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Regio- and Stereoselective Allylic Trifluoromethylation and Fluorination using $CuCF_3$ and CuF Reagents

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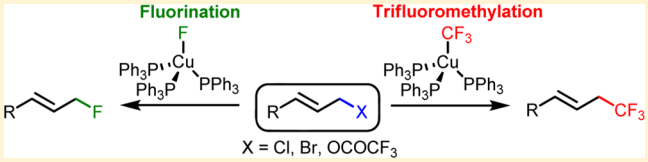
Supporting Information

ABSTRACT: Copper-mediated trifluoromethylation of allylic chlorides and trifluoroacetates was performed using a convenient Cu−CF_3 reagent. The reaction is suitable for selective synthesis of allyl trifluoromethyl species. Mechanistic studies indicate that the reaction proceeds via a nucleophilic substitution mechanism involving allyl copper intermediates. The analogous Cu−F reagent was suitable for fluorination of allyl chlorides. Stereodefined cyclic substrates reacted regio- and stereoselectively.



The trifluoromethyl group is a privileged structural motif in pharmaceutical and agrochemical products.[1] Therefore, the development of new methods for introduction of CF_3 groups has attracted considerable recent attention.[1,2] Most efforts have been concentrated on introducing the CF_3 functional group into aryl,[2−10] alkene[11−18] and alkyne[19,20] substrates. In recent years two main strategies have been developed for these reactions: (i) nucleophilic functionalization based on electron-rich trifluoromethylating reagents, such as complexes **1a**,**b** (Figure 1);[3,7,19] and (ii) electrophilic

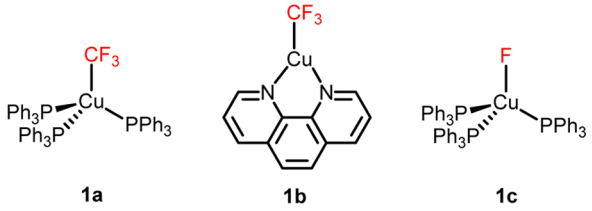
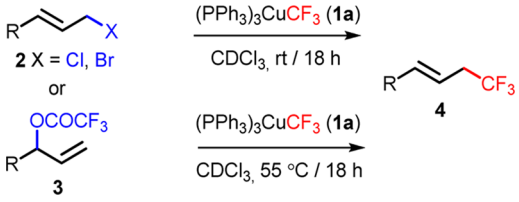


Figure 1. Convenient nucleophilic CF_3 and F transfer reagents.

trifluoromethylation using electron-deficient CF_3 reagents, such as the Togni[8] or other oxidative reagents.[5,11,13−15] Particularly useful methods have appeared for allylic C−H functionalization using the latter method (see, for example, ref 15). Although C−H functionalization is one of the most efficient and atom economic strategies for the introduction of new functional groups, some of the allylic (and other) trifluoromethylation methods suffer from regio- and stereoselectivity and functional group compatibility problems. Therefore, there is still room for development of new substitution methods based on prefunctionalized substrates.[16−18,21]

Recently, Grushin[3] and we[19] have reported efficient methods for the synthesis of organotrifluoromethylated compounds using convenient Cu−CF_3 reagent **1a**. We have shown[19] that propargylic halides and trifluoroacetates can be converted to allenyl- or propargyl-CF_3 derivatives under mild, neutral conditions by **1a**, which is easily accessed via a simple two step synthesis reported by Grushin and co-workers.[3] We have now found that the same method can be extended to allylic derivatives (Scheme 1, Table 1). Allylic halides **2a**−**j** can be

Scheme 1. Allylic Trifluoromethylation with 1a



efficiently and regioselectively trifluoromethylated by copper reagent **1a** in $CDCl_3$ (use of deuterated solvent facilitated the careful analysis of the crude product by ^1H NMR). The reaction provides the linear allylic regioisomer usually with high yield. The reactions can be conducted under mild, neutral conditions (typically at room temperature) without any additives.

Cinnamyl chloride **2a** and its analogues **2b**−**e** reacted smoothly. The aromatic chloro substituent survived the reaction, as only the allylic chloride in **2b** was trifluoromethylated to give **4b** (entry 4). Both linear (**2c**) and branched (**2d**) *para*-nitro cinnamyl chloride gave the corresponding linear regiosiomer **4c** (entries 5−6), suggesting that allylic rearrangement may take place during the trifluoromethylation process. The cinnamyl substrate containing an electron-donating methoxy group (**2e**) reacted faster and with higher yield than its counterpart with an electron-withdrawing nitro group (**2c**). Alkyl substituted allylic halides **2f**−**g** also reacted with high regio- and stereoselectivity (entries 8 and 10). Geranyl bromide **2h** reacted with excellent regioselectivity to give **4g**; however,

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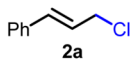
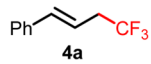
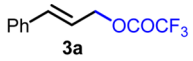
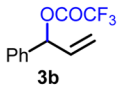
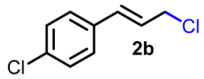
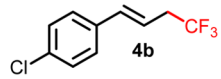
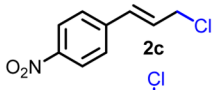
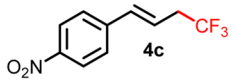
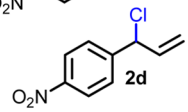
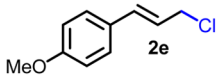
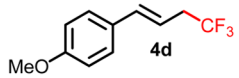
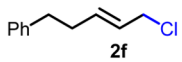
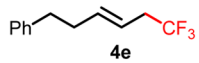
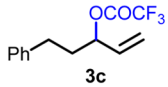
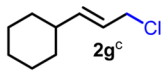
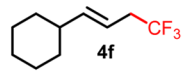
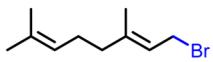
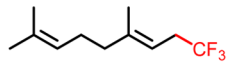
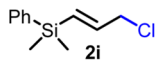
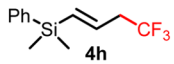
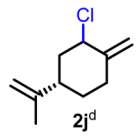
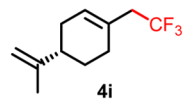
Table 1. Synthesis of Allylic-CF_3 Compounds from Allylic Halides and Trifluoroacetates[a]

