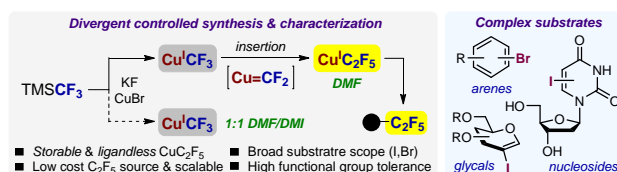


“Ligandless” Pentafluoroethylation of Unactivated (Hetero)Aryl and Alkenyl Halides Enabled by the Controlled Self-Condensation of TMSCF₃-Derived CuCF₃

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Supporting Information Placeholder

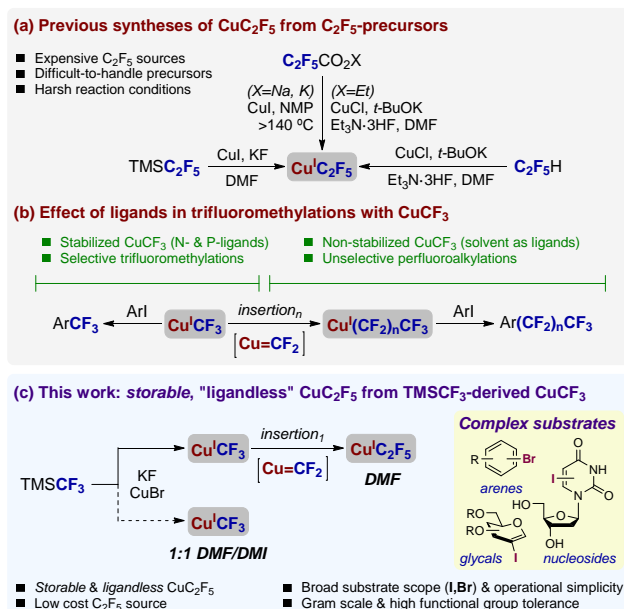


ABSTRACT: Pentafluoroethylation of unactivated C(sp²)-X bonds (X = I, Br) using a *storable*, “ligandless” CuC₂F₅ reagent prepared by controlled self-condensation of ready available TMSCF₃-derived CuCF₃ has been developed. A thorough analysis by ¹⁹F NMR and ESI-MS revealed the nature of this reagent in solution. The operational simplicity and robustness of this system enables the efficient, late-stage incorporation of C₂F₅ units into a variety of (hetero)aryl and complex alkenyl halides such as glycols, nucleosides, and nucleobases.

INTRODUCTION

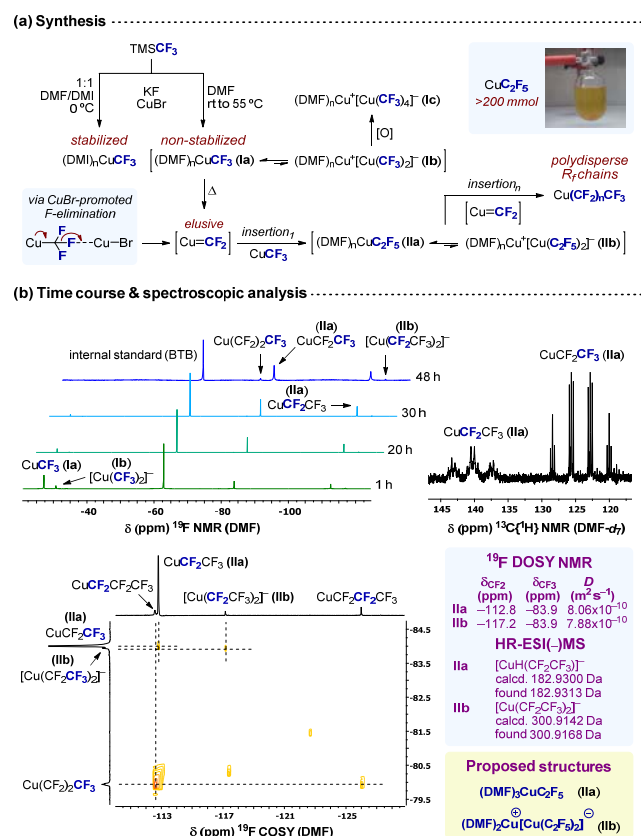
In recent years, numerous reports highlight the importance of incorporating fluorinated motifs into drug candidates to boost their biophysical and/or pharmacological properties.^{1,2} Despite the tremendous progress made in monofluorination³ and trifluoromethylation,⁴ synthetic methods for the late-stage introduction of longer perfluoroalkyl chains (R_f),⁵ and especially the pentafluoroethyl motif (C₂F₅), remain underdeveloped. They typically involve nucleophilic,⁶ electrophilic,⁷ radical,⁸ or metal-mediated/catalyzed transformations^{9,10} via the *in situ* generation of L_n[CuC₂F₅] and subsequent cross-coupling with C(sp²)-X bonds (X = I, Br) (Scheme 1a).¹⁰ Methods to generate CuC₂F₅ from C₂F₅-precursors use the expensive TMS-C₂F₅,¹¹ elevated decarboxylation temperatures (>140 °C) of hygroscopic pentafluoropropionate salts (or esters),¹² and the activation of gaseous C₂F₅H, a non-ozone depleting, greenhouse hydrofluorocarbon (HFC-125).¹³ Moreover, the commercial availability of CuC₂F₅ reagents is limited to Pentafluoroethylator[®] [(Phen)CuC₂F₅]¹⁴ that is still considerably air/moisture-sensitive and too expensive to be implemented in large-scale operations (~83.000 \$/mol).¹⁵ Alternatively, from as early as 1986, Wiemers and Burton detected the formation of CuC₂F₅ species produced after decomposition of non-stabilized CuCF₃.¹⁶ The formation of CuC₂F₅ and longer perfluoroalkyl chains is widely accepted to occur by initial α-fluoride elimination from CuCF₃ and subsequent difluorocarbene insertion into the Cu-CF₃ bond to afford Cu(CF₂)_nCF₃ species (Scheme 1b).

Scheme 1. Syntheses of Cu^I-Pentafluoroethyl Reagents (*upper panel*) and This Work – Synthesis and Characterization of *Storable*, “Ligandless” CuC₂F₅ by Controlled Self-Condensation of TMSCF₃-Derived CuCF₃ (*lower panel*)



TMS = trimethylsilyl, NMP = *N*-methyl-2-pyrrolidone, DMF = *N,N*-dimethylformamide, DMI = 1,3-dimethyl-2-imidazolidinone.

Scheme 2. Synthesis and Characterization of “Ligandless” CuC_2F_5 ^a



^aSee the SI for details. BTB = 1,3-bis(trifluoromethyl)benzene.

This detrimental trifluoromethylation side reaction detected with non-stabilized CuCF_3 delivers unwanted perfluoroalkyl byproducts.¹⁷ Although Yagupolskii¹⁸ reported the deliberate access to CuC_2F_5 via decomposition of CuCF_3 , the resulting organometallic species showed limited reactivity (<4% conv.) with unactivated substrates. During the preparation of this manuscript,¹⁹ the controlled synthesis of a *liganded* CuC_2F_5 from TMSCF_3 -derived CuCF_3 was described by Hu and coworkers.²⁰ Despite this progress, information regarding the nature of the reagent and a broader evaluation of substrate scope focused on using milder reaction conditions specially with more sensitive/complex systems is still needed. To address this challenge, we envisioned a method for taming the uncontrolled generation of CuC_2F_5 , yet balancing its stability/reactivity profile without the necessary use of stoichiometric, conventional dative ligands. The “ligandless”²¹ nature of CuR_f is a key issue in late-stage protocols since its effect in the reactivity/stability balance of the organometallic system is often underestimated (Scheme 1c).

