JOC The Journal of Organic Chemistry



Article

# Trifluoromethylation of Electron-Rich Alkenyl Iodides with Fluoroform-Derived "Ligandless" CuCF

Jordi Mestre, Anton Lishchynskyi, Sergio Castillón, and Omar Boutureira

*J. Org. Chem.*, **Just Accepted Manuscript** • DOI: 10.1021/acs.joc.8b00927 • Publication Date (Web): 19 Jun 2018



ACS Publications

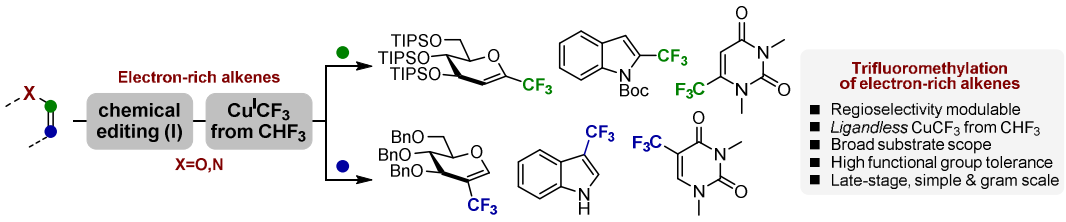
is published by the American Chemical Society. 1155 Sixteenth Street N.W., Washington, DC 20036

# Trifluoromethylation of Electron-Rich Alkenyl Iodides with Fluoroform-Derived "Ligandless" $CuCF_3$

**Jordi Mestre,[†,‡] Anton Lishchynskyi,[‡] Sergio Castillón,[†] and Omar Boutureira*[,†]**

*[†]Departament de Química Analítica i Química Orgànica, Universitat Rovira i Virgili C/Marcel·lí Domingo 1, 43007 Tarragona, Spain*
*[‡]Institute of Chemical Research of Catalonia (ICIQ), The Barcelona Institute of Science and Technology (BIST), Av. Països Catalans 16, 43007 Tarragona, Spain*

**E-mail: omar.boutureira@urv.cat*

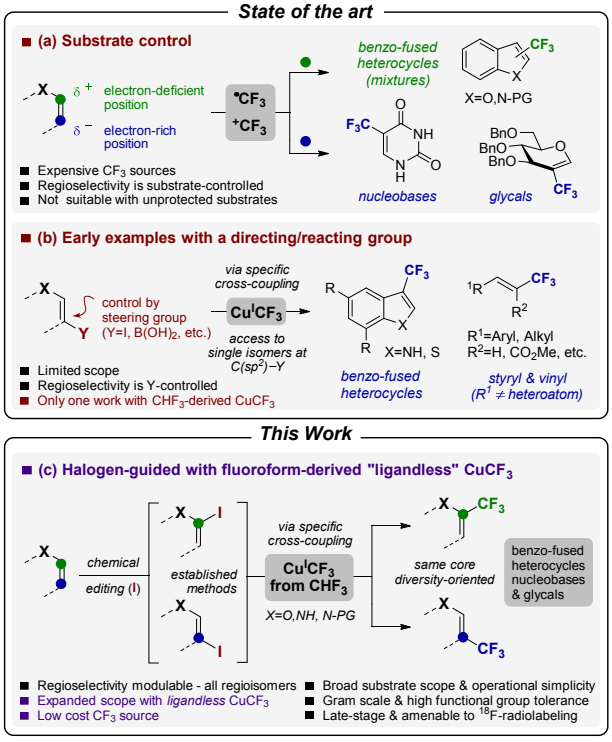



**ABSTRACT:** We herein present a flexible approach for the introduction of $CF_3$ units into a predefined site of electron-rich alkenes that exploits the regiocontrolled introduction of an iodine handle and subsequent trifluoromethylation of the C($sp^2$)–I bond using fluoroform-derived "ligandless" $CuCF_3$. The broad substrate scope and functional group tolerance together with the scalability and purity of the resulting products enabled the controlled, late-stage synthesis of single regioisomers of complex $CF_3$-scaffolds such as sugars, nucleosides (antivirals), and heterocycles (indoles, chromones) with potential for academic and industrial applications.

## INTRODUCTION

The incorporation of $CF_3$ units into unsaturated-C($sp^2$)[1] systems (R-CH=CH-R') using well-established electrophilic,[2,3] radical,[3,4] and metal-mediated[3,5,6] reagents/protocols is now routine. However, the application to the regioselective modification of ubiquitous electron-rich alkenes (X-CH=CH-R, X = heteroatom) and excluding the trifluoromethylation of carbonyl compounds *via* silyl enol ethers or enamines as transient, reactive intermediates,[7] has received less attention (Scheme 1a). While mixtures of regioisomers are typically achieved with benzo-fused heterocycles,[8] modification at the more electron-rich position is exclusive in glycals and nucleobases.[9,10] Alternatively, the rational positioning of a reacting group (Y =

I, $B(OH)_2$, etc.)[11] in combination with a metal-mediated reaction ensures specificity *via* cross-coupling between the $C(sp^2)$–Y and the organometallic partner $CuCF_3$ (Scheme 1b). However, this protocol is so far limited to few examples and certain regioisomers, using simple, electron-rich benzo-fused heterocycles[12] and "non-electron-rich" (X ≠ heteroatom) vinyl[13] and styryl[14,15] halides. Among them, only one report deals with the use of fluoroform-derived $CuCF_3$, which confirms the origin of $CuCF_3$ has not been systematically investigated in such electron-rich systems. Among methods[6] for the preparation of $CuCF_3$, the activation of fluoroform ($CHF_3$),[16] a side-product in Teflon manufacturing, by direct cupration leading to "ligandless"[17] $CuCF_3$ has represented a key milestone in the field.[14,18–20] This reagent provides highly selective transformations overcoming current substrate, functional/protecting group limitations (*e.g.* addition to carbonyls)[21] and reduces potential side reactions (*e.g.* hydrodehalogenation induced by either the formation of metal(0) species and/or the release of P- or N-ligands from organometallic reagents).[22,23]




**Scheme 1.** State-of-the-art trifluoromethylation of electron-rich alkenes (*upper panel*) and this work – metal-mediated halogen-guided with fluoroform-derived "ligandless" $CuCF_3$ (*lower panel*).

Consequently, the development of an effective, mild approach for the

regioselective preparation of $CF_3$-containing electron-rich alkenes using this interesting $CuCF_3$ reagent is particularly attractive. We propose a general two-step methodology for the selective introduction of $CF_3$ units into a predefined position of electron-rich alkenes *via* metal-mediated cross-coupling with fluoroform-derived "ligandless" $CuCF_3$ (Scheme 1c). The overall transformation (from the parent, non-halogenated electron-rich alkene) would allow to program the introduction of a $CF_3$ group based on the availability of well-established methods for the selective introduction of iodine in both carbons and the specificity of Cu-mediated cross-couplings with $C(sp^2)$–I bonds.

## RESULTS AND DISCUSSION

**Optimization of the trifluoromethylation of iodoglycals.** We started our study by exploring the selective incorporation of the $CF_3$ moiety into carbohydrate scaffolds reacting fluoroform-derived "ligandless" $CuCF_3$ reagent ($CuCF_3$-nHF) with 2-iodoglycals[23] as representative examples of building blocks derived from structurally complex natural sources. 3,4,6-Tri-*O*-benzyl-2-iodo-D-glucal **1a** was selected for the optimization studies (Table 1). Treatment of **1a** with stabilized $CuCF_3$ in DMF afforded expected coupling product **2a** in 57% yield after 27 h at room temperature (Table 1, entry 1). In an attempt to improve yield, the effect of "extra" $Et_3N{\cdot}3HF$ (TREAT-HF)[16–19] was evaluated, being the addition of 0.2 "extra" equiv optimal (81%) in terms of balance between reagent's reactivity and stability (Table 1, entries 2–4). No significant differences were observed when moving from 1.2 to 2 equiv of $CuCF_3$-0.6HF (Table 1, entries 5–7). Increasing the temperature up to 50 ºC substantially accelerated the reaction rate (Table 1, entries 8–11). While the use of 1.2 equiv of $CuCF_3$-0.6HF afforded **2a** in 92% yield after 5 h (Table 1, entry 8) and the same reaction with 1.6 equiv resulted in nearly quantitative yield after 13 h (Table 1, entry 9), optimal conditions with 2 equiv reduced the time to 7 h (Table 1, entry 10). The yield and stability of the final vinyl-$CF_3$-product was not compromised upon extending the reaction time from 7 to 13 h once the reaction is completed (Table 1, entry 11). Notably, the formation of undesired by-products such as those found in many metal-mediated reactions with glycals (*e.g.* Ferrier)[24] and 2-iodoglycals (*e.g.* hydrodehalogenation)[23] is suppressed. These findings, together with the fact that microwave-assisted trifluoromethylation at 100 ºC (Table 1, entry 12) reduced the time to *only 10 min* while maintaining practical yields (81%),

**Table 1.** Optimization of trifluoromethylation of **1a**[a]


| entry | $CuCF_3$-nHF (equiv) | "Extra" $Et_3N{\cdot}3HF$ (equiv)[b] | *T* (ºC) | *t* (h) | yield (%)[c] |
|---|---|---|---|---|---|
| 1 | $CuCF_3$ (2)[d] | – | rt | 27 | 57 |
| 2 | $CuCF_3$-0.3HF (2) | 0.1 | rt | 27 | 73 |
| 3 | $CuCF_3$-0.6HF (2) | 0.2 | rt | 21 | 81 |
| 4 | $CuCF_3$-0.9HF (2) | 0.3 | rt | 21 | 80 |
| 5 | $CuCF_3$-0.6HF (1.2) | 0.2 | rt | 39 | 82 |
| 6 | $CuCF_3$-0.6HF (1.6) | 0.2 | rt | 39 | 87 |
| 7 | $CuCF_3$-0.6HF (2) | 0.2 | rt | 39 | 90 |
| 8 | $CuCF_3$-0.6HF (1.2) | 0.2 | 50 | 5 | 92 |
| 9 | $CuCF_3$-0.6HF (1.6) | 0.2 | 50 | 13 | >95 |
| 10 | $CuCF_3$-0.6HF (2) | 0.2 | 50 | 7 | >95 |
| 11 | $CuCF_3$-0.6HF (2) | 0.2 | 50 | 13 | >95 |
| 12[e] | $CuCF_3$-0.6HF (2) | 0.2 | 100 | 10 | 81 |

[a]Reactions were performed in a sealed NMR tube with $CuCF_3$-nHF (up to 2 equiv) in DMF and 2-iodoglucal **1a** (1 equiv) unless otherwise indicated. [b]Mol $Et_3N{\cdot}3HF$/mol CuCl added to stabilized $CuCF_3$. [c]Determined by $^{19}F$ NMR of the crude reaction mixture using 1,3-bis(trifluoromethyl)benzene as internal standard. [d]So-called stabilized $CuCF_3$. [e]The reaction mixture was microwave irradiated in a sealed tube at 100 ºC for 10 min using a CEM-Discover™ single-mode synthesizer (temperature control, fixed hold time off, normal absorption mode, 300 W).

**Table 2.** Trifluoromethylation of **1a** using well-established copper systems

| entry | reaction conditions (equiv) | yield (%)[a,b] |
|---|---|---|
| 1 | $FSO_2CF_2CO_2Me$ (2), CuI (2), DMF, 80 ºC, 8 h | 51(55) |
| 2 | $FSO_2CF_2CO_2Me$ (2), CuI (2), DMF, 100 ºC, 8 h | 84(100)[c] |
| 3 | $TMSCF_3$ (2), Phen (2), CuCl (2), *t*BuOK (2) DMF, 50 ºC, 24 h | 76(92)[d] |
| 4 | $TMSCF_3$ (2), CuBr (2), KF (2), 1:1 DMF/DMI 50 ºC, 20 h | 31(45)[e] |

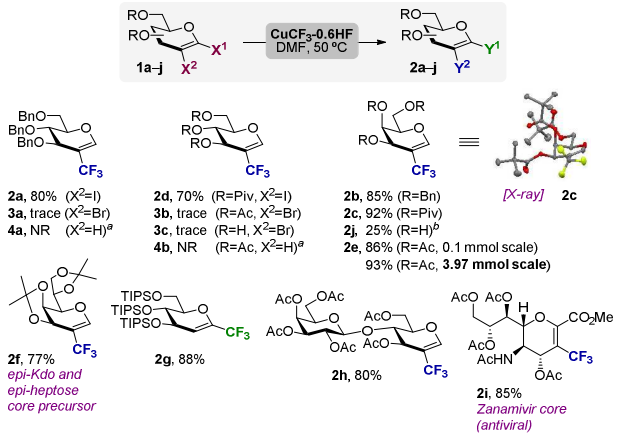
[a]Determined by $^{19}F$ NMR of the crude reaction mixture using 4-fluoroacetophenone (entries 1 and 2) or 1,3-bis(trifluoromethyl)benzene (entries 3 and 4) as internal standard (see SI for details). [b]Conversion in round brackets. [c]Unidentified by-products detected. [d]Hydrodehalogenation detected. [e]Pentafluoroethylation detected. Phen = 1,10-phenanthroline, DMI = 1,3-dimethyl-2-imidazolidinone.

reinforces the potential application of this strategy as a late-stage trifluoromethylation protocol suitable, for example, in the preparation of challenging $^{18}$F-radiolabelled carbohydrates with [$^{18}$F]$CuCF_3$.[25] This is further supported by the *operational simplicity* of the purification step (only an aqueous extraction and/or filtration through a short path of $SiO_2$ was sufficient to afford **2a** in *high-purity*) (SI, Figure S11) and the *scalability* of this reaction as demonstrated for **2e** and **2u**, which also makes our protocol using fluoroform-derived "ligandless" $CuCF_3$ amenable for gram-scale applications. The identity of the resulting product was first confirmed by MS analysis, which showed a mass shift (from 542 to 484 Da) corresponding to the loss of I and the addition of a single $CF_3$ unit (Δmass –58 Da). As expected, $^1$H, $^{13}$C, and $^{19}$F NMR analysis revealed the trifluoromethylation proceed at C-2. Besides the characteristic $CF_3$ peak at –62.6 ppm in the $^{19}$F NMR and the presence of two quaternary centres corresponding to C-2 (q, $^2J_{C,F}$ = 30.7 Hz) and $CF_3$ (q, $^1J_{C,F}$ = 269.9 Hz) in the $^{13}$C NMR, 2D-HMBC experiments also showed key H1-C-2/$CF_3$ cross-peaks that unequivocally confirms the structure of **2a**. Finally, the impact of the $CF_3$ group in the conformation of **2a** was evaluated analysing the characteristic coupling constants $^3J_{3,4}$ and $^3J_{4,5}$ ~ 3.2 Hz. These small values are indicative of a 2-substituted D-glucal adopting the "inverted" $^5H_4$ conformation,[26] probably due to the destabilizing 1,2-allylic ($A^{1,2}$) strain introduced by the bulky $CF_3$ group (supporting information (SI), Figures S12–15).