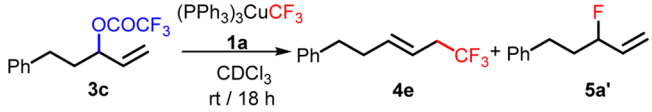
Entry	Substrate	Product	Yield [%]
1	 **2a**	 **4a**	68 / 76[b]
2	 **3a**	**4a**	53
3	 **3b**	**4a**	61
4	 **2b**	 **4b**	85
5	 **2c**	 **4c**	51
6	 **2d**	**4c**	62
7	 **2e**	 **4d**	79
8	 **2f**	 **4e**	75
9	 **3c**	**4e**	30
10	 **2g**[c]	 **4f**	59
11	 **2h**	 E/Z 3:1 **4g**	90
12	 **2i**	 **4h**	41
13	 **2j**[d]	 **4i**	56

[a]A mixture of **2** or **3** (0.15 mmol) and **1a** (1.1 equiv) in $CDCl_3$ (0.6 mL) was stirred for 18 h at room temperature (**2**) or at 55 °C (**3**). [b]The reaction was repeated on 1.6 mmol scale. [c]Linear/branched ratio of the substrate 6:1. [d]Linear/branched ratio of the substrate 1:3.

the *E*/*Z* forms were obtained in a 3:1 ratio. Silyl derivative **2i** reacted with poor yield, affording **4h**. In this process an interesting side reaction was observed, which inspired us to develop a method for allylic fluorination (vide supra). Terpene chloride **2j** could also be converted to trifluoromethyl derivative **4i** without changing the stereogenic carbon. We have also studied application of nonhalide leaving groups for the trifluoromethylation reaction. Allylic acetates (such as cinnamyl acetate) did not react under our conditions or using elevated temperatures. However, allylic trifluoroacetates reacted with **1a** with the same regio- and stereoselectivity as allylic halides. For example, **3a** and **3b** gave the linear regiosiomer **4a** similarly to **2a**. The trifluoroacetates are less reactive than the halides, and therefore slightly elevated temperature (55 °C) had to be applied. In some cases (such as for **3c**), yields with the trifluoroacetate substrate were lower than with the corresponding halides.

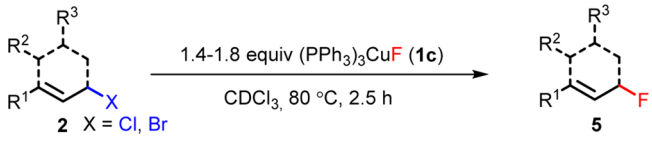
The reaction can easily be scaled up. When we increased the scale of the reaction from 0.15 to 1.6 mmol (11 times) the yield was, in fact, slightly increased from 68 to 76%. As mentioned above, the yield for trifluoromethylation of **2i** (entry 12) was unexpectedly low (41%). Analysis of the reaction mixture by ^{19}F NMR showed that part of the starting material underwent fluorodesilylation to give $PhMe_2Si-F$. Moreover, careful analysis of the reaction mixture of the trifluoromethylation of **3c** showed that allylic fluorination affording **5a′** also occurred using **1a** (Scheme 2). The fluorine in these processes

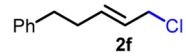
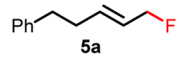
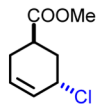
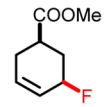
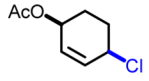
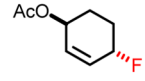
Scheme 2. Allylic Trifluoromethylation and Fluorination with 1a



apparently originated from the CF_3 group. We reasoned that probably α-fluoride elimination of the Cu−CF_3 occurred to give Cu−F and CF_2. α-Fluoride elimination is a well-known process[6,22] for Cu−CF_3 complexes without PPh_3 or other strongly coordinating ligands. These findings gave us the idea to attempt fluorination reactions with the fluoro analogue of **1a** (Table 2). Reagent **1c**[23] is readily available as an intermediate in the synthesis of **1a**.[3]

Table 2. Fluorination of Allylic Halides with 1c[a]



entry	substrate	$(PPh_3)_3CuF·X$[b]	product	trans/cis	yield [%]
1	 **2f**	-	 **5a**	-	53
2	 **2k**	$CHCl_3$	 **5b**	-	92[c]
3	 **2l**	MeOH	 **5c**	1:4	57
4	**2l**	$CHCl_3$	**5c**	1:4	76
5	 **2m**	$CHCl_3$	 **5d**	4:1	64[d]
6	**2m**	MeOH	**5d**	8:1	62

[a]A mixture of **2** (0.30 mmol) and **1c** (1.4−1.8 equiv) in $CDCl_3$ (0.5 mL) was stirred for 2.5 h at 80 °C. [b]Solvent (X) coordinated to **1c**. [c]The reaction was conducted at rt for 10 min. **5b** is unstable; therefore, ^1H NMR yield is given. [d]The isolated product contained 15% of the other regioisomer (2-fluorocyclohex-3-en-1-yl acetate).

