



Coupling of α,α -difluoro-substituted organozinc reagents with 1-bromoalkynes

Artem A. Zemtsov¹, Alexander D. Volodin^{1,2}, Vitalij V. Levin¹, Marina I. Struchkova¹ and Alexander D. Dilman^{*1}

Letter

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Address:

¹N. D. Zelinsky Institute of Organic Chemistry, 119991 Moscow, Leninsky prosp. 47, Russian Federation and ²Higher Chemical College, Russian Academy of Sciences, 125047 Moscow, Miuskaya sq. 9, Russian Federation

Email:

Alexander D. Dilman* - adil25@mail.ru

* Corresponding author

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Abstract

α,α -Difluoro-substituted organozinc reagents generated from conventional organozinc compounds and difluorocarbene couple with 1-bromoalkynes affording *gem*-difluorinated alkynes. The cross-coupling proceeds in the presence of catalytic amounts of copper iodide in dimethylformamide under ligand-free conditions.

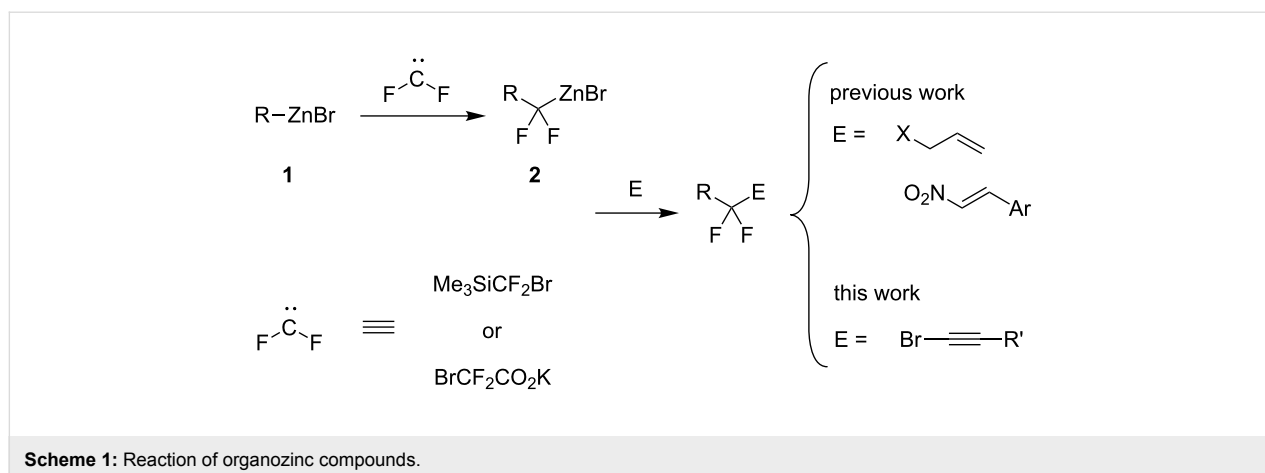
Introduction

gem-Difluorinated organic compounds have attracted increasing attention nowadays due to their applicability in medicinal chemistry [1,2] and other fields. Indeed, unique stereoelectronic properties of the CF₂-unit may be exploited in conformational analysis [3-5], carbohydrate and peptide research [6,7], and reaction engineering [8,9].

Typically, the difluoromethylene fragment is created by deoxy-fluorination, which requires harsh or hazardous conditions [10,11]. Alternatively, functional group manipulations starting from available CF₂-containing building blocks can be considered, but multistep sequences render this approach laborious

[12-14]. Difluoro-substituted cyclopropanes and cyclopropenes constitute a specific class of compounds accessible by difluorocarbene addition to multiple bonds [15].

Recently, we proposed a general method for assembling *gem*-difluorinated structures from organozinc reagents **1**, difluorocarbene, and a terminating electrophile [16-21] (Scheme 1). (Bromodifluoromethyl)trimethylsilane [16-18] or potassium bromodifluoroacetate [19] can be used as precursors of difluorocarbene. In this process, the use of C-electrophiles is particularly important since it allows for the formation of two C–C bonds within one experimental run. Previously, as C-elec-



trophiles in this methodology, only allylic substrates [17] and nitrostyrenes (with the NO₂ serving as a leaving group) [20], were employed. Herein, we report that 1-bromoalkynes, which are known to be involved in reactions with various organometallic compounds [22–27], can be used as suitable coupling partners for difluorinated organozinc compounds **2**. This reaction provides straightforward access to α,α -difluorinated alkynes [13,14,28–31]. Our method is based on facile zinc/copper exchange allowing for versatile couplings described for non-fluorinated organozinc compounds [32–37].

