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Reactions of Difluorocarbene with Organozinc Reagents

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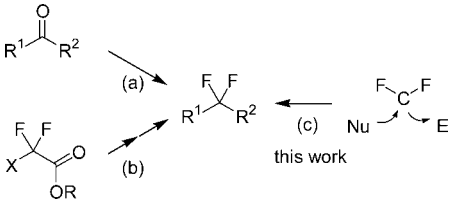
ABSTRACT

Reactions of difluorocarbene with benzyl and alkylzinc halides leading to fluorinated organozinc species have been described. The generated α-difluorinated organozinc reagents are reasonably stable in solution and can be quenched with external electrophiles (iodine, bromine, proton), affording compounds containing the CF_2 fragment.

Due to increasing importance of fluorine-containing organic compounds for the development of new pharmaceuticals and agrochemicals,[1] synthetic methods aimed at the introduction of fluorinated fragments into organic molecules have witnessed exponential growth over the last 5 years.[2] While various methods for the introduction of the CF_3 group have been documented,[2,3] approaches for the synthesis of compounds bearing the CF_2 fragment are notably less abundant.[4−7] In general, the latter compounds can be prepared using a deoxofluorination reaction (path a), which is frequently performed using hazardous sulfur reagents,[8] or from halodifluoroacetic esters and similar CF_2-containing building blocks (path b), which may require a long synthetic sequence.[9] Herein we propose a new efficient approach for assembling CF_2-containing products from three *independent* components—nucleophile, difluorocarbene, and electrophile (path c) (Scheme 1).

Scheme 1. Approaches toward Compounds with a CF_2 Fragment



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(5) For a discussion on challenges in preparation of compounds with RCF_2I and RCF_2Br fragments, see: Zhao, Y.; Gao, B.; Hu, J. *J. Am. Chem. Soc.* **2012**, *134*, 5790–5793.

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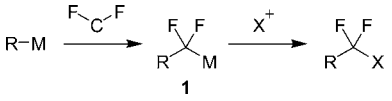
Difluorocarbene is intrinsically electrophilic[10] and, therefore, is capable of interacting with nucleophiles, affording a new nucleophilic species **1** (Scheme 2). While reactions of nucleophiles with difluorocarbene have been known, in all previously reported examples, species **1** were considered as short-lived intermediates undergoing rapid trapping by an electrophile from the reaction medium (proton or halogen). In particular, this scenario is realized in difluoromethylation of alcohols, thiols, amines, and CH acids,[6g,10a,11] bromodifluoromethylation of alkynes and malonates,[12] bromodifluoromethylation of P and S nucleophiles,[13] and, likely, in iododifluoromethylation of lithium enolates.[14] In this work, we demonstrate that reasonably stable reagents **1** can be generated and quenched by subsequent addition of a desired electrophile.

Scheme 2. Addition of Organometallics to Difluorocarbene

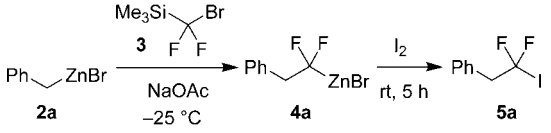


Analogous nonfluorinated homologation of organometallics (i.e., insertion of CH_2) has been described.[15] In the case of CF_2 insertion, the presence of fluorine renders this process challenging. Indeed, the stability of organometallic species **1** is a key issue determining the success of this approach. The stability of reagent **1** is believed to depend on the nature of the metal. For lithium or magnesium, the carbon–metal bond is strongly polarized, whereas the metal–fluorine bond is quite strong, thereby leading to facile decomposition of **1**.[16] We surmised that zinc would present a compromise necessary for noticeable lifetime of species **1**.

