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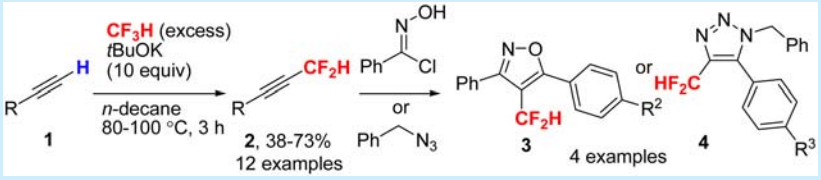
Difluoromethylation of Terminal Alkynes by Fluoroform

Satoshi Okusu,[†] Etsuko Tokunaga,[‡] and Norio Shibata*[,†,‡]

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

Supporting Information



ABSTRACT: The difluoromethylation of terminal alkynes through the use of fluoroform as a source of difluorocarbene is described. The choice of solvents and bases was found to be crucial for the transformation. A series of terminal alkynes **1** were nicely converted into the corresponding difluoromethyl alkynes **2** using potassium *tert*-butoxide in *n*-decane in moderate to good yields. Functional groups such as methoxy, dimethylamino, and bromo as well as phenyl, heteroaryl, and sterically demanding naphthyl were well tolerated under the reaction conditions. One-step transformations of difluoromethyl alkynes **2** to difluoromethylated isoxazoles **3** and 1,2,3-triazoles **4** were also achieved.

The synthesis of organofluorine compounds has attracted a great deal of attention in the past few decades in the pharmaceutical and agrochemical industries.[1] In particular, late-stage direct fluoro-functionalization reactions are advantageous in the synthesis of medicinally attractive fluorinated molecules rather than the use of a fluorinated building block strategy, since they rapidly access a large variety of fluorine-containing drug candidates with structural diversity for prompt use in biological screenings.[2−4] Hence, the development of efficient methods for fluoro-functionalization reactions such as trifluoromethylation[3] and fluorination[4] is becoming a main trend in this field. Among fluoro-functionalization reactions, the difluoromethylation reaction is the next target to be developed from the viewpoint of isosterism in medicinal chemistry.[5] The difluoromethyl (CF_2H) moiety behaves as an isosteric and isopolar group when linked to hydroxy (OH)[6] and thiol (SH)[7] units. Moreover, the CF_2H unit has an acidic proton and thus acts as a more lipophilic hydrogen donor than OH and NH groups through hydrogen bonding.[8] Therefore, the replacement of OH, SH, and NH groups by CF_2H is a useful isosterism strategy for molecular modification of original drugs and novel drug design. Although many methods exist for the direct incorporation of a CF_2H unit into target positions,[9] difluoromethylation of terminal alkynes is generally more challenging than that of *O*-, *S*-, and *N*-nucleophiles since C−H acidity is lower than heteroatom-H acidity.[10] There are only a few reported examples for the difluoromethylation of terminal alkynes.[11] In 1996, Kitazume and Konno succeeded in the difluoromethylation of terminal alkynes using chlorodifluoromethane (HCF_2Cl) and lithium acetylides.[11a] Hu and coworkers showed the difluoromethylation of terminal alkynes with a shelf-stable reagent, *S*-(difluoromethyl)-*S*-phenyl-*N*-tosylsulfoximine.[11c] Furthermore, the same authors also reported that tributyl(difluoromethyl)ammonium chloride is effective for the difluoromethylation of terminal alkynes.[11d] In all these cases, a difluorocarbene mechanism is involved in the transformation.[11a,c,d] Although these methods are useful for the synthesis of difluoromethyl alkynes, HCF_2Cl is a hazardous, ozone-depleting substance. Alternative shelf-stable reagents can also be prepared from HCF_2Cl.[11c,d] Burton and Hartgraves reported an organometallic approach for the direct difluoromethylation of alkynes using a (difluoromethyl)cadmium reagent. This method also required environmentally toxic HCF_2I.[11b] Hence, a more efficient and sustainable method for the difluoromethylation of alkynes is required. As part of our research program on the development of difluoromethylation reactions,[12] we eventually turned to the recently focused fluorinated raw material, fluoroform (HCF_3, HFC-23).