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Selective allylic fluorination reactions have attracted much attention in the last couple of years.[24−27] These reactions are very challenging as some of the allylic fluorides are unstable[27] and the control of the regio- and stereoselectivity of the process is usually very difficult. In general, the Pd- and Ir-catalyzed reactions are suitable for achieving high levels of selectivity.[24−26] However, the Cu-catalyzed/mediated allylic fluorination is rather unusual. During the revision of this paper an independent study on copper-catalyzed fluorination of allyl chlorides and bromides was published by Liu and co-workers.[28]

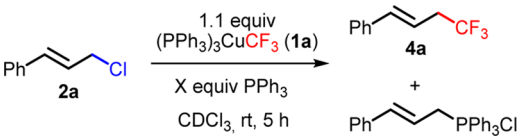
The fluorination of allylic halides with **1c** (Table 2) required higher temperature (80 °C) than the corresponding trifluoromethylation (room temperature). When **2f** was employed, the linear product **5a** was formed (Table 2, entry 1). Cyclic allylic bromide **2k** reacted readily with high NMR yield to give **5b**. As **5b** is both volatile and unstable,[27] it was not isolated. However, cyclic allylic fluorides with electron-withdrawing substituents, such as **5c**,**d**, are stable compounds that are fairly easy to isolate. When stereodefined allylic chlorides[29] **2l**,**m** were reacted with **1c**, we obtained allylic fluorides **5c**,**d** stereoselectively. Formation of methoxy ether byproducts from reaction of **2l** with MeOH coordinated to **1c** somewhat lowered the yield of **5c** (Table 2, entry 3). Gouverneur and co-workers[30] found that **5c** undergoes Pd-catalyzed allylic nucleophilic substitution with malonate derivatives. However, according to our studies allylic fluoride **5c** does not undergo the analogous reaction with MeOH, and thus the methoxy byproduct is proposed to form from allylic chloride **2l**. Replacement of MeOH with $CHCl_3$ in **1c** eliminated this side reaction, and the yield of **5c** thereby increased (Table 2, entry 4). Additionally, the stereoselectivity of formation of **5d** was somewhat dependent on the solvents coordinated to **1c**. In the case of MeOH coordination (entry 6) the *trans*/*cis* ratio was higher (8:1) than with coordinated $CHCl_3$ (entry 5) (4:1). The reactions (entries 3−6) proceeded with inversion of configuration in a formal S_N2 reaction. Palladium-catalyzed synthesis of **5c** from allylic chlorides was previously described by Doyle and Katcher.[24] This reaction proceeds via allyl palladium intermediates by (overall) retention of configuration.[24]

Gouverneur and co-workers[30] described the synthesis of **5d** from the corresponding allylic silane and Selectfluor, which reacts through an S_E2' mechanism. Thus, our copper-mediated process complements the stereochemistry of the Pd-catalyzed reaction to **5c** and somewhat simplifies access to **5d** via substitution of easily accessible allylic chloride[29] **2m** (entries 5−6). When the reaction was attempted with **2m** and simple inorganic fluoride salts, such as CsF and LiF, no reaction took place. Using AgF a complex mixture including **5d** and its possible regio- and stereoisomers was obtained. Application of CuF_2 and PPh_3 resulted in formation of **5d** and its stereoisomer, albeit in low (^{1}H NMR) yield (28%).

When cyclic substrates **2k** and **2m** were reacted with CF_3 complex **1a**, mainly fluorinated products **5b** and **5d** were obtained, albeit with much lower conversion than with fluoride complex **1c**. Under the applied reaction conditions, allylic trifluoroacetates did not give allyl fluoride products with **1c**. The trifluoromethylation of **2a** was also attempted using complex **1b**.[7] However, the (^{1}H NMR) yield (30%) was much lower than with **1a**. Interestingly, we could observe formation of allylic fluorides even with this reagent.

We have briefly studied the mechanistic aspects of the trifluoromethylation reaction. Addition of PPh_3 to the trifluoromethylation of **2a** (Table 1, entry 1, Table 3) strongly inhibited the reaction, suggesting that the substitution is initiated by PPh_3 dissociation followed by coordination of the allylic halide. This is in line with the findings by Grushin[3] for trifluoromethylation of aromatic halides with **1a**.

Table 3. Inhibition Experiment with PPh_3



Equiv of PPh_3 added:	0	1	2	10
		Product ratios [%]		
4a	>99	11	9	-
Ph, PPh3Cl	-	18	30	62
2a (unreacted)	-	71	61	38

Suprisingly, including TEMPO (**6**) in the trifluoromethylation resulted in formation of TEMPO derivatives **7** and **8** and a decrease in the yield of **4a** (Scheme 3). Although formation of **7** and **8** may indicate a radical process, 2 equiv of TEMPO did not completely inhibit the reaction, as in the oxidative trifluoromethylation.[11] Furthermore, control experiments showed that **2a** or **1a** alone do not react with TEMPO. This suggests formation of a reaction intermediate from **1a** and **2a**, which could react with TEMPO (**6**).

Considering the fact that allylic isomers **2c**,**d** and **3a**,**b** regioselectively gave linear products **4c** and **4b**, respectively, we suggest that the allylic substrate **2** and **1a** form an allyl copper intermediate, such as **9a** (Scheme 4). This complex may rearrange to the η^3-allyl form **9b**, and thus the unsubstituted terminus may approach the CF_3 group. Product **4** is proposed to be formed by reductive elimination. Complex **9a** may undergo a single-electron reduction to form Cu(II) complexes and CF_3 or allylic radicals. This process may be promoted in the presence of radical acceptors, such as TEMPO (**6**). However, we suggest that formation of the allyl-CF_3 products **4** proceeds via an ionic mechanism.

