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Deoxygenative nucleophilic difluoromethylselenylation of carboxylic acids and alcohols with BT-$SeCF_2H$†

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The benzothiazolium salt BT-$SeCF_2H$ is introduced as an efficient nucleophilic reagent for transferring difluoromethylselenyl groups onto organic molecules. $SeCF_2H$-Containing selenoesters could be prepared upon deoxygenative substitution of readily available carboxylic acids, while silver catalysis allowed for efficient formation of (difluoromethyl)selenoethers, including the established electrophilic reagent $BnSeCF_2H$, directly from simple alcohols. To the best of our knowledge, these deoxygenative reactions represent the first reported nucleophilic difluoromethylselenylation processes and thus open up new approaches to prepare valuable fluorinated compounds.

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Introduction

Incorporating fluorine atoms and larger fluorine-containing functional groups is a tried and tested method for modulating the physical characteristics, biological activity and bioavailability of organic compounds.[1] While well-established moieties such as the CF_3 group remain the most widely studied, the investigation of alternative fluorinated motifs that offer new possibilities for fine-tuning a molecule's properties has become a major area of research.[2] Organoselenium derivatives are fundamental for many biological functions, with selenium itself being an essential human micronutrient. Multiple selenoethers and selenoesters have accordingly attracted attention as potential therapeutics including as anticancer, anti-microbial and anti-viral agents.[3] Selenium derivatives have also found applications in materials science[4] and as versatile synthetic intermediates and catalysts, especially in oxidation and radical chemistry.[5]

Combining the beneficial effects of fluorine substitution with organoselenium chemistry is an attractive approach for developing new functional (bio)molecules and materials. In recent years, significant research interest has focused on fluoroalkylselenyl groups with the $SeCF_3$ moiety in particular being the subject of several studies.[6] The difluoromethylselenyl group ($SeCF_2H$), on the other hand, has been less extensively investigated despite the well-known advantages partially fluorinated groups can offer over the corresponding perfluoro analogues (*e.g.* lipophilicity modulation, conformational effects, potential for hydrogen bonding).[1,7] One reason for the lack of studies on the $SeCF_2H$ group is the scarcity of synthetic routes to access it. Traditionally, indirect methods involving either insertion of difluorocarbene into a selenol[8] or formal nucleophilic difluoromethylation of a diselenide or cyanoselenide were employed.[9] Direct difluoromethylselenylation methods, in which $SeCF_2H$ is installed as a whole group, do not require access to a selenium-containing precursor and allow $SeCF_2H$ to be more readily studied alongside other fluorinated or non-fluorinated groups in structure–activity relationship (SAR) investigations. To date, however, only two reagent classes have been developed for direct difluoromethylselenylation, with both serving as electrophilic or radical sources of the $SeCF_2H$ group. The selenoether $BnSeCF_2H$ (**A**, Scheme 1a), which is itself produced only in low yield (13–36%) from BnSeCN, typically requires *in situ* activation with SO_2Cl_2, with $ClSeCF_2H$ serving as the actual difluoromethylselenylation reagent.[10] Sulfonyl derivatives **B** (Ar = Ph, *p*-Tol, Scheme 1a) react under milder conditions but are themselves synthesised from **A**.[11] While nucleophilic approaches are commonly employed to install the $SeCF_3$ group, to the best of our knowledge, no direct nucleophilic difluoromethylselenylation method has been reported and there are currently no sources of the $^-SeCF_2H$ anion available.

In 2019, we introduced 2-fluoroalkylchalcogenyl-substituted benzothiazolium salts as new reagents for installing fluorine-containing groups onto organic molecules. These BT-reagents can be prepared from relatively inexpensive starting materials and serve as practical sources of fluoroalkylchalcogenyl anions in synthetically appealing deoxygenative functionalisation reac-

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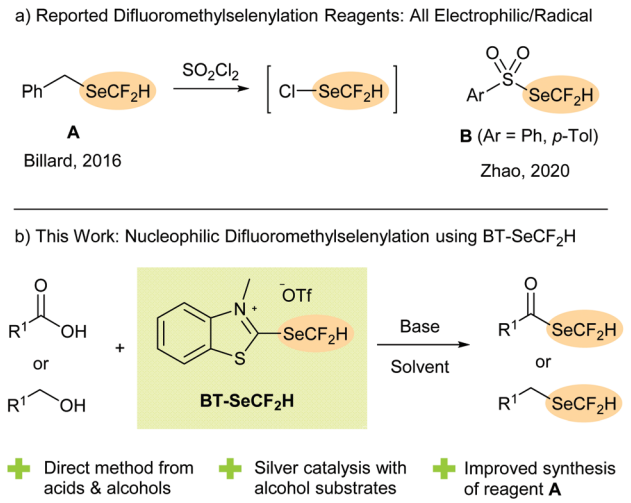


