Application of $PhSCF_2CF_2SiMe_3$ as a Tandem Anion and Radical Tetrafluoroethylene Equivalent: Fluoride-Catalyzed Addition to N-Substituted Cyclic Imides Followed by Radical Cyclization

Yana Chernykh, Stanislav Opekar, Blanka Klepetářová, Petr Beier*

Institute of Organic Chemistry and Biochemistry, Academy of Sciences of the Czech Republic, Flemingovo nám. 2, 166 10 Prague, Czech Republic
Fax +420(220)183578; E-mail: beier@uochb.cas.cz

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Abstract: $PhSCF_2CF_2SiMe_3$ undergoes a fluoride-catalyzed nucleophilic addition to N-substituted cyclic amides affording adducts in moderate to good yields. Reductive cleavage of the phenylsulfanyl group of N-methylated adducts under radical conditions yields the corresponding tetrafluoroethyl-containing adducts in excellent yields. Under the same reduction conditions, N-allylated adducts undergo 6-*exo* radical cyclization to afford the corresponding tetrafluorinated 1-azabicyclic compounds in moderate to good yields and *cis* selectivities.

Key words: nucleophilic addition, radical reaction, fluorine, heterocycles, imides

Many advances in modern medicinal, synthetic, and material chemistries are connected with compounds of the most electronegative atom – fluorine. For example, in drug design, incorporation of fluorine atom(s) or fluorine-containing moieties into organic molecules modulates their biological properties. As a result, selective introduction of fluorinated moieties (fluoroalkylation) into organic molecules has become an important and fast-growing research field. While the introduction of perfluoroalkyl (including trifluoromethyl),[1] difluoromethyl, difluoromethylene,[2] and $–(CF_2)_n–$ groups,[3] where $n > 2$ by nucleophilic, radical, or electrophilic alkylations is well established, reports of the introduction of tetrafluoroethyl ($–CF_2CF_2H$) and tetrafluoroethylene ($–CF_2CF_2–$) moieties are relatively rare. This is due to unavailability or high price of halotetrafluoroethanes for the generation of tetrafluoroethyl radical or carbanion, or facile β-halogen elimination of organometallic species derived from 1,2-dihalotetrafluoroethanes.[4] However, radical chain reactions of 1,2-dihalotetrafluoroethanes with alkenes or alkynes are known.[5] This chemistry has been applied, for example, by Linclau and co-workers[6] in their enantioselective synthesis of tetrafluorinated glucose and galactose derivatives starting with radical addition of bromoiodotetrafluoroethane to an alkene. Other approaches towards tetrafluoroethylene-containing compounds such as the reaction of 1,2-dicarbonyls with SF_4/HF use highly toxic reagents and high-pressure reaction conditions,[7] while with less aggressive Deoxofluor the reaction is limited to simple aromatic benzil derivatives.[8]

Recently, we have reported the development of trimethyl(1,1,2,2-tetrafluoro-2-phenylsulfanylethyl)silane ($PhSCF_2CF_2SiMe_3$) as a tandem anion and radical tetrafluoroethylene synthon ($^{\cdot}CF_2CF_2^-$) and used it to convert aldehydes and ketones into tetrafluoroethyl-substituted alcohols and tetrafluoro-tetrahydropyrans.[9] As an extension of the scope of this methodology we now wish to report our findings on application of $PhSCF_2CF_2SiMe_3$ in the reaction with cyclic imides to give either the corresponding tetrafluoroethyl-containing adducts (after reductive phenyl sulfanyl group removal) or the corresponding tetrafluorinated 1-azabicyclic compounds (after radical 6-*exo* cyclization). These cyclizations should be relatively fast judging from Dolbier's observation of a remarkable rate-enhancement effect in 5-*exo*, 6-*exo*, and 6-*endo* cyclizations when using fluorinated radicals compared to their hydrocarbon analogues.[10] Both compound types have not been previously reported. 1-Azabicyclic ring systems having angular substituents adjacent to nitrogen are structural motifs found in a variety of alkaloid natural products and biologically active agents.[11]

