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Synthesis of *gem*-Difluorinated Nitroso Compounds

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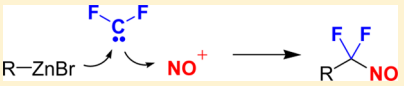
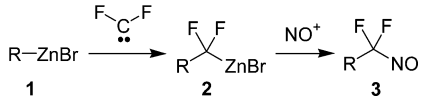
Supporting Information

ABSTRACT: A method for the synthesis of *gem*-difluorinated nitroso compounds is described. The reaction involves interaction of organozinc reagents with (bromodifluoromethyl)trimethylsilane followed by nitrosation of difluorinated organozinc species with an *n*-butyl nitrite/chlorotrimethylsilane system.



Nitroso compounds constitute a class of versatile intermediates which can be involved in cycloaddition and redox processes, as well as in reactions with radicals and nucleophiles.[1] While methods for the preparation of nitroso arenes[2,3] and α-bromo and α-chloro nitroso alkanes[4] are well developed, approaches to fluorinated aliphatic nitroso compounds are scarce. In particular, perfluorinated nitroso alkanes can be obtained by electrophilic nitrosation of perfluorinated mercury,[5] cadmium,[6] and silicon reagents.[7] Several other specific reactions involving harsh conditions and affording polyfluorinated nitroso alkanes have been reported.[8] At the same time, there is steadily growing interest in partially fluorinated molecules and reagents due to their utility in drug design.[9] In this regard, herein we describe a general method for the synthesis of *gem*-difluorinated nitroso compounds starting from conventional organozincs, difluorocarbene, and a nitrosating reagent (Scheme 1). The approach is based on our

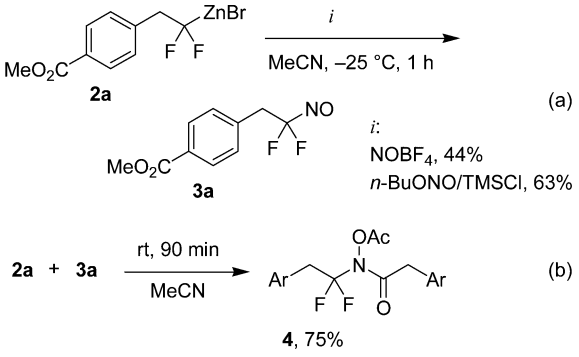
Scheme 1. Synthesis of Nitroso Compounds



recent discovery that treatment of reagents **1** with a difluorocarbene source leads to difluorinated reagents **2** which can be coupled with various electrophiles.[10,11]

Treatment of organozinc reagent **2a**[10a] with nitrosonium tetrafluoroborate (1.1 equiv) in acetonitrile gave the expected product **3a** in 44% yield (Scheme 2, eq a). ^{19}F NMR analysis of the crude product showed the presence of small amounts of other fluorinated materials, indicating partial decomposition of the starting organozinc **2a** under the reaction conditions. Fortunately, by switching to a milder nitrosating system, the combination of *n*-butyl nitrite (1.3 equiv) and chlorotrimethylsilane (1.2 equiv), which generates nitrosyl chloride,[12] allowed isolation of nitroso compound **3a** in 63% yield. Further attempts to improve the product yield were unsuccessful.[13] Presumably, the decreased yield is associated with the reaction

Scheme 2. Transformations of Organozinc 2a



of electrophilic nitroso product **3a** with starting organozinc reagent **2a**. Thus, when reagent **2a** was treated with half the amount of the nitrosating system under standard conditions (−25 °C, 1 h), the crude material contained only small amounts of an unidentified fluorine-containing product, and no nitroso compound **3a** was detected (according to ^{19}F NMR). However, when reagent **2a** was reacted with presynthesized nitroso compound **3a** at room temperature, product **4** was obtained in 75% yield[14] (Scheme 2, eq b).

