Organic Letters
Letter
pubs.acs.org/OrgLett

Nucleophilic Difluoromethylation Using (Bromodifluoromethyl)trimethylsilane

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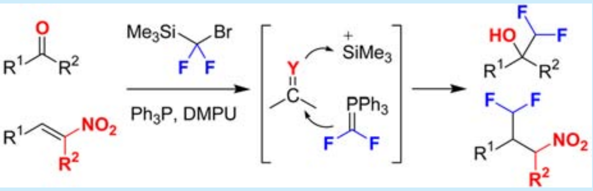
Supporting Information

ABSTRACT: A combination of (bromodifluoromethyl)trimethylsilane (Me_3SiCF_2Br), triphenylphosphine, and DMPU serves as a source of difluorinated phosphorus ylide $Ph_3P{=}CF_2$ under mild conditions. The system was used to effect nucleophilic difluoromethylation of ketones and nitro alkenes. The reaction efficiency is believed to be associated with Lewis acidic activation of the substrates by a silylium species formed upon generation of the phosphorus ylide.



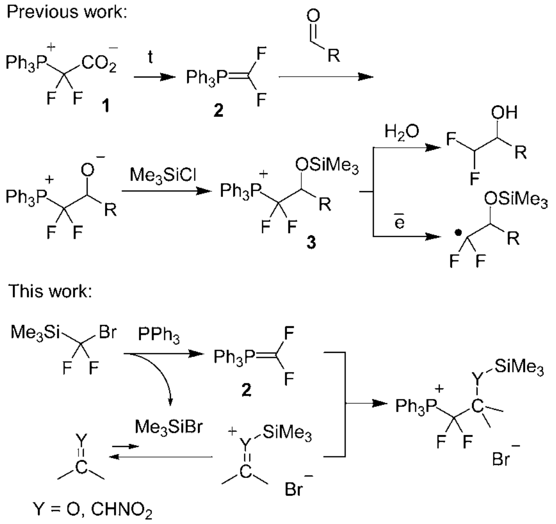
Among a wide variety of methods to obtain valuable organofluorine compounds,[1] nucleophilic fluoroalkylation reactions have attracted the attention of many research groups.[2] Indeed, addition of a fluorinated carbanion at C═O, C═N, and C═C bonds constitutes an efficient approach to synthesize molecules bearing a fluorinated fragment in a specified position. While trifluoromethylation reactions, typically performed with the Ruppert−Prakash reagent (Me_3SiCF_3),[2a−c] have been very well studied, similar processes using difluoromethyl silane (Me_3SiCHF_2) are still rare,[3,4] likely due to strongly basic conditions for the activation of the Si−C bond of the latter silane. Correspondingly, various equivalents of difluoromethyl carbanion have been developed.[2e,f,5,6]

Recently, we reported that phosphobetaine **1** serves as the equivalent of the difluoromethylcarbanion[6] (Scheme 1). In this process, unstable phosphorus ylide **2** generated by decarboxylation of betaine **1** at elevated temperatures[7,8] behaves as a nucleophile, leading to phosphonium salts **3**. These salts either undergo hydrolytic cleavage of the C−P bond[6] or can serve as sources of radicals under photoredox conditions.[9,10] However, owing to the instability of ylide **2** and its moderate reactivity, the scope of electrophiles was limited to aldehydes and other biased substrates such as highly electrophilic azomethines and Michael acceptors bearing two electron-withdrawing groups.[6] Herein we report a different method for the generation of ylide **2** accompanied by formation of Lewis acidic silicon species capable of activating the electrophilic substrate. The reaction was applied to difluoromethylation of nitro alkenes and ketones, electrophiles which are typically problematic for nucleophilic fluoroalkylation under basic conditions.