Fluoroform is an ozone-friendly, nontoxic, and cheap trifluoromethyl compound available in large quantities. Although the use of HCF_3 for organic synthesis had been problematic, taming HCF_3 for trifluoromethylation has been realized in the past few years.[13−16] One of the difficulties of treating HCF_3 for trifluoromethylation is the lability of the trifluoromethyl carbanion ($^-CF_3$), which rapidly transforms to more stabilized difluorocarbene.[17] The electrostatic repulsions between carbanion and the *p*-orbital of the fluorine atom in $^-CF_3$ induce the formation of difluorocarbene with the release of a fluoride anion, which is stabilized by the overlap between a vacant carbene orbital and fluorine *p*-orbitals (Figure 1a).

Researchers have overcome the issue of lability of trifluoromethyl carbanion by using copper[13] or potassium salts[14] and a sterically demanding superbase[15] as well as a classical method using DMF hemiacetal stabilization (Figure 1b).[16] In this context, we came up with the idea of using HCF_3 as an

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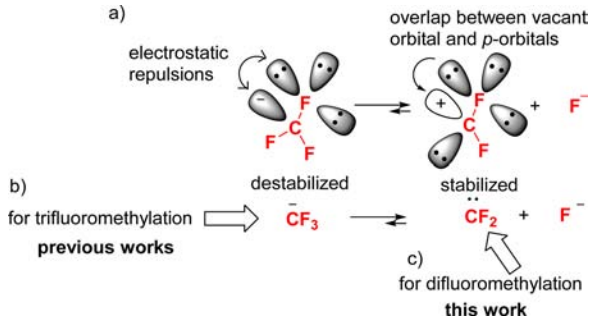
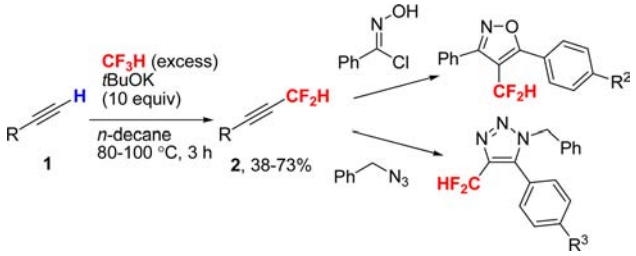


Figure 1. (a) Rapid transformation of trifluoromethyl carbanion to difluorocarbene due to electrostatic repulsions. (b) Fluoroform for trifluoromethylation vs (c) difluoromethylation.

inexpensive, environmentally benign source of difluorocarbene, and not trifluoromethyl carbanion, for organic synthesis (Figure 1c).

During an early stage of our investigation on this topic,[18] Dolbier et al. reported very nice contributions for the difluoromethylation of heterocentered nucleophiles using HCF_3 via in situ generation of difluorocarbene to furnish *O*-, *N*- and *S*-CF_2H products.[18] However, there is no report on the difluoromethylation of terminal alkenes by HCF_3.[19] We disclose herein the first example of difluoromethylation of terminal alkynes **1** by HCF_3 to provide difluoroalkynes **2** in good yields. The selection of both solvent and base is of prime importance to obtain good yields for this transformation. Difluoromethylated products **2** serve as precursors for medicinally attractive difluoromethylated heterocycles such as isoxazoles and triazoles via 1,3-cycloaddition and click reactions (Scheme 1).

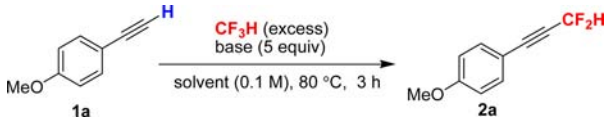
Scheme 1. Difluoromethylation of Terminal Alkynes 1 with HCF_3 and Their Transformation to Heterocycles



