Organic LETTERS

Letter

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Geminal Silicon/Zinc Reagent as an Equivalent of Difluoromethylene Bis-carbanion

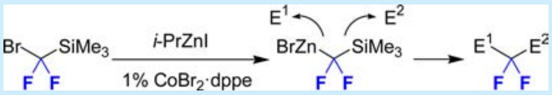
Mikhail D. Kosobokov,[†] Vitalij V. Levin,[†] Artem A. Zemtsov,[†] Marina I. Struchkova,[†]
Alexander A. Korlyukov,[‡] Dmitry E. Arkhipov,[‡] and Alexander D. Dilman*,[†]

[†]N. D. Zelinsky Institute of Organic Chemistry, Leninsky prosp. 47, 119991 Moscow, Russian Federation

[‡]A. N. Nesmeyanov Institute of Organoelement Compounds, Vavilov str. 28, 119991 Moscow, Russian Federation

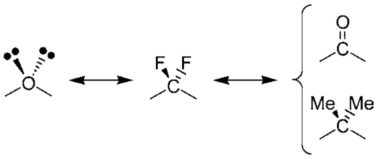
S *Supporting Information*

ABSTRACT: A new difluorinated reagent, [difluoro(trimethylsilyl)-methyl]zinc bromide, bearing C−Zn and C−Si bonds is described. The reagent is conveniently prepared by cobalt-catalyzed halogen/zinc exchange. It can be coupled with two different C-electrophiles in a stepwise manner (with allylic halides for C−Zn bond and aldehydes for C−Si bond) affording products containing a difluoromethylene fragment.



The ability of fluorine to affect biological properties of organic compounds[1] has led to the discovery and successful use of numerous fluorine-containing drugs.[1,2] In the majority of these molecules, the fluorine is present either as a substituent or in the form of a trifluoromethyl group. At the same time, compounds bearing difluoromethylene units are less frequent among marketed medicines, but interest in this structural motive is growing. Indeed, it has been noted that the CF_2 fragment is isosteric to ethereal oxygen[1a,b,3] and, in some cases, even to carbonyl or *gem*-dimethylmethylene groups[4] (Scheme 1).

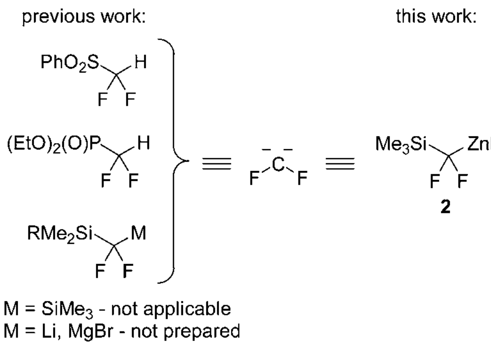
Scheme 1. Bioisosterism of CF_2 Fragment



Typically, synthesis of CF_2-containing products either involves a deoxofluorination reaction, which requires harsh reagents,[5] or relies on a building block approach, which is laborious.[6,7] Recently, we described a strategy for assembling *gem*-difluorinated compounds from difluorocarbene, nucleophile, and electrophile.[8] Herein, we report a reagent for coupling of binucleophilic CF_2 unit with two electrophilic species.

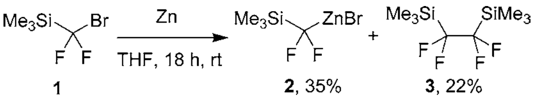
Previously, sulfur[9] and phosphorus[10] reagents were shown to act as equivalents of $-CF_2-$ synthon in reactions with two aldehydes affording 1,3-diols (Scheme 2). However, the use of fluorinated silanes would be desirable, since the carbon−silicon bond is readily cleaved by fluoride anion or even weaker bases.[11] To this end, the bis-silicon reagent $(TMS)_2CF_2$ was reported but failed to serve as the bis-carbanion in reaction with aldehydes.[12] Concerning polar organometallics, preparation of α-lithiated and α-magnesiated silanes was attempted but was unsuccessful.[13] In this work, we describe the silicon/zinc reagent with C−Zn and C−Si bonds being sequentially involved in coupling with suitable electrophiles.

