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PII: S0040-4020(19)30454-5

DOI: https://doi.org/10.1016/j.tet.2019.04.042

Reference: TET 30287

To appear in: *Tetrahedron*

Received Date: 14 March 2019

Revised Date: 13 April 2019

Accepted Date: 16 April 2019

Please cite this article as: Barrett C, Krishnamurti V, Oliveira AP, Prakash GKS, One-pot preparation of $(RSe)_2CF_2$ and $(RS)_2CF_2$ compounds *via* insertion of $TMSCF_3$-derived difluorocarbene into diselenides and disulfides, *Tetrahedron* (2019), doi: https://doi.org/10.1016/j.tet.2019.04.042.

Graphical Abstract

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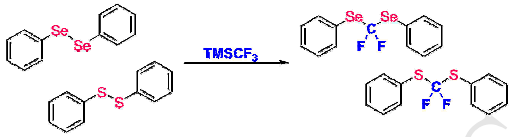

Tetrahedron
journal homepage: www.elsevier.com

One-pot preparation of $(RSe)_2CF_2$ and $(RS)_2CF_2$ compounds *via* insertion of $TMSCF_3$-derived difluorocarbene into diselenides and disulfides

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Dedicated to Professor. John Hartwig as a joint recipient of the 2018 Tetrahedron Prize for Creativity in Organic Chemistry.

ARTICLE INFO

Article history:
Received
Received in revised form
Accepted
Available online

Keywords:
difluorocarbene
$TMSCF_3$
insertion
diselenides
disulfides

ABSTRACT

A method for the first direct insertion of difluorcarbene, generated from $TMSCF_3$, into diselenides and disulfides is disclosed, producing novel difluoromethyl diselenoacetals and difluoromethyl dithioacetals. The reaction conditions tolerate a range of synthetically useful and biologically relevant functional groups. The process is scalable, with two representative compounds prepared at a gram-scale in good yields, and it utilizes cheap and available reagents.

1. Introduction

Fluorofunctionalization is an effective means of tuning the lipophilicity, bioavailability, and metabolic stability of molecules.[1–7] Direct introduction of a $-CF_2-$ group is a highly sought after transformation[8] due to the heightened biological activity of some $-CF_2-$ derivatives over their parent compounds.[9,10] In this context, the generation and utilization of difluorocarbene from fluoroalkylsilanes has emerged as a powerful tool for the difluoromethylation of nucleophilic substrates.[11,12] $TMSCF_2Br$ has been widely used as a difluorocarbene source for CF_2 incorporation into various nucleophiles.[13,14] The Ruppert-Prakash reagent ($TMSCF_3$) is arguably the cheapest source of CF_2 carbene (**Figure 1**). It has been employed in the difluoromethylation of olefins and alkynes to afford difluorocyclopropanes and difluorocyclopropenes respectively.[15] Mikami and co-workers have reported the siladifluoromethylation of carbon[16,17] and boron[18] nucleophiles. Our group has previously disclosed difluoromethylation reactions on various nucleophiles including imidazoles,[19] thiols,[20] phosphonates and phosphine oxides,[21] and stannyl hydrides.[22]

Difluoromethyl thioethers have been prepared through nucleophilic[23] and electrophilic[24] difluoromethylation, difluorocarbene reaction with thiols,[14,20,25] and direct $C(sp^3)$-H fluorination[26] of thioethers. Bromodifluoromethyl thioethers have been synthesized from thiolates and CF_2Br_2.[27–29] Bromodifluoromethyl selenoethers are prepared through reaction of selenols with CF_2Br_2.[30] The only reported synthesis of difluoromethyl thioacetals is from the reaction $TMSCF_2H$ with

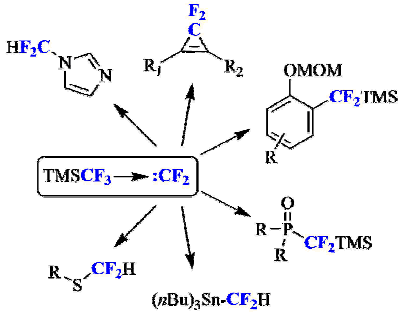

Figure 1. Reported difluoromethylation reactions using $TMSCF_3$.

disulfides.[31] No analogous transformation has been performed on diselenides to afford difluoromethyl selenoacetals. The reported strategy utilizes $TMSCF_2H$ to transfer CF_2H^- to disulfides, forming a difluoromethyl thioether, which attacks another equivalent of disulfide upon deprotonation to form a difluoromethyl thioacetal (**Figure 2**). Conducting an analogous transformation using $TMSCF_3$ would be desirable, since

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$TMSCF_2H$ is prepared from $TMSCF_3$ and is not nearly as cost-effective or available as $TMSCF_3$. Considering this, and our previous experience with CF_2 insertion reactions, we set out to develop a direct CF_2 insertion reaction into chalcogen-chalcogen bonds. We believe that access to such sulfur and selenium compounds would provide potentially useful building blocks for the fluorofunctionalization-thio/selenolation of organic molecules.

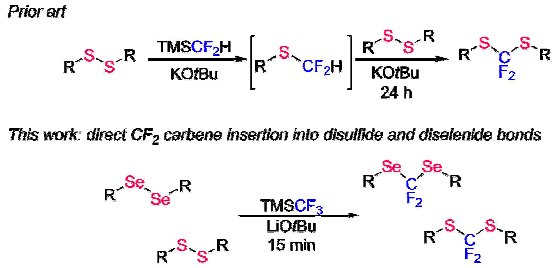
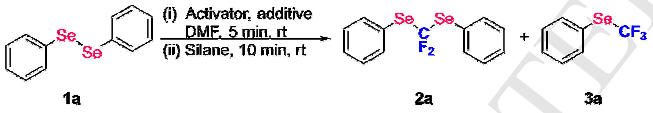


Figure 2. Prior art on the synthesis of difluoromethyl dithioacetals from $TMSCF_2H$ and this work from $TMSCF_3$.