$PhSCF_2CF_2SiMe_3$ was prepared in excellent yield according to literature procedure by a two-step reaction starting from thiophenol and 1,2-dibromotetrafluoroethane.[12] Nucleophilic additions of twofold excess of this silane to *N*-methyl- or *N*-allyl-substituted succinimides or phthalimides (**1a**–**d**) proceeded smoothly in the presence of catalytic tetrabutylammonium triphenyldifluorosilicate (TBAT) in THF at ambient temperature giving the adducts as TMS ethers, which after silyl-group removal using excess of aqueous hydrofluoric acid gave compounds **2** in moderate to good yields (Scheme 1).[13] Cyclic imides were found to be less reactive than aldehydes presumably due to their lower electrophilicity and higher steric hindrance. Using 10 mol% of TBAT or TMAF initiator was found to be satisfactory, while with TBAF no desired adduct was formed and the silyl reagent transferred to $PhSCF_2CF_2H$. Reducing the amount of TBAT to 1 mol%, which is the amount of initiator sufficient for reactions with aldehydes, did not provide good conversions of cyclic imides. The hydrolysis of TMS ether adduct to compounds **2** with HCl works only in the case of **2d**, for other examples HF with slight heating had to be used.

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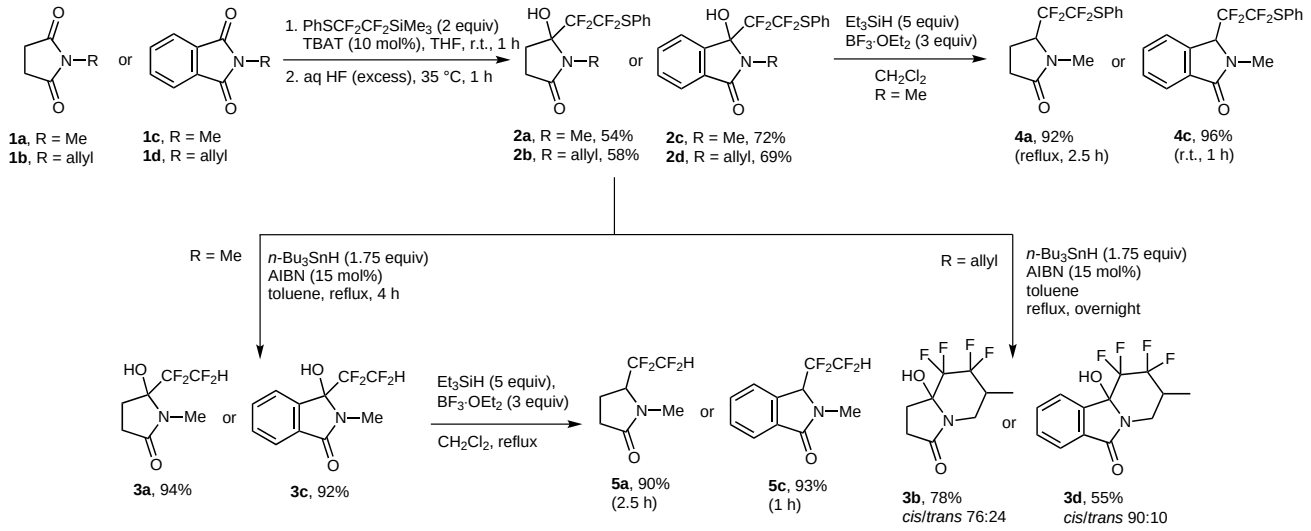


Scheme 1 Fluoride-initiated nucleophilic tetrafluoro(phenylsulfanyl)ethylenation of cyclic imides **1**, radical-mediated cleavage of the phenylsulfanyl group or cyclization, and hydroxy reduction

Reductive cleavage of the phenylsulfanyl group in adducts **2** was investigated. In adducts **2a** and **2c** (R = Me) the PhS group was readily substituted with hydrogen by using an excess amount of *n*-Bu_3SnH and a catalytic amount of AIBN [2,2′-azobis(2-methylpropionitrile)] in refluxing toluene, giving the corresponding tetrafluoroethyl-containing hydroxy lactams **3a** and **3c**, respectively, in excellent yields.[14] For adducts **2b** and **2d** (R = allyl) similar free-radical conditions gave products of 6-*exo* cyclization **3b** and **3d**, respectively, in good yields.[15] Formation of the product of phenylsulfanyl group reduction was minimized to less than 10% conversion by slow addition of *n*-Bu_3SnH and AIBN. The major compound **3b** was formed as a mixture of *cis* and *trans* isomers in an 76:24 ratio (determined by GC–MS analysis of the crude reaction mixture). A single *cis*-**3b** was obtained by crystallization from methanol, and its relative stereochemistry was determined by X-ray crystallography (Figure 1).[16] The phthalimide derived cyclized product **3d** was also formed as a mixture of *cis* and *trans* isomers in a ratio of 90:10. The major isomer of **3d** was assigned as *cis* by comparison of ^{1}H NMR and ^{19}F NMR data with *cis*-**3b**.

