

Addition of thiols to *gem*-difluoroalkenes under photoactivation conditions

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Abstract *gem*-Difluoroalkenes interact with thiols in the presence of catalytic amounts of disulfides affording α,α -difluorosubstituted sulfides. The reaction proceeds at room temperature upon irradiation with 400 nm light.

Keywords *gem*-difluoroalkenes, thiols, photocatalysis

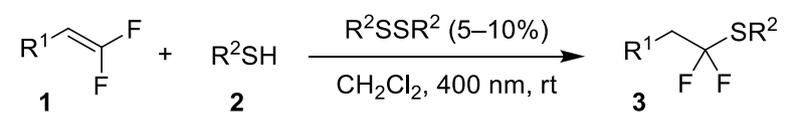
gem-Difluoroalkenes constitute an interesting class of organofluorine compounds. They can be used in medicinal chemistry, and several biologically active molecules bearing the difluorovinyl fragment have been described [1]. On the other hand, difluoroalkenes can serve as precursors in the synthesis of monofluoro- [2], difluoro- [3], and trifluorosubstituted compounds [4]. The difluoroolefines can be readily obtained from carbonyl compounds [5], diazoalkanes [6], and by other methods [2,7].

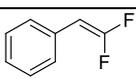
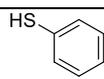
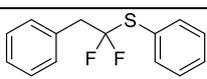
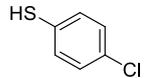
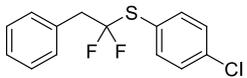
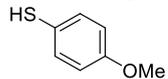
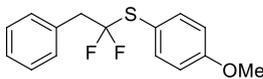
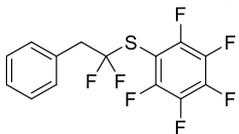
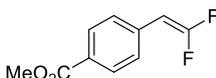
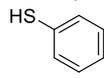
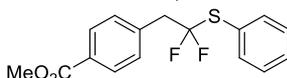
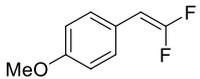
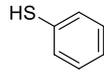
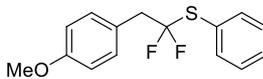
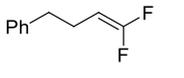
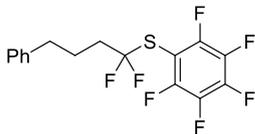
Recently, an addition reaction of thiols to difluoroalkenes mediated by base 1,1,3,3-tetramethylguanidine was described [8]. The reaction involves nucleophilic attack of the thiolate anion at the electronefficient double bond with subsequent protonation and proceeds at elevated temperature. Previously, it was also reported that the addition of thiols to difluoroalkenes can be performed in the presence of benzoyl peroxide, though the heating was required, and the products were obtained in moderate yields [9]. In the present work, we report that the addition reaction can be efficiently performed under mild neutral conditions if the process is mediated by light.

The reaction of difluoroalkenes **1** with thiols **2** was performed in dichloromethane at room temperature upon irradiation with a strip of light emitting diodes with the wavelength of 400 nm (Table 1). Corresponding disulfides were used as catalysts in amount of 5-10 mol %. The reactions with difluoroalkenes bearing aromatic group gave products in more than 90% yields, with the fastest reaction observed with pentafluorothiophenol **2d**. At the same time, the interaction of alkyl-

substituted substrate **1d** with pentafluorothiophenol was very slow, and even after two days, the yield of product **3g** was only 45%.

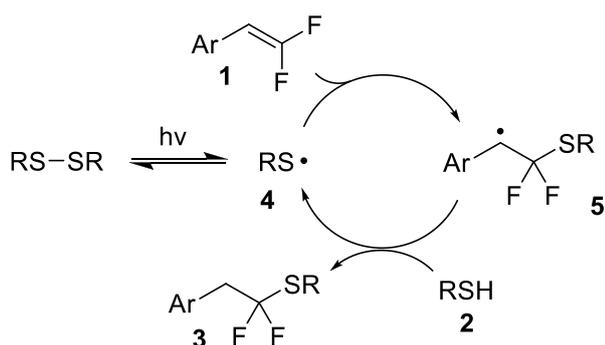
Table 1. Reaction of difluoroalkenes with thiols.



Alkene	Thiol	RSSR, mol %	Time, h	Product	Yield, %
	1a 	2a 5	2		3a 99
	1a 	2b 10	4		3b 99
	1a 	2c 5	3		3c 90
	1a 	2d 5	1		3d 95
	1b 	2a 5	6		3e 99
	1c 	2a 5	2		3f 97
	1d 	2d 10	48		3g 45

The proposed mechanism involves the generation of S-centered radical **4** upon irradiation of the disulfide. Subsequent addition of the radical at the double bond of the difluoroalkene leads to intermediate **5**, which abstracts the hydrogen atom from the starting thiol with the formation of the product and regeneration of radical **4**.

Scheme 1. Proposed reaction mechanism.



