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Short Communication

Synthesis of trifluoromethyl moieties by late-stage copper (I) mediated nucleophilic fluorination

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ABSTRACT

The nucleophilic fluorination of bromodifluoromethyl derivatives mediated by the complex $(PPh_3)_3CuF$ is described. Under the reaction conditions, different trifluoroacetates, trifluoroketones, trifluoroarenes and trifluoroacetamides were obtained in good yields.

1. Introduction

The introduction of a fluorine atom into a moiety can considerably affect the physicochemical properties of bioactive molecules. In particular, the trifluoromethyl group (CF_3) is an important substituent in medicinal chemistry that is widely represented in drugs and druglike molecules [1]. Late-stage introduction of fluorine into organic compounds has kept the attention of synthetic organic chemists in the last years due to the applicability of the artificial ^{18}F isotope in positron emission tomography (PET) [2–4]. While an enormous amount of new fluorination reactions have been developed [5], late-stage nucleophilic introduction of fluorine still remains as a challenge [2]. This could be attributed to the decreased nucleophilicity of the fluoride anion due to its high solvation energy [6]. For this reason the use of harsh reaction conditions including high temperatures [7] (>140 °C) and/or activators are usually required [8–11]. This difficulty is accentuated when the nucleophilic fluorination is desired at a fluorinated carbon center. The presence of one or two fluorine atoms in the carbon center will hinder such substitution owing to the electrostatic effect of the current fluorine substitution [18].

The $(PPh_3)_3CuF$ complex was reported for the first time in 1970 [12] and it is considered to be the closest related compound to Cu(I)F [13,14]. Although $(PPh_3)_3CuF$ has been used as intermediate in the synthesis of the well-known trifluoromethylating agent $(PPh_3)_3CuCF_3$ [15], its reactivity as nucleophilic fluorinating agent has not been studied in detail. To the best of our knowledge, there are only two reports in this context. First, the group of Konovalov reported the synthesis of 1-fluoro-2-nitrobenzene from 1-bromo-2-nitrobenzene using $(PPh_3)_3CuF$ [16]. Another paper was published by the Szabó group on regio- and stereoselective nucleophilic fluorination of allyl chlorides using the same $(PPh_3)_3CuF$ complex, showing the promising properties of this complex as a nucleophilic fluorine source [17].

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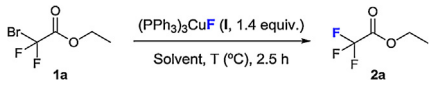
Table 1
Screening of reaction conditions.[a]



Entry	Solvent	Temperature (°C)	Conversion (%)[b]
1	$CDCl_3$	40	<1
2	$CDCl_3$	80	5
3	THF	80	11
4	1,4-Dioxane	80	11
5	Toluene	80	3
6	DMF	80	69
7	DMF	100	90

[a] Reaction conditions: **1a** (0.1 mmol), solvent (0.3 mL), dissolved and heated in the corresponding solvent and temperature under an argon atmosphere for 2.5 h.
[b] Conversion determined by ^{19}F NMR spectroscopy from the reaction crude.

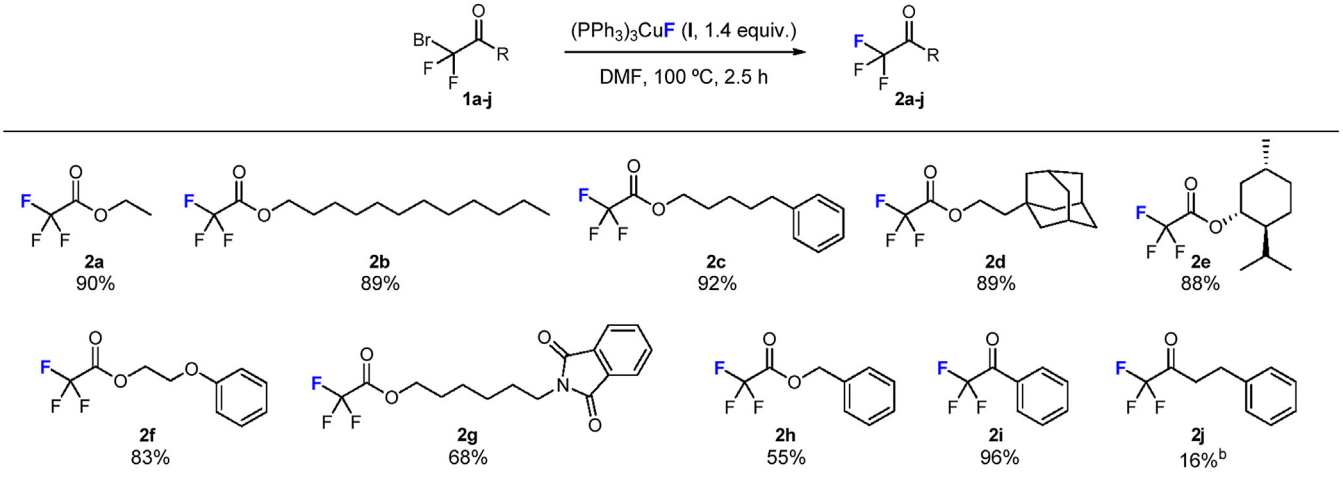
In this paper we present a new late-stage nucleophilic fluorination process for the synthesis of trifluoromethyl moieties (CF_3). This method is based on the halogen exchange reaction between the corresponding difluorobromomethyl derivative (R-CF_2Br) and the easily available copper (I) complex $(PPh_3)_3CuF$.