We initiated our investigation with the reaction of ethynylanisole (**1a**) by HCF_3 in solvent at 80 °C (Table 1). The difluoromethylation of **1a** by HCF_3 in the presence of *t*-BuOK (5.0 equiv) in mesitylene was attempted, and a desired difluoromethyl alkyne **2a** was obtained in 33% yield (run 1). The base was next screened to improve yield (runs 2−8). However, the reaction did not proceed when other bases, such as *t*-BuONa, *t*-BuOLi, KOH, P_2-Et, and PhOK, were used. Compound **1a** was decomposed to give a complex mixture under KHMDS conditions (run 5). Upon screening solvents, we found that the choice of solvent is very important in this transformation, and *n*-decane produced a good result with 52% yield of **2a** in the presence of *t*-BuOK at 80 °C (run 13). Further improvement was observed by using 10 equiv of *t*-BuOK (run 14). When the reaction was carried out at 100 °C, the yield decreased slightly (run 15).

With suitable conditions in hand, the scope of the difluoromethylation of terminal alkynes **1** using HCF_3 was

Table 1. Optimization of Difluoromethylation of 1a by HCF_3[a]

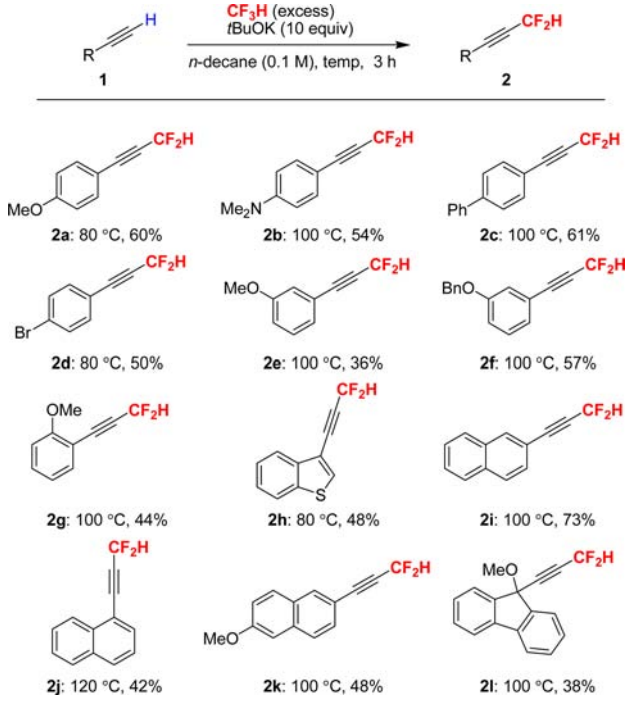


run	base	solvent	yield[b] (%)
1	*t*-BuOK	mesitylene	33
2	*t*-BuONa	mesitylene	NR
3	*t*-BuOLi	mesitylene	NR
4	KOH	mesitylene	NR
5	KHMDS	mesitylene	0
6	NaH	mesitylene	NR
7	P_2-Et	toluene	NR
8	PhOK	toluene	NR
9	*t*-BuOK	toluene	18
10	*t*-BuOK	*p*-xylene	32
11	*t*-BuOK	*n*PrCN	NR
12	*t*-BuOK	1,4-dioxane	NR
13	*t*-BuOK	*n*-decane	52
14[d]	*t*-BuOK	*n*-decane	85 (60)[c]
15[d,e]	*t*-BuOK	*n*-decane	72

[a]The reaction of **1** with HCF_3 (excess) was carried out in the presence of base (5 equiv) in solvent (0.1 M) at 80 °C. [b]Determined by ^{19}F NMR using a crude mixture with trifluorotoluene as the internal standard. [c]Isolated yield. [d]10 equiv of *t*BuOK was used. [e]The reaction was carried out at 100 °C.

explored with a variety of substrates selected in order to establish the generality of the process (Scheme 2). Aromatic rings substituted with either electron-donating or -withdrawing substituents, such as methoxy **2a**, dimethylamino **2b**, phenyl

Scheme 2. Difluoromethylation of Terminal Alkynes 1 Using HCF_3[a,b]



[a]The reaction of **1** with HCF_3 (excess) was carried out in the presence of *t*-BuOK (10 equiv) in *n*-decane (0.1 M) at 80−120 °C. [b]Isolated yield.