2. Results/Discussion

Reaction optimization (**Table 1**) focused on the use of $TMSCF_3$ as the difluorocarbene source and diphenyl diselenide (**1a**) as the model substrate. The liberation of difluorocarbene from $TMSCF_3$ proceeds through decomposition of trifluoromethide, CF_3^-, which is released from the silicate formed upon addition of a nucleophile to $TMSCF_3$. The presence of Li cation has been shown to promote the formation of CF_2 carbene, and in many cases is necessary for the success of the reaction.[21,32] Conveniently, our first trial with LiO*t*Bu, LiCl and $TMSCF_3$ yielded 95% of **2a**. In the absence of LiCl, a slightly diminished

Table 1. Optimization trials on **1a**.



Entry[a]	Activator (equiv)	Silane (equiv)	Yield %	
			2a	**3a**
1	LiO*t*Bu (1.0)	$TMSCF_3$ (2.0)	95	5
2[b]	LiO*t*Bu (1.0)	$TMSCF_3$ (2.0)	89	6
3[b]	NaO*t*Bu (1.0)	$TMSCF_3$ (2.0)	83	8
4[b]	KO*t*Bu (1.0)	$TMSCF_3$ (2.0)	4	50
5	LiO*t*Bu (1.0)	$TMSCF_2Br$ (2.0)	1	5[c]

[a]Reactions performed with 0.5 mmol of **2a**, in 0.63 mL of DMF, with 1.2 equiv LiCl. Yields provided were determined by ^{19}F NMR using PhF (0.5 mmol) as internal standard. [b]No LiCl added. [c]yield of $PhSeCF_2Br$.

yield was observed. Performing the reaction with NaO*t*Bu in place of LiO*t*Bu decreased the conversion of **2a**. KO*t*Bu provided no reasonable conversion to **2a**, with a 50% conversion to **3a** (100% consumption of **1a**), clearly demonstrating the effect of the cation in directing the chemoselectivity of the transformation. This cation dependence stems from the identity of the fluoride salt (**Figure 3**). Li^+ and Na^+ both form very strong bonds with fluoride. Effectively, this makes the reactions irreversible (**Figure 3 eq.1, eq.2**). Lithium and sodium cations are both hard Lewis acids that bind strongly to hard Lewis bases, such as F^-. In contrast, fluoride's weaker bond with the softer K^+ allows for its recombination with CF_2 carbene (**Figure 3 eq.3**).[33] The persistence[34] of and preference for CF_3^- explains the selectivity for trifluoromethylation with KO*t*Bu. Finally, substituting $TMSCF_2Br$ in place of $TMSCF_3$ afforded no favorable amount of the desired product. It is likely that when using $TMSCF_2Br$ under these conditions, the difluorocarbene generation is too fast, which results in carbene dimerization or oligomerization products.

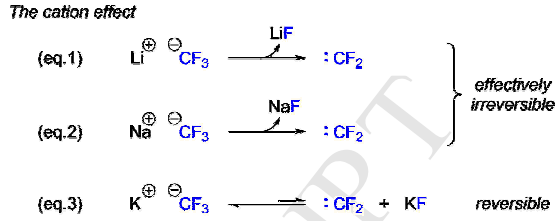


Figure 3. Effect of the cation on CF_2 carbene formation.

The optimized conditions were then applied to a series of diselenides (**Figure 4**). **2a** was isolated in excellent yield (86%). To test the effects of substituent position, 2-,3- and 4-methoxyphenyl derivatives were chosen. Despite the steric bulk of the methoxy group, and its inability to donate significantly by resonance when in the *meta* position, **2b**, **2d**, and **2f** were isolated in near-identical yields (80%, 80%, and 82%, respectively), indicating that substituent position may not significantly influence the difluorocarbene insertion. Both **2a** and **2b** were prepared at a 1 g scale in good yields, showing the potential for scalability. 1-naphthyl derivative **2c** could also be isolated in high yield (96%). The yield was lower (63%) in the case of a 2-dimethylamino substituent (**2e**). This may be due to strong coordination of the N-lone pair with Li^+ in the system, which would make the corresponding ammonium-type species a strong electron withdrawing group, thus promoting the S_N2-type addition of CF_3^- to the Se-Se bond, producing the corresponding Se-CF_3 compound. Difluoromethyl diselenoacetal **2g**, with a 4-Cl substituent, was obtained in excellent isolated yield, which provides a handle for further functionalization. However, 4-OCF_3

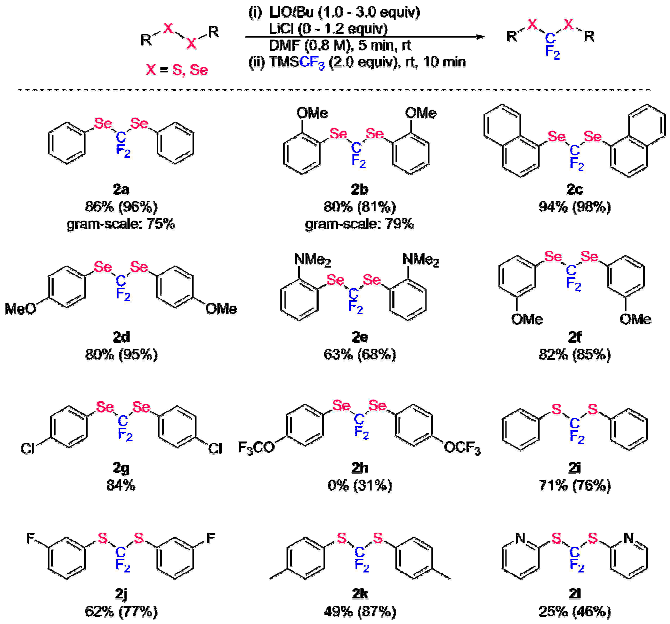


Figure 4: Products of difluorocarbene insertion into Se-Se and S-S bonds. All reactions performed at 0.5 mmol scale, with isolated yields shown outside parentheses. Yields provided in parentheses were determined by ^{19}F NMR spectroscopy using PhF as internal standard.

substituted product **2h** could not be isolated and was only observed by ^{19}F NMR. The diminished conversion and instability may be attributed to the good leaving group ability of -OCF_3, permitting an S_NAr reaction by an equivalent of $ArSeCF_2^-$ or $ArSe^-$. Unfortunately, dimethyl and dibenzyl diselenides did not yield the corresponding products. Dimethyl diselenide selectively gave the methyl trifluoromethyl selenide in 66% yield based on ^{19}F NMR. This is likely due to a much less hindered steric environment around selenium, allowing for more facile nucleophilic addition of the trifluoromethide anion. In the case of dibenzyl diselenide, deprotonation of a benzylic C(sp^3)-H bond, followed by elimination of a phenyl selenolate and a phenyl selenoaldehyde moiety may be responsible for the loss of starting material.[35]