**Comparision with other trifluoromethylation systems.** Trifluoromethylation of **1a** was also compared with well-established Cu-mediated protocols (Table 2). The $FSO_2CF_2CO_2Me$/CuI/KF system afforded **2a** in up to 84% yield upon increasing the temperature from 50 to 100 ºC, which may compromise the stability of sensitive substrates, as confirmed by the presence of unidentified by-products (Table 2, entries 1 and 2).[27] The *in situ* preparation of Phen$CuCF_3$ gave **2a** (76%), although hydrodehalogenation was also detected (Table 2, entry 3).[28] Finally, reaction with $TMSCF_3$/CuBr/KF[29] yielded **2a** (31%) after 20 h at 50 ºC together the formation of undesired pentafluoroethyl by-products due to $CuCF_3$ decomposition (Table 2, entry 4).[30] Collectively, these results suggest a slight benefit of the "ligandless" system used herein over traditional Cu-based protocols in terms of mildness and/or reduced by-products profile.

**Substrate scope.** With the optimal conditions in hand, the scope of this transformation was evaluated with a series of haloglycals featuring representative

protecting groups (Bn, Ac, Piv, and TIPS), multiple stereocenters/configurations (D-gluco, D-galacto, etc.), and high degree of complexity (disaccharides) (Scheme 2).




**Scheme 2.** Trifluoromethylation scope with haloglycals and control reactions. Isolated yields given (see SI for details). [a]Reactions conducted with 3,4,6-tri-*O*-benzyl and 3,4,6-tri-*O*-acetyl-D-glucal **4a** and **4b**, respectively. [b]Some degradation of **1j** observed. $X^1$ and $X^2$ refer to I, Br or H and the superscript indicates position. NR = no reaction, Piv = pivaloyl, TIPS = triisopropylsilyl. ORTEP drawing of **2c** with thermal ellipsoids drawn at the 50% probability level (H atoms omitted for clarity).

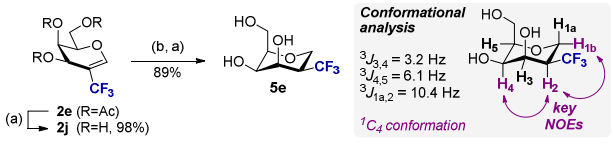
$CF_3$-products **2a**–**j** were consistently obtained in high isolated yields and purity. Benzyl 2-iodoglycals **1a** (D-Glc) and **1b** (D-Gal) afforded **2a** and **2b** in good yields (up to 85%). Unlike protocols using nucleophilic $R_3SiCF_3$ reagents that can react with the electrophilic C($sp^2$) of carbonyl moieties,[21] the combination of mild reaction conditions and specific cross-coupling allowed $CuCF_3$ to react in the presence of acetyl and pivaloyl esters **2c**–**e** and **2h**,**i** (up to 93%), even in gram scale for **2e** (93%). Diagnostic coupling constants $^3J_{3,4}$ and $^3J_{4,5}$ in 2-$CF_3$-D-galactals **2b**,**c** and **2e** ranged from 4.3 to 3.0 Hz,[26,31], indicating certain ring-flattening induced by the 2-$CF_3$ (distorted between $^4H_5$ and $^5H_4$) as evidenced by X-ray analysis of **2c**.[32] Acid-sensitive isopropylidene moiety was also well tolerated in **2f** (77%). Indeed, this represents a successful example of a complex carbohydrate $CF_3$-building block that contains the core structure of important heptosides found in bacterial glycolipids such as the epimers of 3-deoxy-D-manno-2-octulosonic acid (Kdo) and L-*glycero*-D-*manno*-heptopyranose (heptose).[33]

We next evaluated the reactivity (I *vs.* Br) and selectivity (C-1 *vs.* C-2) of this transformation. 2-Bromoglucals **3a**–**c** were unreactive under the conditions used for iodides in contrast to what is observed with vinyl[13] and styryl[14,15] halides where both I and Br react. Moreover, the selective introduction of I at C-1 enables access to 1-$CF_3$-glucal **2g** in 88% yield. The method also tolerates fluoride-labile silyl ethers

(TIPS) as protecting groups. Controls to further confirm the importance of I using D-glucals **4a** and **4b** resulted in recovery of the starting materials. Again, no Ferrier products were observed with neither iodoglycals nor glycals. Collectively, the synthetic flexibility of the overall transformation has been validated with 2-$CF_3$ **2a**,**d** and 1-$CF_3$ **2g** since this strategy allows the selective preparation of complementary 1- and 2-$CF_3$-regioisomers from a single/common-configuration precursor in a diversity-oriented manner. Of benefit is also the smooth preparation of complex D-lactose **2h** (80%) with an acid-sensitive glycosidic linkage and Neu5Ac2en **2i** (85%), containing the core structure of the antiviral zanamivir (Relenza®). The fast kinetics for **2i** under very mild conditions (without "extra" TREAT-HF, rt, 1 h), probably due to the strongly coordinating and/or electron-withdrawing ester at C-2,[19,34] and the fast product isolation (filtration through a short path of $SiO_2$) suggests a good potential for large-scale operations.

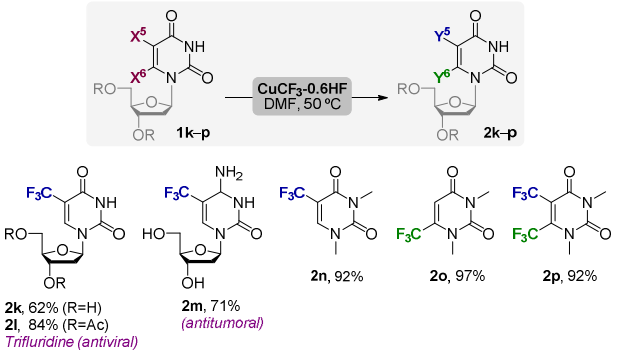
Finally, a key advantage of our method is the specificity of the cross-coupling between the $CuCF_3$/C($sp^2$)–I pair that prevents, unlike methods using electrophilic/radical-$CF_3$ sources, the generation of reactive glycosyl oxocarbenium ions incompatible with many free nucleophiles (OH, $NH_2$), which are indeed frequent in many late-stage protocols.[35] Thus, trifluoromethylation of unprotected 2-iodogalactal **1j** afforded **2j** albeit in 25% yield. However, the inertness of 2-bromo **3c** and the successful results with unprotected nucleosides **2k** and **2m** suggest the reduced yield is due to the instability of the starting unprotected vinyl iodide moiety under the conditions tested.

**Derivatization of 2-trifluoromethylglycals.** A second round of scaffold elaboration further demonstrated the synthetic value of the vinyl-$CF_3$ motif (Scheme 3). While conventional Zemplén deacetylation afforded **2j** in excellent yield (98%), consecutive hydrogenation (10% Pd/C, 10 atm $H_2$) and deacetylation yielded 1,5-anhydro-2-$CF_3$-2-deoxy alditol **5e** (89%) as sole diastereoisomer ($^1C_4$ conformation) as indicated by the analysis of diagnostic coupling constants and key NOE signals.




**Scheme 3.** Elaboration of **2e**. *Conditions:* (a) NaOMe, MeOH, rt, 12 h, 98%; (b) $H_2$ (10 atm), 10% Pd/C, MeOH, rt, 72 h.

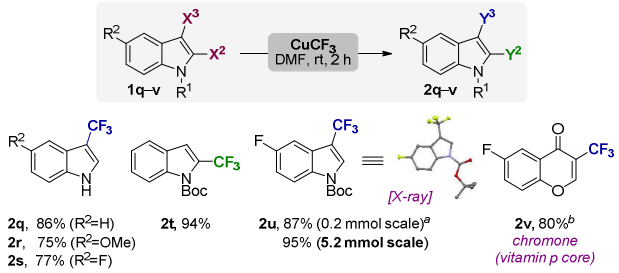
**Trifluoromethylation of iodinated nucleosides and nitrogenous bases.** Having established conditions for the efficient site-selective trifluoromethylation of iodoglycals, we next extended the scope of this approach to iodinated nucleosides and nitrogenous bases (Scheme 4). Since $CF_3$-nucleosides are attractive antiviral compounds, our trifluoromethylation strategy with commercially available 5-iodonucleosides represents an interesting alternative to methods using radical reactions (*e.g.* $CF_3SO_2Na$ – Langlois reagent). Thus, the antiviral trifluridine **2k** (Viroptic®) used in the treatment of herpes simplex virus-1 and -2 (HSV-1 and -2)[36] and its precursor **2l** were obtained in 62% and 84% yield, respectively and 5-$CF_3$-2'-deoxycytidine **2m**, which displays activity against certain tumours[37] was prepared in a fair 71% yield. Indeed, our results are in line with classic radical strategies (62% *vs.* 57% for **2k** and 71 *vs.* 73% for **2m**).[10,38] Finally, our method allowed the preparation in excellent yields (up to 97%) of the two regioisomers of trifluoro-1,3-dimethyluracil **2n**,**o** and the rare bis-trifluoromethyl derivative **2p** (92%) obtained from its diiodinated precursor **1p**.




**Scheme 4.** Trifluoromethylation of iodinated nucleosides and nitrogenous bases. Isolated yields given (see SI for details). $X^5$ and $X^6$ refer to I or H and the superscript indicates position.

**Trifluoromethylation of iodinated benzo-fused heterocycles.** Next, the method was extended to iodinated benzo-fused heterocycles (Scheme 5). Unlike that observed with iodoglycals and nucleosides, preliminary experiments with 3-iodoindole **1q** using optimized conditions ($CuCF_3$-0.6HF, 50 ºC) resulted in the formation of small amounts of hydrodehalogenation products (<15%) (SI, Table S1). Gratifyingly, this side reaction was nearly suppressed by conducting reactions at room temperature and without the addition of "extra" TREAT-HF. Thus, 2-$CF_3$ indole **2t** (94%) and 3-$CF_3$-indoles **2q**–**s** were obtained in good yields (up to 86%) after 2 h at room temperature regardless the electronic properties of their

substituents (*e.g.* F *vs.* OMe). Unlike previous reactions with unprotected indoles **1q**–**s** that proceed smoothly at room temperature, trifluoromethylation of *N*-Boc **1u** required heating up to 50 ºC to afford **2u** in 87% yield (up to 95% in gram scale, suitable for X-ray).[32] This together with the *in situ* $^{19}$F NMR monitoring of the reaction with **1q**, which indicates a putative N–Cu(I) coordination, suggest this event plays a role in the enhancement of the trifluoromethylation rate with unprotected indoles (SI, Scheme S1). Finally, the versatility of this protocol to access advanced heterocyclic $CF_3$-building blocks was demonstrated with the preparation of **2v** (80%), a fluorinated analog containing the vitamin p core (chromone), using 0.2 equiv of "extra" TREAT-HF.




**Scheme 5.** Trifluoromethylation of iodinated benzo-fused heterocycles. Isolated yields given (see SI for details). [a]Conducted from room temperature up to 50 ºC, 24 h. [b]$CuCF_3$-0.6HF, rt, 15 h. $X^2$ and $X^3$ refer to I or H and the superscript indicates position. Boc=*tert*-butoxycarbonyl. ORTEP drawing of **2u** with thermal ellipsoids drawn at the 50% probability level (H atoms and the minor disordered part are omitted for clarity).

## CONCLUSION

In summary, we have implemented a flexible metal-mediated strategy for the precise introduction of $CF_3$ units into a predefined position of electron-rich alkenes using fluoroform-derived "ligandless" $CuCF_3$. The present transformation enables the preparation of all regioisomers by combining the possibility of selective introduction of iodine at both carbons using well-established methods and the specificity of the reaction with "ligandless" $CuCF_3$. Given the broad substrate scope (sugars, nucleosides, and heterocycles) and functional group tolerance (including the presence of free nucleophilic/chelating moieties) together with other "practical" aspects such as mildness (reduced side-reactions profile), scalability, and processability (only an aqueous extraction and/or filtration through a short path of $SiO_2$), we expect this strategy to be broadly applicable to other homogeneous late-stage metal-mediated fluorinations and cross-couplings with electron-rich alkenes bearing C($sp^2$)–I bonds in the fields of agrochemistry,[39] medicinal chemistry, and

drug development.[40]

## EXPERIMENTAL SECTION

**General remarks.** Proton ($^1$H NMR), carbon ($^{13}$C NMR), and fluorine ($^{19}$F NMR) nuclear magnetic resonance spectra were recorded on a 400 MHz (for $^1$H), 100.6 MHz (for $^{13}$C) and 376.5 MHz (for $^{19}$F) spectrometer. Spectra were fully assigned using COSY, HSQC, HMBC, and NOESY. All chemical shifts are quoted on the $\delta$ scale in ppm using the residual solvent as internal standard ($^1$H NMR: $CDCl_3$ = 7.26, $CD_3OD$ = 3.31 and $^{13}$C NMR: $CDCl_3$ = 77.16, $CD_3OD$ = 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 ($\nu_{max}$) 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 $10^{-1}$ deg $cm^2$ $g^{-1}$. 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). Nominal and exact *m/z* values are reported in Daltons (Da). 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 ($\lambda_{max}$ = 254 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). HPLC grade dichloromethane ($CH_2Cl_2$) and tetrahydrofuran (THF) were dried using standard methods, acetonitrile was dried using activated 3Å molecular sieves, and anhydrous DMF was stored over freshly calcined 4 Å molecular sieves in a glove box. All other solvents were used as supplied (Analytical or HPLC grade), without prior purification. All reagents were used as received from commercial suppliers. All reactions using anhydrous conditions were performed using flame-dried apparatus under an atmosphere of argon. Brine refers to a saturated solution of sodium chloride. Anhydrous sodium sulfate ($Na_2SO_4$) was used as drying agent after reaction work-up, as indicated.

