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# Copper-mediated tetrafluoroethylation of unsaturated organotrifluoroborates *via* generation of the $HCF_2CF_2$-radical from zinc 1,1,2,2-tetrafluoroethanesulfinate†

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**A copper-mediated synthetic method for the incorporation of the 1,1,2,2-tetrafluoroethyl ($CF_2CF_2H$) group into unsaturated potassium organotrifluoroborate systems using the zinc 1,1,2,2-tetrafluoroethanesulfinate reagent has been developed. The $HCF_2CF_2$-radical, derived *in situ* from $(HCF_2CF_2SO_2)_2Zn$ using TBHP as an oxidant, combines with a copper-catalyst to promote the replacement of the $BF_3K$ group on alkenes and alkynes. The reactions are carried out under ambient air, using mild and practical conditions. The method provides access to tetrafluoroethylated alkene and alkyne products in moderate to good yields.**

Organofluorine compounds play important roles in the fields of pharmaceuticals, materials sciences, and agrochemicals due to their recognized enhancement of physical, chemical, and medicinal properties.[1] The difluoromethyl group ($CF_2H$) is recognized as a bioisostere of the SH and OH groups,[2] and methodologies for the incorporation of the difluoromethyl ($CF_2H$) group into organic compounds have expanded dramatically over the past decade.[3] The 1,1,2,2-tetrafluoroethyl group ($CF_2CF_2H$), a homolog of the $CF_2H$ group, has the potential to combine the physiochemical properties of the difluoromethyl and perfluoroalkyl groups. To date, there have been studies demonstrating that tetrafluoroethylated compounds exhibit antiparasitic activity, and such compounds have emerged as potentially important candidates for application in the field of agrochemicals (Fig. 1).[4] Recently, the incorporation of the tetrafluoroethyl group into organic molecules has begun to attract significant and sustained attention.[5] Nevertheless, to date, only a handful of methodologies have been reported for this purpose, and these methodologies, for the most part, are limited to arene/heteroarene substrates (Scheme 1A).[6]

Recently, Baker, Boutureira, and co-workers reported a copper-mediated tetrafluoroethylation of electron-rich alkenyl iodides using an *in situ* generated, ligandless $[CuCF_2CF_2H]$ active species (Scheme 1B).[7]

However, this noteworthy approach requires pre-formation of the tetrafluoroethylating reagent and the use of a glove box throughout the two-stage process. We believe that our current,

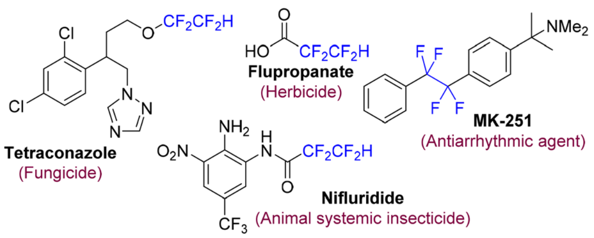
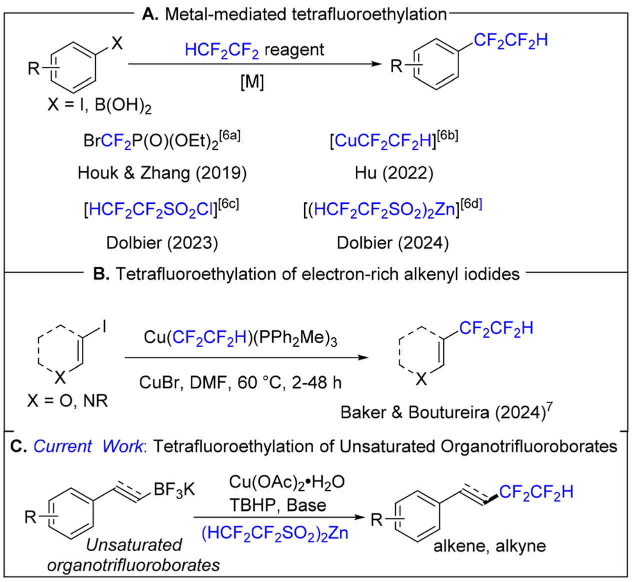


**Fig. 1** Drugs and agrochemicals containing a tetrafluoroethyl group.



**Scheme 1** Aryl tetrafluoroethylation methodologies.

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operationally simple method for direct vinylic and acetylenic tetrafluoroethylation will constitute a worthy addition to the synthetic chemist's toolbox.