Results and Discussion

Organozinc compound **2a** generated from benzylzinc bromide was first evaluated in a reaction with haloalkynes derived from phenylacetylene (Table 1). First, most reactive iodo-substituted alkyne **3a-I** (X = I) was evaluated in the presence of copper iodide (10 mol %). Expected product **4a** was formed in 12% yield, but its yield was tripled simply by adding 2 equiv of DMF additive (Table 1, entries 1 and 2). However, in these experiments, the reaction mixtures contained about 40% of (2,2-

difluoro-2-iodoethyl)benzene (PhCH₂CF₂I) arising from zinc/iodine exchange between **2a** and the iodoalkyne. Chloroalkyne **3a-Cl** was markedly less reactive, likely because of the strong carbon–chlorine bond. Fortunately, bromoalkyne **3a-Br** provided the best results, with the optimal conditions involving the use of DMF as a solvent and only 5 mol % of copper iodide at 0 °C to room temperature, which afforded the coupling product in 79% isolated yield (Table 1, entry 5). The addition of various ligands, as well as the use of other copper salts, did not have a beneficial effect.

Under the optimized conditions, a series of organozinc compounds **2** were coupled with bromoalkynes **3** (Table 2). Good yields of coupling products **4** were typically achieved. The reaction tolerates ester groups or TBS-protected hydroxy groups. Aromatic iodide also remains unaffected (Table 2, entry 2).

As for the mechanism, we believe that the reaction starts with the zinc/copper exchange resulting in the formation of fluorinated organocopper species **5** (Scheme 2). Compound **5** inter-

Table 1: Optimization studies.

| Entry | X | 2a (equiv) | Conditions | Solvent | CuI (equiv) | Additive (equiv) | Yield of 4a , % ^a |
|-------|----|-------------------|------------------------|---------|-------------|------------------|-------------------------------------|
| 1 | I | 2 | –50 °C → rt; 4 h at rt | MeCN | 0.1 | – | 12 |
| 2 | I | 1.3 | –50 °C → rt; 4 h at rt | MeCN | 0.1 | DMF (2) | 35 |
| 3 | Cl | 2 | 0 °C → rt; 16 h at rt | MeCN | 0.1 | DMF (2) | 32 |
| 4 | Br | 1.5 | 0 °C → rt; 16 h at rt | MeCN | 0.1 | DMF (2) | 60 |
| 5 | Br | 1.5 | 0 °C → rt; 16 h at rt | DMF | 0.05 | – | 79 ^b |

^aDetermined by ¹⁹F NMR with internal standard. ^bIsolated yield.

Table 2: Reaction of organozinc compounds **2** with bromoalkynes **3**.

