JOC The Journal of Organic Chemistry

Article

pubs.acs.org/joc

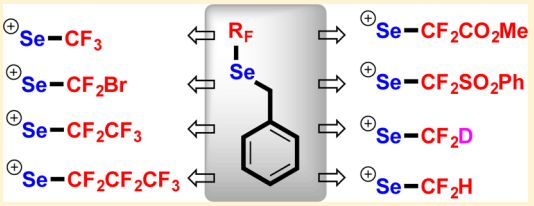
Benzyltrifluoromethyl (or Fluoroalkyl) Selenide: Reagent for Electrophilic Trifluoromethyl (or Fluoroalkyl) Selenolation

Quentin Glenadel,[†] Ermal Ismalaj,[†] and Thierry Billard*

Institute of Chemistry and Biochemistry (ICBMS−UMR CNRS 5246), Université Lyon 1, CNRS, 43 Bd du 11 novembre 1918, F-69622 Villeurbanne, France

Supporting Information

ABSTRACT: Trifluoromethylseleno substituent (CF_3Se) is an emerging group, but its direct introduction onto organic molecules is still quite limited and mainly restricted to nucleophilic methods. Herein, we describe a new approach to easily and safely perform electrophilic trifluoromethylselenolation starting from a simple and easily accessible reagent, namely, benzyltrifluoromethyl selenide. This strategy can be generalized to various fluoroalkylselanyl groups, even functionalized ones.

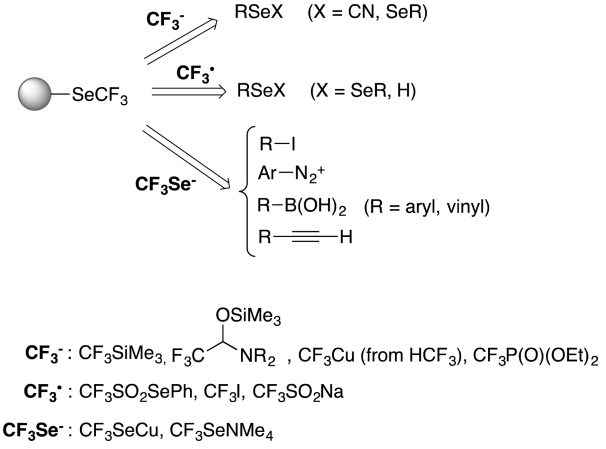


INTRODUCTION

In recent decades, fluorinated compounds have received extraordinary growing interest mainly due to the very specific properties from fluorine addition inside their structures.[1,2] Such specificities could find a large panel of various applications, from materials to life sciences.[3−11] More recently, it has been well-demonstrated that new properties such as high electron-withdrawing characteristics and high lipophilicity can be expected from the association of fluorinated moieties with a heteroatom. This paved the way for the development of new molecules, in particular, as agrochemicals and pharmaceuticals. This associative concept has been particularly illustrated with the growing interest in the trifluoromethylsulfanyl group (CF_3S).[12,13] In the same chalcogen family, the selenium atom possesses properties similar to those of sulfur. Selenium belongs to the essential oligo-elements for living species,[14,15] and some endogenous compounds are selenylated as, for instance, selenocysteine and selenoproteins.[16−21] Furthermore, selenium has demonstrated beneficial roles in human health.[22−26] Organoselenium compounds can also be used for interesting applications in material sciences and nanotechnology.[27] This has focused some interests to the synthesis of trifluoromethylselenolated molecules. Indeed, from an electronic point of view, the CF_3Se group presents properties similar to those of CF_3S (Hammett constants $\sigma_p = 0.45$, $\sigma_m = 0.44$; Swain−Lupton constants $F = 0.43$, $R = 0.02$)[28] but with a lower resonance effect, which could offer some modulations in molecular properties.

Because such molecules are relatively unknown, only a few methods have been described in the literature to obtain CF_3Se molecules. These strategies can be divided into two parts (Scheme 1). The indirect way, consisting in the trifluoromethylation of selenylated substrates. The most useful procedure is based on the nucleophilic trifluoromethylation of diselenides[29] or, more interestingly, selenocyanates.[30] The main variations of this technique were the nucleophilic trifluoromethylating reagents.[31−34] Even if this strategy was recently

Scheme 1. Previous Syntheses of Trifluoromethyl Selenides



improved in aromatic series with a one-pot process,[35] the required preformation of selenylated substrates can constitute a major drawback. It should be noticed that some radical trifluoromethylations of diselenides or selenols have also been reported but are generally more limited.[36−41] From a retrosynthetic point of view, the direct way provides the most elegant approach because the introduction of the CF_3Se group can be envisaged without preliminary introduction of a selenium atom. Thus, recently, trifluoromethylselenolate anion (CF_3Se^-) chemistry has been revisited and has furnished good results in some nucleophilic substitutions or coupling reactions with alkyl,[42] vinyl,[43−45] and aryl[46−50] halogenides, boronic acids,[51] terminal alkynes,[51,52] or aromatic diazonium salts.[53] The reagents used in these reactions are mainly CF_3SeCu[42−46,48,52] or CF_3SeNMe_4,[49,51,53] which have been generally prepared from CF_3SiMe_3 and selenium metal. It is noteworthy that a one-pot process has been developed by an in

Received: June 3, 2016
Published: August 29, 2016

DOI: 10.1021/acs.joc.6b01344
J. Org. Chem. 2016, 81, 8268−8275

situ preforming CF_3Se^- species.[47] However, these methods require the use of a stoichiometric amount of selenium metal and sometimes a stoichiometric amount of copper when CF_3SeCu is used. Furthermore, in aromatic series, prefunctionalized substrates (halogenides, boronic acids, diazoniums, etc.) are necessary.

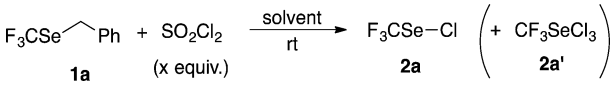
One of the best ways to functionalize aromatic compounds is electrophilic aromatic substitution, which is formally a hydrogen substitution. To extend such a strategy to trifluoromethylselenolation, an electrophilic reagent is then required. Some years ago, CF_3SeCl was described with such purpose. Nevertheless, its synthesis was performed in harsh conditions, with toxic reagents and with poor yields.[54,55] Furthermore, by analogy with CF_3SCl,[56] we can suppose that this highly volatile reagent must be toxic, explaining its very few applications.[57−61] In 2002, Magnier et al.[62] published a very elegant and mild procedure to prepare CF_3SeCl, which was more efficient than the previous methods. This approach is based on the oxidative chlorination of benzyltrifluoromethyl selenide.

RESULTS AND DISCUSSION

This last compound is very easy to synthesize starting from CF_3SiMe_3 and benzylselenocyanate,[30] which is obtained from potassium selenocyanate, an inexpensive source of selenium. Consequently, we decided to develop a procedure based on this starting material, avoiding the isolation of CF_3SeCl, to perform electrophilic aromatic substitutions.

In Magnier's procedure, CF_3SeCl is formed by reaction of SO_2Cl_2 with benzyltrifluoromethyl selenide (**1a**) in solvent-free conditions. To extrapolate this strategy to a one-pot procedure, without isolation of CF_3SeCl (**2a**), optimization of this reaction with a solvent was first studied (Table 1). If the formation of **2a** is nearly instantaneous in THF (entries 1 and 2), the kinetics of the reaction in CH_2Cl_2 is rather low (entries 7−10). This kinetic difference can be rationalized by the promoted SO_2Cl_2 dissociation with basic solvents[63] (DN_{THF} = 20, $DN_{CH_2Cl_2}$ = 1).[64,65] The use of 2 equiv of SO_2Cl_2 can accelerate the formation of CF_3SeCl (**2a**) in CH_2Cl_2 (entries 11−13). In THF, the formation of CF_3SeCl_3 (**2a′**),[66] arising from chlorination of **2a**, is observed with an excess of SO_2Cl_2 (entries 3−6). This side reaction seems to be an equilibrium because, after 1 h, a steady-state appears to be achieved (entries 4−6). Finally, the best solvent to form CF_3SeCl efficiently and rapidly is THF, with only 1 equiv of sulfuryl chloride.

Table 1. Formation of CF_3SeCl

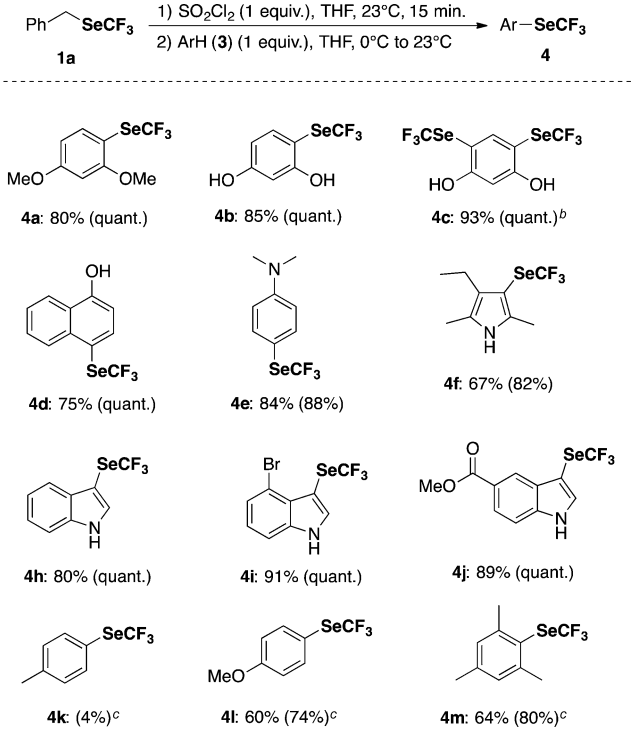


entry	SO_2Cl_2 (x)	solvent	time	**2a** (%)[a]	**2a′** (%)[a]
1	1	THF	4 min	95	
2	1	THF	15 min	95	
3	2	THF	4 min	82	10
4	2	THF	15 min	58	40
5	2	THF	1.5 h	46	52
6	2	THF	3 h	59	41
7	1	CH_2Cl_2	15 min	19	
8	1	CH_2Cl_2	1.5 h	62	
9	1	CH_2Cl_2	3 h	67	
10	1	CH_2Cl_2	4 h	67	
11	2	CH_2Cl_2	15 min	34	
12	2	CH_2Cl_2	1.5 h	83	
13	2	CH_2Cl_2	3 h	88	

[a]Yields as determined by ^{19}F NMR spectroscopy using $PhOCF_3$ as an internal standard.