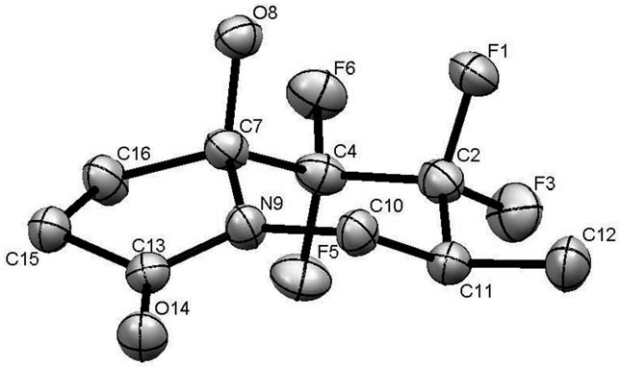
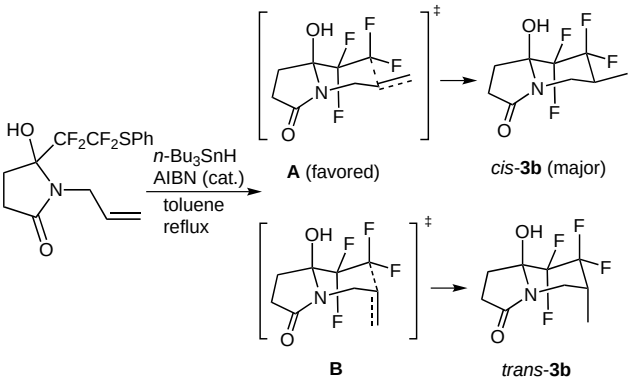


Figure 1 X-ray crystal structure of the major isomer of **3b** crystallizing in centrosymmetric space group. Hydrogen atoms are omitted for clarity, and thermal ellipsoids are set as 50% probability.

The stereochemistry assumed by compound **3b** can be rationalized as shown in Scheme 2, where radical-mediated cyclization proceeds through a 6-*exo*-trig cyclization mode. The forming fused bicyclic structure adopts a conformation with pseudoaxial hydroxy group. Transition state **A**, which leads to *cis*-**3b**, should be energetically more favorable than transition state **B** because it does not involve unfavorable 1,3-diaxial interactions between the fluorine atom and the methyl group. Conceptually, similar models were used to explain the stereochemistry of 5-*exo* and 6-*exo* cyclization to *gem*-difluoromethylenated 1-azabicyclic compounds in an analogous reaction sequence starting from cyclic imides and $PhSCF_2SiMe_3$.[17]



Scheme 2 Proposed transition states for 6-*exo* radical cyclization of **2b** to **3b**

We expected that the presence of hydroxy group in adducts **2** and **3** will provide convenient access to an iminium intermediated, which can be reacted with various nucleophiles. However, the compounds **2a** or **2c** could not be efficiently allylated with allyltrimethylsilane (Scheme 3), and the cyclized compounds **3b** and **3d** did not undergo reduction with Et_3SiH in the presence of $BF_3{\cdot}OEt_2$ (Scheme 4). This lack of reactivity is probably due to the

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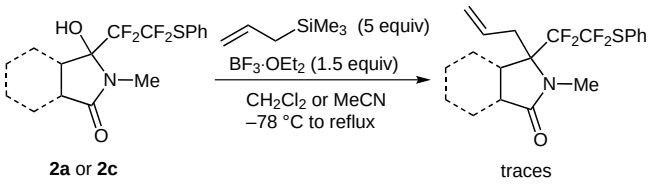
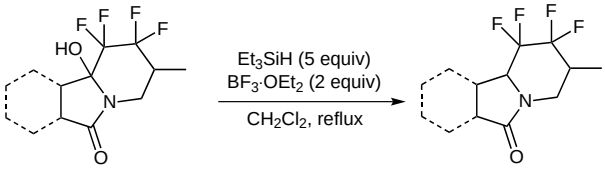
presence of the electron-withdrawing tetrafluoroethyl group, which destabilize the iminium intermediates.