A series of fluorinated organozinc reagents generated from organozinc bromides by CF_2-insertion were nitrosated using the *n*-BuONO/TMSCl system furnishing *gem*-difluorinated nitroso compounds **3** in reasonable yields (Table 1). The ester group, as well as the carbon−boron bond, remained unaffected upon nitrosation.[15]

Nitroso compounds **3** appear as blue or green-blue crystals or oils, with the color being characteristic for the monomeric nitroso form. For **3f**, the structure was confirmed by single crystal X-ray diffraction analysis.[16] However, upon prolonged storage (from week to month, 0 °C) the crystals have a tendency to gradually form a colorless microcrystalline powder. The latter material, being dissolved in $CDCl_3$, affords a blue

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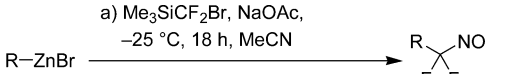
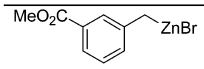
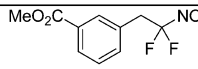
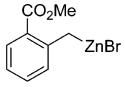
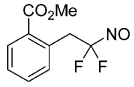
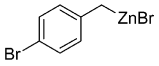
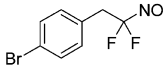
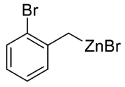
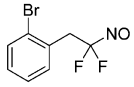
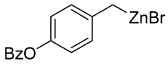
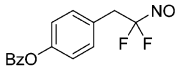
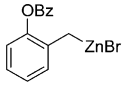
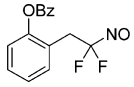
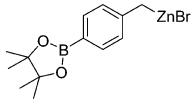
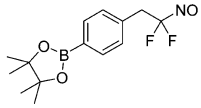
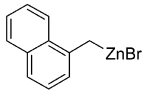
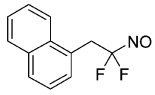
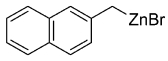
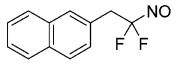
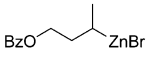
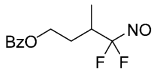
Table 1. Nitrosation of Organozinc Reagents



1	3	Yield of 3, %[a]
	 **3b**	73
	 **3c**	46
	 **3d**	66
	 **3e**	65
	 **3f**	75
	 **3g**	56
	 **3h**	61
	 **3i**	32
	 **3j**	40
	 **3k**	58

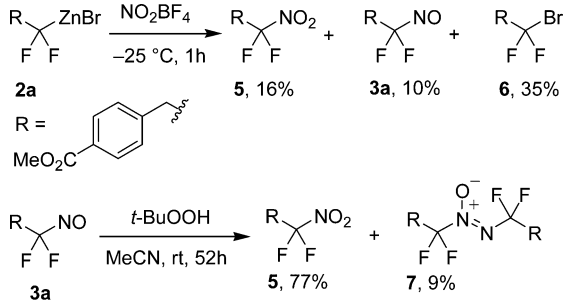
[a]Isolated yield based on organozinc bromide.

solution having identical NMR spectra to those of the freshly prepared product, while evaporation of the solvent leads back to blue crystals. This behavior is indicative of a monomer/dimer equilibrium typical for nitroso compounds.[17]

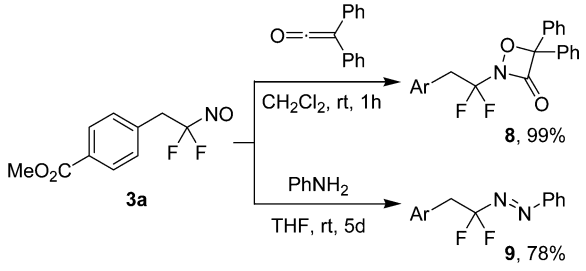
Similar to nitrosation, we attempted to perform nitration of fluorinated oragnozinc **2a** (Scheme 3). When nitronium tetrafluoroborate was used, a mixture was formed containing small amounts of nitro and nitroso compounds, along with bromination product **6** being a major component (yields were determined by ^{19}F NMR; compound **6** was previously described[10a]). The formation of product **6** is likely due to the oxidative reactivity of the nitrating agent.[18] Nevertheless, the nitro compound **5** can be isolated in 77% yield after oxidation of the nitroso group with *tert*-butyl hydroperoxide, though azoxy product **7** was also obtained after chromatographic separation as a minor byproduct.

We also briefly investigated the reactivity of the nitroso group attached to the *gem*-difluorinated carbon (Scheme 4).

