Copper-Mediated Direct Functionalization of Unsaturated C–C Bonds with Ethyl Bromo(difluoro)acetate: A Straightforward Access to Highly Valuable Difluoromethylated Alkenes

Marie-Charlotte Belhomme,[1] Delphine Dru,[1] Heng-Ying Xiong, Dominique Cahard, Tatiana Besset,* Thomas Poisson,* Xavier Pannecoucke

Normandie Université, COBRA, UMR 6014 et FR 3038, Université de Rouen, INSA Rouen, CNRS, 1 rue Tesnière, 76821 Mont Saint-Aignan, France
Fax +33(2)35522959; E-mail: tatiana.besset@insa-rouen.fr; E-mail: thomas.poisson@insa-rouen.fr

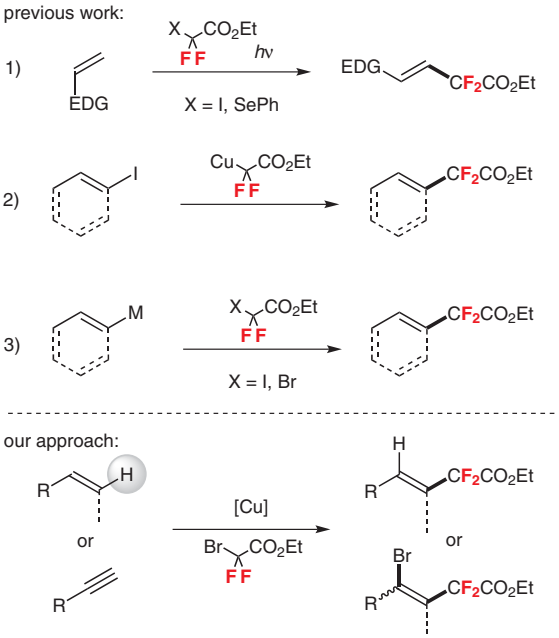
Received: 27.02.2014; Accepted after revision: 13.04.2014

Abstract: A copper-mediated fluorofunctionalization of alkenes and alkynes has been developed. This method provides ready access to trisubstituted difluoromethylated olefins (from dihydropyrans, glycal derivatives, or terminal alkynes) or to tetrasubstituted olefins (from disubstituted alkynes). The products were obtained in good to high yields with acceptable *E*/*Z* selectivities. Finally, a first direct route to difluoromethylated alkynes is reported, albeit with low yields.

Key words: copper, fluorine, alkenes, alkynes, carbohydrates

Transition-metal-promoted carbon–carbon or carbon–heteroatom (e.g., C–O or C–N) bond formation is well recognized as a powerful method for the functionalization of organic molecules.[2] As a result, this field of research was recognized by the award of the Nobel Prize in Chemistry to Heck, Suzuki, and Negishi in 2010 for their development of palladium-catalyzed cross-coupling reactions. Among the transition metals, copper has particular appeal for performing new transformations because of its high abundance, low cost, and low toxicity compared with its congeners. It is therefore not surprising that copper chemistry is a field showing tremendous expansion. Indeed, since the discovery of the venerable Glaser and Ullman–Goldberg reactions in 1869 and 1901, respectively, much attention has been paid to developing new transformations mediated or catalyzed by copper.[3] These efforts have resulted in several elegant and efficient processes to achieve new transformations, permitting novel retrosynthetic disconnections.

Fluorinated compounds are of great interest in medicinal chemistry, materials, and agrochemical research.[4] The development of new and efficient methods for preparing these compounds is therefore a relevant challenge. Several recent efforts have focused on the selective introduction of fluorinated moieties, particularly by direct and selective C–H bond-functionalization reactions.[5,6] Although the introduction of the trifluoromethyl group has been widely explored, the selective introduction of other functionalized fluorinated motifs remains in its infancy despite the considerable possibilities for post-functionalization.[7] Surprisingly, the direct introduction of the ethoxycarbonyl(difluoro)methyl moiety into non-prefunctionalized substrates is underexplored.[8] Indeed, the usual methods generally require the use of prefunctionalized substrates. For instance, most of the well-established methods rely on radical addition of halo or chalcogeno-fluorinated reagents to alkenes,[9] reductive coupling of aryl or vinyl iodides with halo or silylated ethoxycarbonyl(difluoro)methyl derivatives in the presence of copper bronze,[10] or transition-metal-catalyzed Suzuki or Negishi cross couplings of halogenated ethoxycarbonyl(difluoro)methyl derivatives (Scheme 1).[11]



Scheme 1 State-of-the-art methods for introducing ethoxycarbonyl(difluoro)methyl group

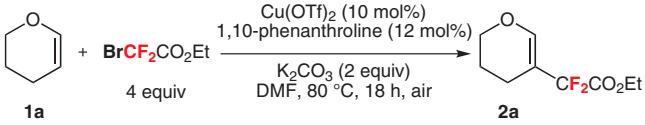
Therefore, as part of our ongoing research program devoted to the design and synthesis of new fluorinated building blocks,[12] we were interested in the direct and selective introduction of the ethoxycarbonyl(difluoro)methyl group

SYNTHESIS 2014, 46, 1859–1870
Advanced online publication: 28.05.2014
DOI: 10.1055/s-0033-1338637; Art ID: ss-2014-c0137-st

by using copper as a promoter.[8,13] Here, we report the direct copper-mediated functionalization of alkenes and alkynes.

At the outset of the project, we focused our attention on the direct and selective introduction of the ethoxycarbonyl(difluoro)methyl moiety onto a dihydropyran backbone,[8] and we examined the effects of various changes in the reaction conditions. Under the optimized conditions, the fluorinated product **2a** was obtained in 73% isolated yield by using copper(II) triflate as a catalyst (Table 1, entry 1). Although a palladium catalyst promoted the reaction, the isolated yield was only 19% (entry 2); this result highlights the efficiency of the copper catalyst in comparison with a palladium catalyst. The base played a crucial role in the outcome of the reaction. Indeed, the replacement of potassium carbonate by an organic base (triethylamine) had a marked effect on the reaction, affording product **2a** in only 21% yield (entry 3); another inorganic base (cesium carbonate) also gave a lower yield (entry 4). We found that two equivalents of base were required to ensure a reasonable yield (entry 5). Pleasingly, the replacement of the copper(II) catalyst by a copper(I) catalyst provided the fluorinated dihydropyran **2a** in good yield (entries 6 and 7). These two results suggested that copper(I) species might be the real active catalytic species in this transformation. Finally, control experiments showed that no reaction occurred in the absence of a base or a copper catalyst (entries 8 and 9).

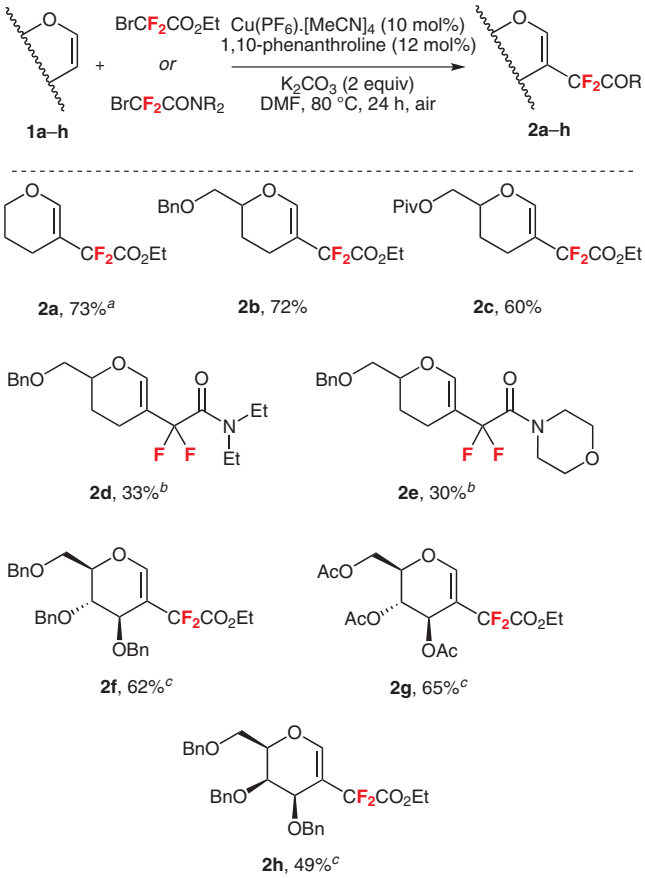
Table 1 Optimization of the Reaction of 3,4-Dihydro-2*H*-pyran



Entry	Deviations from standard conditions	Yield[a] (%)
1	none	73
2	$Pd(PPh_3)_4$ instead of $Cu(OTf)_2$	19
3	Et_3N instead of K_2CO_3	21[b]
4	Cs_2CO_3 instead of K_2CO_3	47
5	K_2CO_3 (1 equiv)	18[b]
6	CuI instead of $Cu(OTf)_2$	70
7	$[Cu(OTf)]_2{\cdot}C_6H_6$ instead of $Cu(OTf)_2$	62[b]
8	no base	NR[b,c]
9	no metal	NR[b,c]

[a] Isolated yield.
[b] Determined by ^{19}F NMR using $PhCF_3$ as an internal standard.
[c] NR = no reaction.

