Copper-Mediated Fluoroalkylation Reactions with [(Phenylsulfonyl)difluoromethyl]trimethylsilane: Synthesis of PhSO₂CF₂-Containing Allenes and Alkynes

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Abstract: Copper-mediated (phenylsulfonyl)difluoromethylation of propargyl chlorides and alkynyl halides with $PhSO_2CF_2TMS$ reagent was successfully achieved to give $PhSO_2CF_2$ -containing allenes and alkynes, respectively. It is believed that the in situ formed $PhSO_2CF_2Cu$ species is involved in the present (phenylsulfonyl)difluoromethylation reactions.

Key words: fluoroalkylation, copper, allenes, alkynes, (phenylsulfonyl)difluoromethyl

Selective incorporation of fluorine atom(s) or fluorinecontaining moieties into organic molecules has been widely recognized as a powerful strategy in drug design and material development, since fluorine causes minimal structural changes and maximal shifts in electron distribution and can often bring about many beneficial properties (such as increased stability, lipophilicity, and bioavailability) to a target molecule.¹ A variety of fluorination and fluoroalkylation methods have been developed during the past decades.² In this context, selective (phenylsulfonyl)difluoromethylation reactions [the transfer of the PhSO₂CF₂ group(s) into organic substrates] have caught much attention, owing to the fact that PhSO₂CF₂ is a versatile functional group that can be readily transformed into other highly useful fluorinated functionalities such as difluoromethyl (CF2H), difluoromethylene (-CF2-), and difluoromethylidene (=CF₂) groups.³ Currently, although the nucleophilic, electrophilic, and free radical (phenylsufonyl)difluoromethylations have all been achieved by using different reagents such as PhSO₂CF₂H, PhSO₂CF₂TMS, PhSO₂CF₂I, or I(III)CF₂SO₂Ph,^{3a} the transition-metal-mediated (phenylsulfonyl)difluoromethylation through a C-C bond-formation protocol has never been reported.

Copper-mediated trifluoromethylation of aryl or alkenyl halides via CF₃Cu intermediates has been well documented,⁴ and a catalytic version of this process was also reported recently.^{5,6} The success of the cross-coupling reaction between aryl (or alkeneyl) halides and CF₃Cu species can be partly attributed to the easy formation and high thermal stability of CF₃Cu species,^{7,8} which tolerates the high reaction temperatures (usually above 80 °C) required for overcoming the high activation barrier for reduction elimination process to give RCF₃ products (R = Ar, alkenyl).⁴ For instance, trifluoromethyl iodide (CF₃I) reacts readily with copper powder (Cu⁰) to form CF₃Cu species, which serves as an in situ generated trifluoromethylation reagent towards aryl (or alkenyl) halides.4a,b Considering that the same protocol might be used for the preparation of PhSO₂CF₂Cu species, we attempted the reaction between iododifluoromethyl phenyl sulfone (PhSO₂CF₂I)⁹ and copper powder in DMF solution. Much to our surprise, PhSO₂CF₂I was found to be almost inert to Cu⁰ even when the reaction temperature was raised to 110 °C, which indicates that the reactivity of PhSO₂CF₂I is remarkably different from that of many other fluoroalkyl iodides.^{4,10,11} After many unsuccessful experiments, finally we found that PhSO₂CF₂Cu species could be prepared by a reaction between $PhSO_2CF_2TMS$ (1)¹² and CuI in the presence of CsF (Scheme 1).^{13,14} In a typical experiment (under N_2 atmosphere), reagent 1 (1 equiv) was added into the mixture of CuI (1 equiv) and CsF (1.1 equiv) in DMF at -30 °C, and the reaction mixture was stirred for 4 h. The formation of the expected PhSO₂CF₂Cu species 2 could be monitored by ¹⁹F NMR, which showed two singlets at $\delta = -93.5$ and -96.7 ppm with a ratio of 1.7:1 (corresponding to two forms of 2).¹⁴ We also found that unlike CF₃Cu, species 2 possesses lower thermal stability, and it decomposed even at room temperature. The prepared solution of 2 decomposed completely after stirring at room temperature for 2 hours.15



Scheme 1 Preparation of PhSO₂CF₂Cu species

Based on the above observation, we decided to investigate the chemical reactivity of the PhSO₂CF₂Cu species **2**. Therefore, the (phenylsulfonyl)difluoromethylation reaction of propargyl chlorides **3** with pregenerated PhSO₂CF₂Cu species **2** was first tested at low temperature.¹⁶ We examined the different reaction conditions by

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 Table 1
 Survey of Reaction Conditions