RESULTS AND DISCUSSION

Optimization of the Synthesis and Characterization of “Ligandless” CuC_2F_5 . We started with the divergent preparation of *stable*, “ligandless” CuCF_3 and CuC_2F_5 reagents by pre-generating CuCF_3 from TMSCF_3 (Scheme 2a and Table 1). Although initial attempts with CuI , TMSCF_3 , and KF using strong coordinating CH_3CN hampered the formation of CuCF_3 , the latter was smoothly afforded in 70% yield by conducting the reaction in pure DMF (Table 1, entry 1 vs. 2). Grushin and coworkers²² also noticed that increasing the Lewis acidity of CuX ,

which is in the order $\text{CuCl} > \text{CuBr} > \text{CuI}$ (Table 1, entry 2 vs. 3, 4 vs. 5), promotes decomposition of CuCF_3 by favoring the α -fluoride elimination to difluorocarbene species that can insert into $\text{Cu}(\text{CF}_2)_n\text{CF}_3$ to produce $\text{Cu}(\text{CF}_2)_{n+1}\text{CF}_3$ species (Scheme 2a and SI, Scheme S1). To limit the production of CuC_2F_5 , the reaction was conducted at 0 °C in 5:1 DMF/DMI to improve the stability of CuCF_3 . Certainly, the yield of CuCF_3 increased to 87% while that of CuC_2F_5 decreased to 8% providing an 11:1 $\text{CuCF}_3/\text{CuC}_2\text{F}_5$ selectivity ratio (Table 1, entry 4). Under the same conditions, the use of CuCl gave worse results in terms of yield of CuCF_3 (46%) with a 4.6:1 $\text{CuCF}_3/\text{CuC}_2\text{F}_5$ ratio and also afforded $[\text{Cu}(\text{CF}_3)_4]^-$ (**Ic**) in 11% yield. This can be explained by the greater acidity of CuCl compared to CuBr (Table 1, entry 5). Using DMI and DMF/DMI mixtures with CuBr afforded CuCF_3 in 88% and 84% yield, respectively and reduced the yield of CuC_2F_5 to *ca.* 1% (Table 1, entries 6 and 7). Finally, after optimization (Table 1, entries 1–7), best results for CuCF_3 were obtained using 1:1:1 $\text{TMSCF}_3/\text{CuBr}/\text{KF}$ system in 1:1 DMF/DMI as stabilizing solvent system at 0 °C (Table 1, entry 8). ¹⁹F NMR showed signals at -27.3 ppm and -30.8 ppm, typically assigned to neutral CuCF_3 (**Ia**) and $[\text{Cu}(\text{CF}_3)_2]^-$ (**Ib**), respectively (Scheme 2a). Since the anionic species that are readily oxidized to $[\text{Cu}(\text{CF}_3)_4]^-$ (**Ic**) are indeed less effective towards trifluoromethylation reactions,^{23,24} a higher proportion of neutral CuCF_3 (**Ia**) is desired. While stability studies revealed no detectable changes after storing the reagent solution at -30 °C for at least 1.5 months, decomposition to CuC_2F_5 and higher order CuR_f species occurred at rt within days (Supporting information (SI), Figure S3).

Next, we optimized this CuCF_3 -to- CuC_2F_5 conversion by small adjustments on essential parameters (solvent, CuX , T , and t). Thus, CuC_2F_5 was preferentially obtained conducting the reaction in pure, non-deoxygenated DMF, adding a slight excess of CuBr , and applying a gradient heating from rt to 55 °C (Table 1, entry 9). The control of the temperature was crucial since a too fast conversion of CuCF_3 increase the yield of longer perfluoroalkyl CuR_f species. Similarly, addition of >1.25 equiv of CuBr also lowered the selectivity and longer perfluoroalkyl chains were obtained. The amount of DMF was also relevant since concentrated reaction mixtures resulted in the formation of longer perfluoroalkyl chains and too diluted reactions slowed down the conversion of CuCF_3 . The use of $\text{CuBr}/\text{TMSCF}_3/\text{KF}$ in a 1:2:1 ratio (considering that two equivalents of CuCF_3 are required for the formation of one CuC_2F_5) delivered higher concentrations of CuCF_3 and Cu_3F_7 presumably due to the slow formation of CuCF_3 and competing insertion of difluoromethylene to CuC_2F_5 (Table 1, entry 10). We monitored the progress by ¹⁹F NMR in DMF to confirm purity and selectivity, and ¹⁹F COSY determined $\text{CF}_2\text{-CF}_3$ spin systems for each species (Scheme 2b and SI, Figure S2). While ¹H NMR only showed a doublet ($J = 7.5$ Hz) at 0.22 ppm, which was assigned to TMSF , ¹³C{¹H} NMR showed the characteristic multiplicity pattern according to the fluoroalkyl moiety, a triplet of quartets ($^1J = 285.0$ Hz, $^2J = 53.8$ Hz) at 140.3 ppm and a quartet of triplets ($^1J = 281.2$ Hz, $^2J = 29.8$ Hz) at 124.2 ppm, assigned to CF_2 and CF_3 , respectively. Next, the nature and composition of the complex was carefully evaluated by ¹⁹F diffusion-ordered spectroscopy (DOSY) NMR ($D = 8.06 \times 10^{-10} \text{ m}^2 \text{ s}^{-1}$ for **Ia**, $D = 7.88 \times 10^{-10} \text{ m}^2 \text{ s}^{-1}$ for **Ib**) and ESI-MS (182.9213 Da for **Ia** $[\text{M}+\text{H}]^+$, 300.9168 Da for **Ib** $[\text{M}]^-$) revealing the presence of species with a molecular weight compatible with the coordination of ~3 DMF for **Ia** and ~2 DMF for **Ib** (Scheme 2b and SI, Table S1 and Figures S5–8).

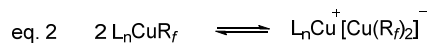
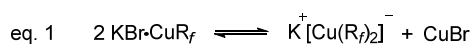
Table 1. Optimization of the Divergent Preparation of CuCF₃ and CuC₂F₅ from TMSCF₃^a

$$\text{TMSCF}_3 + \text{KF} \xrightarrow[\text{Solvent}]{\text{CuX, } T, t} \text{Cu}[(\text{CF}_2)_n\text{CF}_3]_m$$

entry	solvent (v/v)	CuX (equiv)	T (°C)	t (h)	yield (%) ^{b,c} of CuR _f		
					CF ₃ ^d	C ₂ F ₅ ^e	C ₃ F ₇
1 ^f	CH ₃ CN	CuI (1)	rt	3	17(13)	0	0
2	DMF	CuI (1)	rt	3	70(44)	2	0
3	DMF	CuBr (1.25)	rt	3	67(9)	26	0
4	DMF/DMI (5:1)	CuBr (1.25)	0	3	87(20)	8	0
5	DMF/DMI (5:1)	CuCl (1.25)	0	3	46(5) ^g	10	0
6	DMI	CuBr (1.25)	0	3	88(26)	<1	0
7	DMF/DMI (1:1)	CuBr (1.25)	0	3	86(20)	2	0
8	DMF/DMI (1:1)	CuBr (1)	0	3	91(19)	<1	0
9	DMF	CuBr (1.25)	rt → 55	33	0	87(4)	7 ^h
10	DMF	CuBr (0.5)	rt → 55	10	2	74(15)	10 ^h

^aConducted in a Schlenk flask with TMSCF₃ (1 equiv) and KF (1 equiv) in DMF (0.4 M) unless otherwise indicated (see the SI for details). ^bAll Cu[(CF₂)_nCF₃]_m species **Ia,b** (n=0, m=1,2) and **IIa,b** (n=1, m=1,2) included. ^cDetermined by ¹⁹F NMR using 1,3-bis(trifluoromethyl)benzene (BTB) as internal standard. ^dYield of [Cu(CF₃)₂]⁻ species (**Ib**, n=0, m=2) in round brackets. ^eYield of [Cu(C₂F₅)₂]⁻ species (**IIb**, n=1, m=2) in round brackets. ^f61% conversion of TMSCF₃ determined by ¹⁹F NMR. ^g[Cu(CF₃)₄]⁻ species (**Ic**, n=0, m=4) detected in 11% yield. ^hThe selectivity defined as the molar ratio CuC₂F₅/CuC₃F₇ is ~10.

Equilibration of CuR_f Species. Both monomeric compounds CuR_f and [Cu(R_f)X]⁻ are in equilibrium with the corresponding ionic form [Cu(R_f)₂]⁻. The coordination sphere of neutral CuR_f species in ligand-free conditions has been mainly formulated in the literature in two different forms: (a) MX·CuR_f (metal halide adduct), usually KBr·CuR_f^{2□} and (b) L_nCuR_f (solvent stabilized organocopper). Thus, KBr·CuR_f adduct is expected to equilibrate with ionic K⁺[Cu(R_f)₂]⁻ (eq. 1) whereas the solvent stabilized L_nCuR_f will predictably equilibrate with L_nCu⁺[Cu(R_f)₂]⁻ (eq. 2).

