Reactions of *gem*-difluoro-substituted organozinc reagents with propargyl halides

A. A. Zemtsov, N. S. Kondratyev, V. V. Levin, M. I. Struchkova, and A. D. Dilman*

N. D. Zelinsky Institute of Organic Chemistry Russian Academy of Sciences,
47 Leninsky prosp., 119991 Moscow, Russian Federation.
Fax: +7 (499) 135 5328. E-mail: dilman@ioc.ac.ru

gem-Difluoro-substituted organozinc reagents undergo cross-coupling reaction with propargyl halides in the presence of catalytic amounts of copper cyanide. The reaction leads to the formation of 4,4-difluoroallenes in high yields.

Key words: organozinc reagents, cross-coupling, allenes.

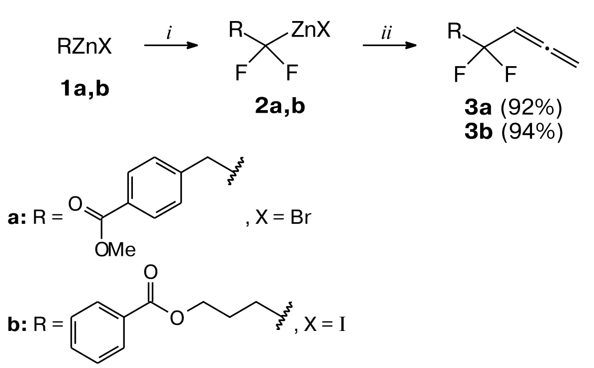
Fluoro-substituted organoelement compounds have found wide applications as nucleophilic reagents nowadays.[1,2] Usually, fluorine-containing derivatives of silicon[3] and copper[4,5] are used for this purpose, but recently organozinc reagents gained much attention.[6] However, wide application of the latter is still limited by low accessibility and moderate reactivity.

Recently, we have developed a new way to obtain *gem*-difluoro-substituted organozinc reagents via CF_2-unit insertion into a carbon—zinc bond.[7] Reagents thus obtained react with heteroatom electrophiles[7,8] and are cross-coupled with allyl halides,[9] 1-bromoalkynes,[10] and nitrostyrenes.[11] In the present work, we describe the results of cross-coupling of *gem*-difluoro-substituted organozinc reagents with propargyl halides. Similar cross-coupling of fluoro-substituted organocopper nucleophiles with propargyl halides was previously studied.[5]

The reaction of organozinc compounds **1a**,**b** with (bromodifluoromethyl)trimethylsilane in the presence of sodium acetate leads to reagents **2a**,**b** (Scheme 1). They react with propargyl bromide in the presence of copper cyanide (10 mol.%) to give high yields of allenes **3a**,**b**. We have found that addition of 2 equivalents of DMF to the reaction mixture is necessary to stabilize *gem*-difluoro-substituted organometallic intermediates.

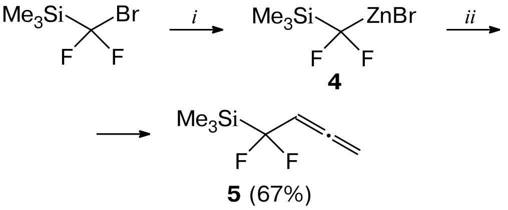
We have also shown that compound **4**, which was obtained from (bromodifluoromethyl)trimethylsilane upon halogen—zinc exchange,[12] can be involved in the cross-coupling reaction in the presense of 5 mol.% of copper cyanide (Scheme 2). Corresponding allene **5** was obtained in 67% yield after vacuum distillation.

Scheme 1



Reagents and conditions: *i*. Me_3SiCF_2Br, AcONa, MeCN; *ii*. $\equiv\!\!-\!\!\diagup^{Br}$, DMF (2 equiv.), CuCN (10%).