Having tested the reaction conditions on diselenides, attempts to extend the conditions to disulfides were made. The optimized conditions for diselenides did not furnish the desired difluoromethyl dithioacetals in appreciable yields, and instead displayed high conversions to the corresponding trifluoromethyl thioethers. This can be attributed to the fact that S, as a harder electrophile, would react more readily with the hard nucleophile, CF_3^-, as opposed to the analogous reaction with diselenides (wherein the Se atom would likely be a softer electrophile). To circumvent this problem, a higher loading of Li*O*t*Bu (3 equiv) was used to increase the Li^+ concentration. This should hasten the decomposition of CF_3^- to difluorocarbene, driven by the formation of LiF. Applying this strategy, product **2i**, derived from diphenyl disulfide, was furnished in 71% yield. Compounds **2j** and **2k**, with a 3-F and 4-Me substituent, could also be produced in good yields. Finally, product **2l** was obtained, albeit in lower yield, showing compatibility with pyridyl moieties.

Figure 5: Proposed reaction pathway.

The first step of the reaction pathway (**Figure 5**) is likely the activation of $TMSCF_3$ by Li*O*t*Bu, forming lithium (tert-butyloxy)(trifluoromethyl)trimethylsilicate (**I**), which would liberate lithium trifluoromethide ($LiCF_3$) and TMS-O*t*Bu. Due to the inherent electrophilicity of the chalcogen center, trifluoromethylation to form trifluoromethyl selenoether **3** is a non-constructive pathway. Decomposition of $LiCF_3$ gives LiF and CF_2 carbene. The CF_2 carbene could be trapped by the diselenide, generating a difluoromethyl selenonium ylide (**II**). Rearrangement of the ylide would afford product **2**. The same reaction pathway can be envisioned with disulfides in place of diselenides.

3. Conclusion

In summary, we have developed a novel difluoromethylenation of diselenides and disulfides, yielding difluoromethyl diselenoacetals and dithioacetals. The method tolerates a number of commonly encountered functional groups. The transformation is scalable, with **2a** and **2b** having been prepared in good yields on a 1-gram scale.

4. Acknowledgements

The authors would like to thank the Loker Hydrocarbon Research Institute for funding.

5. Experimental section

5.1. General

Unless otherwise mentioned, all the chemicals were purchased from commercial sources and used without further purification. N,N-dimethylformamide (DMF) was distilled from CaH_2 under N_2 and stored over activated 3 Å molecular sieves in a Strauss flask. Where applicable, flash column chromatography was performed to isolate the compounds. Solid starting materials were dried under high vacuum (< 0.1 Torr) with a P_2O_5 trap for at least 12 hours prior to use. ^{1}H, ^{13}C, and ^{19}F NMR spectra were recorded on 400 MHz or 500 MHz Varian NMR spectrometers. All chemical shifts are given in units of ppm relative to an internal standard. ^{1}H NMR chemical shifts were determined relative to $CHCl_3$ at δ 7.26. ^{13}C NMR shifts were determined relative to $CDCl_3$ at δ 77.16. ^{19}F NMR chemical shifts were determined relative to $CFCl_3$ at δ 0.00. Mass spectral data were recorded on a high-resolution mass spectrometer, EI or ESI mode.

5.2. Starting materials

Note on diselenide synthesis using Grignard reagents and selenium metal: If the Grignard reagent is prepared *in situ* from aryl halides and magnesium metal, it is important to make sure that the aryl halide is fully consumed before adding the selenium. The aryl selenolate formed can perform nucleophilic substitution on any residual aryl halide to give the diaryl selenoether. This not only lowers yields of the product diselenides, often they are also difficult to separate. GCMS works well to confirm full consumption of aryl halide.

1b: 1,2-Bis(2-methoxyphenyl) diselenide

Adapted from a reported procedure. To a 500 mL, oven-dried, three-neck flask fitted with a glass stopper, rubber septum and nitrogen inlet, equipped with a magnetic stir-bar, Mg (30 mmol, 720 mg) and THF (180 mL) were added under N_2. Keeping the vessel under N_2, 2-bromoanisole (30 mmol, 3.75 mL) was added slowly *via* syringe. The mixture was stirred for 45 minutes and subsequently cooled to 0˚C. Under N_2, Se (20 mmol, 1.58 g) was added in one portion, the bath was removed, and the suspension was allowed to stir at room temperature for 4 hours. The reaction mixture was then quenched with aqueous NH_4Cl (saturated solution, 80 mL) and extracted with Et_2O (40 mL, three times). The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. **1b** was obtained after column chromatography (gradient of 0% to 10% EtOAc in hexanes) was a light-brown solid in 81% yield (2.26 g). **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 7.55 (d, *J* = 7.8 Hz, 2H), 7.21 (t, *J* = 8.0 Hz, 2H), 6.87 (t, *J* = 7.6 Hz, 2H), 6.82 (d, *J* = 8.2 Hz, 2H), 3.91 (s, 6H). The NMR data matches previous reports.[36]

1c: 1,2-Di(naphthalen-1-yl) diselenide

Adapted from a reported procedure. To a 500 mL, oven-dried, three-neck flask fitted with a glass stopper, rubber septum and nitrogen inlet, equipped with a magnetic stir-bar, Mg (2.5 equiv, 600 mg) and LiCl (2.5 equiv, 1.1 g) were added, and the vessel was evacuated and heated for 5 mins with a heat gun. Next, the vessel was allowed to cool down to room temperature, re-pressurized with N_2, and THF (50 mL) was added *via* syringe. TMSCl (5 mol %, 64 µL) and 1,2-dibromoethane (5 mol %, 43 µL) were added under N_2, and the mixture was stirred at room temperature for 10 minutes. The vessel was cooled to 0˚C in an ice bath (still under N_2), and 1-bromonaphthalene (10 mmol, 1,4 mL) was added slowly *via* syringe. The bath was removed, and the mixture was stirred at room temperature until all the bromoarene was consumed (monitored by taking a GC-MS spectrum of a worked-up aliquot of the reaction mix) (45 minutes), and the vessel was once again cooled to 0˚C. Se (1.0 equiv, 790 mg) was added in one portion, the bath was removed, and the mixture was stirred at room temperature for 2 hours. The crude product was extracted with $CHCl_3$ (50 mL, three times)

