

Tetrafluoroethylation of Electron-Rich Alkenyl Iodides Enabled by *in situ* Generation of Solvent-Stabilized “Ligandless” $\text{CuCF}_2\text{CF}_2\text{H}$

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Manuscript received: December 5, 2023; Revised manuscript received: March 6, 2024;

Version of record online: May 23, 2024



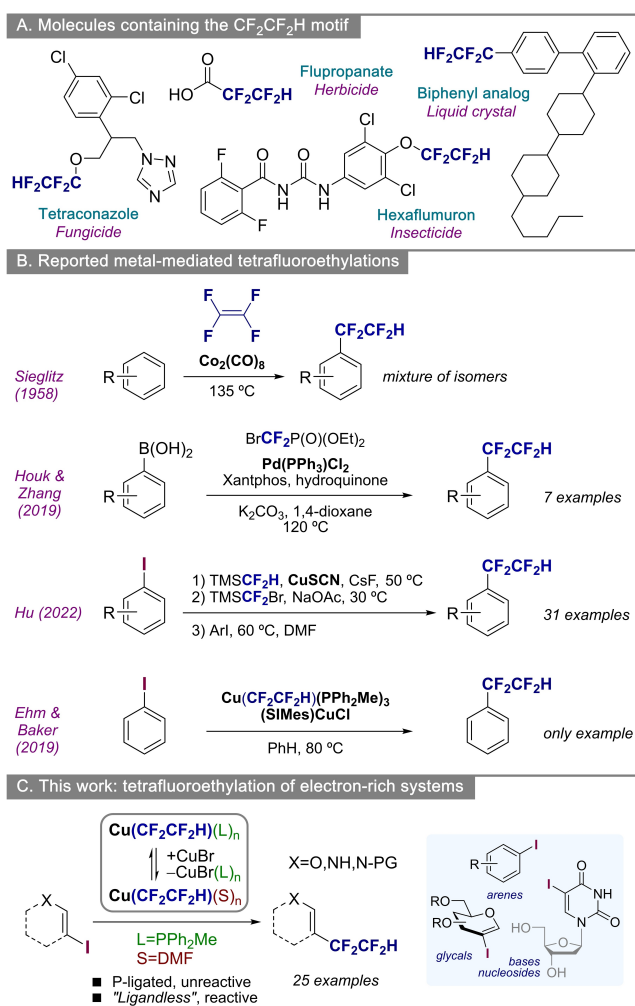
Supporting information for this article is available on the WWW under <https://doi.org/10.1002/adsc.202301409>

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Abstract: In this study, we have developed a metal-mediated synthetic method for incorporating the 1,1,2,2-tetrafluoroethyl ($\text{CF}_2\text{CF}_2\text{H}$) motif into unactivated, electron-rich alkenyl iodides using cross-coupling reactions. We discovered that the stable $\text{Cu}(\text{CF}_2\text{CF}_2\text{H})(\text{PPh}_2\text{Me})_3$ complex, while unreactive with these substrates, serves as a P-ligated reservoir for the formation of solvent-stabilized “ligandless” and reactive $\text{CuCF}_2\text{CF}_2\text{H}$ species. This transformation occurs upon addition of CuBr , which partially scavenges the P-ligand in the form of $\text{CuBr}(\text{PPh}_2\text{Me})_3$. The resulting *in situ* generated solvent stabilized “ligandless” system significantly enhances the reactivity of the complex, particularly towards challenging electron-rich substrates. This advancement enables the synthesis of HCF_2CF_2 -glycols, as well as nucleosides/nucleobases and arenes.

