Supporting Information for

Second-Generation Tags for Fluorous Chemistry Exemplified with a New Fluorous Mitsunobu Reagent

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I. General Methods

All experiments were done under an atmosphere of argon. All proton, carbon, and fluorine NMR spectra were recorded at 300 MHz, 75 MHz, and 121.5 MHz. Chemical shifts are reported in parts per million (ppm) and the spectra were calibrated from the residual solvent signal of CDCl₃ (¹³C NMR, t 77.23 ppm, ¹H NMR 7.27 ppm) or acetone-d₆ (¹³C NMR 29.92 ppm (septet), ¹H NMR 2.04 (quintet)). All the fluorine NMR spectra were calibrated using CFCl₃ (0 ppm (singlet)). In reporting spectral data, the following abbreviations are used: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, b = broad. Infrared (IR) spectra were recorded on an IBM IR/32 spectrometer and ran as neat films or chloroform solutions on sodium chloride plates. Unless otherwise stated, high and low resolution mass spectra were taken under EI mode and are reported in units of m/e. Flash chromatography was performed using silica gel (230-400 mesh). Melting points were measured on a Temp-Melt apparatus and were uncorrected. GC analyses were performed on a Hewlett-Packard 5890 instrument (column: 30 m x 0.32 mm x 0.25 µm HP-1 methyl siloxane).
II. Experimental Procedures

**Synthesis of Bis(perfluoro-t-butyloxypropyl)diazodicarboxylate (7p).**

3-(2′,2′,2′-Trifluoro-1′,1′-bis-trifluoromethylethoxy)propanol (3p): In 100 mL flask equipped with magnetic stirrer and ice bath, argon gas inlet, and addition funnel, KOH (1.4 g, 25 mmol) was suspended in methylethyl ketone (30 mL). (CF₃)₂COH (2, 3.5 mL, 25 mmol) was added dropwise over 20 min at 0 °C. The ice bath was removed and the mixture was stirred vigorously for 2 h at room temperature. BrCH₂CH₂CH₂OH (2.5 mL, 28.5 mmol) was added by a syringe. The mixture was under reflux for 12 hours. Then, it was cooled to r.t. Ice water (50 mL) was added. The mixture was exacted with ether (60 mL x 3). The organic layer was dried over MgSO₄, filtered, concentrated and distilled at ambient pressure to afford perfluoro-t-butyloxypropyl alcohol (3p, 5.8 g, 79 % yield) as a colorless oil (b.p. 70 °C/80 mmHg). ¹H NMR (CDCl₃) δ 4.27 (b, 1H), 4.16 (t, 2H, J₃H = 5.5 Hz), 3.75-3.83 (m, 2H), 1.88-1.99 (m, 2H). ¹³C NMR (CDCl₃) δ 120.4 (q, JCF = 288 Hz), 79.6 (m), 68.1 (s), 59.6 (s), 32.0 (s); ¹⁹F NMR (CDCl₃) δ –71.2 (s); IR (thin film) 3362, 1255, 1164 cm⁻¹; MS 294 (M⁺, 2%), 317 (M⁺+23, 5%), 215 (100%).

**Bis(perfluoro-t-butyloxypropyl)carboxyhydrazide (5p):** In a 1-neck, 100 mL flask equipped with magnetic stirrer, argon gas inlet, and addition funnel, carbonyl diimidazole (1.6 g, 9.6 mmol) was suspended in THF (15 mL, anhydrous). A solution of 3p (2.4 g, 8 mmol) in THF (10 mL, anhydrous) was added dropwise over 1 h. The mixture was stirred vigorously for 2 h. Water (0.1 ml) was added to quench, and the mixture stirred for 10 minutes. The mixture was
concentrated in vacuo to dryness to give crude 4p. The crude intermediate 4p was taken up in BTF (20 ml, dried over 4 Å MS). Hydrazine monohydrogen chloride (0.27 g, 4 mmol) was added, followed by addition of triethylamine (4.8 mL, 35 mmol). This was stirred at 70 °C overnight. It was then cooled to room temperature. The mixture was diluted with ether (100 mL). After transfer to a 250 mL separatory funnel, the mixture was washed with 2N HCl (2 x 15 mL) and brine (1 x 15 mL). The organic layer was dried over MgSO₄, filtered, and concentrated. The crude product was loaded on a silica chromatography column. Hexane/ethyl acetate (6:1) was used to elute pure diperfluoro-t-butyloxypropyl carboxyhydrazide (5p, 2.3 g, 83 % yield for two steps) as a white solid (m.p. 29-31 °C). \( ^1H \) NMR (CDCl₃) \( \delta \) 6.54 (b, 2H), 4.35 (t, J = 5.0 Hz, 4H), 4.11 (t, J = 5.8 Hz, 4H), 2.00-2.08 (m, 4H); \( ^{13}C \) NMR (CDCl₃) \( \delta \) 156.6 (s), 121.5 (q, J = 290.5 Hz), 79.8 (m), 66.3 (s), 62.1 (s), 29.4 (s); \( ^{19}F \) NMR (CDCl₃) \( \delta \) –71.2 (s); IR (thin film) 3310, 1732 cm⁻¹; LRMS 673 (M⁺+1, 75%), 695 (M⁺+23, 100%), 711 (M⁺+39, 67%), 279 (16%); HRMS calculated 673.0643, found 673.0673.