from aqueous HCl (0.15 M, 150 mL). The combined organic layer was washed with brine (75 mL, one time) and dried over $MgSO_4$. The crude product (*caution: STENCH!*) was re-dissolved in EtOH (200 mL), 11 pellets of NaOH (excess) were added, and the suspension was stirred for 2 hours at room temperature. The observed precipitate was collected and confirmed to be pure **1c**. The EtOH solution was concentrated, and a second portion of **1c** was obtained by column chromatography (hexanes). Overall, **1c** was obtained in 74% yield (1.53 g) was a pale-yellow solid. **^{1}H NMR** (399 MHz, Chloroform-*d*) δ 8.21 (ddd, *J* = 8.4, 1.3, 0.7 Hz, 2H), 7.85 – 7.80 (m, 4H), 7.77 (dd, *J* = 7.2, 1.2 Hz, 2H), 7.49 (ddd, *J* = 8.1, 6.9, 1.3 Hz, 2H), 7.42 (ddd, *J* = 8.3, 6.9, 1.4 Hz, 2H), 7.32 – 7.23 (m, 2H). The data matches reported values.[37]

1d: 1,2-Bis(4-methoxyphenyl) diselenide

Adapted from a reported procedure. To a 500 mL, oven-dried, three-neck flask fitted with a glass stopper, rubber septum and nitrogen inlet, equipped with a magnetic stir-bar, Mg (2.5 equiv, 300 mg) and LiCl (2.5 equiv, 551 mg) were added, and the vessel was evacuated and heated for 5 mins with a heat gun. Next, the vessel was allowed to cool down to room temperature, re-pressurized with N_2, and THF (20 mL) was added *via* syringe. TMSCl (5 mol %, 30 µL) and 1,2-dibromoethane (5 mol %, 20 µL) were added under N_2, and the mixture was stirred at room temperature for 10 minutes. The vessel was cooled to 0˚C in an ice bath (still under N_2), and 4-bromoanisole (5 mmol, 625 µL) was added slowly *via* syringe. The bath was removed, and the mixture was stirred at room temperature until all the bromoarene was consumed (monitored by taking a GC-MS spectrum of a worked-up aliquot of the reaction mix) (45 minutes), and the vessel was once again cooled to 0˚C. Se (2.0 equiv, 790 mg) was added in one portion, the bath was removed, and the mixture was stirred at room temperature for 2 hours. The crude product was extracted with $CHCl_3$ (50 mL, three times) from aqueous HCl (0.15 M, 150 mL). The combined organic layer was washed with brine (75 mL, one time) and dried over $MgSO_4$. The crude product (*caution: STENCH!*) was re-dissolved in EtOH (200 mL), 11 pellets of NaOH (excess) were added, and the suspension was stirred for 2 hours at room temperature. The solution was concentrated under reduced pressure, and the crude product was purified by column chromatography (gradient of 0% to 5% EtOAc in hexanes) to give **1d** in 60% yield (558 mg) as a pale-yellow solid. **^{1}H NMR** (399 MHz, Chloroform-*d*) δ 7.61 – 7.37 (m, 4H), 6.95 – 6.61 (m, 4H), 3.81 (s, 6H). The NMR data matches previous reports.[36]

1e: 1,2-Bis(4-(*N*,*N*-dimethylamino)phenyl) diselenide

Adapted from a reported procedure. To a 500 mL, oven-dried, three-neck flask fitted with a glass stopper, rubber septum and nitrogen inlet, equipped with a magnetic stir-bar, Mg (2.5 equiv, 600 mg) and LiCl (2.5 equiv, 1.1 g) were added, and the vessel was evacuated and heated for 5 mins with a heat gun. Next, the vessel was allowed to cool down to room temperature, re-pressurized with N_2, and THF (20 mL) was added *via* syringe. TMSCl (5 mol %, 30 µL) and 1,2-dibromoethane (5 mol %, 20 µL) were added under N_2, and the mixture was stirred at room temperature for 10 minutes. The vessel was cooled to 0˚C in an ice bath (still under N_2), and 2-bromo-N,N-dimethylaniline (10 mmol, 2.0 g) was added slowly. The bath was removed, and the mixture was stirred at room temperature until all the bromoarene was consumed (monitored by taking a GC-MS spectrum of a worked-up aliquot of the reaction mix) (60 minutes), and the vessel was once again cooled to 0˚C. Se (1.0 equiv, 395 mg) was added in one portion, the bath was removed, and the mixture was stirred at room temperature for 2 hours. The crude product was extracted with $CHCl_3$ (50 mL, three times) from water (150 mL). The combined organic layer was washed with brine (75 mL, one time) and dried over $MgSO_4$. The crude product (*caution: STENCH!*) was re-dissolved in EtOH (200 mL), 11 pellets of NaOH (excess) were added, and the suspension was stirred for 2 hours at room temperature. The solution was concentrated under reduced pressure. **1e** was obtained after column chromatography (gradient of 0% to 90% EtOAc in hexanes) was a yellow solid on storing in a freezer (-20 ˚C) for 2 days, in 73% yield (1.45 g). **^{1}H NMR** (399 MHz, Chloroform-*d*) δ 7.52 (dd, *J* = 7.9, 1.5 Hz, 2H), 7.22 – 7.12 (m, 4H), 7.00 (ddd, *J* = 7.8, 7.0, 1.5 Hz, 2H), 2.80 (s, 12H). The data matches reported values.[38]