Scheme 3. Synthesis of Nitro Compound 5



Scheme 4. Reactions of Compound 3a



Thus, nitroso compound **3a** readily reacted at room temperature with diphenylketene affording [2 + 2] cycloaddition product **8** as a single regioisomer (the structure of **8** was confirmed by X-ray analysis[16]). High regioselectivity of the cycloaddition may be associated with the strong electron-withdrawing character of a difluorinated substituent adjacent to the nitroso group.[19] At the same time, the reaction of **3a** with aniline was slow, and corresponding azo compound **9** was obtained in 78% yield after 5 days.[20]

In summary, a method for the synthesis of *gem*-difluorinated nitroso compounds by combining organozinc reagents, a difluorocarbene source, and a nitrosating electrophile has been developed. Despite variable yields, the reaction features straightforward assembly of the nitroso compounds, which are difficult to access by other means.

EXPERIMENTAL SECTION

General Methods. All reactions were performed in Schlenk flasks under an argon atmosphere. Column chromatography was carried out employing silica gel (230–400 mesh). Acetonitrile was distilled from CaH_2 and stored over MS 4A. Organozinc reagents **1a–f,h**[10a] and (bromodifluoromethyl)trimethylsilane[11d] were prepared according to literature procedures.

Preparation of Organozinc Reagents ***1g,k.*** To a stirred suspension of zinc dust (for **1g**, 10.0 mmol, 654 mg; for **1k**, 15.0 mmol, 981 mg) in THF (5.0 mL) a drop of 1,2-dibromoethane was added. The mixture was heated to reflux, and then two drops of Me_3SiCl were added to a hot suspension, and the mixture was vigorously stirred for 15 min at 60 °C. During this period the formation of gas was observed and the zinc dust appeared to become a dark-gray fuzzy material (if this does not happen, an additional drop of Me_3SiCl should be added). Then, the reaction mixture was cooled in an ice/water bath, and the organic bromide [5 mmol; for **1g**, 2-(bromomethyl)phenyl benzoate; for **1k**, 3-bromobutyl benzoate[10c]] was added portionwise within 5 min. The mixture was stirred for 1 h at 0 °C and at room temperature (for **1g**, 18 h; for **1k**, 72 h). The stirring was discontinued, and the unreacted zinc was allowed to settle out. The concentration of the organozinc reagent was determined by iodometric titration.[10a]

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Preparation of Organozinc Reagents ***1i,j.*** To a stirred suspension of zinc dust (15.0 mmol, 981 mg) in THF (5.0 mL) a drop of 1,2-dibromoethane was added. The mixture was heated to reflux, and then two drops of Me_3SiCl were added to a hot suspension, which was followed by vigorous stirring of the mixture for 15 min at 60 °C. During this period the formation of gas was observed, and zinc dust appeared as a dark-gray fuzzy material (if this does not happen, an additional drop of Me_3SiCl should be added). Then, the reaction mixture was cooled to −25 °C, and a solution of the organic bromide (1.11 g, 5.0 mmol; for **1i**, 1-bromomethylnaphthalene; for **1j**, 2-bromomethylnaphthalene) in THF (4.0 mL) was added dropwise within 20 min. The mixture was allowed to warm gradually (within approximately 1 h) to 0 °C, followed by cooling in a bath substituted with ice/water, with continued stirring for 1 h. The cooling bath was removed, and the mixture was stirred for 18 h at room temperature. Then the stirring was discontinued, and unreacted zinc was allowed to settle out. The concentration of organozinc reagent was determined by iodometric titration.[10a]

General Procedure. A freshly titrated THF solution of **1** (1.5 mmol) was concentrated under vacuum until a solid or viscous residue was formed. The residue was dissolved in freshly distilled MeCN (1.5 mL). To the resulting solution was added sodium acetate (148 mg, 1.8 mmol) at room temperature, the reaction flask was immersed in a cold bath at −25 °C, and the mixture was stirred for 10 min at −25 °C. Then, Me_3SiCF_2Br (365 mg, 1.8 mmol) was added dropwise at −25 °C, and the reaction mixture was stirred at this temperature for 18 h. Then, *n*-BuONO (200 mg, 1.94 mmol) and Me_3SiCl (192 mg, 1.77 mmol) were successively added at −25 °C, and the reaction mixture was stirred at −25 °C for 1 h. The green-blue reaction mixture was quenched by addition of methyl *tert*-butyl ether (5 mL) and saturated aqueous $NaHCO_3$ (3 mL), and the reaction mixture was allowed to reach room temperature with stirring. The layers were separated, and the aqueous layer was washed with methyl *tert*-butyl ether (2 × 5 mL). The combined organic phases were dried over Na_2SO_4 and concentrated on a rotary evaporator, and the residue was purified by column chromatography on silica gel.