Bis(perfluoro-t-butyloxypropyl)diazodicarboxylate (7p): In a 100 mL flask equipped with magnetic stirrer, argon gas inlet, addition funnel, 5p (2 g, 2.4 mmol) was suspended in BTF (20 mL). Pyridine (0.6 mL, 7.5 mmol) was added, and the mixture was purged with dry argon for five minutes while stirring vigorously. A solution of bromine (0.21 mL, 3.9 mmol) in BTF (10 mL) was added dropwise slowly. The mixture was stirred at room temperature for 3 h. The mixture was filtered in fume hood. The solid was washed with BTF (2 x 10 mL) filtered. The solid waste was then washed with Na₂S₂O₃ solution for disposal. The all BTF was combined and concentrated. A little yellow precipitation stick to the bottle after concentration was removed by transferring the product into another container. The product was further dried under high
vacuum overnight to provide diperfluoro-t-butylxyethyl carboxyhydrazide (7p, 2.0 g, 100%) as yellow oil. $^1$H NMR (CDCl$_3$) $\delta$ 4.60 (t, $J = 6.1$ Hz, 4H), 4.18 (t, $J = 5.7$ Hz, 4H), 2.16-2.27 (m, 4H); $^{13}$C NMR (CDCl$_3$) $\delta$ 160.2, 120.5 (q, $J = 290.7$ Hz), 79.9 (m), 65.6 (s), 65.0 (s), 29.0 (s); $^{19}$F NMR (CDCl$_3$) $\delta$ –71.1 (s); IR (thin film) 1782 cm$^{-1}$; MS 670 (M$^+$, $3\%$), 693 (M$^+$+23, $2\%$), 356 (100%).

Synthesis of Bis(perfluoro-t-butylxyethyl) carboxyhydrazide (5e).

2-(2',2',2'-Trifluoro-1',1'-bis-trifluoromethylethoxy)ethanol: In 100 mL flask equipped with magnetic stirrer and ice bath, argon gas inlet, and addition funnel, KOH (1.4 g, 25 mmol) was suspended in methylethyl ketone (30 mL). (CF$_3$)$_3$COH (2, 3.5 mL, 25 mmol) was added dropwise over 20 min at 0°C. The ice bath was removed and the mixture was stirred vigorously for 2 h at room temperature. BrCH$_2$CH$_2$OH (2.0 mL, 28.5 mmol) was added by a syringe. The mixture was under reflux for 12 hours. Then, it was cooled to r.t. Ice water (50 mL) was added. The mixture was exacted with ether (60 mL x 3). The organic layer was dried over MgSO$_4$, filtered, concentrated and distilled at ambient pressure to afford perfluoro-t-butylxyethyl alcohol (3b, 5.4 g, 77 % yield) as a colorless oil (b.p. 125°C, lit.$^1$: 124°C).

Synthesis of Bis(perfluoro-t-butylxyethyl) carboxyhydrazide (5e): In a 1-neck, 100 mL flask equipped with magnetic stirrer, argon gas inlet, and addition funnel, carbonyl diimidazole (1.6 g, 9.6 mmol) was suspended in THF (15 mL, anhydrous). A solution of 3e (2.2 g, 8 mmol) in THF (10 mL, anhydrous) was added dropwise over 1 h. The mixture was stirred vigorously
for 2 h. Water (0.1 ml) was added to quench, and the mixture stirred for 10 minutes. The mixture was concentrated in vacuo to dryness give crude 4e.

The crude intermediate 4e was taken up in BTF (20 ml, dried over 4 Å MS). Hydrazine monohydrogen chloride (0.27 g, 4 mmol) was added, followed by addition of triethylamine (4.8 mL, 35 mmol). This was stirred at 70 °C overnight. It was then cooled to room temperature. The mixture was diluted with ether (100 mL). After transfer to a 250 mL separatory funnel, the mixture was washed with 2N HCl (2 x 15 mL) and brine (1 x 15 mL). The organic layer was dried over MgSO₄, filtered, and concentrated. The crude product was loaded on a silica chromatography column. Hexane/ethyl acetate (6:1) was used to elute pure diperfluoro-t-butyloxyethyl carboxyhydrazide (5b, 2.1 g, 82 % yield for two steps) as white oil. ¹H NMR (acetone-d₆) δ 8.47 (b, 2H), 4.26 (t, J = 4.2 Hz, 4H), 2.83 (t, J = 4.3 Hz, 4H); ¹³C NMR (acetone-d₆) δ 157.1, 121.2 (q, J = 289.9 Hz), 80.5 (m), 69.7 (s), 64.2 (s); ¹⁹F NMR (acetone-d₆) δ −71.6 (s); IR (thin film) 3296, 1740 cm⁻¹; MS 645 (M⁺+1, 60%), 667 (M⁺+23, 100%), 683 (M⁺+39, 45%).