Trifluoromethylselenolation of aromatic compounds with the preformed CF_3SeCl (**2a**) was then investigated. To our delight, by simply adding aromatic substrates **3**, the SE_{Ar} reaction was observed (Scheme 2). With electron-rich substrates, the reaction gave good to excellent yields, even in heteroaromatic series. By doubling the amount of reagents, bis-trifluoromethylselenolation could also be observed (**4c**). With less electron-rich aromatic compounds, the reaction failed in these conditions. To try to activate CF_3SeCl, to obtain a better electrophile, some Lewis acid was screened as catalyst. With $BF_3{\cdot}Et_2O$ in 1,2-dichloroethane at 80 °C, good yields with anisole (**4l**) and mesitylene (**4m**) were obtained. Nevertheless, only low yield was observed with toluene (**4k**). A stronger Lewis acid, such as $AlCl_3$ or $TiCl_4$, failed to favor this reaction.

Scheme 2. Trifluoromethylselenolation of Aromatic Compounds[a]

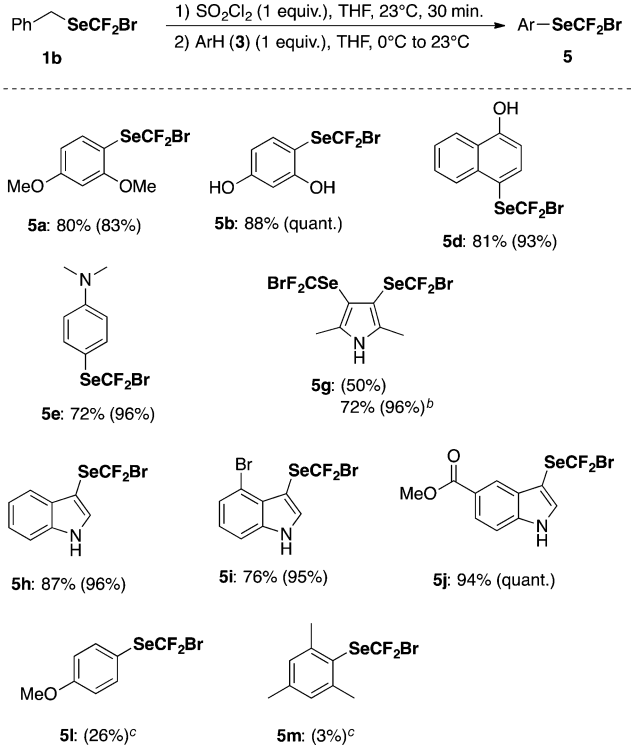


[a]Yields shown are of isolated products; values in parentheses are yields as determined by ^{19}F NMR spectroscopy using $PhOCF_3$ as an internal standard. [b]**1a** (2.2 equiv), SO_2Cl_2 (2.2 equiv). [c]**1a** (1.2 equiv), SO_2Cl_2 (1.2 equiv), $BF_3{\cdot}Et_2O$ (0.3 equiv), $ClCH_2CH_2Cl$, 80 °C.

Because it could be interesting to modulate properties of targeted molecules, depending on the field of applications, modulation of the fluorinated part could be of interest. Consequently, this efficient method has been extended to other fluoroalkylselenolations. Thus, bromodifluoromethaneselenylated molecules were obtained starting from benzylbromodifluoromethyl selenide **1b**, obtained from bromodifluoromethylsilane (Scheme 3). Similar to **1a**, good to excellent results were achieved. The only difference between both procedures is the preforming time of reactive species $BrCF_2SeCl$ (**2b**), which

DOI: 10.1021/acs.joc.6b01344
J. Org. Chem. 2016, 81, 8268−8275

Scheme 3. Bromodifluoromethylselenolation of Aromatic Compounds[a]



[a]Yields shown are of isolated products; values in parentheses are yields as determined by ^{19}F NMR spectroscopy using $PhOCF_3$ as an internal standard. [b]**1b** (2.2 equiv), SO_2Cl_2 (2.2 equiv). [c]**1b** (1.2 equiv), SO_2Cl_2 (1.2 equiv), $BF_3{\cdot}Et_2O$ (0.3 equiv), $ClCH_2CH_2Cl$, 80 °C.

requires slightly more time. With highly reactive pyrrole **3g**, only bis-substituted product **5g** was obtained. Less electron-rich aromatic compounds also required $BF_3{\cdot}Et_2O$ catalysis with heating. Nevertheless, lower yields were observed possibly due to a partial decomposition of the $SeCF_2Br$ by interaction with the Lewis acid.

To validate the generality of this strategy, various other benzylfluoroalkyl selenides were synthesized and engaged in fluoroalkylselenolation reactions (Figure 1). This strategy appears very versatile and furnishes good to excellent yields of fluoroalkaneselenylated aromatic compounds. The only adaptation of the procedure was the preforming time of reacting species **2**, depending on the reagent **1**. This preformation of **2** is summarized in Table 2.

Therefore, difluoromethylated (**10**) and higher fluorinated homologues (**6** and **7**) have been obtained. Some functionalized groups were also introduced (**8** and **9**). To the best of our knowledge, these last substituents have never been described to this day.

Inspired by the "chemical chameleon" characteristic of the $PhSO_2$ group,[67] we have recently demonstrated the easy access to deuterated molecules,[68] which have received some recent interest in medicinal chemistry.[69−71] Consequently, an example of synthesis of a molecule bearing the substituent DCF_2Se was performed (Scheme 4). Thus, difluorodeuteriomethylselanyl indole [**D**]**10h** was obtained with satisfactory yield from **9h**. Except during a mechanistic study,[72] this DCF_2Se group was never described, and molecules bearing it were never isolated. Such a strategy opens access to a new substituent for screening in drug design.

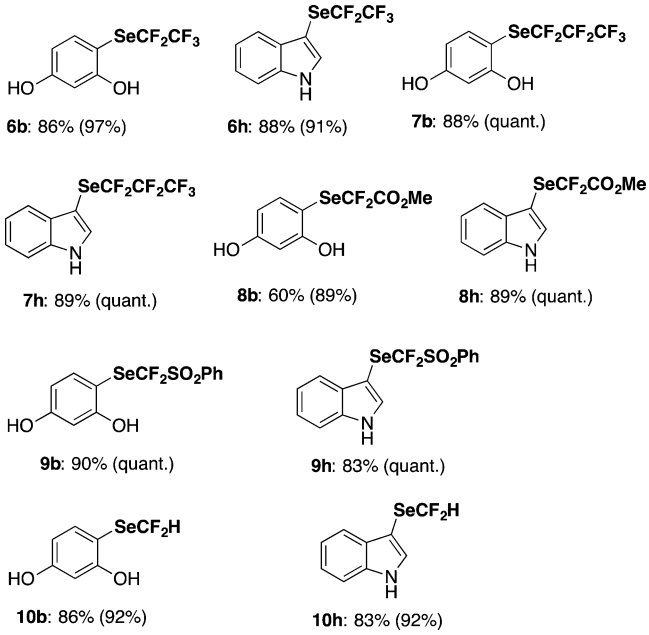
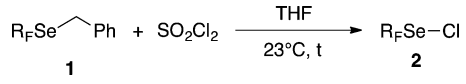


Figure 1. Fluoroalkylselenolation of aromatic compounds. Yields shown are of isolated products; values in parentheses are yields as determined by ^{19}F NMR spectroscopy using $PhOCF_3$ as an internal standard.

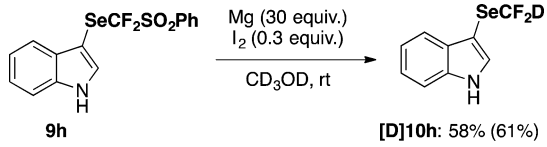
Table 2. Preformation of Reagents 2



entry	R_FSeBn	time (min)
1	$R_F = CF_3$	15
2	$R_F = CF_2CF_3$	15
3	$R_F = CF_2CF_2CF_3$	15
4	$R_F = CF_2Br$	30
5	$R_F = CF_2COOMe$	30
6	$R_F = CF_2SO_2Ph$	30
7[a]	$R_F = CF_2H$	45

[a]Reaction performed at 0 °C.

Scheme 4. Synthesis of Difluorodeuteriomethylselanyl Indole ([D]10h)



CONCLUSION

To conclude, electrophilic trifluoro- and fluoroalkylselenolations of aromatic and heteroaromatic compounds can be easily performed starting from corresponding benzylfluoroalkyl selenides. These simple reagents, easily obtained from a common and moderately toxic source of selenium, constitute valuable electrophilic sources of fluoroalkylseleno groups and should favor the development of new substrates bearing such substituents. Furthermore, the possibility to also introduce functionalized moieties opens the way to post-transformations. By this method, molecules with a DCF_2Se group could be

DOI: 10.1021/acs.joc.6b01344
J. Org. Chem. 2016, 81, 8268−8275

obtained for the first time. No doubt that these reagents should find their place in the toolbox of emerging fluorinated groups.

