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Cu-Promoted difluorocarbene-derived trifluoromethylselenolation of benzyl halides with the $Ph_3P^+CF_2CO_2^-/S_e/F^-$ system is described. Three new carbon-heteroatom bonds, a Se-CF₂ bond, SeCF₂-F bond, and C-SeCF₃ bond, were sequentially formed in the reaction. This work represents the first trifluoromethylselenolation protocol involving an external fluoride for the generation of the key intermediate, CF₃Se⁻ anion.

of benzyl halides[†]

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Trifluoromethylchalcogeno groups, such as trifluoromethoxy $(CF_3O)^1$ and trifluoromethylthio $(CF_3S)^2$, usually possess unique electronic properties which are of particular interest in life sciences, and thus trifluoromethylchalcogeno-containing pharmaceuticals and agrochemicals have been continuously developed.^{1,2} A trifluoromethylseleno group (CF₃Se) also shows valuable electronic properties such as strong electron-withdrawing nature (Hammett constants $\sigma_{\rm p} = 0.45$, $\sigma_{\rm m} = 0.44$),³ and its Hansch–Leo parameter $(\pi = 1.29)$ measured recently by Billard is reflective of high lipophilicity.⁴ Compared with CF₃O and CF₃S, CF₃Se has received much less attention in agrochemical and pharmaceutical research, probably because it is usually believed that selenium is toxic to humans.⁵ However, at low doses selenium is an essential nutrient to humans and selenium substances have found applications in drug design,⁶ such as the drug ebselen.⁷ Therefore, determined efforts have been directed towards the development of efficient methods for the incorporation of a CF₃Se group into organic molecules.

Two strategies have been well established for CF_3Se incorporation, trifluoromethylation of selenocyanates⁸ or diselenides⁹ (Scheme 1, eqn (1)), and direct trifluoromethylselenolation with a CF_3Se -containing reagent¹⁰ or a CF_3^-/Se system¹¹ (eqn (2)).



Difluorocarbene-derived trifluoromethylselenolation

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Trifluoromethylation of selenocyanates or diselenides suffers from the need for the tedious synthesis of selenium-substrates and a narrow substrate scope. Apparently, direct trifluoromethylselenolation is a straightforward and attractive strategy (eqn (2)). Since a Cu complex could catalyze trifluoromethylselenolation with a CF_3^{-}/Se system and $[CuSeCF_3]$ was proposed to be a key intermediate,¹¹ Weng prepared CuSeCF₃-type reagents and applied them to direct trifluoromethylselenolation.¹² [Me₄N⁺⁻SeCF₃] was found to be an effective reagent and has been used in trifluoromethylselenolation of a wide range of substrates under Pd-catalyzed,¹³ Ni-catalyzed,¹⁴ Cu-catalyzed¹⁵ or transition-metalfree¹⁶ conditions. Based on Wakselman's approach for the synthesis of CF₃SeCl,¹⁷ Billard developed a one-pot method for trifluoromethylselenolation of arenes,¹⁸ alkynyl copper,¹⁹ alkenes,²⁰ boronic acids,²¹ organometallic reagents,⁴ and carbonyl compounds²² via the in situ generation of CF₃SeCl. Interestingly, they further used this one-pot strategy to synthesize a new reagent, TsSeCF₃, and achieved various trifluoromethylselenolation reactions by using this reagent.²³ Despite this extensive progress, current trifluoromethylselenolation methods still have significant limitations. For example, the reactions may involve the generation and use of the toxic and highly volatile CF₃SeCl reagent, the [Me₄N⁺⁻SeCF₃] reagent is air sensitive, and both the CuSeCF₃-type reagents and $[Me_4N^{+-}SeCF_3]$ have to be prepared from volatile Ruppert-Prakash reagent (TMSCF₃). Therefore, the development of efficient trifluoromethylselenolation protocols by using readily accessible and easily handled reagents is highly desirable.

Phosphobetaine salt $Ph_3P^+CF_2CO_2^-$, a reagent that was developed by us recently²⁴ and also used by others,²⁵ could be

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easily prepared via a one-step reaction. A convenient work-up procedure simply by washing could afford the pure phosphobetaine salt, which is bench-stable and easy to handle. As a difluorocarbene reagent, $Ph_3P^+CF_2CO_2^-$ could react with elemental sulfur (S₈) to generate thiocarbonyl fluoride in situ, which is electrophilic and would be readily trapped by a nucleophile such as F⁻ anions.^{24f-h} Therefore, the Ph₃P⁺CF₂CO₂^{-/}S₈/F⁻ system was used as the CF₃S⁻ source to achieve trifluoromethylthiolation.^{24e-g} Since the reaction occurred rapidly, ¹⁸F-trifluoromethylthiolation by replacing F⁻ with ¹⁸F⁻ was investigated and successfully achieved. On the basis of this unprecedented trifluoromethylthiolation process, we envisioned that the Ph₃P⁺CF₂CO₂^{-/}Se/F⁻ system might be able to act as a CF₃Se⁻ source to realize trifluoromethylselenolation. In this case, although the reaction involved the sequential formation of three new carbonheteroatom bonds, a Se-CF2 bond, SeCF2-F bond, and C-SeCF3 bond, it occurred fast and was completed within 1.5 h (Scheme 1, eqn (3)).