Scheme 2



Reagents and conditions: *i*. Pr^iZnI, $CoBr_2 \cdot dppe$ (0.5%), THF/DME; *ii*. $\equiv\!\!-\!\!\diagup^{Cl}$, DMF (2 equiv.), CuCN (5%).

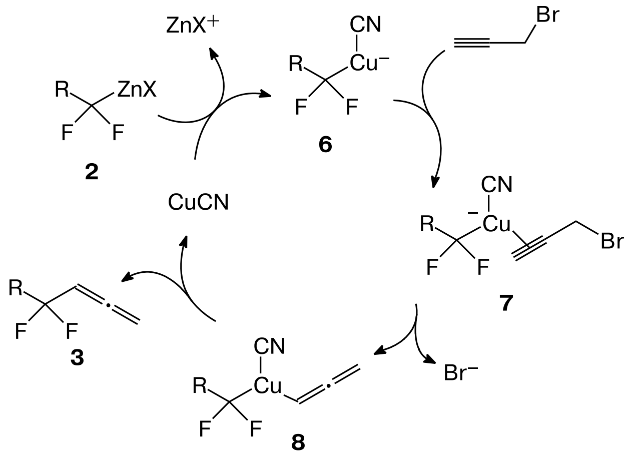
The proposed reaction mechanism is depicted in Scheme 3. Initially, organozinc reagent reacts with copper salt giving intermediate **6**. Then the cuprate complex coordinates to the triple bond leading to complex **7**. This is followed by elimination of the halide-anion and formation of Cu^{III} complex **8**. Finally, product **3** is formed upon reductive elimination and the copper catalyst is regenerated.

In conclusion, we have shown that *gem*-difluoro-substituted organozinc reagents can be used in cross-coupling reaction with propargyl halides. As a result, fluoro-substi-

---

Published in Russian in *Izvestiya Akademii Nauk. Seriya Khimicheskaya,* No. 11, pp. 2760—2762, November, 2016.

Scheme 3



tuted allenes, hardly accessible by other methods, can be readily obtained.

Experimental

All reactions were performed under dry argon. DMF was purified by vacuum distillation from P_2O_5 and was kept under MS 4Å. MeCN was purified by successive distillations from P_2O_5 and CaH_2, and was kept under MS 3Å. ^{1}H, ^{13}C and ^{19}F NMR spectra were recorded on Bruker AM300 spectrometer. High-resolution electrospray ionization (ESI) mass spectra were measured on a Bruker micrOTOF II instrument.[13] Starting compounds Me_3SiCF_2Br,[14] **1a**,**b**,[7a] and **4**[12] were prepared according to the literature procedures.

Synthesis of allenes 3 (general procedure). Anhydrous sodium acetate (197 mg, 2.4 mmol) was placed in a flask and heated at 150 °C for 15 min. Then the flask was cooled to room temperature and filled with argon. Organozinc reagent **1** (2.0 mmol in THF) was added and the suspension formed was concentrated in vacuo to get a viscous oil. The mixture was diluted with MeCN (2.0 mL) and cooled to –25 °C. Me_3SiCF_2Br (487 mg, 2.4 mmol) was added dropwise and the reaction mixture was stirred at –25 °C for 18 h. After that DMF (0.31 mL, 4.0 mmol), propargyl bromide (4.8 mmol, 0.53 mL, 80% solution in toluene) and copper cyanide (0.2 mmol, 18 mg) were added. The cooling bath was replaced by a cold water bath (3—5 °C) and the mixture was allowed to warm up to room temperature during next 2 h and then stirred at ~20 °C for additional 12 h. The reaction was quenched with HCl (8 mL, 0.5 *M* water solution) and the product was extracted with ethyl acetate (3×5 mL). The organic phase was dried over Na_2SO_4 and concentrated in vacuo. Product was purified by column chromatography on silica gel.