EXPERIMENTAL SECTION

General Information. Commercial reagents were used as supplied. Anhydrous solvents were used as supplied. NMR spectra were recorded at 400 MHz (^{1}H NMR), 101 MHz (^{13}C NMR), 376 MHz (^{19}F NMR), or at 300 MHz (^{1}H NMR) and 282 MHz (^{19}F NMR). Multiplicities are indicated as follows: s (singlet), d (doublet), t (triplet), q (quartet), p (quintet), sext (sextet), m (multiplet). The term massif is used to define a group of different protons. All coupling constants were reported in hertz. Melting points were determined using a Köfler bench apparatus (calibration substances were specified).

(Benzylselanyl)carbonitrile. To a dry round-bottom flask equipped with a magnetic stirrer were added potassium selenocyanate (12.6 g, 87.7 mmol, 1.1 equiv), dry THF (60 mL), and benzylbromide (13.6 g, 79.7 mmol, 1.0 equiv). The reaction mixture was stirred at 60 °C for 17 h. The reaction mixture was then partitioned between water and Et_2O, and the organic layer was dried over $MgSO_4$, filtered, and concentrated to dryness to afford the desired product: ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.39−7.33 (massif, 5H), 4.31 (s, 2H), in accordance with literature.[73]

*{[(Trifluoromethyl)selanyl]methyl}benzene (**1a**).* To a dry round-bottom flask equipped with a magnetic stirrer were added (benzylselanyl)carbonitrile (13.7 g, 70.0 mmol, 1.0 equiv) and dry THF (140 mL). The flask was evacuated and refilled with nitrogen three times, and $TMSCF_3$ (20.7 mL, 140 mmol, 2.0 equiv) was added. The reaction mixture was cooled to 0 °C, and TBAF in 1 M THF (14.0 mL, 14.0 mmol, 0.2 equiv) was added dropwise. After 10 min at 0 °C under nitrogen, the reaction was allowed to warm to 23 °C and stirred for 7 h. The conversion was checked by ^{19}F NMR with $PhOCF_3$ as internal standard. The reaction mixture was then partitioned between water and pentane, and the aqueous layer was extracted with pentane. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered through a pad of silica (rinsed with pentane), and concentrated to dryness (under moderate vacuum). The crude residue was purified by chromatography (pentane: 100) to afford the desired product **1a** as a colorless liquid (11.7 g, 70% yield): ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.37−7.27 (massif, 5H), 4.26 (s, 2H); ^{19}F NMR (282 MHz, $CDCl_3$) δ = −34.47 (s, 3F), in accordance with literature.[30]

*{[(Bromodifluoromethyl)selanyl]methyl}benzene (**1b**).* To a dry round-bottom flask equipped with a magnetic stirrer was added (benzylselanyl)carbonitrile (3.92 g, 20 mmol, 1.0 equiv). The flask was evacuated and refilled with nitrogen three times before adding THF (40 mL, 0.5 M) and $TMSCF_2Br$ (6.2 mL, 40 mmol, 2.0 equiv) to the flask. The reaction mixture was cooled to 0 °C, and TBAF in 1 M THF (4.0 mL, 4.0 mmol, 0.2 equiv) was added dropwise. After 10 min at 0 °C under nitrogen, the reaction was allowed to warm to 23 °C and stirred for 4 h. The reaction mixture was then partitioned between water and pentane, and the aqueous layer was extracted with pentane. The combined organic layers were washed with water and brine, dried over $MgSO_4$, filtered, and concentrated to dryness (under moderate vacuum). The crude residue was purified by chromatography (pentane: 100) to afford the desired product **1b** as a colorless liquid (5.28 g, 88% yield): ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.36−7.28 (massif, 5H), 4.31 (s, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 135.6, 129.3, 129.0, 127.8, 107.9 (t, ^1J(C,F) = 355 Hz), 32.7; ^{19}F NMR (376 MHz, $CDCl_3$) δ = −16.54 (s, 2F). Anal. Calcd (%) for $C_8H_7BrF_2Se$: C, 32.03; H, 2.35; Br, 26.63; Se, 26.32. Found: C, 31.95; H, 2.47; Se, 26.11.

*{[(Pentafluoroethyl)selanyl]methyl}benzene (**1c**).* To a dry round-bottom flask equipped with a magnetic stirrer were added (benzylselanyl)carbonitrile (2.8 g, 14.2 mmol, 1.0 equiv) and dry THF (30 mL). The flask was evacuated and refilled with nitrogen three times, and $TMSCF_2CF_3$ (4.9 mL, 28.5 mmol, 2.0 equiv) was added. The reaction mixture was cooled to 0 °C and TBAF in 1 M THF (2.8 mL, 2.8 mmol, 0.2 equiv) was added dropwise. After 10 min at 0 °C under nitrogen, the reaction was allowed to warm to 23 °C and stirred for 16 h. The conversion was checked by ^{19}F NMR with $PhOCF_3$ as internal standard. The reaction mixture was then partitioned between water and pentane, and the aqueous layer was extracted with pentane. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered through a pad of silica (rinsed with pentane), and concentrated to dryness (under moderate vacuum). The crude residue was purified by chromatography (pentane: 100) to afford the desired product **1c** as a colorless liquid (3.21 g, 78% yield): ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.39−7.28 (massif, 5H), 4.28 (s, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 135.5, 129.3, 129.1, 128.0, 119.1 (qt, ^1J(C,F) = 285 Hz, ^2J(C,F) = 35 Hz), 116.5 (tq, ^1J(C,F) = 303 Hz, ^2J(C,F) = 43 Hz), 28.6 (t, ^3J(C,F) = 3 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ = −83.66 (t, ^3J(F,F) = 4.3 Hz, 3F), −91.75 (q, ^3J(F,F) = 4.3 Hz, 2F). Anal. Calcd (%) for $C_9H_7F_5Se$: C, 37.39; H, 2.44; Se, 27.31. Found: C, 37.54; H, 2.53; Se, 27.10.

*{[(Heptafluoropropyl)selanyl]methyl}benzene (**1d**).* To a dry round-bottom flask equipped with a magnetic stirrer were added (benzylselanyl)carbonitrile (720 mg, 3.7 mmol, 1.0 equiv) and dry THF (7 mL). The flask was evacuated and refilled with nitrogen three times, and $TMSCF_2CF_2CF_3$ (1.5 mL, 7.3 mmol, 2.0 equiv) was added. The reaction mixture was cooled to 0 °C and TBAF in 1 M THF (0.73 mL, 0.73 mmol, 0.2 equiv) was added dropwise. After 10 min at 0 °C under nitrogen, the reaction was allowed to warm to 23 °C and stirred for 16 h. The conversion was checked by ^{19}F NMR with $PhOCF_3$ as internal standard. The reaction mixture was then partitioned between water and pentane, and the aqueous layer was extracted with pentane. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered through a pad of silica (rinsed with pentane), and concentrated to dryness (under moderate vacuum). The crude residue was purified by chromatography (pentane: 100) to afford the desired product **1d** as a colorless liquid (1.09 g, 87% yield): ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.38−7.27 (massif, 5H), 4.30 (s, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 135.5, 129.4, 129.1, 128.1, 119.4 (tt, ^1J(C,F) = 304 Hz, ^2J(C,F) = 38 Hz), 117.8 (qt, ^1J(C,F) = 288 Hz, ^2J(C,F) = 35 Hz), 108.9 (tsext, ^1J(C,F) = 262 Hz, ^2J(C,F) = 36 Hz), 28.6 (m); ^{19}F NMR (376 MHz, $CDCl_3$) δ = −79.78 (t, ^4J(F,F) = 9.3 Hz, 3F), −87.74 (m, 2F), −122.77 (br s, 2F). Anal. Calcd (%) for $C_{10}H_7F_7Se$: C, 35.42; H, 2.08; Se, 23.28. Found: C, 35.18; H, 2.23; Se, 23.13.

*Methyl 2-(Benzylselanyl)-2,2-difluoroacetate (**1e**).* To a dry round-bottom flask equipped with a magnetic stirrer was added (benzylselanyl)carbonitrile (392 mg, 2.0 mmol, 1.0 equiv). The flask was evacuated and refilled with nitrogen three times before adding THF (4 mL, 0.5 M) and $TMSCF_2COOMe$ (0.71 mL, 4 mmol, 2.0 equiv) to the flask. The reaction mixture was cooled to 0 °C, and TBAF in 1 M THF (0.4 mL, 0.4 mmol, 0.2 equiv) was added dropwise. After 10 min at 0 °C under nitrogen, the reaction was allowed to warm to 23 °C and stirred for 15 h. The reaction mixture was then partitioned between water and EtOAc, and the aqueous layer was extracted with EtOAc. The combined organic layers were washed with water and brine, dried over $MgSO_4$, filtered, and concentrated to dryness. The crude residue was purified by chromatography (pentane/Et_2O 99/1 to 98/2) to afford the desired product **1e** as a pale yellow liquid (350 mg, 62% yield): ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.36−7.24 (massif, 5H), 4.24 (s, 2H), 3.88 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 163.0 (t, ^2J(C,F) = 31 Hz), 136.4, 129.3, 128.9, 127.7, 115.1 (t, ^1J(C,F) = 302 Hz), 54.0, 28.8 (t, ^3J(C,F) = 3 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ = −83.07 (s, 2F). Anal. Calcd (%) for $C_{10}H_{10}F_2O_2Se$: C, 43.03; H, 3.61; Se, 28.29. Found: C, 43.32; H, 3.92; Se, 28.10.