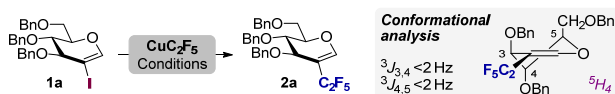


To determine the presence of adducts in CuR_f and the nature of the counterion in M⁺[Cu(R_f)₂]⁻, a precipitation test was performed. Inspired by Grushin's procedure for the stabilization of CuCF₃ by neutralization of *t*-BuOK with HF,^{2□} we decided to

add Et₃N·3HF to the CuCF₃ and CuC₂F₅ reagent solutions expecting to promote precipitation of MF. After addition of the acid, a white precipitate was instantaneously formed from both reagents and, although the ¹⁹F NMR signals from CuC₂F₅ were unchanged, CuCF₃ resulted unstable under acidic conditions and progressively evolved to CuC₂F₅. The solid was separated and tried to redissolve in H₂O but resulted poorly soluble and the slurry gradually turned deep blue. Analysis by ¹⁹F NMR showed no more signals than that from BTB, which was remarkably broader than usual. Given that KF is highly soluble in water, the precipitate was certainly composed of another fluoride salt. The blue color appearance and the deterioration of the quality of the spectra may be explained by the formation of Cu^{II} salts. Moreover, the presence of CuF₂ could not be detected by ¹⁹F NMR owing to its paramagnetic nature. Then, we presume that the species involved in the equilibrium are those illustrated in eq. 2. It should be noted that this equilibration is usually proposed in recent reports²⁷ and the composition of the species involved in the equilibrium is related to those proposed by Vicic and co-workers.²⁴ Moreover, this behavior is also found in other Cu–Nu species.²⁸ The complexity of the system was evidenced after observing the diversification of the species detected by ¹⁹F NMR in different experiments and their apparent correlation (SI, Figure S4 and Scheme S4). Thus, CuCF₃ (**Ia**) equilibrates with [Cu(CF₃)₂]⁻ (**Ib**) (SI, Scheme S4a) and the same applies to CuC₂F₅ (SI, Scheme S4b). Compounds CuC₂F₅ (**IIa**) and [Cu(C₂F₅)₂]⁻ (**IIb**) are easily discernible by the difluoromethylene moiety, which appears in this system at –112.8 ppm and –117.2 ppm, respectively. Typically, the equilibrium is strongly shifted towards the neutral organocopper reagent with, for example, *ca.* 20:1 **IIa/IIb** ratio. Notably, after addition of TMSCF₃ and KF to a solution containing only CuC₂F₅, newly formed CuCF₃ was observed and meaningfully, the **IIa/IIb** ratio was equilibrated to 1.2:1. Two new singlets appeared around –30.6 ppm and –116.9 ppm (SI, Figure S4). This was also observed in the following situations: (a) in intermediate stages during conversion of CuCF₃ to CuC₂F₅ and (b) after addition of HF to a solution of CuCF₃ and gradual formation of CuC₂F₅. The common feature of these scenarios is the coexistence of CuCF₃ and CuC₂F₅, thus, their equilibration to give mixed [Cu(CF₃)(CF₂CF₃)]⁻ (**III**) seems reasonable. Moreover, **III** could be directly produced by the nucleophilic attack of CF₃⁻ liberated from TMSCF₃/KF to neutral **IIa**, ultimately affecting the initial **IIa/IIb** ratio (SI, Scheme S4c). The full picture can be described as a series of comproportion/disproportion reactions.

Optimization of the Pentafluoroethylation of 2-Iodoglycals. With our “ligandless” CuC₂F₅ in hand, we evaluated its synthetic value starting with 2-iodoglycals²⁹ as examples of complex/sensitive electron-rich alkenyl halides. 3,4,6-Tri-*O*-benzyl-2-iodo-*D*-glucal **1a** was selected for both optimization studies and comparison of Cu-mediated pentafluoroethylations (Table 2). We initially assessed the effect of the reaction temperature and dilution (Table 2, entries 1–4). Raising the temperature to 80 °C was sufficient to afford **2a** quantitatively after 19 h, whereas moderate heating at 60 °C provided the same yield after 39 h (Table 2, entry 2 vs. 3). Dilution from 0.4 to 0.06 M of the CuC₂F₅ lowered the rate of the reaction and **2a** was afforded in 60% yield after 75 h (Table 2, entry 4). Although traces of perfluoropropyl byproducts (3–5%) were occasionally detected (¹⁹F NMR showed signals at *ca.* –80 ppm), the absence of hydrodehalogenation³⁰ and Ferrier³¹ side reactions and the high purity of the crude reaction simplified isolation steps (SI, Figure S9).

Table 2. Optimization of Pentafluoroethylation of **1a and Comparison of Copper-Mediated Transformations^a**



entry	CuC ₂ F ₅ (equiv)	additive (equiv)	T (°C)	t (h)	yield (%) ^b
1	TMSCF ₃ -derived CuC ₂ F ₅ (1.5)	–	rt	14	5
2	TMSCF ₃ -derived CuC ₂ F ₅ (1.5)	–	60	39	>95 ^c
3	TMSCF ₃ -derived CuC ₂ F ₅ (1.5)	–	80	19	>95 ^c
4 ^{d,e}	TMSCF ₃ -derived CuC ₂ F ₅ (1.5)	–	60 → 80	75	60(90) ^f
5 ^{d,e}	TMSCF ₃ -derived CuC ₂ F ₅ (1.5)	Py (40)	60 → 80	75	6(>98) ^{f,g}
6 ^{d,e}	TMSCF ₃ -derived CuC ₂ F ₅ (1.5)	Phen (1.5)	60 → 80	75	11(>98) ^{f,g}
7 ^{d,e}	TMSCF ₃ -derived CuC ₂ F ₅ (1.5)	Bipy (1.5)	60 → 80	75	16(77) ^{f,g}
8 ^{d,e}	TMSCF ₃ -derived CuC ₂ F ₅ (1.5)	Phen (1.5) PPh ₃ (1.5)	60 → 80	75	6(78) ^{f,g}
9	C ₂ F ₅ H-derived CuC ₂ F ₅ (2)	Et ₃ N·3HF (0.33) ^h	60	24	<5
10	C ₂ F ₅ H-derived CuC ₂ F ₅ (2)	Et ₃ N·3HF (0.43) ^h	60	24	<5
11	C ₂ F ₅ H-derived CuC ₂ F ₅ (2)	Et ₃ N·3HF (0.53) ^h	60	24	<5 ⁱ

^aConducted in a Schlenk flask with **1a** (1 equiv) and CuC₂F₅ (1.5–2 equiv) in DMF (0.4 M for TMSCF₃-derived and 0.7 M for C₂F₅H-derived CuC₂F₅) unless otherwise indicated (see the SI for details).

^bDetermined by ¹⁹F NMR using 1,3-bis(trifluoromethyl)benzene (BTB) as internal standard. ^cIsolated yields. ^dConducted in DMF (0.06 M). ^e68 h at 60 °C, 7 h at 80 °C. ^fConversion of CuC₂F₅ indicated in round brackets. ^gDecomposition to C₂F₅H detected. ^hMol Et₃N·3HF/mol CuCl. ⁱUnidentified decomposition byproducts detected after 40 h. Py = pyridine, Phen = 1,10-phenanthroline, Bipy = 2,2'-Bipyridine.

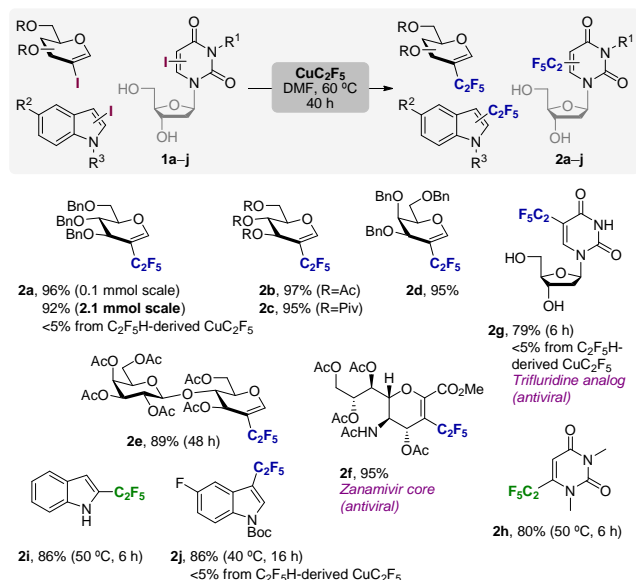
Identification and Conformational Analysis of **2a.** While **2a** was initially identified by ESI–MS analysis (I→C₂F₅, Δmass –8 Da), ¹H, ¹³C{¹H}, and ¹⁹F NMR unequivocally proved the introduction of the C₂F₅ unit at C-2. H-1 was shifted downfield from 6.74 ppm in **1a** to 7.02 ppm in **2a**. Moreover, the ¹⁹F NMR spectrum showed the appearance of three new signals at –84.4