Benzylzinc bromide (**2a**), which can be obtained in different solvents, was selected as a starting nucleophile. Among various sources of difluorocarbene,[17] we preferred to use (bromodifluoromethyl)trimethylsilane (**3**)[18] since, supposedly, it can generate difluorocarbene at low temperatures under mildly basic conditions.[19] Additionally, silane **3** can be readily prepared in large quantities.[18b]

The reaction of 1.5 mmol of benzylzinc bromide with the silane was performed at −25 °C using sodium acetate as a Lewis base, and the resulting solution was treated with iodine to produce compound **5a** (Table 1). Rewardingly, the reaction worked well in various solvents, with the best result being obtained in MeCN. Increasing the amount of silane and sodium acetate consistently gave decreased product yields, which may be associated with some transformations of fluorinated zinc species. Addition of LiCl did not have a beneficial effect[20] (entry 8). Finally, the use of 1.2 equiv of reagents for the generation of difluorocarbene was optimal, affording product **5a** in 85% isolated yield[21] (entry 4).

Table 1. Reaction of Benzylzinc Bromide



no.	silane **3** (equiv)	NaOAc (equiv)	solvent	time[a] (h)	yield[b] (%)
1	1.33	1.33	DMF	6	71
2	1.33	1.33	MeCN	6	58
3	1.33	1.33	MeCN	18	79 (74[c])
4	1.2	1.2	MeCN	18	95 (85[c])
5	1.2	1.2	glyme	18	82
6	1.2	1.2	THF	18	78
7	1.1	1.1	MeCN	18	81 (76[c])
8[d]	1.1	1.1	MeCN	18	53

[a] For the formation of **4a**. [b] Determined by NMR spectroscopy of crude material using $PhCF_3$ as internal standard. [c] Isolated yield. [d] LiCl (1 equiv) was added upon the preparation of **2a**.

The formation of reagent **4a** was supported by ^{19}F NMR data, which demonstrates the presence of two species due to the Schlenk equilibrium (−96.8 and −95.4 ppm in a ratio of 5:1, respectively). The reagent **4a** in acetonitrile solution slowly decomposes at room temperature (ca. 75% of the reagent decomposed after 2 h).[22] However, addition of 2 equiv of dimethylformamide increases its stability (ca. 30% of decomposition after 2 h at room temperature). Addition

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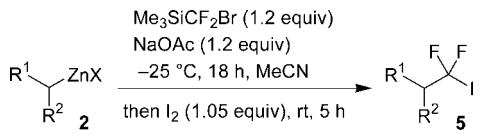
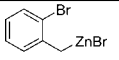
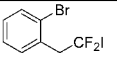
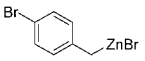
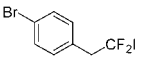
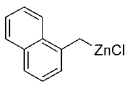
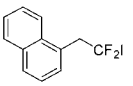
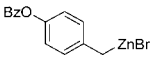
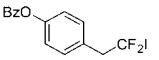
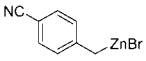
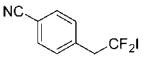
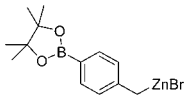
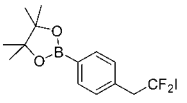
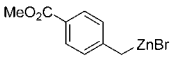
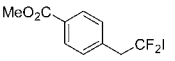
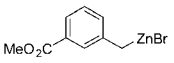
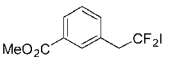
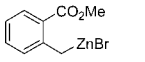
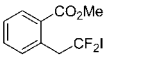
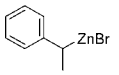
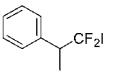
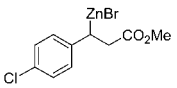
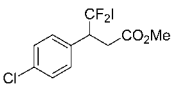
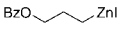
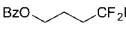
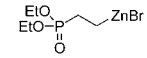
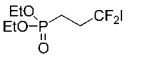
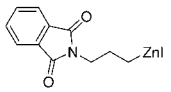
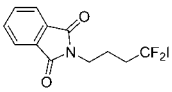
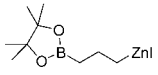
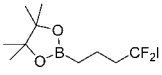
(19) It has previously been reported that Me_3SiCF_2Br can generate difluorocarbene even in the presence of chloride ion, though at elevated temperatures, see ref 17i.

