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Coupling of *N*-acyliminium chlorides with *gem*-difluorinated organozinc reagents

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General Methods. All reactions were performed under an argon atmosphere. 1,2-Dimethoxyethane (DME) was distilled from $LiAlH_4$. Column chromatography was carried out employing silica gel (230-400 mesh). Precoated silica gel plates F-254 were used for thin-layer analytical chromatography visualizing with UV and aq. KMnO4 solution. High resolution mass spectra (HRMS) were measured using electrospray ionization (ESI) and time-of-flight (TOF) mass analyzer. The measurements were done in a positive ion mode (interface capillary voltage – 4500 V) or in a negative ion mode (3200 V); mass range from m/z 50 to m/z 3000. Me_3SiCF_2Br was obtained according to a literature procedure.[1]

General procedure for the synthesis of compounds 5a-e.

*Prepartion of organozinc reagents **4***. A solution of organozinc reagent $RZnBr$[2] in THF (1.5 mmol) was concentrated under vacuum, the residue was dissolved in DME (2.3 mL), and sodium acetate (149 mg, 1.8 mmol) was added at room temperature. The mixture was cooled to –25 °C, Me_3SiCF_2Br (366 mg, 1.8 mmol) was added dropwise, and the mixture was stirred for at –25 °C for 18 h to give a solution of reagent **4**.

*Coupling of N-acyliminium chlorides with reagents **4***. A mixture of acid acyl chloride **2** (1.1 mmol), imine **1** (1.0 mmol) and CuCl (10 mg, 0.1 mmol) in DME (1 ml) was stirred at room temperature for 10 min and then immersed in an ice/water bath. A cold (about 0 °C) solution of RCF_2ZnBr **4** was added dropwise. After stirring for 30 min at 0 °C, the cooling bath was removed, and a homogeneous solution was stirred for 18 h. For the work-up, water (7 mL) was added, the mixture was extracted with methyl *tert*-butyl ether/hexane (1/1, 3×5 mL). The combined organic layers were filtered through Na_2SO_4, concentrated under vacuum, and the residue was purified by column chromatography.

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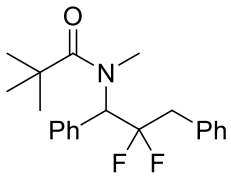
[1] M. D. Kosobokov, A. D. Dilman, V. V. Levin and M. I. Struchkova, *J. Org. Chem.*, 2012, **77**, 5850.

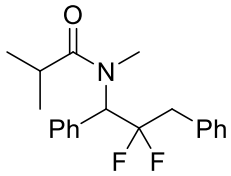
[2] V. V. Levin, A. A. Zemtsov, M. I. Struchkova and A. D. Dilman, *Org. Lett.*, 2013, **15**, 917.

***N*-(2,2-Difluoro-1,3-diphenylpropyl)-*N*-methylpivalamide (5a).**



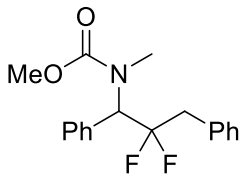
Yield 190 mg (55%). Colorless crystals. Mp 100–101 °C. R_f 0.32 (Hexanes/EtOAc, 8/1). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.35 (s, 9H), 3.02 (s, 3H), 3.08–3.39 (m, 2H), 6.51 (t, 1H, *J* = 15.6), 7.20–7.58 (m, 10H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 28.3, 33.2 (t, *J* = 3.4), 39.4, 41.9 (t, *J* = 24.3), 59.3 (dd, *J* = 27.0, 22.4), 123.9 (t, *J* = 250.1), 127.5, 128.2, 128.4, 128.8, 129.9 (t, *J* = 2.3), 132.3 (dd, *J* = 4.0, 1.7), 134.5, 178.6. ^{19}F NMR (282 MHz, $CDCl_3$) δ: –102.1 (dm, 1F, *J* = 250.1), –99.9 (dm, 1F, *J* = 250.1). HRMS (ESI): calcd for $C_{21}H_{26}F_2NO$ (M+H): 346.1977; found 346.1971.

***N*-(2,2-Difluoro-1,3-diphenylpropyl)-*N*-methylisobutyramide (5b).**



Yield 99 mg (30%). Colorless crystals. Mp 78–79 °C, R_f 0.22 (Hexanes/EtOAc, 8/1). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.13 (d, 3H, *J* = 11.9), 1.32 (d, 3H, *J* = 11.9), 2.78–3.01 (m, 5H), 3.05–3.41 (m, 2H), 6.40 (t, 1H, *J* = 6.1), 7.17–7.60 (m, 10H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 19.0, 19.5, 30.7, 31.4 (t, *J* = 2.3), 41.9 (t, *J* = 24.4), 57.9 (dd, *J* = 27.5, 23.0), 123.8 (t, *J* = 250.1), 128.3, 128.4, 128.8, 129.9, 130.0, 130.7, 132.3 (d, *J* = 5.7), 134.3, 178.2. ^{19}F NMR (282 MHz, $CDCl_3$) δ: –102.4 (dm, *J* = 123.9), –100.3 (dm, *J* = 123.9). HRMS (ESI): calcd for $C_{20}H_{24}F_2NO$ (M+H) 332.1820; found 332.1824.