Methyl 4-(2,2-difluoropenta-3,4-dien-1-yl)benzoate (3a). Yield 438 mg (92%). Colorless oil. R_f 0.23 (hexane—EtOAc, 12 : 1). ^{1}H NMR (300 MHz, $CDCl_3$), δ: 3.32 (t, 2 H, CH_2, J = 15.3 Hz); 3.91 (s, 3 H, CH_3); 5.05 (td, 2 H, $=CH_2$, J = 6.5 Hz, J = 6.3 Hz); 5.38 (tt, 1 H, CH, J = 8.7 Hz, J = 6.3 Hz); 7.36 (d, 2 H, CH_{Ar}, J = 8.2 Hz); 7.99 (d, 2 H, CH_{Ar}, J = 8.2 Hz). ^{13}C {^{1}H} NMR (75 MHz, $CDCl_3$), δ: 43.5 (t, CH_2, J = 26.9 Hz); 52.2 (CH_3); 80.5 ($=CH_2$); 90.4 (t, CH, J = 33.1 Hz); 119.7 (t, CF_2, J = 240.9 Hz); 129.4 (C—CO_2Me); 129.6 (C_{Ar}); 130.8 (C_{Ar}); 138.1 (t, C_{Ar}, J = 3.6 Hz); 167.0 (CO); 208.4 (t, =C=, J = 9.5 Hz). ^{19}F NMR (282 MHz, $CDCl_3$), δ: –88.7 (tdt, CF_2, J = 15.3 Hz, J = 8.7 Hz, J = 6.5 Hz). HRMS (ESI), found *m/z*: 239.0885. $C_{13}H_{13}F_2O_2$. Calculated, *m/z*: 239.0878 [M + H].

4,4-Difluorohepta-5,6-dien-1-yl benzoate (3b). Yield 474 mg (94%). Colorless oil. R_f 0.22 (hexane—EtOAc, 12 : 1). ^{1}H NMR (300 MHz, $CDCl_3$), δ: 1.94—2.08 (m, 2 H, CH_2); 2.09—2.25 (m, 2 H, CH_2CF_2); 4.36 (t, 2 H, CH_2O, J = 6.2 Hz); 5.09 (dt, 2 H, $=CH_2$, J = 7.2 Hz, J = 6.5 Hz); 5.44 (tt, 1 H, CH, J = 7.9 Hz, J = 7.2 Hz); 7.39—7.48 (m, 2 H, CH_{meta}); 7.51—7.60 (m, 1 H, CH_{para}); 8.04 (dd, 2 H, CH_{ortho}, J = 8.1 Hz, J = 1.1 Hz). ^{13}C {^{1}H} NMR (75 MHz, $CDCl_3$), δ: 22.2 (t, CH_2, J = 4.2 Hz); 33.6 (t, $\underline{C}H_2CF_2$, J = 26.3 Hz); 64.1 (CH_2O); 80.2 ($=CH_2$); 90.5 (t, CH, J = 33.8 Hz); 121.1 (t, CF_2, J = 238.5 Hz); 128.4 (C_{Ar}); 129.6 (C_{Ar}); 130.2 ($\underline{C}$—CO_2); 133.0 (C_{Ar}); 166.5 (CO); 208.3 (t, $=CH_2=$, J = 10.1 Hz). ^{19}F NMR (282 MHz, $CDCl_3$), δ: –90.1 (dtt, CF_2, J = 7.9 Hz, J = 7.6 Hz, J = 6.5 Hz). HRMS (ESI), found *m/z*: 275.0859. $C_{14}H_{14}F_2O_2Na$. Calculated, *m/z*: 275.0854 [M + Na].