Methyl 4-(2,2-Difluoro-2-nitrosoethyl)benzoate ***(3a).*** 217 mg (63%). Blue crystals. Mp 44−47 °C. R_f 0.25 (EtOAc/hexane, 1/8). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.99 (d, J = 8.2 Hz, 2H), 7.26 (d, J = 8.1 Hz, 2H), 3.91 (s, 3H), 3.19 (t, J = 15.5 Hz, 2H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ: 166.6, 134.1 (t, J = 2.5 Hz), 130.6, 130.2, 130.1, 125.4 (t, J = 274.8 Hz), 52.3, 35.2 (t, J = 23.8 Hz). ^{19}F NMR (282 MHz, $CDCl_3$) δ: −100.6 (t, J = 15.5 Hz). Anal. Calcd for $C_{10}H_9F_2NO_3$ (229.18): C, 52.41; H, 3.96; N, 6.11. Found: C, 52.48; H, 4.07; N, 6.04.

Methyl 3-(2,2-Difluoro-2-nitrosoethyl)benzoate ***(3b).*** 251 mg (73%). Blue crystals. Mp 27−29 °C. R_f 0.27 (EtOAc/hexane, 1/8). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.99 (d, J = 6.9 Hz, 1H), 7.88 (s, 1H), 7.50−7.33 (m, 2H), 3.92 (s, 3H), 3.19 (t, J = 15.6 Hz, 2H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ: 166.6, 134.9, 131.7, 130.9, 129.50, 129.45 (t, J = 2.8 Hz), 129.0, 125.5 (t, J = 274.5 Hz), 52.3, 35.0 (t, J = 23.9 Hz). ^{19}F NMR (282 MHz, $CDCl_3$) δ: −100.8 (t, J = 15.6 Hz). Anal. Calcd for $C_{10}H_9F_2NO_3$ (229.18): C, 52.41; H, 3.96; N, 6.11. Found: C, 52.26; H, 4.01; N, 5.99.

Methyl 2-(2,2-Difluoro-2-nitrosoethyl)benzoate ***(3c).*** 158 mg (46%). Blue oil. R_f 0.36 (EtoAc/hexane, 1/8). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.97 (d, J = 7.6 Hz, 1H), 7.48 (t, J = 7.6 Hz, 1H), 7.39 (t, J = 7.6 Hz, 1H), 7.28 (d, J = 7.6 Hz, 1H), 3.87 (s, 3H), 3.76 (t, J = 15.7 Hz, 2H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ: 167.4, 133.1, 132.3, 131.3, 130.9, 130.8 (t, J = 2.8 Hz), 128.4, 126.0 (t, J = 274.9 Hz), 52.3, 32.6 (t, J = 23.6 Hz). ^{19}F NMR (282 MHz, $CDCl_3$) δ: −100.4 (t, J = 15.7). Anal. Calcd for $C_{10}H_9F_2NO_3$ (229.18): C, 52.41; H, 3.96; N, 6.11. Found: C, 52.43; H, 4.03; N, 6.09.

1-Bromo-4-(2,2-difluoro-2-nitrosoethyl)benzene ***(3d).*** 247 mg (66%). Blue oil. R_f 0.25 (hexane). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.46 (d, J = 8.3 Hz, 2H), 7.05 (d, J = 8.1 Hz, 2H), 3.10 (t, J = 15.5 Hz, 2H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ: 132.2, 132.1, 128.0 (t, J = 2.8 Hz), 125.3 (t, J = 274.8 Hz), 122.6, 34.7 (t, J = 23.9 Hz). ^{19}F NMR (282 MHz, $CDCl_3$) δ: −100.9 (t, J = 15.5 Hz). Anal. Calcd for $C_8H_6BrF_2NO$ (250.04): C, 38.43; H, 2.42; N, 5.60. Found: C, 38.62; H, 2.55; N, 5.41.

