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Graphical Abstract

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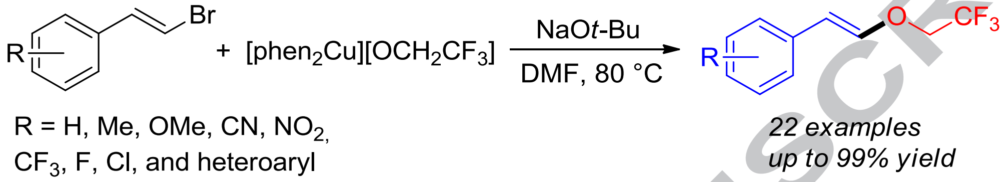

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Copper-mediated trifluoroethoxylation of vinyl bromides

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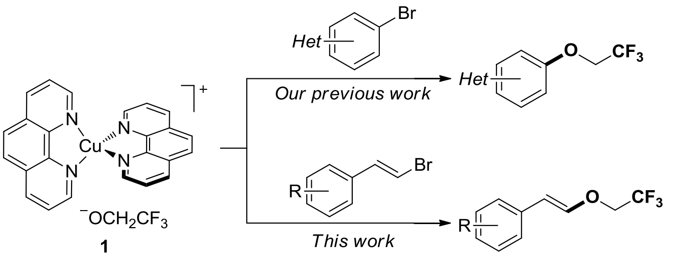
ABSTRACT

Vinyl bromides were subjected to the trifluoroethoxylation reactions with copper reagent $[(phen)_2Cu][OCH_2CF_3]$ at 80 °C in DMF with the presence of NaO*t*-Bu to afford the trifluoroethyl vinyl ethers in good yields. A range of functional groups, such as cyano, nitro, alkoxy, trifluoromethyl, halide, and heterocyclic groups were well tolerated. This approach is also amenable to being performed out on gram scales.

The incorporation of fluorine atoms into organic molecules can highly affect their physical and chemical properties, such as lipophilicity, metabolic stability, and bioavailability, conformation, electrostatic potential, dipole moment, pK_a, etc.[1,2,3,4] As a consequence, intensive efforts have been directed in recent years toward the development of efficient protocols for the incorporation of fluorine-containing groups into functional organic molecules.[5,6-10,11,12,13] In particular, introducing a trifluoroethoxy (CF_3CH_2O-) moiety has attracted the attention of chemists in the pharmaceutical and agrochemical industries, because of its great stability, high electronegativity, and improved lipophilicity.[14,15]

Conventionally, the trifluoroethyl aryl ethers were synthesized through the nucleophilic substitution of a phenol or phenoxide with suitable 2,2,2-trifluoroethyl iodide or methanesulphonate.[16] However, this procedure is limited by the low S_N2 reactivity of the β-carbon atom due to the presence of fluorine substituents[17] and the competing β-fluorine eliminations.[18] Alternative procedures include the cross-coupling of aryl halides with trifluoroethanol in the presence of an excess of copper salts under harsh reaction conditions.[19,20] The catalytic version of the reaction was developed by Legros and Crousse and co-workers using neat fluoro alcohols as both reactant and solvent at reflux conditions.[21] Another example in this area was recently disclosed by Singh and co-workers, who reported the use of Pd/BrettPhos catalyst system for the cross-coupling of primary fluoroalkyl alcohols with activated aryl halides.[22,23]

Recently we reported a convenient, and practical route to synthesize copper(I) fluoroalkoxide complexes, $[(phen)_2Cu][OCH_2R_F]$.[24,25] These complexes reacted with aryl and heteroaryl bromides to furnish the corresponding trifluoroethyl, pentafluoropropyl and tetrafluoropropyl (hetero)aryl ethers in good to excellent yields (Scheme 1).



Scheme 1. Trifluoroethoxylation with $[(phen)_2Cu][OCH_2CF_3]$ **1**.

With a desire to increase the scope of the trifluoroethoxylation further, we decided to explore a general procedure with which to synthesize trifluoroethyl vinyl ethers. Herein, we report an efficient synthesis of trifluoroethyl vinyl ethers via copper-mediated trifluoroethoxylation of vinyl bromides.

When β-bromostyrene **2a** was subjected to the reaction conditions that we found effective for aryl bromides,[24] that is, DMF, 80 °C, in the presence of NaO*t*-Bu (1.0 equiv.), we witnessed the complete consumption of the starting material in