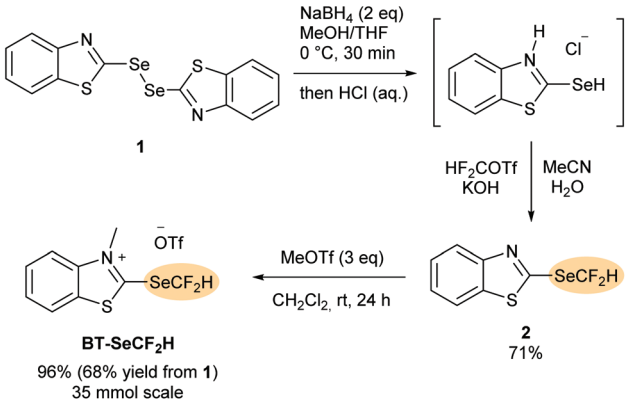
Scheme 1 (a) Established electrophilic and radical difluoromethylselenylation reagents. (b) This work: BT-$SeCF_2H$ as a nucleophilic reagent in deoxygenative substitution reactions of carboxylic acids and aliphatic alcohols.

tions of readily available aliphatic alcohols[12] and carboxylic acids.[13,14] In addition to perfluoroalkyl derivatives such as BT-SR_F ($R_F = C_nF_{2n-1}$) and BT-$SeCF_3$, recent work showed that the partially fluorinated analogue BT-SCF_2H could be successfully engaged in efficient deoxygenative difluoromethylthiolation reactions, providing (difluoromethyl)thioesters directly from carboxylic acids under mild conditions.[13] Inspired by these results, we considered whether a (difluoromethyl)selenium analogue could be accessed and, if so, whether it would act as a source of hitherto unexplored $^-SeCF_2H$ anions for nucleophilic transformations. Herein, we report the successful synthesis of BT-$SeCF_2H$ and its application as a reagent in unprecedented deoxygenative difluoromethylselenylation reactions (Scheme 1b). In addition to providing $SeCF_2H$-containing selenoesters from diverse carboxylic acids, silver catalysis allowed for the efficient synthesis of (difluoromethyl)selenoethers, including the established electrophilic reagent Bn$SeCF_2H$ (**A**), directly from unactivated alcohols.

Results and discussion

Synthesis of BT-$SeCF_2H$

The synthesis of the new benzothiazolium salt BT-$SeCF_2H$ is shown in Scheme 2. As for the other BT-reagents,[12–14] a two-stage approach was envisaged proceeding through a neutral non-methylated benzothiazole intermediate. In the first step, bis(benzothiazole)diselenide **1**[15] was reduced to the corresponding selenol using $NaBH_4$. Following precipitation as the benzothiazolium chloride adduct, subsequent treatment with difluorocarbene generated under basic conditions from HCF_2OTf afforded the stable heteroarene **2**, which could be isolated in 71% yield upon column chromatography.



Scheme 2 Synthesis of BT-$SeCF_2H$.

N-Methylation using methyl trifluoromethanesulfonate in CH_2Cl_2 at rt followed by precipitation with diethyl ether afforded BT-$SeCF_2H$ in 96% yield (overall yield of 68% from **1**, 35 mmol scale). BT-$SeCF_2H$ was obtained as an off-white solid that required no further purification and is stable at least over several months when stored under air at room temperature.