2. Results and discussion

Our initial investigation started with the transformation of a model substrate, ethyl 2-bromo-2,2-difluoroacetate (**1a**) into the corresponding trifluoroacetate (**2a**) using the $(PPh_3)_3CuF$ complex **I** (Table 1). First, we screened different solvent and temperatures. When $CDCl_3$ was used as solvent, low conversions were observed at 40 or 80 °C (Table 1, entries 1 and 2). The use of more polar solvents, such as THF or 1,4-dioxane, gave similar results and 11% of conversion was observed for both solvents (Table 1, entries 3 and 4). The use of the non-polar solvent toluene did not improve the conversion (Table 1, entry 5). Notably, the conversion of the reaction was increased up to 69% at 80 °C for 2.5 h when using DMF as solvent (Table 1, entry 6). When increasing the temperature from 80 to 100 °C the reaction proceed with a 90% conversion (Table 1, entry 7).

With these results in hand, we investigated the scope of the reaction (Scheme 1). All trifluoromethylated products obtained in the fluorination reactions with $(PPh_3)_3CuF$ were relatively unpolar and by consequence difficult to separate from PPh_3 (arising from the decomposition of the Cu-F complex). Thus, even after careful purification the product samples usually contained varying amounts of PPh_3. Hence, for practical reasons and because this is not a problem for a possible PET application due to the use of HPLC purifications, the yields provided in Scheme 1 were determined by ^{19}F NMR using an internal standard. All products were prepared by alternative methods and fully characterized (see Experimental Section 4.8) before being identified by ^{1}H and ^{19}F NMR spectroscopy in the crude reaction mixtures. Different bromodifluoroacetates with alkyl chains (**1a–d**) were well tolerated in the reaction, yielding the corresponding trifluoroacetates **2a–d** in excellent yields (89–92%). Substrates containing bulky substituents as **1e**, derived from (−)-menthol, also gave excellent results (88% yield). Substrates with phenoxy or *N*-phthalimide substituents (**1f–g**) gave the corresponding trifluoroacetates (**2f–g**) in good yields (83% and 68%, respectively). Only in the case of the benzyl derivative **1h** the yield was diminished to 55%, due to the formation of by products in the reaction mixture. We obtained an excellent yield in the fluorination of 2,2,2-bromodifluoroketone **1i** (96%). However, the enolyzable 2,2,2-bromodifluoroketone **1j** provided low yield of the product **2j** in a complex mixture of decomposition products.

Next, we turned our attention to the nucleophilic fluorination of benzylic positions with the purpose of synthesizing trifluoromethyl arenes in a late-stage fashion (Table 2). For this particular reaction, we found that there was no single solvent suitable for all tested substrates. For the *p*-Ph substituted substrate **3a**, a 93% was obtained using $CDCl_3$ at 70 °C (Table 2, entry 1). With this promising result in hand, we focused our attention into more challenging substrates such as electron deficient arenes [8,9,18]. When a *p*-CN group was incorporated in the substrate (**3b**), only 25% was obtained using toluene at 120 °C (Table 2, entry 2). Substrates bearing a *p*-Br or *p*-OCF_3 substituent gave moderate yields, 49% and 40%, respectively using 1,2-dichloroethane at 100 °C (Table 2, entries 3 and 4). Substrates with the strong electron-withdrawing groups *p*-CF_3 and *p*-CF_2Br (**3e** and **3f**, respectively) yielded the corresponding trifluoromethyl arenes

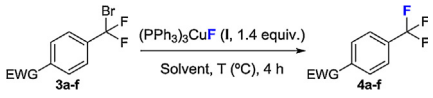


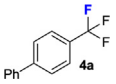
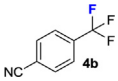
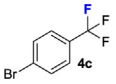
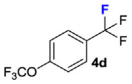
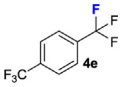
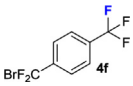
Scheme 1. Substrate scope of trifluoroacetates and trifluoroketones.[a]
[a]Reaction conditions (unless otherwise noted): **1a–j** (0.1 mmol), DMF (0.3 mL), heated at the 100 °C under an argon atmosphere for 2.5 h. Yield determined by ^{19}F NMR spectroscopy using 2,2,2-trifluorotoluene as internal standard. [b]Using $CDCl_3$ at 70 °C.

4e and **4f** in low to moderate yields using DMF at 100 °C (Table 2, entries 5 and 6).

We also tested the complex **I** in the transformation of bromodifluoroacetamides (**5a–j**) into the corresponding trifluoroacetamides (**6aj**). Low yields (36–52%, Scheme 2) were obtained for the model substrates **5a–c** (Scheme 2). Recently, we have reported the use of nucleophilic organoactivators (i.e. DBU) for the debrominative ^{18}F-fluorination of bromodifluoroacetamides using $Bu_4NF[^{18}F]$ as nucleophilic fluorinating agent [10]. In this case a similar effect was observed when DBU was added as additive in the nucleophilic fluorination using $(PPh_3)_3CuF$. Thus, *N*,*N*-dialkyltrifluoroacetamides **6a–c** were obtained in good yields (74–87%, Scheme 2). In this case, substrates with benzyl derivatives substituents (**5d–e**) were well tolerated, yielding the corresponding trifluoroacetamides (**6d–e**) in good yields (73–81%). Oxygen containing substrates, such as the morpholine derivative **5f** or the ketal protected carbonyl **5g** were tolerated, yet they provided somewhat lower yields of the trifluoromethylated analogues (**6f–g**). Other bromodifluoroacetamides such as fluorenone derivative **5 h** and *N*-methyl-*N*-tosylacetamide **5i** provided very low yields of the corresponding trifluoroacetamides (**6h–j**) when DBU was used. In these cases hydrolysis of the amides could occur in the basic media. However, good to moderate yields were obtained (88% and 56% respectively) when DBU was not present. The Weinreb amide derivative **6j** was obtained in similar yields with and without DBU.

