Synthesis and Reactions of the First Fluorine-Containing 1,3-Bis(trimethylsilyloxy)-1,3-butadienes

Muhammad Adeel,[a] Stefanie Reim,[a] Verena Wolf,[a] Mirza A. Yawer,[a] Ibrar Hussain,[a] Alexander Villinger,[a] Peter Langer*[a,b]

[a] Institut für Chemie, Universität Rostock, Albert Einstein Str. 3a, 18059 Rostock, Germany

[b] Leibniz-Institut für Katalyse an der Universität Rostock e.V., Albert Einstein Str. 29a, 18059 Rostock, Germany
E-mail: peter.langer@uni-rostock.de

Received 6 May 2008

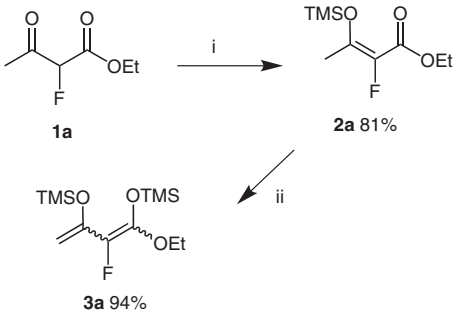
Abstract: The first fluorine-containing 1,3-bis(silyl enol ethers), 2-fluoro-1,3-bis(trimethylsilyloxy)-1,3-butadienes, have been prepared. Their reaction with electrophiles allows a convenient synthesis of various open-chain and cyclic organofluorine compounds which are not readily available by other methods.

Key words: arenes, organofluorine compounds, regioselectivity, silyl enol ethers

Organofluorine compounds play an important role in drug discovery.[1] They exhibit unique stereoelectronic properties: on the one hand the fluorine atom is fairly small, on the other hand its high electronegativity often results in a great improvement of drug-receptor interactions. The carbon–fluorine bond is chemically and biologically stable which avoids undesired metabolic transformations. In addition, the high lipophilicity of organofluorine compounds improves their in vivo transport. They also show a very good solubility in fluorophilic solvents. Therefore, organofluorine compounds are used as ligands[2] for catalytic reactions in fluorous biphasic systems and supercritical carbon dioxide.[3] The unique electronic properties of fluorinated arenes are widely used for applications in organocatalysis.[4] Last but not least, fluorinated arenes and heteroarenes are versatile building blocks in transition-metal-catalyzed cross-coupling reactions.[5]

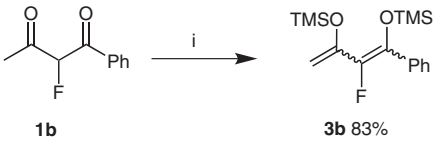
The direct fluorination of arenes, heteroarenes and several open-chained molecules often suffers from several drawbacks, such as low chemo- and regioselectivity or multiple fluorination. An alternative strategy for the regioselective synthesis of organofluorine compounds relies on the use of appropriate fluorine-containing building blocks in condensation and cyclization reactions. For example, aryl fluorides have been prepared by [4+2]-cycloaddition reactions of 2-fluoro-1-methoxy-3-trimethylsilyloxybuta-1,3-diene, 2-fluoro-3-methoxybuta-1,3-diene and related dienes with alkenes or alkynes.[6] Portella et al. reported the synthesis of fluorophenols by annulation reactions of 2,2-difluoro-1,5-diketones which were prepared from trifluoromethyltrimethylsilane, acylsilanes and enones.[7]

SYNLETT 2008, No. 17, pp 2629–2632
Advanced online publication: 01.10.2008
DOI: 10.1055/s-0028-1083440; Art ID: D14608ST



1a **2a** 81% **3a** 94%

Scheme 1 Synthesis of diene **3a**. *Reagents and conditions*: (i) TMSCl, Et_3N, benzene, 20 °C, 48 h; (ii) 1. LDA, THF, –78 °C, 1 h; 2. TMSCl, –78 °C → 20 °C, 14 h.

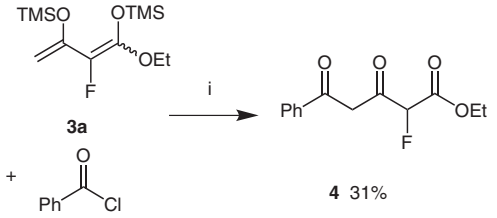


1b **3b** 83%

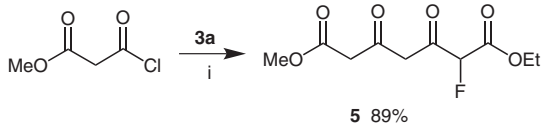
Scheme 2 Synthesis of dienes **3b**. *Reagents and conditions*: (i) TMSOTf, Et_3N, Et_2O, 0 °C → 20 °C, 4 h.