(t, ³J_{H,F} = 2.4 Hz, 3F, CF₃), –112.4 (d, ²J_{H,F} = 273.6 Hz, 1F, CF_{2a}), and –113.38 (d, ²J_{H,F} = 273.6 Hz, 1F, CF_{2b}), the first assigned to CF₃ and the other two signals to diastereotopic fluorine atoms. Finally, C-1 and C-2 appeared in the ¹³C{¹H} NMR spectra as triplets at 149.7 ppm (³J_{C,F} = 10.5 Hz) and 101.4 ppm (²J_{C,F} = 24.7 Hz), respectively, and two new quaternary carbon signals corresponding to CF₃ at 119.4 ppm (qt, ¹J_{C,F} = 286.0 Hz, ²J_{C,F} = 39.6 Hz) and CF₂ at 114.0 ppm (tq, ¹J_{C,F} = 254.9 Hz, ²J_{C,F} = 39.6 Hz) were also detected. Notably, the presence of C₂F₅ had an impact on the conformation adopted by 2-substituted-glycals (from ⁴H₅ in D-glucal to “inverted” ⁵H₄ in **2a**) as revealed by analysis of diagnostic coupling constants J_{3,4} and J_{4,5} < 2 Hz, probably due to the strong 1,2-allylic (A^{1,2}) strain observed with C₂F₅>CF₃>I>H (SI, Figure S10).³²

Comparison with Other Cu-Systems. Next, the effect of common ligands in Cu-mediated fluoroalkylations was addressed (Table 2, entries 5–8). Reactions in the presence of pyridine, phenanthroline, bipyridine, and PPh₃ ligands suffered from very low yields (6–16%) after heating from 60 °C to 80 °C for prolonged reaction times (up to 75 h in total) along with the unproductive consumption of CuC₂F₅ to form C₂F₅H (Table 2, entries 5–8). Finally, we also compared the performance of our system with another “ligandless” reagent, the C₂F₅H-derived CuC₂F₅ (Table 2, entries 9–11).¹³ No substantial differences were observed when increasing from 0.33 to 0.53 equiv of Et₃N·3HF that afforded only traces of **2a**. Collectively, these results suggest that our “ligandless” system performs better over traditional Cu-based systems, especially with sensitive substrates.

Substrate Scope. With the optimal conditions in hand, the scope of this reaction was evaluated with a series of differently protected (Bn, Ac, and Piv) 2-iodoglycals of different configurations (D-glucal, D-galacto) including disaccharides with acid-labile linkages (D-lactose) and Neu5Ac2en, analog of the antiviral zanamivir (Relenza[®]) (Scheme 3). All afforded pure C₂F₅-derivatives **2a–f** in high isolated yields (up to 97%, 92% in gram scale for **2a**). We next studied the scope with other electron-rich iodinated scaffolds (Scheme 3). Thus, the C₂F₅-analog **2g** of the antiviral trifluridine³³ (Viroptic[®]) was obtained in 79% yield after only 6 h at 60 °C in contrast to previous low-yielding protocols based on radical perfluoroalkylations with R₂CO₂H/XeF₂³⁴ or Cu-mediated systems (Cu/C₂F₅/HMPA).³⁵ 6-C₂F₅-Pyrimidine derivative **2h** (80%) was nicely obtained under even milder conditions (50 °C, 6 h), probably due to the facilitated oxidative addition at the more electron-deficient C-6 position. Next, the regioselective preintroduction of iodine at electronically different positions (C-2 vs. C-3) enabled the selective preparation of isomeric C₂F₅-indoles **2i** (86%) and **2j** (86%) under very mild conditions (40–50 °C), which provides a synthetic alternative to perfluoroalkyl indoles obtained by cyclization of fluorinated building blocks.³⁶ Of note is the fact that our system is amenable to free OH and NH groups as demonstrated with **2g** and **2i**. Finally, similar to **1a** (Table 2, entries 9–11), reactions of C₂F₅H-derived “ligandless” CuC₂F₅ with **1g** and **1j** were unsuccessful at 60 °C and only decomposition was observed using excess of Et₃N·3HF and higher temperatures. The high performance of our system towards electron-rich alkenyl/heterocyclic iodides prompted us to evaluate its reactivity with aryl and heteroaryl iodides along with the more challenging bromides (Scheme 4). Thus, a series of *p*-substituted aryl iodides and bromides afforded C₂F₅-derivatives **2k–p** in good yields (up to >98%) after 48 h at 60 °C (X = I) and 90 °C (X = Br) regardless their electronic properties.

Scheme 3. Pentafluoroethylation of Electron-Rich Alkenyl and Heterocyclic Iodides^a



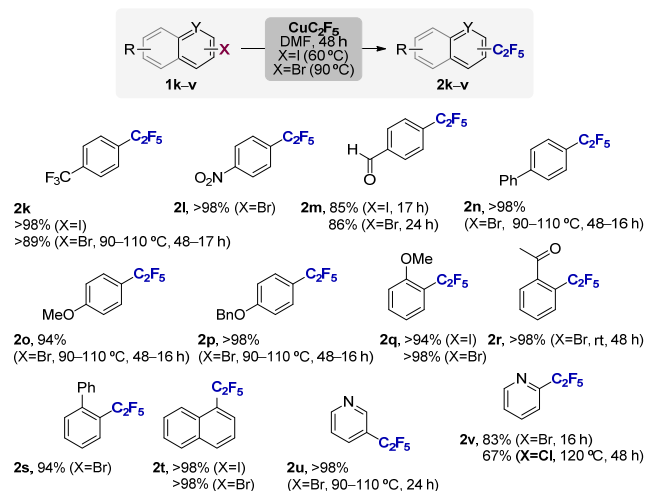
^aConducted in a Schlenk flask with **1a–j** (1 equiv) and “ligandless” CuC_2F_5 (1.5 equiv) in DMF (0.4 M) unless otherwise indicated. Isolated yields given. Deviation from standard conditions indicated in round brackets. Reactions using $\text{C}_2\text{F}_5\text{H}$ -derived CuC_2F_5 (2 equiv) stabilized with $\text{Et}_3\text{N}\cdot 3\text{HF}$ (0.33–0.53 mol $\text{Et}_3\text{N}\cdot 3\text{HF}$ /mol CuCl) in DMF (0.7 M) were conducted at 60 °C, 24 h (see the SI for details). Color code; electron-rich position (blue) and electron-deficient (green).

o-Isomers **2q–s** also provided the expected products in nearly quantitative yields under mild reaction conditions for both I and Br, including the example of **2r** (X = Br, >98%, rt, 48 h) in which the so-called *ortho*-effect²² may be operative. Finally, reaction with activated pyridines afforded **2u** (X = Br, >98%) and **2v** (X = Br, 83%), including an example with a chloride that yielded the same 2- C_2F_5 -pyridine **2v** in a fair 67% yield after 48 h at 120 °C.

CONCLUSIONS

In summary, we have developed a selective method for the preparation of a *storable*, “ligandless” CuC_2F_5 reagent from readily available CuCF_3 . Evaluation of the nature and composition of this reagent in solution provided evidence of the species involved in the subsequent cross-coupling reaction. Its high reactivity enabled the efficient pentafluoroethylation of challenging alkenyl iodides and unactivated (hetero)aryl halides, including readily available bromides (and an example with a 2-Cl-pyridine). Collectively, our complex proves particularly effective for the late-stage incorporation of C_2F_5 units into complex/sensitive products including sugars, nucleosides, and nitrogenous bases, along with the more robust (hetero)arenes compared to other CuC_2F_5 systems bearing dative ligands.

Scheme 4. Pentafluoroethylation of Aryl and Heteroaryl Halides^a



^aConducted in an NMR tube with **2k–v** (1 equiv) and “ligandless” CuC_2F_5 (1.5 equiv) in DMF (0.4 M) unless otherwise indicated. All yields were determined by ¹⁹F NMR using 1,4-difluorobenzene (for **2k**) or 1,3-bis(trifluoromethyl)benzene (for **2l–v**) as internal standard. Deviation from standard conditions indicated in round brackets (see the SI for details).