Keywords: Carbohydrates; Copper; Cross-coupling; Fluorine; Tetrafluoroethylation

The 1,1,2,2-tetrafluoroethyl ($\text{CF}_2\text{CF}_2\text{H}$) motif belongs to the family of polyfluoroalkyl groups ($\text{R}_f=\text{CF}_3$, CF_2H , CF_2CF_3), which have gained significant interest in the pharmaceutical, agrochemical, and electronics industries.^[1] This fragment is commonly found in fungicides, insecticides, herbicides, and liquid crystal components owing to its exceptional biophysical properties and versatile applications. It contributes to enhanced drug potency, bioavailability, metabolic stability, and target selectivity, primarily due to the ability of the CF_2H end to form hydrogen bonds (Scheme 1A).^[2] Among methods for the incorporation of the 1,1,2,2-tetrafluoroethyl moiety,^[3] metal-mediated cross-coupling approaches leading to $\text{C}(sp^2)\text{-R}_f$ bonds are particularly appealing due to the achieved site-selectivity resulting from the specific interaction between the metal complex and its aryl/alkenyl halide partner. Existing metal-mediated methods currently rely on either $\text{Co}_2(\text{CO})_8$,^[4] the *in situ* generation of $\text{M}(\text{C}_2\text{F}_4\text{H})\text{L}_n$ ($\text{M}=\text{Cu}$, Pd),^[5,6] and the preformed complex $\text{Cu}(\text{CF}_2\text{CF}_2\text{H})(\text{PPh}_2\text{Me})_3$ (**1**)^[7] (Scheme 1B). However, these methods often have limitations, such as being restricted to simple substrates (arene/heteroarene) and requiring harsh reaction conditions ($T > 100^\circ\text{C}$). Moreover, some of them rely on expensive and/or difficult-to-handle gaseous reagents (*e.g.*, tetra-



Scheme 1. (A) Selected bioactive molecules containing the CF₂CF₂H fragment. (B) Reported metal-mediated methodologies for the incorporation of the CF₂CF₂H group into simple (hetero)arenes, and (C) This work. TMS = trimethylsilyl, SIMes = 1,3-bis(2,4,6-trimethylphenyl)-4,5-dihydroimidazol-2-ylidene, Xantphos = 9,9-dimethyl-4,5-bis(diphenylphosphino)xanthene, PG = protecting group.

fluoroethylene-TFE), which restricts their broader applicability.

Previous investigations in one of our groups have demonstrated the synthesis of CF₃^[8] and CF₃CF₂-glycols,^[9] as well as nucleosides and nucleobases, through cross-coupling reactions involving electron-rich alkenyl iodides. These substrates were unreactive when using standard preformed ligated complexes but showed reactivity when solvent-stabilized Cu-complexes were employed. These solvent-stabilized Cu-complexes, also known as “ligandless”, “ligand-free”, or “naked” complexes,^[8–11] refer to copper (or other metal)^[12] species that exist in solution without the presence of traditional P- or N-ligands and have exhibited exceptional effectiveness in modifying deli-

cate substrates. Without such strongly coordinating ligands, the reactivity of the copper complex in cross-coupling reactions is enhanced compared to traditional ligated copper complexes.

In this study, our goal was to broaden the application of solvent-stabilized “ligandless” Cu-complexes to incorporate the 1,1,2,2-tetrafluoroethyl (CF₂CF₂H) motif into organic molecules. We particularly focused on their generation from preformed ligated complexes, such as Cu(CF₂CF₂H)(PPh₂Me)₃ (**1**), using challenging electron-rich alkenyl iodides derived from natural products, including glycols, nucleosides, and nucleobases, as the starting materials (Scheme 1C).

Building on our previous work with “ligandless” CuR_F (R_F=CF₃, CF₂CF₃) complexes,^[8,9] our initial investigations began by generating the corresponding “ligandless” CuCF₂CF₂H species from Cu-(CF₂CF₂H)(PPh₂CH₃)₃ (**1**) and optimizing the Cu(I) halide salts and the solvent system for the tetrafluoroethylation of model 4-iodobenzonitrile **21** (Table 1).

With these conditions in hand (CuBr and DMF), we moved to electron-rich alkenyl iodides derived from natural products, including glycols, nucleosides, and nucleobases (Supporting information (SI), Scheme S1). Thus, the preliminary evaluation of complex **1** under “ligandless” reaction conditions, either as a stoichiometric or limiting reagent, demonstrated the viability of this metal-mediated transformation with such unactivated substrates. The addition of CuBr (2 equiv.) in dry DMF (0.03 M) triggers this transformation by partially scavenging the P-ligand presumably in the form of CuBr(PPh₂Me)₃, leading to the formation of an

Table 1. Optimization of the CuX and solvent for the tetrafluoroethylation of model 4-iodobenzonitrile **21** with “ligandless” CuCF₂CF₂H.

entry ^[a]	solvent	DMSO (equiv.)	CuX	yield (%) ^[b]
1	benzene	25	CuCl	16
2	benzene	25	CuBr	11
3	benzene	25	CuI	9
4	DMF	–	CuCl	12
5	DMF	–	CuBr	80
6	DMF	–	CuI	26

^[a] 4-Iodobenzonitrile **21** (0.013 mmol), Cu-(CF₂CF₂H)(PPh₂CH₃)₃ (**1**) (0.013 mmol), and CuBr (0.026 mmol) in dry DMF (0.03 M) unless otherwise indicated.