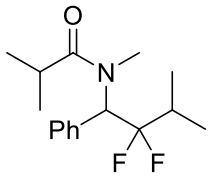
Methyl *N*-(2,2-difluoro-1,3-diphenylpropyl)-*N*-methylcarbamate (5c).



Yield 169 mg (53%). Colorless oil. R_f 0.24 (Hexanes/EtOAc, 10/1). Mixture of rotamers, 2:1. ^{1}H NMR (300 MHz, $CDCl_3$) δ: major rotamer, 2.81 (s, 3H), 3.11–3.43 (m, 2H), 3.77 (s, 3H), 5.85 (t, 1H, *J* = 15.6), 7.17–7.61 (m, 10H); minor rotamer, 2.88 (s, 3H), 3.73 (s, 3H), 5.52 (t, 1H, *J* = 14.7). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 30.5, 41.9 (t, *J* = 24.7), 53.2, 61.0 (dd, *J* = 26.4, 23.5), 123.9 (t, *J* = 250.1), 127.5, 128.4, 128.5, 128.8, 129.9, 130.6, 132.3 (dd, *J* = 9.6, 4.6), 134.0, 158.0. ^{19}F NMR (282 MHz, $CDCl_3$) δ: major rotamer, –102.5 (dm, *J* = 257.5), –100.5 (dm, *J* = 257.5); minor

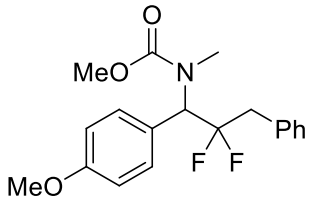
rotamer –101.2 (dm, *J* = 250.1), –99.5 (dm, *J* = 250.1). HRMS (ESI): calcd for $C_{18}H_{20}F_2NO_2$ (M+H) 320.1457; found 320.1448.

_N_-(2,2-Difluoro-3-methyl-1-phenylbutyl)-_N_-methylisobutyramide (5d).



Yield 105 mg (37%). Colorless oil. R_f 0.32 (Hexanes/EtOAc, 10/1). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.03 (d, 3H, *J* = 13.7), 1.08 (d, 3H, *J* = 13.7), 1.11 (d, 3H, *J* = 13.7), 1.19 (d, *J* = 13.7), 1.99–2.22 (m, 1H), 2.84 (sept, 1H, *J* = 13.7), 2.90 (s, 3H), 6.50 (dd, 1H, *J* = 31.1, 34.8), 7.30–7.40 (m, 3H), 7.46–7.53 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 15.4 (t, *J* = 4.6), 15.7 (t, *J* = 4.6), 18.9, 19.4, 30.7, 31.5 (t, *J* = 3.4), 33.1 (t, *J* = 23.0), 55.9 (dd, *J* = 26.4, 23.0), 126.5 (t, *J* = 250.5), 128.2, 128.7, 129.9, 134.5, 178.1. ^{19}F NMR (282 MHz, $CDCl_3$) δ: –112.3 (dt, 1F, *J* = 250.1, 17.0), –110.0 (dt, 1F, *J* = 250.1, 17.0). HRMS (ESI): calcd for $C_{16}H_{24}F_2NO$ (M+H) 284.1820; found 284.1825.

Methyl _N_-[2,2-difluoro-1-(4-methoxyphenyl)-3-phenylpropyl]-_N_-methylcarbamate (5e).



Yield 188 mg (54%). Colorless oil. R_f 0.24 (Hexanes/EtOAc, 5/1). Mixture of rotamers, 2:1. ^{1}H NMR (300 MHz, $CDCl_3$) δ: major rotamer, 2.81 (s, 3H), 3.10–3.40 (m, 2H), 3.76 (s, 3H), 3.81 (s, 3H), 5.79 (t, *J* = 15.7) 6.92 (d, 1H, *J* = 8.2), 6.98–7.16 (m, 2H), 7.17–7.40 (m, 6H); minor rotamer, 2.87 (s, 3H), 3.18 (s, 3H), 5.47 (br t, *J* = 14.7). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 41.9 (t, *J* = 25.1), 53.2, 55.3, 61.0 (t, *J* = 24.7), 113.9, 115.8, 122.1, 123.8 (t, *J* 250.1), 127.5, 128.4, 129.8, 130.6, 132.2 (m), 135.3, 159.8. ^{19}F NMR (282 MHz, $CDCl_3$) δ: major rotamer, –102.4 (dm, 1F, *J* = 250.1), –100.7 (dm, 1F, *J* = 250.1); minor rotamer, –101.0 (dm, 1F, *J* = 252.1), –99.8 (dm, 1F, *J* = 252.1). HRMS (ESI): calcd for $C_{19}H_{22}F_2NO_3$ (M+H) 350.1562; found 350.1555.