EXPERIMENTAL SECTION

General Remarks. Proton (¹H NMR), carbon (¹³C NMR), and fluorine (¹⁹F NMR) nuclear magnetic resonance spectra were recorded on a 400 MHz (for ¹H), 100.6 MHz (for ¹³C) and 376.5 MHz (for ¹⁹F) spectrometer. Spectra were fully assigned using COSY, HSQC, HMBC, and NOESY. Fluorine diffusion-ordered spectroscopy (¹⁹F DOSY) experiments were recorded at 300 K operating at a proton frequency of 500.13 MHz using a 5 mm PBBO gradient probe. All chemical shifts are quoted on the δ scale in ppm using the residual solvent as internal standard (¹H NMR: $\text{CDCl}_3 = 7.26$, $\text{CD}_3\text{OD} = 3.31$ and ¹³C NMR: $\text{CDCl}_3 = 77.16$, $\text{CD}_3\text{OD} = 49.0$). Coupling constants (*J*) are reported in Hz with the following splitting abbreviations: s = singlet, d = doublet, t = triplet, q = quartet, quin = quintet, and app = apparent. Melting points (m.p.) were determined on a melting point apparatus and are uncorrected. Infrared (IR) spectra were recorded on a FTIR–ATR spectrophotometer. Absorption maxima (ν_{max}) are reported in wavenumbers (cm^{-1}). Optical rotations were measured on a polarimeter with a path length of 1.0 dm and are reported with implied units of $10^{-1} \text{ deg cm}^2 \text{ g}^{-1}$. Concentrations (*c*) are given in g/100 mL. High-resolution mass spectra (HRMS) were recorded on a LC/MSD mass spectrometer with electrospray ionization (ESI) or a GC/MSD apparatus with electronic impact ionization (EI, 70 eV). Nominal and exact *m/z* values are reported in Daltons (Da). MS spectra of organometallic complexes were acquired both in positive and negative ionization with a 6550-qTOF. Thin layer chromatography (TLC) was carried out using commercial aluminium backed sheets coated with silica gel. Visualization of the silica plates was achieved using a UV lamp ($\lambda_{\text{max}} = 254 \text{ nm}$) and/or staining with a 6% H_2SO_4 in EtOH or cerium molybdate solution dip followed by heating. Flash column chromatography was carried out using silica gel (230–400 mesh). Mobile phases are reported in relative composition (e.g., 1:1 EtOAc/hexane v/v). All reagents and solvents (Analytical or HPLC grade) were used as received from commercial suppliers. All reactions using anhy-

drous conditions were performed using flame-dried apparatus under an atmosphere of argon. Brine refers to a saturated solution of sodium chloride. Anhydrous sodium sulfate (Na₂SO₄) was used as drying agent after reaction work-up, as indicated. CuBr was stirred overnight under argon with an excess of glacial acetic acid, and after filtration, the solid was washed with absolute ethanol, dry diethyl ether (Et₂O), and the white CuBr was dried under vacuum at 60 °C for at least 8 h and stored under argon.

Preparation of “Ligandless” TMSCF₃-Derived CuC₂F₅. KF (1 mmol) and CuBr (1.25 mmol) were dried under vacuum overnight at 150 °C and 80 °C, respectively. The solids and a magnetic stir bar were added into a two-neck round-bottom flask with PTFE stopcock and the system was evacuated under vacuum and refilled with argon three times. Dry DMF (0.4 M) was added under argon and the mixture vigorously stirred for 10 min. TMSCF₃ (1 mmol) was slowly added *via* a syringe under argon while the reaction mixture was stirred at room temperature. Next, the mixture was gradually warmed up to 55 °C until the reaction was complete (*ca.* 33 h). 1,3-Bis(trifluoromethyl)benzene (BTB, 0.5 mmol) was added as internal standard. After mixing well the components, the stirring was stopped and the reaction was left undisturbed until all solids settled on the bottom of the flask. An aliquot (0.7 mL) of the supernatant was transferred under argon to a NMR tube for quantitative ¹⁹F NMR analysis.

General Procedure for the Pentafluoroethylation of Unactivated (Hetero)aryl and Alkenyl Halides. A Schlenk flask charged with the corresponding (hetero)aryl/alkenyl halide (0.1–0.17 mmol) was purged and backfilled with argon three times. TMSCF₃-derived CuC₂F₅ solution (0.4 M, 0.15–0.26 mmol) and 1,3-bis(trifluoromethyl)benzene (BTB, 0.05–0.08 mmol) were sequentially added under argon and the Schlenk flask was capped with a rubber septum. The reaction mixture was heated in a silicon oil bath at the indicated temperature and monitored by ¹⁹F NMR for quantitative analysis. The reaction crude was extracted with Et₂O, the solvent evaporated, supported on SiO₂ and filtrated through a short path of SiO₂.

1,5-Anhydro-3,4,6-tri-O-benzyl-2-deoxy-2-pentafluoroethyl-D-arabino-hex-1-enitol (2a). The title compound was prepared following the general procedure above, starting from 3,4,6-tri-O-benzyl-2-iodo-D-glucal **1a**²⁹ (57 mg, 0.105 mmol) and CuC₂F₅ (0.4 M in DMF, 0.5 mL, 0.22 mmol). After 39 h at 60 °C, standard workup and filtration through a short path of SiO₂ (1:9 EtOAc/hexane) afforded **2a** (54 mg, 96%) as a colorless syrup. *R_f* (1:9 EtOAc/hexane): 0.33; [α]_D²⁰ –21.9 (*c* 0.75, CH₂Cl₂); ¹H NMR (400 MHz, CDCl₃) δ 7.41–7.17 (m, 15H), 7.02 (bs, 1H), 4.64–4.57 (m, 1H), 4.56–4.38 (m, 6H), 4.02 (bs, 1H), 3.87 (bs, 1H), 3.78 (dd, *J* = 10.4 Hz, *J* = 7.4 Hz, 1H), 3.63 (dd, *J* = 10.4 Hz, *J* = 5.5 Hz, 1H); ¹³C{¹H} NMR (100.6 MHz, CDCl₃) δ 149.7 (t, *J* = 10.5 Hz), 137.8, 137.5, 137.4, 128.7, 128.5, 128.2, 128.1, 128.0, 127.9, 127.9, 127.8, 119.4 (qt, *J* = 286.0 Hz, *J* = 39.6 Hz), 114.0 (tq, *J* = 254.9 Hz, *J* = 39.6 Hz), 101.4 (t, *J* = 24.7 Hz), 76.5, 73.4, 72.2, 71.7, 70.3, 67.8, 67.8; ¹⁹F NMR (376.5 MHz, CDCl₃) δ –84.4 (t, *J* = 2.8 Hz, 3F), –112.4 (d, *J* = 273.6 Hz, 1F), –113.38 (d, *J* = 273.6 Hz, 1F); FTIR–ATR (neat, *v*_{max}) 3032, 2923, 2855, 1656, 1455, 1198, 1069, 1027, 800, 736, 696; HRMS (TOF ES⁺) *m/z*: [M+Na]⁺ Calcd for C₂₉H₂₇F₅NaO₄⁺ 557.1722; Found 557.1724.

Large Scale Preparation of 2a. The title compound was prepared following the general procedure above, starting from 3,4,6-tri-O-benzyl-2-iodo-D-glucal **1a**²⁹ (1.125 g, 2.074 mmol)

and CuC₂F₅ (0.4 M in DMF, 10.3 mL, 4.14 mmol). After 40 h at 60 °C, standard workup and filtration through a short path of SiO₂ (1:9 EtOAc/hexane) afforded **2a** (1.024 g, 92%) as a colorless syrup.

1,5-Anhydro-3,4,6-tri-O-acetyl-2-deoxy-2-pentafluoroethyl-D-arabino-hex-1-enitol (2b). The title compound was prepared following the general procedure above, starting from 3,4,6-tri-O-acetyl-2-iodo-D-glucal **1b**²⁹ (40 mg, 0.1 mmol) and CuC₂F₅ (0.4 M in DMF, 0.48 mL, 0.2 mmol). After 40 h at 60 °C, standard workup and filtration through a short path of SiO₂ (3:7 EtOAc/hexane) afforded **2b** (37.9 mg, 97%) as a colorless syrup. *R_f* (3:7 EtOAc/hexane): 0.38; [α]_D²⁰ –14.4 (*c* 0.25, CH₂Cl₂); ¹H NMR (400 MHz, CDCl₃) δ 7.12 (bt, *J* = 1.4 Hz, 1H), 4.50–5.47 (m, 1H), 5.14 (appt, *J* = 2.9 Hz, 1H), 4.60–4.54 (m, 1H), 4.45 (dd, *J* = 11.9 Hz, *J* = 7.8 Hz, 1H), 4.19 (dd, *J* = 11.9 Hz, *J* = 4.7 Hz, 1H), 2.09 (s, 3H), 2.08 (s, 3H), 2.05 (s, 3H); ¹³C{¹H} NMR (100.6 MHz, CDCl₃) δ 170.4, 169.3, 169.2, 151.3 (t, *J* = 10.3 Hz), 119.0 (qt, *J* = 286.3 Hz, *J* = 40.4), 113.1 (tq, *J* = 252.6 Hz, *J* = 39.1 Hz), 99.8 (t, *J* = 24.3 Hz), 74.3, 65.4, 61.0, 60.7, 20.8, 20.8, 20.7; ¹⁹F NMR (376.5 MHz, CDCl₃) δ –84.8 (t, *J* = 2.6 Hz, 3F), –113.4 (d, *J* = 276.0 Hz, 1F), –114.6 (d, *J* = 276.0 Hz, 1F); FTIR–ATR (neat, *v*_{max}) 2965, 1746, 1655, 1371, 1196, 1077, 1024, 906; HRMS (TOF ES⁺) *m/z*: [M+Na]⁺ Calcd for C₁₄H₁₅F₅NaO₇⁺ 413.0630; Found 413.0634.