^[b] Determined by ¹⁹F NMR using α,α,α-trifluorotoluene as internal standard. DMSO = dimethylsulfoxide, DMF = N,N-dimethylformamide.

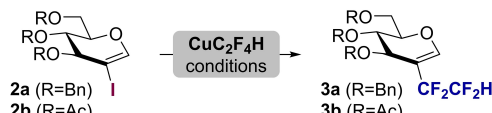
observable solid precipitate. This behaviour has been also noticed in a similar complex, $\text{CuBr}(\text{PPh}_3)_3$, which was insoluble in most of the available solvents for NMR analysis.^[13] The consequent generation of a “ligandless” system *in situ*, which retains its activity for at least four months when stored at -30°C , substantially boosts the reactivity of the complex, particularly when confronted with electron-rich substrates (up to 96% yield).

A major drawback of these conditions is that the purification of final products is very challenging due to the presence of unreacted starting material. Therefore, in order to improve the practicality of this transformation and reduce the substrate equivalents needed (to simplify the challenging chromatographic separation between the final product and starting iodide), we proceeded to optimize the $\text{CuCF}_2\text{CF}_2\text{H}$ system and reaction conditions using 1 equiv. of 3,4,6-tri-*O*-benzyl- and 3,4,6-tri-*O*-acetyl-2-iodo-D-glucal **2a**^[14,15] and **2b**,^[14] respectively, as sensitive, electron-rich model substrates, while keeping them as the limiting reagents (Table 2). First, the reaction of complex **1** with **2a** proceeded only under “ligandless” conditions, upon addition of 2 equiv. of CuBr and after 24 h from room temperature to 70°C , affording **3a** in 64% yield (Table 2, entry 1 vs. entry 2). Notably, increasing both the reaction temperature and time from 3 h at 50°C to 6 h at 70°C , and finally to 24 h at 70°C , not only enhances the yield (from 9% to 31% and ultimately 64%) but also significantly accelerates the production of $\text{HCF}_2\text{CF}_2\text{H}$ (from 0% to 11%), as evidenced by the integration of signals observed in the ^{19}F NMR spectrum (*ca.* -141 ppm, d, $J=57.8$ Hz). This com-

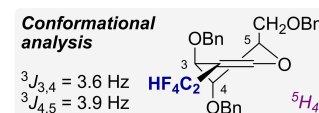
pound results from the decomposition of the $\text{CuCF}_2\text{CF}_2\text{H}$ complex (SI, Figures S1, S2).

To comparatively determine the performance of our system, we then explored alternative protocols that could potentially generate the solvent-stabilized “ligandless” complex $\text{CuCF}_2\text{CF}_2\text{H}$ (Table 2, entries 3, 4). Preliminary attempts to generate $\text{CuCF}_2\text{CF}_2\text{H}$ *in situ* from $\text{Cu}(0)$ ^[16] and commercially available 1,1,2,2-tetrafluoroethyl iodide **4**, followed by its reaction with model iodobenzene in dry/degassed DMF, afforded the corresponding 1,1,2,2-tetrafluoroethylbenzene^[17] in a 65% yield (SI, Figure S5). However, this Ullmann-type reaction required harsh conditions (130°C , 19 h) that may not be suitable for 2-iodo-D-glycals, which are sensitive substrates. As expected, applying the same protocol to 3,4,6-tri-*O*-acetyl-2-iodo-D-glucal **2b** resulted in a poor 15% yield of the desired product **3b** after 24 h at 100°C (Table 2, entry 3 and SI, Figure S6). Likewise, the reaction with the more electron-rich 5-iodo-2'-deoxyuridine **2f** was entirely suppressed, with no conversion observed even after 19 h at 80°C (SI, Figure S7). Next, based on literature transmetalation protocols that typically proceed under milder reaction conditions,^[11,18] we attempted the reaction using **2b** (Table 2, entry 4). We began by optimizing the synthesis of DMPU-stabilized $\text{Zn}(\text{CF}_2\text{CF}_2\text{H})_2$ (SI, Table S1). This species exhibited resonances at -123.4 (bs, 4F, CF_2) and -131.9 ppm (d, $J_{\text{FH}}=57.6$ Hz, 4F, CF_2H) in the ^{19}F NMR spectrum when prepared from ZnEt_2 (1 M in hexane) and $\text{ICF}_2\text{CF}_2\text{H}$ **4** in dry DMPU (SI, Figure S8). Subsequent treatment of this mixture with CuBr afforded the $\text{CuCF}_2\text{CF}_2\text{H}$ complex (-108.2 ppm, bs, 2F, CF_2 and

