Synthesis of 1,1-Difluoroalkanes via Phase Transfer Catalysed Reaction of 1,1-*bis*-Triflates with KF in the Presence of Cocatalyst – Ph_3SnF

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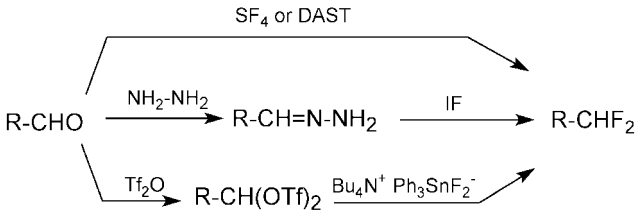
Abstract: 1,1-*bis*-Triflates treated with KF in the presence of triphenyltin fluoride and tetrabutylammonium hydrogen sulfate give 1,1-difluoroalkanes

Key words: phase transfer catalysis, tin compound, fluorination

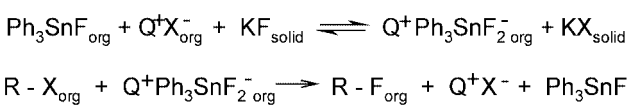
Fluoro substituents modify biological activity of organic molecules hence numerous drugs and plant protection agents contain fluorine.[1] Introduction of fluorine into organic molecules, is a rather difficult task for which typical methods of synthesis of other halo derivatives usually are not applicable, thus there is a continuous interest in methods of fluorination of organic compounds.

1,1-Difluoroalkanes are usually prepared from aldehydes via direct reaction with SF_4[2] or DAST[3,4] or in two-step processes: conversion of the aldehydes into hydrazones followed by reaction of the latter with IF[5] or conversion into *gem*-*bis*-trifluoromethanesulfonates (triflates), which are subsequently treated with $Bu_4N^+Ph_3SnF_2^-$[6] (Scheme 1).



Scheme 1

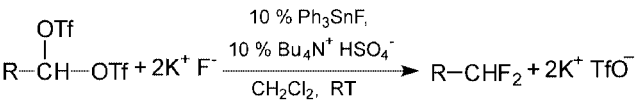
All these methods are inconvenient due to high cost, difficulties in handling and availability of the required reagents. In particular, the reaction of the *gem*-*bis*-triflates with $Bu_4N^+Ph_3SnF_2^-$, a commercially available and stable compound, is prohibitive for practical synthesis, because of its high cost and high molecular weight. Since for complete conversion of the *bis*-triflates into 1,1-difluoroalkanes at least three equivalents of the salt is necessary, in order to prepare 1 g of difluoroalkane, more than 12 g of the reagent has to be used. In our previous communication[7] we have reported that instead of using this salt as a stoichiometric reagent for replacement of a nucleofugal group in an aliphatic compound with fluorine, the reaction can be performed in a cocatalytic liquid-solid phase-transfer catalysis (PTC) system, in which the PT catalyst is assisted by Ph_3SnF and analogous compounds. The system operates thanks to the possibility of continuous formation of the $Ph_3SnF_2^-$ anion in the reaction of Ph_3SnF with solid KF and is efficient for the synthesis of fluoroalkanes, including secondary derivatives (Scheme 2).



Scheme 2

Application of this system to the synthesis of 1,1-difluoroalkanes from 1,1-*bis*-triflates was not obvious. Earlier attempts to prepare 1,1-difluoroalkanes via the reaction with tetrabutylammonium fluoride or F^- anions in solid-liquis PTC system: CsF/18-crown-6 failed – the *bis*-triflates underwent decomposition to produce aldehydes and unidentified products.[6]

On the other hand when a solution of the *gem*-*bis*-triflates obtained from various aldehydes was treated with solid anhydrous KF in the presence of 10% molar $Bu_4N^+HSO_4^-$ and Ph_3SnF the replacement of the triflic groups with fluorine proceeded smoothly giving the expected 1,1-difluoroalkanes usually in good yields (Scheme 3, Table).



Scheme 3

Yield determined by GLC are usually good – somewhat lower when there is a secondary carbon in vicinity of the reaction center. In the latter case the reaction is slower and accompanied with β-elimination process giving vinyl triflates.

All the reactions presented in the Table were carried out under identical standard conditions, without optimization.[8] As usually in the case of volatile products prepared in small scale experiments, isolated yields were substantially lower than those determined by GLC analyses due to losses during isolation and purification.

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Table 1 Yields of 1,1-Difluoroalkanes in the Reaction of *bis*-Triflates with KF in Cocatalytic PTC System

Entry	Product	Time [h]	Yield [%][a]
1	1,1-Difluorooctane	30	68 (50)
2	1,1-Difluorodecane	30	72 (57)
3	1,1-Difluoro-2-phenyl-ethane	30	65
4	1,1-Difluoro-3-phenyl-propane	30	70
5	2-Ethyl-1,1-difluorohexane	48	48
6	Difluoromethylcyclohexane	48	58

[a] Determined by GLC using biphenyl as internal standard; isolated yields are given in parentheses.