1f: 1,2-Bis(3-methoxyphenyl) diselenide

Adapted from a reported procedure. To a 500 mL, oven-dried, three-neck flask fitted with a glass stopper, rubber septum and nitrogen inlet, equipped with a magnetic stir-bar, Mg (2.5 equiv, 600 mg) and LiCl (2.5 equiv, 1.1 g) were added, and the vessel was evacuated and heated for 5 mins with a heat gun. Next, the vessel was allowed to cool down to room temperature, re-pressurized with N_2, and THF (20 mL) was added *via* syringe. TMSCl (5 mol %, 30 µL) and 1,2-dibromoethane (5 mol %, 20 µL) were added under N_2, and the mixture was stirred at room temperature for 10 minutes. The vessel was cooled to 0˚C in an ice bath (still under N_2), and 3-bromoanisole (10 mmol, 1.87 g) was added slowly. The bath was removed, and the mixture was stirred at room temperature until all the bromoarene was consumed (monitored by taking a GC-MS spectrum of a worked-up aliquot of the reaction mix) (60 minutes), and the vessel was once again cooled to 0˚C. Se (1.0 equiv, 395 mg) was added in one portion, the bath was removed, and the mixture was stirred at room temperature for 2 hours. The crude product was extracted with $CHCl_3$ (50 mL, three times) from water (150 mL). The combined organic layer was washed with brine (75 mL, one time) and dried over $MgSO_4$. The crude product (*caution: STENCH!*) was re-dissolved in EtOH (200 mL), 11 pellets of NaOH (excess) were added, and the suspension was stirred for 2 hours at room temperature. The solution was concentrated under reduced pressure. **1f** was obtained after column chromatography (gradient of 0% to 20% EtOAc in hexanes) was a yellow solid on storing in a freezer (-20 ˚C) for 2 days, in 66% yield (1.45 g). The NMR data matches previous reports.[39]

1g: 1,2-Bis(4-chlorophenyl) diselenide

Adapted from a reported procedure. To a 500 mL, oven-dried, three-neck flask fitted with a glass stopper, rubber septum and nitrogen inlet, equipped with a magnetic stir-bar, Mg (2.5 equiv, 600 mg) and LiCl (2.5 equiv, 1.1 g) were added, and the vessel was evacuated and heated for 5 mins with a heat gun. Next, the vessel was allowed to cool down to room temperature, re-pressurized with N_2, and THF (20 mL) was added *via* syringe. TMSCl (5 mol %, 30 µL) and 1,2-dibromoethane (5 mol %, 20 µL) were added under N_2, and the mixture was stirred at room temperature for 10 minutes. The vessel was cooled to 0˚C in an ice bath (still under N_2), and 4-chloro-1-bromobenzene (10 mmol, 1.91 g) was added slowly. The bath was removed, and the mixture was stirred at room temperature until all the bromoarene was consumed (monitored by taking a GC-MS spectrum of a worked-up aliquot of the reaction mix) (60 minutes), and the vessel was once again cooled to 0˚C. Se (1.0 equiv, 395 mg) was added in one portion, the bath was removed, and the mixture was stirred at room temperature for 2 hours. The crude product was extracted with $CHCl_3$ (50 mL, three times) from HCl (1 M, 150 mL). The combined organic layer was washed with brine (75 mL, one time) and dried over $MgSO_4$. The crude product (*caution: STENCH!*) was re-dissolved in EtOH (200 mL), 11 pellets of NaOH (excess) were added, and the suspension was stirred for 2

hours at room temperature. The solution was concentrated under reduced pressure. **1g** was obtained after column chromatography (gradient of 0% to 20% EtOAc in hexanes) as a yellow solid in 72% yield (3.6 g). The NMR data matches previous reports.[40]

1h: 1,2-Bis(4-(trifluoromethoxy)phenyl) diselenide

Adapted from a reported procedure. To a 500 mL, oven-dried, three-neck flask fitted with a glass stopper, rubber septum and nitrogen inlet, equipped with a magnetic stir-bar, Mg (2.5 equiv, 600 mg) and LiCl (2.5 equiv, 1.1 g) were added, and the vessel was evacuated and heated for 5 mins with a heat gun. Next, the vessel was allowed to cool down to room temperature, re-pressurized with N_2, and THF (20 mL) was added *via* syringe. TMSCl (5 mol %, 30 µL) and 1,2-dibromoethane (5 mol %, 20 µL) were added under N_2, and the mixture was stirred at room temperature for 10 minutes. The vessel was cooled to 0˚C in an ice bath (still under N_2), and 4-bromo-1-trifluoromethoxybenzene (10 mmol, 2.41 g) was added slowly. The bath was removed, and the mixture was stirred at room temperature until all the bromoarene was consumed (monitored by taking a GC-MS spectrum of a worked-up aliquot of the reaction mix) (60 minutes), and the vessel was once again cooled to 0˚C. Se (1.0 equiv, 395 mg) was added in one portion, the bath was removed, and the mixture was stirred at room temperature for 2 hours. The crude product was extracted with $CHCl_3$ (50 mL, three times) from water (150 mL). The combined organic layer was washed with brine (75 mL, one time) and dried over $MgSO_4$. The crude product (*caution: STENCH!*) was re-dissolved in EtOH (200 mL), 11 pellets of NaOH (excess) were added, and the suspension was stirred for 2 hours at room temperature. The solution was concentrated under reduced pressure. **1h** was obtained after column chromatography (gradient of 0% to 20% EtOAc in hexanes) as a yellow oil in 59% yield (1.42 g). The NMR data matches previous reports.[40]

*5.3. Products (**2**)*

2a: **Difluorobis(phenylselanyl)methane**

In an argon glovebox, Li*O*t*Bu (0.5 mmol, 1.0 equiv, 40.0 mg), LiCl (0.6 mmol, 1.2 equiv, 25.4 mg) and 1,2-diphenyl diselenide (0.5 mmol, 156.1 mg) were weighed into an oven-dried, crimp-top vial equipped with a magnetic stir bar and sealed. Under N_2, DMF (0.63 mL) was added by syringe, and the solution was stirred for 5 mins, followed by dropwise addition of $TMSCF_3$ (1.0 mmol, 2 equiv, 148 µL). The solution was stirred for 10 mins, diluted with EtOAc (5 mL) and poured into aqueous HCl (12 mL, 1 M concentration). The organic layer was decanted, and the crude product was extracted from the aqueous layer two more times (5 mL EtOAc each time). The organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated. Flash column chromatography (n-pentane) of the crude mixture afforded **2a** in 86% isolated yield (156 mg) as a colorless liquid. **^{1}H NMR** (500 MHz, Chloroform-*d*) δ 7.80 – 7.69 (m, 4H), 7.46 (td, *J* = 7.4, 1.4 Hz, 2H), 7.39 (td, *J* = 7.4, 1.2 Hz, 4H). **^{13}C NMR** (101 MHz, Chloroform-*d*) δ 137.0, 129.9, 129.4, 126.4, 119.1 (t, *J* = 347.1 Hz). **^{19}F NMR** (376 MHz, Chloroform-*d*) δ -43.8. **FT-IR (cm^{-1})** 3073, 3056, 1577, 1561, 1476, 1438, 1329, 1310, 1075, 1032, 1019, 999, 804, 737, 688, 472. **HRMS (M)** 362.9014.