**1,5-Anhydro-3,4,6-tri-*O*-pivaloyl-2-deoxy-2-iodo-D-*lyxo*-hex-1-enitol (1c).** *N*-iodosuccinimide (NIS) (423 mg, 1.88 mmol) was added to a solution of 3,4,6-tri-*O*-

pivaloyl-D-galactal[41] (500 mg, 1.25 mmol) in 10:1 (v/v) $CH_3CN/H_2O$ (22 mL) at 0 ºC. The reaction mixture was warmed up to room temperature and stirred for 3 h. The crude was then diluted with EtOAc and washed with saturated aqueous $Na_2S_2O_3$, saturated aqueous $NaHCO_3$, and brine. The combined organic layers were dried over $Na_2SO_4$, filtered, and concentrated under reduced pressure. The residue was azeotropically dried with toluene and used in the next step without further purification. The crude was dissolved in dry $CH_2Cl_2$ (12 mL) and treated with a mixture of $Ph_2SO$ (758 mg, 3.75 mmol), 2,4,6-tri-*tert*-butylpyrimidine (TTBP) (932 mg, 3.75 mmol), and 4 Å molecular sieves (0.8 g) in dry $CH_2Cl_2$ (12 mL) at –78 ºC for 30 min. $Tf_2O$ (0.25 mL, 1.5 mmol) was then added and the reaction gradually warmed up to room temperature and stirred for 5 h. The reaction mixture was quenched with $Et_3N$ and the solvent evaporated. The residue was purified by column chromatography (1:20 EtOAc/hexane) to afford **1c** (344 mg, 52% over two steps) as a pale yellow solid. $R_f$ (1:9 EtOAc/hexane): 0.51; m.p: 53–55 ºC; $[\alpha]_D^{20}$ +17.7 (*c* 9.1, $CH_2Cl_2$); $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 6.72 (d, $J$ = 1.5 Hz, 1H), 5.57 (dd, $J$ = 4.4 Hz, $J$ = 1.5 Hz, 1H), 5.46 (dd, $J$ = 4.4 Hz, $J$ = 2.5 Hz, 1H), 4.46–4.43 (m, 1H), 4.26 (dd, $J$ = 12.0 Hz, $J$ = 8.2 Hz, 1H), 4.06 (dd, $J$ = 12.0 Hz, $J$ = 5.0 Hz, 1H), 1.20 (s, 9H), 1.17 (s, 9H), 1.15 (s, 9H); $^{13}$C NMR (100.6 MHz, $CDCl_3$) $\delta$ 178.0, 177.0, 176.7, 148.7, 73.3, 67.0, 64.4, 61.2, 60.4, 39.1, 39.0, 38.8, 27.3, 27.14, 27.12; FTIR–ATR (neat, $\nu_{max}$) 2972, 2934, 2871, 1739, 1624, 1480, 1280, 1138, 1036; HRMS (TOF ES$^+$) *m/z*: $[M+Na]^+$ Calcd for $C_{21}H_{33}INaO_7^+$ 547.1163; Found 547.1149.

**1,5-Anhydro-3,4,6-tri-*O*-pivaloyl-2-deoxy-2-iodo-D-*arabino*-hex-1-enitol (1d).** NIS (110 mg, 0.44 mmol) was added to a solution of 3,4,6-tri-*O*-pivaloyl-D-glucal[42] (110 mg, 0.28 mmol) in 10:1 (v/v) $CH_3CN/H_2O$ (5.5 mL) at 0 ºC. The reaction mixture was warmed up to room temperature and stirred for 3 h. The crude was then diluted with EtOAc and washed with saturated aqueous $Na_2S_2O_3$, saturated aqueous $NaHCO_3$, and brine. The combined organic layers were dried over $Na_2SO_4$, filtered, and concentrated under reduced pressure. The residue was azeotropically dried with toluene and used in the next step without further purification. The crude was dissolved in dry $CH_2Cl_2$ (7 mL) and treated with a mixture of $Ph_2SO$ (190 mg, 0.92 mmol), 2,4,6-tri-*tert*-butylpyrimidine (TTBP) (230 mg, 0.92 mmol), and 4 Å molecular sieves (0.5 g) in dry $CH_2Cl_2$ (5 mL) at –78 ºC for 30 min. $Tf_2O$ (78 µL, 0.46 mmol) was then added and the reaction gradually warmed up to room temperature and stirred for 5 h. The reaction mixture was quenched with $Et_3N$ and the solvent evaporated. The residue was purified by column chromatography (1:60 EtOAc/hexane) to afford **1d** (15 mg, 10% over two

steps) as a pale yellow solid. $R_f$ (1:9 EtOAc/hexane): 0.68; m.p: 104–105 ºC; $[\alpha]_D^{20}$ +53.5 (*c* 2.5, $CH_2Cl_2$); $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 6.78 (d, $J$ = 1.1 Hz, 1H), 5.57–5.55 (m, 1H), 5.27 (dd, $J$ = 7.9 Hz, $J$ = 5.8 Hz, 1H), 4.38 (ddd, $J$ = 7.9 Hz, $J$ = 5.5 Hz, $J$ = 2.8 Hz, 1H), 4.30 (dd, $J$ = 12.3 Hz, $J$ = 5.5 Hz, 1H), 4.19 (dd, $J$ = 12.3 Hz, $J$ = 2.8 Hz, 1H), 1.23 (s, 9H), 1.20 (s, 9H), 1.17 (s, 9H); $^{13}$C NMR (100.6 MHz, $CDCl_3$) $\delta$ 178.1, 177.3, 176.4, 149.6, 74.6, 70.6, 67.2, 67.0, 61.1, 39.2, 39.0, 38.9, 27.4, 27.2, 27.1; FTIR–ATR (neat, $\nu_{max}$) 2960, 2923, 2852, 1742, 1480, 1280, 1135; HRMS (TOF ES$^+$) *m/z*: $[M+Na]^+$ Calcd for $C_{21}H_{33}INaO_7^+$ 547.1163; Found 547.1156.

**1,5-Anhydro-3,6-di-*O*-acetyl-2-deoxy-4-*O*-(2,3,4,6-tetra-*O*-acetyl-*β*-D-galactopyranosyl)-2-iodo-D-*arabino*-hex-1-enitol (1h).** NIS (224 mg, 0.99 mmol) and $AgNO_3$ (42 mg, 0.25 mmol) were added under argon atmosphere to a solution of 3,6-di-*O*-acetyl-4-*O*-(2,3,4,6-tetra-*O*-acetyl-*β*-D-galactopyranosyl)-D-glucal (470 mg, 0.83 mmol) in dry $CH_3CN$ (2 mL) at room temperature. The reaction mixture was warmed up to 80 ºC and stirred for 4 h. The crude was filtered through a short path of Celite® 545 and the solvent evaporated. The residue was purified by column chromatography (1:1 EtOAc/hexane) to afford **1h** (385 mg, 68%) as a white solid. $R_f$ (1:1 EtOAc/hexane): 0.25; m.p: 43–45 ºC; $[\alpha]_D^{20}$ +5.5 (*c* 0.14, $CHCl_3$); $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 6.76 (bs, 1H), 5.59 (d, $J$ = 4.4 Hz, 1H), 5.38 (d, $J$ = 3.3 Hz, 1H), 5.19 (dd, $J$ = 10.7 Hz, $J$ = 7.8 Hz, 1H), 5.00 (dd, $J$ = 10.7 Hz, $J$ = 3.3 Hz, 1H), 4.62 (d, $J$ = 7.8 Hz, 1H), 4.37–4.31 (m, 2H), 4.24 (dd, $J$ = 12.8 Hz, $J$ = 7.9 Hz, 1H), 4.17–4.01 (m, 2H), 4.02 (appt, $J$ = 4.4 Hz, 1H), 4.94 (appt, $J$ = 6.5 Hz, 1H), 2.17 (s, 3H), 2.13 (s, 3H), 2.11 (s, 3H), 2.06 (s, 3H), 2.05 (s, 3H), 1.98 (s, 3H); $^{13}$C NMR (100.6 MHz, $CDCl_3$) $\delta$ 170.6, 170.5, 170.4, 170.2, 169.8, 169.3, 148.8, 101.5, 75.4, 74.2, 71.1, 71.0, 70.8, 68.9, 66.9, 65.5, 61.3, 61.2, 21.1, 20.94, 20.88, 20.83, 20.81, 20.7; FTIR–ATR (neat, $\nu_{max}$) 2979, 1740, 1368, 1215, 1170, 1046; HRMS (TOF ES$^+$) *m/z*: $[M+NH_4]^+$ Calcd for $C_{24}H_{35}INO_{15}^+$ 704,1046; Found 704.1035.

**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 (1i).** NIS (105 mg, 0.47 mmol) and $AgNO_3$ (18.3 mg, 0.107 mmol) were added under argon atmosphere to a solution of methyl 5-acetamido-4,7,8,9-tetra-*O*-acetyl-2,6-anhydro-3,5-dideoxy-D-*glycero*-α-D-*galacto*-non-2-enonate (170 mg, 0.359 mmol) in dry $CH_3CN$ (2 mL) at room temperature. The reaction mixture was warmed up to 80 ºC and stirred for 6 h. A second batch of NIS (105 mg, 0.47 mmol) and $AgNO_3$ (18.3 mg, 0.107 mmol) was added and the mixture stirred at 80 ºC for 6 h. The crude was filtered through a short path of Celite® 545 and

the solvent evaporated. The residue was purified by column chromatography (4:1 EtOAc/hexane) to afford **1i** (100 mg, 46%) as a white foam. $R_f$ (EtOAc): 0.42; $[\alpha]_D^{20}$ – 0.96 (*c* 6.4, $CH_2Cl_2$); $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 6.30–6.21 (m, 1H), 5.68–5.62 (m, 1H), 5.47–5.41 (m, 1H), 5.25–5.17 (m, 1H), 4.54 (dd, *J* = 12.5 Hz, *J* = 2.7 Hz, 1H), 4.49–4.42 (m, 2H), 4.07 (dd, *J* = 12.5 Hz, *J* = 6.9 Hz, 1H), 3.78 (s, 3H), 2.10 (s, 3H), 2.07 (s, 3H), 2.03 (s, 3H), 2.00 (s, 3H), 1.85 (s, 3H); $^{13}$C NMR (100.6 MHz, $CDCl_3$) $\delta$ 170.7, 170.5, 170.3, 170.1, 169.9, 161.3, 145.9, 77.0, 75.3, 73.7, 70.6, 67.1, 61.9, 52.8, 47.7, 22.9, 20.9, 20.8, 20.7, 20.6; FTIR–ATR (neat, $\nu_{max}$) 3274, 3058, 2956, 1739, 1662, 1535, 1436, 1370, 1210, 1029, 734; HRMS (TOF ES$^+$) *m/z*: $[M+Na]^+$ Calcd for $C_{20}H_{26}INNaO_{12}^+$ 622.0392; Found 622.0394.

**1,5-Anhydro-2-deoxy-2-iodo-D-*lyxo*-hex-1-enitol (1j).** 3,4,6-tri-*O*-acetyl-2-iodo-D-galactal[43] **1e** (78 mg, 0.195 mmol) was dissolved in MeOH (2 mL) and NaOMe (8.5 mg, 0.16 mmol) was added at room temperature. The reaction mixture was stirred at the same temperature for 5 h and neutralized with Dowex® ($H^+$ 50WX8-200). The ion exchanger was filtered off and washed with MeOH. The resulting solution was concentrated under reduced pressure and the residue purified by column chromatography (1:9 MeOH/$CH_2Cl_2$) to afford **1j** (45 mg, 85%) as a white solid. $R_f$ (1:9 MeOH/$CH_2Cl_2$): 0.13; m.p: 135–137 ºC; $[\alpha]_D^{20}$ +31.5 (*c* 1.2, MeOH); $^1$H NMR (400 MHz, $CD_3OD$) $\delta$ 6.71 (d, *J* = 1.5 Hz, 1H), 4.18–4.16 (m, 1H), 4.09–4.03 (m, 2H), 3.81 (dd, *J* = 11.6 Hz, *J* = 6.9 Hz, 1H), 3.74 (dd, *J* = 11.6 Hz, *J* = 5.1 Hz, 1H); $^{13}$C NMR (100.6 MHz, $CD_3OD$) $\delta$ 149.3, 79.6, 77.5, 69.3, 67.6, 62.0; FTIR–ATR (neat, $\nu_{max}$) 3343, 2926, 1736, 1627, 1373, 1227, 1164, 1022; HRMS (TOF ES$^+$) *m/z*: $[M+Na]^+$ Calcd for $C_6H_9INaO_4^+$ 294.9438; Found 294.9434.

**Synthesis of stabilized $CuCF_3$ with "extra" $Et_3N{\cdot}3HF$.** The fluoroform-derived reagent $CuCF_3$ stabilized with $Et_3N{\cdot}3HF$ (TREAT-HF) was prepared in a 0.1 mol scale in DMF using the following reported procedure.[16b] In a glove box, CuCl (1.5 g, 15 mmol) was added to a solution of *t*-BuOK (3.54 g, 30.6 mmol) in DMF (20 mL). The reaction mixture was stirred at room temperature for 30 min and KCl precipitated. The solid was filtered off and washed with additional DMF (10 mL). The DMF solution was transferred to a 3-oz Fischer–Porter tube equipped with a pressure gauge, a needle valve, and a Teflon-coated magnetic stir-bar. The tube was sealed, brought out, and quickly evacuated under vacuum to ~1 mm Hg. Next, fluoroform was introduced to ~50 psi at vigorous stirring followed by a rapid drop of pressure to 5–10 psi. After 5 min, a solution of TREAT-HF (0.83 mL, 5 mmol) in DMF (3 mL) was added under vigorous

stirring. The tube was introduced to the glove box and unsealed. Next, the suspension was left on standing for 1 h to allow KF to precipitate. Finally, the pale yellow supernatant (~6 mL) was carefully separated by a syringe and the solution of $CuCF_3$ stored at –30 ºC. At the moment of use, the concentration of the reagent (referred to as $CuCF_3$) was 0.34 M. $CuCF_3$ reagents with "extra" TREAT-HF were prepared as follows. In a glove box, three different vials were charged with 5 mL of the $CuCF_3$ solution and different volumes of TREAT-HF (purity 99%) were added to the vials. TREAT-HF (35 μL, 0.215 mmol) to obtain $CuCF_3$-0.3HF, TREAT-HF (70 μL, 0.430 mmol) to obtain $CuCF_3$-0.6HF, and TREAT-HF (105 μL, 0.645 mmol) to obtain $CuCF_3$-0.9HF. All reagents were stored at –30 ºC and left undisturbed for several hours prior to use.

**Optimization experiments for the trifluoromethylation of 1a.** In a glove box, the corresponding $CuCF_3$ TREAT-HF reagent was added to 3,4,6-tri-*O*-benzyl-2-iodo-D-glucal[23a] **1a** (54 mg, 0.1 mmol) in an NMR tube. The tube was sealed, brought out of the glove box, and 1,3-bis(trifluoromethyl)benzene (internal standard; 0.05 mmol, 7.7 μL) was added. The reaction was monitored by $^{19}F$ NMR at the selected temperature and quenched by extraction with $Et_2O$. The solvent was evaporated under reduced pressure and the crude analyzed by $^{1}H$ NMR to determine the conversion.

**Trifluoromethylation using the $FSO_2CF_2CO_2Me$/CuI system.** To a flame-dried Schlenk flask equipped with a magnetic stir bar was added CuI (38 mg, 0.2 mmol) under argon. DMF (1.5 mL), $FSO_2CF_2CO_2Me$ (25.4 μL, 0.2 mmol) and **1a** (54 mg, 0.1 mmol) were consecutively added and the resulting mixture was stirred at the indicated temperature for 8 h. 4′-Fluoroacetophenone (internal standard; 36.4 μL, 0.3 mmol) was added to the crude mixture and an aliquot was transferred to an NMR tube for quantitative $^{19}F$ NMR analysis.