Scheme 2. Equivalents of CF_2 Bis-carbanion Synthon



In the initial experiment, (bromodifluoromethyl)trimethylsilane (Me_3SiCF_2Br, **1**)[14] was treated with zinc dust. Reagent **2** was detected in small amounts along with homocoupling product **3**, as determined by ^{19}F NMR spectroscopy[15] (Scheme 3). Attempts to improve this reductive protocol failed despite extensive variation of reaction conditions.[16,17]

Scheme 3. Attempted Reductive Zincation of 1

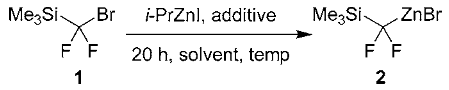


Then, the generation of organozinc species **2** was evaluated by means of bromine/zinc exchange using isopropylzinc iodide (Table 1). The reaction of silane **1** with 1.6 equiv of *i*-PrZnI was slow at room temperature, providing modest yields of **2** (entries

Received: January 22, 2014
Published: February 19, 2014

dx.doi.org/10.1021/ol5002297 | *Org. Lett.* 2014, 16, 1438−1441

Table 1. Preparation of Reagent 2



no.	solvent	RZnI (equiv)	additive (equiv)	temp (°C)	conv of **1**^{b} (%)	yield of **2**^{b} (%)
1	THF	1.6	none	20	65	30
2	THF/NMP	1.6	none	20	65	15
3	THF	1.6	LiCl (1.6)	20	100	0
4	THF	1.2	Ni(acac)$_2$ (0.01)	5	29	12
5	THF	1.2	NiBr$_2$·(PPh$_3$)$_2$ (0.01)	5	49	24
6	THF	1.2	CoBr$_2$·(PPh$_3$)$_2$ (0.01)	5	62	38
7	THF	1.2	CoBr$_2$·dppe (0.01)	5	95	30
8	**THF/DG**	**1.2**	**CoBr$_2$·dppe (0.01)**	**5**	**100**	**90**
9	**THF/DG**	**1.0**	**CoBr$_2$·dppe (0.01)**	**5**	**95**	**88**
10^c	THF/DG	1.0	CoBr$_2$·dppe (0.01)	5	95	87
11	THF/DG	1.2	CoBr$_2$·dppe(0.005)	5	97	88
12	THF/DG	1.2	CoBr$_2$·dppp (0.01)	5	86	60
13	THF/DG	1.2	CoBr$_2$·dppb (0.01)	5	78	63
14	THF/DG	1.2	CoBr$_2$ (0.01)	5	43	28
15^d	THF/DG	1.2	CoBr$_2$·dppe (0.01)	5	69	34

[a] THF: tetrahydrofuran. NMP: *N*-methylpyrrolidone. DG: diglyme. [b] Determined by ^{19}F NMR using PhCF$_3$ as internal standard. [c] Reaction time 48 h. [d] *i*-PrZnBr was used.

1 and 2). Then, the effect of various catalysts was evaluated.[18] The significant rate acceleration was observed by adding 1 mol % of CoBr$_2$·dppe complex (dppe, 1,2-bis(diphenylphosphino)ethane), which allowed the temperature to decrease as well the amount of *i*-PrZnI (to 1.2 equiv, entry 7). Rewardingly, the addition of diglyme as a cosolvent (THG/diglyme, 1/1) led to complete conversion together with 90% yield of **2** (entry 8). The use of a precisely stoichiometric amount of *i*-PrZnI afforded almost the same yield of **2** at 95% conversion (entry 9). Other evaluated cobalt and nickel salts and complexes were notably less efficient. When isopropylzinc *bromide* was employed instead of isopropylzinc *iodide*, the reaction was slow (entry 15).

We also investigated the stability, composition, and structure of organozinc reagent **2**. The obtained THF/diglyme solutions of **2** are reasonably stable and can even be stored at low temperatures. For example, after 72 h at −30 °C, no decrease of reagent concentration was noted, whereas after the same time at room temperature only 25% of **2** decomposed (^{19}F NMR control).

^{19}F NMR analysis of **2** in THF/diglyme solution showed two close signals (−130.4 and −130.7 in a ratio 93:7, respectively), likely owing to Schlenk equilibrium. Interestingly, when isolated crystals of **2**·diglyme (vide infra) were dissolved in CD$_3$CN, only one signal was observed.

It was surprising to find that reagent **2** contains *bromide* at zinc despite using isopropylzinc *iodide* for the halogen/zinc exchange. Indeed, such a halogen distribution pattern was established by identification of isopropyl iodide byproduct.[19] Furthermore, we were fortunate to obtain highly air-sensitive crystals of **2** coordinated with diglyme, and X-ray analysis unambiguously demonstrated the presence of bromide (Figure 1).

We suggest a tentative mechanism of bromine/zinc exchange accounting for unusual halogen redistribution (Scheme 4). At first, the cobalt(II) complex is reduced to generate catalytically active Co(I) iodide species.[20] Subsequently, oxidative addition leads to Co(III) intermediate,[21] which serves as iodinating reagent with respect to isopropylzinc iodide. At the latter step the isopropyl iodide is formed along with generation of the Zn−Br bond. The final step involves Co/Zn transmetalation providing reagent **2**.