Deoxydifluoromethylselenylation of carboxylic acids

With BT-$SeCF_2H$ in hand, we sought to investigate its reactivity as a nucleophilic difluoromethylselenylating reagent. Inspired by the successful application of BT-SCF_2H in deoxygenative substitution reactions of carboxylic acids,[13] BT-$SeCF_2H$ (1.25 eq.) was first reacted with *n*-dodecanoic acid **3a** and NaH (2 eq.) in THF. After 2 h at rt, we were delighted to observe clean formation of the (difluoromethyl)selenoester **4a** in 45% NMR yield. Selenoesters have found multiple applications as pharmaceutical candidates and synthetic reagents, but studies on difluoromethyl derivatives are lacking.[16] In 2020, Wang and co-workers reported the only methodology for preparing (difluoromethyl)selenoesters; a radical process from aldehydes employing Bn$SeCF_2H$ (**A**) together with AIBN.[10f] The successful synthesis of (difluoromethyl)selenoesters using BT-$SeCF_2H$ not only offers a complementary route starting from readily available carboxylic acids, it also represents the first reported nucleophilic difluoromethylselenylation process. Mechanistically, **4a** likely results from an initial attack of the carboxylate to the 2-position of BT-$SeCF_2H$ followed either by elimination of $^-SeCF_2H$ and subsequent addition/elimination to a 2-carboxybenzothiazolium intermediate, or alternatively through a concerted rearrangement process.‡ Increasing the amount of BT-$SeCF_2H$ to 2 eq. and raising the reaction temperature to 45 °C improved the NMR yield to 81%, with **4a** being isolated in 78% yield after column chromatography.

The scope of the deoxygenative difluoromethylselenylation reaction was then tested with a range of carboxylic acid derivatives **3** (Scheme 3). A wide selection of aliphatic substrates

‡A concerted mechanism proceeding through a 4-membered transition state was suggested by DFT studies on the related deoxydifluoromethylthiolation of carboxylic acids with BT-SCF_2H (see ref. 13).

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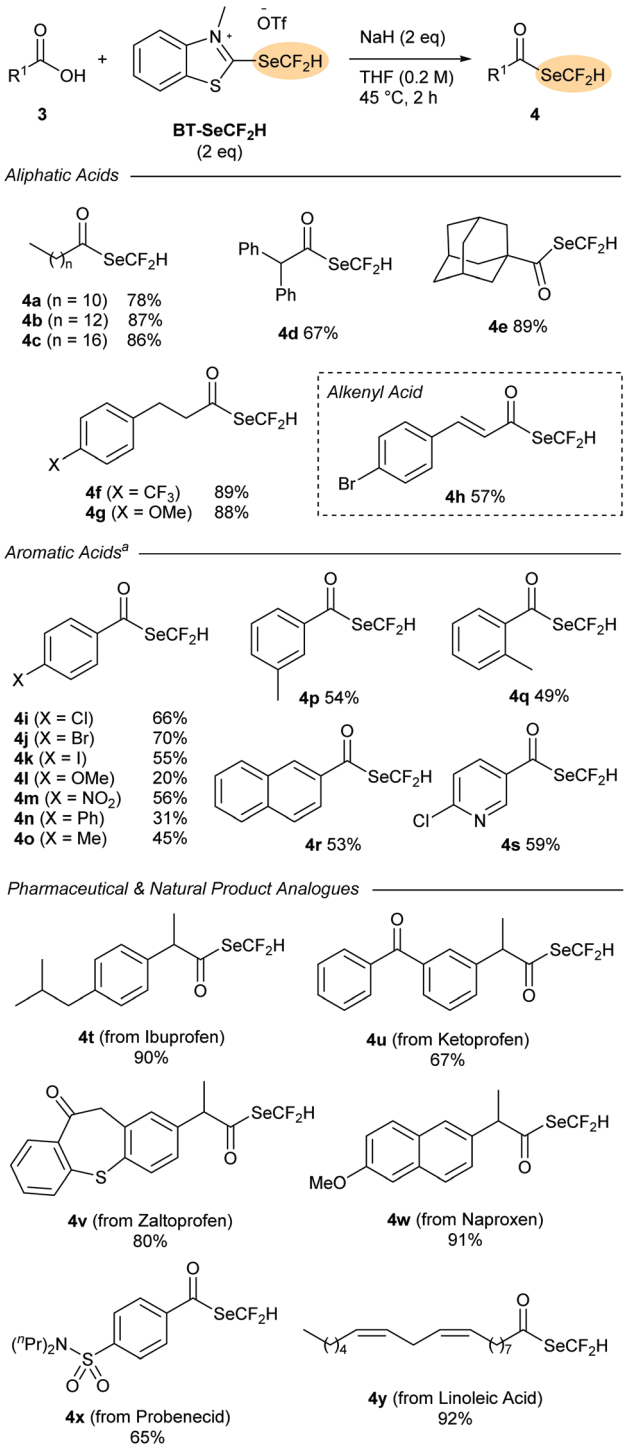

Scheme 3 Scope of the deoxydifluoromethylselenylation of carboxylic acids. Conditions: **3** (0.3 mmol), BT-$SeCF_2H$ (2 eq.), NaH (2 eq.) in THF (0.2 M), 45 °C, 2 h. Isolated yields. [a]Reactions conducted at rt.