This conclusion is also supported by our competition experiments (Scheme 5). Thus, the reaction is faster with a substrate bearing an electron-donating substituent (**2e**) than with a substrate with an electron-withdrawing substituent (**2c**). This suggests that CF_3 is transferred in a nucleophilic substitution process. However, it should be noted that the difference in the rate of trifluoromethylation between the *p*-methoxy (**2e**) and the *p*-nitro substituted (**2c**) cinnamyl derivatives is relatively small (about 2.5 times), which means that a radical mechanism cannot be excluded.

In summary, we have shown that allylic chlorides and trifluoroacetates can be trifluoromethylated by reagent **1a**. The reaction is highly stereo- and regioselective and tolerates several functional groups. At elevated temperature **1a** undergoes α-elimination to give **1c**, which has proved to be a useful fluorinating reagent. Using complex **1c**, regio- and stereoselective fluorination of some stereodefined allylic chlorides could be performed. Our procedure broadens the reagent scope in trifluoromethylation and fluorination methods, and complements the chemo- and stereoselectivity of existing methods.

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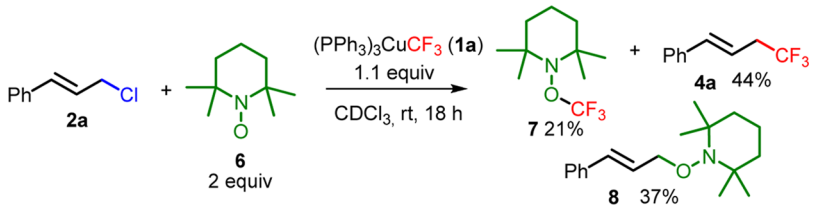
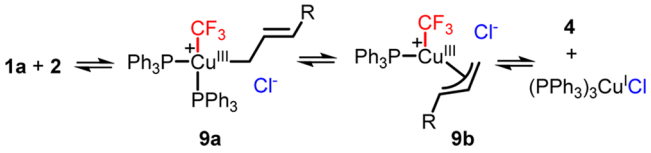
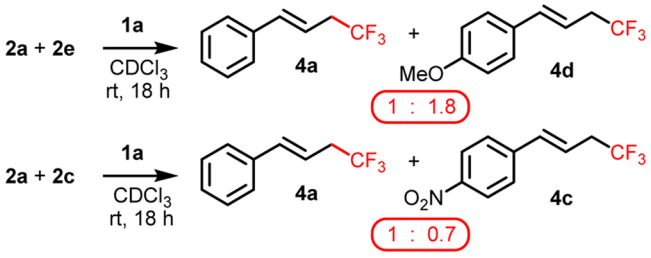
Scheme 3. Inhibition Experiment with TEMPO 6



Scheme 4. Suggested Mechanism for the Trifluoromethylation



Scheme 5. Competition Experiments: All Components Have Been Used in Equal Amounts



EXPERIMENTAL SECTION

General Information. Starting materials **1a**,[3] **3a**,[31] **2b**,[32] **2c**,[33] **2d**,[33] **2e**,[32] **2f**,[32] **3c**,[31] **2g**,[34] **2i**,[34] **2j**,[35] **2l**,[36] and **2m**[29] were prepared according to literature procedures. All other chemicals were obtained from commercial suppliers and were used without further purification. All reactions were prepared in a glovebox and performed under argon unless otherwise stated. ^{1}H NMR, ^{13}C NMR and ^{19}F NMR spectra were recorded in $CDCl_3$ on 400 or 500 MHz instruments. All ^{1}H NMR spectra are measured relative to the signals for residual $CHCl_3$ (7.26 ppm), and all ^{13}C NMR spectral data are reported relative to $CDCl_3$ (77.16 ppm). For ^{19}F NMR, α,α,α-trifluorotoluene was used as an external standard (−63.7 ppm). HRMS data were recorded on a micrOTOF instrument using ESI technique. Attempts to obtain a HRMS spectrum was unsuccessful because of a combination of low polarity and high volatility for compounds **4e**, **4f**, **4h**, **4i**, and **5a**. All column chromatography was performed using silica gel (35−70 μm).

General Procedure for Trifluoromethylation of 2a−2j, 3a−3c. To a screw top vial were added **2** or **3** (0.15 mmol), $(PPh_3)_3CuCF_3$ (**1a**, 152 mg, 0.165 mmol) and $CDCl_3$ (0.6 mL) inside the glovebox. The reaction mixture was stirred for 18 h at room temperature for substrates **2** and at 55 °C for substrates **3**. The crude mixture was thereafter purified by column chromatography.

General Procedure for Fluorination of 2f, 2k−2m. To a screw top vial were added **2** (0.30 mmol), $(PPh_3)_3CuF$ (**1b**, 1.4 equiv/0.43 mmol or 1.8 equiv/0.54 mmol) and $CDCl_3$ (1 mL) inside the glovebox. The number of solvent molecules coordinated to $(PPh_3)_3CuF$ was determined by ^{1}H NMR spectroscopy in $CDCl_3$ or C_6D_6. Using this information, the molecular weights of $(PPh_3)_3CuF{\cdot}x$MeOH and $(PPh_3)_3CuF{\cdot}x$CHCl$_3$ were calculated (see below). The reaction mixture was heated at 80 °C for 2.5 h. The solvent volume was thereafter reduced under a vacuum, and pentane was added. The organic solvent was separated from the precipitated PPh_3, and the solid was washed with pentane 2 additional times. The organic phases were then joined, and the product was purified by column chromatography.