1-Bromo-2-(2,2-difluoro-2-nitrosoethyl)benzene ***(3e).*** 244 mg (65%). Blue oil. R_f 0.34 (hexane). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.58 (d, J = 7.9 Hz, 1H), 7.35−7.25 (m, 2H); 7.24−7.13 (m, 1H), 3.41 (t, J = 15.3, 2H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ: 133.5, 132.4, 130.0, 129.4 (t, J = 2.4 Hz), 127.8, 125.9 (t, J = 275.8 Hz), 125.8, 35.0 (t, J = 24.0 Hz). ^{19}F NMR (282 MHz, $CDCl_3$) δ: −100.3 (t, J = 15.3 Hz). Anal. Calcd for $C_8H_6BrF_2NO$ (250.04): C, 38.43; H, 2.42; N, 5.60. Found: C, 38.23; H, 2.39; N, 5.43.

4-(2,2-Difluoro-2-nitrosoethyl)phenyl Benzoate ***(3f).*** 327 mg (75%). Blue crystals. Mp 89−92 °C. R_f 0.39 (EtOAc/hexane, 1/8). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.21 (d, J = 7.5 Hz, 2H), 7.65 (t, J = 7.4 Hz, 1H), 7.52 (t, J = 7.6 Hz, 2H), 7.31−7.17 (m, 4H), 3.18 (t, J = 15.6 Hz, 2H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ: 165.1, 151.0, 133.8, 131.7, 130.3, 129.5, 128.7, 126.5 (t, J = 2.7 Hz), 125.6 (t, J = 274.8 Hz), 122.2, 34.7 (t, J = 23.9 Hz). ^{19}F NMR (282 MHz, $CDCl_3$) δ: −100.8 (t, J = 15.6 Hz). Anal. Calcd for $C_{15}H_{11}F_2NO_3$ (291.25): C, 61.86; H, 3.81; N, 4.81. Found: C, 61.78; H, 4.01; N, 4.65.

2-(2,2-Difluoro-2-nitrosoethyl)phenyl Benzoate ***(3g).*** 246 mg (56%). Blue crystals. Mp 41−43 °C. R_f 0.33 (EtOAc/hexane, 1/8). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.21 (d, J = 7.6 Hz, 2H), 7.69 (t, J = 7.3 Hz, 1H), 7.56 (t, J = 7.6 Hz, 2H), 7.41 (td, J = 7.6, 1.7 Hz, 1H), 7.36−7.22 (m, 3H), 3.21 (t, J = 15.1 Hz, 2H). ^{13}C{^{1}H} NMR (50 MHz, $CDCl_3$) δ: 164.7, 149.9, 134.1, 132.5, 130.3, 129.8, 129.1, 128.9, 126.4, 125.9 (t, J = 275.2 Hz), 123.2, 121.5 (t, J = 2.9 Hz), 29.9 (t, J = 24.5 Hz). ^{19}F NMR (282 MHz, $CDCl_3$) δ: −100.3 (t, J = 15.1 Hz). Anal. Calcd for $C_{15}H_{11}F_2NO_3$ (291.25): C, 61.86; H, 3.81; N, 4.81. Found: C, 61.71; H, 3.94; N, 4.76.

2-[4-(2,2-Difluoro-2-nitrosoethyl)phenyl]-4,4,5,5-tetramethyl-1,3,2-dioxaborolane ***(3h).*** 272 mg (61%). Blue crystals. Mp 76−80 °C. R_f 0.42 (EtOAc/hexane, 1/8). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.77 (d, J = 7.9 Hz, 2H), 7.19 (d, J = 7.8 Hz, 2H), 3.18 (t, J = 15.5 Hz, 2H), 1.35 (s, 12H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ: 135.3, 132.0 (t, J = 2.7 Hz), 129.9, 125.8 (t, J = 274.4 Hz), 84.1, 35.5 (t, J = 23.7 Hz), 25.0. ^{19}F NMR (282 MHz, $CDCl_3$) δ: −100.6 (t, J = 15.5 Hz). Anal. Calcd for $C_{14}H_{18}BF_2NO_3$ (297.11): C, 56.60; H, 6.11; N, 4.71. Found: C, 56.46; H, 5.98; N, 4.73.