Zinc 1,1,2,2-tetrafluoroethanesulfinate $(HCF_2CF_2SO_2)_2Zn$ is a bench-stable, easy-to-prepare and handle reagent, which was first introduced by our group in 2024,[6d] when it was demonstrated to be a versatile reagent for the direct transfer of the $CF_2CF_2H$ group into organic substrates. This reagent serves as a precursor for tetrafluoroethyl radicals upon oxidative treatment with *t*-butyl hydroperoxide (TBHP), as demonstrated in the aforementioned study of the copper-mediated tetrafluoroethylation of arylboronic acids.[6d] A key feature of this chemistry is the reaction of the $HCF_2CF_2$-radical generated from $(HCF_2CF_2SO_2)_2Zn$ with a copper–aryl intermediate to provide $ArCF_2CF_2H$ products. The mild conditions and high selectivity associated with these reactions led us to consider additional applications of this chemistry. With that in mind, consistent with our long-standing interest in the development of fluoroalkylation methodologies,[8] and inspired by multiple papers related to the trifluoromethylation of vinylic boronic acids using the $NaSO_2CF_3$ reagent,[9] we sought to develop a mild and operationally simple protocol for the tetrafluoroethylation of potassium organovinyltrifluoroborates (Scheme 1C).

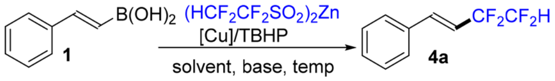
Unsaturated potassium organotrifluoroborate salts have gained increased attention due to their bench stability, high functional group tolerance, and ease of preparation from commercially available sources.[10]

Our initial experiments, however, were carried out using the commercially available *E*-β-styreneboronic acid **1** using conditions virtually identical to those used in our 2024 paper on tetrafluoroethylation of arylboronic acids (Table 1).[6d] We were pleased to observe the formation of product **4a** in 48% yield (by $^{19}F$ NMR) under the following conditions: $(HCF_2CF_2SO_2)_2Zn$, TBHP, $K_2CO_3$ and CuCl (1.0 equiv.) in a $DCM/MeOH/H_2O$ solvent system at 0 °C to room temperature (entry 1). A product derived from protodeborylation constituted the main byproduct, along with formation of trace amounts of the homocoupling product.

Optimizing the reaction involved carrying out experiments using various copper-catalysts, including CuI, $(MeCN)_4CuPF_6$, $CuCl_2·H_2O$, $Cu(OAc)_2·H_2O$, $Cu(OTf)_2$, $CuSO_4$, and CuI with added ligands. This led to variable yields of the desired product (see the ESI† for details of the optimization), with the best yields for conversion of the boronic acid obtained using: (a) $Cu(OAc)_2·H_2O$ (65%, entry 6) and (b) CuI with the ligand 1,10-phenanthroline (66%, entry 11). Using no base or increasing the reaction temperature to 50 °C led to lower yields (entries 9 and 10). Also, interestingly, when the reaction was carried out with no added catalyst, a reasonable yield of 33% was obtained. Such a non-catalyzed substitution reaction was never mentioned in related $CF_3SO_2Na$-based studies.[9]

We then extended our optimization experiments to include other styreneboronic acid derivatives. Potassium organovinyl trifluoroborates have been shown to have some advantages for cross-coupling chemistry in terms of ease of preparation and greater nucleophilicity compared to organovinylboronic acids and esters.[11] Using *E*-β-styryl potassium trifluoroborate **3a** provided the best yield (72%; entry 14) under the otherwise same reaction conditions (Scheme 2). In contrast, pinacol ester **2** provided a lower yield (42%, entry 15) of the desired product.