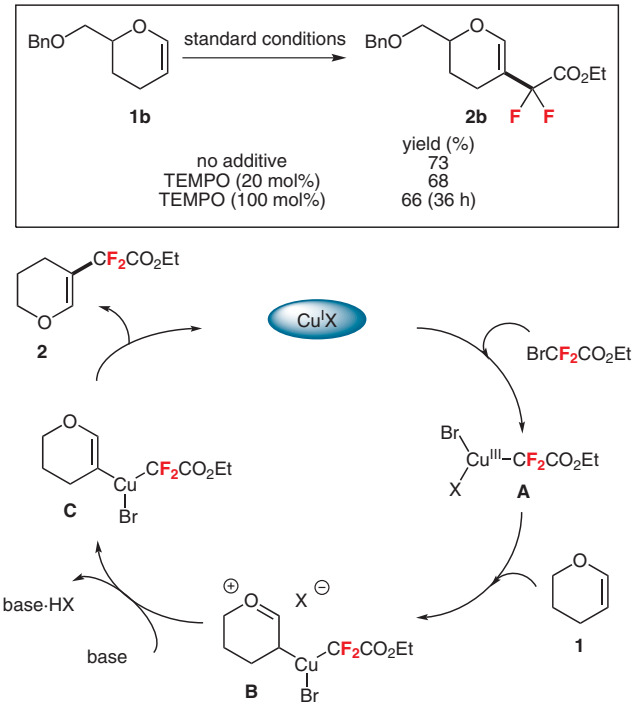
We then applied our optimized reaction conditions to other dihydropyran derivatives and to several carbohydrate derivatives (Scheme 2). First, we extended the reaction to dihydropyrans **1b** and **1c** containing different protecting groups. Pleasingly, the benzyl-protected 2-hydroxydihydropyran **1b** reacted smoothly to give the fluorinated adduct **2b** in 72% yield. A pivaloyl protecting group was also compatible, and the corresponding product **2c** was obtained in 60% isolated yield. We then turned our attention to amide derivatives. Treatment of dihydropyran **1b** with the 2-bromo-*N*,*N*-diethyl-2,2-difluoroacetamide under slightly modified conditions (5 mol% of Cu_2O with Cs_2CO_3 as the base at 90 °C) gave the corresponding product **2d** in a modest 33% isolated yield. Similarly, treatment of an *N*-morpholino derivative under our modified conditions gave the coupling product **2e** in 30% isolated yield. These lower yields might be explained by the lower electrophilicity of the intermediate copper complex (see below) compared with the one derived from ethyl bromo(difluoro)acetate. Finally, because of the importance of fluorinated carbohydrates, we decided to apply our reaction conditions to glycal derivatives. To our delight, after a slight modification of the reaction temperature and the stoichiometry of ethyl bromo(difluoro)acetate, tri-*O*-benzyl-D-glucal (**1f**) reacted smoothly to give the fluori-



Scheme 2 Difluoromethylation reactions of dihydropyrans and glycal derivatives. *Reagents and conditions*: **1** (0.24 mmol), $BrCF_2CO_2Et$ or $BrCF_2CONR_2$ ($NR_2 = NEt_2$ or morpholino) (4 equiv), $Cu(PF_6){\cdot}[MeCN]_4$ (0.024 mmol), 1,10-phenanthroline (0.029 mmol), K_2CO_3 (0.48 mmol), DMF (1.2 mL), 80 °C. [a] $Cu(OTf)_2$ was used. [b] The reaction was performed at 90 °C with 5 mol% of Cu_2O and with Cs_2CO_3 as the base. [c] Reaction was performed at 110 °C with 8 equiv of $BrCF_2CO_2Et$.

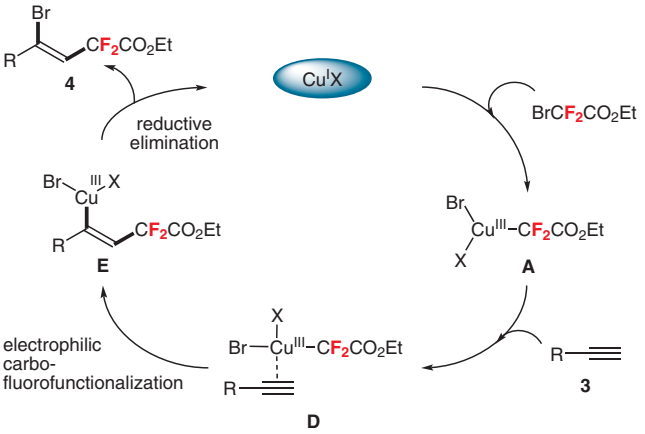
nated carbohydrate **2f** in 62% yield, and D-glucal triacetate (**1g**) gave a similar yield (65%) of the corresponding product. When tri-*O*-benzyl-D-galalactal (**1h**) reacted under the same conditions, the corresponding product **2h** was isolated in 49% yield.

We were intrigued by the mechanism of this new transformation, so we performed some mechanistic experiments and, as a result, we proposed the following catalytic cycle (Scheme 3). To elucidate the reaction pathway, we carried out the reaction in the presence of radical inhibitors or radical scavengers.[14] The addition of (2,2,6,6-tetramethylpiperidin-1-yl)oxyl (TEMPO) did not have any marked effect on the transformation, and the corresponding product **2b** was obtained in a similar yield. On the basis of these results, we proposed a mechanism involving a highly electrophilic copper(III) species.[15] First, the copper(I) catalyst undergoes an oxidative addition to the C–Br bond of ethyl bromo(difluoro)acetate to give the copper(III) intermediate **A**. A nucleophilic attack of the dihydropyran derivative **1** then generates the oxonium species **B**, which is released as the enol ether **C** by the base. Finally, reductive elimination regenerates the catalyst and delivers the desired product **2**.[16]



Scheme 3 Mechanistic study and proposed mechanism. *Reagents and conditions*: **1b** (0.24 mmol), $BrCF_2CO_2Et$ (4 equiv), $Cu(PF_6)\cdot[MeCN]_4$ (0.024 mmol), 1,10-phenanthroline (0.029 mmol), K_2CO_3 (0.48 mmol), DMF (1.2 mL), 80 °C.

On the basis of this proposed mechanism, which involves an electrophilic copper(III) species, we wondered if such process might be further applied in the direct functionalization of another important class of versatile compounds: the alkynes. Indeed, this hypothesis was supported by recent report from Gaunt's group,[17] who found that alkynes and alkenes are suitable reaction partners for a highly electrophilic species (an iodonium salt) in the presence of a copper catalyst. Accordingly, the copper(III) species **A** might form a copper π-complex **D**, which would then performs an electrophilic carbofluorofunctionalization, generating a new copper(III) species **E**. The latter would undergo a reductive elimination to release the bromofluorinated alkene **4** with regeneration of the copper species (Scheme 4).



Scheme 4 Proposed reaction pathway for the functionalization of alkynes

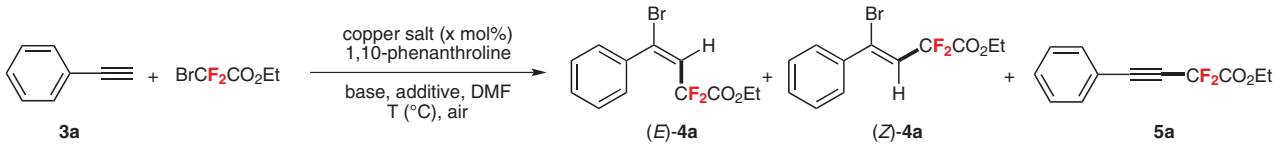
Because of the importance of fluorinated alkenes, the design of innovative and straightforward synthetic pathways to these highly valuable compounds is an interesting challenge that has recently attracted growing interest from several research groups.[18] The application of the strategy described above to the functionalization of alkynes should give the corresponding difluoromethylated alkenes, compounds that are usually obtained by radical addition of iodo- or seleno-substituted difluoroacetates.[9,19] If our strategy proved successful, the resulting difluoromethylated vinyl bromides would constitute highly valuable trisubstituted olefin building blocks, capable of undergoing further synthetic transformations.

We began by studying the reaction of ethyl bromodifluoroacetate with phenylacetylene (**3a**) as a model substrate (Table 2). After extensive investigations, we were pleased to discover that alkene **4a** could be obtained in the presence of a catalytic amount of copper(II) triflate in *N*,*N*-dimethylformamide under air at 120 °C (Table 2, entry 1). Although (*E*)-**4a** was obtained in low yield, this preliminary result demonstrated the potential of the approach. Encouraged by this observation, we decided to pursue our investigations by using a stoichiometric amount of the copper salt to improve the conversion of alkyne **3a** into the corresponding alkene **4a**. For this purpose, several copper sources were examined with a shorter reaction time at 140 °C (entries 2–4). Both copper(II) and copper(I) salts provided the expected alkene **4a**, but the copper(II) complexes were far more efficient. In particular, when the reaction was performed with copper(II) triflate, alkene **4a** was obtained in a high yield as an inseparable

68:32 mixture of the *E*- and *Z*-diastereoisomers (entry 3). The geometry of the double bond was established unequivocally by means of NOESY experiments.[19] Decreasing the temperature to 120 °C (entry 5) had a beneficial effect on the reactivity while the selectivity remained unchanged (*E*/*Z* 68:32). In contrast, the use of another base (sodium acetate) did not have a significant effect on the outcome of the reaction (entry 6; *E*/*Z* 74:26), whereas the use of bathophenanthroline as a ligand gave a lower yield of **4a** (entry 7). Finally, control experiments revealed that the fluorinated containing olefin **4a** was not obtained in the absence of a copper salt or of a base.[20]