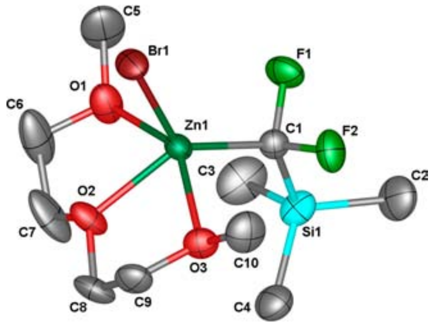
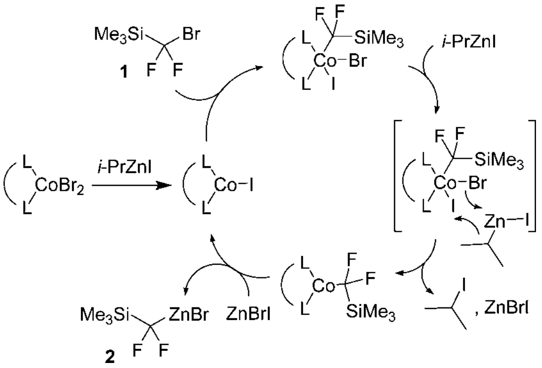


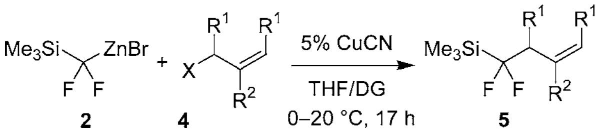
Figure 1. X-ray structure of **2**·diglyme. Hydrogen atoms are omitted for clarity.

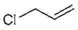
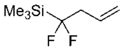
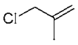
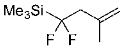
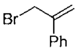
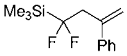
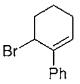
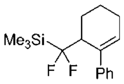
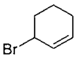
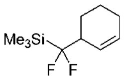
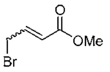
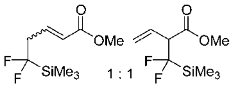
Scheme 4. Proposed Mechanism of Halogen/Zinc Exchange



Having developed a method for the preparation of reagent **2**, we proceeded with exploration of its properties as equivalent of difluoromethylene bis-carbanion. Given the greater polarity of C−Zn bond compared to that of C−Si bond, reactions of **2** as organozinc species were first evaluated. For fluorinated organozinc reagents, copper(I)-catalyzed arylation[22] and allylation[8b,23] have been reported. Since arylations are performed under harsh conditions (elevated temperatures, long times), we focused on allylation reactions. Thus, reagent **2** was coupled with allylic halides in the presence of 5 mol % of copper cyanide[24] (Table 2).

Table 2. Allylation of Reagent 2[a]



no.	starting		product		yield of **5**, %[b]
1		**4a**		**5a**	88
2		**4b**		**5b**	68
3		**4c**		**5c**	70
4		**4d**		**5d**	80
5		**4e**		**5e**	79
6		**4f**[c]		**5f**	74[d]

[a] Ratio **2**:**4** is equal to 1:1.2 (entries 1 and 2) or 1:1 (entries 3−5). [b] Isolated yield based on reagent **2**. [c] *E*/*Z* mixture 13:1. [d] Combined yield of α and γ regioisomers, ratio 1:1. The α-regioisomer is formed as *E*/*Z* mixture in a ratio of 13:1.

Silanes **5a**−**e** were obtained in good yields after purification of crude material either by distillation or by chromatography.[25] At the same time, the reaction of unsymmetrical substrate **4f** bearing an ester group afforded a 1:1 mixture of regioisomers (entry 6).

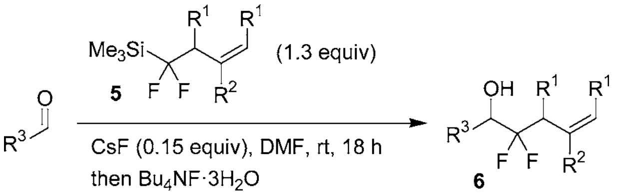
It should be pointed out that *gem*-difluorinated silanes Me_3SiCF_2R, where R is a nonfluorinated group, are difficult to synthesize, and only a limited number of examples were documented.[26] The use of reagent **2** as a source of nucleophilic silyldifluoromethyl group opens up opportunities for the synthesis of novel partially fluorinated silanes.