**Trifluoromethylation using the *in situ* generated (Phen)$CuCF_3$.** In a glove box, to a vial equipped with a magnetic stir bar was added CuCl (35 mg, 0.35 mmol), *t*BuOK (39 mg, 0.35 mmol) phenanthroline (63 mg, 0.35 mmol) and DMF (0.7 mL). The resulting red mixture was stirred 30 min at room temperature followed by addition of $TMSCF_3$ (51.7 μL, 0.35 mmol). After stirring 1 h at room temperature, **1a** (95 mg, 0.175 mmol) was added, the vial was capped with a rubber septum and taken out of the glove box and the reaction mixture was heated 24 h at 50 ºC without stirring. 1,3-Bis(trifluoromethyl)benzene (internal standard; 13.6 μL, 0.087 mmol) was added to the crude mixture and an aliquot was transferred to an NMR tube for quantitative $^{19}F$ NMR analysis.

**Trifluoromethylation using the $TMSCF_3$/KF/CuBr system.** Dry KF (12 mg, 0.2 mmol) and CuBr (30 mg, 0.2 mmol) were added to a Schlenk flask and the reaction vessel was evacuated and refilled with argon three times. DMF (0.2 mL) and 1,3-dimethyl-2-imidazolidinone (DMI, 0.2 mL) were then added followed by addition of $TMSCF_3$ (29.6 μL, 0.2 mmol) at 0 ºC and the reaction mixture was stirred at this temperature for 3 h. Then **1a** (54 mg, 0.1 mmol) was added and the reaction mixture was heated for 24 h at 50 ºC without stirring. 1,3-Bis(trifluoromethyl)benzene (internal standard; 7.7 μL, 0.05 mmol) was added to the crude mixture and an aliquot was transferred to an NMR tube for quantitative $^{19}F$ NMR analysis.

**General procedure for the trifluoromethylation of electron-rich vinyl iodides.** In a glove box, $CuCF_3$-0.6HF (0.34 M, 0.59 mL, 0.2 mmol) was added at room temperature to a vial containing the corresponding vinyl iodide (0.1 mmol). The concentration of $CuCF_3$-0.6HF at the moment of use ranged between 0.33–0.38 M. The vial was sealed, brought out of the glove box, and stirred at 50 ºC for 7 h. The crude was extracted with $Et_2O$, the solvent evaporated, and the crude analyzed by $^1H$ NMR. The residue was purified using chromatographic techniques.

*1,5-Anhydro-3,4,6-tri-O-benzyl-2-deoxy-2-trifluoromethyl-D-arabino-hex-1-enitol* ***(2a)***.[9b] The title compound was prepared following the general procedure above, starting from 3,4,6-tri-*O*-benzyl-2-iodo-D-glucal[23a] **1a** (200 mg, 0.36 mmol) and $CuCF_3$-0.6HF (2.2 mL, 0.74 mmol). After standard work-up, the crude was purified by column chromatography (1:15 EtOAc/hexane) to afford **2a** (139 mg, 80%) as a colorless syrup. $R_f$ (1:4 EtOAc/hexane): 0.43; $[\alpha]_D^{20}$ –11.2 (*c* 1.26, $CH_2Cl_2$); $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 7.40–7.21 (m, 15H), 7.07 (bq, $J$ = 1.5 Hz, 1H), 4.59–4.44 (m, 7H), 4.10 (bs, 1H), 3.90 (appt, $J$ = 3.2 Hz, 1H), 3.78 (dd, $J$ = 10.5 Hz, $J$ = 6.9 Hz, 1H), 3.67 (dd, $J$ = 10.5 Hz, $J$ = 5.1 Hz, 1H); $^{13}C$ NMR (100.6 MHz, $CDCl_3$) $\delta$ 148.1 (q, $J$ = 7.2 Hz), 137.8, 137.6, 137.4, 128.7, 128.6, 128.5, 128.4, 128.2, 128.11, 128.06, 128.0 127.9, 127.8, 125.0 (q, $J$ = 269.9 Hz), 103.6 (q, $J$ = 30.7 Hz), 76.5, 73.4, 72.4, 72.2, 71.2, 68.9, 71.2, 68.9, 67.7; $^{19}F$ NMR (376.5 MHz, $CDCl_3$,) $\delta$ –62.6 (s); FTIR–ATR (neat, $\nu_{max}$) 3030, 2866, 1667, 1497, 1454, 1323, 1213, 1109; HRMS (TOF $ES^+$) *m/z*: $[M+Na]^+$ Calcd for $C_{28}H_{27}F_3NaO_4^+$ 507.1754; Found 507.1752.

*1,5-Anhydro-3,4,6-tri-O-benzyl-2-deoxy-2-trifluoromethyl-D-lyxo-hex-1-enitol* ***(2b)***.[9b] The title compound was prepared following the general procedure above, starting from 3,4,6-tri-*O*-benzyl-2-iodo-D-galactal[23a] **1b** (63.4 mg, 0.12 mmol) and $CuCF_3$-0.6HF (0.71 mL, 0.23 mmol). After standard work-up, the crude was purified by column

chromatography (1:15 EtOAc/hexane) to afford **2b** (49.6 mg, 85%) as a colorless syrup. $R_f$ (1:4 EtOAc/hexane): 0.53; $[\alpha]_D^{20}$ –20.7 (*c* 2.1, $CH_2Cl_2$); $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.40–7.21 (m, 15H), 7.07 (bq, $J$ = 1.5 Hz, 1H), 4.59–4.44 (m, 7H), 4.10 (bs, 1H), 3.90 (appt, $J$ = 3.2 Hz, 1H), 3.78 (dd, $J$ = 10.5 Hz, $J$ = 6.9 Hz, 1H), 3.67 (dd, $J$ = 10.5 Hz, $J$ = 5.1 Hz, 1H); $^{13}$C NMR (100.6 MHz, $CDCl_3$) $\delta$ 147.9 (q, $J$ = 7.1 Hz), 138.2, 138.0, 137.7, 128.6, 128.5, 128.4, 128.1, 128.0, 127.9, 127.8, 124.7 (q, $J$ = 269.6 Hz), 104.8 (q, $J$ = 30.8 Hz), 76.6, 74.2, 73.5, 72.9, 72.7, 68.5, 67.8; $^{19}$F NMR (376.5 MHz, $CDCl_3$) $\delta$ –62.1 (s); FTIR–ATR (neat, $\nu_{max}$) 3063, 3031, 2867, 1662, 1497, 1454, 1326, 1211, 1108, 1063, 1027; HRMS (TOF ES$^+$) *m/z*: $[M+Na]^+$ Calcd for $C_{28}H_{27}F_3NaO_4^+$ 507.1754; Found 507.1750.

*1,5-Anhydro-3,4,6-tri-O-pivaloyl-2-deoxy-2-trifluoromethyl-D-lyxo-hex-1-enitol (**2c**).* The title compound was prepared following the general procedure above, starting from **1c** (54 mg, 0.10 mmol) and $CuCF_3$-0.6HF (0.57 mL, 0.20 mmol). After standard work-up, the crude was purified by column chromatography (1:9 EtOAc/hexane) to afford **2c** (43 mg, 92%) as a white solid. $R_f$ (1:9 EtOAc/hexane): 0.50; m.p: 96–98 ºC; $[\alpha]_D^{20}$ +6.0 (*c* 0.17, $CH_2Cl_2$); $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.09 (bs, 1H), 5.86 (bdq, $J$ = 4.1 Hz, $J$ = 0.9 Hz, 1H), 5.46 (dd, $J$ = 4.1 Hz, $J$ = 3.3 Hz, 1H), 4.49 (m, 1H), 4.41 (dd, $J$ = 11.8 Hz, $J$ = 8.9 Hz, 1H), 4.18 (dd, $J$ = 11.8 Hz, $J$ = 4.1 Hz, 1H), 1.22 (s, 9H), 1.21 (s, 9H), 1.20 (s, 9H); $^{13}$C NMR (100.6 MHz, $CDCl_3$) $\delta$ 178.2, 177.2, 176.8, 149.0 (q, $J$ = 7.1 Hz), 123.8 (q, $J$ = 271.6 Hz), 103.0 (q, $J$ = 31.5 Hz), 74.0, 63.5, 61.3, 61.2, 39.1, 39.0, 38.9, 27.2, 27.2, 27.1; $^{19}$F NMR (376.5 MHz, $CDCl_3$) $\delta$ –62.5 (s); FTIR–ATR (neat, $\nu_{max}$) 2975, 1738, 1666, 1481, 1280, 1111; HRMS (TOF ES$^+$) *m/z*: $[M+Na]^+$ Calcd for $C_{22}H_{33}F_3NaO_7^+$ 489.2071; Found 489.2072.

*1,5-Anhydro-3,4,6-tri-O-pivaloyl-2-deoxy-2-trifluoromethyl-D-arabino-hex-1-enitol (**2d**).* The title compound was prepared following the general procedure above, starting from **1d** (15 mg, 0.028 mmol) and $CuCF_3$-0.6HF (0.16 mL, 0.056 mmol). After standard work-up, the crude was purified by column chromatography (1:40 EtOAc/hexane) to afford **2d** (9.1 mg, 70%) as a pale yellow syrup. $R_f$ (1:9 EtOAc/hexane): 0.57; $[\alpha]_D^{20}$ –13.3 (*c* 0.1, $CH_2Cl_2$); $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.18 (bs, 1H), 5.56 (bd, $J$ = 3.3 Hz, 1H), 5.13 (bd, $J$ = 3.3 Hz, 1H), 4.53–4.43 (m, 2H), 4.05 (dd, $J$ = 17.6 Hz, $J$ = 7.9 Hz, 1H), 1.23 (s, 9H), 1.20 (s, 9H), 1.19 (s, 9H); $^{13}$C NMR (100.6 MHz, $CDCl_3$) $\delta$ 178.1, 176.8, 176.6, 149.3 (q, $J$ = 6.6 Hz), 124.0 (q, $J$ = 271.8 Hz), 102.3 (q, $J$ = 31.8 Hz), 74.6, 65.6, 61.3, 61.0, 38.98, 38.97, 38.96, 27.3, 27.0; $^{19}$F NMR (376.5 MHz, $CDCl_3$) $\delta$ –62.5 (s); FTIR–ATR (neat, $\nu_{max}$) 2978, 2963, 1740, 1669,

1327, 1279, 1122; HRMS (TOF ES$^+$) *m/z*: [M+Na]$^+$ Calcd for $C_{22}H_{33}F_3NaO_7^+$ 489.2071; Found 489.2092.

*1,5-Anhydro-3,4,6-tri-O-acetyl-2-deoxy-2-trifluoromethyl-D-lyxo-hex-1-enitol (**2e**).*[9b] The title compound was prepared following the general procedure above, starting from 3,4,6-tri-*O*-acetyl-2-iodo-D-galactal[43] **1e** (1.58 g, 3.97 mmol) and $CuCF_3$-0.6HF (20.9 mL, 7.94 mmol).. After standard work-up, the crude was purified by column chromatography (1:4 EtOAc/hexane) to afford **2e** (1.25 g, 93%) as a white solid. $R_f$ (1:4 EtOAc/hexane): 0.41; m.p: 54–56 ºC; $[\alpha]_D^{20}$ +23.5 (*c* 0.2, $CHCl_3$); $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.06 (bs, 1H), 5.80 (d, *J* = 4.3 Hz, 1H), 5.41 (dd, *J* = 4.3 Hz, *J* = 3.0 Hz, 1H), 4.43 (m, 1H), 4.34 (dd, *J* = 11.9 Hz, *J* = 8.1 Hz, 1H), 4.23 (dd, *J* = 11.9 Hz, *J* = 4.1 Hz, 1H), 2.08 (s, 3H), 2.06 (s, 3H), 2.02 (s, 3H); $^{13}$C NMR (100.6 MHz, $CDCl_3$) $\delta$ 170.5, 169.8, 169.7, 149.3 (q, *J* = 6.9 Hz), 123.6 (q, *J* = 270.0 Hz), 102.9 (q, *J* = 31.5 Hz), 73.8, 63.5, 61.3, 60.8, 20.7, 20.5; $^{19}$F NMR (376.5 MHz, $CDCl_3$) $\delta$ –62.7 (s); FTIR–ATR (neat, $\nu_{max}$) 2940, 1747, 1666, 1455, 1371, 1328, 1213, 1151, 1112, 1046; HRMS (TOF ES$^+$) *m/z*: [M+Na]$^+$ Calcd for $C_{13}H_{15}F_3NaO_7^+$ 363.0662; Found 363.0658.

*1,5-Anhydro-2-deoxy-2-trifluoromethyl-3,4:6,7-di-O-isopropylidene-D-glycero-D-talo-hept-1-enitol (**2f**).* The title compound was prepared following the general procedure above, starting from 1,5-anhydro-2-deoxy-2-iodo-3,4:6,7-di-*O*-isopropylidene-D-*glycero*-D-*talo*-hept-1-enitol[23b] **1f** (24 mg, 0.06 mmol) and $CuCF_3$-0.6HF (0.34 mL, 0.12 mmol).. After standard work-up, the crude was purified by column chromatography (1:8 EtOAc/hexane) to afford **2f** (15 mg, 77%) as a pale yellowish oil. $R_f$ (1:8 EtOAc/hexane): 0.37; $[\alpha]_D^{20}$ +0.55 (*c* 0.2, $CH_2Cl_2$); $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 6.96 (bq, *J* = 1.5 Hz, 1H), 4.86 (d, *J* = 6.2 Hz, 1H), 4.54 (dd, *J* = 6.2 Hz, *J* = 1.0 Hz, 1H), 4.41 (ddd, *J* = 8.1 Hz, *J* = 6.1 Hz, *J* = 4.6 Hz, 1H), 4.13 (dd, *J* = 9.1 Hz, *J* = 6.1 Hz, 1H), 4.08 (dd, *J* = 9.1 Hz, *J* = 4.6 Hz, 1H), 3.84 (bd, *J* = 8.1 Hz, 1H), 1.44 (s, 3H), 1.43 (s, 3H), 1.42 (s, 3H), 1.38 (s, 3H); $^{13}$C NMR (100.6 MHz, $CDCl_3$) $\delta$ 148.3 (q, *J* = 6.7 Hz), 124.6 (q, *J* = 270.0 Hz), 111.7, 109.9, 107.0 (appd, *J* = 30.5 Hz), 76.2, 73.8, 71.5, 67.0, 66.6, 29.9, 27.8, 27.0, 25.3; $^{19}$F NMR (376.5 MHz, $CDCl_3$) $\delta$ –62.5 (s); FTIR–ATR (neat, $\nu_{max}$) 2986, 2933, 2361, 2331, 1774, 1724, 1668, 1373, 1334, 1225, 1146, 1115, 1043, 993, 844; HRMS (TOF ES$^+$) *m/z*: [M+Na]$^+$ Calcd for $C_{14}H_{19}F_3NaO_5^+$ 347.1077; Found 347.1082.