*({[(Benzenesulfonyl)difluoromethyl]selanyl}methyl)benzene (**1f**).* To a dry round-bottom flask equipped with a magnetic stirrer was added (benzylselanyl)carbonitrile (1.08 g, 5.5 mmol, 1.0 equiv). The flask was evacuated and refilled with nitrogen three times before adding diglyme (11 mL, 0.5 M) and $TMSCF_2SO_2Ph$ (11.0 mmol, 2.0 equiv) to the flask. The reaction mixture was cooled to 0 °C, and CsF (166 mg, 1.1 mmol, 0.2 equiv) was carefully added. After 10 min at 0 °C under nitrogen, the reaction was allowed to warm to 23 °C and stirred for 15 h. The reaction mixture was then partitioned between water and Et_2O, and the aqueous layer was extracted with Et_2O. The combined organic layers were washed with water and brine, dried over

DOI: 10.1021/acs.joc.6b01344
J. Org. Chem. 2016, 81, 8268−8275

$MgSO_4$, filtered, and concentrated to dryness. The crude residue was purified by chromatography (pentane/Et_2O 9/1) to afford the desired product **1f** as a white solid (2.64 g, 80% yield): mp 63−65 °C, calibration substance: azobenzol at 68.0 °C; ^1H NMR (400 MHz, $CDCl_3$) δ = 8.02 (m, 2H), 7.77 (m, 1H), 7.64 (m, 2H), 7.40−7.27 (massif, 5H), 4.45 (s, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 135.59, 135.57, 131.9, 131.0, 129.5, 129.4, 129.0, 128.0, 126.0 (t, ^1J(C,F) = 339 Hz), 30.7 (t, ^3J(C,F) = 3 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ = −78.53 (s, 2F). Anal. Calcd (%) for $C_{14}H_{12}F_2O_2SSe$: C, 46.55; H, 3.35; Se, 21.86, S 8.87. Found: C, 46.65; H, 3.58; Se, 21.64, S 9.07.

*{[(Difluoromethyl)selanyl]methyl}benzene (**1g**).* To a dry round-bottom flask equipped with a magnetic stirrer were added (benzylselanyl)carbonitrile (2.05 g, 10.45 mmol, 1.0 equiv) and dry THF (20 mL). The flask was evacuated and refilled with nitrogen three times, and $TMSCF_2H$ (2.85 mL, 20.9 mmol, 2.0 equiv) was added. The reaction mixture was cooled to 0 °C, and CsF (1.59 g, 10.45 mmol, 1.0 equiv) was carefully added. After 30 min at 0 °C under nitrogen, the reaction was allowed to warm to 23 °C and stirred for 15 h. The conversion was checked by ^{19}F NMR with $PhOCF_3$ as internal standard. The reaction mixture was then partitioned between water and pentane, and the aqueous layer was extracted with pentane. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated to dryness (under moderate vacuum). The crude residue was purified by chromatography (pentane/DCM 97/3 to 95/5) to afford the desired product **1g** as a colorless liquid (450 mg, 19% yield): ^1H NMR (400 MHz, $CDCl_3$) δ = 7.37−7.31 (massif, 4H), 7.27 (m, 1H), 7.08 (t, ^2J(H,F) = 55.2 Hz, 1H), 4.12 (s, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 137.4, 129.1, 128.9, 127.5, 115.8 (t, ^1J(C,F) = 287 Hz), 26.4 (t, ^3J(C,F) = 3 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ = −92.95 (d, ^2J(F,H) = 55.3 Hz, 2F). Anal. Calcd (%) for $C_8H_8F_2Se$: C, 43.46; H, 3.65; Se, 35.71. Found: C, 43.29; H, 3.40; Se, 35.63.

General Procedure 1 for Fluoroalkylselenolation without BF_3·Et_2O. To a flask equipped with a magnetic stirrer were added **1** (0.5 mmol, 1.0 equiv), sulfuryl chloride (0.5 mmol, 1.0 equiv), and dry THF (0.5 mL, 1 M). The reaction mixture was stirred at 23 °C until complete formation of the intermediate **2** (cf Table 2); it was then cooled to 0 °C, followed by the addition of **3** (0.5 mmol, 1.0 equiv). The reaction mixture was stirred at 0 °C for 15 min, and it was then allowed to warm to 23 °C until complete conversion of the intermediate **2** (the conversion takes between 15 min and 3 h, as checked by ^{19}F NMR with $PhOCF_3$ as internal standard). The reaction mixture was then partitioned between water and Et_2O, and the aqueous layer was extracted with Et_2O. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated to dryness. The crude residue was purified by chromatography to afford the desired product **4**, **5**, **6**, **7**, **8**, or **9**.

General Procedure 2 for Fluoroalkylselenolation with BF_3·Et_2O. To a flask equipped with a magnetic stirrer were added **1** (0.6 mmol, 1.2 equiv), sulfuryl chloride (0.6 mmol, 1.2 equiv), and dry DCE (0.5 mL, 1 M). The reaction mixture was stirred at 23 °C for 3.5 h followed by the addition of **3** (0.5 mmol, 1.0 equiv) and BF_3·Et_2O (0.15 mmol, 30 mol). The reaction mixture was heated to 80 °C for 15 h. The conversion was checked by ^{19}F NMR with $PhOCF_3$ as internal standard. The reaction mixture was then partitioned between water and pentane, and the aqueous layer was extracted with pentane. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated to dryness. The crude residue was purified by chromatography to afford the desired product **4** or **5**.

General Procedure 3 for Difluoromethylselenolation. To a flask equipped with a magnetic stirrer were added **1g** (0.4 mmol, 1.0 equiv) and dry THF (0.2 mL). The solution was cooled to 0 °C, and sulfuryl chloride (0.4 mmol, 1.0 equiv) and dry THF (0.2 mL) were added. The reaction mixture was stirred at 0 °C for 45 min, and **3** (0.4 mmol, 1.0 equiv) was added. The reaction mixture was stirred at 0 °C until complete conversion of the intermediate **2g** (the conversion takes around 2 h; it was checked by ^{19}F NMR with $PhOCF_3$ as internal standard). The reaction mixture was then partitioned between water and Et_2O, and the aqueous layer was extracted with Et_2O. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated to dryness. The crude residue was purified by chromatography to afford the desired product **10**.

*2,4-Dimethoxy-1-[(trifluoromethyl)selanyl]benzene (**4a**). Procedure 1.* Eluent for the flash chromatography: pentane/toluene 90/10 to 85/15; ^1H NMR (300 MHz, $CDCl_3$) δ = 7.61 (d, J = 8.1 Hz, 1H), 6.52−6.48 (massif, 2H), 3.87 (s, 3H), 3.84 (s, 3H); ^{19}F NMR (282 MHz, $CDCl_3$) δ = −36.54 (s, 3F), in accordance with literature.[35]

*4-[(trifluoromethyl)selanyl]benzene-1,3-diol (**4b**). Procedure 1.* White solid (mp 68−70 °C, calibration substance: azobenzol at 68.0 °C). Eluent for the flash chromatography: pentane/acetone 80/20; ^1H NMR (400 MHz, $CDCl_3$) δ = 7.52 (d, J = 8.5 Hz, 1H), 6.58 (d, J = 2.7 Hz, 1H), 6.45 (dd, J = 8.5, 2.7 Hz, 1H), 6.25 (br s, 1H), 5.44 (br s, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 160.6, 158.8, 140.3, 121.9 (q, ^1J(C,F) = 336 Hz), 109.8, 102.7, 100.3; ^{19}F NMR (376 MHz, $CDCl_3$) δ = −36.74 (s, 3F). Anal. Calcd (%) for $C_7H_5F_3O_2Se$: C, 32.71; H, 1.96; Se, 30.72. Found: C, 32.59; H, 1.91; Se, 30.48.

*4,6-Bis[(trifluoromethyl)selanyl]benzene-1,3-diol (**4c**).* To a flask equipped with a magnetic stirrer were added **1a** (274 mg, 1.15 mmol, 2.2 equiv), sulfuryl chloride (93 μL, 1.15 mmol, 2.2 equiv), and dry THF (1.1 mL, 1 M). The reaction mixture was stirred at 23 °C for 15 min, and it was cooled to 0 °C. Resorcinol **3c** (57 mg, 0.52 mmol, 1.0 equiv) was added, and the reaction was stirred at 0 °C for 15 min and then at 23 °C for 22 h (the conversion was checked by ^{19}F NMR with $PhOCF_3$ as internal standard). The reaction mixture was then partitioned between an aqueous 10% NaOH solution and EtOAc. The aqueous layer was acidified with an aqueous 1 M HCl solution and twice extracted with EtOAc. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated to dryness. The crude residue was purified by chromatography (pentane/acetone 80/20) to afford the desired product **4c** as a white solid (195 mg, 93% yield): mp 64−66 °C, calibration substance: azobenzol at 68.0 °C; ^1H NMR (400 MHz, $CDCl_3$) δ = 8.01 (s, 1H), 6.84 (s, 1H), 6.47 (br s, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 162.1, 149.3, 121.7 (q, ^1J(C,F) = 336 Hz), 102.6, 101.9 (br s); ^{19}F NMR (376 MHz, $CDCl_3$) δ = −36.47 (s, 6F). Anal. Calcd (%) for $C_8H_4F_6O_2Se_2$: C, 23.78; H, 1.00; Se, 39.09. Found: C, 23.67; H, 0.89; Se, 39.14.