In summary, we demonstrated that addition of thiols to *gem*-difluoroalkenes can be effected upon light irradiation. Mild conditions and simplicity of the reaction set-up make this method attractive for the synthesis of α,α -difluorosubstituted sulfides.

Experimental part

Synthesis of disulfides 3 (general procedure). Under argon atmosphere, a solution of difluoroalkene **1** (0.75 mmol), thiol **2** (0.94 mmol) and disulfide (for **3a,c-f**, 0.038 mmol; for **3b,g**, 0.075 mmol) in dichloromethane (2 mL) was stirred upon irradiation with light emitting diodes (2x smd 3528, Arlight RT 2-5000 12V UV400 2X), with cooling of the reaction vessel with room temperature water. The reaction time is shown in Table 1. Then, the reaction mixture was concentrated under vacuum, and the residue was purified by column chromatography on silica gel.

[(1,1-Difluoro-2-phenylethyl)thio]benzene (**3a**) [10].

Yield 190 mg (99%), colorless oil, R_f 0.30 (EtOAc/hexane, 1/30). ^1H NMR (300 MHz, CDCl_3) δ : 3.52 (t, 2H, $J = 14.8$ Hz) 7.36–7.50 (m, 8H), 7.68 (dd, 2H, $J = 7.8, 1.4$ Hz). ^{13}C NMR (75 MHz, CDCl_3) δ : 45.3 (t, $J = 24.3$ Hz), 127.1 (t, $J = 2.2$ Hz), 127.8, 128.5, 128.8 (t, $J = 280.0$ Hz), 129.1, 129.8, 130.6, 132.1 (t, $J = 3.3$ Hz), 136.2. ^{19}F NMR (282 MHz, CDCl_3) δ : -72.5 (t, $J = 14.8$ Hz).

1-Chloro-4-[(1,1-difluoro-2-phenylethyl)thio]benzene (**3b**).

Yield 215 mg (99%), white crystals, mp 63–64 °C, R_f 0.40 (EtOAc/hexane, 1/25). ^1H NMR (300 MHz, CDCl_3) δ : 3.49 (t, 2H, $J = 14.8$ Hz), 7.30–7.45 (m, 7H), 7.55 (d, 2H, $J = 8.5$ Hz). ^{13}C NMR (75 MHz, CDCl_3) δ : 45.3 (t, $J = 24.2$ Hz), 125.5 (t, $J = 2.1$), 128.0, 128.6, 128.6 (t, $J = 280.6$), 129.4, 130.6, 131.9 (t, $J = 3.4$ Hz), 136.4, 137.5. ^{19}F NMR (282 MHz, CDCl_3) δ : -72.1 (t, $J = 14.8$ Hz). Calcd for $\text{C}_{14}\text{H}_{11}\text{ClF}_2\text{S}$ (284.02): C 59.05, H 3.89. Found: C 59.07, H 3.80.

1-[(1,1-Difluoro-2-phenylethyl)thio]-4-methoxybenzene (**3c**).

Yield 190 mg (90%), colorless oil, R_f 0.39 (EtOAc/hexane, 1/10). ^1H NMR (300 MHz, CDCl_3) δ : 3.51 (t, 2H, $J = 14.9$ Hz), 3.85 (s, 3H), 6.97 (d, 2H, $J = 8.8$ Hz), 7.37–7.47 (m, 5H), 7.61 (d, 2H, $J = 8.8$ Hz). ^{13}C NMR (75 MHz, CDCl_3) δ : 45.0 (t, $J = 24.5$), 55.3, 114.7, 117.5 (t, $J = 2.4$), 127.7, 128.5, 128.7 (t, $J = 279.3$ Hz), 130.6, 132.3 (t, $J = 3.2$ Hz), 138.2, 161.2. ^{19}F NMR (282 MHz, CDCl_3) δ : -73.2 (t, $J = 14.9$ Hz). HRMS (ESI): calcd for $\text{C}_{15}\text{H}_{14}\text{F}_2\text{OSNa}$ [$\text{M}+\text{Na}$] 303.0626; found 303.0638.

[(1,1-Difluoro-2-phenylethyl)thio]pentafluorobenzene (**3d**).

Yield 244 mg (95%), white crystals, mp 49–51 °C, R_f 0.36 (EtOAc/hexane, 1/25). ^1H NMR (300 MHz, CDCl_3) δ : 3.57 (t, 2H, $J = 14.7$ Hz), 7.38–7.48 (m, 5H). ^{13}C NMR (75 MHz, CDCl_3) δ : 45.2

(t, $J = 23.2$ Hz), 101.2 (tm, $J = 21.7$ Hz), 128.3, 128.4 (t, $J = 285.5$ Hz), 128.8, 130.6, 131.1 (t, $J = 3.5$ Hz), 137.9 (dm, $J = 256.2$ Hz), 143.5 (dtt, $J = 258.7, 13.4, 5.0$ Hz), 148.9 (dm, $J = 249.6$ Hz). ^{19}F NMR (282 MHz, CDCl_3) δ : -161.2 (m, 2F), -148.7 (tt, 1F, $J = 20.8, 4.5$ Hz), -129.9 (m, 2F), -70.1 (tt, 2F, $J = 14.7, 5.8$ Hz). Calcd for $\text{C}_{14}\text{H}_7\text{F}_7\text{S}$ (340.02): C 49.42, H 2.07. Found: C 49.28, H 2.01.