*1,5-Anhydro-2-deoxy-1-trifluoromethyl-3,4,6-tris-O-(triisopropylsilyl)-D-arabino-hex-1-enitol (**2g**).* The title compound was prepared following the general procedure above, starting from 1-iodo-3,4,6-tris-*O*-(triisopropylsilyl)- D-glucal[44] **1g** (74.1 mg, 0.10

mmol) and $CuCF_3$-0.6HF (0.57 mL, 0.20 mmol).. After standard work-up, the crude was purified by column chromatography (hexane) to afford **2g** (60 mg, 88%) as a glassy syrup. $R_f$ (hexane): 0.74; $[\alpha]_D^{20}$ –7.9 (*c* 0.28, $CH_2Cl_2$); $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 5.47 (dd, *J* = 5.6 Hz, 1H), 4.45–4.42 (m, 1H), 4.15 (bs, 1H), 4.09–3.86 (m, 1H), 3.99 (dd, *J* = 11.4 Hz, *J* = 7.5 Hz, 1H), 3.88 (dd, *J* = 11.4 Hz, *J* =4.8 Hz, 1H), 1.13–0.96 (m, 63H); $^{13}$C NMR (100.6 MHz, $CDCl_3$) $\delta$ 142.0 (q, *J* = 35.0 Hz), 119.9 (q, *J* = 273.2 Hz), 100.9 (q, *J* = 3.7 Hz), 82.2, 69.4, 65.0, 61.4, 18.2–18.1, 12.6, 12.4, 12.1; $^{19}$F NMR (376.5 MHz, $CDCl_3$) $\delta$ –72.9 (s); FTIR–ATR (neat, $\nu_{max}$) 2944, 2867, 1735, 1463, 1370, 1192, 1103, 882; HRMS (TOF ES$^+$) *m/z*: $[M+NH_4]^+$ Calcd for $C_{34}H_{73}F_3NO_4Si_3^+$ 700.4794; Found 700.4782.

*1,5-Anhydro-3,6-di-O-acetyl-2-deoxy-4-O-(2,3,4,6-tetra-O-acetyl-β-D-galactopyranosyl)-2-trifluoromethyl-D-arabino-hex-1-enitol (**2h**).*[9b] The title compound was prepared following the general procedure above, starting from **1h** (60.9 mg, 0.087 mmol) and $CuCF_3$-0.6HF (0.45 mL, 0.17 mmol). The reaction mixture was stirred at 50 ºC for 16 h. After standard work-up, the crude was purified by column chromatography (1:1 EtOAc/hexane) to afford **2h** (44 mg, 80%) as a white solid. $R_f$ (1:1 EtOAc/hexane): 0.15; m.p: 50–52 ºC; $[\alpha]_D^{20}$ +1.9 (*c* 0.2, $CHCl_3$); $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.13 (bq, *J* = 1.5 Hz, 1H), 5.59 (bs, 1H), 5.37 (dd, *J* = 3.6 Hz, *J* = 1.0 Hz, 1H), 5.18 (dd, *J* = 10.5 Hz, *J* = 7.5 Hz, 1H), 5.01 (dd, *J* = 10.5 Hz, *J* = 3.6 Hz, 1H), 4.69 (d, *J* = 7.5 Hz, 1H), 4.46 (m, 1H), 4.31 (dd, *J* = 12.0 Hz, *J* = 8.1 Hz, 1H), 4.18 (dd, *J* = 12.0 Hz, *J* = 4.8 Hz, 1H), 4.15 (dd, *J* = 11.4 Hz, *J* = 6.7 Hz, 1H), 4.11 (dd, *J* = 11.4 Hz, *J* = 6.5 Hz, 1H), 4.02–3.96 (m, 2H), 2.14 (s, 3H), 2.10 (s, 3H), 2.05 (s, 3H), 2.04 (s, 3H), 2.02 (s, 3H), 2.00 (s, 3H); $^{13}$C NMR (100.6 MHz, $CDCl_3$) $\delta$ 170.6, 170.5, 170.4, 170.2, 169.7, 169.2, 149.0 (q, *J* = 6.5 Hz), 124.2 (q, *J* = 271.8 Hz), 101.7, 101.1 (q, *J* = 31.3 Hz), 74.9, 73.2, 71.4, 70.9, 68.9, 67.0, 61.4, 61.3, 61.1, 20.9, 20.84, 20.78, 20.77, 20.7, 20.6; $^{19}$F NMR (376.5 MHz, $CDCl_3$) $\delta$ –64.0 (s); FTIR–ATR (neat, $\nu_{max}$) 2980, 1740, 1667, 1369, 1328, 1211, 1115, 1047, 1020; HRMS (TOF ES$^+$) *m/z*: $[M+Na]^+$ Calcd for $C_{25}H_{31}F_3NaO_{15}^+$ 651.1507; Found 651.1509.

*Methyl 5-Acetamido-4,7,8,9-tetra-O-acetyl-2,6-anhydro-3,5-dideoxy-3-trifluoromethyl-D-glycero-α-D-galacto-non-2-enonate (**2i**).*[9b] The title compound was prepared following the general procedure above, starting from **1i** (40 mg, 0.067 mmol) and $CuCF_3$-0.6HF (0.36 mL, 0.13 mmol). The reaction mixture was stirred at room temperature for 1 h. After standard work-up, the crude was purified by column chromatography (1:4 EtOAc/hexane) to afford **2i** (30.7 mg, 85%) as a white foam. $R_f$

(1:1 EtOAc/hexane): 0.23; $[\alpha]_D^{20}$ +9.0 (*c* 0.62, $CH_2Cl_2$); $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 5.87 (d, *J* = 7.5 Hz, 1H), 5.73 (d, *J* = 9.2 Hz, 1H), 5.48 (dd, *J* = 6.9 Hz, *J* = 2.7 Hz, 1H), 5.25 (ddd, *J* = 6.9 Hz, *J* = 6.0 Hz, *J* = 2.9 Hz, 1H), 4.48 (dd, *J* = 9.7 Hz, *J* = 2.7 Hz, 1H), 4.44–3.35 (m, 2H), 4.09 (dd, *J* = 12.5 Hz, *J* = 6.0 Hz, 1H), 3.86 (s, 3H), 2.11 (s, 3H), 2.08 (s, 3H), 2.04 (s, 3H), 1.92 (s, 3H); $^{13}$C NMR (100.6 MHz, $CDCl_3$) $\delta$ 170.72, 170.70, 170.6, 170.0, 169.8, 161.0, 151.2 (q, *J* = 3.8 Hz), 122.5 (q, *J* = 272.3 Hz), 104.9 (q, *J* = 33.0 Hz), 77.45, 69.8, 66.7, 66.2, 61.8, 53.6, 47.3, 23.2, 20.92, 20.85, 20.80, 20.78; $^{19}$F NMR (376.5 MHz, $CDCl_3$) $\delta$ –58.6 (s); FTIR–ATR (neat, $\nu_{max}$) 3273, 3060, 2961, 1746, 1663, 1540, 1370, 1208, 1131, 1008; HRMS (TOF ES$^+$) *m/z*: $[M+Na]^+$ Calcd for $C_{21}H_{26}F_3NNaO_{12}^+$ 564.1299; Found 564.1307.

**Deacetylation of 2e.** 1,5-Anhydro-3,4,6-tri-*O*-acetyl-2-deoxy-2-trifluoromethyl-D-*lyxo*-hex-1-enitol **2e** (20 mg, 0.058 mmol) was dissolved in MeOH (0.5 mL) and NaOMe (1.6 mg, 0.03 mmol) was added at room temperature. The reaction mixture was stirred at the same temperature for 12 h and neutralized with Dowex® ($H^+$ 50WX8-200). The ion exchanger was filtered off and washed with MeOH. The resulting solution was concentrated under reduced pressure to afford **2j** (12.2 mg, 98%) as a white solid. $R_f$ (1:9 MeOH/$CH_2Cl_2$): 0.55; m.p: 93–95 ºC; $[\alpha]_D^{20}$ +8.0 (*c* 0.1, MeOH); $^1$H NMR (400 MHz, $CD_3OD$) $\delta$ 7.03 (bs, 1H), 4.46 (bdq, *J* = 4.4 Hz, *J* = 0.9 Hz, 1H), 4.08 (m, 1H), 3.99 (dd, *J* = 4.4 Hz, *J* = 2.5 Hz, 1H), 3.90 (dd, *J* = 12.0 Hz, *J* = 6.8 Hz, 1H), 3.80 (dd, *J* = 12.0 Hz, *J* = 4.6 Hz, 1H); $^{13}$C NMR (100.6 MHz, $CD_3OD$) $\delta$ 149.4 (q, *J* = 7.6 Hz), 126.4 (q, *J* = 269.2 Hz), 107.0 (q, *J* = 29.0 Hz), 80.1, 66.3, 63.4, 61.4; $^{19}$F NMR (376.5 MHz, $CD_3OD$) $\delta$ –63.0 (s); FTIR–ATR (neat, $\nu_{max}$) 3537, 3349, 3185, 1669, 1346, 1214, 1103, 1040; HRMS (TOF ES$^+$) *m/z*: $[M+Na]^+$ Calcd for $C_7H_9F_3NaO_4^+$ 237.0345; Found 237.0341.

**5-Trifluoromethyl-2'-deoxyuridine (2k).**[9c] To a vial containing 5-iodo-2'-deoxyuridine **1k** (47 mg, 0.13 mmol), three portions of $CuCF_3$-0.6HF (0.36 mL, 0.13 mmol) was added every 2 h and stirred at 50 ºC. After 2 h from the last addition, the residue was azeotropically dried with toluene and the crude purified by column chromatography (1:9 MeOH/$CH_2Cl_2$) to afford **2k** (23.8 mg, 62%) as a white solid. $R_f$ (4:1 EtOAc/hexane): 0.38; $^1$H NMR (400 MHz, $CD_3OD$) $\delta$ 8.80 (bs, 1H), 6.24 (t, *J* = 6.2 Hz, 1H), 4.42 (m, 1H), 3.97 (m, 1H), 3.84 (dd, *J* = 11.9 Hz, *J* = 2.9 Hz, 1H), 3.75 (dd, *J* = 11.9 Hz, *J* = 2.9 Hz, 1H), 2.37 (ddd, *J* = 13.7 Hz, *J* = 6.3 Hz, *J* = 4.4 Hz, 1H), 2.27 (m, 1H); $^{13}$C NMR (100.6 MHz, $CD_3OD$) $\delta$ 161.2, 151.3, 143.8 (q, *J* = 5.9 Hz),

123.9 (q, $J$ = 268.8 Hz), 105.3 (q, $J$ = 32.9 Hz), 87.3, 87.5, 71.7, 62.1, 42.1; $^{19}$F NMR (376.5 MHz, $CD_3OD$) $\delta$ –64.5 (s).

*5-Trifluoromethyl-3',5'-di-O-acetyl-2'-deoxyuridine (**2l**).*[45] The title compound was prepared following the general procedure above, starting from 3',5'-di-*O*-acetyl-5-iodo-2'-deoxyuridine[46] **1l** (43 mg, 0.10 mmol) and $CuCF_3$-0.6HF (0.55 mL, 0.20 mmol). The reaction mixture was stirred at 50 ºC for 4 h. After standard work-up, the crude was purified by column chromatography (1:30 MeOH/$CH_2Cl_2$) to afford **2l** (32 mg, 84%) as a white solid. $R_f$ (4:1 EtOAc/hexane): 0.38; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.08 (bs, 1H), 6.27 (dd, $J$ = 8.1 Hz, $J$ = 5.5 Hz, 1H), 5.23 (appdt, $J$ = 6.2 Hz, $J$ = 2.1 Hz, 1H), 4.42 (dd, $J$ = 11.2 Hz, $J$ = 2.3 Hz, 1H), 4.36–4.28 (m, 2H), 2.62 (ddd, $J$ = 14.5 Hz, $J$ = 5.5 Hz, $J$ = 2.1 Hz, 1H), 2.22–2.07 (m, 7H); $^{13}$C NMR (100.6 MHz, $CDCl_3$) $\delta$ 170.5, 170.3, 158.3, 149.4, 140.1 (q, $J$ = 5.9 Hz), 121.8 (q, $J$ = 269.8 Hz), 105.9 (q, $J$ = 33.2 Hz), 86.2, 83.2, 74.1, 63.8, 38.7, 21.0, 20.6; $^{19}$F NMR (376.5 MHz, $CDCl_3$) $\delta$ –63.5 (s).

*5-Trifluoromethyl-2'-deoxycytidine (**2m**).*[38] The title compound was prepared following the general procedure above, starting from 5-iodo-2'-deoxycytidine **1m** (16 mg, 0.045 mmol) and $CuCF_3$-0.6HF (0.55 mL, 0.20 mmol). The reaction mixture was stirred at 50 ºC for 4 h. The residue was azeotropically dried with toluene and the crude purified by column chromatography (from 1:20 to 1:4 MeOH/$CH_2Cl_2$) to afford **2m** (9.5 mg, 71%) as a white solid. $^1$H NMR (400 MHz, $CD_3OD$) $\delta$ 8.83 (bs, 1H), 6.19 (appt, $J$ = $J$ = 5.9 Hz, 1H), 4.38 (m, 1H), 3.97 (m, 1H), 3.86 (dd, $J$ = 12.0 Hz, $J$ = 2.9 Hz, 1H), 3.74 (dd, $J$ = 12.0 Hz, $J$ = 2.9 Hz, 1H), 2.44 (ddd, $J$ = 13.6 Hz, $J$ = 6.3 Hz, $J$ = 5.0 Hz, 1H), 2.21 (m, 1H); $^{13}$C NMR (100.6 MHz, $CD_3OD$) $\delta$ 162.5, 157.0, 144.7 (q, $J$ = 6.1 Hz), 124.7 (q, $J$ = 268.9 Hz), 98.0 (q, $J$ = 34.5 Hz), 89.2, 88.3, 71.1, 61.9, 42.6; $^{19}$F NMR (376.5 MHz, $CD_3OD$) $\delta$ –63.8 (s).

*5-Trifluoromethyl-1,3-dimethyluracil (**2n**).*[47] The title compound was prepared following the general procedure above, starting from 5-iodo-1,3-dimethyluracil[48] **1n** (30 mg, 0.11 mmol) and $CuCF_3$-0.6HF (0.59 mL, 0.22 mmol). The reaction mixture was stirred at 50 ºC for 3 h. After standard work-up, the crude was purified by column chromatography (3:7 EtOAc/hexane) to afford **2n** (21.1 mg, 92%) as a white solid. $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.68 (bs, 1H), 3.48, 3.36 (s, 6H); $^{13}$C NMR (100.6 MHz, $CDCl_3$) $\delta$ 158.8, 151.0, 143.2 (q, $J$ = 5.9 Hz), 122.1 (q, $J$ = 268.8 Hz), 104.1 (q, $J$ = 32.9 Hz), 37.9, 28.1; $^{19}$F NMR (376.5 MHz, $CDCl_3$) $\delta$ –63.9 (s).