Table 2. Optimization of the $\text{CuCF}_2\text{CF}_2\text{H}$ system and reaction conditions using **2a** and **2b**.



Conformational analysis



entry	substrate (equiv.)	conditions (equiv.)	yield (%) ^[a]	
			product	$\text{HCF}_2\text{CF}_2\text{H}$
1	2a (1)	$\text{Cu}(\text{CF}_2\text{CF}_2\text{H})(\text{PPh}_2\text{Me})_3$ 1 (1.5), dry DMF (0.1 M), rt→ 70°C , 24 h	3a , 0	48
2	2a (1)	$\text{Cu}(\text{CF}_2\text{CF}_2\text{H})(\text{PPh}_2\text{Me})_3$ 1 (1.5), CuBr (6), dry DMF (0.1 M), rt→ 70°C , 24 h	3a , 64	11
3	2b (1)	$\text{Cu}(0)$ (3), $\text{ICF}_2\text{CF}_2\text{H}$ 4 (1.2 equiv.), dry/deoxy DMF (0.3 M), 100°C , 24 h	3b , 15	57
4	2b (1)	1) ZnEt_2 (1 M in hexane, 2.5 equiv.), $\text{ICF}_2\text{CF}_2\text{H}$ 4 (1.5 equiv.) dry DMPU (1.5 M), 60°C , 68 h 2) CuBr (1.2 equiv.), rt, 30 min 3) 2b (1), dry DMF (0.3 M), 60°C , 30 min	3b , < 5 ^[b]	28
5	2a (1)	$\text{Cu}(\text{CF}_2\text{CF}_2\text{H})(\text{PPh}_2\text{Me})_3$ 1 (1.5), Bipy (1.6), dry DMF (0.1 M), rt→ 70°C , 24 h	3a , 0	52
6	2a (1)	$\text{Cu}(\text{CF}_2\text{CF}_2\text{H})(\text{PPh}_2\text{Me})_3$ 1 (1.5), Phen (1.6), dry DMF (0.1 M), rt→ 70°C , 24 h	3a , 0	56

^[a] Determined by ^{19}F NMR using 1,3-bis(trifluoromethyl)benzene (entries 1, 2, 5, 6) or 1,4-difluorobenzene (entry 3) as internal standard unless otherwise indicated.

^[b] Conversion determined by ^{19}F NMR with respect to the starting $\text{CuCF}_2\text{CF}_2\text{H}$. DMF = *N,N*-dimethylformamide, DMPU = *N,N'*-dimethylpropyleneurea, Bipy = 2,2'-bipyridine, Phen = 1,10-phenanthroline.

–128.6 ppm, d, $J_{\text{FH}} = 59.1$ Hz, 2F, CF₂H), which is typically in equilibrium with the corresponding anionic species [Cu(CF₂CF₂H)₂][–] (–120.7 ppm, bs, 4F, CF₂ and –130.8 ppm, d, $J_{\text{FH}} = 57.6$ Hz, 4F, CF₂H), as evidenced by ¹⁹F NMR. However, the addition of iodo-substrate **2b** to this mixture only gave very low conversions to product **3b** under the tested conditions (SI, Figures S9, S10).