2b: Difluorobis((2-methoxyphenyl)selanyl)methane

In an argon glovebox, Li*O*t*Bu (0.5 mmol, 1.0 equiv, 40.0 mg), LiCl (0.6 mmol, 1.2 equiv, 25.4 mg) and 1,2-bis(2-methoxyphenyl) diselenide (0.5 mmol, 186.1 mg) were weighed into an oven-dried, crimp-top vial equipped with a magnetic stir bar and sealed. Under N_2, DMF (0.63 mL) was added by syringe, and the solution was stirred for 5 mins, followed by dropwise addition of $TMSCF_3$ (1.0 mmol, 2 equiv, 148 µL). The solution was stirred for 10 mins, the vial was opened, the solution was diluted with EtOAc (5 mL) and poured into aqueous HCl (12 mL, 1 M concentration). The organic layer was decanted, and the crude product was extracted from the aqueous layer two more times (5 mL EtOAc each time). The organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated. Flash column chromatography (gradient of 0% to 10% EtOAc in hexanes) of the crude mixture afforded **2b** in 80% isolated yield (218 mg) as a pale-yellow solid. **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 7.72 (d, *J* = 7.6 Hz, 2H), 7.38 (d, *J* = 7.8 Hz, 2H), 6.98 – 6.90 (m, 4H), 3.85 (s, 6H). **^{13}C NMR** (101 MHz, Chloroform-*d*) δ 159.0, 137.4 (t, *J* = 1.5 Hz), 131.3, 121.4, 119.0 (t, *J* = 348.6 Hz), 116.5, 111.3, 56.0. **^{19}F NMR** (376 MHz, Chloroform-*d*) δ -43.0. **FT-IR (cm^{-1})** 3062, 3005, 2956, 2935, 2835, 1579, 1474, 1463, 1431, 1289, 1271, 1245, 1179, 1163, 1125, 1056, 1020, 941, 803, 748, 657, 458. **HRMS (M-H$^+$)** 420.9196.

2c: Difluorobis(naphthalen-1-ylselanyl)methane

In an argon glovebox, Li*O*t*Bu (0.5 mmol, 1.0 equiv, 40.0 mg), LiCl (0.6 mmol, 1.2 equiv, 25.4 mg) and 1,2-di(naphthalen-1-yl) diselenide (0.5 mmol, 206.1 mg) were weighed into an oven-dried, crimp-top vial equipped with a magnetic stir bar and sealed. Under N_2, DMF (0.63 mL) was added by syringe, and the solution was stirred for 5 mins, followed by dropwise addition of $TMSCF_3$ (1.0 mmol, 2 equiv, 148 µL). The solution was stirred for 10 mins, the vial was opened, the solution was diluted with EtOAc (5 mL) and poured into aqueous HCl (12 mL, 1 M concentration). The organic layer was decanted, and the crude product was extracted from the aqueous layer two more times (5 mL EtOAc each time). The organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated. Flash column chromatography (gradient of 0% to 5% EtOAc in hexanes) of the crude mixture afforded **2c** in 94% isolated yield (169 mg) as a pale-yellow solid. **^{1}H NMR** (399 MHz, Chloroform-*d*) δ 8.38 – 8.31 (m, 2H), 8.03 – 7.93 (m, 4H), 7.89 – 7.82 (m, 2H), 7.56 – 7.47 (m, 4H), 7.48 – 7.40 (m, 2H). **^{13}C NMR** (100 MHz, Chloroform-*d*) δ 138.2, 135.6, 134.3, 131.5, 128.7, 128.6, 127.3, 126.6, 126.0, 125.8, 119.5 (t, *J* = 349.0 Hz). **^{19}F NMR** (376 MHz, Chloroform-*d*) δ -41.6. **FT-IR (cm^{-1})** 3055, 3040, 2932, 2851, 1588, 1559, 1499, 1455, 1375, 1364, 1335, 1251, 1201, 1142, 1133, 1033, 1019, 979, 952, 910, 861, 812, 793, 763, 733, 650, 622, 599, 531, 525, 511. **HRMS (M-H$^+$)** 462.9313.

2d: Difluorobis((4-methoxyphenyl)selanyl)methane

In an argon glovebox, Li*O*t*Bu (0.23 mmol, 1.0 equiv, 18.4 mg), LiCl (0.28 mmol, 1.2 equiv, 1.7 mg) and 1,2-bis(4-methoxyphenyl) diselenide (0.23 mmol, 86.1 mg) were weighed into an oven-dried, crimp-top vial equipped with a magnetic stir bar and sealed. Under N_2, DMF (0.30 mL) was added by syringe, and the solution was stirred for 5 mins, followed by dropwise addition of $TMSCF_3$ (1.0 mmol, 2 equiv, 68 µL). The solution was stirred for 10 mins, the vial was opened, the solution was diluted with EtOAc (5 mL) and poured into aqueous HCl (12 mL, 1 M concentration). The organic layer was decanted, and the crude product was extracted from the aqueous layer two more times (5 mL EtOAc each time). The organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated. Flash column chromatography (gradient of 0% to 10% EtOAc in hexanes) of the crude mixture afforded **2d** in 80% isolated yield (77 mg) as a yellow solid. **^{1}H NMR** (399 MHz, Chloroform-*d*) δ 7.8 – 7.4 (m, 4H), 7.0 – 6.5 (m, 4H), 3.8 (s, 6H). **^{13}C NMR** (100 MHz, Chloroform-*d*) δ 161.1, 138.9, 119.4 (t, *J* = 347.1 Hz), 116.9 (t, *J* = 1.3 Hz), 115.0, 55.4. **^{19}F NMR** (376 MHz,

Chloroform-*d*) δ -45.5. **FT-IR (cm^{-1})** 3067, 2969, 2942, 2889, 2837, 2541, 2367, 2284, 1895, 1583, 1571, 1489, 1462, 1434, 1406, 1299, 1289, 1249, 1190, 1179, 1104, 1021, 823, 793, 762, 707, 604, 517, 484. **HRMS (M-H$^+$)** 420.9215.