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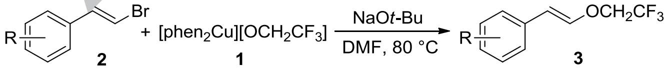
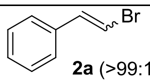
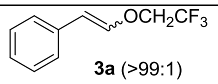
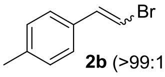
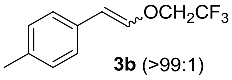
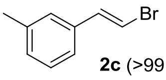
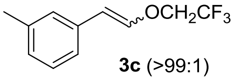
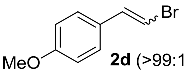
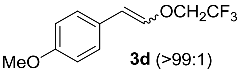
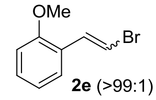
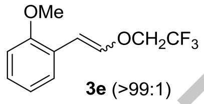
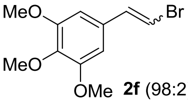
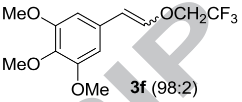
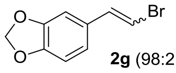
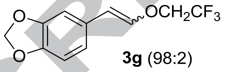
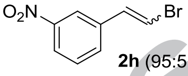
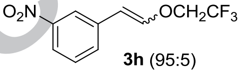
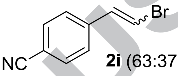
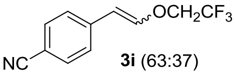
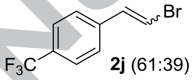
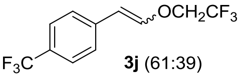
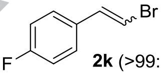
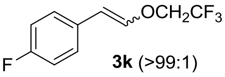
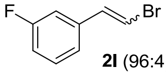
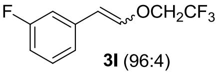
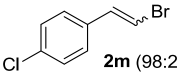
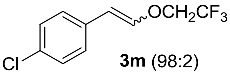
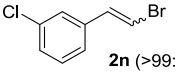
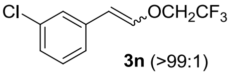
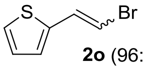
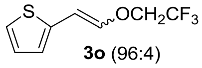
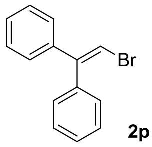
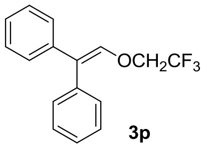
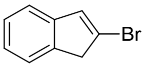
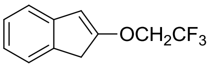
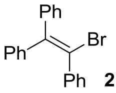
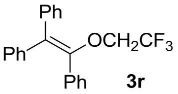
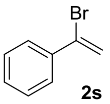
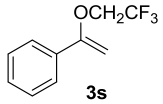
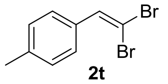
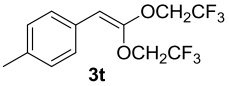
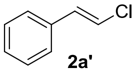
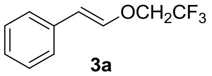
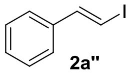
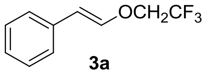
12 h and the formation of good yields of expected (2-(2,2,2-trifluoroethoxy)vinyl)benzene **3a** (89%; Table 1, entry 1).

To explore the scope of the trifluoroethoxylation reaction, various substituted alkenyl bromides were examined under the reaction conditions (Table 1). The vinyl bromides containing the *para*- or *meta*-substituted methyl afforded the trifluoroethylated products **3b** and **3c** in 84% and 83% yields, respectively (Entries 2 and 3). The vinyl bromides with methoxy substituent were well tolerated under the present reaction conditions and furnished the corresponding products **3d**-**3f** in good to excellent yields (Entries 4-6). 5-(2-Bromovinyl)benzo[*d*][1,3]dioxole also underwent this reaction well and provided the desired product **3g** in 81% yield (Entry 7). The vinyl bromide having the *meta*-substituted nitro group was transformed into the desired product **3h** in 80% yield (Entry 8). Furthermore, the trifluoroethoxylation reaction with vinyl bromides with the *para*-nitrile, or trifluoromethyl substituents on the phenyl ring gave the corresponding products **3i** and **3j** with slightly compromised yields (Entries 9 and 10). It was found that vinyl bromides with halogen substituents such as fluoro and chloro reacted smoothly to provide the corresponding products **3k**–**3n** in 62–76% yields (Entries 11–14). The reaction was compatible with the presence of a halogen atom on the aromatic core, allowing further synthetic functionalization. When hetero-aromatic vinyl halides such as 2-(2-bromovinyl)thiophene were used, the desired product **3o** was reached in 78% yield (Entry 15). The reaction was also amenable to substrate possessing a disubstitution in α-position; with (2-bromoethene-1,1-diyl)dibenzene (**2p**) the corresponding product **3p** was formed in 92% yields (Entry 16). Noteworthy, under the reaction conditions, cyclic vinyl bromides, such as 2-bromo-1*H*-indene (**2q**) participated the reaction even though the corresponding product **3q** was obtained in low yield of 8% (Entry 17). The sterically highly demanding arylvinyl bromides, such as 2-bromo-1,1,2-triphenylethylene (**2r**) also participated in the trifluoroethoxylation reaction to give the corresponding product **3r** in 56% yield (Entry 18). To assess the versatility of this methodology, the reaction was evaluated on α-bromostyrene **2s**. In this case, the expected trifluoroethoxylated styrene **3s** was obtained in 9% yield (Entry 19). Unfortunately, when 1-(2,2-dibromovinyl)-4-methylbenzene (**2t**) was used as a substrate, the product **3t** was obtained in only 2% yield (^{19}F NMR; Entry 20). Finally, the reaction also proceeded with the use of vinyl chlorides, albeit in lower yields: for instance under the reaction conditions, the trifluoroethoxylation of β-chlorostyrene furnished (2-(2,2,2-trifluoroethoxy)vinyl)benzene **3a** in 38% yield (^{19}F NMR; Entry 21). The use of β-iodostyrene led to excellent yield of the corresponding product **3a** (Entry 22).