Table 1 Optimization of the reaction conditions[a]

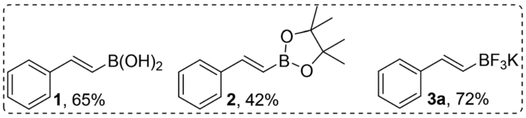


| Entry | [Cu]-catalyst | Base | **4a** % yield[b] ($^{19}F$ NMR) |
|---|---|---|---|
| 1 | CuCl | $K_2CO_3$ | 48 |
| 2 | CuCl | $NaHCO_3$ | 51 |
| 3 | CuI | $NaHCO_3$ | 49 |
| 4 | $(MeCN)_4CuPF_6$ | $NaHCO_3$ | 46 |
| 5 | $CuCl_2·H_2O$ | $NaHCO_3$ | 56 |
| 6 | $Cu(OAc)_2·H_2O$ | $NaHCO_3$ | 65 |
| 7 | $Cu(OTf)_2$ | $NaHCO_3$ | 31 |
| 8 | $CuSO_4$ | NaHCO3 | 29 |
| 9 | $Cu(OAc)_2·H_2O$ | None | 59 |
| 10[c] | $Cu(OAc)_2·H_2O$ | $NaHCO_3$ | 58 |
| 11[d] | CuI/1,10-phen | $NaHCO_3$ | 66 |
| 12[e] | CuI/TMEDA | $NaHCO_3$ | 50 |
| 13 | $Cu(OAc)_2·H_2O$/1,10-phen | $NaHCO_3$ | 51 |
| 14[f] | **$Cu(OAc)_2·H_2O$** | **$NaHCO_3$** | **72** |
| 15[g] | $Cu(OAc)_2·H_2O$ | $NaHCO_3$ | 42 |
| 16[h] | None | $NaHCO_3$ | 33 |

[a] General conditions: **1** (0.2 mmol, 1 equiv.), [Cu]-catalyst (1 equiv.), base (1 equiv.), TBHP (70% in $H_2O$, 5 equiv.), $DCM/MeOH/H_2O$ (4 : 4 : 3 ratio), 0 °C–rt, 15 h, under a nitrogen atmosphere. [b] Yields were determined by $^{19}F$ NMR analysis using $PhCF_3$ as an internal standard. [c] The reaction was conducted at 50 °C. [d] 2 equiv. of 1,10-phenanthroline. [e] 3 equiv. of TMEDA. [f] (*E*) PhCH = $CHBF_3K$ was used as the starting material. [g] (*E*) PhCH = CHBPin was used as the starting material. [h] No copper.

With the development of a mild optimized reaction procedure, the substrate scope of the reaction was then investigated. The transformations were equally effective for a variety of substituents on the phenyl ring (Scheme 3). Although trifluoromethylations of arylboronic acids bearing strong electron-deficient substituents have been shown to be less reactive, due to slower transmetalation,[12] in our case, substrates with electron-rich and electron-poor aromatic rings provided similar results in the reaction. Additionally, C-3 substituted heteroaromatic pyridine (**4i**, 74%) and thiophene (**4j**, 53%) also led to the desired product in good yields.

It should be noted that the tetrafluoroethylation reactions occurred with generally high selectivity, with no (*Z*) isomeric product being observed by NMR, except in the case of substrate **3k**, which features an extended conjugation. As expected, a substrate with a sterically hindering β-methyl substituent (**3l**) led to no product formation. Also, our methodology did not



Scheme 2 Comparison of styrene boronic acid derivatives.