2e: 2,2'-((Difluoromethylene)bis(selanediyl))bis(*N*,*N*-dimethylaniline)

In an argon glovebox, LiO*t*Bu (0.5 mmol, 1.0 equiv, 40.0 mg), LiCl (0.6 mmol, 1.2 equiv, 25.4 mg) and 1,2-bis(4-(*N*,*N*-dimethylamino)phenyl) diselenide (0.5 mmol, 199.1 mg) were weighed into an oven-dried, crimp-top vial equipped with a magnetic stir bar and sealed. Under N_2, DMF (0.63 mL) was added by syringe, and the solution was stirred for 5 mins, followed by dropwise addition of $TMSCF_3$ (1.0 mmol, 2 equiv, 148 µL). The solution was stirred for 10 mins, the vial was opened, the solution was diluted with EtOAc (5 mL) and poured into saturated K_2CO_3 (12 mL). The organic layer was decanted, and the crude product was extracted from the aqueous layer two more times (5 mL EtOAc each time). The organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated. Flash column chromatography (gradient of 0% to 10% EtOAc in hexanes) of the crude mixture afforded **2e** in 63% isolated yield (141 mg) as a pale-yellow oil. **^{1}H NMR** (399 MHz, Chloroform-*d*) δ 7.81 (d, *J* = 7.9 Hz, 2H), 7.30 – 7.25 (m, 2H), 7.16 (dd, *J* = 8.0, 1.5 Hz, 2H), 7.07 (ddd, *J* = 7.9, 7.2, 1.4 Hz, 2H), 2.69 (s, 12H). **^{13}C NMR** (100 MHz, Chloroform-*d*) δ 153.4, 133.3 (t, *J* = 2.2 Hz), 128.7, 128.2, 125.2, 120.9, 120.6 (t, *J* = 346.5 Hz), 45.3. **^{19}F NMR** (376 MHz, Chloroform-*d*) δ -46.6. **FT-IR (cm^{-1})** 2940, 2824, 2785, 1570, 1491, 1473, 1291, 1250, 1173, 1018, 1013, 940, 794, 760, 731, 651, 518, 491. **HRMS (M-H$^+$)** 447.2703.

2f: Difluorobis((3-methoxyphenyl)selanyl)methane

In an argon glovebox, LiO*t*Bu (0.5 mmol, 1.0 equiv, 40.0 mg), LiCl (0.6 mmol, 1.2 equiv, 25.4 mg) and 1,2-bis(3-methoxyphenyl) diselenide (0.5 mmol, 186.1 mg) were weighed into an oven-dried, crimp-top vial equipped with a magnetic stir bar and sealed. Under N_2, DMF (0.63 mL) was added by syringe, and the solution was stirred for 5 mins, followed by dropwise addition of $TMSCF_3$ (1.0 mmol, 2 equiv, 148 µL). The solution was stirred for 10 mins, the vial was opened, the solution was diluted with EtOAc (5 mL) and poured into aqueous HCl (12 mL, 1 M concentration). The organic layer was decanted, and the crude product was extracted from the aqueous layer two more times (5 mL EtOAc each time). The organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated. Flash column chromatography (gradient of 0% to 10% EtOAc in hexanes) of the crude mixture afforded **2f** in 82% isolated yield (174 mg) as a pale-yellow oil. **^{1}H NMR** (399 MHz, Chloroform-*d*) δ 7.30 – 7.27 (m, 4H), 7.25 – 7.23 (m, 2H), 7.01 – 6.95 (m, 2H), 3.82 (s, 6H). **^{13}C NMR** (100 MHz, Chloroform-*d*) δ 159.8, 130.1, 129.0, 126.9, 121.9, 119.1 (t, *J* = 347.4 Hz), 115.9, 55.5. **^{19}F NMR** (376 MHz, Chloroform-*d*) δ -43.5. **FT-IR (cm^{-1})** 3085, 3053, 3017, 2964, 2938, 2837, 2518, 2059, 1587, 1571, 1477, 1465, 1455, 1440, 1421, 1301, 1286, 1232, 1184, 1169, 1035, 1013, 899, 877, 830, 800, 770, 684, 664, 574, 557, 453. **HRMS (M-H$^+$)** 420.9156.

2g: Bis((4-chlorophenyl)selanyl)difluoromethane

In an argon glovebox, LiO*t*Bu (0.5 mmol, 1.0 equiv, 40.0 mg), LiCl (0.6 mmol, 1.2 equiv, 25.4 mg) and 1,2-bis(4-chlorophenyl) diselenide (0.5 mmol, 191.0 mg) were weighed into an oven-dried, crimp-top vial equipped with a magnetic stir bar and sealed. Under N_2, DMF (0.63 mL) was added by syringe, and the solution was stirred for 5 mins, followed by dropwise addition of $TMSCF_3$ (1.0 mmol, 2 equiv, 148 µL). The solution was stirred for 10 mins, the vial was opened, the solution was diluted with EtOAc (5 mL) and poured into aqueous HCl (12 mL, 1 M concentration). The organic layer was decanted, and the crude product was extracted from the aqueous layer two more times (5 mL EtOAc each time). The organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated. Flash column chromatography (hexanes) of the crude mixture afforded **2g** in 84% isolated yield (181 mg) as a colorless solid. **^{1}H NMR** (399 MHz, Chloroform-*d*) δ 7.64 – 7.57 (m, 1H), 7.38 – 7.30 (m, 1H). **^{13}C NMR** (100 MHz, Chloroform-*d*) δ 138.3 (d, *J* = 1.1 Hz), 136.7, 129.7, 124.3 (t, *J* = 1.2 Hz), 118.8 (t, *J* = 348.2 Hz). **^{19}F NMR** (376 MHz, Chloroform-*d*) δ -44.1. **FT-IR (cm^{-1})** 3084, 2923, 2851, 2761, 2645, 2359, 1909, 1645, 1579, 1558, 1470, 1435, 1387, 1350, 1291, 1267, 1084, 1023, 1009, 951, 801, 732, 486.