1,3-Bis(trimethylsilyloxy)-1,3-butadienes (e.g., Chan's diene)[8,9] represent important synthetic building blocks which have been used in formal [3+2], [3+3], [4+2] and [4+3] cyclizations and other transformations.[10] Herein, we report the synthesis and reactions of 2-fluoro-1,3-bis(silyloxy)-1,3-butadienes which represent, to the best of our knowledge, the first fluorine-containing 1,3-bis(silyl enol ethers).[11] Their reactions with electrophiles provide a convenient and regioselective approach to a variety of organofluorine compounds which are not readily available by other methods.

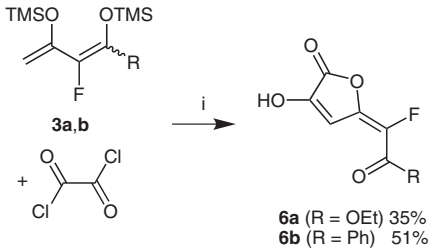
The silylation of commercially available ethyl 2-fluoroacetoacetate (**1a**) afforded silyl enol ether **2a**. The latter was transformed, by deprotonation (LDA) at –78 °C and subsequent addition of trimethylchlorosilane, into novel 1-ethoxy-2-fluoro-1,3-bis(trimethylsilyloxy)-1,3-butadiene (**3a**) (Scheme 1). The fluorine substituent proved to be compatible with the reaction conditions. 2-Fluoro-1-phenyl-1,3-bis(silyloxy)-1,3-butadiene (**3b**) was prepared by reaction of an Et_2O solution of **1b** with two equivalents of trimethylsilyl-trifluoromethanesulfonate (TMSOTf) and triethylamine (Scheme 2). Dienes **3a** and **3b** can be stored at –20 °C under an inert atmosphere for several weeks.



Scheme 3 Synthesis of **4**. *Reagents and conditions*: (i) CH_2Cl_2, –78 °C → 20 °C; (ii) $NaHCO_3$, H_2O.



Scheme 4 Synthesis of **5**. *Reagents and conditions*: (i) TMSOTf (0.2 equiv), CH_2Cl_2, –78 °C → 20 °C; (ii) $NaHCO_3$, H_2O.



Scheme 5 Synthesis of butenolides **6a**,**b**. *Reagents and conditions*: (i) TMSOTf (0.3 equiv), CH_2Cl_2, –78 °C → 20 °C, 14 h.

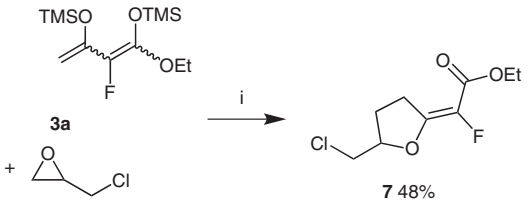
The reaction of **3a** with benzoyl chloride, following our recently reported protocol,[12] afforded ethyl 2-fluoro-5-phenyl-3,5-dioxopentanoate (**4**; Scheme 3). The best yields were obtained when the reactions were carried out in the absence of Lewis acid. It is noteworthy that products such as **4** are not available by direct fluorination of 3,5-dioxoalkanoates, due to the formation of a mixture of regioisomers.

The TMSOTf-catalyzed condensation of **3a** with methyl malonyl chloride afforded dimethyl 2-fluoro-3,5-dioxopimelate (**5**; Scheme 4). The synthesis of **5** is again not possible by fluorination of dimethyl 3,5-dioxopimelate, due to the formation of regioisomers.

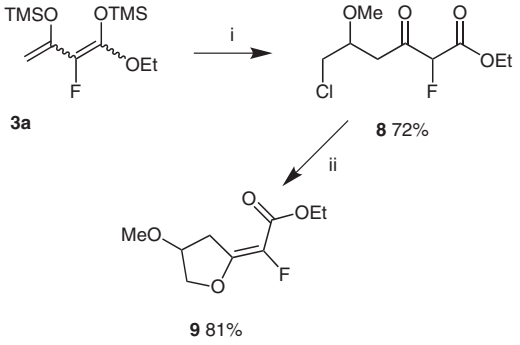
The TMSOTf-catalyzed cyclization[13] of 1,3-bis(silyl enol ethers) **3a**,**b** with oxalyl chloride afforded the novel fluorinated γ-alkylidenebutenolides **6a**,**b** (Scheme 5). The exocyclic double bond was formed with excellent *Z*-diastereoselectivity.