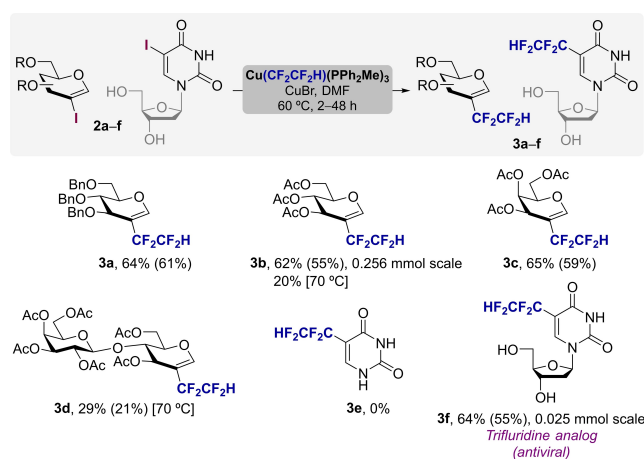
Finally, the performance of complex **1**, when subjected to additional conventional ligands such as phenanthroline and bipyridine,^[8,9,19] further highlighted the superiority of our “ligandless” system in facilitating the cross-coupling of these electron-rich substrates (Table 2, entries 5, 6). The use of these ligands not only inhibited the transformation of the complex CuCF₂CF₂H to form HCF₂CF₂H (14–52%). This effect was further accelerated with increases in both reaction temperature and time (SI, Figures S3, S4).

Products **3a** and **3b** were identified through initial analysis using ESI-MS (I → C₂F₄H, Δmass + 26 Da). Subsequent analysis using ¹H, ¹³C{¹H}, and ¹⁹F NMR confirmed the presence of the C₂F₄H unit at C-2, which influenced the conformation adopted by 2-substituted glycols, resulting in a change from the ⁴H₅ conformation in D-glucal to an “inverted” ⁵H₄ conformation, for example, in **3a** (SI, Figure S11).^[20]

The substrate scope of the reaction using our solvent-stabilized “ligandless” CuCF₂CF₂H reagent, with the optimized reaction conditions employing 1.5 equiv. of complex **1** to simplify purification (Table 2, entry 2), was further evaluated with **2a–f** (Scheme 2).

We employed different protected 2-iodoglycals^[14,21] (Bn vs. Ac), including various configurations (*gluco* vs. *galacto*) and a disaccharide derived from D-lactose, as well as a nucleoside and a nucleobase. While the reaction with the unprotected nucleoside derivative **2f** (an analog of the antiviral Trifluridine) was successful, yielding **3f** (64%), the reaction with 5-iodouracil **2e** presented challenges under standard conditions (0%). This difficulty may be attributed to coordination of the NH moiety to CuBr. As a result, the reaction had to be briefly optimized to obtain the final product **3e** in 78% yield (64% isolated and performed at a 0.630 mmol scale) (Table 3, entry 11).

Practical yields (up to 64%) of C₂F₄H-derivatives **3a–f** were obtained for all substrates tested under mild reaction conditions (60 °C, 2–48 h). Although no Ferrier side reactions were observed, occasionally, we detected traces of D-glycals (or bases/nucleosides) as challenging-to-separate hydrodehalogenated byproducts (3–22%).^[22] If necessary, and to ensure the generation of pure analytical samples for potential biological testing, an additional step was employed to eliminate these impurities. This step involves treating the reaction mixture with *N*-iodosuccinimide (NIS) and



Scheme 2. Tetrafluoroethylation of electron-rich alkenyl iodides derived from glycols, nucleosides, and nucleobases. *General conditions:* alkenyl iodide (0.1 mmol), Cu(CF₂CF₂H)(PPh₂Me)₃ (**1**) (0.15 mmol), and CuBr (0.6 mmol) in dry DMF (0.1 M) unless otherwise indicated. All yields were determined by ¹⁹F NMR using 1,3-bis(trifluoromethyl)benzene (BTB) as internal standard. Isolated yields given in round brackets. Deviation from standard conditions indicated in square brackets.

Table 3. Optimization of the tetrafluoroethylation of 5-iodouracil **2e** with “ligandless” CuCF₂CF₂H.

entry ^[a]	solvent (v/v)	1:CuBr:2e (equiv.)	yield (%) ^[b]
1	DMF	2:6:1	0
2	DMF	1.5:0.5:1	0
3	DMF	1.5:1:1	0
4	DMF	1:1:1.5	0
5	DMF	1:2.5:1.5	0
6	DMF/Et ₂ O (1:200)	1:2:1.5	0
7	DMF/Et ₂ O (1:200)	1:2:1	0
8	DMF/THF (1:200)	1:2:1.5	0
9	DMF/toluene (1:200)	1:2:1	44
10	DMF/toluene (1:200)	1:3:1	43
11 ^[c]	DMSO/toluene (1:200)	1:2:1	78 (64)
12	DMSO/toluene (1:20)	2:6:1	0

^[a] *General conditions:* 5-iodouracil **2e** (1–1.5 equiv.), Cu(CF₂CF₂H)(PPh₂CH₃)₃ (**1**) (1–2 equiv.), and CuBr (0.5–6 equiv.) in dry solvent (0.03 M) unless otherwise indicated.