Next, we examined the scope of the reaction for the synthesis of alkenes **4** from terminal and internal alkynes **3**. The desired products were generally isolated in high yields and in moderate to good *E*/*Z* ratios (Scheme 5). Initially, we tested aryl-substituted terminal alkynes, which gave the corresponding trisubstituted alkenes. We were delighted to find that the reaction proceeded with a broad tolerance to various functional groups. Electron-rich (**3b** and **3c**) and electron-deficient (**3d**, **3e**, and **3f**) arylacetylene derivatives were suitable substrates for this reaction. Notably, even a bromine atom on the aryl group was tolerated, thereby providing the dibromo derivative **4f**, which offers new possibilities for further functionalization, for example, by cross-coupling reactions. Arylalkynes with various substitution patterns, such as *meta*- or *ortho*-substitution (**3g**, **3h** and **3i**), were also efficiently converted into the corresponding difluoromethylated olefins (**4g**, **4h** and **4i**). Steric hindrance on the aromatic ring had no effect on the outcome of the reaction, except in the case of the *o*-methoxy-substituted derivative **4h**. Pleasingly, the reaction was also compatible with hetaryl groups such as 3-thienyl (**3j**) or 2-pyridyl (**3k**). These results highlight the broad scope of this transformation. Note that in the case of the pyridyl compound **4k**, a reverse selectivity was observed (*E*/*Z* ratio of 41:59), probably as a result of coordination of the pyridine ring to the copper species. The benzylic-substituted alkyne **3l** was functionalized with a moderate yield of 23% and with loss of diastereoselectivity. Finally, to assess the effectiveness of our reaction, more-challenging disubstituted alkynes, such as **3m** and **3n**, were also tested. Gratifyingly, under the standard conditions, 1-phenylbutyne and diphenylacetylene gave

Table 2 Optimization Study for the Preparation of Fluoroalkene **4a**[a]



3a (*E*)-**4a** (*Z*)-**4a** **5a**

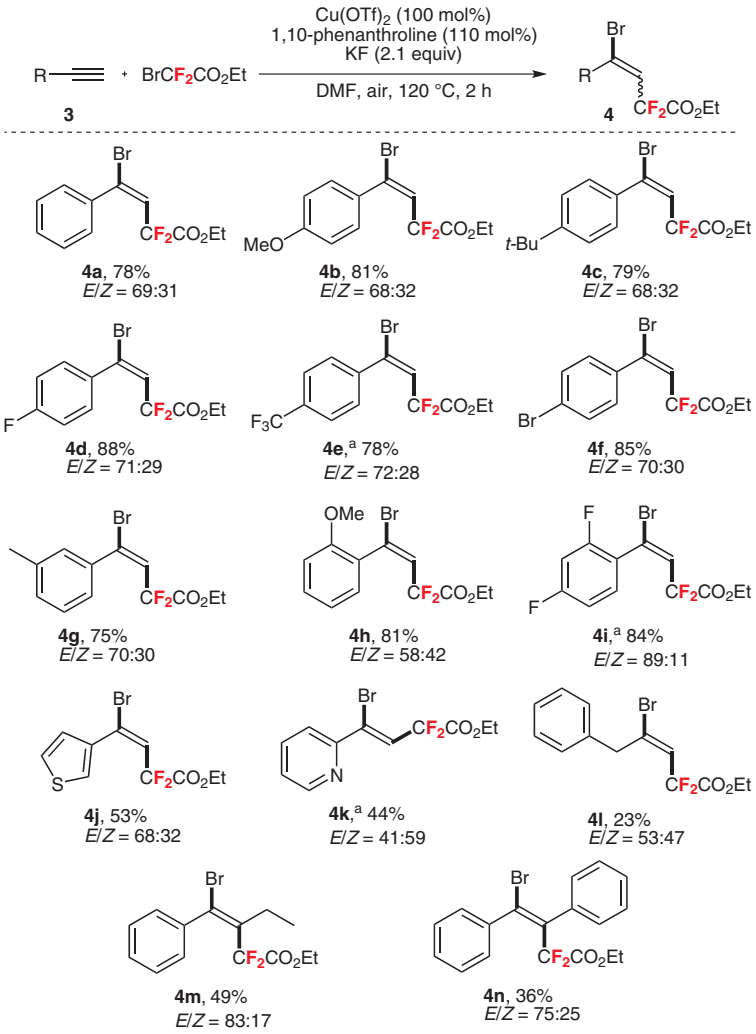
Entry	Copper salt	x mol%	Base	Additive	Yield[b] of **4a** (%)	*E*/*Z* ratio[c]	Yield[b] of **5a** (%)
1[d,e]	$Cu(OTf)_2$	10	KF	–	12	–	–
2[f]	$CuCl_2$	100	KF	–	55	73:27	–
3[f]	$Cu(OTf)_2$	100	KF	–	76	68:32	–
4[f]	CuBr	100	KF	–	30	90:10	–
5[d,g]	$Cu(OTf)_2$	100	KF	–	94 (78)[h]	69:31	–
6[d,g]	$Cu(OTf)_2$	100	NaOAc	–	84	74:26	–
7[d,g,i]	$Cu(OTf)_2$	100	KF	–	62	63:37	–
8[d,g]	$Cu(acac)_2$	100	KF	–	52	69:31	3
9[j]	$Cu(acac)_2$	10	KF	$Cu(OAc)_2$	–	–	18
10[j]	$Cu(acac)_2$	10	CsOPiv	$Cu(OAc)_2$	–	–	28
11[j]	$Cu(acac)_2$	10	NaOAc	$Cu(OAc)_2$	–	–	29
12[j]	–	–	KF	$Cu(OAc)_2$	–	–	3

[a] Reaction conditions: **3a** (1 equiv), $BrCF_2CO_2Et$ (5 equiv), 1,10-phenanthroline (1.1x mol%), base (2.1 equiv), additive (1.5 equiv), [DMF] = 0.125 mol/L, air.
[b] Yields determined by ^{19}F NMR with $PhCOCF_3$ as internal standard.
[c] Determined by ^{19}F NMR spectroscopy on the crude reaction mixture.
[d] At 120 °C.
[e] 16 h.
[f] 140 °C for 2 h.
[g] 2 h.
[h] Isolated yield.
[i] Bathophenanthroline was used instead of 1,10-phenanthroline.
[j] 100 °C for 16 h, [DMF] = 0.1 mol/L.

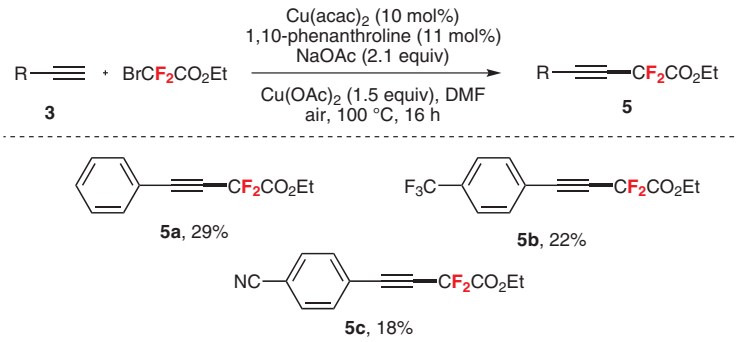
the otherwise relatively inaccessible tetrasubstituted olefins **4m** and **4n**, with good *E*/*Z* selectivity (83:17) in the case of **4m**.

Surprisingly, during the course of our optimization study, we observed that when the reaction was mediated by bis(acetylacetonate)copper, traces (3%) of the difluoromethylated alkyne **5a** were obtained (Table 2, entry 8). The direct fluorination of terminal alkynes with trifluoromethyl, (trifluoromethyl)sulfide or fluoro groups is challenging, and the development of such transformations is of considerable interest.[21] Furthermore, there is no report of a direct route to difluoromethylated terminal alkynes. Therefore, a straightforward synthesis of fluorinated scaffolds such as **5** would be extremely valuable because of their potential use in various transformations.[22] Such compounds are normally prepared by multistep syntheses involving the use of difluoropropargyl bromide derivatives. These derivatives are usually obtained by the addition of phenylacetylene to dibromodifluoromethane in the presence of butyllithium; however, dibromodifluoromethane is an ozone-depleting substance that presents difficulties in handling.[23]

Consequently, we sought to optimize the reaction conditions to give difluoromethylated alkyne **5a** selectively. Pleasingly, when we performed the reaction with a catalytic amount of bis(acetylacetonato)copper (10 mol%) in the presence of copper(II) acetate at 100 °C, the desired alkyne **5a** was obtained in 18% yield (Table 2, entry 9). Note that the presence of copper(II) acetate as an additive was required to ensure the formation of alkyne **5a**.[24] Further experiments with various bases showed that the use of cesium pivalate or sodium acetate gave **5a** with slightly improved yields (28% and 29%, respectively; entries 10 and 11). Finally, we performed a control experiment without bis(acetylacetonate)copper (entry 12), and this gave traces of the desired product **5a**, suggesting that copper(II) acetate is not the active catalytic species. Although its role has not yet been clearly defined, our observations highlight the fact that copper(II) acetate is a key additive for the success of this transformation.[25]



Scheme 5 Difluoromethylation of alkynes **3** to give alkenes **4**. *Reagents and conditions*: **3** (0.4 mmol, 1 equiv), $BrCF_2CO_2Et$ (5 equiv), $Cu(OTf)_2$ (100 mol%), 1,10-phenanthroline (110 mol%), KF (2.1 equiv), [DMF] = 0.125 mol/L, air, 120 °C, 2 h. The major isomers are shown, and the isolated yields for the two stereoisomers are reported. The *E*/*Z* ratios were determined by ^{19}F NMR spectroscopy of the crude mixture.
[a] This compound and its isomer were isolated together with an inseparable impurity.