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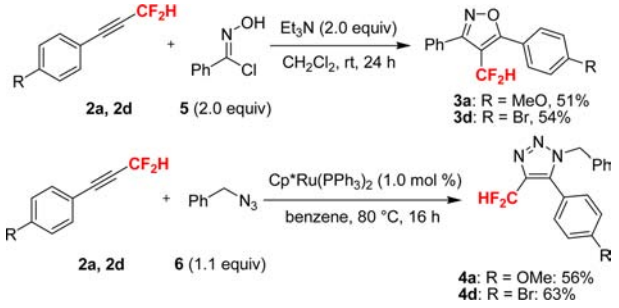
2c, and bromo **2d**, were tolerated. *Meta*- and *ortho*-substituted aryl alkyne derivatives were also accepted (**2e**−**g**). A benzothiophene-substituted alkyne **2h** was compatible with the same reaction conditions. The sterically demanding naphthyl-substituted alkynes also afforded the corresponding products **2j** and **2k** in moderate yields. Furthermore, the fluorene-substituted alkyne also produced the desired product **2l** in 38% yield.

Finally, a regioselective one-step conversion of **2** into the medicinally attractive heterocycles was carried out to show the utility of **2** (Scheme 3). First, the 1,3-dipolar cycloaddition of

Scheme 3. Transformations of 2 to Medicinally Attractive Isoxazoles 3 and Triazoles 4



difluoromethylalkynes **2a** and **2d** with imidoyl chloride **5** in the presence of NEt_3 regioselectively provided isoxazoles **3a** and **3d** in 51% and 54% yield, respectively. Triazoles **4** were also obtained regioselectively from **2a** and **2d** with benzylazide **6** in the presence of a catalytic amount of $Cp^*Ru(PPh_3)_2$ in 56% and 63% yield, respectively.[20] The structures and geometries of **3d** and **4d** were clearly determined by X-ray crystallographic analyses (Figure 2).

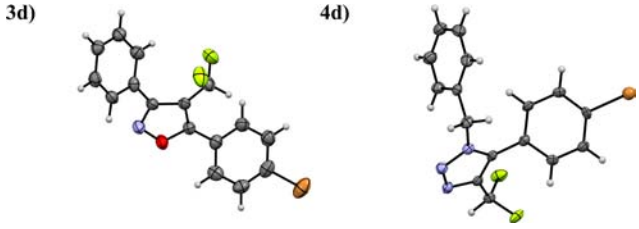


Figure 2. X-ray crystallographic analyses of **3d** (left, CCDC 1406862) and **4d** (right, CCDC 1406861).

In conclusion, we have developed the first example of difluoromethylation of terminal alkynes **1** by HCF_3. In situ generation of difluorocarbene from ozone-friendly HCF_3 is advantageous for this transformation instead of using HCF_2Cl or related derivatized reagents. Wide substrate generality was observed in good to moderate yields. Key to successful transformation is the suitable selection of solvent and base (*t*-BuOK in *n*-decane) at a high reaction temperature. The utility of the product difluoromethylalkynes **2** was shown by examples of regioselective cycloaddition reactions to medicinally attractive difluoromethylated isoxazoles **3** and 1,2,3-triazoles **4**. Although the yields of present reaction are still moderate, the difluoromethylation of carbon nucleophiles is rather tough[19] compared to the heterocentered nucleophiles.[18] Further extension of HCF_3 chemistry to difluoromethylation and trifluoromethylation of other substrates is currently underway.

■ ASSOCIATED CONTENT

Supporting Information

Experimental details, analytical data (HRMS), CIF information, and copies of ^1H, ^{13}C, and ^{19}F NMR spectra. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b01778.