^[b] Determined by ¹⁹F NMR using α,α,α-trifluorotoluene as internal standard. Isolated yield given in round brackets.

^[c] Larger scale reaction conducted with **2e** (0.630 mmol).

H₂O, resulting in formation of the corresponding 2-deoxy-2-iodolactol (only from the D-glycal).^[21] This product can be easily separated from the reaction

mixture, allowing for the isolation of the desired pure 2-(1,1,2,2-tetrafluoroethyl)-glycol that remains inert under these conditions. This behaviour is consistent with previous observations made for related 2-CF₃-glycols.^[23]

Having demonstrated the success of the cross-coupling reaction with 2-iodoglycols and other electron-rich substrates, we proceeded to explore the conversion of simpler aryl halides **2g–r** (Scheme 3). Notably, the *p*-isomers **2l–o**, which bear coordinating groups (CN, CHO, C(O)Me, and CO₂Me),^[24] performed the best, affording the desired C₂F₄H-derivatives **3l–o** in moderate to good yields (Scheme 3 and SI, Table S2). The synthetic value of our protocol was further demonstrated with reactions at a larger scale (0.2 mmol) with the best performers **2n** and **3o**, which afforded pure **3n** and **3o** in 75% and 79% isolated yields, respectively. Unlike similar methods for which the ortho-effect^[24] was invoked to explain enhanced reactivity of *o*-isomers, in our case, *o*-isomers **2p** and **2q** yielded the expected products **3p** and **3q** in lower yields, suggesting that the ortho-effect may not be significant in this case. This was more pronounced for **2q**, which possesses a strongly coordinating ester moiety (81% or >99% at a 0.2 mmol scale for *p*-**3o** vs. 31% for *o*-**3q**). Aryl bromides (X=Br), including **2g-Br** and **2i-Br**, as well as chlorides **2r**, showed low or no reactivity. Only some activated systems contain-

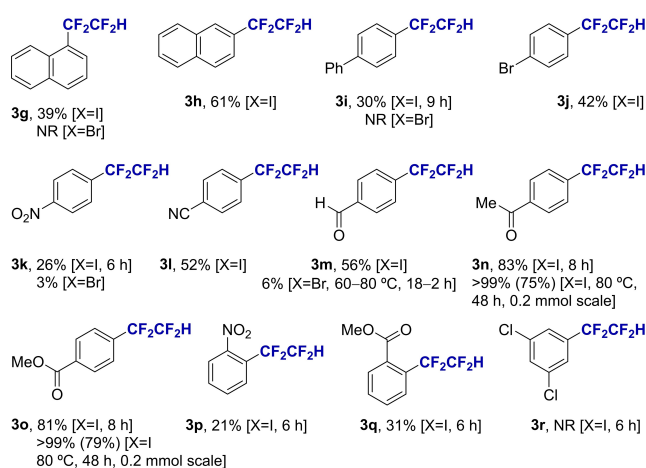
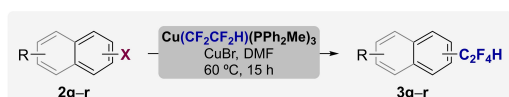
ing electron-withdrawing substituents such as **2k-Br** (NO₂) and **2m-Br** (CHO), yielded small amounts of the corresponding final products, **3k** (3%) and **3m** (6%). This phenomenon was applied to a scaffold simultaneously containing iodine (I) and bromine (Br) atoms, enabling the selective tetrafluoroethylation of **2j** at the I site, resulting in **3j** (42%). Importantly, **3j** still retains a Br handle for further functionalizations. This discovery opens the door to exploring this technology for other chemoselective (I vs. Br) synthetic applications.