2a or **2c** traces

Scheme 3 Attempted allylation of **2a** and **2c**



3b or **3d** traces

Scheme 4 Attempted reduction of **3b** and **3d**

In contrast, reduction of adducts **2a**,**c** and **3a**,**c** with Et_3SiH in the presence of $BF_3{\cdot}OEt_2$ to the corresponding *N*-methyl pyrrolidinones and isoindolinones **4** and **5** proceeded in excellent yields (Scheme 1).[18]

In summary, $PhSCF_2CF_2SiMe_3$ was successfully used as a tandem anion and radical tetrafluoroethylene equivalent for introduction of $–CF_2CF_2H$ and $–CF_2CF_2–$ moieties to cyclic *N*-methyl- and *N*-allyl-substituted succinimides and phthalimides. Fluoride-mediated nucleophilic addition of the reagent to cyclic imides provided (after hydrolysis of the intermediate TMS ether) N-substituted 5-hydroxy-5-[1,1,2,2-tetrafluoro-2-(phenylthio)ethyl]pyrrolidin-2-ones and 3-hydroxy-3-[1,1,2,2-tetrafluoro-2-(phenylthio)ethyl]isoindolin-1-ones **2** in moderate to good yields. Under free-radical conditions, compounds **2** underwent either substitution of the phenylsulfanyl group for hydrogen to **3a** and **3c** in high yields or 6-*exo* radical cyclization to the corresponding tetrafluorinated 1-azabicyclic compounds **3b** and **3d** in moderate to good yields and *cis* selectivities. Substitution of the hydroxy group for hydrogen in adducts **2a**,**c**, and **3a**,**c** with triethylsilane gave the corresponding *N*-methyl pyrrolidinones and isoindolinones **4** and **5** in high yields.

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Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

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(13) (a) **5-Hydroxy-1-methyl-5-[1,1,2,2-tetrafluoro-2-(phenylthio)ethyl]pyrrolidin-2-one (2a′)**
A solution of TBAT (108 mg, 10 mol%) in dry THF (2 mL) was added dropwise to a solution of $PhSCF_2CF_2SiMe_3$ (1.13 g, 4 mmol) and **1a** (226 mg, 2 mmol) in dry THF (10 mL). The mixture was stirred at r.t. under argon for 1 h, followed by the addition of aq HF (4 mL, 1 M), and stirred at 35 °C for another hour. The reaction product was extracted in Et_2O (3 × 25 mL), the combined organic phase was washed with brine (15 mL), dried ($MgSO_4$), and concentrated under reduced pressure. The resulting residue was purified by flash column chromatography (SiO_2, PE–EtOAc) to give the desired product **2a** (349 mg, 54% yield); white solid; mp 116–118 °C; R_f = 0.26 (PE–EtOAc, 50:50). ^1H NMR (400 MHz, $CDCl_3$): δ = 2.10–2.18 (m, 1 H), 2.39–2.45 (m, 2 H), 2.67–2.74 (m, 1 H), 2.87 (s, 3 H), 5.34 (br s, 1 H), 7.38–7.43 (m, 2 H), 7.46–7.50 (m, 1 H), 7.62–7.65 (m, 2 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 26.3, 28.8, 29.5, 90.7–91.2 (m),

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116.0 (tt, $^1J_{CF}$ = 262.2 Hz, $^2J_{CF}$ = 30.9 Hz), 123.8, 124.8 (tt, $^1J_{CF}$ = 289.0 Hz, $^2J_{CF}$ = 35.1 Hz), 129.2, 130.6, 137.2, 175.7. ^{19}F NMR (376 MHz, $CDCl_3$): δ = –118.7 (dd, 1 F, $^2J_{FF}$ = 273.2 Hz, $^3J_{FF}$ = 8.0 Hz), –117.5 (dd, 1 F, $^2J_{FF}$ = 273.2 Hz, $^3J_{FF}$ = 3.4 Hz), –85.4 (dd, 1 F, $^2J_{FF}$ = 224.5 Hz, $^3J_{FF}$ = 8.0 Hz), –83.6 (d, 1 F, $^2J_{FF}$ = 224.5 Hz, $^3J_{FF}$ = 3.4 Hz). IR (film): ν_{max} = 3191, 1680, 1578, 1105, 753, 691 cm^{-1}. MS (EI): *m/z* (%) = 190 (5), 114 (100), 109 (11), 86 (9), 58 (13). HRMS (ESI$^+$): *m/z* calcd for $C_{13}H_{14}F_4NO_2S$ [MH]$^+$: 324.06759; found: 324.06760.