As we have found that a copper source may be necessary to enable the trifluoromethylthiolation with the $Ph_3P^+CF_2CO_2^{-/}S_8/F^-$ system, CuI was then used to promote the trifluoromethylselenolation of substrate **1a** with the $Ph_3P^+CF_2CO_2^{-/}S_8/F^-$ system (Table 1). A brief survey of the reaction solvent (entries 1–4) revealed that DMA appeared to be a superior choice (entry 4). Almost no product was detected by using CuBr instead of CuI (entry 5). The yield was slightly increased by

 Table 1
 Optimization of the reaction conditions^a

$Br + Ph_3P^+CF_2COO^- + Se + CsF - $ 1a			<u>[Cu], [Ag], 2.2'-bpy</u> DMA, 70 °C, 1.5 h Ph 2a	
Entry	[Cu] (equiv.)	[Ag] (equiv.)	Additive (equiv.)	$\operatorname{Yield}^{b}(\%)$
$ \frac{1^{cd}}{2^{ce}} \\ \frac{2^{ce}}{3^{cf}} \\ \frac{4^{c}}{5^{c}} \\ \frac{5^{c}}{6^{c}} \\ \frac{7}{8} \\ 9 \\ 10 \\ 11^{g} \\ 12^{h} \\ 13^{i} \\ 14 \\ 15 \\ 16 \\ 17 \\ 18 \\ 19 \\ 19 \\ 18 \\ 19 \\ 10 \\ 19 \\ 10 \\ 10 \\ 10 \\ 10 \\ 10 \\ 10 \\ 10 \\ 10$	CuI (0.5) CuI (0.5) CuI (0.5) CuI (0.5) CuI (1) CuI (3)	$\begin{array}{c} - \\ - \\ - \\ - \\ - \\ - \\ - \\ - \\ - \\ - $	$ \begin{array}{c} - \\ - \\ - \\ - \\ - \\ - \\ - \\ - \\ - \\ - \\$	Trace ND ND 14 Trace 19 28 26 7 37 20 12 36 17 54 34 35 57 80
20 21 22 ^j	CuI (3) — CuI (3)	$\begin{array}{c} \\ Ag_2CO_3 (0.2) \\ Ag_2CO_3 (0.2) \end{array}$	n Bu ₄ NCl (2) n Bu ₄ NCl (2) n Bu ₄ NCl (2)	45 ND 62

^{*a*} Reaction conditions: substrate **1a** (0.2 mmol), Ph₃P⁺CF₂CO₂⁻ (2 equiv.), Se (6 equiv.), CsF (3 equiv.), 2,2'-bpy(2,2'-bipyridine) (2 equiv.), Cu complex, and Ag complex in DMA (3 mL) at 70 °C for 1.5 h; ND = not detected. ^{*b*} The yields were determined by ¹⁹F NMR spectroscopy. ^{*c*} No 2,2'-bpy was used. ^{*d*} DMF was used as the reaction solvent. ^{*e*} THF was used as the reaction solvent. ^{*f*} DMSO was used as the reaction solvent. ^{*g*} KF was used instead of CsF. ^{*h*} 1,10-Phenanthroline was used instead of 2,2'-bpy. ^{*i*} The reaction temperature was 90 °C. ^{*j*} No 2,2'-bpy was used.

increasing the loading of CuI to 1 equiv. (entry 6 vs. 4). The presence of a ligand (2,2'-bipyridine) and a suitable Ag complex (2 equiv.) such as Ag₂CO₃ or AgF further increased the yield (entries 7 and 8). Interestingly, decreasing the loading of Ag_2CO_3 led to an increase in the yield (entry 10 vs. 7). KF was an inferior fluoride source compared with CsF (entry 11 vs. 10). A lower yield was obtained by using another ligand instead of 2,2'-bipyridine (entry 12). Increasing the reaction temperature did not give a higher yield (entry 13). The use of an ammonium salt ("Bu₄NCl) as an additive, which may stabilize the in situ generated CF₃Se⁻ anion, gave a 54% yield of the desired product (entry 15). A slightly higher yield was given by increasing the loading of this ammonium salt (entry 18). To our delight, using a substoichiometric amount of Ag₂CO₃ could also give a good vield (80%) when using excessive CuI (entry 19). But the vield was decreased dramatically without the presence of Ag₂CO₃ (entry 20). CuI is essential for this conversion and no desired product was observed without using this complex (entry 21). The ligand 2,2'-bipyridine also played an important role, as evidenced by the lower yield (62%) in its absence (entry 22).