1-(2,2-Difluoro-2-nitrosoethyl)naphthalene ***(3i).*** 106 mg (32%). Green-blue crystals. Mp 37−41 °C. R_f 0.24 (hexane). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.97−7.80 (m, 3H), 7.61−7.47 (m, 2H), 7.42 (t, J = 7.6 Hz, 1H), 7.33 (d, J = 7.0 Hz, 1H), 3.64 (t, J = 15.4 Hz, 2H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ: 134.1, 132.5, 129.9, 129.3, 129.0, 126.8, 126.5 (t, J = 275.3 Hz), 126.0, 125.33, 125.26 (t, J = 2.3 Hz), 123.7, 31.8 (t, J = 24.1 Hz). ^{19}F NMR (282 MHz, $CDCl_3$) δ: −99.7 (t, J = 15.4). Anal. Calcd for $C_{12}H_9F_2NO$ (221.20): C, 65.16; H, 4.10; N, 6.33. Found: C, 65.19; H, 4.04; N, 6.21.

2-(2,2-Difluoro-2-nitrosoethyl)naphthalene ***(3j).*** 134 mg (40%). Green-blue crystals. Mp 35−36 °C. R_f 0.25 (hexane). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.87−7.75 (m, 3H), 7.65 (s, 1H), 7.54−7.45 (m, 2H), 7.28 (d, J = 8.4 Hz, 1 H), 3.33 (t, J = 15.6 Hz, 2H). ^{13}C{^{1}H} NMR (50 MHz, $CDCl_3$) δ: 133.4, 133.0, 130.0, 128.6, 127.9, 127.8, 126.6, 126.5, 126.4 (t, J = 2.8 Hz), 126.0 (t, J = 274.7 Hz), 35.5 (t, J = 23.4 Hz). ^{19}F NMR (282 MHz, $CDCl_3$) δ: −100.4 (t, J = 15.6 Hz). Anal. Calcd for $C_{12}H_9F_2NO$ (221.20): C, 65.16; H, 4.10; N, 6.33. Found: 65.29; H, 4.27; N, 6.27.

4,4-Difluoro-3-methyl-4-nitrosobutyl Benzoate ***(3k).*** 225 mg (58%). Blue oil. R_f 0.16 (EtOAc/hexane, 1/30). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.02 (d, J = 7.4 Hz, 2H), 7.58 (t, J = 7.4 Hz, 1H), 7.45 (t, J = 7.6 Hz, 2H), 4.46−4.31 (m, 2H), 2.68−2.46 (m, 1H), 2.22−2.07 (m, 1H), 1.83−1.67 (m, 1H), 1.08 (d, J = 7.0 Hz, 3H).^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ: 166.4, 133.3, 130.0, 129.7, 128.6, 128.2 (t, J = 276.4 Hz), 61.7, 32.1 (t, J = 22.4 Hz), 28.1 (t, J = 3.1 Hz), 11.7 (t, J = 4.1 Hz). ^{19}F NMR (282 MHz, $CDCl_3$) δ: −107.4 (dd, J = 191.8, 12.3 Hz, 1F), −110.0 (dd, J = 191.8, 14.6 Hz, 1F). Anal. Calcd for $C_{12}H_{13}F_2NO_3$ (257.23): C, 56.03; H, 5.09; N, 5.45. Found: C, 56.10; H, 5.10; N, 5.46.