The $TiCl_4$-mediated cyclization of **3a** with epichlorohydrin, following our recently reported protocol,[14] afforded the halogenated 2-alkylidenetetrahydrofuran **7** (Scheme 6). The exocyclic double bond was again formed with excellent *Z* diastereoselectivity.

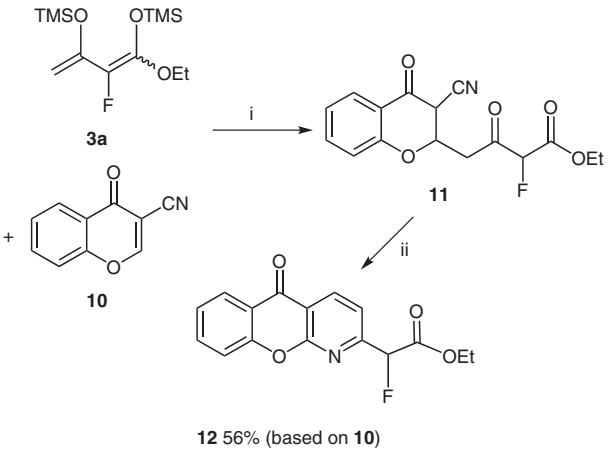
The TMSOTf-catalyzed condensation of **3a** with 1-chloro-2,2-dimethoxyethane gave the 2-fluoro-6-chloro-5-methoxy-3-oxohexanoate **8** (Scheme 7). The DBU-mediated cyclization[15] of **8** afforded the *Z*-configured 4-methoxy-2-alkylidenetetrahydrofuran **9**.[16]



Scheme 6 Synthesis of 2-alkylidenetetrahydrofuran **7**. *Reagents and conditions*: (i) $TiCl_4$ (2.0 equiv), CH_2Cl_2, –78 °C → 20 °C.

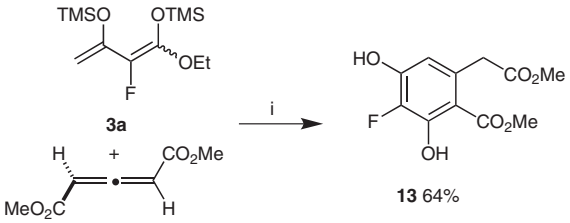


Scheme 7 Synthesis of **9**. *Reagents and conditions*: (i) TMSOTf (0.5 equiv), CH_2Cl_2, –78 °C → 20 °C; (ii) DBU (2.0 equiv), THF, 20 °C.



Scheme 8 Synthesis of 1-azaxanthone **12**. *Reagents and conditions*: (i) 1. 3-cyanochromone, TMSOTf, 1 h, 20 °C; 2. **3a**, CH_2Cl_2, 0 °C → 20 °C, 12 h; 3. HCl (10%); (ii) 1. Et_3N, EtOH, 20 °C, 12 h; 2. HCl (1 M).

The TMSOTf-mediated reaction of **3a** with 3-cyanochromone (**10**) gave condensation product **11**. The latter was formed by regioselective attack of the terminal carbon atom of the diene onto C-2 of the cyanochromone and subsequent hydrolysis upon aqueous workup. Treatment of an ethanol solution of crude **11** with triethylamine afforded the novel fluorinated 1-azaxanthone **12** (Scheme 8). This type of product is again not available by direct fluorination. The transformation of **11** into **12** can be explained by a domino 'retro-Michael/nitrile-addition/heterocyclization' reaction.[17]



Scheme 9 Synthesis of homophthalate **13**. *Reagents and conditions*: (i) 1. neat, 20–80 °C; 2. $NEt_3(HF)_3$, EtOH.