Scheme 6 Difluoromethylation of alkynes **3** to give alkynes **5**. *Reagents and conditions*: **3** (0.2 mmol, 1 equiv), $BrCF_2CO_2Et$ (5 equiv), $Cu(acac)_2$ (10 mol%), 1,10-phenanthroline (11 mol%), NaOAc (2.1 equiv), $Cu(OAc)_2$ (1.5 equiv), [DMF] = 0.1 mol/L, air, 100 °C, 16 h. Yields were determined by ^{19}F NMR with $PhCOCF_3$ as internal standard.

Next, we focused on the scope of the reaction toward the synthesis of alkynes **5** from three terminal alkynes **3** (Scheme 6). In general, yields were quite moderate, probably due to competition from the homocoupling reaction.[26] The reaction was compatible with electron-withdrawing substituents, such as the trifluoromethyl (**5b**) or nitrile group (**5c**); electron-rich groups, such as methoxy, gave poorer results. Although alkynes **5** were obtained in low yields, these examples showcase the potential of this strategy and constitute the first example of the direct introduction of an ethoxycarbonyl(difluoro)methyl group onto alkynes.

Finally, to gain further insight into the mechanism of the formation of the bromodifluoromethylated olefin, we carried out the reaction in the presence of one equivalent of TEMPO. No effect on either the reactivity or the selectivity was observed, thereby ruling out a plausible radical pathway. Consequently, in agreement with previous reports,[17] we assume that our initial hypothesis of a mechanism involving an electrophilic copper(III) intermediate is plausible (Scheme 4). With respect to the mechanism for the synthesis of the difluoromethylated alkyne, we assume that the reaction proceeds through another pathway, because **4a** is not an intermediate for the formation of alkyne **5a**.[27]

In conclusion, we have developed a copper-mediated direct fluorofunctionalization of unsaturated derivatives by using commercially available ethyl bromo(difluoro)acetate. By this method, we obtained a panel of trisubstituted difluoromethylated olefins, including dihydropyrans, glycal derivatives, and tetrasubstituted olefins, in good to high yields. Because various functional groups are tolerated, this copper-promoted transformation has considerable synthetic potential and constitutes a versatile method for the direct introduction of difluoro moieties onto non-prefunctionalized alkenes or alkynes. Moreover, we developed a new route to difluoroacetylated alkynes. Although the fluorinated alkynes were obtained in modest yields, this method represents the first direct access to ethoxycarbonyl(difluoro)methyl-substituted alkynes. Finally, both these strategies pave the way for the synthesis of highly valuable functionalized fluorinated olefins and alkynes. Indeed, these substrates might easily be engaged in further post-functionalizations on the bromine atom or the ester moiety to give more-complex fluorinated molecules.

All reactions were carried out using oven-dried glassware with magnetic stirring under an atmosphere of air unless otherwise stated. Flash chromatography was performed on silica gel (0.040–0.060 nm or 0.060–0.200 nm) unless otherwise stated. Analytical TLC was performed on silica gel coated aluminum plates with F-254 indicator with visualization by UV irradiation (254 nm) and/or chemical staining with $KMnO_4$ solution. ^1H NMR spectra were recorded on a Bruker DXP 300 spectrometer; ^{13}C NMR spectra were recorded at 75 MHz, and ^{19}F NMR spectra at 282 MHz. Chemical shifts (δ) are quoted in ppm relative to the residual solvent ($CHCl_3$: δ = 7.26 for ^1H, δ = 77.0 for ^{13}C) or to external ($CFCl_3$; δ = 0 ppm). High-resolution mass spectra were recorded on a Waters LCT Premier spectrometer. IR spectra were recorded on a Perkin-Elmer Spectrum 100. Optical rotations were measured in $CHCl_3$ on a Perkin-Elmer 341 polarimeter with a 1 cm cell. Melting points are uncorrected. All anhydrous solvents were dried by standard techniques. Dry DMF (sealed bottles) was purchased from Acros Organics. Dihydropyran and ethyl bromodifluoroacetate were distilled before use. 3,4,6-Tri-*O*-benzyl-D-glucal[28] and 3,4,6- tri-*O*-benzyl-D-galactal,[29] were prepared by known procedures. All the solid bases (KF, CsOPiv, Cs_2CO_3, and NaOAc) were dried over P_2O_5 under vacuum before use.

Ethyl 3,4-Dihydro-2*H*-pyran-5-yl(difluoro)acetates 2a–e; General Procedure

The appropriate Cu complex (0.036 mmol), 1,10-phenanthroline (0.043 mmol), and K_2CO_3 (0.72 mmol) were dissolved in DMF (1.8 mL) under air. Enol ether **1** (0.36 mmol) and $BrCF_2CO_2Et$ or $BrCF_2CONR_2$ (NR_2 = NEt_2, morpholino; 1.44 mmol) were added, and the tube was sealed. The mixture was heated at 80 or 90 °C for 18 h. The solution was then cooled and extracted with Et_2O (3 × 10 mL). The organic layer was washed successively with H_2O (2 × 10 mL) and brine (2 × 10 mL) then dried ($MgSO_4$). The solvent was removed under vacuum and the residue was purified by flash chromatography.

Ethyl 3,4-Dihydro-2*H*-pyran-5-yl(difluoro)acetate (2a)

Prepared by following the general procedure from dihydropyran **1a** and $BrCF_2CO_2Et$ on a 0.36 mmol scale with $Cu(OTf)_2$ (13 mg, 0.036 mmol) as catalyst. Flash chromatography (silica gel) gave a colorless oil (***Caution:*** *highly volatile*); yield: 0.054 g (73%); R_f = 0.34 (pentane–Et_2O, 19:1).

IR (neat): 2941, 1760, 1662, 1256, 1009 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.84 (br s, 1 H), 4.33 (q, $J_{H,H}$ = 7.1 Hz, 2 H), 4.00 (dd, $J_{H,H}$ = 5.3, 5.1 Hz, 2 H), 2.14 (dt, $J_{H,H}$ = 6.3, 1.1 Hz, 2 H), 1.93–1.85 (m, 2 H), 1.35 (t, $J_{H,H}$ = 7.1 Hz, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 164.0 (t, $J_{C,F}$ = 35.8 Hz), 146.3 (t, $J_{C,F}$ = 11.0 Hz), 114.3 (t, $J_{C,F}$ = 248.1 Hz), 105.9 (t, $J_{C,F}$ = 24.8 Hz), 66.0, 62.8, 21.0, 17.8 (t, $J_{C,F}$ = 2.8 Hz), 13.9.

^{19}F NMR (282 MHz, $CDCl_3$, $CFCl_3$): δ = –105.3 (s, 2 F).

HRMS (AP+): *m*/*z* calcd for $[M + H]^+$ $C_9H_{13}F_2O_3$: 207.0833; found: 207.0827 (–2.9 ppm).

Ethyl {2-[(Benzyloxy)methyl]-3,4-dihydro-2*H*-pyran-5-yl}(difluoro)acetate (2b)

Prepared by following the general procedure from 2-(benzyloxymethyl)-3,4-dihydro-2*H*-pyran (**1b**) and $BrCF_2CO_2Et$ on a 0.24 mmol scale with $Cu(MeCN)_4PF_6$ (9 mg, 0.024 mmol) as catalyst. Flash chromatography (silica gel) gave a colorless oil; yield: 0.056 g (72%); R_f = 0.37 (pentane–Et_2O, 19:1).

IR (neat): 2859, 1760, 1662, 1271, 1198, 1089 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.40–7.28 (m, 5 H), 6.88 (br s, 1 H), 4.64–4.55 (m, 2 H), 4.33 (q, $J_{H,H}$ = 7.2 Hz, 2 H), 4.10–4.03 (m, 1 H), 3.62 (dd, $J_{H,H}$ = 10.2, 5.7 Hz, 1 H), 3.56 (dd, $J_{H,H}$ = 10.2, 4.5 Hz, 1 H), 2.21–2.16 (m, 2 H), 2.00–1.92 (m, 1 H), 1.80–1.66 (m, 1 H), 1.35 (t, $J_{H,H}$ = 7.2 Hz, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 164.0 (t, $J_{C,F}$ = 35.8 Hz), 146.0 (t, $J_{C,F}$ = 11.0 Hz), 137.8, 128.4, 127.8 (2 C), 127.7 (2 C), 114.2 (dd, $J_{C,F}$ = 248.7, 248.7 Hz), 105.8 (t, $J_{C,F}$ = 25.3 Hz), 74.9, 73.5, 71.6, 62.8, 23.0, 17.7 (t, $J_{C,F}$ = 2.8 Hz), 14.0.

^{19}F NMR (282 MHz, $CDCl_3$, $CFCl_3$): δ = –104.5 (d, $J_{F,F}$ = 253.4 Hz), –105.9 (d, $J_{F,F}$ = 253.4 Hz).

HRMS (AP+): *m*/*z* $[M + H]^+$ calcd for $C_{17}H_{21}F_2O_4$: 327.1408; found: 327.1401 (–2.1 ppm).