Modified Synthesis of 1c. Complex **1c** was synthesized according to a previously reported literature procedure[37] or with a slight modification in the purification process. Using the original procedure,[37] we obtained $(PPh_3)_3CuF{\cdot}2.8$MeOH in which the MeOH is coordinated to the complex. It has previously been noted[23] that the number of MeOH molecules retained in the product, $(PPh_3)_3CuF{\cdot}x$MeOH, after prolonged drying under a vacuum at room temperature varies. A value of x less than 1 could not be achieved. However, the coordinated MeOH could be removed using a modified purification method. After completion of the reaction, the crude was concentrated at reduced pressure and thereafter dissolved in $CHCl_3$. To ensure complete removal of MeOH, the solvent was once again removed at reduced pressure. Recrystallization of the residue from $CHCl_3$/pentane produced $(PPh_3)_3CuF{\cdot}0.46CHCl_3$ (**1c**) in 54% (4.997 g, 5.406 mmol, MW = 924.31 g/mol) yield. The number of $CHCl_3$ molecules coordinated to **1c** after drying the complex overnight in a vacuum varied from 2 to complete removal of the solvent. The amounts of the coordinated solvent molecules were determined by ^{1}H NMR. The spectral data for **1c** is in agreement with previously reported literature values.[23,37]

***(E)*-(4,4,4-Trifluorobut-1-en-1-yl)benzene (4a).** The product was synthesized from **2a** (0.15 mmol, 23 mg and 1.6 mmol, 258 mg) according to the general procedure for trifluoromethylation. The title compound was purified by column chromatography (pentane) and isolated as an oil in 68% yield (19 mg and 232 mg in the scaled-up version of the reaction). Compound **4a** was also synthesized from allylic trifluoroacetates **3a** (0.15 mmol, 35 mg) and **3b** (0.15 mmol, 35 mg) according to the general procedure for trifluoromethylation. Additionally, in the trifluoromethylation of **3b**, 1.2 equiv (0.18 mmol) of **1a** was used. The title compound was purified by column chromatography (pentane) and isolated in 53% yield (15 mg) from **3a** and in 61% yield (17 mg) from **3b**. The NMR data obtained are in agreement with literature values.[15] Spectral data for **4a**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41−7.36 (m, 2H), 7.36−7.30 (m, 2H), 7.30−7.24 (m, 1H), 6.61 (d, J = 15.8 Hz, 1H), 6.11 (dt, J = 15.8, 7.3 Hz 1H), 3.06−2.93 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.8, 136.4, 128.8, 128.3, 126.6, 126.1 (q, J_{C-F} = 277.2 Hz), 117.3 (q, J_{C-F} = 3.6 Hz), 37.8 (q, J_{C-F} = 29.9 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ −66.2 (t, J = 10.7 Hz).

***(E)*-1-Chloro-4-(4,4,4-trifluorobut-1-en-1-yl)benzene (4b).** The product was synthesized from **2b** (0.15 mmol, 28 mg) according to the general procedure for trifluoromethylation. The title compound was purified by column chromatography (pentane) and isolated as an oil in 85% yield (28 mg). The NMR data obtained are in agreement with literature values.[16] Spectral data for **4b**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30 (br s, 4H), 6.56 (d, J = 15.8 Hz, 1H), 6.09 (dt, J = 15.8, 7.3 Hz, 1H), 3.06−2.92 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.6, 134.8, 134.0, 129.0, 127.8, 125.9 (q, J_{C-F} = 277.2 Hz), 118.1 (q, J_{C-F} = 3.6 Hz), 37.8 (q, J_{C-F} = 30.0 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ −66.2 (t, J = 10.6 Hz).

***(E)*-1-Nitro-4-(4,4,4-trifluorobut-1-en-1-yl)benzene (4c).** The product was synthesized from **2c** (0.15 mmol, 30 mg) and **2d** (0.15 mmol, 30 mg) according to the general procedure for trifluoromethylation except that pentane was added to the reaction mixture after completion of the reaction. The organic solvent was separated from the precipitated PPh_3, and the solid was washed with pentane two additional times. The organic phases were then joined, and the product was purified by column chromatography (pentane/diethylether 10:1) and isolated as an oil in 51% yield (18 mg) from **2c** and

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in 62% (22 mg) yield from **2d**. Spectral data for **4c**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.24−8.16 (m, 2H), 7.56−7.48 (m, 2H), 6.69 (d, J = 15.9, 1H), 6.30 (dt, J = 15.9, 7.2 Hz, 1H), 3.13−2.99 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.5, 142.5, 134.8, 127.2, 125.7 (q, J_{C-F} = 276.8 Hz), 124.2, 122.3 (q, J_{C-F} = 3.6 Hz), 37.9 (q, J_{C-F} = 30.3 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ −65.9 (t, J = 10.5 Hz); HRMS (ESI) m/z calcd. for $[C_{10}H_8F_3NO_2Na]^+$ 254.0399, found 254.0391.

(*E*)-1-Methoxy-4-(4,4,4-trifluorobut-1-en-1-yl)benzene (4d). The product was synthesized from **2e** (0.15 mmol, 27 mg) according to the general procedure for trifluoromethylation except that pentane was added to the reaction mixture after completion of the reaction. The organic solvent was separated from the precipitated PPh_3, and the solid was washed with pentane two additional times. The organic phases were then joined, and the product was purified by column chromatography (pentane/diethylether 20:1) and isolated as an oil in 79% yield (26 mg). The NMR data obtained are in agreement with literature values.[20] Spectral data for **4d**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.35−7.29 (m, 2H), 6.89−6.83 (m, 2H), 6.54 (d, J = 15.9 Hz, 1H), 5.96 (dt, J = 15.9, 7.3 Hz, 1H), 3.81 (s, 3H), 3.01−2.91 (m, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 159.7, 136.2, 129.2, 127.8, 126.1 (q, J_{C-F} = 276.6 Hz), 115.0 (q, J_{C-F} = 3.6 Hz), 114.2, 55.5, 37.8 (q, J_{C-F} = 29.8 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ −66.3 (t, J = 10.7 Hz).