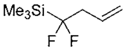
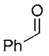
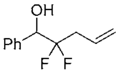
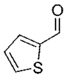
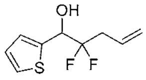
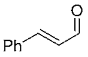
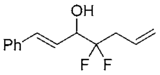
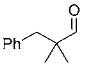
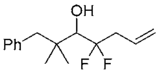
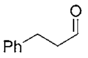
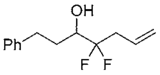
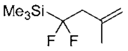
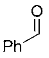
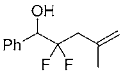
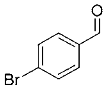
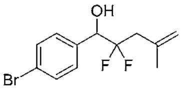
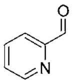
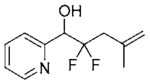
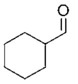
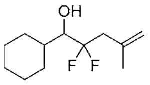
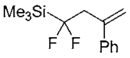
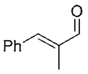
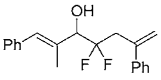
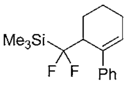
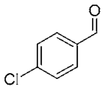
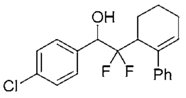
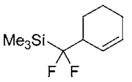
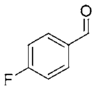
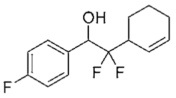
Silanes **5a**−**e** were employed as nucleophilic reagents with a range of aldehydes (Table 3). Aromatic and α,β-unsaturated, as well as tertiary and α-branched aliphatic aldehydes, gave *gem*-difluorinated alcohols **6** in high yields. However, hydrocinnamaldehyde afforded product in moderate yield (entry 5), presumably owing to facile enolization under basic conditions.

Reactions of ketones with silane **5a** were also briefly investigated. Under standard conditions, benzophenone afforded the expected alcohol **6m** in modest yield along with fluorodiene **7** (Scheme 5). It is likely that diene **7** is formed by elimination of HF from the primary product. In the reaction of acetophenone, a enolizable ketone, neither conventional *gem*-difluorinated alcohol, nor fluorodiene was detected.

In summary, a new fluorinated organometallic reagent serving as an equivalent of difluoromethylene bis-carbanion is described. The key feature of the reagent is Si−CF_2−Zn functionality, which enables successive coupling with two different electrophiles by exploiting nucleophilic reactivities of C−Zn and C−Si bonds. Furthermore, the intermediate silanes Me_3SiCF_2R, produced after coupling with a first electrophile, may find their own use in synthesis of organofluorine compounds.

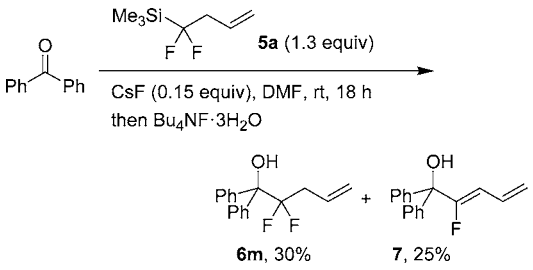
Table 3. Reaction of Silanes 5 with Aldehydes



no.	silane		substrate	product		yield of **6**, %[a]
1		**5a**			**6a**	89
2		**5a**			**6b**	75
3		**5a**			**6c**	92
4		**5a**			**6d**	72
5		**5a**			**6e**	27
6		**5b**			**6f**	93
7		**5b**			**6g**	88
8		**5b**			**6h**	45
9		**5b**			**6i**	82
10		**5c**			**6j**	77
11		**5d**			**6k**[b]	98
12		**5e**			**6l**[b]	88

[a] Isolated yield. [b] Mixture of diastereoisomers 1:1.

Scheme 5. Reaction of Benzophenone



■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Experimental procedures, compound characterization data, copies of NMR spectra for all compounds, and X-ray data for **2**·diglyme (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: adil25@mail.ru.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work was supported by the Ministry of Science (project MD-1151.2011.3), Russian Foundation for Basic Research (projects 13-03-12074, 14-03-00293, 14-03-31253_mol_a, 14-03-31265_mol_a), and the Russian Academy of Sciences. We are grateful to R. Novikov (N. D. Zelinsky Institute of Organic Chemistry) for 2D-NMR measurements and to G. Ivanov (Higher Chemical College, Russian Academy of Sciences) for experimental assistance.

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(25) For the synthesis of silanes **5**, we employed reagent **2** prepared with 1.2 equiv of *i*-PrZnI (entry 8, Table 1). If reagent **2** prepared under the conditions of entry 9 is employed, the residual starting silane Me_3SiCF_2Br hampers purification of silanes **5**.

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