could be successfully converted into the corresponding (difluoromethyl)selenoesters **4a–g** in excellent yields (67–89%). Primary, secondary and even tertiary derivatives were all tolerated with 1-adamantanecarboxylic acid **3e** providing selenoester **4e** in 89% yield after column chromatography. Aromatic acids could also be successfully employed with these reactions being conducted at room temperature. A wide range of functional groups were tolerated with electron-neutral and comparatively electron-deficient moieties leading to the highest yields. The successful formation of the halogen-substituted products **4i–k** is particularly noteworthy as these compounds could serve as $SeCF_2H$-containing building blocks amenable to subsequent functionalisation through cross-coupling. As demonstrated by the series **4o–q**, substituents at the *ortho*-, *meta*- and *para*-positions were tolerated with little difference in the product yields observed.

Finally, the applicability of the deoxydifluoromethylselenylation method to the synthesis of $SeCF_2H$-containing pharmaceutical analogues was evaluated. A range of (difluoromethyl)selenoesters of common non-steroidal anti-inflammatory drugs (NSAIDs) could be prepared in excellent yields directly from the pharmaceutical compound (**4t–w**, 67–91%). The sulphonamide probenecid (**3x**), which is used to treat gout, could also be converted in 65% yield, while the naturally occurring fatty acid linoleic acid (**3y**) provided selenoester **4y** in 92% yield.

Deoxydifluoromethylselenylation of alcohols

Having established the reactivity of BT-$SeCF_2H$ as a nucleophilic reagent for the difluoromethylselenylation of carboxylic acids, we next turned our attention to the synthesis of selenoethers directly from aliphatic alcohols. Although more widely studied than (difluoromethyl)selenoesters, synthetic routes to alkyl-$SeCF_2H$ compounds are largely limited to indirect methods that require pre-installation of a diselenide or cyanoselenide motif onto the substrate.[9] To date, only a handful of direct difluoromethylselenylation reactions affording aliphatic products have been disclosed involving either nucleophilic attack onto *in situ*-activated $BnSeCF_2H$ (**A**)[10c,e] or, in a very recent report from Zhang and co-workers, radical group transfer from $PhSO_2SeCF_2H$ (**B**).[11c]

In an initial test reaction, 4-nitrobenzyl alcohol **5a** was reacted with BT-$SeCF_2H$ (1.25 eq.) and $NEt(^iPr)_2$ (2 eq.) in MeCN at rt. After 2 h, ^1H and ^{19}F NMR indicated the formation of the desired selenoether **6a** in 42% yield. Increasing the amount of reagent and base and adding them in portions, as well as the optimisation of the temperature (−40 °C) and reaction time (4 h) allowed for an increase in the NMR yield of **6a** to 65% with the pure product being isolated in 62% yield after column chromatography. At this stage, the generality of the method was tested with a selection of benzylic alcohols (Scheme 4). While a series of substrates bearing electron-withdrawing substituents such as –CN, $–CF_3$ and $–CO_2Me$ provided the corresponding (difluoromethyl)selenoethers **6a–e** in good yields, more electron-rich derivatives reacted only with low efficiency. Addition of these alcohols to the BT-reagent followed by elimination of $^-SeCF_2H$ would lead to a comparatively less electrophilic 2-alkoxybenzothiazolium intermediate. Nucleophilic substitution at this species is likely less favoured, and decomposition of the $^-SeCF_2H$ anion may outcompete product formation. With the aim of providing a stabilising