Table 2
Substrate scope of trifluoromethyl arenes.[a]



Entry	Product	Solvent	Temperature (°C)	Yield (%)
1		$CDCl_3$	70	93
2		Toluene	120	25
3		DCE	100	49
4		DCE	100	40
5		DMF	100	27
6		DMF	100	40

[a] Reaction conditions: **3a–f** (0.1 mmol), solvent (0.3 mL), heated at the indicated temperature under an argon atmosphere for 4 h. Yield determined by ^{19}F NMR spectroscopy using 2,2,2-trifluoroacetophenone as internal standard.

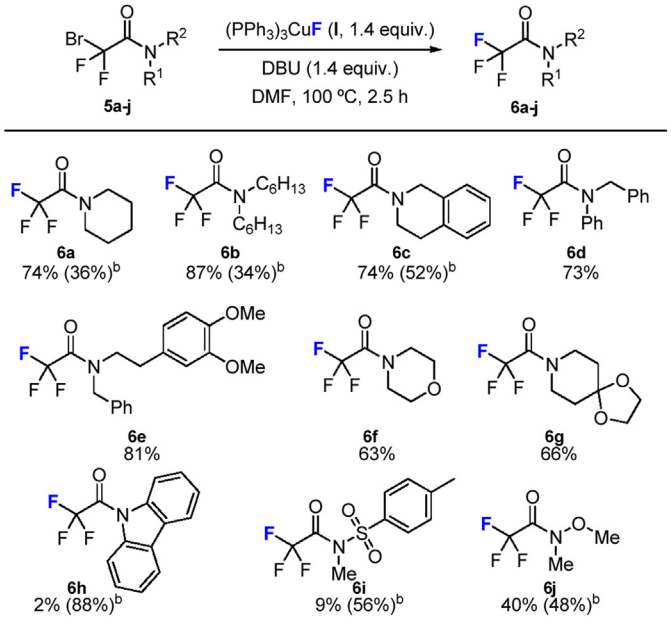
3. Conclusion

In summary, we have demonstrated that the complex $(PPh_3)_3CuF$ is an excellent nucleophilic fluorination agent in the synthesis of trifluoromethyl moieties from the corresponding bromodifluoro derivatives. In general, the reaction proceeds in DMF as the solvent at 100 °C in short reaction times and without the addition of external ligands. In the case of less reactive substrates, the use of activators as DBU has a beneficial effect accelerating the reaction.

4. Experimental

4.1. General information

All reactions were carried out in closed glass reaction vials under an atmosphere of dry Ar. Reagents were used as obtained from commercial suppliers without further purification. Complex **I** was synthetized according to the reported procedure [17]. Compounds **1a**, **2a, 2i, 3f, 4a–e** were obtained from a commercial suppliers and used or analyzed as received. Compounds **2j** [19], **3a–b** [9], **3e** [9], **4f** [9], **5a–j** [10], **6a–j** [10] were synthetized according to the reported procedures and the spectroscopic data agree with the published ones. Dry DMF was used as obtained from a commercial supplier (puriss p. a.). Flash chromatography was carried out on 60 Å (35–70 μm) silica gel (Acros Kieselgel 60) using pentane or pentane/EtOAc, pentane/Et_2O or pentane/acetone mixtures as eluent. Analytical TLC was carried out on aluminum-backed plates (1.5 Å, ~5 cm) pre-coated (0.25 mm) with silica gel (Merck, Silica Gel 60 F254). Compounds were visualized by exposure to UV light or by dipping the plates in a solution of 0.75% $KMnO_4$ (w/v) in a aqueous solution of K_2CO_3 0.36 M. Melting points were recorded in a metal block and are uncorrected. ^{1}H NMR spectra were recorded at 400 MHz; ^{13}C NMR spectra were recorded



Scheme 2. Substrate scope of trifluoroacetamides.[a]
[a] Reaction conditions (unless otherwise noted): **5a-j** (0.1 mmol), DMF (0.3 mL), heated at the 100 °C under an argon atmosphere for 2.5 h. Yield determined by ^{19}F NMR spectroscopy using 2,2,2-trifluorotoluene as internal standard. [b] Yield without DBU as additive.

at 100 MHz, ^{19}F NMR spectra were recorded at 377 MHz with a Bruker Advance spectrometer. ^{1}H and ^{13}C NMR chemical shifts (δ) are reported in ppm from tetramethylsilane, using the residual solvent resonance ($CHCl_3$: δ_H 7.26 and $CDCl_3$: δ_C 77.0) as an internal reference. Coupling constants (J) are given in Hz. High-resolution mass spectra (HRMS) were recorded with a Bruker microTOF ESI-TOF mass spectrometer. We were not able to obtain high-resolution mass data for some of the substrates/products. Therefore, we provide EI mass data in the characterization. NMR yields were calculated using α,α,α-trifluorotoluene or 2,2,2-trifluoroacetophenone as internal standards.