*2-[(Trifluoromethyl)selanyl]naphthalen-1-ol (**4d**). Procedure 1.* Brown solid (mp 64−66 °C, calibration substance: azobenzol at 68.0 °C). Eluent for the flash chromatography: pentane/EtOAc 95/5 to 85/15; ^1H NMR (400 MHz, $CDCl_3$) δ = 8.46 (br d, J = 8.4 Hz, 1H), 8.26 (ddd, J = 8.3, 1.4, 0.7 Hz, 1H), 7.91 (d, J = 7.8 Hz, 1H), 7.66 (ddd, J = 8.4, 6.8, 1.4 Hz, 1H), 7.57 (ddd, J = 8.3, 6.8, 1.2 Hz, 1H), 6.80 (d, J = 7.8 Hz, 1H), 5.84 (br s, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 154.8, 139.4, 136.8, 128.3, 128.3, 126.1, 125.3, 122.7 (q, ^1J(C,F) = 335 Hz), 122.4, 113.2 (q, ^3J(C,F) = 2 Hz), 108.9; ^{19}F NMR (376 MHz, $CDCl_3$) δ = −36.38 (s, 3F). Anal. Calcd (%) for $C_{11}H_7F_3OSe$: C, 45.38; H, 2.42; Se, 27.12. Found: C, 45.59; H, 2.65; Se, 27.31.

*N,N-Dimethyl-4-[(trifluoromethyl)selanyl]aniline (**4e**). Procedure 1.* Eluent for the flash chromatography: pentane/EtOAc 99/1 to 98/2; ^1H NMR (300 MHz, $CDCl_3$) δ = 7.57 (m, 2H), 6.68 (m, 2H), 3.01 (s, 6H); ^{19}F NMR (282 MHz, $CDCl_3$) δ = −37.84 (s, 3F), in accordance with literature.[35]

*3-Ethyl-2,5-dimethyl-4-[(trifluoromethyl)selanyl]-1H-pyrrole (**4f**). Procedure 1.* Dark brown liquid. Eluent for the flash chromatography: pentane/Et_2O 100/0 to 98/2; ^1H NMR (400 MHz, $CDCl_3$) δ = 7.85 (br s, 1H), 2.44 (q, J = 7.6 Hz, 2H), 2.24 (s, 3H), 2.16 (s, 3H), 1.10 (t, J = 7.6 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 129.6, 129.4, 123.0, 122.3 (q, ^1J(C,F) = 338 Hz), 100.5 (q, ^3J(C,F) = 2 Hz), 18.2, 15.4, 11.4, 10.8; ^{19}F NMR (376 MHz, $CDCl_3$) δ = −38.58 (s, 3F). Anal. Calcd (%) for $C_9H_{12}F_3NSe$: C, 40.01; H, 4.48, N 5.18; Se, 29.23. Found: C, 39.76; H, 4.71, N 5.46; Se, 29.52.

*3-[(Trifluoromethyl)selanyl]-1H-indole (**4h**). Procedure 1.* Brown solid (mp 63−65 °C, calibration substance: azobenzol at 68.0 °C). Eluent for the flash chromatography: pentane/EtOAc 90/10 to 85/15; ^1H NMR (400 MHz, $CDCl_3$) δ = 8.44 (br s, 1H), 7.82 (m, 1H), 7.48 (d, J = 2.7 Hz, 1H), 7.43 (m, 1H), 7.36−7.30 (massif, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 136.1, 133.0, 130.1, 123.4, 122.4 (q, ^1J(C,F) = 335 Hz), 121.6, 120.1, 111.7, 93.2 (q, ^3J(C,F) = 2 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ = −37.54 (s, 3F). Anal. Calcd (%) for $C_9H_6F_3NSe$: C,

DOI: 10.1021/acs.joc.6b01344
J. Org. Chem. 2016, 81, 8268−8275

40.93; H, 2.29, N 5.30; Se, 29.90. Found: C, 41.02; H, 2.48, N 5.13; Se, 29.74.

*4-Bromo-3-[(trifluoromethyl)selanyl]-1H-indole (**4i**). Procedure 1.* Brown solid (mp 98−100 °C, calibration substance: benzil at 95.0 °C). Eluent for the flash chromatography: pentane/EtOAc 85/15 to 80/20; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.65 (br s, 1H), 7.56 (d, J = 2.8 Hz, 1H), 7.43−7.38 (massif, 2H), 7.10 (t, J = 7.9 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 137.1, 135.5, 126.6, 126.2, 124.2, 122.0 (q, ^1J(C,F) = 335 Hz), 115.0, 111.3, 93.3 (q, ^3J(C,F) = 2 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ = −38.70 (s, 3F). Anal. Calcd (%) for $C_9H_5BrF_3NSe$: C, 31.51; H, 1.47, Br 23.30, N 4.08; Se, 23.02. Found: C, 31.70; H, 1.70, Br 23.22, N 4.21; Se, 22.96.

*Methyl 3-[(Trifluoromethyl)selanyl]-1H-indole-5-carboxylate (**4j**). Procedure 1.* Pale pink solid (mp 169−171 °C, calibration substance: benzanilide at 163.0 °C). Eluent for the flash chromatography: pentane/EtOAc 80/20 to 70/30; ^{1}H NMR (400 MHz, $(CD_3)_2CO$) δ = 11.34 (br s, 1H), 8.42 (s, 1H), 7.95−7.92 (massif, 2H), 7.64 (d, J = 8.9 Hz, 1H), 3.91 (s, 3H); ^{13}C NMR (101 MHz, $(CD_3)_2CO$) δ = 167.8, 140.3, 137.1, 130.6, 124.7, 124.2, 123.4 (q, ^1J(C,F) = 334 Hz), 122.6, 113.1, 93.5, 52.2; ^{19}F NMR (376 MHz, $(CD_3)_2CO$) δ = −38.93 (s, 3F). Anal. Calcd (%) for $C_{11}H_8F_3NO_2Se$: C, 41.01; H, 2.50, N 4.35; Se, 24.51. Found: C, 40.88; H, 2.66, N 4.16; Se, 24.81.

*1-Methoxy-4-[(trifluoromethyl)selanyl]benzene (**4l**). Procedure 2.* Eluent for the flash chromatography: cyclohexane/toluene 98/2; ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.66 (m, 2H), 6.91 (m, 2H), 3.83 (s, 3H); ^{19}F NMR (282 MHz, $CDCl_3$) δ = −37.18 (s, 3F), in accordance with literature.[35]

*1,3,5-Trimethyl-2-[(trifluoromethyl)selanyl]benzene (**4m**). Procedure 2.* Eluent for the flash chromatography: pentane: 100; ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.05 (s, 2H), 2.60 (s, 6H), 2.34 (s, 3H); ^{19}F NMR (282 MHz, $CDCl_3$) δ = −35.16 (s, 3F), in accordance with literature.[48]

*1-[(Bromodifluoromethyl)selanyl]-2,4-dimethoxybenzene (**5a**). Procedure 1.* Off white solid (mp <46 °C, calibration substance: azobenzol at 68.0 °C). Eluent for the flash chromatography: cyclohexane/toluene 9/1; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.63 (m, 1H), 6.52−6.49 (massif, 2H), 3.86 (s, 3H), 3.84 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 163.8, 161.2, 140.5, 109.3 (t, ^1J(C,F) = 359 Hz), 106.9, 105.8, 99.2, 56.2, 55.6; ^{19}F NMR (376 MHz, $CDCl_3$) δ = −18.20 (s, 2F). Anal. Calcd (%) for $C_9H_9BrF_2O_2Se$: C, 31.24; H, 2.62, Br 23.09; Se, 22.82. Found: C, 31.49; H, 2.92, Br 23.17; Se, 22.96.

*4-[(Bromodifluoromethyl)selanyl]benzene-1,3-diol (**5b**). Procedure 1.* Pale yellow solid (mp 116−118 °C, calibration substance: acetanilide 114.5 °C). Eluent for the flash chromatography: cyclohexane/EtOAc 8/2; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.52 (d, J = 8.5 Hz, 1H), 6.58 (dd, J = 2.7, 0.5 Hz, 1H), 6.45 (ddd, J = 8.5, 2.7, 0.5 Hz, 1H), 6.27 (br s, 1H), 5.52 (br s, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 161.0, 158.8, 140.3, 109.7, 108.8 (t, ^1J(C,F) = 359 Hz), 104.4, 102.7; ^{19}F NMR (376 MHz, $CDCl_3$) δ = −18.98 (s, 2F). Anal. Calcd (%) for $C_7H_5BrF_2O_2Se$: C, 26.44; H, 1.59, Br 25.13; Se, 24.83. Found: C, 26.53; H, 1.87, Br 25.39; Se, 24.97.

*4-[(Bromodifluoromethyl)selanyl]naphthalen-1-ol (**5d**). Procedure 1.* Brown solid (mp 95−97 °C, calibration substance: azobenzol at 68.0 °C). Eluent for the flash chromatography: cyclohexane/EtOAc 95/5; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.46 (br d, J = 8.5 Hz, 1H), 8.26 (ddd, J = 8.2, 1.4, 0.7 Hz, 1H), 7.92 (d, J = 7.8 Hz, 1H), 7.65 (ddd, J = 8.5, 6.8, 1.4 Hz, 1H), 7.56 (ddd, J = 8.2, 6.8, 1.2 Hz, 1H), 6.82 (d, J = 7.8 Hz, 1H), 5.99 (br s, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 155.1, 139.5, 136.7, 128.4, 128.3, 126.1, 125.3, 122.4, 117.2, 109.4 (t, ^1J(C,F) = 359 Hz), 108.9; ^{19}F NMR (376 MHz, $CDCl_3$) δ = −18.09 (s, 2F). Anal. Calcd (%) for $C_{11}H_7BrF_2OSe$: C, 37.53; H, 2.00, Br 22.70; Se, 22.43. Found: C, 37.28; H, 1.87, Br 22.82; Se, 22.73.