Recently, we reported[11] that (bromodifluoromethyl)trimethylsilane (Me_3SiCF_2Br, **5**) serves as a source of difluorocarbene in the presence of neutral Lewis basic activators.[12−14] Correspondingly, we combined 4-bromoacetophenone **4a** with silane **5**, triphenylphosphine, and 2 equiv of DMPU (1,3-dimethylpropyleneurea) in acetonitrile and within 1 h observed clean formation of addition species **6a** by ^{19}F NMR (Scheme 2). There was no reaction without DMPU. Decreasing the amount of DMPU to 0.2 equiv led to addition product in only 8% yield. Hexamethylphosphoramide (HMPA) showed similar activity as a basic activator,[15] but because of its toxicity further experiments were performed with DMPU.

A series of ketones were reacted with silane **5**/Ph_3P/DMPU system, and the reaction mixture was treated with potassium hydroxide to effect protodephosphorylation of intermediate salts **6** (Table 1). Aromatic and heteroaromatic methyl ketones

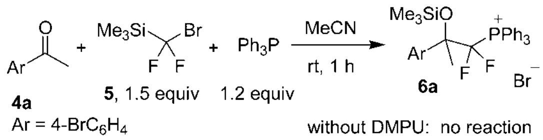
Scheme 1. Reactions of Fluorinated Ylide



Received: June 7, 2016
Published: June 23, 2016

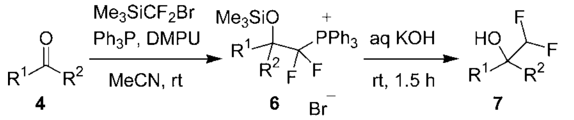
DOI: 10.1021/acs.orglett.6b01641
Org. Lett. 2016, 18, 3458−3461

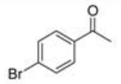
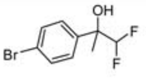
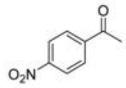
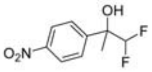
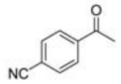
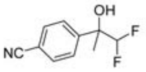
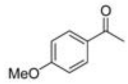
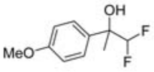
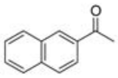
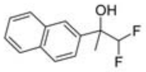
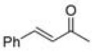
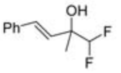
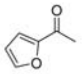
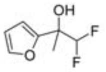
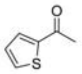
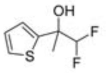
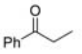
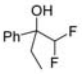
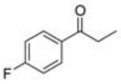
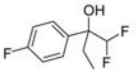
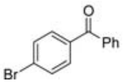
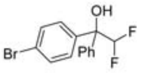
Scheme 2. Reactions of 4-Bromoacetophenone



without DMPU: no reaction
DMPU (2 equiv): 85%
DMPU (0.2 equiv): 8%

Table 1. Reactions of Ketones[a]



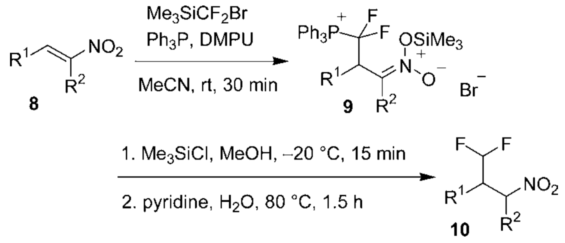
entry	substrate	product		time, h	yield (%)[b]
1			7a	1	84
2			7b	1	80
3			7c	1	98
4			7d	16	80
5			7e	1	95
6			7f	1	81
7			7g	1	90
8			7h	2	82
9			7i	16	54
10			7j	16	67
11			7k	16	86

[a] Ratio: Me$_3$SiCF$_2$Br (1.5 equiv), PPh$_3$ (1.2 equiv), DMPU (2 equiv). [b] Isolated yield.

provided good yields of products **7**. Reactions are typically complete within 1 h, except for methoxy-substituted ketone, which required a long reaction time (entry 4). An α,β-unsaturated ketone afforded the carbonyl addition product exclusively (entry 6). Ethyl ketones were less reactive, and besides the expected products, reaction mixtures contained noticeable amounts of silyl enol ethers, originating from silylation of the starting substrates. Nevertheless, the corresponding difluorinated alcohols **7i,j** were isolated in acceptable yields (entries 9 and 10). Similarly, an attempted reaction of β-tetralone, an easily enolizable ketone, exclusively provided its silyl enol ether. In the reaction of 2-decanone, the addition product was formed in less than 10% yield (^{19}F NMR control). The nonenolizable and less reactive ketone, 4-bromobenzophenone, gave product **7k** in high yield (entry 11).