1,5-Anhydro-3,4,6-tri-O-pivaloyl-2-deoxy-2-pentafluoroethyl-D-arabino-hex-1-enitol (2c). The title compound was prepared following the general procedure above, starting from 3,4,6-tri-O-pivaloyl-2-iodo-D-glucal **1c**³² (23 mg, 0.043 mmol) and CuC₂F₅ (0.4 M in DMF, 0.23 mL, 0.088 mmol). After 40 h at 60 °C, standard workup and filtration through a short path of SiO₂ (1:9 EtOAc/hexane) afforded **2c** (21.5 mg, 95%) as a colorless syrup. *R_f* (1:9 EtOAc/hexane): 0.36; [α]_D²⁰ –16.4 (*c* 1.13, CH₂Cl₂); ¹H NMR (400 MHz, CDCl₃) δ 7.14 (bd, *J* = 1.9 Hz, 1H), 5.45 (bs, 1H), 5.08 (m, 1H), 4.60–4.51 (m, 2H), 4.06 (dd, *J* = 9.9 Hz, *J* = 2.2 Hz, 1H), 1.22 (s, 9H), 1.21 (s, 9H), 1.18 (s, 9H); ¹³C{¹H} NMR (100.6 MHz, CDCl₃) δ 178.2, 176.7, 176.6, 151.2 (t, *J* = 10.8 Hz), 99.6 (dd, *J* = 25.7, *J* = 22.75 Hz), 74.27, 65.14, 61.27, 60.64, 39.0, 39.0, 38.9, 27.3, 27.0, 27.0; ¹⁹F NMR (376.5 MHz, CDCl₃) δ –84.70 (t, *J* = 2.3 Hz, 3F), –112.9 (d, *J* = 275.8 Hz, 1F), –114.8 (d, *J* = 275.8 Hz, 1F); FTIR–ATR (neat, *v*_{max}) 2975, 2936, 2875, 1737, 1657, 1481, 1278, 1201, 1115, 1031, 800; HRMS (TOF ES⁺) *m/z*: [M+Na]⁺ Calcd for C₂₃H₃₃F₅NaO₇⁺ 539.2039; Found 539.2047.

1,5-Anhydro-3,4,6-tri-O-benzyl-2-deoxy-2-pentafluoroethyl-D-hexo-hex-1-enitol (2d). The title compound was prepared following the general procedure above, starting from 3,4,6-tri-O-benzyl-2-iodo-D-galactal **1d**²⁹ (43 mg, 0.079 mmol) and CuC₂F₅ (0.4 M in DMF, 0.37 mL, 0.16 mmol). After 40 h at 60 °C, standard workup and filtration through a short path of SiO₂ (1:9 EtOAc/hexane) afforded **2d** (40 mg, 95%) as a colorless syrup. *R_f* (1:4 EtOAc/hexane): 0.39; [α]_D²⁰ –56.4 (*c* 0.22, CH₂Cl₂); ¹H NMR (400 MHz, CDCl₃) δ 7.40–7.22 (m, 15H), 6.86 (bs, 1H), 4.84–4.41 (m, 7H), 4.24 (bd, *J* = 2.6 Hz, 1H), 4.05–3.94 (m, 2H), 3.90 (dd, *J* = 11.7 Hz, *J* = 2.0 Hz, 1H); ¹³C{¹H} NMR (100.6 MHz, CDCl₃) δ 149.4 (t, *J* = 10.5 Hz), 138.3, 138.0, 137.4, 128.7, 128.5, 128.3, 128.2, 128.1, 127.9, 127.8, 127.7, 127.6, 119.2 (qt, *J* = 286.4 Hz, *J* = 41.1 Hz), 113.6 (tq, *J* = 252.6 Hz, *J* = 38.8 Hz), 102.9 (t, *J* = 23.7 Hz), 76.4, 73.4, 73.4, 73.5, 72.4, 67.8, 67.8; ¹⁹F NMR (376.5 MHz, CDCl₃) δ –84.5 (bs, 3F), –111.6 (d, *J* = 274.0 Hz, 1F), –112.8 (d, *J* = 274.0 Hz, 1F); FTIR–ATR (neat, *v*_{max}) 3064, 3032, 2920, 2865, 1773,

1724, 1651, 1455, 1196, 1071, 735, 697; HRMS (TOF ES⁺) *m/z*: [M+Na]⁺ Calcd for C₂₉H₂₇F₅NaO₄⁺ 557.1722; Found 557.1724.

1,5-Anhydro-3,6-di-O-acetyl-2-deoxy-4-O-(2,3,4,6-tetra-O-acetyl-β-D-galactopyranosyl)-2-pentafluoroethyl-D-arabino-hex-1-enitol (2e). The title compound was prepared following the general procedure above, starting from 3,6-di-O-acetyl-2-iodo-4-O-(2,3,4,6-tetra-O-acetyl-β-D-galactopyranosyl)-D-glucal **1e**³² (59 mg, 0.086 mmol) and CuC₂F₅ (0.4 M in DMF, 0.39 mL, 0.17 mmol). After 48 h at 60 °C, standard workup and filtration through a short path of SiO₂ (1:1 EtOAc/hexane) afforded **2e** (52 mg, 89%) as a colorless syrup. *R_f* (1:1 EtOAc/hexane): 0.25; [α]_D²⁰ +4.6 (*c* 1.02, CHCl₃); ¹H NMR (400 MHz, CDCl₃) δ 7.09 (bs, 1H), 5.73 (bs, 1H), 5.37 (d, *J* = 3.4 Hz, *J* = 1.0 Hz, 1H), 5.17 (dd, *J* = 10.4 Hz, *J* = 7.9 Hz, 1H), 5.01 (dd, *J* = 10.4 Hz, *J* = 3.4 Hz, 1H), 4.70 (d, *J* = 7.9 Hz, 1H), 4.53–4.47 (m, 1H), 4.32 (dd, *J* = 12.0 Hz, *J* = 8.4 Hz, 1H), 4.21–4.07 (m, 3H), 4.02–3.97 (m, 2H), 2.14 (s, 3H), 2.11 (s, 3H), 2.03 (s, 6H), 2.02 (s, 3H), 1.97 (s, 3H); ¹³C{¹H} NMR (100.6 MHz, CDCl₃) δ 170.6, 170.5, 170.4, 170.2, 169.6, 169.2, 150.8 (t, *J* = 10.2 Hz), 119.0 (qt, *J* = 286.6 Hz, *J* = 40.4 Hz), 113.2 (tq, *J* = 253.9 Hz, *J* = 40.4 Hz), 101.7, 99.1 (t, *J* = 24.0 Hz), 74.8, 72.7, 71.3, 70.9, 68.9, 67.0, 61.4, 61.3, 61.2, 20.9, 20.8, 20.7, 20.7, 20.6; ¹⁹F NMR (376.5 MHz, CDCl₃) δ -84.7 (bs, 3F), -112.9 (d, *J* = 275.2 Hz, 1F), -115.6 (d, *J* = 274.3 Hz, 1F); FTIR–ATR (neat, *v*_{max}) 2984, 1742, 1656, 1369, 1204, 1075, 1046, 1019, 956, 899, 736; HRMS (TOF ES⁺) *m/z*: [M+Na]⁺ Calcd for C₂₆H₃₁F₅NaO₁₅⁺ 701.1475; Found 701.1476.

Methyl 5-acetamido-4,7,8,9-tetra-O-acetyl-2,6-anhydro-3,5-dideoxy-3-pentafluoroethyl-D-glycero-D-galacto-non-2-enonate (2f). The title compound was prepared following the general procedure above, starting from methyl 5-acetamido-4,7,8,9-tetra-O-acetyl-2,6-anhydro-3,5-dideoxy-3-iodo-D-glycero-α-D-galacto-non-2-enonate **1f**³² (40 mg, 0.066 mmol) and CuC₂F₅ (0.4 M in DMF, 0.30 mL, 0.13 mmol). After 40 h at 60 °C, standard workup and filtration through a short path of SiO₂ (7:3 EtOAc/hexane) afforded **2f** (38.1 mg, 95%) as a white foam. *R_f* (EtOAc): 0.47; [α]_D²⁰ -14.4 (*c* 0.25, CH₂Cl₂); ¹H NMR (400 MHz, CDCl₃) δ 5.82 (d, *J* = 8.4 Hz, 1H), 5.76 (d, *J* = 6.5 Hz, 1H), 5.54 (dd, *J* = 6.0 Hz, *J* = 3.6 Hz, 1H), 5.22 (td, *J* = 6.0 Hz, *J* = 3.0 Hz, 1H), 4.55–4.46 (m, 2H), 4.36 (dd, *J* = 12.5 Hz, *J* = 3.0 Hz, 1H), 4.11 (dd, *J* = 12.5 Hz, *J* = 6.0 Hz, 1H), 3.83 (s, 3H), 2.10 (s, 3H), 2.07 (s, 3H), 2.05 (s, 3H), 2.03 (s, 3H), 1.93 (s, 3H); ¹³C{¹H} NMR (100.6 MHz, CDCl₃) δ 170.7, 170.4, 169.8, 169.8, 161.2, 153.3 (dd, *J* = 7.1 Hz, *J* = 7.1 Hz), 118.8 (qt, *J* = 287.7 Hz, *J* = 40.2 Hz), 113.0 (dd, *J* = 256.9 Hz, *J* = 40.2 Hz), 101.2 (dd, *J* = 25.3 Hz, *J* = 21.8 Hz), 77.7, 69.8, 66.8, 65.1, 61.8, 53.5, 47.1, 23.1, 20.9, 20.8, 20.7, 20.6; ¹⁹F NMR (376.5 MHz, CDCl₃) δ -81.6 (bs, 3F), -106.1 (d, *J* = 281.0 Hz, 1F), -110.6 (d, *J* = 281.0 Hz, 1F); FTIR–ATR (neat, *v*_{max}) 3276, 1749, 1656, 1541, 1438, 1371, 1207, 1048, 1027, 965; HRMS (TOF ES⁺) *m/z*: [M+Na]⁺ Calcd for C₂₁H₂₆F₃NNaO₁₂⁺ 564.1299; Found 564.1307.