[5-(2-Ethoxy-1,1-difluoro-2-oxoethyl)-3,4-dihydro-2*H*-pyran-2-yl]methyl Pivalate (2c)

Prepared by following the general procedure from 2-(pivaloyloxymethyl)-3,4-dihydro-2*H*-pyran (**1b**) and $BrCF_2CO_2Et$ on a 0.24 mmol scale with $Cu(MeCN)_4PF_6$ (9 mg, 0.024 mmol) as catalyst. Flash chromatography [silica gel, pentane–Et_2O (9:1)] gave a colorless oil; yield: 0.046 g (60%); R_f = 0.34 (pentane–Et_2O, 9:1).

IR (neat): 2971, 1755, 1737, 1659, 1283, 1156, 1096 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.86 (br s, 1 H), 4.33 (q, $J_{H,H}$ = 7.2 Hz, 2 H), 4.22 (dd, $J_{H,H}$ = 11.7, 4.7 Hz, 1 H), 4.17 (dd, $J_{H,H}$ = 11.7, 5.3 Hz, 1 H), 4.12–4.04 (m, 1 H), 2.23–2.19 (m, 2 H), 2.00–1.92 (m, 1 H), 1.77–1.67 (m, 1 H), 1.36 (t, $J_{H,H}$ = 7.2 Hz, 3 H), 1.22 (s, 9 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 178.2, 163.9 (t, $J_{C,F}$ = 35.8 Hz), 145.8 (dd, $J_{C,F}$ = 11.0, 11.0 Hz), 114.1 (dd, $J_{C,F}$ = 248.7, 248.7 Hz), 105.9 (t, $J_{C,F}$ = 24.8 Hz), 73.5, 65.1, 62.9, 38.8, 27.1 (3 C), 22.8, 17.6 (t, $J_{C,F}$ = 2.8 Hz), 13.9.

^{19}F NMR (282 MHz, $CDCl_3$, $CFCl_3$): δ = –103.9 (d, $J_{F,F}$ = 253.4 Hz), –105.6 (d, $J_{F,F}$ = 253.4 Hz).

HRMS (AP+): *m*/*z* $[M + H]^+$ calcd for $C_{15}H_{23}F_2O_5$: 321.1514; found: 321.1520 (+1.9 ppm).

2-{2-[(Benzyloxy)methyl]-3,4-dihydro-2*H*-pyran-5-yl}-*N*,*N*-diethyl-2,2-difluoroacetamide (2d)

Prepared by following the general procedure from 2-(benzyloxymethyl)-3,4-dihydro-2*H*-pyran (**1b**) and $BrCF_2CONEt_2$ at 90 °C on a 0.24 mmol scale with Cu_2O (2 mg, 0.012 mmol) as catalyst. Flash chromatography [silica gel, PE–EtOAc (4:1)] gave a colorless oil; yield: 0.028 g (33%); R_f = 0.25 (PE–EtOAc, 4:1).

IR (neat): 2856, 1660, 1264, 1103, 1069 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.34–7.30 (m, 5 H), 6.75 (s, 1 H), 4.63–4.54 (m, 2 H), 4.11–4.04 (m, 1 H), 3.64–3.54 (m, 2 H), 3.45–3.33 (m, 4 H), 2.23–2.21 (m, 2 H), 2.00–1.92 (m, 1 H), 1.80–1.67 (m, 1 H), 1.21–1.14 (m, 6 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 162.4 (t, $J_{C,F}$ = 29.7 Hz), 145.6 (t, $J_{C,F}$ = 10.5 Hz), 137.7, 128.4 (2 C), 127.8, 127.7 (2 C), 116.6 (t, $J_{C,F}$ = 243.7 Hz), 107.3 (t, $J_{C,F}$ = 25.9 Hz), 74.9, 73.5, 71.7, 42.4, 41.3, 23.1, 17.3, 14.0, 12.2.

^{19}F NMR (282 MHz, $CDCl_3$, $CFCl_3$): δ = –96.5 (d, $J_{F,F}$ = 265.7 Hz), –97.7 (d, $J_{F,F}$ = 265.7 Hz).

HRMS (ESI+): *m*/*z* $[M + H]^+$ calcd for $C_{19}H_{26}F_2NO_3$: 354.1881; found: 354.1881 (0 ppm).

4-[{2-[(Benzyloxy)methyl]-3,4-dihydro-2*H*-pyran-5-yl}(difluoro)acetyl]morpholine (2e)

Prepared by following the general procedure from 2-(benzyloxymethyl)-3,4-dihydro-2*H*-pyran (**1b**) and 4-[bromo(difluoro)acetyl]morpholine at 90 °C on a 0.24 mmol scale with Cu_2O (2 mg, 0.012 mmol) as catalyst. Flash chromatography (silica gel) gave a colorless oil; yield: 0.026 g (30%); R_f = 0.30 (PE–EtOAc, 3:1).

IR (neat): 2860, 1663, 1254, 1101, 1022 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.37–7.30 (m, 5 H), 6.81 (s, 1 H), 4.63–4.55 (m, 2 H), 4.13–4.06 (m, 1 H), 3.71–3.59 (m, 10 H), 2.22–2.20 (m, 2 H), 2.01–1.93 (m, 1 H), 1.81–1.68 (m, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 161.8 (t, $J_{C,F}$ = 30.3 Hz), 145.7 (t, $J_{C,F}$ = 11.0 Hz), 137.7, 128.4 (2 C), 127.8, 127.7 (2 C), 116.6 (t, $J_{C,F}$ = 245.4 Hz), 106.9 (t, $J_{C,F}$ = 24.8 Hz), 75.0, 73.5, 71.6, 66.7, 66.5, 46.9, 43.3, 23.0, 17.5 (t, $J_{C,F}$ = 2.2 Hz).

^{19}F NMR (282 MHz, $CDCl_3$, $CFCl_3$): δ = –96.3 (d, $J_{F,F}$ = 268.7 Hz), –97.3 (d, $J_{F,F}$ = 268.7 Hz).

HRMS (AP+): *m*/*z* $[M + H]^+$ calcd for $C_{19}H_{24}F_2NO_4$: 368.1673; found: 368.1661 (–3.3 ppm).

Glycal Derivatives 2f–h; General Procedure

$Cu[MeCN]_4PF_6$ (9 mg, 0.024 mmol), 1,10-phenanthroline (5 mg, 0.029 mmol), and K_2CO_3 (66 mg, 0.48 mmol) were dissolved in DMF (1.2 mL) under air . The appropriate glycal derivative (0.24 mmol) and $BrCF_2CO_2Et$ (0.25 mL, 1.92 mmol) were added, the tube was sealed, and the mixture was heated at 110 °C for 24 h. The solution was then cooled and extracted with Et_2O (3 × 8 mL). The organic layer was washed successively with H_2O (2 × 8 mL) and brine (2 × 8 mL) then dried ($MgSO_4$). The solvent was removed under vacuum and the residue was purified by flash chromatography (silica gel, pentane–Et_2O).

1,5-Anhydro-3,4,6-tri-*O*-benzyl-2-deoxy-2-[ethoxycarbonyl(difluoro)methyl]-D-*arabino*-hex-1-enitol (2f)

Prepared by following the general procedure from 3,4,6-tri-*O*-benzyl-D-glucal (**1f**) as a colorless oil; yield: 0.080 g (62%); $[\alpha]_D^{20}$ –9.2 (*c* 0.25, $CHCl_3$); R_f = 0.30 (pentane–Et_2O, 4:1).

IR (neat): 2928, 2869, 1762, 1291, 1202, 1088, 1068 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.37–7.19 (m, 15 H), 6.97 (d, $J_{H,F}$ = 2.6 Hz, 1 H), 4.61–4.60 (m, 2 H), 4.50–4.49 (m, 4 H), 4.45–4.40 (m, 1 H), 4.14–4.01 (m, 3 H), 3.89–3.86 (m, 1 H), 3.78 (dd, $J_{H,H}$ = 10.6, 6.4 Hz, 1 H), 3.66 (dd, $J_{H,H}$ = 10.6, 4.5 Hz, 1 H), 1.15 (t, $J_{H,H}$ = 7.2 Hz, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 163.9 (dd, $J_{C,F}$ = 37.9, 33.6 Hz), 146.6 (dd, $J_{C,F}$ = 12.7, 9.4 Hz), 137.6, 137.5, 137.3, 128.5 (2 C), 128.4 (2 C), 128.2 (2 C), 128.0, 127.8 (2 C), 127.73 (2 C), 127.69 (2 C), 127.63 (2 C), 113.4 (t, $J_{C,F}$ = 250.3 Hz), 105.7 (dd, $J_{C,F}$ = 26.4, 22.0 Hz), 76.3, 73.3, 72.5, 72.2, 71.9, 70.0 (d, $J_{C,F}$ = 3.9 Hz), 67.6, 62.6, 13.7.

^{19}F NMR (282 MHz, $CDCl_3$, $CFCl_3$): δ = –103.2 (d, $J_{F,F}$ = 256.5 Hz), –109.4 (d, $J_{F,F}$ = 256.5 Hz).

HRMS (ESI+): *m*/*z* $[M + Na]^+$ calcd for $C_{31}H_{32}F_2O_6Na$: 561.2065; found: 561.2063 (–0.4 ppm).