■ AUTHOR INFORMATION

Corresponding Author

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

Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) (a) Chambers, R. D. *Fluorine in Organic Chemistry*; Wiley: New York, 1973. (b) Ishikawa, N.; Kobayashi, Y. *Fusso Kagoubustu (Compounds of Fluorine)*; Kodansha, Ltd.: Tokyo, 1979. (c) Kirk, K. L. *Biochemistry of Halogenated Organic Compounds*; Plenum: New York, 1991; pp 65−103 and 145−150. (d) Kitazume, T.; Ishihara, T.; Taguchi, T. *Fusso No Kagaku (Chemistry of Fluorine)*; Scientific, Ltd.: Tokyo, 1993; pp 151−192. (e) Banks, R. E.; Smart, B. E.; Tatlow, J. C. *Organofluorine Chemistry: Principles and Commercial Applications*; Plenum: New York, 1994. (f) Kirsch, P. *Modern Fluoroorganic Chemistry: Synthesis, Reactivity, Applications*; Wiley-VCH: Weinheim, 2004. (g) Thayer, A. M. *Chem. Eng. News* **2006**, *84*, 15−25. (h) Bégué, J.-P.; Bonnet-Delpon, D. *Bioorganic and Medicinal Chemistry of Fluorine*; Wiley-VCH: Weinheim, 2008. (i) Kirk, K. L. *Org. Process Res. Dev.* **2008**, *12*, 305−321. (j) Ojima, I. *Fluorine in Medicinal Chemistry and Chemical Biology*; Blackwell: Oxford, 2009. (k) Meanwell, N. A. *J. Med. Chem.* **2011**, *54*, 2529−2591. (l) Kirsch, P. *Modern Fluoroorganic Chemistry*; Wiley-VCH: Weinheim, 2013. (o) Wang, J.; Sánchez-Roselló, M.; Aceña, J. L.; del Pozo, C.; Sorochinsky, A. E.; Fustero, S.; Soloshonok, V. A.; Liu, H. *Chem. Rev.* **2014**, *114*, 2432−2506.

(2) For selected reviews, see: (a) Schlosser, M. *Angew. Chem., Int. Ed.* **2006**, *45*, 5432−5446. (b) Ma, J.-A.; Cahard, D. *Chem. Rev.* **2008**, *108*, PR1−PR43. (c) Smits, R.; Cadicamo, C. D.; Burger, K.; Koksch, B. *Chem. Soc. Rev.* **2008**, *37*, 1727−1739. (d) Nie, J.; Guo, H.-C.; Cahard, D.; Ma, J.-M. *Chem. Rev.* **2011**, *111*, 455−529. (e) Liang, T.; Neumann, C. N.; Ritter, T. *Angew. Chem., Int. Ed.* **2013**, *52*, 8214−8264. (f) Xu, X.-H.; Matsuzaki, K.; Shibata, N. *Chem. Rev.* **2015**, *115*, 731−764. (g) Yang, X.; Wu, T.; Phipps, R. J.; Toste, F. D. *Chem. Rev.* **2015**, *115*, 826−870. (r) Huang, Y.-Y.; Yang, X.; Chen, Z.; Verpoort, F.; Shibata, N. *Chem. - Eur. J.* **2015**, *21*, 8664−8684.

(3) (a) Prakash, G. K. S.; Yudin, A. K. *Chem. Rev.* **1997**, *97*, 757−786. (b) Shibata, N.; Mizuta, S.; Kawai, H. *Tetrahedron: Asymmetry* **2008**, *19*, 2633−2644. (c) Tomashenko, O. A.; Grushin, V. V. *Chem. Rev.* **2011**, *111*, 4475−4521. (d) Chu, L.; Qing, F.-L. *Acc. Chem. Res.* **2014**, *47*, 1513−1522. (e) Liu, X.; Xu, C.; Wang, M.; Liu, Q. *Chem. Rev.* **2015**, *115*, 683−730.

(4) (a) Nyffeler, P. T.; Durón, S. G.; Burkart, M. D.; Vincent, S. P.; Wong, C.-H. *Angew. Chem., Int. Ed.* **2005**, *44*, 192−212. (b) Shibata, N.; Ishimaru, T.; Nakamura, S.; Toru, T. *J. Fluorine Chem.* **2007**, *128*, 469−483. (c) Campbell, M. G.; Ritter, T. *Org. Process Res. Dev.* **2014**, *18*, 474−480. (d) Wu, J. *Tetrahedron Lett.* **2014**, *55*, 4289−4294. (e) Cresswell, A. J.; Davies, S. G.; Roberts, P. M.; Thomson, J. E. *Chem. Rev.* **2015**, *115*, 566−611. (f) Campbell, M. G.; Ritter, T. *Chem. Rev.* **2015**, *115*, 612−633.