With the optimized reaction conditions in hand, we then investigated the Cu-mediated trifluoromethylselenolation of benzyl halides with the $Ph_3P^+CF_2CO_2^-/Se/F^-$ system. As shown in Scheme 2, electron-deficient, -neutral and -rich benzyl bromides could all be well converted into the desired products in moderate to good yields (**2a–2m**). Although the mixture of $Ph_3P^+CF_2CO_2^-$, F^- source, and a Cu complex could generate the active trifluoromethylation intermediate [CuCF₃],²⁶ trifluoromethylation byproduct was not observed in these reactions. Interestingly, the aryl C–X bond (X = Cl, Br or I) remained intact (**2c–2g**), even though aryl halides are reactive toward Cu-mediated trifluoromethylselenolation, as



$$\begin{array}{c} \mbox{Cul, Ag_2CO_3} \\ \mbox{Ph}_3 \mbox{Ph}_2 \mbox{C}_2 \mbox{Cu}_2 \mbox{ + Se} + \mbox{Cs} \frac{2.2 \mbox{-bpy}, \mbox{"Bu}_4 \mbox{Cl}_4 \mbox{Cl}_5}{\mbox{DMA, 70 °C, 0.5 h}} \mbox{ [CuSeCF_3]} \frac{4 \mbox{-Ph} \mbox{C}_6 \mbox{H}_4 \mbox{CH}_2 \mbox{Be}_4 \mbox{H}_4 \mbox{CH}_2 \mbox{Be}_4 \mbox{H}_4 \mbox{CH}_2 \mbox{Be}_4 \mbox{H}_4 \mbox{CH}_2 \mbox{Be}_4 \mbox{Be}_4 \mbox{H}_4 \mbox{Be}_4 \mbox{Be}$$

 $\mbox{Scheme 3}$ The generation of [CuSeCF_3] intermediate. a The yield was determined by $^{19}{\rm F}$ NMR spectroscopy.



has been reported previously.¹¹ Low yields were obtained for the conversion of allyl bromides and alkyl bromides (**2n–2o**). Although benzyl chlorides show lower reactivity compared with benzyl bromides, the conversion of benzyl chlorides gave the desired products in moderate to good yields. Low reactivity of secondary benzyl chlorides was observed (**2p**).

The [CuSeCF₃] should be the key intermediate for this transformation. Without the presence of a substrate, [CuSeCF₃] species were generated from the reaction of CuI with the $Ph_3P^+CF_2CO_2^-/Se/CsF$ system (Scheme 3) (please see ESI† for details). After $Ph_3P^+CF_2CO_2^-$ was completely consumed, the subsequent addition of substrate **1a** gave the desired product in 48% yield, indicating the important role of the [CuSeCF₃] intermediate.

The plausible reaction mechanism is proposed as shown in Scheme 4. Decarboxylation of $Ph_3P^+CF_2CO_2^-$ under warming conditions generates a difluorocarbene intermediate.^{24c} On the basis of our observation that difluorocarbene can react with elemental sulfur to produce thiocarbonyl fluoride,^{24f-h} we propose that difluorocarbene could also be trapped by elemental selenium to form selenocarbonyl fluoride (CF₂==Se), which is an electrophilic species and would be attacked by a fluoride anion to give a trifluoromethyl-seleno anion (CF₃Se⁻ Cs⁺). The CF₃Se⁻ anion could be stabilized by the ammonium cation ⁿBu₄N⁺, the source of which is ⁿBu₄NCl or [(ⁿBu₄N⁺)₂ CO₃²⁻] that is produced *via* the reaction of ⁿBu₄NCl with Ag₂CO₃, to form the [ⁿBu₄N⁺ CF₃Se⁻] intermediate. Ligand exchange of the copper complex with [ⁿBu₄N⁺ CF₃Se⁻] provides the key trifluoromethylselenolation intermediate, CuSeCF₃, which would easily convert the substrates into the final products.¹¹

In summary, we have described the Cu-mediated trifluoromethylselenolation of benzyl halides with the $Ph_3P^+CF_2CO_2^{-/}$ Se/F⁻ system. This work represents the first protocol for trifluoromethylselenolation by using the combination of a difluorocarbene intermediate, elemental selenium and fluoride anions as the trifluoromethylseleno anion source. The use of the F⁻ anion for the construction of CF_3Se^- anions may allow the application of this strategy in ¹⁸F-trifluoromethylselenolation. As the difluorocarbene reagent ($Ph_3P^+CF_2CO_2^-$) could be easily prepared and is easy to handle, this trifluoromethylselenolation protocol may find utility in the synthesis of CF_3Se -containing biologically active molecules.

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Conflicts of interest

The authors declare no competing financial interest.

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