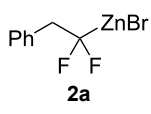
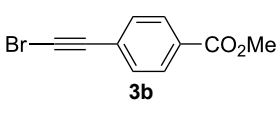
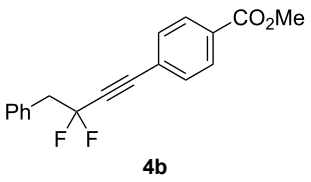
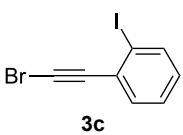
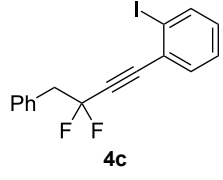
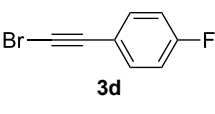
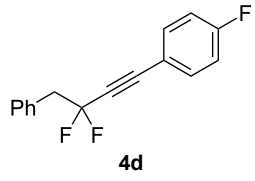
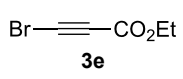
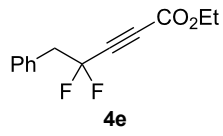
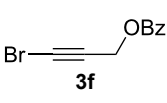
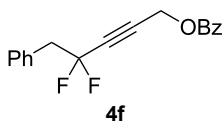
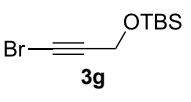
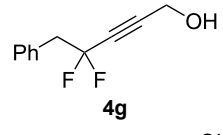
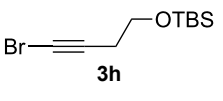
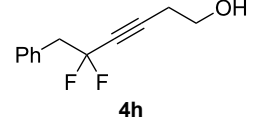
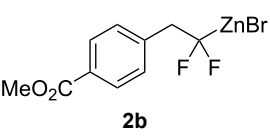
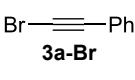
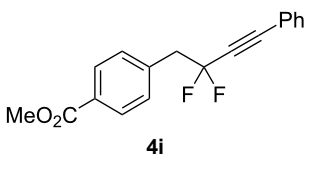
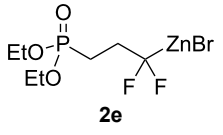
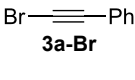
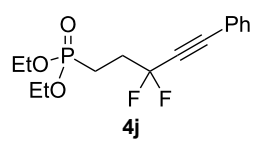
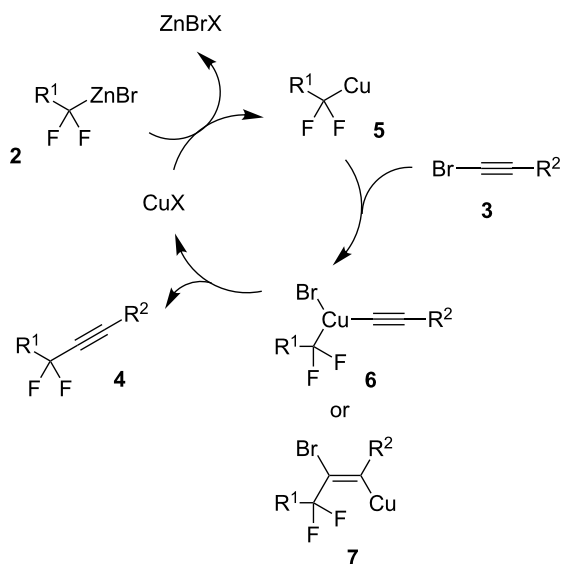
| Entry | 2 | 3 | 4 | Yield of 4 , % ^a |
|----------------|--|---|--|------------------------------------|
| | $ \begin{array}{c} \text{R}^1 \\ \\ \text{C}(\text{F})_2\text{ZnBr} \\ \\ \text{F} \end{array} + \text{Br}-\text{C}\equiv\text{C}-\text{R}^2 \xrightarrow[\text{DMF, 0 }^\circ\text{C to rt, 18 h}]{\text{CuI (5\%)}} \begin{array}{c} \text{R}^1 \\ \\ \text{C}(\text{F})_2-\text{C}\equiv\text{C}-\text{R}^2 \\ \\ \text{F} \end{array} $ | | | |
| | 2 (1.5 equiv) | 3 | 4 | |
| 1 |  |  |  | 84 |
| 2 | 2a |  |  | 82 |
| 3 | 2a |  |  | 70 |
| 4 | 2a |  |  | 84 |
| 5 | 2a |  |  | 67 |
| 6 ^b | 2a |  |  | 80 |
| 7 ^b | 2a |  |  | 75 |
| 8 |  |  |  | 80 |
| 9 |  |  |  | 81 |

Table 2: Reaction of organozinc compounds **2** with bromoalkynes **3**. (continued)

| | | | | |
|-----------------|--|--|--|----|
| 10 | | | | 72 |
| 11 ^b | | | | 71 |
| 12 ^b | | | | 62 |

^aIsolated yield. ^bThe crude product was desilylated.

acts with bromoalkyne **3** either by oxidative addition generating copper(III) intermediate **6** or by triple bond carbometallation [38] generating copper(I) intermediate **7**. Subsequent reductive elimination (from **6**) or β -elimination (from **7**) leads to the product and regenerates the copper(I) catalyst.

**Scheme 2:** Proposed mechanism.

Conclusion

In summary, a method for the copper-catalyzed coupling of α,α -difluoro-substituted organozinc compounds with 1-bromoalkynes has been developed. The reaction is performed under mild conditions affording *gem*-difluoro-substituted alkynes in good yields.

Supporting Information

Supporting Information File 1

Full experimental details, compound characterization, and copies of NMR spectra.

[<http://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-11-231-S1.pdf>]

Acknowledgements

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