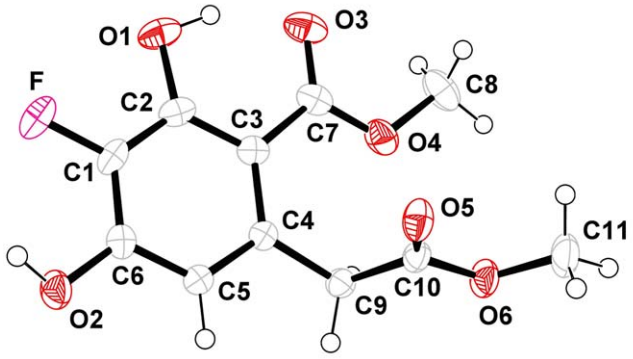
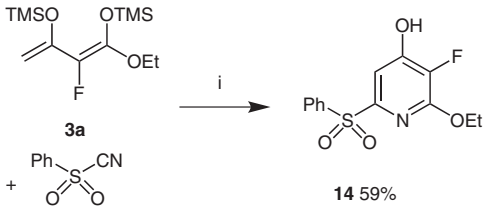


Figure 1 Crystal structure of **13**



Scheme 10 Synthesis of pyridine **14**. *Reagents and conditions*: (i) 1. neat, –78 °C, then 45 °C, 48 h; 2. NH_4Cl, H_2O.

The [4+2]-cycloaddition[18] of 1,3-bis(trimethylsiloxy)-1,3-butadiene **3a** with dimethyl allene-1,3-dicarboxylate afforded the novel fluorinated 2,4-dihydroxyhomophthalate **13** in good yield and with very good regioselectivity (Scheme 9). Product **13** is not available by direct fluorination of the corresponding homophthalate because of the formation of a regioisomeric mixture. The structure of **13** was independently confirmed by X-ray crystal structure analysis (Figure 1).[19]

The hetero-Diels–Alder reaction[20] of 1,3-bis(silyloxy)-1,3-butadiene **3a** with phenylsulfonylcyanide afforded the fluorinated 4-hydroxy-2-(arylsulfonyl)pyridine **14** (Scheme 10).[21] This type of product is again not available by direct fluorination.

In conclusion, we have reported a building block strategy for the synthesis of novel organofluorine compounds based on reactions of 2-fluoro-1,3-bis(trimethylsilyloxy)-1,3-butadienes, the first fluorinated 1,3-bis(silyl enol ethers). The products are not available by direct fluorination reactions.

Acknowledgment

Financial support by the State of Pakistan (HEC scholarship for I.H. and M.A.Y.) and by the State of Mecklenburg-Vorpommern is gratefully acknowledged.

References and Notes

(1) (a) *Fluorine in Bioorganic Chemistry*; Filler, R.; Kobayasi, Y.; Yagupolskii, L. M., Eds.; Elsevier: Amsterdam, **1993**. (b) Filler, R. *Fluorine-Containing Drugs in Organofluorine Chemicals and their Industrial Application*; Pergamon: New York, **1979**, Chap. 6. (c) Hudlicky, M. *Chemistry of Organic Compounds*; Ellis Horwood: Chichester, **1992**. (d) Kirsch, P. *Modern Fluoroorganic Chemistry*; Wiley-VCH: Weinheim, **2004**. (e) See also: Chambers, R. D. *Fluorine in Organic Chemistry*; Blackwell: Oxford, **2004**. (f) Ryckmanns, T.; Balancon, L.; Berton, O.; Genicot, C.; Lamberty, Y.; Lallemand, B.; Passau, P.; Pirlot, N.; Quéré, L.; Talaga, P. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 261. (g) Malamas, M. S.; Sredy, J.; Moxham, C.; Katz, A.; Xu, W.; McDevitt, R.; Adebayo, F. O.; Sawicki, D. R.; Seestaller, L.; Sullivan, D.; Taylor, J. R. *J. Med. Chem.* **2000**, *43*, 1293. (h) Ciha, A. J.; Ruminski, P. G. *J. Agric. Food Chem.* **1991**, *39*, 2072. (i) Albrecht, H. A.; Beskid, G.; Georgopapadakou, N. H.; Keith, D. D.; Konzelmann, F. M.; Pruess, D. L.; Rossman, P. L.; Wei, C. C.; Christenson, J. G. *J. Med. Chem.* **1991**, *34*, 2857. (j) Albrecht, H. A.; Beskid, G.; Christenson, J. G.; Deitcher, K. H.; Georgopapadakou, N. H.; Keith, D. D.; Konzelmann, F. M.; Pruess, D. L.; Wie, C. C. *J. Med. Chem.* **1994**, *37*, 400. (k) Song, C. W.; Lee, K. Y.; Kim, C. D.; Chang, T.-M.; Chey, W. Y. *J. Pharmacol. Exp. Ther.* **1997**, *281*, 1312. (l) De Voss, J. J.; Sui, Z.; DeCamp, D. L.; Salto, R.; Babe, L. M.; Craik, C. S.; Ortiz de Montellano, P. R. *J. Med. Chem.* **1994**, *37*, 665. (m) Anjaiah, S.; Chandrasekhar, S.; Gree, R. *Adv. Synth. Catal.* **2004**, *346*, 1329. (n) Iorio, M. A.; Paszkowska, R. T.; Frigeni, V. *J. Med. Chem.* **1987**, *30*, 1906. (o) Popp, J. L.; Musza, L. L.; Barrow, C. J.; Rudewicz, P. J.; Houck, D. R. *J. Antibiot.* **1994**, *47*, 411. (p) Chen, T. S.; Petuch, B.; MacConnell, J.; White, R.; Dezeny, G. *J. Antibiot.* **1994**, *47*, 1290. (q) Lam, K. S.; Schroeder, D. R.; Veitch, J. M. J. M.; Colson, K. L.; Matson, J. A.; Rose, W. C.; Doyle, T. W.; Forenza, S. *J. Antibiot.* **2001**, *54*, 1.