2i: Difluorobis(phenylthio)methane

In an argon glovebox, LiO*t*Bu (1.5 mmol, 3.0 equiv, 120.0 mg), and 1,2-diphenyl disulfide (0.5 mmol, 109.0 mg) were weighed into an oven-dried, crimp-top vial equipped with a magnetic stir bar and sealed. Under N_2, DMF (0.63 mL) was added by syringe, and the solution was stirred for 5 mins, followed by dropwise addition of $TMSCF_3$ (1.0 mmol, 2 equiv, 148 µL). The solution was stirred for 10 mins, the vial was opened, the solution was diluted with EtOAc (5 mL) and poured into aqueous HCl (12 mL, 1 M concentration). The organic layer was decanted, and the crude product was extracted from the aqueous layer two more times (5 mL EtOAc each time). The organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated. Flash column chromatography (hexanes) of the crude mixture afforded **2i** in 71% isolated yield (95 mg) as a pale-yellow oil. **^{1}H NMR** (399 MHz, Chloroform-*d*) δ 7.66 – 7.56 (m, 4H), 7.49 – 7.43 (m, 2H), 7.43 – 7.36 (m, 4H). **^{13}C NMR** (100 MHz, Chloroform-*d*) δ 136.3, 132.4 (t, *J* = 312.4 Hz), 130.3, 129.2, 127.4. **^{19}F NMR** (376 MHz, Chloroform-*d*) δ -49.5. The NMR data matches previous reports.[31]

2j: Difluorobis((3-fluorophenyl)thio)methane

In an argon glovebox, LiO*t*Bu (1.5 mmol, 3.0 equiv, 120.0 mg), and bis(3-fluorophenyl) disulfide (0.5 mmol, 127.2 mg) were weighed into an oven-dried, crimp-top vial equipped with a magnetic stir bar and sealed. Under N_2, DMF (0.63 mL) was added by syringe, and the solution was stirred for 5 mins, followed by dropwise addition of $TMSCF_3$ (1.0 mmol, 2 equiv, 148 µL). The solution was stirred for 10 mins, the vial was opened, the solution was diluted with EtOAc (5 mL) and poured into aqueous HCl (12 mL, 1 M concentration). The organic layer was decanted, and the crude product was extracted from the aqueous layer two more times (5 mL EtOAc each time). The organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated. Flash column chromatography (gradient of 0% to 10% EtOAc in hexanes) of the crude mixture afforded **2j** in 62% isolated yield (94 mg) as a pale-yellow oil. **^{1}H NMR** (399 MHz, Chloroform-*d*) δ 7.4 – 7.3 (m, 6H), 7.2 (m, 2H). **^{13}C NMR** (100 MHz, Chloroform-*d*) δ 162.5 (d, *J* = 250.2 Hz), 132.1 (t, *J* = 315.5 Hz), 131.8 (d, *J* = 3.2 Hz), 130.5 (d, *J* = 8.3 Hz), 129.0 (dt, *J* = 7.9, 1.4 Hz), 122.9 (d, *J* = 22.1 Hz), 117.7 (d, *J* = 21.0 Hz). **^{19}F NMR** (376 MHz, Chloroform-*d*) δ -49.2, -110.5 – -113.3 (m). **HRMS (M-H$^+$)** 303.0011.

2k: Difluorobis(*p*-tolylthio)methane

In an argon glovebox, LiO*t*Bu (1.5 mmol, 3.0 equiv, 120.0 mg), and di-*p*-tolyl disulfide (0.5 mmol, 123.2 mg) were weighed into an oven-dried, crimp-top vial equipped with a magnetic stir bar and sealed. Under N_2, DMF (0.63 mL) was added by syringe, and the solution was stirred for 5 mins, followed by dropwise addition of $TMSCF_3$ (1.0 mmol, 2 equiv, 148 µL). The solution

was stirred for 10 mins, the vial was opened, the solution was diluted with EtOAc (5 mL) and poured into aqueous HCl (12 mL, 1 M concentration). The organic layer was decanted, and the crude product was extracted from the aqueous layer two more times (5 mL EtOAc each time). The organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated. Flash column chromatography (gradient of 0% to 15% EtOAc in hexanes) of the crude mixture afforded **2k** in 49% isolated yield (73 mg) as a pale-yellow solid. **^{1}H NMR** (399 MHz, Chloroform-*d*) δ 7.51 (d, *J* = 8.2 Hz, 4H), 7.27 – 7.18 (m, 4H), 2.40 (s, 6H). **^{13}C NMR** (100 MHz, Chloroform-*d*) δ 140.7, 136.4 (d, *J* = 1.1 Hz), 132.4 (t, *J* = 314.1 Hz), 130.0, 124.0 (t, *J* = 1.4 Hz), 21.5. **^{19}F NMR** (376 MHz, Chloroform-*d*) δ -50.2. **HRMS (M-H$^+$)** 295.0436.

2l: Difluorobis(pyridin-2-ylthio)methane

In an argon glovebox, LiO*t*Bu (1.5 mmol, 3.0 equiv, 120.0 mg), and di(pyridin-2-yl) disulfide (0.5 mmol, 110.2 mg) were weighed into an oven-dried, crimp-top vial equipped with a magnetic stir bar and sealed. Under N_2, DMF (0.63 mL) was added by syringe, and the solution was stirred for 5 mins, followed by dropwise addition of $TMSCF_3$ (1.0 mmol, 2 equiv, 148 µL). The solution was stirred for 10 mins, the vial was opened, the solution was diluted with EtOAc (5 mL) and poured into water (12 mL). The organic layer was decanted, and the crude product was extracted from the aqueous layer two more times (5 mL EtOAc each time). The organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated. Flash column chromatography (hexanes) of the crude mixture afforded **2l** in 25% isolated yield (34 mg) as a light-brown oil. **^{1}H NMR** (399 MHz, Chloroform-*d*) δ 8.60 (ddd, *J* = 4.8, 1.9, 1.0 Hz, 2H), 7.78 – 7.59 (m, 4H), 7.28 (ddd, *J* = 7.1, 4.8, 1.5 Hz, 2H). **^{19}F NMR** (376 MHz, Chloroform-*d*) δ -47.5. The NMR data matches previous reports.[31]

6. References

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