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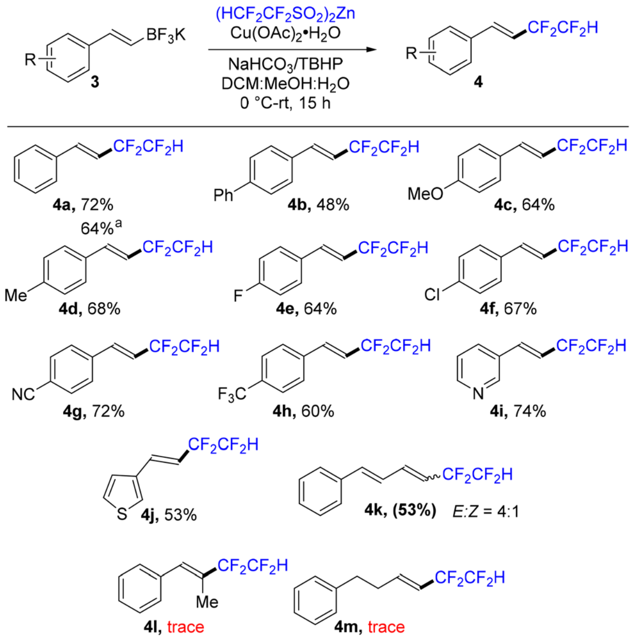
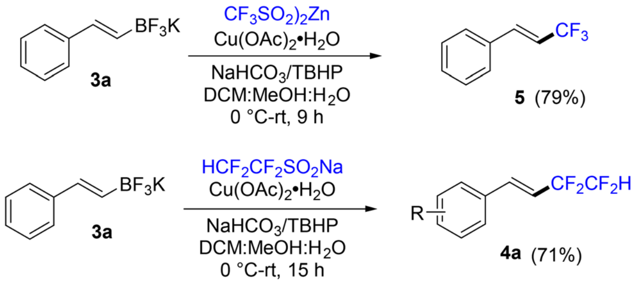


**Scheme 3** Substrate scope of alkenyltrifluoroborates. Reaction conditions: **3** (0.2 mmol), $Cu(OAc)_2 \cdot H_2O$ (1 equiv.), $NaHCO_3$ (1 equiv.), TBHP (70% in $H_2O$, 5 equiv.), $(HCF_2CF_2SO_2)_2Zn$ (2 equiv.), DCM/MeOH/$H_2O$ (4 : 4 : 3 ratio), 0 °C–rt, 15 h, under a nitrogen atmosphere; yields were determined by $^{19}F$ NMR using $PhCF_3$ as an internal standard. [a] 1 mmol scale.

tolerate the substitution of an alkyl group for the aryl group (**3m**). Finally, a scale-up reaction using potassium styryltrifluoroborate **3a** and $(HCF_2CF_2SO_2)_2Zn$ was performed. This reaction proceeded smoothly to give the desired product **4a** with only a modest decrease in yield (64%).

A possible mechanism for this reaction would be one analogous to that proposed by Beller *et al.* in their paper on the Cu-mediated trifluoromethylation of aryl and vinyl boronic acids using the $CF_3SO_2Na$ reagent.[9a] However, this mechanism does not readily explain the lack of reactivity of **3l** and **3m**. Instead, a mechanism involving addition of the radical to the terminal vinylic carbon, followed by oxidation of the radical by TBHP and subsequent elimination of the $BF_3$ group, with or without Cu complexation, makes more sense, especially since the reaction was shown to occur in the absence of the Cu catalyst.

In a brief comparative study, the reactions of the analogous trifluoromethyl reagent $(CF_3SO_2)_2Zn$ and $HCF_2CF_2SO_2Na$ (Langlois-type) reagent with *E*-β-styryl potassium trifluoroborate (**3a**) were examined under identical reaction conditions to those shown in Scheme 3. The results of these reactions are provided in Scheme 4. The successful reaction of zinc bis(trifluoromethylsulfinate) with **3a** demonstrates that diverse fluoroalkyl zinc reagents should be effective for fluoroalkylation of potassium styryltrifluoroborates under our conditions. The likewise productive reaction of the tetrafluoroethyl Langlois-type reagent $HCF_2CF_2SO_2Na$ suggests a similarity in reactivity between Na and Zn fluoroalkylsulfinates in this reaction.