1,5-Anhydro-3,4,6-tri-*O*-acetyl-2-deoxy-2-[ethoxycarbonyl(difluoro)methyl]-D-*arabino*-hex-1-enitol (2g)

Prepared by following the general procedure from 3,4,6-tri-*O*-acetyl-D-glucal (**1g**) as a colorless oil; yield: 0.062 g (65%); $[\alpha]_D^{20}$ +31.2 (*c* 0.25, $CHCl_3$); R_f = 0.22 (pentane–Et_2O, 3:2).

IR (neat): 2990, 1743, 1661, 1369, 1216, 1198, 1021 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.08 (br s, 1 H), 5.61 (d, $J_{H,H}$ = 4.3 Hz, 1 H), 5.16 (t, $J_{H,H}$ = 4.3 Hz, 1 H), 4.47–4.18 (m, 5 H), 2.10 (s, 3 H), 2.09 (s, 3 H), 2.03 (s, 3 H), 1.36 (t, $J_{H,H}$ = 7.2 Hz, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 170.3, 169.4, 169.3, 163.3 (dd, $J_{C,F}$ = 35.8, 35.8 Hz), 148.7 (t, $J_{C,F}$ = 10.5 Hz), 112.6 (dd, $J_{C,F}$ = 250.9, 250.9 Hz), 104.0 (t, $J_{C,F}$ = 24.8 Hz), 74.1, 66.1, 63.1, 62.8 (dd, $J_{C,F}$ = 3.3, 2.2 Hz), 60.8, 20.7, 20.6, 20.5, 13.7.

^{19}F NMR (282 MHz, $CDCl_3$, $CFCl_3$): δ = –104.3 (d, $J_{F,F}$ = 262.6 Hz), –105.4 (d, $J_{F,F}$ = 262.6 Hz).

HRMS (ESI+): *m*/*z* $[M + Na]^+$ calcd for $C_{16}H_{20}F_2O_9Na$: 417.0980; found: 417.0973 (–1.7 ppm).

1,5-Anhydro-3,4,6-tri-*O*-benzyl-2-deoxy-2-[ethoxycarbonyl(difluoro)methyl]-D-*lyxo*-hex-1-enitol (2h)

Prepared following the general procedure from 3,4,6-tri-*O*-benzyl-D-galactal (**1h**) as a colorless oil; yield: 0.063 g (49%); $[\alpha]_D^{20}$ –11.5 (*c* 0.4, $CHCl_3$); R_f = 0.29 (pentane–Et_2O, 9:1).

IR (neat): 2923, 2863, 1761, 1296, 1211, 1096 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.37–7.28 (m, 15 H), 6.89 (d, $J_{H,F}$ = 2.8 Hz, 1 H), 4.79–4.39 (m, 7 H), 4.33–4.32 (m, 1 H), 4.04 (q, $J_{H,H}$ = 7.2 Hz, 2 H), 4.00–3.97 (m, 1 H), 3.73 (dd, $J_{H,H}$ = 10.6, 6.6 Hz, 1 H), 3.60 (dd, $J_{H,H}$ = 10.6, 4.5 Hz, 1 H), 1.09 (t, $J_{H,H}$ = 7.2 Hz, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 163.8 (dd, $J_{C,F}$ = 38.5, 33.0 Hz), 146.2 (dd, $J_{C,F}$ = 13.2, 9.4 Hz), 137.9, 137.8, 137.7, 128.48 (2 C), 128.45 (2 C), 128.2 (2 C), 128.0 (2 C), 127.94, 127.92 (2 C), 127.8, 127.73 (2 C), 127.67, 113.3 (dd, $J_{C,F}$ = 249.8, 248.1 Hz), 106.7 (dd, $J_{C,F}$ = 26.4, 20.4 Hz), 76.1, 73.9, 73.5, 72.9, 72.1, 69.5, 67.8, 62.6, 13.7.

^{19}F NMR (282 MHz, $CDCl_3$, $CFCl_3$): δ = –101.9 (d, $J_{F,F}$ = 257.5 Hz), –109.8 (d, $J_{F,F}$ = 257.5 Hz).

HRMS (ESI+): *m*/*z* $[M + NH_4]^+$ calcd for $C_{31}H_{36}F_2NO_6$: 556.2511; found: 556.2527 (+2.9 ppm).

Difluoromethylated Vinyl Bromides 4a–n: General Procedure

$Cu(OTf)_2$ (1 equiv), 1,10-phenanthroline (1.1 equiv), and KF (2.1 equiv) were dissolved in DMF (3.2 mL) under air, $BrCF_2CO_2Et$ (5 equiv) was added, and the tube was sealed. The mixture was stirred for 15 min at 120 °C in a preheated oil bath then cooled (~15 min). Alkyne **3** (0.4 mmol, 1 equiv) was added and the mixture was heated at 120 °C for 2 h. The tube was then cooled to r.t. and the mixture was diluted with Et_2O (15 mL) and H_2O (15 mL). The organic layer was washed successively with H_2O (2 × 20 mL) and brine (2 × 20 mL) then extracted with Et_2O (2 × 20 mL). The organic layer was dried ($MgSO_4$) and carefully concentrated under vacuum (***Caution**: the products are highly volatile*) to give a residue that was purified by column chromatography. The *E*/*Z* ratio was determined by ^{19}F NMR spectrometric analysis of the crude reaction mixture.

Ethyl (3*E*)- and (3*Z*)-4-Bromo-2,2-difluoro-4-phenylbut-3-enoate (4a)

Prepared by following the general procedure from phenylacetylene (**3a**) as a mixture of stereoisomers in an *E*/*Z* ratio of 69:31. The crude mixture was purified by column chromatography (silica gel) to give a colorless oil; yield: 0.119 g (78%); R_f = 0.37 (pentane–Et_2O, 9:1).

IR (neat): 2988, 1769, 1641, 1446, 1299, 1193, 1067 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.63–7.33 (m, 7.87 H, *E* and *Z*), 6.67 (t, $J_{H,F}$ = 11.1 Hz, 0.45 H, *Z*), 6.51 (t, $J_{H,F}$ = 11.1 Hz, 1 H, *E*), 4.39 (q, $J_{H,H}$ = 7.2 Hz, 1.14 H, *Z*), 3.97 (q, $J_{H,H}$ = 7.2 Hz, 2 H, *E*), 1.38 (t, $J_{H,H}$ = 7.2 Hz, 1.76 H, *Z*), 1.19 (t, $J_{H,H}$ = 7.2 Hz, 3 H, *E*).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 162.7 (t, $J_{C,F}$ = 33.8 Hz, *Z*), 162.4 (t, $J_{C,F}$ = 33.2 Hz, *E*), 137.8 (*Z*), 137.1 (*E*), 133.5 (t, $J_{C,F}$ = 10.1 Hz, *E*), 132.9 (t, $J_{C,F}$ = 10.4 Hz, *Z*), 130.4 (*Z*), 129.9 (*E*), 128.5 (*Z*), 128.4 (t, $J_{C,F}$ = 2.2 Hz, *E*), 128.1 (*E*), 127.6 (*Z*), 125.0 (t, $J_{C,F}$ = 28.5 Hz, *E*), 123.3 (t, $J_{C,F}$ = 30.0 Hz, *Z*), 112.0 (t, $J_{C,F}$ = 246.0 Hz, *Z*), 111.0 (t, $J_{C,F}$ = 247.5 Hz, *E*), 63.3 (*Z*), 63.1 (*E*), 13.8 (*Z*), 13.6 (*E*).

^{19}F NMR (282 MHz, $CDCl_3$, $CFCl_3$): δ = –93.6 (d, J_{FH} = 11.1 Hz, CF_2, *E*), –97.6 (d, J_{FH} = 11.1 Hz, CF_2, *Z*).

MS (EI): *m*/*z* = 306 $[M^+]$.

HRMS (EI): *m*/*z* $[M - CO_2Et]^+$ calcd for $C_9H_6BrF_2$: 232.9600; found: 232.9607 (+2.7 ppm).

Ethyl (3*E*)- and (3*Z*)-4-Bromo-2,2-difluoro-4-(4-methoxyphenyl)but-3-enoate (4b)

Prepared by following the general procedure from 4-ethynylanisole (**3b**; 0.394 mmol) as a mixture of stereoisomers in an *E*/*Z* ratio of 68:32. The crude mixture was purified by column chromatography (silica gel) to give a yellow oil; yield: 0.106 g (81%); R_f = 0.36 (pentane–Et_2O, 9:1).