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(8) **Typical Procedure**: Dried powdered KF (3.094 g, 53.3 mmol), Ph_3SnF (98 mg, 0.27 mmol) $Bu_4N^+HSO_4^-$ (91 mg, 0.27 mmol) and a freshly prepared solution of $RCH(OTf)_2$ in CH_2Cl_2 (2.7 mmol in 4.5 mL) were vigorously stirred at r.t. till the reaction was completed (16–48 h). The reaction mixture was diluted with ether (25 mL), the solid was filtered off, washed with diethyl ether (3 × 8 mL). The ether extracts were combined and the solvent was distilled using a 20 cm Vigreux column. The products were purified by chromatography (silica gel, *n*-pentane or *n*-pentane/CH_2Cl_2).

1,1-Difluorooctane: ^{1}H NMR (200 MHz, $CDCl_3$): 0.89 (t, *J* [^{1}H-^{1}H] = 6.5 Hz, 3 H CH_3), 1.25–1.50 (m, 10 H), 1.65–1.95 (m, 2 H), 5.79 (tt, ^2J [^{19}F–^{1}H] = 57 Hz; *J* [^{1}H–^{1}H] = 4.5 Hz, 1 H, CHF_2). ^{19}F NMR (178 MHz, $CDCl_3$): –116.2 (dt, ^2J [^{19}F–^{1}H] = 57 Hz; ^3J [^{19}F–^{1}H] = 17.5 Hz), MS (EI, 70 eV): 150 (M^+, <1), 130 (M–HF, 1); 84(20), 81(17), 73(15), 71(21), 69(14), 68(12), 59(12), 57(60), 56(36), 55(37), 43(100), 42(23), 41(65).

1,1-Difluorodecane: ^{1}H NMR (200 MHz, $CDCl_3$): 0.88 (t, *J* [^{1}H–^{1}H] = 6.5 Hz, 3 H CH_3), 1,23–1,50 (m, 14 H), 1.65–1.95 (m, 2 H), 5.79 (tt, ^2J [^{19}F–^{1}H] = 57 Hz; *J* [^{1}H–^{1}H] = 4.5 Hz, 1 H, CHF_2). ^{19}F NMR (178 MHz, $CDCl_3$): –116.2 (dt; ^2J [^{19}F–^{1}H] = 57 Hz, ^3J [^{19}F–^{1}H] = 17.5 Hz). MS (EI, 70 eV): 178 (M^+, 3), 107(13), 85(31), 84(16), 83(11), 82(15), 81(10), 73(16), 71(34), 70(21), 69(17), 57(80), 56(24), 55(34), 43(100), 42(15), 41(43).

1,1-Difluoro-2-phenyl-ethane: ^{1}H NMR (200 MHz, $CDCl_3$): 3.07 (td, ^3J [^{19}F–^{1}H] = 17.3 Hz, *J* [^{1}H–^{1}H] = 4.6 Hz, 2 H; Ph-CH_2-CHF_2), 5.85 (tt, ^2J [^{19}F–^{1}H] = 56 Hz, *J* [^{1}H–^{1}H] = 4.6 Hz, 1 H, CHF_2), 7.15–7,32 (m, 5 H, Ph). ^{19}F NMR (178 MHz, $CDCl_3$): –115,5 (dt, ^2J [^{19}F–^{1}H] = 56.6 Hz, ^3J [^{19}F–^{1}H] = 17.3 Hz). MS (EI, 70 eV): 142 (M^+, 33), 91(100), 65(14).

1,1-Difluoro-3-phenyl-propane: ^{1}H NMR (200 MHz, $CDCl_3$): 2.01– 2.29 (m, 2 H, CH_2-CHF_2), 2.78 (t, *J* [^{1}H–^{1}H] = 7.9 Hz, 2 H, Ph-CH_2), 5.80 (tt, ^2J [^{19}F–^{1}H] = 56.7 Hz, *J* [^{1}H–^{1}H] = 4.5 Hz, 1 H, CHF_2), 7.16–7.36 (m, 5 H, Ph). ^{19}F NMR (178 MHz, $CDCl_3$): –117.7 (dt, ^2J [^{19}F–^{1}H] = 56.8 Hz, ^3J [^{19}F–^{1}H] = 17.1 Hz). MS (EI, 70 eV): 156 (M^+, 28), 92(11), 91(100), 65(11).

2-Ethyl-1,1-difluorohexane: ^{1}H NMR (200 MHz, $CDCl_3$): 0.85–1.03 (m, 6 H), 1.25–1.55 (m, 8 H), 1.90–2.10 (1 H, $CHCHF_2$), 5.71 (td, ^2J [^{19}F–^{1}H] = 58.0 Hz, *J* [^{1}H–^{1}H] = 4.0 Hz, 1 H, CHF_2). ^{19}F NMR (178 MHz, $CDCl_3$): –123.43 (dd, ^2J [^{19}F–^{1}H] = 57.0 Hz, ^3J [^{19}F–^{1}H] = 15.7 Hz). MS (EI, 70 eV): 130 (M^+ – HF, 1), 57(100), 56(11), 55(16), 43(49), 42(22), 41(48), 39(13).

Difluoromethylcyclohexane: ^{1}H NMR (200 MHz, $CDCl_3$): 1.01–1.38 (m, 6 H), 1.61–1.84 (m, 5 H), 5.52 (td, ^2J [^{19}F–^{1}H] = 56.7 Hz, *J* [^{1}H–^{1}H] = 4.2 Hz, 1 H, CHF_2). ^{19}F NMR (178 MHz, $CDCl_3$): –123.82 (dd, ^2J [^{19}F–^{1}H] = 56.8 Hz, ^3J [^{19}F–^{1}H] = 14.1 Hz).