(2) (a) Schmidbaur, H.; Kumberger, O. *Chem. Ber.* **1993**, *126*, 3. (b) Dinger, M. B.; Henderson, W. *J. Organomet. Chem.* **1998**, *560*, 233. (c) Liedtke, J.; Loss, S.; Widauer, C.; Grützmacher, H. *Tetrahedron* **2000**, *56*, 143.

(3) See, for example: (a) Schneider, S.; Tzschucke, C. C.; Bannwarth, W. *Multiphase Homogeneous Catalysis*; Cornils, B.; Herrmann, W. A.; Horvath, I. T.; Leitner, W.; Mecking, S.; Olivier-Booubigou, H.; Vogt, D., Eds.; Wiley-VCH: Weinheim, **2005**, Chap. 4, 346. (b) Clarke, D.; Ali, M. A.; Clifford, A. A.; Parratt, A.; Rose, P.; Schwinn, D.; Bannwarth, W.; Rayner, C. M. *Curr. Top. Med. Chem.* **2004**, *7*, 729.

(4) Reviews: (a) Wittkopp, A.; Schreiner, P. R. In *The Chemistry of Dienes and Polyenes*, Vol. 2; Rappoport, Z., Ed.; John Wiley & Sons: New York, **2000**. (b) See also: Schreiner, P. R. *Chem. Soc. Rev.* **2003**, *32*, 289. (c) Wittkopp, A.; Schreiner, P. R. *Chem. Eur. J.* **2003**, *9*, 407. (d) Kleiner, C. M.; Schreiner, P. R. *Chem. Commun.* **2006**, 4315. (e) Kotke, M.; Schreiner, P. R. *Synthesis* **2007**, 779. (f) Review: Tsogoeva, S. B. *Eur. J. Org. Chem.* **2007**, 1701.

(5) *Metal-Catalyzed Cross-Coupling Reactions*; de Meijere, A.; Diederich, F., Eds.; Wiley-VCH: Weinheim, **2004**.