General Procedure for the Mitsunobu Reactions: Synthesis of 4-Cyanophenyl 4-Fluorobenzyl Ether (10a): 4-Cyanophenol (8, 51 mg, 0.42 mmol), p-fluorobenzyl alcohol (9, 26 µL, 0.23 mmol), F-TPP (300 mg, 0.35 mmol) and F-DEAD (355 mg, 0.42 mmol) were combined by procedure B₂ in THF (10 mL) (procedure B: A solution of F-DEAD in THF (5 mL) was slowly added to a solution of phenol, alcohol, and F-TPP in THF (5 mL) at room temperature over 30 mins.). After the reaction was completed, the crude reaction mixture was concentrated and taken up in ether (100 mL) and washed with aqueous 1 M sodium hydroxide solution (2 x 10 mL) and brine (2 x 10 mL). The ether layer was dried with magnesium sulfate

S  
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and concentrated. The crude reaction mixture was loaded onto a 20 g FluoroFlash cartridge using MeOH (<1 mL). Washing with 80:20 MeOH:H₂O (30 mL) eluted the organic product. A second wash with MeOH (100 mL) eluted the fluorous byproducts. The MeOH:water fraction was concentrated and dried to give 47 mg 4-cyanophenyl 4-fluorobenzyl ether (10a, 90 % yield; 96 % GC purity), which is a known compound. Its CAS registry number is [56442-14-9].

**Recycling of the reagents:** The crude fluorous fraction from the spe was purified by flash chromatography, as previously described.² The recovered hydrazide 5b was reconverted to 7p by the above procedure. The recovered phosphine oxide was reconverted to the phosphine by the published procedure.³
III. Apparatus for F-SPE

Designed by Mr. Simon Nielsen, visiting graduate student from the Danish University of Pharmaceutical Sciences.

As shown in Figure 1, the new F-SPE apparatus consists of 1) a FluoroFlash cartridge; 2) a septum stopper with its top part cropped; 3) a needle; 4) a vacuum adapter; 5) a separatory funnel.
IV. References


$^1$H NMR, Acetone-d$_6$
$^1$H, $^13$C NMR, Acetone-d$_6$

![NMR Spectrum]

$\text{CH}_2\text{CH}_{\text{2}}\text{O}N$($\text{CH}_2\text{O})_3$O-N$\text{CH}_2\text{CH}_{\text{2}}\text{O}\text{H}$

$\text{CH}_2\text{CH}_{\text{2}}\text{O}N$($\text{CH}_2\text{O})_3$O-N$\text{CH}_2\text{CH}_{\text{2}}\text{O}$

$\text{CH}_2\text{CH}_{\text{2}}\text{O}N$($\text{CH}_2\text{O})_3$O-N$\text{CH}_2\text{CH}_{\text{2}}\text{O}$

$\text{CH}_2\text{CH}_{\text{2}}\text{O}N$($\text{CH}_2\text{O})_3$O-N$\text{CH}_2\text{CH}_{\text{2}}\text{O}$
$^{19}$F NMR, Acetone-d$_6$
$^{59}$Sn (Control), $^1$H NMR, Acetone-d$_6$

$\text{n-C}_4\text{F}_9(\text{CH}_2)_3\text{O NH O(CH}_2)_3\text{n-C}_4\text{F}_9$
5n (Control), $^{13}$C NMR, Acetone-d$_6$
$^{19}$F NMR, Acetone-d$_6$ n-C$_4$F$_9$(CH$_2$)$_3$O NH O(CH$_2$)$_3$-n-C$_4$F$_9$
$^7$H NMR, CDCl$_3$

$\text{I-C}_{4}\text{F}_9\text{O}\left(\text{CH}_2\right)_3\text{O-N=}
\text{N=O(\text{CH}_2\text{O})_4\text{C}_4\text{F}_9}$
$^{7}J_{19F-NMR}, \text{CDCl}_3$

$t$-$C_4F_9O(CH_2)_3O$ $N$

$O$ $N$ $O(CH_2)_3O-t-C_4F_9$

$t$-$C_4F_9O(CH_2)_3O$ $N$

$O$ $N$ $O(CH_2)_3O-t-C_4F_9$

$^{17}S$
10c, 1H NMR, Acetone-d$_6$ (After F-SPE)