*6-Trifluoromethyl-1,3-dimethyluracil (**2o**).*[49] The title compound was prepared following the general procedure above, starting from 6-iodo-1,3-dimethyluracil[48] **1o** (84

mg, 0.31 mmol) and $CuCF_3$-0.6HF (1.66 mL, 0.62 mmol). The reaction mixture was stirred at room temperature for 5 h. After standard work-up, the crude was purified by column chromatography (1:4 EtOAc/hexane) to afford **2o** (63 mg, 97%) as a white solid. $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 6.22 (s, 1H), 3.49 (q, $J$ = 1.3 Hz, 3H), 3.34 (s, 3H; $^{13}$C NMR (100.6 MHz, $CDCl_3$) $\delta$ 161.1, 151.7, 140.6 (q, $J$ = 34.3 Hz), 119.6 (q, $J$ = 275.1 Hz), 102.7 (q, $J$ = 5.6 Hz), 32.6 (q, $J$ = 3.6 Hz), 28.5 ($CH_3$); $^{19}$F NMR (376.5 MHz, $CDCl_3$) $\delta$ –66.0 (s).

*5,6-bis(Trifluoromethyl)-1,3-dimethyluracil (**2p**).* The title compound was prepared following the general procedure above, starting from 5,6-diiodo-1,3-dimethyluracil[48] **1p** (22 mg, 0.056 mmol) and $CuCF_3$-0.6HF (0.59 mL, 0.22 mmol). The reaction mixture was stirred at 50 ºC for 5 h. After standard work-up, the crude was purified by column chromatography (3:7 EtOAc/hexane) to afford **2p** (14.3 mg, 92%) as a yellowish syrup. $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 3.57 (q, $J$ = 2.6 Hz, 3H), 3.39 (s, 3H); $^{13}$C NMR (100.6 MHz, $CDCl_3$) $\delta$ 157.1, 150.1, 144.2 (q, $J$ = 37.0 Hz), 121.0 (q, $J$ = 273.5 Hz), 119.2 (q, $J$ = 279.6 Hz), 107.9 (q, $J$ = 33.7 Hz), 35.8 (m), 29.0 (appd, $J$ = 2.1 Hz); $^{19}$F NMR (376.5 MHz, $CDCl_3$) $\delta$ –56.53 (q, $J$ = 14.8 Hz), –58.45 (qq, $J$ = 14.6, $J$ = 2.15 Hz); FTIR–ATR (neat, $\nu_{max}$) 2960, 2923, 2852, 1732, 1670, 1442, 1366, 1200, 1160; HRMS (EI) *m/z*: $[M]^+$ Calcd for $C_8H_6F_6N_2O_2^+$ 276.0333; Found 276.0339.

*3-(Trifluoromethyl)-1H-indole (**2q**).*[12d] The title compound was prepared following the general procedure above, starting from 3-iodo-1*H*-indole[50] **1q** (37 mg, 0.15 mmol) and $CuCF_3$ (0.82 mL, 0.3 mmol). The reaction mixture was stirred at room temperature for 2 h. After standard work-up, the crude was purified by column chromatography (1:9 EtOAc/hexane) to afford **2q** (24 mg, 86%) as a white solid. $^1$H NMR (400 MHz, $CDCl_3$,) $\delta$ 8.36 (bs, 1H), 7.78 (d, $J$ = 7.9 Hz, 1H), 7.56–7.52 (m, 1H), 7.44 (d, $J$ = 8.1 Hz, 1H), 7.35–7.23 (m, 2H); $^{13}$C NMR (100.6 MHz, $CDCl_3$) $\delta$ 135.9, 124.4 (q, $J$ = 5.3 Hz), 124.3 (q, $J$ = 265.9 Hz), 123.68, 123.66 (q, $J$ = 2.1 Hz), 121.7, 119.6, 111.7, 107.9 (q, $J$ = 36.9 Hz); $^{19}$F NMR (376.5 MHz, $CDCl_3$) $\delta$ –57.4 (s); FTIR–ATR (neat, $\nu_{max}$) 2940, 1747, 1666, 1455, 1371, 1328, 1213, 1151, 1112, 1046.

*5-Methoxy-3-(trifluoromethyl)-1H-indole (**2r**).* The title compound was prepared following the general procedure above, starting from 5-methoxy-3-iodo-1*H*-indole[50] **1r** (69 mg, 0.25 mmol) and $CuCF_3$ (1.6 mL, 0.5 mmol). The reaction mixture was stirred at room temperature for 2 h. After standard work-up, the crude was purified by column chromatography (1:9 EtOAc/hexane) to afford **2r** (40 mg, 75%) as a brownish solid. M.p: 62–65 ºC; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.30 (bs, 1H), 7.51–7.48 (m, 1H), 7.31

(d, $J$ = 8.9 Hz, 1H), 7.17 (bs, 1H), 6.95 (dd, $J$ = 8.9 Hz, $J$ = 2.4 Hz, 1H), 3.88 (s, 3H); $^{13}$C NMR (100.6 MHz, $CDCl_3$,) $\delta$ 155.4, 130.9, 124.8 (q, $J$ = 5.2 Hz), 124.5 (q, $J$ = 265.9 Hz), 124.2 (q, $J$ = 1.9 Hz), 114.4, 112.6, 107.5 (q, $J$ = 36.8 Hz), 100.7, 55.9; $^{19}$F NMR (376.5 MHz, $CDCl_3$) $\delta$ –57.5 (s); FTIR–ATR (neat, $\nu_{max}$) 3325, 2950, 2843, 1734, 1631, 1595, 1559, 1492, 1450, 1374, 1284, 1216, 1116, 1072, 993, 924, 727; HRMS (TOF ES$^+$) *m/z*: $[M+H]^+$ Calcd for $C_{10}H_9F_3NO^+$ 216.0631; Found 216.0632.

*5-Fluoro-3-(trifluoromethyl)-1H-indole (**2s**).* The title compound was prepared following the general procedure above, starting from 5-fluoro-3-iodo-1*H*-indole[50] **1s** (26 mg, 0.1 mmol) and $CuCF_3$ (0.56 mL, 0.2 mmol). The reaction mixture was stirred at room temperature for 2 h. After standard work-up, the crude was purified by column chromatography (1:9 EtOAc/hexane) to afford **2s** (15.6 mg, 77%) as a yellowish solid. M.p: 62–64 ºC; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.41 (bs, 1H), 7.59–7.55 (m, 1H), 7.44–7.39 (m, 1H), 7.36 (dd, $J$ = 8.9 Hz, $J$ = 4.3 Hz, 1H), 7.06 (td, $J$ = 9.0 Hz, $J$ = 2.5 Hz, 1H); $^{13}$C NMR (100.6 MHz, $CDCl_3$) $\delta$ 158.8 (d, $J$ = 237.5 Hz), 132.4, 125.9 (q, $J$ = 5.1 Hz), 124.2 (dq, $J$ = 10.6 Hz, $J$ = 2.2 Hz), 124.1 (q, $J$ = 266.0 Hz), 112.6, 112.5 (d, $J$ = 36.6 Hz), 108.1 (appdd, $J$ = 37.3 Hz, $J$ = 4.7 Hz), 104.9 (d, $J$ = 25.0 Hz); $^{19}$F NMR (376.5 MHz, $CDCl_3$) $\delta$ –57.7 (s, 3F), –121.7 (td, $J$ = 9.2 Hz, $J$ = 4.3 Hz, 1F); FTIR–ATR (neat, $\nu_{max}$) 3363, 2977, 1735, 1370, 1096, 992, 801; HRMS (TOF ES$^-$) *m/z*: $[M+H]^-$ Calcd for $C_9H_4F_4N^-$ 202.0285; Found 202.0285.

*tert-Butyl-2-(trifluoromethyl)-1H-indole-1-carboxylate (**2t**).*[51] The title compound was prepared following the general procedure above, starting from *tert*-butyl-2-iodo-1*H*-indole-1-carboxylate[52] **1t** (46 mg, 0.13 mmol) and $CuCF_3$ (0.73 mL, 0.32 mmol). The reaction mixture was stirred at room temperature for 16 h. After standard work-up, the crude was purified by column chromatography (hexane) to afford **2t** (36 mg, 94%) as a colorless syrup. $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.29 (bdq, $J$ = 8.6, $J$ = 0.8 Hz, 1H), 7.62 (d, $J$ = 7.8 Hz, 1H), 7.49–7.42 (m, 1H), 7.33–7.27 (m, 1H), 7.14 (s, 1H), 1.68 (s, 9H); $^{13}$C NMR (100.6 MHz, $CDCl_3$) $\delta$ 148.7, 137.8, 127.1, 127.0 (q, $J$ = 39.2 Hz) 126.6, 123.7, 122.1, 120.9 (q, $J$ = 267.8 Hz), 116.2, 113.6 (q, $J$ = 5.1 Hz), 85.6, 28.0; $^{19}$F NMR (376.5 MHz, $CDCl_3$) δ in ppm: –58.2 (s).

*tert-Butyl-5-fluoro-3-(trifluoromethyl)-1H-indole-1-carboxylate (**2u**).* The title compound was prepared following the general procedure above, starting from *tert*-butyl-5-fluoro-3-iodo-1*H*-indole-1-carboxylate[50] **1u** (1.88 g, 5.2 mmol) and $CuCF_3$ (22 mL, 8.32 mmol). The reaction mixture was stirred 16 h at room temperature and 8 h at 50 ºC. After standard work-up, the crude was purified by column chromatography

(hexane) to afford **2u** (1.50 g, 95%) as a white solid. M.p: 81–83 ºC; $^{1}$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.13 (dd, $J$ = 9.1 Hz, $J$ = 4.5 Hz, 1H), 7.97 (bd, $J$ = 1.2 Hz, 1H), 7.34–7.28 (m, 1H), 7.10 (td, $J$ = 9.1 Hz, $J$ = 2.6 Hz, 1H), 1.71 (s, 9H); $^{13}$C NMR (100.6 MHz, $CDCl_3$) $\delta$ 159.7 (d, $J$ = 241.2 Hz), 148.7, 131.8, 127.5 (q, $J$ = 5.4 Hz), 126.3 (dq, $J$ = 10.5 Hz, $J$ = 1.8 Hz), 123.2 (q, $J$ = 267.1 Hz), 116.8 (d, $J$ = 9.2 Hz), 113.7 (d, $J$ = 25.2 Hz), 111.4 (qd, $J$ = 37.3 Hz, $J$ = 4.2 Hz), 105.4 (d, $J$ = 25.2 Hz), 85.6, 28.1; $^{19}$F NMR (376.5 MHz, $CDCl_3$) $\delta$ –59.5 (s, 3F), –118.7 (m, 1F); FTIR–ATR (neat, $\nu_{max}$) 3133, 2982, 1739, 1454, 1371, 1251, 1138, 1093, 844; HRMS (EI) *m/z*: $[M]^+$ Calcd for $C_{14}H_{13}F_4NO_2^+$ 303.0882; Found 303.0872.

*6-Fluoro-3-(trifluoromethyl)-4H-chromen-4-one (**2v**).* The title compound was prepared following the general procedure above, starting from 6-fluoro-3-iodo-4*H*-chromen-4-one **1v** (54 mg, 0.186 mmol) and $CuCF_3$-0.6HF (0.98 mL, 0.36 mmol). The reaction mixture was stirred at room temperature for 15 h. After standard work-up, the crude was purified by column chromatography (1:9 EtOAc/hexane) to afford **2v** (34.5 mg, 80%) as a white solid. M.p: 80–82 ºC; $^{1}$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.32 (q, $J$ = 1.3 Hz, 1H), 7.91 (dd, $J$ = 7.9 Hz, $J$ = 3.0 Hz, 1H), 7.55 (ddd, $J$ = 9.2 Hz, $J$ = 4.2 Hz, $J$ = 0.4 Hz, 1H), 7.48 (ddd, $J$ = 9.2 Hz, $J$ = 7.9 Hz, $J$ = 3.0 Hz, 1H); $^{13}$C NMR (100.6 MHz, $CDCl_3$) $\delta$ 172.2, 160.3 (q, $J$ = 249.6 Hz), 156.0 (q, $J$ = 6.8 Hz), 152.3 (d, $J$ = 2.1 Hz), 125.8 (d, $J$ = 6 Hz), 123.2 (d, $J$ = 25.5 Hz), 122.2 (q, $J$ = 272.3 Hz), 120.7 (d, $J$ = 8.2 Hz), 115.6 (appd, $J$ = 31.1Hz), 111.3 (d, $J$ =24.2 Hz); $^{19}$F NMR (376.5 MHz, $CDCl_3$) $\delta$ –64.5 (s, 3F), –112.7 (m, 1F); FTIR–ATR (neat, $\nu_{max}$) 3086, 2925, 1655, 1479, 1389, 1333, 1139, 1101, 961, 831, 716; HRMS (TOF ES$^+$) *m/z*: $[M+H]^+$ Calcd for $C_{10}H_5F_4O_2^+$ 233.0220; Found 233.0217.

**Hydrogenation/deacetylation of 2e.** 10% Pd/C (90 mg, 0.08 mmol Pd) was added to a solution of **2e** (55 mg, 0.162 mmol) in dry and deoxygenated methanol (1mL) at room temperature. The mixture was stirred under $H_2$ (10 atm) at the same temperature for 72 h, filtered through a short path of Celite® 545, and concentrated under reduced pressure. The crude was redissolved in MeOH (2 mL) and NaOMe (4.32 mg, 0.08 mmol) was added at room temperature. The reaction mixture was stirred at the same temperature for 12 h and neutralized with Dowex® ($H^+$ 50WX8-200). The ion exchanger was filtered off and washed with MeOH. The crude material was purified by column chromatography (1:9 MeOH/EtOAc) to afford 1,5-anhydro-2-deoxy-2-trifluoromethyl-D-talitol **5e** (31.0 mg, 89% over two steps) as a white solid. $R_f$ (1:9 MeOH/$CH_2Cl_2$): 0.15; m.p: 137–139 ºC; $[\alpha]_D^{20}$ +49.3 (*c* 0.1, MeOH); $^{1}$H NMR (400 MHz, $CD_3OD$) $\delta$ 4.81 (appt, $J$ = 3.2 Hz,

1H), 4.15 (dd, $J$ = 12.7 Hz, $J$ = 8.6 Hz, 1H), 4.03 (dd, $J$ = 11.4 Hz, $J$ = 10.4 Hz, 1H), 3.87 (ddd, $J$ = 8.6 Hz, $J$ = 6.1 Hz, $J$ = 2.8 Hz, 1H), 3.79 (dd, $J$ = 6.1 Hz, $J$ = 3.2 Hz, 1H), 3.73 (dd, $J$ = 12.7 Hz, $J$ = 2.8 Hz, 1H), 3.64 (dd, $J$ = 11.4 Hz, $J$ = 4.1 Hz, 1H), 4.63–4.56 (m, 1H); $^{13}$C NMR (100.6 MHz, $CD_3OD$) $\delta$ 125.2 (q, $J$ = 280.1 Hz), 79.3, 66.6, 69.3 (q, $J$ = 2.3 Hz), 59.1, 55.9 (q, $J$ = 3.1 Hz), 45.8 (q, $J$ = 25.8 Hz); $^{19}$F NMR (376.5 MHz, $CD_3OD$) $\delta$ –68.0 (d, $J$ = 9.3 Hz); FTIR–ATR (neat, $\nu_{max}$) 3366, 2926, 1664, 1398, 1325, 1262, 1110, 1036; HRMS (TOF ES$^+$) *m/z*: $[M+Na]^+$ Calcd for $C_7H_{11}F_3NaO_4^+$ 239.0502; Found 239.0506.