4.2. General procedure A for the synthesis of bromodifluoroacetates **1b–f, 1h**

In a 20 mL glass vial the corresponding alcohol (3.08 mmol, 1 equiv.) was dissolved in hexane (5 mL) under an atmosphere of air. Ethyl 2-bromo-2,2-difluoroacetate (12.3 mmol, 4 equiv., 2.5 g) was added followed by 2 drops of concentrated H_2SO_4 and the reaction was stirred at room temperature for 16 h. The reaction was quenched with Na_2CO_3 (satd. aq, 10 mL), extracted with EtOAc (3 × 10 mL) and washed with Na_2CO_3 (satd. aq). The combined organic phases were dried over $MgSO_4$ and the solvent was removed under reduced pressure. Purification by column chromatography afforded the desired esters.

4.2.1. Dodecyl 2-bromo-2,2-difluoroacetate (**1b**)

Following the general procedure A from dodecanol (573 mg). Purification by column chromatography (SiO_2; EtOAc/Pentane 1:10) afforded the title compound as a colorless oil (801 mg, 76%). ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ = 4.35 (t, J(H,H) = 6.7 Hz, 2H), 1.78–1.71 (m, 2H), 1.43-1.26 (m, 18H), 0.90–0.86 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$, TMS): δ = 159.8 (t, J(C,F) = 31.1 Hz), 108.9 (t, J(C,F) = 314.3 Hz), 68.7, 32.1, 29.8, 29.7, 29.6, 29.5, 29.2, 28.3, 25.7, 22.8, 14.3. ^{19}F NMR (377 MHz, $CDCl_3$): δ = −60.66.

HRMS (ESI): m/z calcd for $C_{14}H_{24}O_2{}^{79}BrF_2 + Na^+$: 364.0820 $[M+Na]^+$; found: 364.0821.

4.2.2. 5-Phenylpentyl 2-bromo-2,2-difluoroacetate (**1c**)

Following the general procedure A from 5-phenylpentan-1-ol (505 mg). Purification by column chromatography (SiO_2; EtOAc/Pentane 1:10) afforded the title compound as a colorless oil (744 mg, 75%). ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ = 7.30–7.26 (m, 2H), 7.20–7.16 (m, 3H), 4.35 (t, J(H,H) = 6.6 Hz, 2H),), 2.66–2.62 (m, 2H), 1.82–1.75 (m, 2H), 1.72–1.64 (m, 2H), 1.48–1.41 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$, TMS): δ = 159.8 (t, J(C,F) = 31.2 Hz), 142.2, 128.5, 128.4, 125.9, 108.9 (t, J(C,F) = 314.3 Hz), 68.4, 35.8, 30.9, 28.1, 25.2. ^{19}F NMR (377 MHz, $CDCl_3$): δ = −60.72. HRMS (ESI): m/z calcd for $C_{13}H_{15}O_2{}^{79}BrF_2 + Na^+$: 343.0116 $[M+Na]^+$; found: 343.0113.

4.2.3. 1-Adamantaneethyl 2-bromo-2,2-difluoroacetate (**1d**)

Following the general procedure A from 1-adamantaneethanol (554 mg). Purification by column chromatography (SiO_2; EtOAc/Pentane 1:10) afforded the title compound as a colorless oil (732 mg, 71%). ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ = 4.41 (t, J(H,H) = 7.3 Hz, 2H), 2.00–1.95 (m, 3H), 1.75–1.69 (m, 3H), 1.66–1.61 (m, 3H), 1.56–1.52 (m, 8H). ^{13}C NMR (100 MHz, $CDCl_3$, TMS): δ = 159.8 (t, J(C,F) = 31.1 Hz), 109.0 (t, J(C,F) = 314.4 Hz), 65.3, 42.5, 41.9, 37.0, 31.9, 28.6. ^{19}F NMR (377 MHz, $CDCl_3$): δ = −60.66. HRMS (ESI): m/z calcd for $C_{14}H_{19}O_2{}^{79}BrF_2 + Na^+$: 359.0429 $[M+Na]^+$; found: 359.0433.

4.2.4. (−)-Menthyl 2-bromo-2,2-difluoroacetate (**1e**)

Following the general procedure A from (−)-menthol (554 mg). Purification by column chromatography (SiO_2; EtOAc/Pentane 1:10) afforded the title compound as a light yellow oil (186 mg, 19%). ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ = 4.84 (td, J(H,H) = 11.0, 4.5 Hz, 1H), 2.09–2.04 (m, 1H), 1.97–1.87 (m, 1H), 1.77–1.69 (m, 2H), 1.58–1.47 (m, 2H), 1.18–1.07 (m, 2H), 0.97–0.85 (m, 1H), 0.95 (d, J(H,H) = 6.6 Hz, 3H), 0.92 (d, J(H,H) = 7.0 Hz, 3H), 0.79 (d, J(H,H) = 7.0 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$, TMS): δ = 159.4 (t, J(C,F) = 30.8 Hz), 109.1 (t, J(C,F) = 314.8 Hz), 79.7, 46.9, 40.0, 34.1, 31.6, 26.3, 23.5, 22.0, 20.7, 16.3. ^{19}F NMR (377 MHz, $CDCl_3$): δ = −60.63 (d, J(F,F) = 162.7 Hz, 1F), −61.04 (d, J(F,F) = 162.8 Hz, 1F). HRMS (ESI): m/z calcd for $C_{12}H_{19}O_2{}^{79}BrF_2 + Na^+$: 335.0429 $[M+Na]^+$; found: 335.0429.