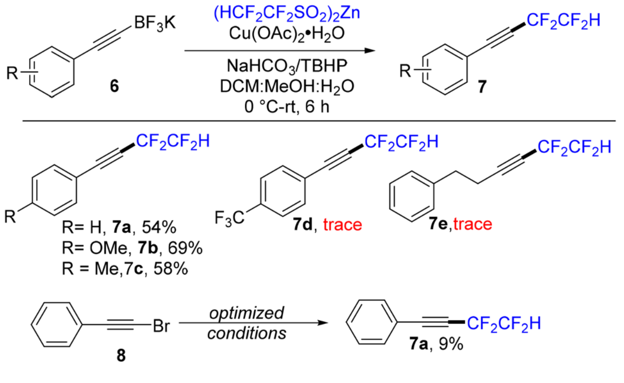
**Scheme 4** Brief exploratory comparisons of reagents.

Alkynes continue to be versatile synthons in synthetic organic chemistry,[13] and tetrafluoroethyl-substituted alkynes hold promise as valuable synthetic intermediates.

Buoyed by the success of the potassium styryltrifluoroborate chemistry, we endeavoured to extend it to the study of potassium alkynyl trifluoroborates (Scheme 5). Potassium alkynyl trifluoroborates are readily prepared and are stable under ambient laboratory conditions.[14] They are convenient to handle and useful as synthetic intermediates for further transformations.[15]

Using our previously optimized conditions with potassium phenylethynyltrifluoroborate (**6a**) as the substrate, the desired product was only obtained in a modest (32%) yield. Using different copper catalysts, such as CuCl, $CuSO_4$, CuI, $Cu(OTf)_2$, and $(MeCN)_4CuPF_6$, led to diminished yields, with protodeboronation being the main alternative observed pathway. Also, when using a haloalkyne, such as (bromoethynyl)benzene **8**, as a substrate, the desired product was obtained in a very poor yield of only 9%.[16] However, when using a shorter (6 h) reaction time along with a modified solvent ratio (DCM, MeOH, $H_2O$/1 : 1 : 2 ratio), the desired product **7a** could be obtained in a synthetically useful isolated yield (54%).

Neutral and electron-rich aryl alkynes were found to give satisfactory results in the reaction, but unfortunately, the electron-deficient trifluoromethyl-substituted phenyl compound



**Scheme 5** Substrate scope of alkynyltrifluoroborates. Reaction conditions: **6** (0.2 mmol), $Cu(OAc)_2 \cdot H_2O$ (1 equiv.), $NaHCO_3$ (1 equiv.), TBHP (70% in $H_2O$, 5 equiv.), $(HCF_2CF_2SO_2)_2Zn$ (2 equiv.), DCM/MeOH/$H_2O$ (1 : 1 : 2 ratio), 0 °C–rt, 6 h, under a nitrogen atmosphere; yields were determined by $^{19}F$ NMR using $PhCF_3$ as an internal standard.

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(**6d**) and a simple alkyl-substituted alkyne (**6e**) failed to produce more than trace amounts of the product. In a final experiment to assess side product formation under optimized conditions, substrate **6a** produced, in addition to the desired product **7a** (55%), the protodeborylation (20%) and homocoupling (5%) products.

## Conclusions

In conclusion, we report a convenient copper-mediated radical tetrafluoroethylation of unsaturated potassium organotrifluoroborates using the bench-stable $(HCF_2CF_2SO_2)_2Zn$ reagent as the source of the $HCF_2CF_2$ group. Thus, using a convenient reaction procedure, the synthesis of a diverse group of *E*-β-tetrafluoroethylstyrenes was achieved with modest to good yields. This chemistry has also been successfully extended to the synthesis of aryl tetrafluoroethylalkynes.

## Author contributions

The synthetic work was carried out largely by Md N. A., with significant assistance from S. M. and T. U. W. R. D. Jr. supervised the work and wrote the manuscript with feedback from the other authors.

## Conflicts of interest

There are no conflicts to declare.

## Data availability

The data supporting this article have been included as part of the ESI.†

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