## ASSOCIATED CONTENT

**Supporting Information.** $^1$H, $^{13}$C, and $^{19}$F NMR spectra for all new compounds and additional optimization and Cu(I) coordination experiments with 3-iodoindole **1q**. X-ray crystallographic analysis of **2c** and **2u**. This material is available free of charge via the Internet at http://pubs.acs.org.

## AUTHOR INFORMATION

**Corresponding Author**

*E-mail: omar.boutureira@urv.cat

**Notes**

The authors declare no competing financial interest.

## ACKNOWLEDGEMENTS

We thank the European Commission (Marie Curie CIG to O.B.), the Spanish Government (CTQ2014-58664-R and RYC-2015-17705), the European Regional Development Fund, and the Universitat Rovira i Virgili (Martí Franquès Research Fellowship Programme to J.M.) for financial support. We also thank Dr. Vladimir V. Grushin for providing the fluoroform-derived $CuCF_3$ reagent and for helpful discussions and Dr. Eddy Martin (ICIQ) for the crystallographic studies. O.B. is a Ramón y Cajal Fellow.

## REFERENCES

(1) (a) Landelle, G.; Panossian, A.; Pazenok, S.; Vors, J.-P.; Leroux, F. R. Recent advances in transition metal-catalyzed Csp$^2$-monofluoro-, difluoro-,

perfluoromethylation and trifluoromethylthiolation. *Beilstein J. Org. Chem*. **2013,** *9,* 2476–2536. (b) Wu, X.-F.; Neumann, H.; Beller, M. Recent developments on the trifluoromethylation of (hetero)arenes. *Chem. Asian J.* **2012**, *7*, 1744–1754.

(2) (a) Li, M.; Xue, X.-S.; Guo, J.; Wang, Y.; Cheng, J.-P. An energetic guide for estimating trifluoromethyl cation donor abilities of electrophilic trifluoromethylating reagents: computations of X–$CF_3$ bond heterolytic dissociation enthalpies. *J. Org. Chem.* **2016**, *81*, 3119–3126. (b) Charpentier, J.; Früh, N.; Togni, A. Electrophilic trifluoromethylation by use of hypervalent iodine reagents. *Chem. Rev*. **2014**, *115*, 650–682.

(3) (a) Yang, X.; Wu, T.; Phipps, R. J.; Toste, F. D. Advances in catalytic enantioselective fluorination, mono-, di-, and trifluoromethylation, and trifluoromethylthiolation reactions. *Chem. Rev.* **2015**, *115*, 826–870. (b) Wang, S.-M.; Han, J.-B.; Zhang, C.-P.; Qin, H.-L.; Xiao, J.-C. An overview of reductive trifluoromethylation reactions using electrophilic '$^{+}CF_3$' reagents. *Tetrahedron* **2015**, *71*, 7949–7976.

(4) (a) Lefebvre, Q. Toward sustainable trifluoromethylation reactions: sodium triflinate under the spotlight. *Synlett* **2017**, *28*, 19–23. (b) Chatterjee, T.; Iqbal, N.; You, Y.; Cho, E. J. Controlled fluoroalkylation reactions by visible-light photoredox catalysis. *Acc. Chem. Res.* **2016**, *49*, 2284–2294. (c) Koike, T.; Akita, M. Fine design of photoredox systems for catalytic fluoromethylation of carbon–carbon multiple bonds. *Acc. Chem. Res.* **2016**, *49*, 1937–1945. (d) Koike, T.; Akita, M. Trifluoromethylation by visible-light-driven photoredox catalysis. *Top. Catal*. **2014**, *57*, 967–974. (e) Zhang, C. Application of Langlois' reagent in trifluoromethylation reactions. *Adv. Synth. Catal*. **2014**, *356*, 2895–2906. (f) Studer, A. A "Renaissance" in radical trifluoromethylation. *Angew. Chem. Int. Ed*. **2012**, *51*, 8950–8958.

(5) (a) Egami, H.; Sodeoka, M. Trifluoromethylation of alkenes with concomitant introduction of additional functional groups. *Angew. Chem. Int. Ed*. **2014**, *53*, 8294–8308. (b) Barata-Vallejo, S.; Lantaño, B.; Postigo, A. Recent advances in trifluoromethylation reactions with electrophilic trifluoromethylating reagents.. *Chem. - Eur. J.* **2014**, *20*, 16806–16829. (c) Besset, T.; Poisson, T.; Pannecoucke, X. Recent progress in direct introduction of fluorinated groups on alkenes and alkynes by means of C–H bond functionalization. *Chem. - Eur. J.* **2014**, *20*,

16830–16845. (d) Liu, G.; Chen, P. Recent advances in transition-metal-catalyzed trifluoromethylation and related transformations. *Synthesis* **2013**, *45*, 2919–2939. (e) Hollingworth, C.; Gouverneur, V. Transition metal catalysis and nucleophilic fluorination. *Chem. Commun.* **2012**, *48*, 2929–2942. (f) Tomashenko, O. A.; Grushin, V. V. Aromatic trifluoromethylation with metal complexes. *Chem. Rev.* **2011**, *111*, 4475–4521. (g) Furuya, T.; Kamlet, A. S.; Ritter, T. Catalysis for fluorination and trifluoromethylation. *Nature* **2011**, *473*, 470–477.

(6) (a) Liu, T.; Shen, Q. Progress in copper-mediated formation of trifluoromethylated arenes. *Eur. J. Org. Chem.* **2012**, 6679–6687. (b) García-Monforte, M. A.; Martínez-Salvador, S.; Menjón, B. The trifluoromethyl group in transition metal chemistry. *Eur. J. Inorg. Chem.* **2012**, 4945–4966.

(7) (a) Prieto, A.; Baudoin, O.; Bouyssi, D.; Monteiro, N. Electrophilic trifluoromethylation of carbonyl compounds and their nitrogen derivatives under copper catalysis. *Chem. Commun.* **2016**, *52*, 869–881. (b) Ando, A.; Kumadaki, I.; Sato, K.; Tarui, A.; Omote, M. Trifluoromethylation of organic compounds and related reactions. *Synthesis* **2010**, 1865–1882.

(8) (a) Usachev, B. I. 1-/2-/3-Fluoroalkyl-substituted indoles, promising medicinally and biologically beneficial compounds: Synthetic routes, significance and potential applications. *J. Fluorine Chem*. **2016**, *185*, 118–167. (b) Jacquet, J.; Blanchard, S.; Derat, E.; Desage-El Murr, M.; Fensterbank, L. Redox-ligand sustains controlled generation of $CF_3$ radicals by well-defined copper complex. *Chem. Sci.* **2016**, *7*, 2030–2036. (c) Zheng, J.; Lin, J.-H.; Deng, X.-Y.; Xiao, J.-C. 1,8-Diazabicyclo[5.4.0]undec-7-ene (DBU)-promoted decomposition of difluorocarbene and the subsequent trifluoromethylation. *Org. Lett.* **2015**, *17*, 532–535. (d) Seo, S.; Taylor, J. B.; Greaney, M. F. Silver-catalysed trifluoromethylation of arenes at room temperature. *Chem. Commun.* **2013**, *49*, 6385–6387. (e) Iqbal, N.; Choi, S.; Ko, E.; Cho, E. J. Trifluoromethylation of heterocycles via visible light photoredox catalysis. *Tetrahedron Lett.* **2012**, *53*, 2005–2008. (f) Mejía, E. ; Togni, A. Rhenium-catalyzed trifluoromethylation of arenes and heteroarenes by hypervalent iodine reagents. *ACS Catal.* **2012**, *2*, 521–527. (g) Shimizu, R.; Egami, H.; Nagi, T.; Chae, J.; Hamashima, Y.; Sodeoka, M. Direct *C*2-trifluoromethylation of indole derivatives catalyzed by copper acetate. *Tetrahedron Lett.* **2010**, *51*, 5947–5949. (h) Kino, T.; Nagase, Y.; Ohtsuka, Y.;

Yamamoto, K.; Uraguchi, D.; Tokuhisa, K.; Yamakawa, T. Trifluoromethylation of various aromatic compounds by $CF_3I$ in the presence of Fe(II) compound, $H_2O_2$ and dimethylsulfoxide. *J. Fluorine Chem*. **2010**, *131*, 98–105.

(9) (a) Rey-Rodriguez, R.; Retailleau, P.; Bonnet, P.; Gillaizeau, I. Iron-catalyzed trifluoromethylation of enamide. *Chem. - Eur. J.* **2015**, *21*, 3572–3575. (b) Wang, B.; Xiong, D.-C.; Ye, X.-S. Direct C–H trifluoromethylation of glycals by photoredox catalysis. *Org. Lett.* **2015**, *17*, 5698−5701. (c) Fang, Z.; Ning, Y.; Mi, P.; Liao, P.; Bi, X. Catalytic C–H *α*-trifluoromethylation of *α,β*-unsaturated carbonyl compounds. *Org. Lett.* **2014,** *16*, 1522–1525. (d) Belhomme, M.-C.; Poisson, T.; Pannecoucke, X. Copper catalyzed *β*-difluoroacetylation of dihydropyrans and glycals by means of direct C–H functionalization. *Org. Lett.* **2013**, *15*, 3428–3431. (e) Feng, C.; Loh, T.-P. Copper-catalyzed olefinic trifluoromethylation of enamides at room temperature. *Chem. Sci.* **2012**, *3*, 3458–3462.

(10) Ji, Y.; Brueckl, T.; Baxter, R. D.; Fujiwara, Y.; Seiple, I. B.; Su, S.; Blackmond, D. G.; Baran, P. S. Innate C–H trifluoromethylation of heterocycles. *Proc. Natl. Acad. Sci. USA* **2011**, *108*, 14411–14415.

(11) (a) Li, Y.; Wu, L.; Neumann, H.; Beller, M. Copper-catalyzed trifluoromethylation of aryl- and vinylboronic acids with generation of $CF_3$-radicals. *Chem. Commun.* **2013**, *49*, 2628–2630. (b) Ye, Y.; Sanford, M. S. Merging visible-light photocatalysis and transition-metal catalysis in the copper-catalyzed trifluoromethylation of boronic acids with $CF_3I$. *J. Am. Chem. Soc.* **2012**, *134*, 9034–9037. (c) Liu, T.; Shen, Q. Copper-catalyzed trifluoromethylation of aryl and vinyl boronic acids with an electrophilic trifluoromethylating reagent. *Org. Lett.* **2011**, *13*, 2342–2345.

(12) (a) Zhang, X.; Wang, J.; Wan, Z. New reagent for highly efficient synthesis of trifluoromethyl-substituted arenes and heteroarenes. *Org. Lett.* **2015**, *17*, 2086–2089. (b) Chen, M.; Buchwald, S. L. Rapid and efficient trifluoromethylation of aromatic and heteroaromatic compounds using potassium trifluoroacetate enabled by a flow system. *Angew. Chem. Int. Ed.* **2013**, *52*, 11628–11631. (c) Liu, T.; Shao, X.; Wu, Y.; Shen, Q. Highly selective trifluoromethylation of 1,3-disubstituted arenes through iridium-catalyzed arene borylation. *Angew. Chem. Int. Ed.* **2012**, *51*, 540–543. (d) Zhang, C.-P.; Wang, Z.-L.; Chen, Q.-Y.; Zhang,

C.-T.; Gu, Y.-C.; Xiao, J.-C. Copper-mediated trifluoromethylation of heteroaromatic compounds by trifluoromethyl sulfonium salts. *Angew. Chem. Int. Ed*. **2011**, *50*, 1896–1900. (e) Nussbaumer, P.; Petranyi, G.; Stuetz, A. Synthesis and structure-activity relationships of benzo[*b*]thienylallylamine antimycotics. *J. Med. Chem.* **1991**, *34*, 65–73.

(13) (a) Qing, F.-L.; Zhang, X.; Peng, Y. The trifluoromethylation of 1,1-dibromo-1-alkenes using trifluoromethylcopper ($CF_3Cu$) generated in situ from methyl fluorosulfonyldifluoroacetate. *J. Fluorine Chem.* **2001**, *111*, 185–187. (b) Zhang, X.; Qing, F.-L.; Yu, Y. Synthesis of 2‘,3‘-dideoxy-2‘-trifluoromethylnucleosides from *α*-trifluoromethyl-*α*,*β*-unsaturated ester. *J. Org. Chem.* **2000**, *65*, 7075–7082. (c) Fei, X.-S.; Tian, W.-S.; Chen, Q.-Y. New, convenient route for trifluoromethylation of steroidal molecules. *J. Chem. Soc. Perkin Trans. 1* **1998**, 1139–1142. (d) Duan, J.; Dolbier, W. R.; Chen, Q.-Y. A new and improved synthesis of *trans*-1,2-diiodoalkenes and their stereospecific and highly regioselective trifluoromethylation. *J. Org. Chem.* **1998**, *63*, 9486–9489. (e) Urata, H.; Fuchikami, T. A novel and convenient method for trifluoromethylation of organic halides using $CF_3SiR'_3$/KF/Cu(I) system. *Tetrahedron Lett.* **1991**, *32*, 91–94.

(14) Grushin, V.; Lishchynskyi, A.; Mazloomi, Z. Trifluoromethylation and pentafluoroethylation of vinylic halides with low-cost $R_fH$-derived $CuR_f$ ($R_f = CF_3, C_2F_5$). *Synlett* **2015**, *26*, 45–50.

(15) (a) Hafner, A.; Bräse, S. Efficient trifluoromethylation of activated and non-activated alkenyl halides by using (trifluoromethyl)trimethylsilane. *Adv. Synth. Catal.* **2011**, *353*, 3044–3048. (b) Nowak, I.; Robins, M. J. Trifluoromethylation of alkenyl bromides and iodides (including 5-iodouracils) with $(CF_3)_2Hg$ and Cu (“trifluoromethylcopper”). *J. Org. Chem.* **2007**, *72*, 2678–2681.

(16) (a) Grushin, V. V. Fluoroform as a feedstock for high-value fluorochemicals: novel trends and recent developments. *Chim. Oggi*. **2014**, *32*, 81–90. (b) Mazloomi, Z.; Bansode, A.; Benavente, P.; Lishchynskyi, A.; Urakawa, A.; Grushin, V. V. Continuous process for production of $CuCF_3$ via direct cupration of fluoroform. *Org. Process Res. Dev.* **2014**, *18*, 1020–1026. (c) Konovalov, A. I.; Benet-Buchholz, J.; Martin, E.; Grushin, V. V. The critical effect of the countercation in the direct cupration of fluoroform with $[Cu(OR)_2]^-$. *Angew.*

*Chem. Int. Ed.* **2013**, *52*, 11637–11641. (d) Zanardi, A.; Novikov, M. A.; Martin, E.; Benet-Buchholz, J.; Grushin, V. V. Direct cupration of fluoroform. *J. Am. Chem. Soc.* **2011***, 133,* 20901–20913.