IR (neat): 2988, 2843, 1768, 1604, 1508, 1294, 1253, 1178, 1067, 1029, 833 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.58–7.50 (m, 0.93 H, *Z*), 7.35–7.29 (m, 2 H, *E*), 6.93–6.82 (m, 3.09 H, *E* and *Z*), 6.57 (t, $J_{H,F}$ = 11.3 Hz, 0.46 H, *Z*), 6.44 (t, $J_{H,F}$ = 11.3 Hz, 1 H, *E*), 4.38 (q, $J_{H,H}$ = 7.2 Hz, 1.20 H, *Z*), 3.99 (q, $J_{H,H}$ = 7.2 Hz, 2 H, *E*), 3.84 (s, 1.48 H, *Z*), 3.81 (s, 3 H, *E*), 1.37 (t, $J_{H,H}$ = 7.2 Hz, 1.68 H, *Z*), 1.19 (t, $J_{H,H}$ = 7.2 Hz, 3 H, *E*).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 162.9 (t, $J_{C,F}$ = 33.8 Hz, *Z*), 162.6 (t, $J_{C,F}$ = 33.2 Hz, *E*), 161.3 (*Z*), 160.8 (*E*), 133.9 (t, $J_{C,F}$ = 10.4 Hz, *E*), 132.7 (t, $J_{C,F}$ = 10.6 Hz, *Z*), 130.3 (t, $J_{C,F}$ = 2.0 Hz, *E*), 130.1 (*Z*), 129.4 (t, $J_{C,F}$ = 28.5 Hz, *Z*), 129.2 (t, $J_{C,F}$ = 30.0 Hz, *E*), 124.3 (t, $J_{C,F}$ = 28.5 Hz, *E*), 121.2 (t, $J_{C,F}$ = 30.0 Hz, *Z*), 113.8 (*Z*), 113.4 (*E*), 112.2 (t, $J_{C,F}$ = 245.3 Hz, *Z*), 111.2 (t, $J_{C,F}$ = 246.8 Hz, *E*), 63.3 (*Z*), 63.1 (*E*), 55.4 (*Z*), 55.3 (*E*), 13.9 (*Z*), 13.7 (*E*).

^{19}F NMR (282 MHz, $CDCl_3$, $CFCl_3$): δ = –93.6 (d, J_{FH} = 11.3 Hz, CF_2, *E*), –97.5 (d, J_{FH} = 11.3 Hz, CF_2, *Z*).

HRMS (EI): *m*/*z* $[M^+]$ calcd for $C_{13}H_{13}BrF_2O_3$: 335.9996; found: 335.9993 (–0.9 ppm).

Ethyl (3*E*)- and (3*Z*)-4-Bromo-2,2-difluoro-4-(4-*tert*-butylphenyl)but-3-enoate (4c)

Prepared by following the general procedure from (4-*tert*-butylphenyl)acetylene (**3c**) as a mixture of stereoisomers in an *E*/*Z* ratio of 68:32. The crude mixture was purified by flash chromatography (silica gel) to give a colorless oil; yield: 0.114 g (79%); R_f = 0.58 (pentane–Et_2O, 19:1).

IR (neat): 2964, 1771, 1641, 1298, 1192, 1068, 686 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.57–7.31 (m, 6.38 H, *E* and *Z*), 6.66 (t, $J_{H,F}$ = 11.3 Hz, 0.49 H, *Z*), 6.49 (t, $J_{H,F}$ = 11.0 Hz, 1 H, *E*), 4.40 (q, $J_{H,H}$ = 7.2 Hz, 1.03 H, *Z*), 3.93 (q, $J_{H,H}$ = 7.2 Hz, 2 H, *E*), 1.38 (t, $J_{H,H}$ = 7.2 Hz, 1.67 H, *Z*), 1.35–1.33 (m, 13.54 H, *E* and *Z*), 1.16 (t, $J_{H,H}$ = 7.2 Hz, 3 H, *E*).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 162.8 (t, $J_{C,F}$ = 34.1 Hz, *Z*), 162.5 (t, $J_{C,F}$ = 33.6 Hz, *E*), 153.9 (*Z*), 153.3 (*E*), 134.9 (t, $J_{C,F}$ = 1.1 Hz, *Z*), 134.2 (t, $J_{C,F}$ = 1.1 Hz, *E*), 133.9 (t, $J_{C,F}$ = 11.0 Hz, *E*), 132.9 (t, $J_{C,F}$ = 10.5 Hz, *Z*), 128.4 (t, $J_{C,F}$ = 2.2 Hz, 2 C, *E*), 127.4 (2 C, *Z*), 125.3 (2 C, *Z*), 125.0 (2 C, *E*), 124.6 (t, $J_{C,F}$ = 28.6 Hz, *E*), 122.4 (t, $J_{C,F}$ = 30.3 Hz, *Z*), 112.1 (t, $J_{C,F}$ = 247.0 Hz, *Z*), 114.1 (t, $J_{C,F}$ = 248.7 Hz, *E*), 63.2 (*Z*), 63.0 (*E*), 34.8 (*Z*), 34.7 (*E*), 31.11 (3 C, *Z*), 31.08 (3 C, *E*), 13.9 (*Z*), 13.6 (*E*).

^{19}F NMR (282 MHz, $CDCl_3$, $CFCl_3$): δ = –93.2 (d, J_{FH} = 11.0 Hz, CF_2, *E*), –97.7 (d, J_{FH} = 11.3 Hz, CF_2, *Z*).

HRMS (EI): *m*/*z* [M$^+$] calcd for $C_{16}H_{19}BrF_2O_2$: 362.0516; found: 362.0518 (+0.6 ppm).

Ethyl (3*E*)- and (3*Z*)-4-Bromo-2,2-difluoro-4-(4-fluorophenyl)but-3-enoate (4d)

Prepared by following the general procedure from 1-ethynyl-4-fluorobenzene (**3d**) as a mixture of stereoisomers in an *E*/*Z* ratio of 71:29. The crude mixture was purified by flash chromatography (silica gel) to give a colorless oil; yield: 0.114 g (88%); R_f = 0.67 (pentane–Et_2O, 19:1).

IR (neat): 2988, 1769, 1600, 1505, 1299, 1161, 1069, 730 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.62–7.57 (m, 0.98 H, *E* and *Z*), 7.40–7.36 (m, 2.06 H, *E* and *Z*), 7.12–7.02 (m, 3.15 H, *E* and *Z*), 6.62 (t, $J_{H,F}$ = 11.0 Hz, 0.46 H, *Z*), 6.50 (t, $J_{H,F}$ = 11.3 Hz, 1 H, *E*), 4.40 (q, $J_{H,H}$ = 7.2 Hz, 1.10 H, *Z*), 4.08 (q, $J_{H,H}$ = 7.2 Hz, 2 H, *E*), 1.38 (t, $J_{H,H}$ = 7.2 Hz, 1.51 H, *Z*), 1.24 (t, $J_{H,H}$ = 7.2 Hz, 3 H, *E*).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 163.9 (d, $J_{C,F}$ = 252.0 Hz, *Z*), 163.3 (d, $J_{C,F}$ = 251.4 Hz, *E*), 162.6 (t, $J_{C,F}$ = 34.1 Hz, *Z*), 162.5 (t, $J_{C,F}$ = 33.0 Hz, *E*), 134.1 (d, $J_{C,F}$ = 3.9 Hz, *Z*), 133.3 (t, $J_{C,F}$ = 4.4 Hz, *E*), 132.4 (t, $J_{C,F}$ = 9.9 Hz, *E*), 131.6 (t, $J_{C,F}$ = 10.5 Hz, *Z*), 130.7 (dt, $J_{C,F}$ = 8.8, 2.2 Hz, 2 C, *E*), 129.7 (dt, $J_{C,F}$ = 8.8, 1.1 Hz, 2 C, *Z*), 125.3 (t, $J_{C,F}$ = 28.1 Hz, *E*), 123.3 (t, $J_{C,F}$ = 30.3 Hz, *Z*), 115.6 (d, $J_{C,F}$ = 22.0 Hz, 2 C, *Z*), 115.3 (d, $J_{C,F}$ = 22.0 Hz, 2 C, *E*), 111.9 (t, $J_{C,F}$ = 247.6 Hz, *Z*), 111.0 (t, $J_{C,F}$ = 249.8 Hz, *E*), 63.4 (*Z*), 63.3 (*E*), 13.9 (*Z*), 13.7 (*E*).

^{19}F NMR (282 MHz, $CDCl_3$, $CFCl_3$): δ = –94.8 (d, J_{FH} = 11.3 Hz, CF_2, *E*), –98.0 (d, J_{FH} = 11.0 Hz, CF_2, *Z*), –110.4 (m, F, *E*), –110.5 (m, F, *Z*).

HRMS (EI): *m*/*z* [M$^+$] calcd for $C_{12}H_{10}BrF_3O_2$: 323.9796; found: 323.9799 (+1.3 ppm).

Ethyl (3*E*)- and (3*Z*)-4-Bromo-2,2-difluoro-4-[4-(trifluoromethyl)phenyl]but-3-enoate (4e)

Prepared by following the general procedure from 1-ethynyl-4-(trifluoromethyl)benzene (**3e**) as a mixture of stereoisomers in an *E*/*Z* ratio of 72:28. The crude mixture was purified by column chromatography (silica gel) to give a light-yellow oil. This compound and its isomer were isolated together with an inseparable impurity; yield: 0.116 g (78%); R_f = 0.66 (pentane–Et_2O, 9:1).