DOI: 10.1021/acs.orglett.5b01778
Org. Lett. 2015, 17, 3802−3805

(5) (a) Furuya, T.; Kuttruff, C.; Ritter, T. *Curr. Opin. Drug Discovery Dev.* **2008**, *11*, 803−819. (b) Rewcastle, G. W.; Gamage, S. A.; Flanagan, J. U.; Frederick, R.; Denny, W. A.; Baguley, B. C.; Kestell, P.; Singh, R.; Kendall, J. D.; Marshall, E. S.; Lill, C. L.; Lee, W.-J.; Kolekar, S.; Buchanan, C. M.; Jamieson, S. M. F.; Sheperd, P. R. *J. Med. Chem.* **2011**, *54*, 7105−7126.
(6) Prakash, G. K. S.; Mandal, M.; Schweizer, S.; Petasis, N. A.; Olah, G. A. *J. Org. Chem.* **2002**, *67*, 3718−3723.
(7) Narjes, F.; Koehler, K. F.; Koch, U.; Gerlach, B.; Colarusso, S.; Steinkühler, C.; Brunetti, M.; Altamura, S.; De Francesco, R.; Matassa, V. G. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 701−704.
(8) (a) Erickson, J. A.; McLoughlin, J. I. *J. Org. Chem.* **1995**, *60*, 1626−1631. (b) Li, Y.; Hu, J. *Angew. Chem., Int. Ed.* **2005**, *44*, 5882−5886. (c) Prakash, G. K. S.; Weber, C.; Chacko, S.; Olah, G. A. *Org. Lett.* **2007**, *9*, 1863−1866.
(9) Ni, C.; Hu, J. *Synthesis* **2014**, *46*, 842−863.
(10) Hu, J.; Zhang, W.; Wang, F. *Chem. Commun.* **2009**, 7465−7478.
(11) (a) Konno, T.; Kitazume, T. *Chem. Commun.* **1996**, 2227−2228. (b) Burton, D. J.; Hartgraves, G. A. *J. Fluorine Chem.* **2007**, *128*, 1198−1215. (c) Zhang, W.; Wang, F.; Hu, J. *Org. Lett.* **2009**, *11*, 2109−2112. (d) Wang, F.; Huang, W.; Hu, J. *Chin. J. Chem.* **2011**, *29*, 2717−2721.
(12) (a) Mizuta, S.; Shibata, N.; Ogawa, S.; Fujimoto, H.; Nakamura, S.; Toru, T. *Chem. Commun.* **2006**, 2575−2577. (b) Liu, G.; Wang, X.; Lu, X.; Xu, X.-H.; Tokunaga, E.; Shibata, N. *ChemistryOpen* **2012**, *1*, 227−231. (c) Liu, G.; Wang, X.; Xu, X.-H.; Lu, X.; Tokunaga, E.; Tsuzuki, S.; Shibata, N. *Org. Lett.* **2013**, *15*, 1044−1047. (d) Wang, X.; Liu, G.; Xu, X.-H.; Shibata, N.; Tokunaga, E.; Shibata, N. *Angew. Chem., Int. Ed.* **2014**, *53*, 1827−1831. (e) Wang, X.; Tokunaga, E.; Shibata, N. *ScienceOpen Res.* **2014**, DOI: 10.14293/S2199-1006.1.SOR-CHEM.-AD1QVW.v2.
(13) (a) Zanardi, A.; Novikov, M. A.; Martin, E.; Benet-Buchholz, J.; Grushin, V. V. *J. Am. Chem. Soc.* **2011**, *133*, 20901−20913. (b) Novák, P.; Lishchynskyi, A.; Grushin, V. V. *Angew. Chem., Int. Ed.* **2012**, *51*, 7767−7770. (c) Novák, P.; Lishchynskyi, A.; Grushin, V. V. *J. Am. Chem. Soc.* **2012**, *134*, 16167−16170. (d) Lishchynskyi, A.; Novikov, M. A.; Martin, E.; Escudero-Adán, E. C.; Novák, P.; Grushin, V. V. *J. Org. Chem.