(*E*)-(6,6,6-Trifluorohex-3-en-1-yl)benzene (4e). The product was synthesized from **2f** (0.15 mmol, 27 mg) according to the general procedure for trifluoromethylation. The title compound was purified by column chromatography (pentane) and isolated in 75% yield (24 mg). Compound **4e** was also synthesized from allylic trifluoroacetate **3c** (0.15 mmol, 39 mg) according to the general procedure for trifluoromethylation except that pentane was added to the reaction mixture after completion of the reaction. The organic solvent was separated from the precipitated PPh_3, and the solid was washed with pentane two additional times. The organic phases were then collected, and **4e** was purified by column chromatography (pentane) and isolated as an oil in 30% yield (10 mg). Compound **5a′** was isolated in 32% yield (8 mg). The spectral data for this compound is in agreement with previously reported literature values.[26] Spectral data for **4e**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32−7.27 (m, 2H), 7.23−7.16 (m, 3H), 5.75 (dt, J = 15.4, 6.7 Hz, 1H), 5.41 (dtt, J = 15.4, 7.0, 1.5 Hz, 1H), 2.85−2.67 (m, 4H), 2.45−2.34 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.6, 137.5, 128.6, 128.5, 126.2 (q, J_{C-F} = 276.5 Hz), 124.8, 118.5 (q, J_{C-F} = 3.6 Hz), 37.5 (q, J_{C-F} = 29.6 Hz), 35.5, 34.4; ^{19}F NMR (376 MHz, $CDCl_3$) δ −66.7 (t, J = 10.8 Hz); (EI) m/z (rel intens) 213 (M+, 10), 181 (31), 131 (23), 117 (8), 91 (100).

(*E*)-(4,4,4-Trifluorobut-1-enyl)cyclohexane (4f). The product was synthesized from **2g** (0.15 mmol, 24 mg) (linear/branched isomeric ratio 6:1) according to the general procedure for trifluoromethylation. The title compound was purified by column chromatography (pentane) and isolated in as an oil 59% yield (17 mg). Spectral data for **4f**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.65 (dd, J = 15.5, 6.7 Hz, 1H), 5.33 (dtd, J = 15.5, 7.0, 1.4 Hz, 1H), 2.81−2.69 (m, 2H), 2.04−1.92 (m, 1H), 1.79−1.69 (m, 4H), 1.69−1.61 (m, 1H), 1.37−1.01 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.3, 126.3 (q, J_{C-F} = 276.5 Hz), 115.2 (q, J_{C-F} = 3.5 Hz), 40.8, 37.6 (q, J_{C-F} = 29.4 Hz), 32.8, 26.3, 26.1; ^{19}F NMR (376 MHz, $CDCl_3$) δ −66.8 (t, J = 10.8 Hz); (EI) m/z (rel intens) 191 (M+, 16), 109 (6), 97 (3), 83 (5), 67 (100).

(*E*)-9,9,9-Trifluoro-2,6-dimethylnona-2,6-diene (4g). The product was synthesized from **2h** (0.15 mmol, 33 mg) according to the general procedure for trifluoromethylation. The title compound was purified by column chromatography (pentane) and isolated as an oil in 90% yield (28 mg, E/Z ratio 3:1, determined from ^{19}F NMR spectroscopy). The NMR data obtained are in agreement with literature values.[16] Spectral data for (*E*)-**4g**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.26−5.01 (m, 2H), 2.87−2.72 (m, 2H), 2.16−2.02 (m, 4H), 1.69 (s, 3H), 1.66 (s, 3H), 1.60 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.5, 132.0, 126.7 (q, J_{C-F} = 276.6 Hz), 123.8, 112.0 (q, J_{C-F} = 3.4 Hz), 39.7, 33.1 (q, J_{C-F} = 29.3 Hz), 26.5, 25.8, 17.8, 16.5; ^{19}F NMR (376 MHz, $CDCl_3$) δ −66.4 (t, J = 11.0 Hz).

(*E*)-Dimethyl(phenyl)(4,4,4-trifluorobut-1-en-1-yl)silane (4h). The product was synthesized from **2i** (0.15 mmol, 32 mg) according to the general procedure for trifluoromethylation. The title compound was purified by column chromatography (pentane) and isolated as an oil in 41% yield (15 mg). The compound $PhMe_2Si-F$[38] was observed to form as a byproduct (ratio **4h**: $PhMe_2Si-F$ 1:1.3 determined from ^{19}F NMR analysis of the crude reaction mixture). Spectral data for **4h**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54−7.48 (m, 2H), 7.40−7.34 (m, 3H), 6.11 (d, J = 18.5 Hz, 1H), 6.00 (dt, J = 18.5, 6.2 Hz, 1H), 3.00−2.86 (m, 2H), 0.36 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.0, 137.3, 135.0 (q, J_{C-F} = 3.4 Hz), 133.9, 129.3, 128.0, 125.9 (q, J_{C-F} = 277.1 Hz), 41.2 (q, J_{C-F} = 28.9 Hz), −2.7; ^{19}F NMR (376 MHz, $CDCl_3$) δ −66.0 (t, J = 10.8 Hz).

(*R*)-4-(Prop-1-en-2-yl)-1-(2,2,2-trifluoroethyl)cyclohex-1-ene (4i). The product was synthesized from **2j** (linear/branched isomeric ratio 1:3, 0.15 mmol, 26 mg) according to the general procedure for trifluoromethylation. The title compound was purified by column chromatography (pentane) and isolated as an oil in 56% yield (17 mg). Spectral data for **4i**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.73−5.66 (m, 1H), 4.76−4.68 (m, 2H), 2.71 (q, J = 11.2 Hz, 2H), 2.24−2.05 (m, 4H), 2.05−1.91 (m, 1H), 1.88−1.78 (m, 1H), 1.74 (s, 3H), 1.56−1.43 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.6, 128.8, 127.5 (q, J_{C-F} = 2.6 Hz), 126.4 (q, J_{C-F} = 277.8 Hz), 109.0, 41.9 (q, J_{C-F} = 28.7 Hz), 40.5, 31.0, 29.3, 27.7, 20.9; ^{19}F NMR (376 MHz, $CDCl_3$) δ −64.8 (t, J = 11.2 Hz).