$1 \xrightarrow{\text{Cul (1.0 equiv)}}_{\text{DMF, -30 °C, 4 h}} \begin{bmatrix} 2 \end{bmatrix} \xrightarrow{\texttt{(3a)}}_{\text{temp, time}} \text{Ph} \xrightarrow{\text{S}}_{\text{F}} \xrightarrow{\text{Cul (1.1 equiv)}}_{\text{temp, time}} \text{Ph} \xrightarrow{\text{S}}_{\text{F}} \xrightarrow{\text{Cul (1.1 equiv)}}_{\text{temp, time}} \text{Ph} \xrightarrow{\text{S}}_{\text{F}} \xrightarrow{\text{Cul (1.1 equiv)}}_{\text{temp, time}} \text{Ph} \xrightarrow{\text{Cul (1.1 equiv)}}_{\text{F}} \xrightarrow{\text{Cul (1.1 equiv)}}_{\text{F}} \xrightarrow{\text{Cul (1.1 equiv)}}_{\text{temp, time}} \text{Ph} \xrightarrow{\text{Cul (1.1 equiv)}}_{\text{F}} \xrightarrow{\text{Cul (1.1 equiv)}}_{\text{F}} \xrightarrow{\text{Cul (1.1 equiv)}}_{\text{temp, time}} \text{Ph} \xrightarrow{\text{Cul (1.1 equiv)}}_{\text{F}} \xrightarrow{\text{Cul (1.1 equiv)}}_{\text{F}} \xrightarrow{\text{Cul (1.1 equiv)}}_{\text{temp, time}} \xrightarrow{\text{Cul (1.1 equiv)}}_{\text{F}} \text{Cul (1.1 equ$								
Entry ^a	Molar ratio (1/3a)	Temp (°C)	Time (h)	Yield (%) ^b				
1	1:1	0	16	44				
2	2:1	0	16	11				
3	1:1.5	0	16	50				
4	1:2	0	16	60				
5	1:3	0	16	59				
6	1:2	25	16	31				
7	1:2	-15	16	21				
8	1:2	0	40	51				
9	1:2	0	7	35				
10 ^c	1:2	0	16	31				

^a Typical reaction procedure: under N₂ atmosphere, CuI (0.25 mmol), CsF (0.27 mmol), **1** (0.25 mmol), and DMF (1.5 mL) were added into a Schlenk flask at -30 °C, and the mixture was stirred for 4 h. Then **3a** was added into the mixture, which was stirred at a desired temperature for a certain period of time.

^b Determined by ¹⁹F NMR using PhCF₃ as internal standard.

^c AuCl (10 mol%) was added.

using 3-chloro-3-methylbut-1-yne (**3a**) as a model substrate. The results are shown in Table 1. It turned out that the product yields were sensitive to the reaction temperature. Both low temperature (-15 °C) and relatively higher temperature (25 °C) led to low product yields (entries 6 and 7, in Table 1), and the medium temperature (0 °C) was found to be ideal for the reaction (entries 3 and 4). We also found that the optimal reaction time was 16 hours

Table 2 Cu-Mediated Reaction between 1 and Propargyl Chlorides 3

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(entries 4, 8, and 9). After a quick scanning of the reactant ratio, an optimal yield of **4a** (60%) was obtained when the reaction proceeded in DMF at 0 °C for 16 hours with a molar ratio 1/3a = 1:2 (entry 4). It should be mentioned that the control experiment showed that in the absence of CuI, the combination of **1** and CsF (in DMF) was unable to undergo the similar C–C bond-formation reaction with **3a**. This indicates that the PhSO₂CF₂Cu species **2** plays an important role for the success of the current nucleophilic fluoroalkylation reaction.

By choosing the above reaction conditions (Table 1, entry 4) as standard, we next investigated the scope of Cumediated (phenylsulfonyl)difluoromethylation of propargyl chlorides **3**. The results are shown in Table 2. It turned out that disubstituted propargylic chlorides could react with pregenerated **2** to give allene products **4** in moderate yields (entries 1, 2, 4, and 5). The reaction with activated monosubstituted propargylic chloride **3c** could afford allene product **4c** in medium yield (entry 3). When **2** was used to react with unsubstituted propargal chloride **3f**, no product was obtained (entry 6).