*4-[(Bromodifluoromethyl)selanyl]-N,N-dimethylaniline (**5e**). Procedure 1.* Yellow solid (mp 76−78 °C, calibration substance: azobenzol at 68.0 °C). After removing volatiles, pentane was added to the residue and the precipitate was filtered off and washed with pentane: ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.60 (d, J = 8.5 Hz, 2H), 6.74 (d, J = 8.5 Hz, 2H), 3.02 (s, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 151.7, 138.8, 112.6, 111.4, 109.9 (t, ^1J (C, F) = 357 Hz), 40.2; ^{19}F NMR (376 MHz, $CDCl_3$) δ = −19.35 (s, 2F). Anal. Calcd (%) for $C_9H_{10}BrF_2NSe$: C, 32.85; H, 3.06, Br 24.28, N 4.26; Se, 24.00. Found: C, 32.69; H, 3.11, Br 24.20, N 4.35; Se, 23.79.

*3,4-Bis[(bromodifluoromethyl)selanyl]-2,5-dimethyl-1H-pyrrole (**5g**).* To a flask equipped with a magnetic stirrer were added **1b** (190 mg, 0.63 mmol, 2.2 equiv), sulfuryl chloride (51 μL, 0.63 mmol, 2.2 equiv), and dry THF (0.6 mL, 1 M). The reaction mixture was stirred at 23 °C for 15 min, and it was cooled to 0 °C. The pyrrole derivative **3g** (29 μL, 0.29 mmol, 1.0 equiv) was added, and the reaction was stirred at 0 °C for 35 min (the conversion was checked by ^{19}F NMR with $PhOCF_3$ as internal standard). The reaction mixture was then partitioned between water and Et_2O, and the aqueous layer was extracted with Et_2O. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated to dryness. The crude residue was purified by chromatography (pentane/Et_2O 80/20 to 70/30) to afford the desired product **5g** as a pale yellow liquid (106 mg, 72% yield): ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.50 (br s, 1H), 2.45 (s, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 136.1, 110.2 (t, ^1J(C,F) = 359 Hz), 109.3, 13.5; ^{19}F NMR (376 MHz, $CDCl_3$) δ = −18.97 (s, 4F). Anal. Calcd (%) for $C_8H_7Br_2F_4NSe_2$: C, 18.81; H, 1.38, Br 31.28, N 2.74; Se, 30.91. Found: C, 19.05; H, 1.57, Br 31.33, N 2.59; Se, 30.98.

*3-[(Bromodifluoromethyl)selanyl]-1H-indole (**5h**). Procedure 1.* Brown solid (mp 49−51 °C, calibration substance: azobenzol at 68.0 °C). Eluent for the flash chromatography: cyclohexane/EtOAc 9/1 to 8/2; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.54 (br s, 1H), 7.81 (m, 1H), 7.53 (d, J = 2.7 Hz, 1H), 7.44 (m, 1H), 7.34−7.27 (massif, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 136.1, 133.2, 130.0, 123.5, 121.7, 120.3, 111.6, 109.9 (t, ^1J(C,F) = 359 Hz), 98.0; ^{19}F NMR (376 MHz, $CDCl_3$) δ = −18.92 (s, 2F). Anal. Calcd (%) for $C_9H_6BrF_2NSe$: C, 33.26; H, 1.86, Br 24.58, N 4.31 Se 24.29. Found: C, 33.18; H, 2.02, Br 24.90, N 4.49; Se, 24.21.

*4-Bromo-3-[(bromodifluoromethyl)selanyl]-1H-indole (**5i**). Procedure 1.* Dark brown solid (mp 90−92 °C, calibration substance: azobenzol at 68.0 °C). Eluent for the flash chromatography: cyclohexane/EtOAc 8/2; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.67 (br s, 1H), 7.60 (d, J = 2.8 Hz, 1H), 7.44−7.40 (massif, 2H), 7.11 (t, J = 7.9 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 137.0, 135.8, 126.7, 126.2, 124.2, 115.1, 111.3, 109.7 (t, ^1J(C,F) = 359 Hz), 98.0; ^{19}F NMR (376 MHz, $CDCl_3$) δ = −20.24 (s, 2F). Anal. Calcd (%) for $C_9H_5Br_2F_2NSe$: C, 26.76; H, 1.25, Br 39.57, N 3.47 Se 19.55. Found: C, 26.52; H, 1.07, Br 39.83, N 3.24; Se, 19.87.

*Methyl 3-[(Bromodifluoromethyl)selanyl]-1H-indole-5-carboxylate (**5j**). Procedure 1.* Pale pink solid (mp 188−190 °C, calibration substance: salophen at 191.0 °C). After removing volatiles, pentane was added to the residue and the precipitate was filtered off and washed with pentane: ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.83 (br s, 1H), 8.51 (br s, 1H), 8.01 (dd, J = 8.5, 1.6 Hz, 1H), 7.64 (d, J = 2.6 Hz, 1H), 7.48 (d, J = 8.5 Hz, 1H), 3.96 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 167.9, 138.8, 134.5, 129.8, 124.9, 124.0, 123.2, 111.5, 109.5 (t, ^1J(C,F) = 359 Hz), 99.5, 52.3; ^{19}F NMR (376 MHz, $CDCl_3$) δ = −19.07 (s, 2F). Anal. Calcd (%) for $C_{11}H_8BrF_2NO_2Se$: C, 34.49; H, 2.11, Br 20.86, N 3.66 Se 20.61. Found: C, 34.37; H, 2.34, Br 21.05, N 3.75; Se, 20.85.

*4-[(Pentafluoroethyl)selanyl]benzene-1,3-diol (**6b**). Procedure 1.* White solid (mp 91−93 °C, calibration substance: benzil at 95.0 °C). Eluent for the flash chromatography: pentane/acetone 80/20; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.49 (d, J = 8.5 Hz, 1H), 6.58 (d, J = 2.7 Hz, 1H), 6.44 (dd, J = 8.5, 2.7 Hz, 1H), 6.22 (br s, 1H), 5.42 (br s, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 160.7, 159.2, 140.8, 118.7 (qt, ^1J(C,F) = 286 Hz, ^2J(C,F) = 34 Hz), 115.4 (tq, ^1J(C,F) = 305 Hz, ^2J(C,F) = 42 Hz), 109.8, 102.7, 99.2 (t, ^3J(C,F) = 3 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ = −82.80 (t, ^3J(F,F) = 3.8 Hz, 3F), −91.61 (q, ^3J(F,F) = 3.8 Hz, 2F). Anal. Calcd (%) for $C_8H_5F_5O_2Se$: C, 31.29; H, 1.64; Se, 25.71. Found: C, 31.19; H, 1.77; Se, 26.03.

*3-[(Pentafluoroethyl)selanyl]-1H-indole (**6h**). Procedure 1.* Pale pink solid (mp 74−76 °C, calibration substance: azobenzol at 68.0 °C). Eluent for the flash chromatography: pentane/EtOAc 90/10; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.51 (br s, 1H), 7.79 (m, 1H), 7.50 (d, J

DOI: 10.1021/acs.joc.6b01344
J. Org. Chem. 2016, 81, 8268−8275

= 2.7 Hz, 1H), 7.43 (m, 1H), 7.34−7.28 (massif, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 136.1, 133.6, 130.4, 123.4, 121.7, 120.2, 119.1 (qt, ^1J(C,F) = 286 Hz, ^2J(C,F) = 35 Hz), 115.4 (tq, ^1J(C,F) = 304 Hz, ^2J(C,F) = 41 Hz), 111.6, 92.1 (t, ^3J(C,F) = 4 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ = −82.75 (t, ^3J(F,F) = 3.9 Hz, 3F), −92.62 (q, ^3J(F,F) = 3.9 Hz, 2F). Anal. Calcd (%) for $C_{10}H_6F_5NSe$: C, 38.24; H, 1.93, N 4.46; Se, 25.14. Found: C, 38.13; H, 2.14, N 4.71; Se, 25.34.

*4-[(Heptafluoropropyl)selanyl]benzene-1,3-diol (**7b**). Procedure 1.* White solid (mp 71−73 °C, calibration substance: azobenzol at 68.0 °C). Eluent for the flash chromatography: pentane/acetone 80/20; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.50 (d, J = 8.5 Hz, 1H), 6.58 (s, J = 2.7 Hz, 1H), 6.45 (dd, J = 8.5, 2.7 Hz, 1H), 6.23 (s, 1H), 5.51 (s, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 160.8, 159.3, 141.0, 118.2 (tt, ^1J(C,F) = 306 Hz, ^2J(C,F) = 40 Hz), 117.5 (qt, ^1J(C,F) = 289 Hz, ^2J(C,F) = 35 Hz), 109.8, 108.8 (tsext, ^1J(C,F) = 263 Hz, ^2J(C,F) = 38 Hz), 102.7, 99.1; ^{19}F NMR (376 MHz, $CDCl_3$) δ = −79.85 (t, ^4J(F,F) = 9.2 Hz, 3F), −87.57 (m, 2F), −122.28 (s, 2F). Anal. Calcd (%) for $C_9H_5F_7O_2Se$: C, 30.27; H, 1.41; Se, 22.11. Found: C, 30.50; H, 1.71; Se, 22.33.