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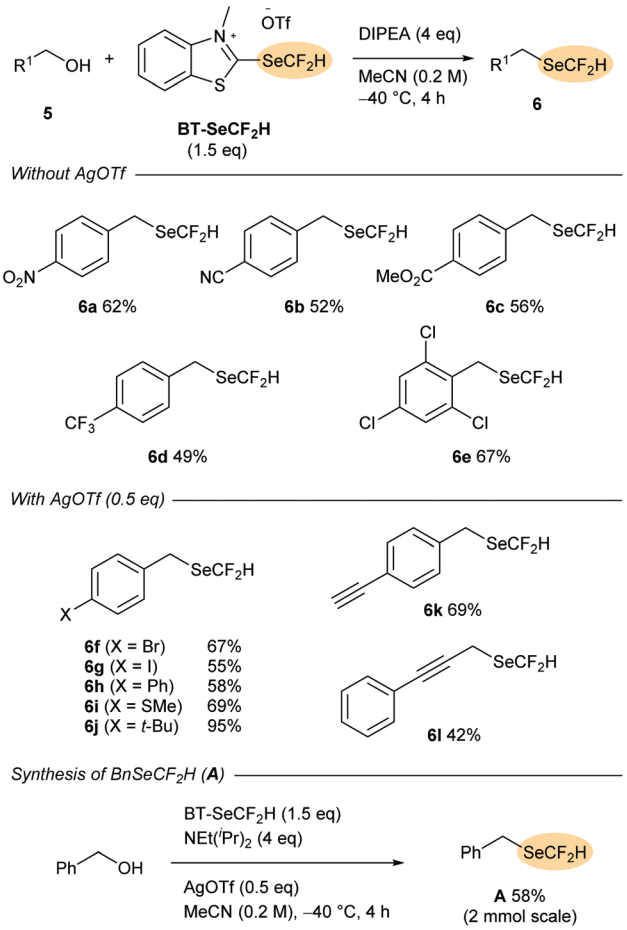

Scheme 4 Scope of the deoxydifluoromethylselenylation of aliphatic alcohols. Conditions: **5** (0.3 mmol), BT-$SeCF_2H$ (2 eq.), $NEt(^iPr)_2$ (2 eq.) and, where indicated AgOTf (0.5 eq.), in MeCN (0.2 M), –40 °C, 2 h then additional BT-$SeCF_2H$ (0.25 eq.), $NEt(^iPr)_2$ (2 eq.) added, stirred for another 2 h at –40 °C. Isolated yields.

counter-cation, which could increase the lifetime of $^-SeCF_2H$ in the reaction medium, silver(I) salts were tested as catalytic additives. While 4-bromobenzyl-containing selenoether **6f** was provided in only 31% yield under the standard conditions described above, addition of Ag_2O (0.25 eq., 0.5 eq. of Ag^+) led to an increase in NMR yield to 63%. Moreover, selenoether **6f** was obtained in 81% NMR yield (67% isolated) when the reaction was conducted in the presence of AgOTf (0.5 eq.).

Under these silver catalysis conditions, good yields were obtained with a selection of electron-neutral and electron-rich benzyl alcohols (**5g–k**, up to 95% with 4-(*tert*-butyl)benzyl alcohol **5h**), while the propargylic substrate **5l** also reacted with moderate efficiency (42% yield of **6l**). Notably, the method is also tolerant of terminal alkynes (**6k**), which are known to be activated by silver(I). Finally, direct deoxytrifluoromethylselenylation of benzyl alcohol was tested as a method for preparing BnSeCF_2H (**A**). This electrophilic and radical difluoromethylselenylation reagent was introduced by Billard and co-workers in 2016[10a] and has been previously synthesised from benzyl bromide in a two-step sequence involving nucleophilic difluoromethylation of BnSeCN.[10a,e,11c] Subjecting BnOH to the optimised conditions with BT-$SeCF_2H$ (1.5 eq.), AgOTf (0.5 eq.) and $NEt(^iPr)_2$ (4 eq.) resulted in smooth formation of the established reagent **A**, which could be isolated in 58% yield after column chromatography on a 2 mmol scale. This yield is notably higher than that obtained in the previously-reported difluoromethylation of BnSeCN (13–36%)[10a,e,11c] and suggests that direct deoxygenative difluoromethylselenylation could serve as a useful complementary approach to prepare reagent **A** and, by extension, its derivatives **B**.

Conclusions

In conclusion, BT-$SeCF_2H$ has been introduced as a practical reagent for hitherto unexplored nucleophilic difluoromethylselenylation reactions. Deoxygenative substitution of carboxylic acids provides (difluoromethyl)selenoesters, while silver catalysis allows for the efficient synthesis of benzylic and propargylic CF_2H-substituted selenoethers, including the established electrophilic reagent Bn$SeCF_2H$ (**A**), directly from unactivated alcohols. In opening up nucleophilic approaches, we believe this work will inspire new routes towards difluoromethylselenylated compounds and accelerate the study of the $SeCF_2H$ group in medicinal and materials chemistry.

Conflicts of interest

M.N.H. and S.D. are co-inventors on a European and International Patent Application concerning the synthesis and use of benzothiazolium reagents for installing fluorine-containing functional groups (EP 3 677 576 A1; WO 2020141195 A1).

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