4.2.5. 2-Phenoxyethyl 2-bromo-2,2-difluoroacetate (**1f**)

Following the general procedure A from 2-phenoxyethanol (425 mg). Purification by column chromatography (SiO_2; EtOAc/Pentane 1:20) afforded the title compound as a colorless oil (405 mg, 45%). ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ = 7.33–7.28 (m, 2H), 7.02–6.98 (m, 1H), 6.94–6.90 (m, 2H), 4.71–4.69 (m, 2H), 4.29–4.26 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$, TMS): δ = 159.7 (t, J(C,F) = 31.7 Hz), 158.2, 129.7, 121.7, 114.9, 108.6 (t, J(C,F) = 314.1 Hz), 66.3, 65.2. ^{19}F NMR (377 MHz, $CDCl_3$): δ = −60.84. HRMS (ESI): m/z calcd for $C_{10}H_9O_3{}^{79}BrF_2 + Na^+$: 316.9595 $[M+Na]^+$; found: 316.9599.

4.2.6. Benzyl 2-bromo-2,2-difluoroacetate (**1h**)

Following the general procedure A from benzyl alcohol (333 mg). Purification by column chromatography (SiO_2; EtOAc/Pentane 1:40) afforded the title compound as a colorless oil (367 mg, 45%). ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ = 7.42–7.38 (m, 5H), 5.36 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$, TMS): δ = 159.6 (t, J(C,F) = 31.5 Hz), 133.6, 129.3, 129.0, 128.7, 108.9 (t, J(C,F) = 314.4 Hz), 69.9. ^{19}F NMR (377 MHz, $CDCl_3$): δ = −60.70.

4.3. 6-(1,3-Dioxoisoindolin-2-yl)hexyl 2-bromo-2,2-difluoroacetate (**1g**)

In a 50 mL bottom flask 2-(6-hydroxyhexyl)isoindoline-1,3-dione (2.0 mmol, 1 equiv., 495 mg) and Et_3N (4.0 mmol, 2 equiv., 405 mg) were dissolved in dichloromethane (20 mL) under an atmosphere of argon. 2-Bromo-2,2-difluoroacetyl chloride (2.8 mmol, 1.4 equiv., 541 mg) was added dropwise and the reaction was stirred at 0 °C for 2 h. The reaction was quenched with NH_4Cl (satd. aq, 10 mL) and extracted with dichloromethane (3 × 10 mL). The combined organic phases were dried over $MgSO_4$ and the solvent was removed under reduced pressure. Purification by column chromatography (SiO_2; EtOAc/Pentane 1:10) afforded the title compound as a colorless oil (492 mg, 61%). ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ = 7.87–7.82 (m, 2H), 7.74–7.69 (m, 2H), 4.34 (t, J(H,H) = 6.6 Hz, 2H), 3.71–3.67 (m, 2H), 1.79–1.67 (m, 4H), 1.50–1.36 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$, TMS): δ = 168.6, 159.7 (t, J(C,F) = 31.2 Hz), 134.0, 132.2, 123.3, 108.9 (t, J(C,F) = 314.3 Hz), 68.4, 37.9, 28.5, 28.1, 26.4, 25.3. ^{19}F NMR (377 MHz, $CDCl_3$): δ = −60.71. HRMS (ESI): m/z calcd for $C_{16}H_{16}O_4N{}^{79}BrF_2 + Na^+$: 426.0123 $[M+Na]^+$; found: 426.0133.

4.4. 2-Bromo-2,2-difluoro-1-phenylethan-1-one (**1i**)

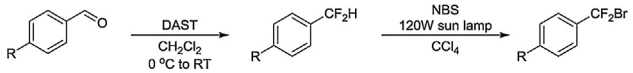
Following the reported procedure with slight modifications [20]: a solution of bromobenzene (15.0 mmol, 1.1 equiv., 2.36 g) in dry Et_2O (3 mL) was added dropwise to a suspension of Mg (18.0 mmol, 1.32 equiv., 437 mg) in dry Et_2O (20 mL) in a sealed MW vial. The reaction was heated at 50 °C after the addition of 1.5 mL of the solution and then it was stirred at room temperature (the reaction is refluxing with the slow addition of the solution of 2-bromoethylbenzene). After the reflux is stopped, the reaction mixture was heated at 50 °C for 2 h. To a solution of ethyl 2-bromo-2,2-difluoroacetate (13.64 mmol, 1.0 equiv., 2.77 g) in dry Et_2O (14 mL) at −78 °C, the readily prepared phenethylmagnesium

bromide was added dropwise and the reaction was stirred at −78 °C for 2.5 h following by 30 min at room temperature. The reaction was quenched with HCl 3 M (10 mL) and extracted with Et_2O (3 × 10 mL). The combined organic phases were dried over $MgSO_4$ and the solvent was removed under reduced pressure. Purification by column chromatography (SiO_2; Pentane) afforded the title compound as a colorless oil (2.23 g, 70%). ^1H NMR (400 MHz, $CDCl_3$, TMS): δ = 8.17–8.14 (m, 2H), 7.71–7.67 (m, 1H), 7.56–7.52 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$, TMS): δ = 181.4 (t, J(C,F) = 25.8 Hz), 135.2, 130.7 (t, J(C,F) = 2.7 Hz), 129.1, 129.0, 113.7 (t, J(C,F) = 318.6 Hz). ^{19}F NMR (377 MHz, $CDCl_3$): δ = −57.76. (EI) m/z (rel intens) 105.05 (M^+-CF_2Br, 64), 77.15 (100).