(6) (a) Shi, G.-Q.; Cottens, S.; Shiba, S. A.; Schlosser, M. A. *Tetrahedron* **1992**, *48*, 10569. (b) Shi, G.-Q.; Schlosser, M. *Tetrahedron* **1993**, *49*, 1445. (c) Patrick, T. B.; Rogers, J.; Gorrell, K. *Org. Lett.* **2002**, *4*, 3155.
(7) Lefebvre, O.; Brigaud, T.; Portella, C. *Tetrahedron* **1998**, *54*, 5939.
(8) For a review of 1,3-bis(silyl enol ethers), see: Langer, P. *Synthesis* **2002**, 441.
(9) Chan, T.-H.; Brownbridge, P. *J. Chem. Soc., Chem. Commun.* **1979**, 578.
(10) For a review of [3+3]-cyclizations, see: Feist, H.; Langer, P. *Synthesis* **2007**, 327.
(11) For [3+3] cyclizations of 1,3-bis(silyloxy)-1,3-dienes with 2-fluoro-3-silyloxy-2-en-1-ones, see: Hussain, I.; Yawer, M. A.; Lau, M.; Pundt, T.; Fischer, C.; Reinke, H.; Görls, H.; Langer, P. *Eur. J. Org. Chem.* **2008**, 503.
(12) Rahn, T.; Nguyen, V. T. H.; Dang, T. H. T.; Ahmed, Z.; Lalk, M.; Fischer, C.; Spannenberg, A.; Langer, P. *J. Org. Chem.* **2007**, *72*, 1957.
(13) Langer, P.; Stoll, M.; Schneider, S. *Chem. Eur. J.* **2000**, *6*, 3204.
(14) Langer, P.; Armbrust, H.; Eckardt, T.; Magull, J. *Chem. Eur. J.* **2002**, *8*, 1443.
(15) (a) Bellur, E.; Görls, H.; Langer, P. *Eur. J. Org. Chem.* **2005**, 2074. (b) See also: Langer, P.; Krummel, T. *Chem. Eur. J.* **2001**, *7*, 1720.
(16) The synthesis of a difluoro(furan-2-yl)acetate by a different approach has been recently reported: (a) Eto, H.; Kanwko, Y.; Sakamoto, T. *Chem. Pharm. Bull.* **2000**, *48*, 982. (b) Murakami, S.; Kim, S.; Ishii, H.; Fuchigami, T. *Synlett* **2004**, 815.
(17) (a) Langer, P.; Appel, B. *Tetrahedron Lett.* **2003**, *44*, 5133. (b) Rashid, M. A.; Rasool, N.; Appel, B.; Adeel, M.; Karapetyan, V.; Mkrtchyan, S.; Reinke, H.; Fischer, C.; Langer, P. *Tetrahedron* **2008**, *64*, 5416.
(18) Langer, P.; Kracke, B. *Tetrahedron Lett.* **2000**, *41*, 4545.
(19) CCDC 684861 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.
(20) Emmrich, T.; Reinke, H.; Langer, P. *Synthesis* **2006**, 2551.
(21) **Synthesis of 2-Ethoxy-3-fluoro-6-(phenylsulfonyl)pyridin-4-ol (14)**: To phenylsulfonyl cyanide was dropwise added **3a** at –78 °C. The neat reaction mixture was subsequently stirred at 45 °C for 48 h. To the mixture was added a sat. aq solution of NH_4Cl (20 mL) and the organic and the aqueous layer were separated. The latter was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were dried (Na_2SO_4), filtered and the filtrate was concentrated in vacuo. The residue was purified by chromatography (silica gel, heptanes–EtOAc) to give **14**. Starting with phenylsulfonyl cyanide (0.167 g, 1.0 mmol) and **3a** (0.589 g, 2.0 mmol), **14** was isolated as a red solid (0.179 g, 59%). ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.22 (t, ^3J = 7.1 Hz, 3 H, OCH_2CH_3), 4.26 (q, ^3J = 7.0 Hz, 2 H, OCH_2CH_3), 7.19 (br s, 1 H, OH_{heter}), 7.43 (m, 1 H, CH_{heter}), 7.46–7.50 (m, 2 H, CH_{Ph}), 7.53–7.56 (m, 1 H, CH_{Ph}), 7.95 (dd, ^3J = 8.4 Hz, ^4J = 1.5 Hz, 2 H, CH_{Ph}). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.1 (OCH_2CH_3), 63.6 (OCH_2CH_3), 107.8 (CH_{heter}), 128.9 (2 × CH_{Ph}), 129.0 (2 × CH_{Ph}), 133.8 (CH_{Ph}), 136.8 (d, ^1J = 252.4 Hz, CF_{heter}), 138.4 (C_{Ph}), 149.4 (d, ^4J = 6.7 Hz, C_{heter}), 151.3 (d, ^2J = 10.2 Hz, COH_{heter}), 153.8 (d, ^2J = 9.9 Hz, C_{heter}). ^{19}F NMR (235 MHz, $CDCl_3$): δ = –162.05 (CF_{heter}). IR (neat): 3354 (w), 1576 (m), 1440 (m), 1353 (m), 1317 (m), 1149 (s), 1076 (m), 1022 (m), 740 (s), 724 (s), 682 (s), 585 (s) cm^{-1}. HRMS (ESI, positive): *m/z* $[M + H]^+$ calcd for $C_{13}H_{13}FNO_4S$: 298.05438; found: 298.05413. HRMS (ESI, positive): *m/z* $[M + Na]^+$ calcd for $C_{13}H_{12}FNO_4SNa$: 320.03652; found: 320.03633. All products gave satisfactory spectroscopic data and correct elemental analyses and/or high resolution mass data.