*3-[(Heptafluoropropyl)selanyl]-1H-indole (**7h**). Procedure 1.* Redish solid (mp 46−48 °C, calibration substance: azobenzol at 68.0 °C). Eluent for the flash chromatography: pentane/EtOAc 90/10; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.49 (br s, 1H), 7.82 (m, 1H), 7.48 (d, J = 2.7 Hz, 1H), 7.42 (m, 1H), 7.36−7.30 (massif, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 136.2, 133.8, 130.5, 123.4, 121.7, 120.2, 118.1 (tt, ^1J(C,F) = 305 Hz, ^2J(C,F) = 38 Hz), 117.7 (qt, ^1J(C,F) = 289 Hz, ^2J(C,F) = 35 Hz), 111.7, 109.0 (tsext, ^1J(C,F) = 263 Hz, ^2J(C,F) = 38 Hz), 92.1 (t, ^3J(C,F) = 4 Hz); ^{19}F NMR (282 MHz, $CDCl_3$) δ = −79.87 (t, ^4J(F,F) = 9.1 Hz, 3F), −88.46 (qt, ^4J(F,F) = 9.1 Hz, ^3J(F,F) = 3.4 Hz, 2F), −122.42 (br s, 2F). Anal. Calcd (%) for $C_{11}H_6F_7NSe$: C, 36.28; H, 1.66, N 3.85; Se, 21.69. Found: C, 36.14; H, 1.49, N 4.12; Se, 21.51.

*Methyl 2-[(2,4-Dihydroxyphenyl)selanyl]-2,2-difluoroacetate (**8b**). Procedure 1.* Yellow oil. Eluent for the flash chromatography: cyclohexane/EtOAc 8/2; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.40 (d, J = 8.5 Hz, 1H), 6.53 (d, J = 2.6 Hz, 1H), 6.40 (dd, J = 8.5, 2.6 Hz, 1H), 6.45−6.35 (massif, 2H), 3.78 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 162.8 (t, ^2J(C,F) = 30 Hz), 160.8, 158.8, 140.4, 115.9 (t, ^1J(C,F) = 304 Hz), 109.8, 102.6, 100.5 (t, ^3J(C,F) = 3 Hz), 54.3; ^{19}F NMR (376 MHz, $CDCl_3$) δ = −82.73 (s, 2F). Anal. Calcd (%) for $C_9H_8F_2O_4Se$: C, 36.38; H, 2.71; Se, 26.58. Found: C, 36.63; H, 2.89; Se, 26.48.

*Methyl 2,2-Difluoro-2-(1H-indol-3-ylselanyl)acetate (**8h**). Procedure 1.* Redish solid (mp 94−96 °C, calibration substance: benzil at 95.0 °C). Eluent for the flash chromatography: pentane/EtOAc 80/20 to 75/25; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.67 (br s, 1H), 7.71 (m, 1H), 7.35−7.31 (massif, 2H), 7.27−7.23 (massif, 2H), 3.62 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 163.2 (t, ^2J(C,F) = 30 Hz), 136.2, 133.4, 130.2, 123.2, 121.3, 119.8, 115.7 (t, ^1J(C,F) = 302 Hz), 111.8, 93.1 (t, ^3J(C,F) = 3 Hz), 53.7; ^{19}F NMR (376 MHz, $CDCl_3$) δ = −84.47 (s, 2F). Anal. Calcd (%) for $C_{11}H_9F_2NO_2Se$: C, 43.44; H, 2.98, N 4.61; Se, 25.96. Found C 43.60; H, 3.22, N 4.36; Se, 26.06.

*4-{[(Benzenesulfonyl)difluoromethyl]selanyl}benzene-1,3-diol (**9b**). Procedure 1.* Off white solid (mp 149−151 °C, calibration substance: acetanilide at 114.5 °C). After removing volatiles, pentane was added to the residue and the precipitate was filtered off and washed with pentane; ^{1}H NMR (400 MHz, CD_3OD) δ = 7.97 (m, 2H), 7.81 (m, 1H), 7.67 (m, 2H), 7.35 (d, J = 8.5 Hz, 1H), 6.39 (d, J = 2.6 Hz, 1H), 6.28 (dd, J = 8.5, 2.6 Hz, 1H); ^{13}C NMR (101 MHz, CD_3OD) δ = 163.2, 162.0, 142.0, 136.8, 133.5, 131.9, 130.6, 126.4 (t, ^1J(C,F) = 340 Hz), 109.3, 103.6, 99.5 (t, ^3J(C,F) = 2 Hz); ^{19}F NMR (376 MHz, CD_3OD) δ = −75.51 (s, 2F). Anal. Calcd (%) for $C_{13}H_{10}F_2O_4SSe$: C, 41.17; H, 2.66, S 8.45 Se 20.82. Found: C, 41.27; H, 2.90, S 8.25; Se, 20.96.

*3-{[(Benzenesulfonyl)difluoromethyl]selanyl}-1H-indole (**9h**). Procedure 1.* Pale brown solid (mp 122−124 °C, calibration substance: acetanilide at 114.5 °C). After removing volatiles, pentane was added to the residue and the precipitate was filtered off and washed with pentane; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.75 (br s, 1H), 7.95 (d, J = 7.7 Hz, 2H), 7.79 (m, 1H), 7.74 (t, J = 7.7 Hz, 1H), 7.57 (t, J = 7.7 Hz, 2H), 7.52 (m, 1H), 7.41 (m, 1H), 7.29−7.25 (massif, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 136.1, 135.5, 134.2, 132.0, 130.8, 130.5, 129.4, 124.9 (t, ^1J(C,F) = 342 Hz), 123.2, 121.5, 120.2, 111.8, 92.3 (m); ^{19}F NMR (376 MHz, $CDCl_3$) δ = −78.03 (s, 2F). Anal. Calcd (%) for $C_{15}H_{11}F_2NO_2SSe$: C, 46.64; H, 2.87, N 3.63, S 8.30 Se 20.44. Found: C, 46.43; H, 2.74, N 3.71, S 8.14; Se, 20.27.

*4-[(Difluoromethyl)selanyl]benzene-1,3-diol (**10b**). Procedure 3.* Pale yellow oil. Eluent for the flash chromatography: pentane/EtOAc 75/25; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.46 (d, J = 8.5 Hz, 1H), 6.95 (t, ^2J(H,F) = 55.2 Hz, 1H), 6.57 (d, J = 2.6 Hz, 1H), 6.43 (dd, J = 8.5, 2.6 Hz, 1H), 6.37 (br s, 1H), 5.75 (br s, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 159.9, 158.5, 140.0, 116.4 (t, ^1J(C,F) = 292 Hz), 109.6, 102.5, 100.5 (t, ^3J(C,F) = 3 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ = −90.05 (d, ^2J(F,H) = 55.4 Hz). Anal. Calcd (%) for $C_7H_6F_2O_2Se$: C, 35.17; H, 2.53; Se, 33.03. Found: C, 34.94; H, 2.62; Se, 32.88.

*3-[(Difluoromethyl)selanyl]-1H-indole (**10h**). Procedure 3.* Pale yellow liquid. Eluent for the flash chromatography: pentane/EtOAc 90/10 to 85/15; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.44 (br s, 1H), 7.79 (m, 1H), 7.44−7.41 (massif, 2H), 7.33−7.26 (massif, 2H), 7.00 (t, ^2J(H,F) = 55.7 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 136.2, 132.2, 130.4, 123.3, 121.3, 120.2, 117.2 (t, ^1J(C,F) = 290 Hz), 111.6, 93.4 (t, ^3J(C,F) = 4 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ = −90.60 (d, ^2J(F,H) = 54.9 Hz). Anal. Calcd (%) for $C_9H_7F_2NSe$: C, 43.92; H, 2.87, N 5.69; Se, 32.08. Found: C, 43.75; H, 3.12, N 5.74; Se, 32.28.

*3-[(Difluorodeuteriomethyl)selanyl]-1H-indole ([**D**]**10h**).* To a flask were added magnesium turnings (93 mg, 3.9 mmol, 10 equiv) and iodine (14.8 mg, 0.12 mmol, 30 mol), and it was heated up with a heat gun for 10 min under stirring. The flask was evacuated and refilled with nitrogen three times before adding a solution of **9h** (150 mg, 0.38 mmol, 1 equiv) in CD_3OD (3.8 mL, 0.1 M). The mixture was stirred for 1.5 h at 23 °C, then a second portion of magnesium (187 mg, 7.8 mmol, 20 equiv) was added and the reaction was stirred for a further 2 h. The conversion was checked by ^{19}F NMR with $PhOCF_3$ as internal standard. A saturated aqueous solution of NH_4Cl (10 mL) was added, and the reaction mixture was extracted with Et_2O (15 mL × 3). The combined organic layers were washed with water and brine, dried over $MgSO_4$, filtered, and concentrated to dryness. The crude residue was purified by chromatography (pentane/Et_2O 85/15 to 75/25) to afford the desired product [**D**]**10h** as a yellow oil (55 mg, 58% yield): ^{1}H NMR (400 MHz $CDCl_3$) δ = 8.43 (br s, 1H), 7.79 (m, 1H), 7.44−7.41 (massif, 2H), 7.33−7.26 (massif, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 136.2, 132.2, 130.4, 123.3, 121.3, 120.2, 116.9 (tt, ^1J(C,F) = 289 Hz, ^1J(C,D) = 32 Hz), 111.6, 93.3 (t, ^3J(C,F) = 4 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ = −91.33 (t, ^2J(F,D) = 8.5 Hz, 2F). Anal. Calcd (%) for $C_9H_6DF_2NSe$: C, 43.74; H, 3.26, N 5.67; Se, 31.95. Found: C, 43.54; H, 2.98, N 5.80; Se, 32.06.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b01344.

Copies of NMR spectra (PDF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: thierry.billard@univ-lyon1.fr.

Author Contributions

†Q.G. and E.I. contributed equally.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work was supported by the CNRS, the RADIOMI project (EU FP7-PEOPLE-2012-ITN-RADIOMI), the French Ministry of Research and the French Fluorine Network.