(14) (a) **5-Hydroxy-1-methyl-5-(1,1,2,2-tetrafluoroethyl)-pyrrolidin-2-one (3a)**
A solution of *n*-Bu_3SnH (470 μL, 1.75 mmol) and AIBN (25 mg, 0.15 mmol) in dry toluene (3 mL) was added over 1 h using a syringe pump to a refluxing solution of **2a** (323 mg, 1 mmol) in dry toluene (5 mL). The resulting mixture was refluxed under argon for 3 h, followed by concentration under reduced pressure and purification by flash column chromatography (SiO_2, PE–EtOAc) to give product **3a** (202 mg, 94% yield); colorless oil; R_f = 0.23 (PE–EtOAc, 60:40). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.90–2.00 (m, 1 H), 2.26–2.38 (m, 2 H), 2.41–2.50 (m, 1 H), 2.73 (d, 3 H, *J* = 2.5 Hz), 6.59 (tdd, 1 H, $^2J_{HF}$ = 51.5 Hz, $^3J_{HF}$ = 9.6, 3.5 Hz), 7.36 (br d, 1 H, *J* = 2.8 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 25.8, 28.4, 28.8, 88.7–90.2 (m), 173.8. ^{19}F NMR (376 MHz, $CDCl_3$): δ = –138.3 (ddd, 1 F, $^2J_{FF}$ = 301.0 Hz, $^3J_{FF}$ = 10.7, 7.1 Hz), –134.3 (ddd, 1 F, $^2J_{FF}$ = 301.0 Hz, $^3J_{FF}$ = 12.5, 1.3 Hz), –130.6 (ddd, 1 F, $^2J_{FF}$ = 265.8 Hz, $^3J_{FF}$ = 12.5, 7.1 Hz), –126.8 (ddd, 1 F, $^2J_{FF}$ = 265.8 Hz, $^3J_{FF}$ = 10.7, 1.3 Hz). IR (film): ν_{max} = 3204, 1687, 1110 cm^{-1}. MS (EI): *m/z* (%) = 198 (6), 114 (100), 101 (8), 86 (20), 58 (45). HRMS (ESI$^+$): *m/z* calcd for $C_7H_{10}F_4NO_2$ [MH]$^+$: 216.06422; found: 216.06417.

