *J. Am. Chem. Soc.* **2011**, *133*, 11482.

(9) (a) We name it CF3-DAST and do not abbreviate it as CF_3-DASD (trifluoromethyl diethylaminosulfur difluoride) because DAST is a popular name, almost a trademark.. (b) Bacque, E.; El-Ahmad, Y.; Billard, T.; Langlois, B.; Ferry. *PCT Int. Appl.* **2008**, 63. (c) Ferry, A.; Billard, T.; Langlois, B.R.; Bacqué, E. *J. Org. Chem.* **2008**, *73*, 9362.

(10) (a) Saidalimu, I.; Suzuki, S.; Tokunaga, E.; Shibata, N. *Chem. Sci.* **2016**, *7*, 2106. (b) Saidalimu, I.; Guo, M.; Tokunaga, E.; Shibata, N. *Asian J. Org. Chem.* **2016**, *5*, 1208.

(11) (a) Xu, X.-H.; Matsuzaki, K.; Shibata, N. *Chem. Rev.* **2015**, *115*, 731. (b) Ni, C.; Hu, M.; Hu, J. *Chem. Rev.* **2015**, *115*, 765.

(12) (a) Shao, X.; Wang, X.; Yang, T.; Lu, L.; Shen, Q. *Angew. Chem., Int. Ed.* **2013**, *52*, 3457. (b) Bauer, M.; Haas, A.; Muth, J. *J. Fluorine Chem.* **1980**, *16*, 129. (c) Bootwicha, T.; Liu, X.; Pluta, R.; Atodiresei, I.; Rueping, M. *Angew. Chem., Int. Ed.* **2013**, *52*, 12856. (d) Baert, F.; Colomb, J.; Billard, T. *Angew. Chem., Int. Ed.* **2012**, *51*, 10382. (e) Boiko, V. N. *Beilstein J. Org. Chem.* **2010**, *6*, 880.

(13) (a) Yang, Y.-D.; Azuma, A.; Tokunaga, E.; Yamasaki, M.; Shiro, M.; Shibata, N. J. *J. Am. Chem. Soc.* **2013**, *135*, 8782. (b) Chachignon, H.; Maeno, M.; Kondo, H.; Shibata, N.; Cahard, D. *Org. Lett.* **2016**, *18*, 2467. (c) Xu, C.; Ma, B.; Shen, Q. *Angew. Chem., Int. Ed.* **2014**, *53*, 9316. (d) Alazet, S.; Ismalaj, E.; Glenadel, Q.; Bars, D. L.; Billard, T. *Eur. J. Org. Chem.* **2015**, *2015*, 4607.

(14) (a) Bayreuther, H.; Haas, A. *Chem. Ber.* **1973**, *106*, 1418. (b) Popov, V. I.; Haas, A.; Lieb, M. J. *J. Fluorine Chem.* **1990**, *47*, 131.