Nitro alkenes **8** were also subjected to the same difluoromethylation conditions (Table 2). The addition reaction proceeded rapidly, and in 30 min phosphonium salts **9** were observed by ^{19}F NMR. Surprisingly, attempted dephosphorylation of salts **9** under basic conditions gave nitro compounds **10** in moderate yields along with recovered

Table 2. Reactions of Nitro Alkenes[a]



entry	substrate	product	yield (%)[b]
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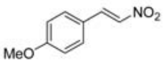
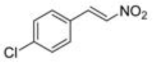
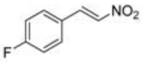
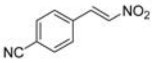
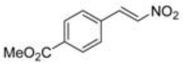
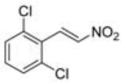
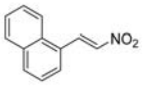
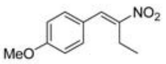
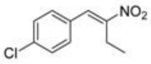
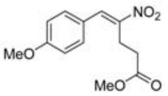
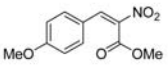
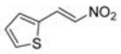
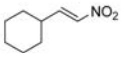
2		10b	86
3		10c	92
4		10d	96
5		10e	82
6[d]		10f	82
7		10g	93
8		10h	87
9		10i[c]	91
10		10j[c]	85
11		10k[c]	83
12		10l[c]	74
13		10m	72
14		10n	81
15		10o	81

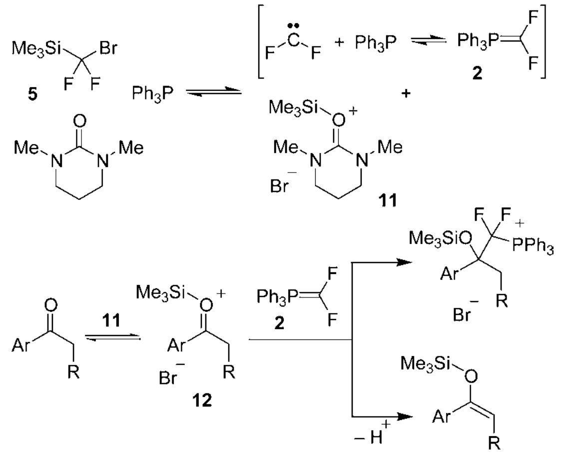
[a] Ratio: Me$_3$SiCF$_2$Br (1.5 equiv), PPh$_3$ (1.2 equiv), DMPU (2 equiv); Me$_3$SiCl (0.2 equiv), MeOH (5 equiv); pyridine (1.2 equiv), H$_2$O (50 equiv). [b] Isolated yield. [c] Mixture of diastereoisomers in a ratio about 1:1. [d] Reaction time for the formation of **9**, 2 h.

DOI: 10.1021/acs.orglett.6b01641
Org. Lett. 2016, 18, 3458−3461

starting nitro alkenes **8**. The latter process is likely associated with rapid base mediated conversion of a silyl nitronate fragment into a nitronate anion followed by a retro-Michael reaction. To avoid this problem, the mixture containing salt **9** was first treated with Me_3SiCl (0.2 equiv) and methanol (5 equiv) at −20 °C to effect formation of the nitro group, followed by heating at 80 °C with water and 1.2 equiv of pyridine. Under these conditions, a wide variety of nitro alkenes were difluoromethylated. Aromatic, heteroaromatic, and aliphatic substrates afforded nitro compounds **10** in high yields.

Concerning the mechanism, we believe that the reaction of silane **5** with phosphine and DMPU generates a small equilibrium concentration of phosphonium ylide **2** (Scheme 3).