(*E*)-(5-Fluoropent-3-en-1-yl)benzene (5a). The product was synthesized from **2f** (0.15 mmol, 27 mg) according to the general procedure for fluorination except that the reaction was performed at half the scale. The copper reagent used, $(PPh_3)_3CuF$ (1.8 equiv, 0.27 mmol, 235 mg, MW = 869.40 g/mol), had no solvent molecule coordinated in solid form. The title compound was purified by column chromatography (pentane/chloroform 9:1) and isolated as an oil in 53% yield (13 mg). Spectral data for **5a**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33−7.27 (m, 2H), 7.23−7.17 (m, 3H), 5.94−5.83 (m, 1H), 5.79−5.67 (m, 1H), 4.80 (dd, J = 47.4, 6.2 Hz, 1H), 2.77−2.70 (m, 2H), 2.46−2.38 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.5, 136.4 (d, J_{C-F} = 12.0 Hz), 128.54, 128.52, 126.1, 125.3 (d, J_{C-F} = 16.5 Hz), 83.7 (d, J_{C-F} = 160.6 Hz), 35.3 (d, J_{C-F} = 3.2 Hz), 34.1 (d, J_{C-F} = 2.1 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ −208.3 (tm, J = 47.4 Hz); (EI) m/z (rel intens) 164 (M, 7), 131 (51), 104 (5), 91 (100), 77 (3).

3-Fluorocyclohex-1-ene (5b). The product was synthesized from **2k** (0.30 mmol, 48 mg) in a soda lime reaction vial according to the general procedure for fluorination using the copper reagent $(PPh_3)_3CuF{\cdot}0.5CHCl_3$ (1.8 equiv, 0.54 mmol, 500 mg, MW = 924.31 g/mmol) except that the reaction was run at room temperature for 10 min. The title compound was formed in 92% NMR yield according to ^{1}H NMR using 1,3,5-trimethyoxybenzene as an internal standard. The NMR data obtained are in agreement with literature values.[27]

***cis*-(Methyl 5-fluorocyclohex-3-enecarboxylate) (5c).** The product was synthesized from **2l** (trans/cis 15:1, 0.30 mmol, 52 mg) according to the general procedure for fluorination, and the product was purified by column chromatography (pentane/diethylether 10:1). Depending on the purification method for **1c** (see above) the complex contained varying amounts of coordinated solvent molecules (MeOH or $CHCl_3$). When using copper reagent $(PPh_3)_3CuF{\cdot}2.8MeOH$ (1.4 equiv, 0.43 mmol, 417 mg, MW = 959.11 g/mol), the product was isolated as an oil in 57% yield (27 mg, cis/trans 4:1) together with methoxy derivative (methyl-5-methoxycyclohex-3-ene-1-carboxylate)[39] in 23% yield (12 mg, cis/trans 1.5:1). When using copper reagent $(PPh_3)_3CuF{\cdot}0.8CHCl_3$ (1.8 equiv, 0.54 mmol, 528 mg, MW = 964.9 g/mol), the product was isolated in 76% yield (36 mg, cis/trans 4:1). The isomeric ratios were determined from ^{1}H and ^{19}F NMR of the crude reaction mixtures. The NMR data obtained are in agreement with literature values.[30] Spectral data for *cis*-**5c**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.92−5.84 (m, 1H), 5.83−5.75 (m, 1H), 5.13 (dm, J = 48.9 Hz, 1H), 3.69 (s, 3H), 2.71−2.61 (m, 1H), 2.47−2.22 (m, 3H), 1.98−1.86 (m, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 174.4, 130.0 (d, J_{C-F} = 9.7 Hz), 126.9 (d, J_{C-F} = 20.8 Hz), 87.3 (d, J_{C-F} = 163.9 Hz), 52.0, 37.4 (d, J_{C-F} = 8.2 Hz), 31.6 (d, J_{C-F} = 20.3 Hz), 27.3 (d, J_{C-F} = 2.1 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ −173.0 (tm, J = 48.9 Hz).

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***trans*-(4-Fluorocyclohex-2-en-1-yl acetate) (5d).** The product was synthesized from **2m** (cis/trans 24:1, 0.30 mmol, 52 mg) according to the general procedure for fluorination, and the product was purified by column chromatography (pentane/diethylether 9:1). When using copper reagent $(PPh_3)_3CuF{\cdot}2.8MeOH$ (1.4 equiv, 0.43 mmol, 417 mg, MW = 959.11 g/mol), the product was isolated as an oil in 62% yield (30 mg, cis/trans 8:1). When using copper reagent $(PPh_3)_3CuF{\cdot}0.5CHCl_3$ (1.8 equiv, 0.54 mmol, 500 mg, MW = 924.31 g/mol), the product was isolated in 77% yield together with the regioisomer of **5d**: 2-fluorocyclohex-3-en-1-yl acetate (37 mg, *cis*-**5d**/*trans*-**5d**/regioisomer of **5d** 16:68:17). The isomeric ratio was determined from ^{19}F NMR of the crude reaction mixture. The NMR data obtained are in agreement with literature values.[40] Spectral data for *trans*-**5d**: ^1H NMR (500 MHz, $CDCl_3$) δ 6.05−5.96 (m, 1H), 5.96−5.89 (m, 1H), 5.37−5.24 (m, 1H), 5.05 (dm, J = 47.8 Hz, 1H), 2.21−2.09 (m, 2H), 2.04 (s, 3H), 1.92−1.79 (m, 1H), 1.72−1.59 (m, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 170.6, 131.1 (d, J_{C-F} = 9.6 Hz), 130.2 (d, J_{C-F} = 19.1 Hz), 85.6 (d, J_{C-F} = 164.5 Hz), 67.5 (d, J_{C-F} = 2.6 Hz), 26.7 (d, J_{C-F} = 20.0 Hz), 25.3 (d, J_{C-F} = 5.2 Hz), 21.3; ^{19}F NMR (376 MHz, $CDCl_3$) δ −172.2 (m).