Methyl 4-[2-((Acetyloxy){1,1-difluoro-2-[4-(methoxycarbonyl)-phenyl]ethyl}amino)-2-oxoethyl]benzoate ***(4).*** A solution of organozinc **2a**[10a] (0.41 mmol, 1.0 mL of 0.41 M in MeCN [a stock solution of

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2a was stabilized with 3 equiv of DMF,[10a] with the concentration of organozinc reagent being determined by ^{19}F NMR using $PhCF_3$ as internal standard]) was added to a solid nitroso compound **3a** (93 mg, 0.406 mmol) at room temperature, and the mixture was stirred for 1.5 h. Then, EtOAc (4.0 mL) and a solution of $NaHSO_4$ (240 mg, 2.0 mmol in 2.0 mL of water) were successively added. The organic layer was separated, and the aqueous phase was washed with EtOAc (4.0 mL). The combined organic phases were dried over Na_2SO_4 and concentrated, and the residue was purified by column chromatography on silica gel to afford 136 mg (75%) of compound **4** as colorless crystals. Mp 128−131 °C. R_f 0.13 (EtOAc/hexane, 1/3). ^1H NMR (300 MHz, $CDCl_3$) δ: 7.98 (d, J = 8.1 Hz, 2H), 7.95 (d, J = 8.1 Hz, 2H), 7.33 (d, J = 8.1 Hz, 2H), 7.21 (d, J = 8.4 Hz, 2H), 3.95−3.53 (m, 4H); 3.89 (s, 6H), 2.16 (s, 3H). $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ: 170.9, 167.3, 166.83, 166.77, 137.6, 136.3 (t, J = 2.5 Hz), 130.7, 130.0, 129.9, 129.7, 129.6, 129.5, 120.2 (t, J = 259 Hz), 52.2, 41.8 (t, J = 26.3 Hz), 41.0 (t, J = 2.1 Hz), 17.9. ^{19}F NMR (282 MHz, $CDCl_3$) δ: −78.2 (br d, J = 198 Hz); −83.1 (br). Anal. Calcd for $C_{22}H_{21}F_2NO_7$ (449.40): C, 58.80; H, 4.71; N, 3.12. Found: C, 58.88; H, 4.80; N, 3.22.

Oxidation of Nitroso Compounds ***3a***. *tert*-Butylhydroperoxide (1.66 mmol, 214 mg of 70% aqueous solution) was added to a solution of **3a** (185 mg, 0.81 mmol) in acetonitrile (1 mL) at room temperature, and the mixture was stirred for 52 h. The precipitate was filtered affording 11 mg of compound **7**, the filtrate was concentrated under vacuum, and the residue was purified by column chromatography on silica gel (EtOAc/hexane, gradient from 1/10 to 1/3) furnishing nitro compound **5** (153 mg, 77%) and an additional 5 mg of compound **7** (combined yield 16 mg, 9%).

*Methyl 4-(2,2-Difluoro-2-nitroethyl)benzoate (**5**).* Colorless crystals. Mp 73−76 °C. R_f 0.39 (EtOAc/hexane, 1/3). ^1H NMR (300 MHz, $CDCl_3$) δ: 8.02 (d, J = 8.2 Hz, 2H), 7.32 (d, J = 8.0 Hz, 2H), 3.90 (s, 3H), 3.70 (t, J = 14.1 Hz, 2H). $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ: 166.4, 132.8 (t, J = 2.8 Hz), 131.0, 130.4, 130.3, 123.9 (t, J = 287.4 Hz), 52.3, 39.5 (t, J = 22.5 Hz). ^{19}F NMR (282 MHz, $CDCl_3$) δ: −86.3 (t, J = 14.1 Hz). Anal. Calcd for $C_{10}H_9F_2NO_4$ (245.18): C, 48.99; H, 3.70; N, 5.71. Found: C, 49.11; H, 3.79; N, 5.69.