Methyl 4-[(2,2-difluoro-2-phenylethyl)thio]-benzoate (3e).

Yield 234 mg (99%), white crystals, mp 70–71 °C, R_f 0.32 (EtOAc/hexane, 1/8). ^1H NMR (300 MHz, CDCl_3) δ : 3.49 (t, 2H, $J = 14.8$ Hz), 3.93 (s, 3H), 7.34–7.49 (m, 5H), 7.60 (d, 2H, $J = 7.4$ Hz), 8.04 (d, 2H, $J = 8.3$ Hz). ^{13}C NMR (75 MHz, CDCl_3) δ : 45.0 (t, $J = 24.6$ Hz), 52.1, 126.7 (t, $J = 2.2$ Hz), 128.3 (t, $J = 280.0$ Hz), 129.1, 129.7, 129.9, 130.6, 136.2, 137.2 (t, $J = 3.0$ Hz), 166.8. ^{19}F NMR (282 MHz, CDCl_3) δ : -72.3 (t, $J = 14.8$ Hz). HRMS (ESI): calcd for $\text{C}_{16}\text{H}_{14}\text{F}_2\text{O}_2\text{SNa}$ [$\text{M}+\text{Na}$] 331.0575; found 331.0575.

1-[(2,2-Difluoro-2-(phenylthio)ethyl)]-4-methoxybenzene (3f) [5].

Starting thiophenol cannot be removed from the product by column chromatography. For the isolation of compound **3f**, the crude product was dissolved in ethanol (5 mL) followed by addition of hydrogen peroxide (25 μl of 30% aqueous solution, 0.3 mmol) and a crystal of iodine, and the mixture was stirred for 30 min. Then, iodine was neutralized by aqueous solution of $\text{Na}_2\text{S}_2\text{O}_3$, the mixture was extracted with methyl *tert*-butyl ether (3 \times 5 mL). The combined organic phases was dried over Na_2SO_4 , concentrated under vacuum, and the residue was purified by chromatography. Yield 204 mg (97%), colorless oil, R_f 0.32 (EtOAc/hexane, 1/10). ^1H NMR (300 MHz, CDCl_3) δ : 3.45 (t, 2H, $J = 14.7$ Hz), 3.85 (s, 3H), 6.96 (d, 2H, $J = 8.5$ Hz), 7.29 (d, 2H, $J = 8.5$ Hz), 7.38–7.49 (m, 3H), 7.67 (d, 2H, $J = 7.0$ Hz). ^{13}C NMR (75 MHz, CDCl_3) δ : 44.4 (t, $J = 24.3$ Hz), 55.2, 114.0, 124.1 (t, $J = 3.5$ Hz), 127.2 (t, $J = 2.1$ Hz), 129.0 (t, $J = 279.6$ Hz), 129.1, 129.7, 131.7, 136.2, 159.4. ^{19}F NMR (282 MHz, CDCl_3) δ : -72.4 (t, $J = 14.7$ Hz).

1,1-Difluoro-4-phenylbutylpentafluorophenylsulfide (3g).

Yield 125 mg (45%), colorless oil, R_f 0.35 (EtOAc/hexane, 1/25). ^1H NMR (300 MHz, CDCl_3) δ : 1.97–2.11 (m, 2H), 2.18–2.37 (m, 2H), 2.77 (t, 2H, $J = 7.5$ Hz), 7.20–7.31 (m, 6H), 7.31–7.41 (m, 4H). ^{13}C NMR (75 MHz, CDCl_3) δ : 24.8 (t, $J = 3.3$ Hz), 35.0, 38.1 (t, $J = 22.4$ Hz), 101.3 (tm, $J = 18.8$ Hz), 126.4, 128.5, 128.7, 129.5 (t, $J = 283.5$ Hz), 137.9 (dm, $J = 256.5$ Hz), 140.9, 143.5 (dtt, $J = 258.7, 13.7, 5.0$ Hz), 148.9 (dm, $J = 250.4$ Hz). ^{19}F NMR (282 MHz, CDCl_3) δ : -161.1 (m, 2F), -148.7 (tt, 1F, $J = 21.2, 4.2$ Hz), -120.0 (m, 2F), -70.9 (tt, 2F, $J = 14.6, 6.3$ Hz). MS (EI), m/z : 368.08 [M^+], 198.94, 169.08, 149.03, 129.02, 127.00, 105.00, 90.99.

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