4.5. 1-Bromo-1,1-difluoro-4-phenylbutan-2-one (**1j**)

Following the reported procedure with slight modifications [20]: a solution of 2-bromoethylbenzene (15.0 mmol, 1.1 equiv., 2.1 mL) in dry Et_2O (3 mL) was added dropwise to a suspension of Mg (18.0 mmol, 1.32 equiv., 437 mg) in dry Et_2O (20 mL) in a sealed MW vial. The reaction was heated at 50 °C after the addition of 1.5 mL of the solution and then it was stirred at room temperature (the reaction is refluxing with the slow addition of the solution of 2-bromoethylbenzene). After the reflux is stopped, the reaction mixture was heated at 50 °C for 2 h. To a solution of ethyl 2-bromo-2,2-difluoroacetate (13.64 mmol, 1.0 equiv., 2.77 g) in dry Et_2O (14 mL) at −78 °C, the readily prepared phenethylmagnesium bromide was added dropwise and the reaction was stirred at −78 °C for 2.5 h following by 30 min at room temperature. The reaction was quenched with HCl 3 M (10 mL) and extracted with Et_2O (3 × 10 mL). The combined organic phases were dried over $MgSO_4$ and the solvent was removed under reduced pressure. Purification by column chromatography (SiO_2; EtOAc/Pentane 1:50) afforded the title compound as a colorless oil (3.01 g, 84%). ^1H NMR (400 MHz, $CDCl_3$, TMS): δ = 7.33-7.29 (m, 2H), 7.25-7.20 (m, 3H), 3.14-3.09 (m, 2H), 3.04-2.99 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$, TMS): δ = 191.3 (t, J(C,F) = 26.5 Hz), 139.5, 128.8, 128.4, 126.8, 114.1 (t, J(C,F) = 319.9 Hz), 36.5, 29.1. ^{19}F NMR (377 MHz, $CDCl_3$): δ = −64.90. HRMS (ESI): m/z calcd for $C_{10}H_9O^{79}BrF_2 + Na^+$: 284.9697 $[M + Na]^+$; found: 284.9710.

4.6. General procedure B for the synthesis of bromo(difluoromethyl) arenes **3a-f**. Following the reported procedure with slight modifications:



To a dry flask containing a solution of aryl aldehyde (1.0 equiv.) in dry CH_2Cl_2 (1.0 M) at 0 °C was added DAST (1.7 equiv.) and catalytic amounts of EtOH (50–100 μL). The reaction mixture was warmed to room temperature and stirred for 2–3 days before it was quenched at 0 °C with $NaHCO_3$ (sat. aq.) and extracted with CH_2Cl_2 (3 × 30 mL). The combined organic layers were washed with brine, dried over $MgSO_4$ and the solvent was removed under reduced pressure. Purification by column chromatography afforded the desired difluoromethyl arenes.

Under an argon atmosphere, degassed CCl_4 (0.35 M) was added to a round bottom flask containing the corresponding difluoromethyl arene (1.0 equiv.) and *N*-Bromosuccinimide (1.7 equiv.). The reaction mixture was irradiated by the light of a 120 W sun lamp (approx. 12 cm distance between lamp and reaction flask) for 1–30 days before being quenched with $Na_2S_2O_3$ (sat. aq.) and extracted with CH_2Cl_2 (3 × 30 mL). The combined organic layers were washed with brine, dried over $MgSO_4$ and the solvent was removed under reduced pressure. Purification by column chromatography afforded the desired bromodifluoromethyl arenes.

4.6.1. 1-Bromo-4-(bromodifluoromethyl)benzene (**3c**)

Following the general procedure B from 4-bromobenzaldehyde with a reaction time of 2 days. Purification by column chromatography (SiO_2; pentane/Et_2O 100:1) afforded 1-Bromo-4-(difluoromethyl)benzene as a colorless oil (1.05 g, 81%). ^1H NMR (400 MHz, $CDCl_3$, TMS): δ = 7.62–7.58 (m, 2H), 7.41–7.36 (m, 2H), 6.61 (t, J(H,F) = 56.3 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$, TMS): δ = 133.4 (t, J(C,F) = 22.8 Hz), 132.1, 127.4 (t, J(C,F) = 6.0 Hz), 125.3 (t, J(C,F) = 2.5 Hz), 114.3 (t, J(C,F) = 239.2 Hz). ^{19}F NMR (377 MHz, $CDCl_3$): δ = −111.10 (d, J(F,H) = 56.3 Hz). (EI) m/z (rel intens) 207.89 (M+, ^{81}Br, 100), 205.98 (M^+, ^{79}Br, 93), 127.23 (M^+-Br, 49). From 1-Bromo-4-(difluoromethyl)benzene with a reaction time of 9 days. Purification by column chromatography (SiO_2; pentane) afforded the title compound as a colorless oil (745 mg, 82%). ^1H NMR (400 MHz, $CDCl_3$, TMS): δ = 7.62–7.58 (m, 2H), 7.50–7.46 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$, TMS): δ = 137.3 (t, J(C,F) = 24.2 Hz), 132.1, 126.1 (t, J(C,F) = 5.1 Hz), 126.0 (t, J(C,F) = 1.7 Hz), 117.8 (t, J(C,F) = 303.7 Hz). ^{19}F NMR (377 MHz, $CDCl_3$): δ = −44.05 (s). (EI) m/z (rel intens) 207.19 (M^{+79}Br-Br, 96), 205.17 (M^{+81}Br-Br, 100), 126.23 (M^+-Br_2, 47).