(1,1-Difluorobuta-2,3-dien-1-yl)(trimethyl)silane (5). DMF (30.0 mmol, 4.65 mL), propargyl chloride (15.8 mmol, 1.15 mL), and copper cyanide (0.75 mmol, 67.5 mg) were added to reagent **4** (15.0 mmol, 19.2 mL 0.78 *M* in diglyme) at 0 °C. The suspension obtained was warmed to ~20 °C under stirring during next 2 h followed by stirring at ~20 °C for additional 12 h. The product was separated by recondensation in vacuo (7 Torr) using a liquid nitrogen trap. The liquid obtained was dissolved in pentane (10 mL), washed with water (5×10 mL), and filtered through Na_2SO_4. Pentane was evaporated under atmospheric pressure and the residue was distilled in vacuo, b.p. 80—82 °C (100 Torr). Yield 1.63 g (67%). ^{1}H NMR (300 MHz, $CDCl_3$), δ: 0.20 (s, 9 H, $SiMe_3$); 5.05 (td, 2 H, CH_2, J = 8.2 Hz, J = 6.9 Hz); 5.40 (tt, 1 H, CH, J = 12.7 Hz, J = 6.9 Hz). ^{13}C {^{1}H} NMR (75 MHz, $CDCl_3$), δ: 4.4 (t, $SiMe_3$, J = 1.7 Hz); 79.4 (t, CH_2, J = 2.2 Hz); 90.7 (t, CH, J = 26.6 Hz); 125.6 (t, CF_2, J = 259.9 Hz); 208.5 (t, =C=, J = 12.9 Hz). ^{19}F NMR (282 MHz, $CDCl_3$), δ: –107.2 (td, CF_2, J = 12.7 Hz, J = 8.2 Hz). Found (%): C, 52.04; H, 7.43. $C_7H_{12}F_2Si$ (162.25). Calculated (%): C, 51.82; H, 7.45.

This study was financially supported by the Ministry of Education and Science of the Russian Federation (Project MK-6724.2016.3) and the Russian Foundation for Basic Research (Project No. 14-03-00293).

References

1. D. J. Burton, Z.-Y. Yang, *Tetrahedron*, 1992, **48**, 189.
2. V. P. Ananikov, L. L. Khemchyan, Y. V. Ivanova, V. I. Bukhtiyarov, A. M. Sorokin, I. P. Prosvirin, S. Z. Vatsadze, A. V. Medved´ko, V. N. Nuriev, A. D. Dilman, V. V. Levin, I. V. Koptyug, K. V. Kovtunov, V. V. Zhivonitko, V. A. Likholobov, A. V. Romanenko, P. A. Simonov, V. G. Nenajdenko, O. I. Shmatova, V. M. Muzalevskiy, M. S. Nechaev, A. F. Asachenko, O. S. Morozov, P. B. Dzhevakov, S. N. Osipov, D. V. Vorobyeva, M. A. Topchiy, M. A. Zotova, S. A. Ponomarenko, O. V. Borshchev, Y. N. Luponosov, A. A. Rempel, A. A. Valeeva, A. Y. Stakheev, O. V. Turova, I. S. Mashkovsky, S. V. Sysolyatin, V. V. Malykhin, G. A. Bukhti-

yarova, A. O. Terent´ev, I. B. Krylov, *Russ. Chem. Rev.* (*Engl. Transl.*), 2014, **83**, 885.