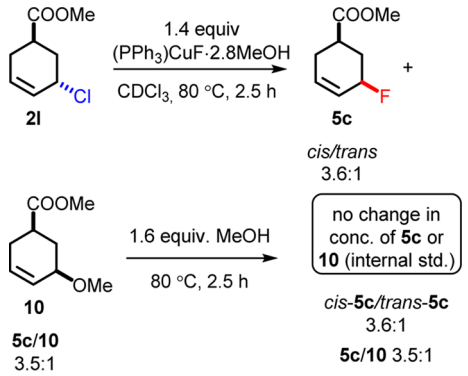
Competition Experiments (Scheme 5). The reaction was performed according to the general procedure for trifluoromethylation using a combination of **2a** (0.15 mmol, 23 mg) and **2e** (0.15 mmol, 27 mg) or **2c** (0.15 mmol, 30 mg) as starting materials and trifluoromethylating reagent $(PPh_3)_3CuCF_3$ (**1a**, 0.15 mmol, 138 mg) in 0.8 mL $CDCl_3$. The ratios between the products formed were determined using ^{19}F NMR to be **4a**/**4d** 1:1.8 and ^{19}F NMR to be **4a**/**4c** 1:0.7.

Inihibition Experiment with PPh_3 (Table 3). The reaction was performed according to the general procedure for trifluoromethylation using **2a** (0.15 mmol, 23 mg) as starting material except that the reaction was performed in 0.5 mL of $CDCl_3$ for 5 h and that different amounts of PPh_3 (0, 1, 2, or 10 equiv) were added. The ratios between the products formed were determined using ^1H NMR analysis of the crude reaction mixtures.

Inihibition Experiment with Radical Scavenger TEMPO (Scheme 3). The reaction was performed according to the general procedure for trifluoromethylation using **2a** (0.15h mmol, 23 mg) as starting material in the presence of TEMPO (**6**) (2 equiv, 0.3 mmol, 47 mg). As the ^1H NMR shifts of **7** and **8** are overlapping, we used both ^1H and ^{19}F spectroscopy to determine the yields. From the ratio of **4a** and **8** in ^1H NMR and from ^{19}F NMR (using α,α,α-trifluorotoluene as an internal standard) the yields were determined to be 44% of **4a**, 37% of **8**[41] (with respect to the amount of **2a** employed) and 19% of **7** (with respect to the amount of **1a** employed). Spectral data for **8**: ^1H NMR (400 MHz, $CDCl_3$) δ 7.43−4.37 (m, 2H), 7.34−7.28 (m, 2H), 7.25−7.20 (m, 1H), 6.60 (d, J = 16.0 Hz, 1H), 6.29 (dt, J = 16.0, 5.9 Hz, 1H), 4.45 (dd, J = 5.9, 1.5 Hz, 2H), 1.64−1.53 (m, 1H), 1.51−1.44 (m, 4H), 1.39−1.30 (m, 1H), 1.21 (s, 6H), 1.14 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.3, 131.5, 128.6, 127.6, 126.6, 125.8, 78.2, 60.0, 39.9, 33.2, 20.4, 17.3.

Control Experiments with TEMPO. The reaction was performed according to the general procedure for trifluoromethylation but without allylic substrate and with the addition of TEMPO (**6**) (0.3 mmol, 47 mg). According to ^{19}F NMR analysis (using α,α,α-trifluorotoluene as an internal standard) <0.5% of **7** was formed. Additionally, only unreacted **1a** can be observed in the crude reaction mixture by ^{19}F NMR in more than trace amounts. The reaction was performed according to the general procedure for trifluoromethylation using **2a** as starting material with the addition of TEMPO (**6**) (2 equiv, 0.3 mmol, 47 mg) but without copper complex **1a**. According to ^1H NMR analysis **2a** is still intact after the reaction, and other products were not formed in more than trace amounts.

Investigation into the Formation of Methoxy Ether By-product 10 during the Fluorination of 2l. To a screw top vial were added **2l** (0.04 mmol, 7 mg), $(PPh_3)_3CuF{\cdot}2.8MeOH$ (1.4 equiv, 0.056 mmol, 54 mg, MW = 959.11 g/mol) and $CDCl_3$ (0.15 mL) inside the glovebox. An internal standard was included in the reaction mixture (1,3,5-trimethyoxybenzene), and the clear solution was heated at 80 °C for 2.5 h. Analysis by ^1H NMR spectroscopy revealed that all **2l** had been consumed. Ratios: **5c**/**10** 3.5:1 and *cis*-**5c**/*trans*-**5c** 3.6:1. MeOH was thereafter added to the reaction mixture (approximately 1.6 equiv, 2 mg), and the solution was heated at 80 °C for another 2.5 h. ^1H NMR analysis revealed that no decomposition of **5c** and **10** had occurred (by comparing the integrals with the integrals of the internal standard) and that the *cis*-**5c**/*trans*-**5c** ratio of 3.6:1 was maintained. These results show that **10** forms from **2l** and not from **5c**.



■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The NMR spectra of the products are given. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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