The cross-coupling reaction between pregenerated 2 and alkynyl halides 5 was also examined (Table 3). We found that most of alkynyl halides 5 could react smoothly with 2 to give cross-coupling products 6 in moderate to good yields. Besides alkynyl iodides, alkynyl bromide (such as 5a') could also give the cross-coupling product 6a in satisfactory yield (entry 2). However, when phenylethynyl chloride (5a") was subjected to the reaction, only trace amount of product was detected (entry 3). Furthermore, the yield decreased when there was an electron-withdrawing group on the phenyl ring (entry 4). For alkyl-substituted alkynyl iodides, the corresponding cross-coupling products could be formed in 59–82% yields (entries 5–7). While the benzylic C-H bond did not significantly interfere with the desired coupling reaction (entries 8 and 9), the existence of acidic proton source (such as a hydroxy

Cul (1.0 equiv) CsF (1.1 equiv) DMF, -30 °C, 4 h	= → [2]	$\xrightarrow{(3)} R^2$ $\xrightarrow{R^2} F$ $\xrightarrow{P} F$	$F = F = \frac{1}{4}$		
Entry	Substrate	R ¹	R ²	Product	Yield (%) ^a
1	3a	Ме	Me	4a	60
2	3b	Et	Me	4b	63
3	3c	Ph	Н	4c	64
4	3d	CH ₂ CH ₂ Ph	Me	4d	56
5	3e	-(CH ₂) ₅ -		4e	42
6	3f	Н	Н	4f	0 ^b

^a Isolated yield.

^b Determined by ¹⁹F NMR using PhCF₃ as internal standard.

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 Table 3
 Cu-Mediated Cross-Coupling Reaction between Compound 1 and Alkynyl Halides 5

1 -	Cul (1.0 equiv) CsF (1.1 equiv) DMF, -30 °C, 4 h	R ³ ────X (5) (2.0 equiv) DMF, 0 °C, 16 h	Ph S F F		
Entry	Substrate	R ³	6 X	Product	Yield (%) ^a
1	5a	Ph	Ι	6a	79
2	5a′	Ph	Br	ба	69
3	5a″	Ph	C1	6a	trace ^b
4	5b	$4-FC_6H_4$	Ι	6b	58
5	5c	<i>n</i> -Bu	Ι	6c	82
6	5d	<i>n</i> -oct	Ι	6d	59
7	5e	c-Hex	Ι	6e	67
8	5f	CH ₂ OBn	I	6f	45
9	5g	Bn	Ι	6g	62
10	5h	CH(OH)Ph	Ι	6h	13 ^b

^a Isolated yield.

^b Determined by ¹⁹F NMR using PhCF₃ as internal standard.

group) in substrate **5h** led to the complete failure of the desired coupling reaction (entry 10).

To demonstrate the synthetic applications of (phenylsulfonyl)difluoromethylated alkynes, we chose product **6a** for further elaborations (Scheme 2). By using Mg/HgCl₂ system,¹⁷ compound **6a** was successfully desulfonylated to give difluoromethylated product **7** in 75% yield (determined by ¹⁹F NMR). Furthermore, considering that furans are important units in many nature products and pharmaceuticals,¹⁸ compound **6a** was used as a nucleophilic fluoroalkylating agent to react with 4-methoxybenzaldehyde in the presence of Mg/HgCl₂(cat.),¹⁷ and the addition product **8** was obtained in 65% isolated yield. Compound **8** could be readily transformed to fluorine-containing furan by the treatment of DBU {1,8-diazabicyclo[5.4.0]undec-7-ene}.¹⁹



Scheme 2 Synthetic applications of product 6a

It is noteworthy that we incidently discovered that when air (ca. 1 equiv of O_2 ; added via a balloon) was present, PhSO₂CF₂Cu/CuI/DMF system will undergo an oxidative coupling reaction to give PhSO₂CF₂I (**10**, 66% yield, determined by ¹⁹F NMR; Scheme 3, equation 1). A similar oxidative chlorination reaction occurred when CuCl₂ was used instead of CuI, and PhSO₂CF₂Cl (**12**) was obtained in 60% isolated yield (Scheme 3, equation 2). In the latter case, CuCl₂ was used not only as a copper source, but also as an oxidant.²⁰



Scheme 3 Oxidative coupling reactions

In conclusion, a new (phenylsulfonyl)difluoromethylation reagent, $PhSO_2CF_2Cu$, was successfully prepared for the first time by using $PhSO_2CF_2TMS/CuI/CsF$ in DMF. It was found that $PhSO_2CF_2Cu$ reagent could efficiently undergo cross-coupling reactions with propargyl chlorides and alkynyl halides to give $PhSO_2CF_2$ -containing allenes and alkynes, respectively. Further investigation of this reagent and related chemistry are currently under way in our laboratory.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

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