(15) (a) **7,7,8,8-Tetrafluoro-8a-hydroxy-6-methylhexahydroindolizin-3(2*H*)-one (3b)**
A solution of *n*-Bu_3SnH (470 μL, 1.75 mmol) and AIBN (25 mg, 0.15 mmol) in dry toluene (3 mL) was added over 3 h using a syringe pump to a refluxing solution of **2b** (349 mg, 1 mmol) in dry toluene (5 mL). The resulting mixture was refluxed under argon overnight, followed by concentration under reduced pressure and purification by flash column chromatography (SiO_2, PE–EtOAc) to give product **3b** (188 mg, 78% yield); white solid; *cis*/*trans* = 76:24; mp (*cis*) 160–162 °C; R_f = 0.42 (PE–EtOAc, 25:75). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.91 (dd, 3 H, $^3J_{HH}$ = 7.3 Hz, $^4J_{HH}$ = 3.8 Hz, *trans*), 1.02 (d, 3 H, $^3J_{HH}$ = 6.7 Hz, *cis*), 1.88–1.97 (m, 2 H, *cis* + *trans*), 2.10–2.25 (m, 2 H, *cis* + *trans*), 2.28–2.35 (m, 1 H, *cis*), 2.37–2.40 (m, 1 H, *trans*), 2.42–2.53 (m, 2 H, *cis* + *trans*), 2.69–2.79 (m, 1 H, *cis*), 3.16–3.23 (m, 1 H, *trans*), 3.61–3.69 (m, 1 H, *trans*), 3.77–3.88 (m, 1 H, *cis*), 7.08 (s, 1 H, *trans*), 7.11 (s, 1 H, *cis*). ^{13}C NMR (100 MHz, $CDCl_3$): δ (*cis*) = 8.0 (d, *J* = 5.6 Hz), 25.9, 28.6, 35.3 (t, $^2J_{CF}$ = 21.4 Hz), 36.1 (d, *J* = 8.3 Hz), 88.1–88.7 (m), 171.8. ^{19}F NMR (376 MHz, $CDCl_3$): δ = –140.9 (ddd, 1 F, $^2J_{FF}$ = 252.4 Hz, $^3J_{FF}$ = 16.1, 10.4 Hz, *cis*), –135.8 (ddd, 1 F, $^2J_{FF}$ = 257.8 Hz, $^3J_{FF}$ = 16.3, 12.1 Hz, *trans*), –124.7 (ddd, 1 F, $^2J_{FF}$ = 255.1 Hz, $^3J_{FF}$ = 16.1, 14.6 Hz, *cis*), –121.2 (ddd, 1 F, $^2J_{FF}$ = 255.1 Hz, $^3J_{FF}$ = 18.1, 10.4 Hz, *cis*), –121.1 (ddd, 1 F, $^2J_{FF}$ = 252.4 Hz, $^3J_{FF}$ = 18.1, 14.6 Hz, *cis*), –120.4 (ddd, 1 F, $^2J_{FF}$ = 257.4 Hz, $^3J_{FF}$ = 17.9, 12.1 Hz, *trans*), –117.2 (ddd, 1 F, $^2J_{FF}$ = 257.8 Hz, $^3J_{FF}$ = 17.9, 12.4 Hz, *trans*), –106.1 (ddd, 1 F, $^2J_{FF}$ = 257.4 Hz, $^3J_{FF}$ = 16.3, 12.4 Hz, *trans*). IR (film): ν_{max} = 3252, 1699, 116 cm^{-1}. MS (EI): *m/z* (%) = 241 (2) [M]$^+$, 221 (58), 201 (22), 173 (12), 112 (100), 84 (77), 55 (35). HRMS (EI$^+$): *m/z* calcd for $C_9H_{11}F_4NO_2$ [M]$^+$: 241.0726; found: 241.0731.

(16) CCDC-860878 (for *cis*-**3b**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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(18) (a) **1-Methyl-5-[1,1,2,2-tetrafluoro-2-(phenylthio)-ethyl]pyrrolidin-2-one (4a)**
To a solution of **2a** (323 mg, 1 mmol) in CH_2Cl_2 (5 mL) was added dropwise triethylsilane (0.8 mL, 5 mmol) and BF_3·OEt_2 (377 μL, 3 mmol) under argon atmosphere. The mixture was refluxed for 2.5 h, followed by the addition of sat. $NaHCO_3$ solution (10 mL), and extracted with CH_2Cl_2 (3 × 25 mL). The combined extracts were washed with brine and dried over anhyd $MgSO_4$. Filtration followed by evaporation gave a crude product, which was purified by flash column chromatography (SiO_2, PE–EtOAc) to give the desired product **4a** (282 mg, 92% yield); colorless oil; R_f = 0.26 (PE–EtOAc, 80:20). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.15–2.34 (m, 3 H), 2.44–2.59 (m, 1 H), 2.95 (d, 3 H, *J* = 2.0 Hz), 4.04–4.13 (m, 1 H), 7.37–7.43 (m, 2 H), 7.44–7.51 (m, 1 H), 7.56–7.68 (m, 2 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 19.6–19.8 (m), 29.0, 30.9–31.0 (m), 60.8–61.4 (m), 129.3, 130.7, 137.2. ^{19}F NMR (376 MHz, $CDCl_3$): δ = –120.7 (dd, 1 F, $^2J_{FF}$ = 270.9 Hz, $^3J_{FF}$ = 20.1 Hz), –111.0 (d, 1 F, $^2J_{FF}$ = 270.9 Hz), –86.3 (s, 2 F). IR (film): ν_{max} = 3063, 1707, 1577, 1108 cm^{-1}. MS (EI): *m/z* (%) = 109 (6), 98 (100), 42 (5). HRMS (ESI$^+$): *m/z* calcd for $C_{13}H_{13}F_4NNaOS$ [MNa]$^+$: 330.05453; found: 330.05462.

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