5-Pentafluoroethyl-2'-deoxyuridine (2g).³⁷ The title compound was prepared following the general procedure above, starting from 5-iodo-2'-deoxyuridine **1g** (44 mg, 0.124 mmol) and CuC₂F₅ (0.4 M in DMF, 0.61 mL, 0.25 mmol). After 6 h at 60 °C, standard workup and filtration through a short path of SiO₂ (9:1 CH₂Cl₂/MeOH) afforded **2g** (34 mg, 79%) as a white solid. *R_f* (9:1 CH₂Cl₂/hexane): 0.26; ¹H NMR (400 MHz, CD₃OD) δ 8.82 (bs, 1H), 6.24 (t, *J* = 6.0 Hz, 1H), 4.41 (dd, *J* = 9.3 Hz, *J* = 4.0 Hz, 1H), 3.98 (bd, *J* = 2.8 Hz, 1H), 3.83 (dd, *J* =

11.8 Hz, *J* = 2.5 Hz, 1H), 3.74 (d, *J* = 11.8 Hz, *J* = 2.5 Hz, 1H), 2.45 (m, 1H), 2.27 (m, 1H); ¹³C{¹H} NMR (100.6 MHz, CD₃OD) δ 160.9, 151.3, 145.9 (t, *J* = 9.4 Hz), 120.5 (appdt, *J* = 285.0 Hz, 37.7 Hz), 103.0 (bs), 89.4, 87.7, 71.8, 62.1, 42.3; ¹⁹F NMR (376.5 MHz, CD₃OD) δ -85.6 (bs, 3F), -114.4 (m, 2F).

6-Pentafluoroethyl-1,3-dimethyluracil (2h). The title compound was prepared following the general procedure above, starting from 6-iodo-1,3-dimethyluracil **1h**³⁸ (30.8 mg, 0.116 mmol) and CuC₂F₅ (0.4 M in DMF, 0.56 mL, 0.23 mmol). After 6 h at 50 °C, standard workup and filtration through a short path of SiO₂ (1:9 EtOAc/hexane) afforded **2h** (24 mg, 80%) as a colorless syrup. *R_f* (1:9 EtOAc/hexane): 0.16; ¹H NMR (400 MHz, CDCl₃) δ 6.20 (s, 1H), 3.52 (t, *J* = 2.2 Hz, 3H), 3.38 (s, 3H); ¹³C{¹H} NMR (100.6 MHz, CDCl₃) δ 160.9, 152.0, 139.9 (t, *J* = 24.3 Hz), 118.2 (qt, *J* = 287.1 Hz, *J* = 40.1 Hz), 110.8 (tq, *J* = 259.4 Hz, *J* = 40.1 Hz), 105.5 (t, *J* = 8.1 Hz), 33.6 (m), 28.7; ¹⁹F NMR (376.5 MHz, CDCl₃) δ -81.6 (bs, 3F), -111.4 (m, 2F); FTIR–ATR (neat, *v*_{max}) 3110, 2960, 2917, 1849, 1719, 1667, 1440, 1369, 1200, 1146, 1078, 998, 938, 831, 744; HRMS (QTOF EI⁺) *m/z*: [M]⁺ Calcd for C₈H₇F₅N₂O₂⁺ 258.0428; Found 258.0430.

2-(Pentafluoroethyl)-1H-indole (2i).³⁹ The title compound was prepared following the general procedure above, starting from 2-iodoindole **1i**⁴⁰ (26 mg, 0.107 mmol) and CuC₂F₅ (0.4 M in DMF, 0.52 mL, 0.22 mmol). After 6 h at 50 °C standard workup and filtration through a short path of SiO₂ (1:9 EtOAc/hexane) afforded **2i** (21.5 mg, 86%) as a white solid. *R_f* (1:9 EtOAc/hexane): 0.37; ¹H NMR (400 MHz, CDCl₃) δ 8.41 (bs, 1H), 7.71 (d, *J* = 8.0 Hz, 1H), 7.46 (m, 1H), 7.35 (m, 1H), 7.22 (m, 1H), 6.98 (bs, 1H); ¹³C{¹H} NMR (100.6 MHz, CDCl₃) δ 136.1, 127.0, 125.0, 124.0 (t, *J* = 29.1 Hz), 122.2, 121.3, 119.0 (qt, *J* = 285.7 Hz, *J* = 38.9 Hz), 111.8, 111.0 (tq, *J* = 251.3 Hz, *J* = 38.9 Hz), 106.2 (t, *J* = 4.9 Hz); ¹⁹F NMR (376.5 MHz, CDCl₃) δ -84.5 (t, *J* = 3.2 Hz, 3F), -111.9 (m, 2F).

tert-Butyl-5-fluoro-3-(pentafluoroethyl)-1H-indole-1-carboxylate (2j). The title compound was prepared following the general procedure above, starting from **1j**⁴¹ (27 mg, 0.076 mmol) and CuC₂F₅ (0.4 M in DMF, 0.43 mL, 0.18 mmol). After 16 h at 40 °C, standard workup and filtration through a short path of SiO₂ (hexane) afforded **2j** (21 mg, 86%) as a white solid. *R_f* (1:9 EtOAc/hexane): 0.50; mp 74–76 °C; ¹H NMR (400 MHz, CDCl₃) δ 8.16 (bdd, *J* = 9.1 Hz, *J* = 4.4 Hz, 1H), 7.94 (bs, 1H), 7.33 (bd, *J* = 8.8 Hz, 1H), 7.10 (td, *J* = 9.1 Hz, *J* = 2.6 Hz, 1H), 1.69 (s, 9H); ¹³C{¹H} NMR (100.6 MHz, CDCl₃) δ 159.7 (d, *J* = 240.9 Hz), 148.7, 131.9, 128.7 (t, *J* = 8.1 Hz), 127.0 (dt, *J* = 11.2 Hz, *J* = 2.6 Hz), 119.3 (qt, *J* = 285.7 Hz, *J* = 40.1 Hz), 116.8 (d, *J* = 9.3 Hz), 113.9 (d, *J* = 25.2 Hz), 113.0 (tq, *J* = 250.4 Hz, *J* = 40.1 Hz), 109.4 (td, *J* = 28.0 Hz, *J* = 4.1 Hz), 106.2 (d, *J* = 26.2 Hz), 85.8, 28.2; ¹⁹F NMR (376.5 MHz, CDCl₃) δ -84.8 (t, *J* = 2.7 Hz, 3F), -111.2 (bs, 2F), -118.63 (td, *J* = 8.8 Hz, *J* = 4.7 Hz, 1F); FTIR–ATR (neat, *v*_{max}) 2984, 1751, 1479, 1454, 1385, 1256, 1203, 1152, 1067, 1026, 962, 854, 811, 738; HRMS (QTOF EI⁺) *m/z*: [M]⁺ Calcd for C₁₅H₁₃F₆NO₂⁺ 353.0850; Found 353.0848.

General Procedure for Quantitative ¹⁹F NMR Analysis.

An NMR tube charged with the corresponding solid (hetero)aryl halide (0.171 mmol) was purged and backfilled with argon three times. CuC₂F₅ (0.4 M in DMF, 0.4 mL, 0.26 mmol) and 1,3-bis(trifluoromethyl)benzene (BTB, 13 μL, 0.084 mmol) were sequentially added under argon and the NMR tube was capped with a rubber septum. The reaction mixture was heated in a silicon oil bath at the indicated temperature and monitored by

^{19}F NMR for quantitative analysis. For liquid compounds, the NMR tube was purged and backfilled with argon three times prior to the addition of all reagents.