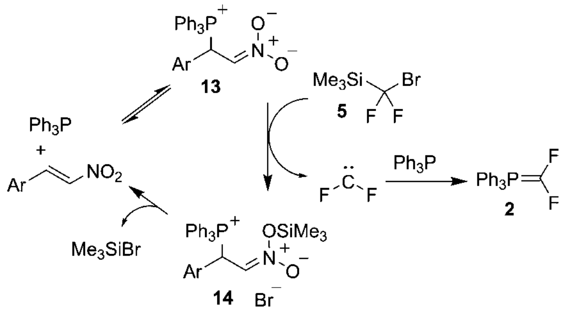
Scheme 3. Proposed Mechanism



Indeed, a mixture of these three reagents remains virtually unaffected during 1 h according to ^{19}F NMR, whereas after addition of a substrate, the reaction takes place leading to an addition product. Serving as a Lewis base, DMPU generates difluorocarbene along with silylium salt **11**.[15] We propose that salt **11** can behave as a Lewis acidic activator of the keto group, providing cationic species **12**,[16] which upon reaction with ylide **2** undergoes either nucleophilic attack, leading to an addition product, or deprotonation, leading to silyl enol ether.

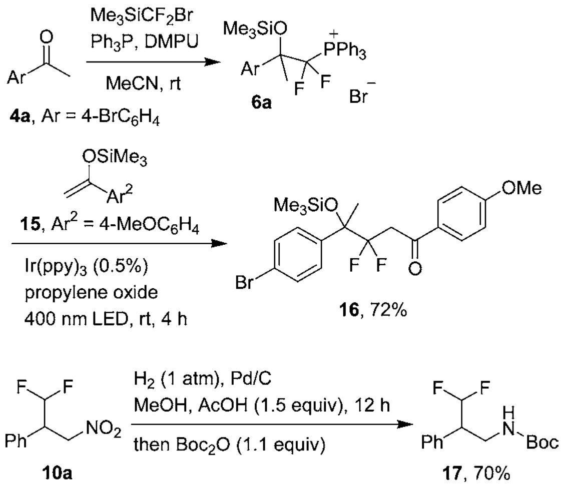
In the case of nitro alkenes, a similar mechanism may work. At the same time, the notably faster reactions compared to those of ketones may suggest an alternative mechanism. Presumably, the combination of phosphine and nitro alkene itself can trigger the decomposition of silane **5**, thereby fostering the generation of ylide **2** (Scheme 4). Thus, phosphine can reversibly add to the nitro alkene, leading to nitronate species **13**, which behaves as a Lewis base toward silane **5** to give difluorocarbene and silyl nitronate **14**. Subsequent fragmentation of **14** recovers the nitro alkene and phosphine along with formation of Lewis acidic bromosilane. In support of this mechanism is the observation that the reaction of nitro alkene with Me_3SiCF_2Br/PPh_3 proceeds without DMPU, but at a slower rate.

Scheme 4. Generation of Ylide 2 with Nitro Alkenes



To demonstrate potential applications of the method, phosphonium salt **6a** was involved in a photoredox reaction with silyl enol ether **15** using an iridium catalyst and irradiating with a strip of LEDs,[9] furnishing ketone **16**[17] (Scheme 5). For product **10a** derived from the nitro alkene, the nitro group was reduced with hydrogen under atmospheric pressure followed by conversion of the resulting amino group into a *N*-Boc protected form. It should be pointed out that fluorinated amines could serve as valuable building blocks in medicinal chemistry.

Scheme 5. Transformations of Addition Products



In summary, a new approach for the generation of difluorinated phosphorus ylide under mild conditions is described. The method was applied to the difluoromethylation of ketones and nitro alkenes, which are usually considered tough substrates for addition of fluorinated carbanions. Relatively fast reaction rates in the present system likely originate from Lewis acidic silylium species, which activates substrates for nucleophilic attack.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b01641.

Experimental procedures, compound characterization data, copies of NMR spectra for all compounds (PDF)

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work was supported by the Russian Science Foundation (Project 14-13-00034).

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