4.6.2. 1-(Bromodifluoromethyl)-4-(trifluoromethoxy)benzene (**3d**)

Following the general procedure B from 4-(trifluoromethoxy) benzaldehyde with a reaction time of 3 days. Purification by column chromatography (SiO_2; pentane/Et_2O 100:1) afforded 1-(difluoromethyl)-4-(trifluoromethoxy)benzene as a colorless volatile liquid (494 mg, 34%). ^1H NMR (400 MHz, $CDCl_3$, TMS): δ = 7.58–7.54 (m, 2H), 7.33–7.28 (m, 2H), 6.66 (t, J(H,F) = 56.3 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$, TMS): δ = 151.0 (q, J(C,F) = 1.9 Hz), 133.1 (t, J(C,F) = 22.9 Hz), 127.5 (t, J(C,F) = 6.0 Hz), 121.2, 120.5 (q, J(C,F) = 258.1 Hz), 114.0 (t, J(C,F) = 239.3 Hz). ^{19}F NMR (377 MHz, $CDCl_3$): δ = −57.84 (s, 3F), −110.79 (d, J(F,H) = 56.2 Hz, 2F). (EI) m/z (rel intens) 211.99 (M^+, 84), 193.19 (M^+-F, 22), 162.19 (20), 145.19 (33), 127.23 (M^+-OCF_3, 100). From 1-(difluoromethyl)-4-(trifluoromethoxy)benzene with a reaction time of 14 days. Purification by column chromatography (SiO_2; pentane) afforded the title compound as a colorless oil (237 mg, 47%). ^1H NMR (400 MHz, $CDCl_3$, TMS): δ = 7.69–7.64 (m, 2H), 7.33–7.28 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$, TMS): δ = 151.2 (p, J(C,F) = 2.1 Hz), 136.7 (t, J(C,F) = 24.4 Hz), 126.5 (t, J(C,F) = 5.1 Hz), 121.0, 120.4 (q, J(C,F) = 258.7 Hz), 117.0 (t, J(C,F) = 303.7 Hz). ^{19}F NMR (377 MHz, $CDCl_3$): δ = −43.70 (s, 2F), −57.80 (s, 3F). (EI) m/z (rel intens) 211.04 (M^+-Br, 100), 145.21 (25).

4.7. General procedure C for the halogen exchange reaction using $(PPh_3)_3CuF$

A reaction vial was charged with the corresponding bromodifluoderivative **1a-i, 5h-*j*** (0.1 mmol, 1 equiv.), $(PPh_3)_3CuF$ (0.14 mmol, 1.4 equiv., 122 mg) and dry DMF (0.3 mL) under an atmosphere of argon. The reaction was stirred at 100 °C for 2.5 h. The reaction was cooled down and α,α,α-trifluorotoluene (3 equiv., 37 μL) was added as internal standard and the yield was calculated by ^{19}F NMR spectroscopy.

4.8. General procedure D for the synthesis of trifluoroacetates **2b-h**

In a 20 mL glass vial the corresponding alcohol (3.0 mmol, 1 equiv.) was dissolved in hexane (5 mL) under an atmosphere of air. Ethyl 2,2,2-trifluoroacetate (12.0 mmol, 4 equiv., 1.7 g) was added followed by 2 drops of concentrated H_2SO_4 and the reaction was stirred at room temperature for 16 h. The reaction was quenched with Na_2CO_3 (satd. aq, 10 mL), extracted with EtOAc (3 × 10 mL) and washed with Na_2CO_3 (satd. aq. 20 mL). The combined organic

phases were dried over $MgSO_4$ and the solvent was removed under reduced pressure. Purification by column chromatography afforded the desired esters.

*4.8.1. Dodecyl 2,2,2-trifluoroacetate (**2b**)*

Following the general procedure D from dodecanol (559 mg). Purification by column chromatography (SiO2; Pentane) afforded the title compound as a colorless oil (700 mg, 83%). ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ = 4.34 (t, J(H,H) = 6.7 Hz, 2H), 1.77–1.70 (m, 2H), 1.42–1.23 (m, 18H), 0.90–0.86 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$, TMS): δ = 157.7 (q, J(C,F) = 42.0 Hz), 114.8 (q, J(C,F) = 285.5 Hz), 68.4, 32.1, 29.8, 29.7, 29.6, 29.5, 29.2, 28.3, 25.7, 22.9, 14.2. ^{19}F NMR (377 MHz, $CDCl_3$): δ = −75.37. (EI) m/z (rel intens) 213.14 (M^+-CF_3, 6), 97.23 (26), 83.33 (47), 69.34 (88), 67.52 (100).

*4.8.2. 5-Phenylpentyl 2,2,2-trifluoroacetate (**2c**)*

Following the general procedure D from 5-phenylpentan-1-ol (493 mg). Purification by column chromatography (SiO_2; EtOAc/Pentane 1:10) afforded the title compound as a colorless oil (520 mg, 67%). ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ = 7.30–7.26 (m, 2H), 7.21–7.16 (m, 3H), 4.34 (t, J(H,H) = 6.7 Hz, 2H),), 2.65–2.61 (m, 2H), 1.81–1.74 (m, 2H), 1.71–1.64 (m, 2H), 1.47–1.39 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$, TMS): δ = 157.7 (q, J(C,F) = 42.0 Hz), 142.2, 128.5, 128.4, 125.9, 114.7 (q, J(C,F) = 285.6 Hz), 68.3, 35.8, 31.0, 28.1, 25.2. ^{19}F NMR (377 MHz, $CDCl_3$): δ = −75.12. (EI) m/z (rel intens) 259.86 (M^+, 20), 146.17 (100), 117.29 (50), 104.56 (75), 91.42 (95).