*Methyl 4-{2-[{1,1-Difluoro-2-[4-(methoxycarbonyl)phenyl]ethyl}-NNO-azoxy]-2,2-difluoroethyl}benzoate (**7**).* Colorless crystals. Mp 158−161 °C. R_f 0.23 (EtOAc/hexane, 1/3). ^1H (300 MHz, $CDCl_3$) δ: 8.01 (d, J = 8.8 Hz, 2H), 7.98 (d, J = 8.8 Hz, 2H), 7.32 (d, J = 7.7 Hz, 2H), 7.29 (d, J = 7.7 Hz, 2H), 3.93 (s, 3H), 3.92 (s, 3H), 3.68 (t, J = 14.1 Hz, 2H), 3.60 (t, J = 14.5 Hz, 2H). $^{13}C\{^1H\}$ NMR (50 MHz, $CDCl_3$) δ: 166.8, 166.5, 135.8 (t, J = 3.0 Hz), 133.4 (t, J = 2.8 Hz), 130.8, 130.6, 130.3, 130.2, 130.1, 129.9, 122.8, 121.1 (t, J = 255.1 Hz), 52.4, 52.3, 39.9 (t, J = 23.1 Hz), 38.6 (t, J = 25.9 Hz). ^{19}F (282 MHz, $CDCl_3$) δ: −86.6 (t, J = 14.1 Hz, 2F), −87.3 (t, J = 14.5 Hz). Anal. Calcd for $C_{20}H_{18}F_4N_2O_5$ (442.36): C, 54.30; H, 4.10; N, 6.33. Found: C: 54.39; H: 4.19; N: 6.29.

*Methyl 4-[2,2-Difluoro-2-(3-oxo-4,4-diphenyl-1,2-oxazetidin-2-yl)ethyl]benzoate (**8**).* A solution of diphenylketene[21] (0.67 mmol, 0.5 mL of 1.3 M in Et_2O) was added dropwise to a solution of **3a** (101 mg, 0.44 mmol) in CH_2Cl_2 at room temperature. The mixture was stirred for 1 h and then diluted with hexane (5 mL), and the resulting solution was chromatographed on silica gel (EtOAc/hexane, 1/12) affording compound **8** as colorless crystals (185 mg, 99%). Mp 66−68 °C. R_f 0.18 (EtOAc/hexane, 1/8). ^1H NMR (300 MHz, $CDCl_3$) δ: 8.00 (d, J = 8.2 Hz, 2H), 7.53−7.37 (m, 12H), 3.91 (s, 3H), 3.63 (t, J = 13.9 Hz, 2H). $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ: 170.2, 166.8, 135.5 (t, J = 2.4 Hz), 135.1, 130.7, 130.0, 129.9, 129.6, 128.9, 126.5, 118.3 (t, J = 258.1 Hz), 103.4, 52.2, 40.4 (t, J = 25.0 Hz). ^{19}F NMR (282 MHz, $CDCl_3$) δ: −85.8 (t, J = 13.9 Hz). Anal. Calcd for $C_{24}H_{19}F_2NO_4$ (423.41): C, 68.08; H, 4.52; N, 3.31. Found: C, 68.05; H, 4.55; N, 3.31.

*Methyl 4-{2,2-Difluoro-2-[(E)-phenyldiazenyl]ethyl}benzoate (**9**).* Aniline (39 mg, 0.42 mmol) was added to a solution of **3a** (92 mg, 0.40 mmol) in THF (2 mL) at 0 °C, and the mixture was stirred at room temperature for 5 days. The mixture was concentrated under vacuum, and the residue was purified by column chromatography on silica gel (EtOAc/hexane, 1/10). 95 mg (78%). Yellow crystals. Mp 98−99 °C. R_f 0.23 (EtOAc/hexane, 1/8). ^1H NMR (300 MHz, $CDCl_3$) δ: 8.00 (d, J = 8.2 Hz, 2H), 7.84 (d, J = 6.8 Hz, 2H), 7.60−7.47 (m, 3H), 7.38 (d, J = 8.0 Hz, 2H), 3.90 (s, 3H), 3.50 (t, J = 14.7 Hz, 2H). $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ: 166.9, 150.8, 136.9 (t, J = 2.3 Hz), 133.4, 130.9, 129.8, 129.6, 129.4, 123.6, 123.6 (t, J = 252.8 Hz), 52.2, 39.9 (t, J = 27.1 Hz). ^{19}F NMR (282 MHz, $CDCl_3$) δ: −90.4 (t, J = 14.7 Hz). Anal. Calcd for $C_{16}H_{14}F_2N_2O_2$ (304.29): C, 63.15; H, 4.64; N, 9.21. Found: C: 63.11; H: 4.59; N: 9.37.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Copies of NMR spectra for all compounds, X-ray ellipsoid plots, and CIF files (for **3f** and **8**). This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(14) For a detailed discussion concerning the mechanism of formation of product **4** and its structural assignment, see Supporting Information.

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