(20) Lithium chloride may affect the reactivity of organozinc species. See: Metzger, A.; Schade, M. A.; Knochel, P. *Org. Lett.* **2008**, *10*, 1107–1110.

(21) The decrease in the yield upon isolation compared to NMR yield is associated with the volatility of **5a**.

Table 2. Difluoroiodomethylation of Organozinc Reagents



no.	reagent		product		yield of **5**,[a] %
1		**2b**		**5b**	84
2		**2c**		**5c**	80
3[b,c]		**2d**		**5d**	70
4		**2e**		**5e**	85
5		**2f**		**5f**	70
6		**2g**		**5g**	70
7		**2h**		**5h**	88
8		**2i**		**5i**	85
9		**2j**		**5j**	57
10		**2k**		**5k**	93
11		**2l**		**5l**	73
12		**2m**		**5m**	82
13[c,d]		**2n**		**5n**	64
14[c]		**2o**		**5o**	46
15[c]		**2p**		**5p**	32

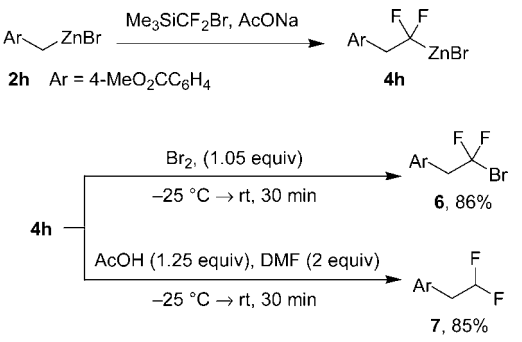
[a] Isolated yield based on organozinc halide. [b] 1.4 equiv of Me_3SiCF_2Br and NaOAc was used. [c] Time for the CF_2 insertion step was 21 h. [d] DMF (2 equiv) was added before the CF_2 insertion step.

of 5 equiv of dimethylformamide allows even moderate heating (ca. 25% of decomposition after 2 h at 40 °C).

(22) It should be noted that iodination of reagent **4a** was carried out at room temperature. The success of iodination can be explained either by formation of zinc salt upon iodination, which can influence the Schlenk equilibrium of **4a**, or by more significant deceleration of decomposition relative to iodination upon decrease of concentration of **4a**. Furthermore, the iodination likely starts at −25 °C, and a longer period at room temperature was applied to achieve complete conversion.

Under the optimized conditions, a variety of organozinc reagents **2** were reacted with silane **3** followed by iodination (Table 2). Benzylzinc halides worked well in this process, furnishing products of difluoroiodomethylation in good yields (entries 1−11). The reaction tolerates halogen, cyano, ester, and boryl groups on the aromatic ring. Importantly, secondary benzylzinc reagents successfully provided final products (entries 10 and 11). The yields with aliphatic organozinc reagents were variable (entries 12−15). However, no products were produced starting from arylzinc halides, presumably, owing to the instability of fluorinated organozinc reagents $ArCF_2ZnX$ under the reaction conditions.

Scheme 3. Bromination and Protonation of Reagent **4h**



Besides iodination, fluorinated organozinc reagents can be brominated and protonated, thereby allowing formation of CF_2Br and CHF_2 groups, respectively (Scheme 3). Thus, the interaction of reagent **4h** with bromine proceeded rapidly, leading to product **6**. To effect protonation, addition of 2 equiv of DMF along with acetic acid was found to be important to achieve a high yield of product **7**. It should be pointed out that overall transformation of **2h** to **7** corresponds to difluoromethylation of the starting organozinc reagent.

In summary, we have proposed a new approach for the synthesis of compounds containing the CF_2 fragment. The key point of the described methodology is the insertion of difluorocarbene into a carbon−zinc bond followed by treatment of newly formed fluorinated organozinc species with an external electrophile. Our further studies will be directed toward extending the scope of this process by variation of organometallic and electrophilic components.

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Supporting Information Available. Experimental procedures, compound characterization data, and copies of NMR spectra for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.