(17) This term refers to those complexes lacking externally added, dative P- or N-ligands and typically involves preparations with oxygenated coordinating solvents such as DMF and DMI, among others.

(18) (a) Lishchynskyi, A.; Berthon, G.; Grushin, V. V. Trifluoromethylation of arenediazonium salts with fluoroform-derived $CuCF_3$ in aqueous media. *Chem. Commun*. **2014**, *50*, 10237–10240. (b) Novák, P.; Lishchynskyi, A.; Grushin, V. V. Fluoroform-derived $CuCF_3$ for low-cost, simple, efficient, and safe trifluoromethylation of aryl boronic acids in air. *Angew. Chem. Int. Ed*. **2012**, *51*, 7767–7770. (c) Novák, P.; Lishchynskyi, A.; Grushin, V. V. Trifluoromethylation of *α*-haloketones. *J. Am. Chem. Soc*. **2012**, *134*, 16167–16170.

(19) Lishchynskyi, A.; Novikov, M. A.; Martin, E.; Escudero-Adán, E. C.; Novák, P.; Grushin, V. V. Trifluoromethylation of aryl and heteroaryl halides with fluoroform-derived $CuCF_3$: scope, limitations, and mechanistic features. *J. Org. Chem*. **2013**, *78*, 11126–11146.

(20) (a) Ye, Y.; Cheung, K. P. S.; He, L.; Tsui, G. C. Domino cyclization/trifluoromethylation of 2-alkynylanilines using fluoroform-derived $CuCF_3$: synthesis of 3-(trifluoromethyl)indoles. *Org. Chem. Front.* **2018**, *5*, 1511–1515. (b) Ye, Y.; Cheung, K. P. S.; He, L.; Tsui, G. C. Synthesis of 2‑(trifluoromethyl)indoles via domino trifluoromethylation/cyclization of 2‑alkynylanilines. *Org. Lett.* **2018**, *20*, 1676–1679. (c) He, L.; Tsui, G. C. Fluoroform-derived $CuCF_3$ for trifluoromethylation of terminal and TMS-protected alkynes. *Org. Lett.* **2016**, *18*, 2800–2803.

(21) Liu, X.; Xu, C.; Wang, M.; Liu, Q. Trifluoromethyltrimethylsilane: nucleophilic trifluoromethylation and beyond. *Chem. Rev.* **2014**, *115*, 683–730.

(22) (a) Moon, J.; Lee, S. Palladium catalyzed-dehalogenation of aryl chlorides and bromides using phosphite ligands. *J. Organomet. Chem.* **2009**, *694*, 473–477. (b) Demchuk, O.; Snieckus, V.; Yoruk, B.; Blackburn, T. A mixed naphthyl-phenyl phosphine ligand motif for Suzuki, Heck, and hydrodehalogenation reactions. *Synlett* **2006**, 2908–2913. (c) Navarro, O.; Kaur, H.; Mahjoor, P.; Nolan, S. P. Cross-coupling and dehalogenation reactions catalyzed by (*N*-heterocyclic

carbene)Pd(allyl)Cl complexes. *J. Org. Chem*. **2004**, *69*, 3173–3180. (d) Kobayashi, Y.; Yamamoto, K.; Asai, T.; Nakano, M.; Kumadaki, I. Studies on organic fluorine compounds. Part 35. Trifluoromethylation of pyrimidine- and purine-nucleosides with trifluoromethyl–copper complex. *J. Chem. Soc., Perkin Trans. 1* **1980**, 2755–2761.

(23) (a) Cobo, I.; Matheu, M. I.; Castillón, S.; Boutureira, O.; Davis, B. G. Phosphine-free Suzuki–Miyaura cross-coupling in aqueous media enables access to 2-*C*-aryl-glycosides. *Org. Lett.* **2012**, *14*, 1728–1731. (b) Rodríguez, M. A.; Boutureira, O.; Díaz, Y.; Matheu, M. I.; Castillón, S.; Seeberger, P. H. Synthesis of 2-iodoglycals, glycals, and 1,1‘-disaccharides from 2-deoxy-2-iodopyranoses under dehydrative glycosylation conditions. *J. Org. Chem.* **2007**, *72*, 8998–9001.

(24) (a) Vankar, Y. D.; Linker, T. Recent developments in the synthesis of 2-*C*-branched and 1,2-annulated carbohydrates. *Eur. J. Org. Chem.* **2015**, 7633–7642. (b) Srinivas, B.; Reddy, T. R.; Krishna, P. R.; Kashyap, S. Copper(II) triflate as a mild and efficient catalyst for Ferrier glycosylation: synthesis of 2,3-unsaturated *O*-glycosides. *Synlett* **2014**, *25*, 1325–1330. (c) Gómez, A. M.; Lobo, F.; Uriel, C.; López, J. C. Recent developments in the Ferrier rearrangement. *Eur. J. Org. Chem.* **2013**, 7221–7262.

(25) (a) Preshlock, S.; Tredwell, M.; Gouverneur, V. $^{18}$F-Labeling of arenes and heteroarenes for applications in positron emission tomography. *Chem. Rev.* **2016**, *116*, 719–766. (b) Van der Born, D.; Sewing, C.; Herscheid, J. K. D. M.; Windhorst, A. D.; Orru, R. V. A.; Vugts, D. J. A universal procedure for the [$^{18}$F]trifluoromethylation of aryl iodides and aryl boronic acids with highly improved specific activity. *Angew. Chem. Int. Ed.* **2014**, *53*, 11046–11050.

(26) Chalmers, A. A.; Hall, R. H. Conformational studies of D-glycals by $^{1}$H nuclear magnetic resonance spectroscopy. *J. Chem. Soc. Perkin Trans. 2*, **1974**, 728–732.

(27) Chen, Q.-Y.; Wu, S.-W. Methyl fluorosulphonyldifluoroacetate; a new trifluoromethylating agent. *J. Chem. Soc., Chem. Commun.* **1989**, 705–706.

(28) Morimoto, H.; Tsubogo, T.; Litvinas, N. D.; Hartwig, J. F. A broadly applicable copper reagent for trifluoromethylations and perfluoroalkylations of aryl iodides and bromides. *Angew. Chem. Int. Ed.* **2011**, *50*, 3793–3798.

(29) Kütt, A.; Movchun, V.; Rodima, T.; Dansauer, T.; Rusanov, E. B.; Leito, I.; Kaljurand, I.; Koppel, J.; Pihl, V.; Koppel, I.; Ovsjannikov, G.; Toom, L.;

Mishima, M.; Medebielle, M.; Lork, E.; Röschenthaler, G.-V.; Koppel, I. A.; Kolomeitsev, A. A. Pentakis(trifluoromethyl)phenyl, a sterically crowded and electron-withdrawing group: synthesis and acidity of pentakis(trifluoromethyl)benzene, -toluene, -phenol, and -aniline. *J. Org. Chem.* **2008**, *73*, 2607–2620.

(30) Wiemers, D. M.; Burton, D. J. Pregeneration, spectroscopic detection and chemical reactivity of (trifluoromethyl)copper, an elusive and complex species. *J. Am. Chem. Soc.* **1986**, *108*, 832–834.

(31) Lemieux, R. U.; Nagabhushan, T. L.; O'Neill, I. K. The reactions of nitrosyl chloride and dinitrogen tetroxide with acetylated glycals. Acetylated 2-deoxy-2-nitroso-α-D-hexopyranosyl chlorides and nitrates and acetylated 2-nitroglycals. *Can. J. Chem.* **1968**, *46*, 413–418.

(32) CCDC 1533215 **2c** and 1533216 **2u** contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

(33) Dohi, H.; Périon, R.; Durka, M.; Bosco, M.; Roué, Y.; Moreau, F.; Grizot, S.; Ducruix, A.; Escaich, S.; Vincent, S. P. Synthesis of ADP-2-fluoroheptose, an inhibitor of the LPS biosynthesis. *Chem. - Eur. J.* **2008**, *14*, 9530–9539.

(34) Konovalov, A. I.; Lishchynskyi, A.; Grushin, V. V. Mechanism of trifluoromethylation of aryl halides with $CuCF_3$ and the ortho effect. *J. Am. Chem. Soc.* **2014**, *136*, 13410–13425.

(35) (a) Neumann, C. N.; Ritter, T. Late-stage fluorination: fancy novelty or useful tool? *Angew. Chem. Int. Ed.* **2015**, *54*, 3216–3221. (b) Campbell, M. G.; Ritter, T. Late-stage fluorination: from fundamentals to application. *Org. Process Res. Dev.* **2014**, *18*, 474–480.

(36) De Clercq, E. Antiviral drugs in current clinical use. *J. Clin. Virol.* **2004**, *30*, 115–133.

(37) Mekras, J. A.; Boothman, D. A.; Greer, S. B. Use of 5-trifluoromethyldeoxycytidine and tetrahydrouridine to circumvent catabolism and exploit high levels of cytidine deaminase in tumors to achieve DNA- and target-directed therapies. *Cancer Res.* **1985**, *45*, 5270–5280.

(38) Musumeci, D.; Irace, C.; Santamaria, R.; Montesarchio, D. Trifluoromethyl derivatives of canonical nucleosides: synthesis and bioactivity studies. *Med.*

*Chem. Commun.* **2013**, *4*, 1405–1410.

(39) Fujiwara, T.; O'Hagan, D. Successful fluorine-containing herbicide agrochemicals. *J. Fluorine Chem*. **2014**, *167*, 16–29.

(40) (a) Zhou, Y.; Wang, J.; Gu, Z.; Wang, S.; Zhu, W.; Aceña, J. L.; Soloshonok, V. A.; Izawa, K.; Liu, H. Next generation of fluorine-containing pharmaceuticals, compounds currently in phase II–III clinical trials of major pharmaceutical companies: new structural trends and therapeutic areas. *Chem. Rev.* **2016**, *116*, 422–518. (b) Yerien, D. E.; Bonesi, S.; Postigo, A. Fluorination methods in drug discovery. *Org. Biomol. Chem.* **2016**, *14*, 8398–8427. (c) Richardson, P. Fluorination methods for drug discovery and development. *Expert Opin. Drug Discov.* **2016**, *11*, 983–999. (d) Gillis, E. P.; Eastman, K. J.; Hill, M. D.; Donnelly, D. J.; Meanwell, N. A. Applications of fluorine in medicinal chemistry. *J. Med. Chem.* **2015**, *58*, 8315–8359. (e) Wang, J.; Sánchez-Roselló, M.; Aceña, J. L.; del Pozo, C.; Sorochinsky, A. E.; Fustero, S.; Soloshonok, V. A.; Liu, H. Fluorine in pharmaceutical industry: fluorine-containing drugs introduced to the market in the last decade (2001–2011). *Chem. Rev*. **2014**, *114*, 2432–2506. (f) Zhu, W.; Wang, J.; Wang, S.; Gu, Z.; Aceña, J. L.; Izawa, K.; Liu, H.; Soloshonok, V. A. Recent advances in the trifluoromethylation methodology and new $CF_3$-containing drugs. *J. Fluorine Chem*. **2014**, *167*, 37–54. (g) Purser, S.; Moore, P. R.; Swallow, S.; Gouverneur, V. Fluorine in medicinal chemistry. *Chem. Soc. Rev*. **2008**, *37*, 320–330. (h) Hagmann, W. K. The many roles for fluorine in medicinal chemistry. *J. Med. Chem*. **2008**, *51*, 4359–4369. (i) Kirk, K. L. Fluorine in medicinal chemistry: recent therapeutic applications of fluorinated small molecules. *J. Fluorine Chem*. **2006**, *127*, 1013–1029.

(41) Kunz, H.; Rueck, K. New bicyclic oxazolidinone carbohydrate derivatives useful in selective synthesis of diastereomers of chiral *N*-acyl analogues. *Ger. Offen.* DE 4113327 A1 19921029, 1992.

(42) Matsushita, Y.; Sugamoto, K.; Kita, Y.; Matsui, T. Silica gel-catalyzed *β*-*O*-glucosylation of alcohols with 1,2-anhydro-3,4,6-tri-*O*-pivaloyl-*α*-D-glucopyranose. *Tetrahedron Lett.* **1997**, *38*, 8709–8712.

(43) Dharuman, S.; Vankar, Y. D. *N*-Halosuccinimide/$AgNO_3$-efficient reagent systems for one-step synthesis of 2-haloglycals from glycals: application in the

synthesis of 2C-branched sugars via Heck coupling reactions. *Org. Lett.* **2014**, *16*, 1172–1175.

(44) Friesen, R. W.; Loo, R. W.; Sturino, C. F. The preparation of *C*-aryl glucals via palladium-catalyzed cross-coupling methods. *Can. J. Chem*. **1994**, *72*, 1262–1272.

(45) Tanabe, Y.; Matsuo, N.; Ohno, N. Direct perfluoroalkylation including trifluoromethylation of aromatics with perfluoro carboxylic acids mediated by xenon difluoride. *J. Org. Chem.* **1988,** *53*, 4582–4585.

(46) Hudson, R. H. E.; Ghorbani-Choghamarani, A. Oligodeoxynucleotides incorporating structurally simple 5-alkynyl-2′-deoxyuridines fluorometrically respond to hybridization. *Org. Biomol. Chem.* **2007**, *5*, 1845–1848.

(47) Serizawa, H.; Aikawa, K.; Mikami, K. Direct synthesis of a trifluoromethyl copper reagent from trifluoromethyl ketones: application to trifluoromethylation. *Chem. - Eur. J*. **2013**, *19*, 17692–17697.

(48) Saito, I.; Ikehira, H.; Matsuura, T. Photochemistry of 5- and 6-iodouracils in the presence of allylsilanes and alkenes. A convenient route to C5- and C6-substituted uracils. *J. Org. Chem.* **1986**, *51*, 5148–5153.

(49) Hocek, M.; Ćerňová, M.; Pohl, R.; Klepetářová, B. C–H trifluoromethylations of 1,3-dimethyluracil and reactivity of the Products in C–H arylations. *Heterocycles*, **2014**, *89*, 1159–1171.

(50) Tasch, B. O. A.; Merkul, E.; Müller, T. J. J. One-pot synthesis of diazine-bridged bisindoles and concise synthesis of the marine alkaloid hyrtinadine A. *Eur. J. Org. Chem*. **2011**, 4532–4535.

(51) Senecal, T. D.; Parsons, A. T.; Buchwald, S. L. Room temperature aryl trifluoromethylation via copper-mediated oxidative cross-coupling. *J. Org. Chem.* **2011**, *76*, 1174–1176.

(52) Kline, T. Preparation of 2-iodotryptamine and 2-iodo-5-methoxytryptamine. *J. Heterocyclic Chem*. **1985**, *22*, 505–509.