*4.8.3. 1-Adamantaneethyl 2,2,2-trifluoroacetate (**2d**)*

Following the general procedure D from 1-adamantaneethanol (541 mg). Purification by column chromatography (SiO_2; Pentane) afforded the title compound as a colorless oil (629 mg, 76%). ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ = 4.39 (t, J(H,H) = 7.4 Hz, 2H), 1.99–1.93 (m, 3H), 1.75-1.69 (m, 3H), 1.67–1.60 (m, 3H), 1.57–1.50 (m, 8H). ^{13}C NMR (100 MHz, $CDCl_3$, TMS): δ = 157.6 (q, J(C,F) = 42.0 Hz), 114.7 (q, J(C,F) = 285.7 Hz), 64.9, 42.5, 41.9, 37.0, 31.9, 28.7. ^{19}F NMR (377 MHz, $CDCl_3$): δ = −75.56. (EI) m/z (rel intens) 207.12 (M^+-CF3, 1), 163.13 (4), 132.12 (100), 93.43 (29), 79.47 (32).

*4.8.4. (−)-Menthyl 2,2,2-trifluoroacetate (**2e**)*

Following the general procedure D from (−)-menthol (444 mg). Purification by column chromatography (SiO_2; Et_2O/Pentane 1:20) afforded the title compound as a colorless oil (249 mg, 35%). ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ = 4.87 (td, J(H,H) = 11.0, 4.5 Hz, 1H), 2.09–2.01 (m, 1H), 1.91–1.78 (m, 1H), 1.77–1.67 (m, 2H), 1.59–1.45 (m, 2H), 1.19–1.03 (m, 2H), 0.97–0.88 (m, 1H), 0.94 (d, J(H,H) = 6.6 Hz, 3H), 0.91 (d, J(H,H) = 7.0 Hz, 3H), 0.78 (d, J(H,H) = 7.0 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$, TMS): δ = 157.3 (q, J(C,F) = 41.6 Hz), 114.8 (q, J(C,F) = 285.7 Hz), 79.5, 46.9, 40.2, 34.1, 31.6, 26.4, 23.6, 21.9, 20.6, 16.3. ^{19}F NMR (377 MHz, $CDCl_3$): δ = −75.30. (EI) m/z (rel intens) 139.02 (M^+-CO_2CF_3, 17), 123.11 (9), 95.13 (44), 81.24 (100), 79.36 (52), 67.41 (54).

*4.8.5. 2-Phenoxyethyl 2,2,2-trifluoroacetate (**2f**)*

Following the general procedure D from 2-phenoxyethanol (409 mg). Purification by column chromatography (SiO_2; EtOAc/Pentane 1:9) afforded the title compound as a colorless oil (184 mg, 27%). ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ = 7.34–7.28 (m, 2H), 7.03–6.98 (m, 1H), 6.93–6.89 (m, 2H), 4.72–4.68 (m, 2H), 4.29–4.25 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$, TMS): δ = 158.2, 157.6 (q, J(C,F) = 42.8 Hz), 129.7, 121.7, 114.8, 114.6 (q, J(C,F) = 285.4 Hz), 66.2, 65.0. ^{19}F NMR (377 MHz, $CDCl_3$): δ = −74.88. (EI) m/z (rel intens) 234.03 (M^+, 29), 141.12 (100).

*4.8.6. 6-(1,3-Dioxoisoindolin-2-yl)hexyl 2,2,2-trifluoroacetate (**2g**)*

Following the general procedure D from 2-(6-hydroxyhexyl) isoindoline-1,3-dione (432 mg). Purification by column chromatography (SiO_2; EtOAc/Pentane 1:4) afforded the title compound as a white solid (243 mg, 41%). M.p. = 57–60 °C. ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ = 7.86–7.82 (m, 2H), 7.73–7.69 (m, 2H), 4.35–4.31 (m, 2H), 3.71–3.67 (m, 2H), 1.78–1.66 (m, 4H), 1.48–1.35 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$, TMS): δ = 168.3, 157.4 (q, J(C,F) = 42.1 Hz), 133.9, 132.1, 123.1, 114.5 (q, J(C,F) = 285.7 Hz), 68.1, 37.7, 28.3, 28.0, 26.3, 25.1. ^{19}F NMR (377 MHz, $CDCl_3$): δ = −75.13. (EI) m/z (rel intens) 234.99 (M^+, 46), 274.16 (1), 230.10 (7), 160.22 (100), 77.48 (18).

*4.8.7. Benzyl 2,2,2-trifluoroacetate (**2h**)*

Following the general procedure D from benzyl alcohol (324 mg). Purification by column chromatography (SiO_2; Pentane) afforded the title compound as a colorless oil (310 mg, 51%). ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ = 7.43–-7.36 (m, 5H), 5.36 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$, TMS): δ = 157.5 (q, J(C,F) = 42.5 Hz), 133.4, 129.4, 129.0, 128.8, 114.7 (q, J(C,F) = 285.7 Hz), 69.7. ^{19}F NMR (377 MHz, $CDCl_3$): δ = −74.96. (EI) m/z (rel intens) 203.93 (M^+, 45), 135.18 (12), 107.23 (30), 91.41 (100).

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