In conclusion, a selective method was developed to prepare a solvent-stabilized “ligandless” CuCF₂CF₂H reagent from Cu(CF₂CF₂H)(PPh₂Me)₃ (**1**) and CuBr. The high reactivity of this system allowed for the tetrafluoroethylation of challenging electron-rich alkenyl iodides. Overall, this complex proved to be particularly effective for incorporating C₂F₄H units into complex and sensitive products such as sugars and nucleosides, outperforming other CuCF₂CF₂H systems with common dative ligands (2,2'-bipyridine and 1,10-phenanthroline). Finally, the study underscores the potential of this metal-mediated synthetic approach for incorporating the 1,1,2,2-tetrafluoroethyl motif into drug candidates and agrochemicals that contain electron-rich alkenyl fragments and expands the scope of available synthetic routes for these compounds.

Experimental Section

General Procedure A1 for Tetrafluoroethylation of Electron-Rich Alkenyl Iodides using “ligandless” CuCF₂CF₂H

In a glove box, Cu(CF₂CF₂H)(PPh₂Me)₃ (**1**)^[7] (0.15 mmol) was added at room temperature to a vial containing the corresponding alkenyl iodide (0.1 mmol) and CuBr (0.6 mmol). Dry DMF (1 mL) and 1,3-bis(trifluoromethyl)benzene as internal standard (BTB, 0.1 mmol) were subsequently added, and the resulting mixture transferred to an NMR tube. The NMR tube was capped with a rubber septum, brought out of the glovebox, and heated to 60 °C (or 70 °C, depending on the substrate). The reaction mixture was then analyzed by quantitative ¹⁹F NMR. After completion, the crude mixture was diluted with Et₂O and washed with saturated aqueous NH₄Cl. The combined organic layers were dried over Na₂SO₄, filtered, and concentrated under reduced pressure. When obtaining a pure analytical sample was required due to the presence of the undesired hydrodehalogenated byproduct, the crude mixture (*ca.* 1 mmol) was redissolved in 10:1 (v/v) CH₃CN/H₂O (0.05 M) and NIS (2.5 mmol) was added at 0 °C. The reaction mixture was warmed to room temperature and monitored by ¹H NMR until the byproduct was consumed. The crude mixture was then diluted with EtOAc and washed with saturated aqueous Na₂S₂O₃, saturated aqueous NaHCO₃, and brine. The combined organic layers were dried over Na₂SO₄, filtered, and concentrated under reduced pressure. The residue was purified using chromatographic techniques.



Scheme 3. Tetrafluoroethylation of aryl halides. *General conditions:* aryl halide (0.01 mmol), Cu(CF₂CF₂H)(PPh₂Me)₃ (**1**) (0.015 mmol), and CuBr (0.06 mmol) in dry DMF (0.02 M) unless otherwise indicated. All yields were determined by ¹⁹F NMR using 1,3-bis(trifluoromethyl)benzene (BTB) as internal standard. Isolated yields given in round brackets. Deviation from standard conditions indicated in square brackets. NR = no reaction.

General Procedure A2 for Tetrafluoroethylation of Aryl Halides using “ligandless” CuCF₂CF₂H

In a glove box, Cu(CF₂CF₂H)(PPh₂CH₃)₃ (**1**)^[7] (0.015 mmol) was added at room temperature to a vial containing the corresponding aryl halide (0.01 mmol) and CuBr (0.06 mmol). Dry DMF (0.6 mL) and 1,3-bis(trifluoromethyl)benzene as internal standard (BTB, 0.01 mmol) were subsequently added, and the resulting mixture transferred to an NMR tube. The NMR tube was capped with a rubber septum, brought out of the glovebox, and heated to the corresponding temperature, depending on the substrate. The reaction mixture was then analyzed by quantitative ¹⁹F NMR. After completion, the crude mixture was diluted with CH₂Cl₂ and washed with brine. The combined organic layers were dried over Na₂SO₄, filtered, and concentrated under reduced pressure. The residue was purified using chromatographic techniques.

Acknowledgements

This work was supported by the Spanish Government-MCIU/MCIN, the national agency of investigation-AEI/10.13039/501100011033, and the European Regional Development Fund-ERDF (projects: CTQ2017-90088-R and PID2020-120584RB-I00 to O.B. FPI Fellowship; PRE2018-085730 to I.B. and FPU Fellowship; FPU19/01969 to M.B.), and the Universitat Rovira i Virgili (Martí i Franquès Research Fellowship Programme; 2022PMF-PIPF-17 to P. C.). We also thank Dr. Núria Fontanals (URV) for assistance with high resolution mass spectrometry experiments. R.T.B. thanks the NSERC (Discovery Grant 2019-05959) and Canada Research Chairs program for generous financial support.

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