1-(Pentafluoroethyl)-4-(trifluoromethyl)benzene (2k).¹² The title compound was prepared following the general procedure above, starting from 1-iodo-4-(trifluoromethyl)benzene **1k** (25.1 μL , 0.171 mmol), Cu_2F_5 (0.4 M in DMF, 0.4 mL, 0.26 mmol), and 1,4-difluorobenzene (17.5 μL , 0.171 mmol). After 48 h at 60 $^\circ\text{C}$, quantitative ^{19}F NMR analysis of the reaction mixture indicated **2k** was obtained in >98% yield. ^{19}F NMR (376.5 MHz, CDCl_3) δ -63.3 (s, 3F), -85.1 (bs, 3F), -115.2 (bs, 2F).

1-(Pentafluoroethyl)-4-nitrobenzene (2l).¹⁸ The title compound was prepared following the general procedure above, starting from 1-bromo-4-nitrobenzene **1l** (34.9 mg, 0.171 mmol), Cu_2F_5 (0.4 M in DMF, 0.4 mL, 0.26 mmol), and 1,3-bis(trifluoromethyl)benzene (BTB, 13 μL , 0.084 mmol). After 48 h at 90 $^\circ\text{C}$, quantitative ^{19}F NMR analysis of the reaction mixture indicated **2l** was obtained in >98% yield. ^{19}F NMR (376.5 MHz, CDCl_3) δ -84.9 (bs, 3F), -115.1 (bs, 2F).

4-(Pentafluoroethyl)benzaldehyde (2m).¹² The title compound was prepared following the general procedure above, starting from 4-bromobenzaldehyde **1m** (32.3 mg, 0.171 mmol), Cu_2F_5 (0.4 M in DMF, 0.4 mL, 0.26 mmol), and 1,3-bis(trifluoromethyl)benzene (BTB, 13 μL , 0.084 mmol). After 24 h at 90 $^\circ\text{C}$, quantitative ^{19}F NMR analysis of the reaction mixture indicated **2m** was obtained in 86% yield. ^{19}F NMR (376.5 MHz, CDCl_3) δ -85.0 (bs, 3F), -115.2 (bs, 2F).

4-(Pentafluoroethyl)-1,1'-biphenyl (2n).¹³ The title compound was prepared following the general procedure above, starting from 4-bromobiphenyl **1n** (39.9 mg, 0.171 mmol), Cu_2F_5 (0.4 M in DMF, 0.4 mL, 0.26 mmol), and 1,3-bis(trifluoromethyl)benzene (BTB, 13 μL , 0.084 mmol). After 48 h at 90 $^\circ\text{C}$ and 16 h at 110 $^\circ\text{C}$, quantitative ^{19}F NMR analysis of the reaction mixture indicated **2n** was obtained in >98% yield. ^{19}F NMR (376.5 MHz, CDCl_3) δ -85.2 (bs, 3F), -114.5 (bs, 2F).

1-Methoxy-4-(pentafluoroethyl)benzene (2o).¹³ The title compound was prepared following the general procedure above, starting from 1-bromo-4-methoxybenzene **1o** (21.6 μL , 0.171 mmol), Cu_2F_5 (0.4 M in DMF, 0.4 mL, 0.26 mmol), and 1,3-bis(trifluoromethyl)benzene (BTB, 13 μL , 0.084 mmol). After 48 h at 90 $^\circ\text{C}$ and 16 h at 110 $^\circ\text{C}$, quantitative ^{19}F NMR analysis of the reaction mixture indicated **2o** was obtained in 94% yield. ^{19}F NMR (376.5 MHz, CDCl_3) δ -85.4 (bs, 3F), -113.5 (bs, 2F).

1-Benzyloxy-4-(pentafluoroethyl)benzene (2p).⁴² The title compound was prepared following the general procedure above, starting from 1-benzyloxy-4-bromobenzene **1p** (46.9 mg, 0.171 mmol), Cu_2F_5 (0.4 M in DMF, 0.4 mL, 0.26 mmol), and 1,3-bis(trifluoromethyl)benzene (BTB, 13 μL , 0.084 mmol). After 48 h at 90 $^\circ\text{C}$ and 16 h at 110 $^\circ\text{C}$, quantitative ^{19}F NMR analysis of the reaction mixture indicated **2p** was obtained in >98% yield. ^{19}F NMR (376.5 MHz, CDCl_3) δ -85.4 (bs, 3F), -113.6 (bs, 2F).

1-Methoxy-2-(pentafluoroethyl)benzene (2q).¹³ The title compound was prepared following the general procedure above, starting from 1-bromo-2-methoxybenzene **1q** (22.0 μL , 0.171 mmol), Cu_2F_5 (0.4 M in DMF, 0.4 mL, 0.26 mmol), and 1,3-bis(trifluoromethyl)benzene (BTB, 13 μL , 0.084 mmol). After 48 h at 90 $^\circ\text{C}$, quantitative ^{19}F NMR analysis of the reaction mixture indicated **2q** was obtained in >98% yield. ^{19}F NMR (376.5 MHz, CDCl_3) δ -84.2 (bs, 3F), -111.5 (bs, 2F).

2'-(Pentafluoroethyl)acetophenone (2r).⁴³ The title compound was prepared following the general procedure above, starting from 2'-bromoacetophenone **1r** (30.7 μL , 0.171 mmol), Cu_2F_5 (0.4 M in DMF, 0.4 mL, 0.26 mmol), and 1,3-bis(trifluoromethyl)benzene (BTB, 13 μL , 0.084 mmol). After 48 h at 90 $^\circ\text{C}$, quantitative ^{19}F NMR analysis of the reaction mixture indicated **2r** was obtained in 98% yield. ^{19}F NMR (376.5 MHz, CDCl_3) δ -83.9 (bs, 3F), -107.7 (bs, 2F).

2-(Pentafluoroethyl)-1,1'-biphenyl (2s).¹⁰ The title compound was prepared following the general procedure above, starting from 2-bromobiphenyl **1s** (39.9 mg, 0.171 mmol), Cu_2F_5 (0.4 M in DMF, 0.4 mL, 0.26 mmol), and 1,3-bis(trifluoromethyl)benzene (BTB, 13 μL , 0.084 mmol). After 48 h at 90 $^\circ\text{C}$ and 16 h at 110 $^\circ\text{C}$, quantitative ^{19}F NMR analysis of the reaction mixture indicated **2s** was obtained in 94% yield. ^{19}F NMR (376.5 MHz, CDCl_3) δ -84.1 (bs, 3F), -106.3 (bs, 2F).

1-(Pentafluoroethyl)naphthalene (2t).¹³ The title compound was prepared following the general procedure above, starting from 1-iodonaphthalene **1t** (25.7 μL , 0.171 mmol), Cu_2F_5 (0.4 M in DMF, 0.4 mL, 0.26 mmol), and 1,3-bis(trifluoromethyl)benzene (BTB, 13 μL , 0.084 mmol). After 48 h at 60 $^\circ\text{C}$, quantitative ^{19}F NMR analysis of the reaction mixture indicated **2t** was obtained in >98% yield. ^{19}F NMR (376.5 MHz, CDCl_3) δ -83.8 (bs, 3F), -108.2 (bs, 2F).

3-(Pentafluoroethyl)pyridine (2u).¹³ The title compound was prepared following the general procedure above, starting from 3-bromopyridine **1u** (16.6 μL , 0.171 mmol), Cu_2F_5 (0.4 M in DMF, 0.4 mL, 0.26 mmol), and 1,3-bis(trifluoromethyl)benzene (BTB, 13 μL , 0.084 mmol). After 24 h at 90 $^\circ\text{C}$ and 24 h at 110 $^\circ\text{C}$, quantitative ^{19}F NMR analysis of the reaction mixture indicated **2u** was obtained in >98% yield. ^{19}F NMR (376.5 MHz, CDCl_3) δ -85.4 (bs, 3F), -115.7 (bs, 2F).

2-(Pentafluoroethyl)pyridine (2v).¹⁸ The title compound was prepared following the general procedure above, starting from 2-bromopyridine **1v** (16.6 μL , 0.171 mmol), Cu_2F_5 (0.4 M in DMF, 0.4 mL, 0.26 mmol), and 1,3-bis(trifluoromethyl)benzene (BTB, 13 μL , 0.084 mmol). After 16 h at 90 $^\circ\text{C}$, quantitative ^{19}F NMR analysis of the reaction mixture indicated **2v** was obtained in 83% yield. ^{19}F NMR (376.5 MHz, CDCl_3) δ -83.4 (bs, 3F), -116.8 (bs, 2F).

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website. ^1H , $^{13}\text{C}\{^1\text{H}\}$, and ^{19}F NMR spectra for all new compounds, stability studies, and additional optimization experiments (PDF).

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