DOI: 10.1021/acs.joc.6b01344
J. Org. Chem. 2016, 81, 8268−8275

REFERENCES

(1) Smart, B. E. *J. Fluorine Chem.* **2001**, *109*, 3.
(2) Kirsch, P. *Modern Fluoroorganic Chemistry: Synthesis, Reactivity, Applications*; Wiley-VCH: Weinheim, Germany, 2013.
(3) Hird, M. *Chem. Soc. Rev.* **2007**, *36*, 2070.
(4) Pagliaro, M.; Ciriminna, R. *J. Mater. Chem.* **2005**, *15*, 4981.
(5) 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.
(6) Hagmann, W. K. *J. Med. Chem.* **2008**, *51*, 4359.
(7) Becker, A. *Inventory of Industrial Fluoro-biochemicals*; Eyrolles: Paris, 1996.
(8) Theodoridis, G. In *Advances in Fluorine Science*; Tressaud, A., Ed.; Elsevier: Amsterdam, 2006; Vol. 2, p 121.
(9) Fujiwara, T.; O'Hagan, D. *J. Fluorine Chem.* **2014**, *167*, 16.
(10) Gillis, E. P.; Eastman, K. J.; Hill, M. D.; Donnelly, D. J.; Meanwell, N. A. *J. Med. Chem.* **2015**, *58*, 8315.
(11) Zhou, Y.; Wang, J.; Gu, Z.; Wang, S.; Zhu, W.; Aceña, J. L.; Soloshonok, V. A.; Izawa, K.; Liu, H. *Chem. Rev.* **2016**, *116*, 422.
(12) Toulgoat, F.; Alazet, S.; Billard, T. *Eur. J. Org. Chem.* **2014**, 2415.
(13) Xu, X.-H.; Matsuzaki, K.; Shibata, N. *Chem. Rev.* **2015**, *115*, 731.
(14) Rayman, M. P. *Lancet* **2000**, *356*, 233.
(15) Schwarz, K.; Foltz, C. M. *J. Am. Chem. Soc.* **1957**, *79*, 3292.
(16) Bodnar, M.; Konieczka, P.; Namiesnik, J. *J. Environ. Sci. Health, Part C: Environ. Carcinog. Ecotoxicol. Rev.* **2012**, *30*, 225.
(17) Brown, K. M.; Arthur, J. R. *Public Health Nutr.* **2001**, *4*, 593.
(18) Holben, D. H.; Smith, A. M. *J. Am. Diet. Assoc.* **1999**, *99*, 836.
(19) Kyriakopoulos, A.; Behne, D. *Rev. Physiol. Biochem. Pharmacol.* **2002**, *145*, 1.
(20) Lu, J.; Holmgren, A. *J. Biol. Chem.* **2009**, *284*, 723.
(21) Wessjohann, L. A.; Schneider, A.; Abbas, M.; Brandt, W. *Biol. Chem.* **2007**, *388*, 997.
(22) Abdulah, R.; Miyazaki, K.; Nakazawa, M.; Koyama, H. *J. Trace Elem. Med. Biol.* **2005**, *19*, 141.
(23) Combs, G. F.; Gray, W. P. *Pharmacol. Ther.* **1998**, *79*, 179.
(24) Ferri, T.; Favero, G.; Frasconi, M. *Microchem. J.* **2007**, *85*, 222.
(25) Hartikainen, H. *J. Trace Elem. Med. Biol.* **2005**, *18*, 309.
(26) Sanz Alaejos, M.; Diaz Romero, F. J.; Diaz Romero, C. *Nutrition* **2000**, *16*, 376.
(27) Romashov, L. V.; Ananikov, V. P. *Chem. - Eur. J.* **2013**, *19*, 17640.
(28) Hansch, C.; Leo, A.; Taft, R. W. *Chem. Rev.* **1991**, *91*, 165.
(29) Billard, T.; Langlois, B. R. *Tetrahedron Lett.* **1996**, *37*, 6865.
(30) Billard, T.; Large, S.; Langlois, B. R. *Tetrahedron Lett.* **1997**, *38*, 65.
(31) Large, S.; Roques, N.; Langlois, B. R. *J. Org. Chem.* **2000**, *65*, 8848.
(32) Blond, G.; Billard, T.; Langlois, B. R. *Tetrahedron Lett.* **2001**, *42*, 2473.
(33) Cherkupally, P.; Beier, P. *Tetrahedron Lett.* **2010**, *51*, 252.
(34) Potash, S.; Rozen, S. *J. Org. Chem.* **2014**, *79*, 11205.
(35) Nikolaienko, P.; Rueping, M. *Chem. - Eur. J.* **2016**, *22*, 2620.
(36) Billard, T.; Langlois, B. R.; Large, S. *Phosphorus, Sulfur Silicon Relat. Elem.* **1998**, *136*, 521.
(37) Billard, T.; Roques, N.; Langlois, B. R. *J. Org. Chem.* **1999**, *64*, 3813.
(38) Magnier, E.; Vit, E.; Wakselman, C. *Synlett* **2001**, 1260.
(39) Pooput, C.; Medebielle, M.; Dolbier, W. R. *Org. Lett.* **2004**, *6*, 301.
(40) Pooput, C.; Dolbier, W. R.; Médebielle, M. *J. Org. Chem.* **2006**, *71*, 3564.
(41) Ma, J.-J.; Yi, W.-B.; Lu, G.-P.; Cai, C. *Catal. Sci. Technol.* **2016**, *6*, 417.
(42) Rong, M.; Huang, R.; You, Y.; Weng, Z. *Tetrahedron* **2014**, *70*, 8872.
(43) Zhu, P.; He, X.; Chen, X.; You, Y.; Yuan, Y.; Weng, Z. *Tetrahedron* **2014**, *70*, 672.
(44) Hou, C.; Lin, X.; Huang, Y.; Chen, Z.; Weng, Z. *Synthesis* **2015**, *47*, 969.
(45) Wu, C.; Huang, Y.; Chen, Z.; Weng, Z. *Tetrahedron Lett.* **2015**, *56*, 3838.
(46) Kondratenko, N. V.; Kolomeytsev, A. A.; Popov, V. I.; Yagupolskii, L. M. *Synthesis* **1985**, 667.
(47) Chen, C.; Hou, C.; Wang, Y.; Hor, T. S. A.; Weng, Z. *Org. Lett.* **2014**, *16*, 524.
(48) Chen, C.; Ouyang, L.; Lin, Q.; Liu, Y.; Hou, C.; Yuan, Y.; Weng, Z. *Chem. - Eur. J.* **2014**, *20*, 657.
(49) Aufiero, M.; Sperger, T.; Tsang, A. S. K.; Schoenebeck, F. *Angew. Chem., Int. Ed.* **2015**, *54*, 10322.
(50) Tian, Q.; Weng, Z. *Chin. J. Chem.* **2016**, *34*, 505.
(51) Lefebvre, Q.; Pluta, R.; Rueping, M. *Chem. Commun.* **2015**, *51*, 4394.
(52) Wang, Y.; You, Y.; Weng, Z. *Org. Chem. Front.* **2015**, *2*, 574.
(53) Matheis, C.; Wagner, V.; Goossen, L. J. *Chem. - Eur. J.* **2016**, *22*, 79.
(54) Dale, J. W.; Emeleus, H. J.; Haszeldine, R. N. *J. Chem. Soc.* **1958**, 2939.
(55) Yarovenko, N. N.; Shemanina, V. N.; Gazieva, G. B. *Russ. J. Gen. Chem.* **1959**, *29*, 924.
(56) Stump, E. C. *Chem. Eng. News* **1967**, *45*, 44.
(57) Haas, A.; Praas, H.-W. *Chem. Ber.* **1992**, *125*, 571.
(58) Yagupol'skii, L. M.; Voloshchuk, V. G. *Russ. J. Gen. Chem.* **1966**, *36*, 173.
(59) Voloshchuk, V. G.; Yagupol'skii, L. M.; Syrova, G. P.; Bystrov, V. P. *Russ. J. Gen. Chem.* **1967**, *37*, 105.
(60) Yagupol'skii, L. M.; Voloshchuk, V. G. *Russ. J. Gen. Chem.* **1967**, *37*, 1463.
(61) Yagupol'skii, L. M.; Voloshchuk, V. G. *Russ. J. Gen. Chem.* **1968**, *38*, 2426.
(62) Magnier, E.; Wakselman, C. *Collect. Czech. Chem. Commun.* **2002**, *67*, 1262.
(63) Masilamani, D.; Rogic, M. M. *J. Org. Chem.* **1981**, *46*, 4486.
(64) Reichardt, C.; Welton, T. *Solvents and Solvent Effects in Organic Chemistry*; Wiley-VCH: Weinheim, Germany, 2011.
(65) Marcus, Y. *The Properties of Solvents*; Wiley: Chichester, UK, 1998.
(66) Marsden, C. J. *J. Fluorine Chem.* **1975**, *5*, 401.
(67) Trost, B. M. *Bull. Chem. Soc. Jpn.* **1988**, *61*, 107.
(68) Ismalaj, E.; Le Bars, D.; Billard, T. *Angew. Chem., Int. Ed.* **2016**, *55*, 4790.
(69) Gant, T. G. *J. Med. Chem.* **2014**, *57*, 3595.
(70) Mullard, A. *Nat. Rev. Drug Discovery* **2016**, *15*, 219.
(71) Thomae, D.; Morley, T. J.; Lee, H. S.; Barret, O.; Constantinescu, C.; Papin, C.; Baldwin, R. M.; Tamagnan, G. D.; Alagille, D. *J. Labelled Compd. Radiopharm.* **2016**, *59*, 205.
(72) Hu, M.; Wang, F.; Zhao, Y.; He, Z.; Zhang, W.; Hu, J. *J. Fluorine Chem.* **2012**, *135*, 45.
(73) Suzuki, H.; Usuki, M.; Hanafusa, T. *Synthesis* **1979**, 705.

DOI: 10.1021/acs.joc.6b01344
J. Org. Chem. 2016, 81, 8268−8275