Table 1. Trifluoroethoxylation of alkenyl bromides by [(phen)$_2$Cu][OCH$_2$CF$_3$] **1** [a]



Entry	Alkenyl halide (*E*/*Z*)	Product (*E*/*Z*)	Yield [b] (%)
1	 **2a** (>99:1)	 **3a** (>99:1)	89
2	 **2b** (>99:1)	 **3b** (>99:1)	84
3	 **2c** (>99:1)	 **3c** (>99:1)	83
4	 **2d** (>99:1)	 **3d** (>99:1)	99
5	 **2e** (>99:1)	 **3e** (>99:1)	92
6	 **2f** (98:2)	 **3f** (98:2)	71
7	 **2g** (98:2)	 **3g** (98:2)	81
8	 **2h** (95:5)	 **3h** (95:5)	80
9	 **2i** (63:37)	 **3i** (63:37)	64
10	 **2j** (61:39)	 **3j** (61:39)	62
11	 **2k** (>99:1)	 **3k** (>99:1)	76
12	 **2l** (96:4)	 **3l** (96:4)	62
13	 **2m** (98:2)	 **3m** (98:2)	68
14	 **2n** (>99:1)	 **3n** (>99:1)	65
15	 **2o** (96:4)	 **3o** (96:4)	78
16	 **2p**	 **3p**	92
17	 **2q**	 **3q**	8
18	 **2r**	 **3r**	56
19	 **2s**	 **3s**	9
20	 **2t**	 **3t**	2 [c]

21	 **2a'**	 **3a**	38[c]
22	 **2a''**	 **3a**	99[c]

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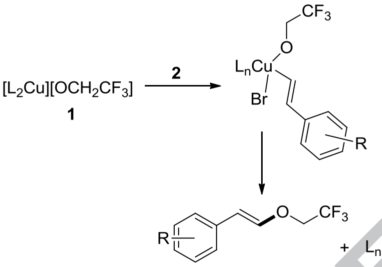
[a] Reaction conditions: **1** (0.60 mmol), **2** (0.50 mmol), NaO*t*-Bu (0.50 mmol), DMF (5.0 mL), under N_2 atmosphere. The *E*/*Z* configuration ratios of products were determined by ^{19}F NMR.

[b] Isolated yields.

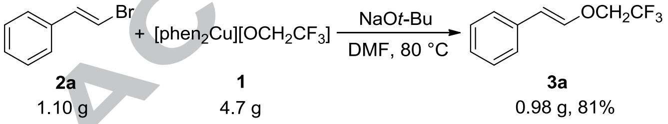
[c] The yield was determined by ^{19}F NMR spectroscopy with $PhOCF_3$ as internal standard.

The stereochemistry of trifluoroethyl vinyl ethers **3** was characterized by the ^1H NMR coupling constant value of the olefinic protons (*trans* configuration: J = 12.6–12.9 Hz; *cis* configuration: J = 7.2 Hz).[26-29] In addition, the *E*/*Z* stereochemistry of the trifluoroethyl vinyl ethers bond corresponds to the alkenyl bromide substrates (Entries 1–15). The complete retention of the double-bond stereochemistry after reaction indicates that the trifluoroethoxylation reaction could proceeds *via* an oxidative addition−reductive elimination pathway (Scheme 2).[28]



Scheme 2. Plausible reaction pathway leading to the trifluoroethyl vinyl ethers.

To highlight the scalability and practicability of our synthesis, the trifluoroethoxylation reaction was performed on a gram scale. Using 1.10 g (6.0 mmol) of β-bromostyrene **2a** as the substrate, the trifluoroethoxylated product **3a** was obtained in 81% yield (Scheme 3).



Scheme 3. Scalability of the trifluoroethoxylation of **2a**.

In conclusion, a convenient synthetic strategy to prepare trifluoroethyl vinyl ethers was explored by the trifluoroethoxylation reactions of copper reagent $[(phen)_2Cu][OCH_2CF_3]$ with vinyl bromides. The strategy afforded the trifluoroethyl vinyl ethers in good yields. Additionally, the reaction tolerated a variety of substituents at the aryl moiety of vinyl halides and is amenable to being carried out on gram scales.

Acknowledgments

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References and notes

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Supplementary Material

Supplementary data associated with this article can be found, in t

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Highlights:

- An efficient method for synthesis of trifluoroethyl vinyl ethers has been developed.
- The procedure tolerates a variety of substituents at the aryl moiety of vinyl halides.
- The reaction is amenable to being carried out on gram scales.