* **2013**, *78*, 11126−11146. (e) Mazloomi, Z.; Bansode, A.; Benavente, P.; Lishchynskyi, A.; Urakawa, A.; Grushin, V. V. *Org. Process Res. Dev.* **2014**, *18*, 1020−1026. (f) Lishchynskyi, A.; Berthon, G.; Grushin, V. V. *Chem. Commun.* **2014**, *50*, 10237−10240. (g) Konovalov, A. I.; Lishchynskyi, A.; Grushin, V. V. *J. Am. Chem. Soc.* **2014**, *136*, 13410−13425. (j) Folléas, B.; Marek, I.; Normant, J.-F.; Saint-Jalmes, L. *Tetrahedron* **2000**, *56*, 275−283.
(14) (a) Prakash, G. K. S.; Jog, P. V.; Batamack, P. T. D.; Olah, G. A. *Science* **2012**, *338*, 1324−1327. (b) Prakash, G. K. S.; Wang, F.; Zhang, Z.; Haiges, R.; Rahm, M.; Christe, K. O.; Mathew, T.; Olah, G. A. *Angew. Chem., Int. Ed.* **2014**, *53*, 11575−11578.
(15) (a) Shibata, N.; Kagawa, T. JP2014091691, 2014. (b) Kawai, H.; Yuan, Z.; Tokunaga, E.; Shibata, N. *Org. Biomol. Chem.* **2013**, *11*, 1446−1450. (c) Zhang, Y.; Fujiu, M.; Serizawa, H.; Mikami, K. *J. Fluorine Chem.* **2013**, *156*, 367−371. (d) Okusu, S.; Hirano, K.; Tokunaga, E.; Shibata, N. *ChemistryOpen* **2015**, DOI: 10.1002/open.201500160.
(16) (a) Shono, T.; Ishifune, M.; Okada, T.; Kashimura, S. *J. Org. Chem.* **1991**, *56*, 2−4. (b) Folléas, B.; Marek, I.; Normant, J.-F.; Jalmes, L. S. *Tetrahedron Lett.* **1998**, *39*, 2973−2976. (c) Barhdadi, R.; Troupel, M.; Périchon, J. *Chem. Commun.* **1998**, 1251−1252. (d) Russell, J.; Roques, N. *Tetrahedron* **1998**, *54*, 13771−13782. (e) Large, S.; Roques, N.; Langlois, B. R. *J. Org. Chem.* **2000**, *65*, 8848−8856. (f) Billard, T.; Bruns, S.; Langlois, B. R. *Org. Lett.* **2000**, *2*, 2101−2103.
(17) (a) Tarrant, P. *The Preparation and Reactions of Fluoromethylenes in Chemistry Reviews*; Marcel Dekker, Inc.: New York, 1977. (b) Langlois, B. R.; Billard, T. *Synthesis* **2003**, 185−194.
(18) (a) Thomoson, C. S.; Dolbier, W. R., Jr. *J. Org. Chem.* **2013**, *78*, 8904−8908. (b) Thomoson, C. S.; Wang, L.; Dolbier, W. R., Jr. *J. Fluorine Chem.* **2014**, *168*, 34−39.
(19) Difluoromethylation of lithium enolates by HCF_3 is reported. See: Iida, T.; Hashimoto, R.; Aikawa, K.; Ito, S.; Mikami, K. *Angew. Chem., Int. Ed.* **2012**, *51*, 9535−9538.
(20) (a) Zhang, L.; Chen, X.; Xue, P.; Sun, H. H. Y.; Williams, I. D.; Sharpless, K. B.; Fokin, V. V.; Jia, G. *J. Am. Chem. Soc.* **2005**, *127*, 15998−15999. (b) Boren, B. C.; Narayan, S.; Rasmussen, L. K.; Zhang, L.; Zhao, H.; Lin, Z.; Jia, G.; Fokin, V. V. *J. Am. Chem. Soc.* **2008**, *130*, 8923−8930.

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