3. (a) G. K. S. Prakash, A. K. Yudin, *Chem. Rev.*, 1997, **97**, 757; (b) X. Liu, C. Xu, M. Wang, Q. Liu, *Chem. Rev.*, 2015, **115**, 683–730; (c) A. D. Dilman, V. V. Levin, *Mendeleev Commun.*, 2015, **25**, 239.
4. (a) H. Morimoto, T. Tsubogo, N. D. Litvinas, J. F. Hartwig, *Angew. Chem., Int. Ed. Engl.*, 2011, **50**, 3793; (b) A. Lishchynskyi, M. A. Novikov, E. Martin, E. C. Escudero-Adan, P. Novak, V. V. Grushin, *J. Org. Chem.*, 2013, **78**, 11126; (c) H. Wang, D. A. Vicic, *Synlett*, 2013, **24**, 1887.
5. (a) T. S. N. Zhao, K. J. Szabo, *Org. Lett.*, 2012, **14**, 3966; (b) Y. Miyake, S. Ota, M. Shibata, K. Nakajima, Y. Nishibayashi, *Chem. Commun.*, 2013, **49**, 7809; (c) J. Zhu, F. Wang, W. Huang, Y. Zhao, W. Ye, J. Hu, *Synlett*, 2011, 899; (d) Y.-L. Ji, J.-J. Kong, J.-H. Lin, J.-C. Xiao, Y.-C. Gu, *Org. Biomol. Chem.*, 2014, **12**, 2903; (e) B. R. Ambler, S. Peddi, R. A. Altman, *Org. Lett.*, 2015, **17**, 2506.
6. (a) L. Xu, D. A. Vicic, *J. Am. Chem. Soc.*, 2016, **138**, 2536; (b) K. Aikawa, Y. Nakamura, Y. Yokota, W. Toya, K. Mikami, *Chem. Eur. J.*, 2015, **21**, 96; (c) K. Aikawa, W. Toya, Y. Nakamura, K. Mikami, *Org. Lett.*, 2015, **17**, 4996; (d) P. T. Kaplan, B. Chen, D. A. Vicic, *J. Fluorine Chem.*, 2014, **168**, 158; (e) I. Popov, S. Lindeman, O. Daugulis, *J. Am. Chem. Soc.*, 2011, **133**, 9286; (f) L.-P. B. Beaulieu, J. F. Schneider, A. B. Charette, *J. Am. Chem. Soc.*, 2013, **135**, 7819; (g) M. M. Kremlev, W. Tyrra, A. I. Mushta, D. Naumann, Y. L. Yagupolskii, *J. Fluorine Chem.*, 2010, **131**, 212.
7. (a) V. V. Levin, A. A. Zemtsov, M. I. Struchkova, A. D. Dilman, *Org. Lett.*, 2013, **15**, 917; (b) V. V. Levin, A. A. Zemtsov, M. I. Struchkova, A. D. Dilman, *J. Fluorine Chem.*, 2015, **171**, 97.
8. (a) V. O. Smirnov, M. I. Struchkova, D. E. Arkhipov, A. A. Korlyukov, A. D. Dilman, *J. Org. Chem.*, 2014, **79**, 11819; (b) V. O. Smirnov, A. S. Maslov, V. V. Levin, M. I. Struchkova, A. D. Dil´man, *Russ. Chem. Bull.* (*Engl. Transl.*), 2014, **63**, 2564 [*Izv. Akad. Nauk, Ser. Khim.*, 2014, 2564].
9. A. A. Zemtsov, N. S. Kondratyev, V. V. Levin, M. I. Struchkova, A. D. Dilman, *J. Org. Chem.*, 2014, **79**, 818.
10. A. A. Zemtsov, A. D. Volodin, V. V. Levin, M. I. Struchkova, A. D. Dilman, *Beilstein J. Org. Chem.*, 2015, **11**, 2145.
11. N. S. Kondratyev, V. V. Levin, A. A. Zemtsov, M. I. Struchkova, A. D. Dilman, *J. Fluorine Chem.*, 2015, **176**, 89.
12. (a) M. D. Kosobokov, V. V. Levin, A. A. Zemtsov, M. I. Struchkova, A. A. Korlyukov, D. E. Arkhipov, A. D. Dilman, *Org. Lett.*, 2014, **16**, 1438; (b) A. D. Volodin, A. A. Zemtsov, V. V. Levin, M. I. Struchkova, A. D. Dilman, *J. Fluorine Chem.*, 2015, **176**, 57.
13. A. M. Tsedilin, A. N. Fakhrutdinov, D. B. Eremin, S. S. Zalesskiy, A. O. Chizhov, N. G. Kolotyrkina, V. P. Ananikov, *Mendeleev Commun.*, 2015, **25**, 454.
14. M. D. Kosobokov, A. D. Dilman, V. V. Levin, M. I. Struchkova, *J. Org. Chem.*, 2012, **77**, 5850.

Received July 14, 2016;
in revised form September 14, 2016