IR (neat): 2988, 1769, 1652, 1408, 1322, 1169, 1128, 1066, 835 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.77–7.43 (m, 8.02 H, *E* and *Z*), 6.73 (t, $J_{H,F}$ = 10.7 Hz, 0.51 H, *Z*), 6.55 (t, $J_{H,F}$ = 11.8 Hz, 1 H, *E*), 4.46–4.31 (m, 1.85 H, *Z*), 4.11 (q, $J_{H,H}$ = 7.2 Hz, 2 H, *E*), 1.44–1.33 (m, 2.69 H, *Z*), 1.24 (t, $J_{H,H}$ = 7.2 Hz, 3 H, *E*).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 163.6 (t, $J_{C,F}$ = 34.3 Hz, *Z*), 162.4 (t, $J_{C,F}$ = 33.2 Hz, *E*), 141.3 (*Z*), 140.8 (*E*), 131.8 (q, $J_{C,F}$ = 32.9 Hz, *Z*), 131.7 (q, $J_{C,F}$ = 32.5 Hz, *E*), 131.4 (t, $J_{C,F}$ = 9.0 Hz, *E*), 131.0 (t, $J_{C,F}$ = 10.5 Hz, *Z*), 128.8 (t, $J_{C,F}$ = 2.3 Hz, *E*), 128.1 (*Z*), 125.9 (t, $J_{C,F}$ = 27.5 Hz, *E*), 125.8 (q, $J_{C,F}$ = 3.6 Hz, *Z*), 125.2 (q, $J_{C,F}$ = 3.8 Hz, *E*), 123.6 (q, $J_{C,F}$ = 270.8 Hz, *E*), 121.5 (t, $J_{C,F}$ = 24.8 Hz, *Z*), 111.7 (t, $J_{C,F}$ = 246.8 Hz, *Z*), 110.9 (t, $J_{C,F}$ = 249.4 Hz, *E*), 63.5 (*Z*), 63.4 (*E*), 13.9 (*Z*), 13.7 (*E*). One carbon of the minor isomer was overlapped.

^{19}F NMR (282 MHz, $CDCl_3$, $CFCl_3$): δ = –63.4 (s, CF_3, *Z*), –63.5 (s, CF_3, *E*), –95.8 (d, J_{FH} = 11.8 Hz, CF_2, *E*), –98.6 (d, J_{FH} = 10.7 Hz, CF_2, *Z*).

MS (EI): *m*/*z* = 354 [M – F]$^+$.

Ethyl (3*E*)- and (3*Z*)-4-Bromo-2,2-difluoro-4-(4-bromophenyl)but-3-enoate (4f)

Prepared by following the general procedure from 4-bromophenylacetylene **3f** as a mixture of stereoisomers in an *E*/*Z* ratio of 70:30. The crude mixture was purified by column chromatography (silica gel) to give a yellow oil; yield: 0.131 g (85%); R_f = 0.82 (pentane–Et_2O, 9:1)

IR (neat): 2988, 1767, 1680, 1591, 1485, 1300, 1097, 1068, 821 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.54–7.10 (m, 6.56 H, *E* and *Z*), 6.58 (t, $J_{H,F}$ = 11.1 Hz, 0.38 H, *Z*), 6.42 (t, $J_{H,F}$ = 11.5 Hz, 1 H, *E*), 4.42–4.26 (m, 1.21 H, *Z*), 4.00 (q, $J_{H,H}$ = 7.2 Hz, 2 H, *E*), 1.37–1.25 (m, 2.03 H, *Z*), 1.16 (t, $J_{H,H}$ = 7.2 Hz, 3 H, *E*).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 162.5 (t, $J_{C,F}$ = 33.3 Hz, *Z*), 162.4 (t, $J_{C,F}$ = 33.1 Hz, *E*), 136.8 (*Z*), 136.1 (*E*), 133.7 (*Z*), 132.1 (t, $J_{C,F}$ = 9.3 Hz, *E*), 131.8 (*Z*), 131.4 (*E*), 130.0 (t, $J_{C,F}$ = 1.9 Hz, *E*), 129.1 (*Z*), 125.4 (t, $J_{C,F}$ = 27.8 Hz, *E*), 124.8 (*Z*), 124.3 (*E*), 123.7 (t, $J_{C,F}$ = 30.2 Hz, *Z*), 111.8 (t, $J_{C,F}$ = 246.2 Hz, *Z*), 110.9 (t, $J_{C,F}$ = 248.6 Hz, *E*), 63.4 (*Z*), 63.3 (*E*), 13.9 (*Z*), 13.7 (*E*).

^{19}F NMR (282 MHz, $CDCl_3$, $CFCl_3$): δ = –94.8 (d, J_{FH} = 11.5 Hz, CF_2, *E*), –97.9 (d, J_{FH} = 11.0 Hz, CF_2, *Z*).

HRMS (EI): *m*/*z* [M$^+$] calcd for $C_{12}H_{10}Br_2F_2O_2$: 383.8995; found: 383.8988 (–2.0 ppm).

Ethyl (3*E*)- and (3*Z*)-4-Bromo-2,2-difluoro-4-(3-methylphenyl)but-3-enoate (4g)

Prepared by following the general procedure from 3-ethynyltoluene (**3g**) as a mixture of stereoisomers in an *E*/*Z* ratio of 70:30. The crude mixture was purified by column chromatography (silica gel) to give a light-yellow oil; yield: 0.095 g (75%); R_f = 0.62 (pentane–Et_2O, 9:1).

IR (neat): 2986, 1771, 1640, 1448, 1300, 1189, 1101, 1071, 783 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.48–7.07 (m, 6.70 H, *E* and *Z*), 6.65 (t, $J_{H,F}$ = 11.1 Hz, 0.43 H, *Z*), 6.48 (t, $J_{H,F}$ = 11.1 Hz, 1 H, *E*), 4.39 (q, $J_{H,H}$ = 7.2 Hz, 1.01 H, *Z*), 3.96 (q, $J_{H,H}$ = 7.2 Hz, 2 H, *E*), 2.39 (s, 1.35 H, *Z*), 2.36 (s, 3 H, *E*), 1.38 (t, $J_{H,H}$ = 7.2 Hz, 1.63 H, *Z*), 1.19 (t, $J_{H,H}$ = 7.2 Hz, 3 H, *E*).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 162.7 (t, $J_{C,F}$ = 33.8 Hz, *Z*), 162.4 (t, $J_{C,F}$ = 33.0 Hz, *E*), 138.4 (*Z*), 137.9 (*E*), 137.8 (*Z*), 137.0 (*E*), 133.8 (t, $J_{C,F}$ = 10.4 Hz, *E*), 133.1 (t, $J_{C,F}$ = 10.4 Hz, *Z*), 131.1 (*Z*), 130.7 (*E*), 129.0 (t, $J_{C,F}$ = 1.9 Hz, *E*), 128.4 (*Z*), 128.2 (*Z*), 128.0 (*E*), 125.6 (t, $J_{C,F}$ = 1.9 Hz, *E*), 124.84 (t, $J_{C,F}$ = 28.5 Hz, *E*), 124.82 (*Z*), 123.0 (t, $J_{C,F}$ = 30.2 Hz, *Z*), 112.0 (t, $J_{C,F}$ = 245.6 Hz, *Z*), 111.1 (t, $J_{C,F}$ = 246.9 Hz, *E*), 63.3 (*Z*), 63.0 (*E*), 21.3 (*Z*), 21.2 (*E*), 13.9 (*Z*), 13.6 (*E*).

^{19}F NMR (282 MHz, $CDCl_3$, $CFCl_3$): δ = –93.9 (d, J_{FH} = 11.1 Hz, CF_2, *E*), –98.0 (d, J_{FH} = 11.1 Hz, CF_2, *Z*).

HRMS (EI): *m*/*z* [M$^+$] calcd for $C_{13}H_{13}BrF_2O_2$: 318.0067; found: 318.0072 (+1.6 ppm).

Ethyl (3*E*)- and (3*Z*)-4-Bromo-2,2-difluoro-4-(2-methoxyphenyl)but-3-enoate (4h)

Prepared by following the general procedure from 2-ethynylanisole (**3h**) as a mixture of stereoisomers in an *E*/*Z* ratio of 58:42. The crude mixture was purified by column chromatography (silica gel) to give a light-yellow oil; yield: 0.109 g (81%); R_f = 0.34 (pentane–Et_2O, 9:1).

IR (neat): 2977, 1770, 1652, 1597, 1490, 1282, 1251, 1067, 752 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.42–7.30 (m, 2.34 H, *E* and *Z*), 7.24–7.16 (m, 0.94 H, *E* and *Z*), 7.04–6.83 (m, 3.40 H, *E* and *Z*), 6.61 (t, $J_{H,F}$ = 11.4 Hz, 0.72 H, *Z*), 6.52 (t, $J_{H,F}$ = 11.4 Hz, 1 H, *E*), 4.40 (q, $J_{H,H}$ = 7.2 Hz, 1.41 H, *Z*), 4.05 (q, $J_{H,H}$ = 7.2 Hz, 2 H, *E*), 3.87 (s, 2.17 H, *Z*), 3.84 (s, 3 H, *E*), 1.40 (t, $J_{H,H}$ = 7.2 Hz, 2.10 H, *Z*), 1.25 (t, $J_{H,H}$ = 7.2 Hz, 3 H, *E*).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 162.8 (t, $J_{C,F}$ = 33.9 Hz, *Z*), 162.5 (t, $J_{C,F}$ = 33.5 Hz, *E*), 156.3 (*Z*), 155.8 (*E*), 131.4 (*E*), 131.2 (*Z*), 130.4 (*Z*), 129.9 (*E*), 129.4 (t, $J_{C,F}$ = 9.7 Hz, *E*), 128.2 (t, $J_{C,F}$ = 11.1 Hz, *Z*), 127.7 (*Z*), 126.6 (t, $J_{C,F}$ = 30.0 Hz, *Z*), 126.3 (t, $J_{C,F}$ = 28.5 Hz, *E*), 125.9 (*E*), 120.4 (*Z*), 120.1 (*E*), 111.9 (t, $J_{C,F}$ = 246.0 Hz, *Z*),

111.4 (*Z*), 111.0 (t, $J_{C,F}$ = 246.8 Hz, *E*), 111.0 (*E*), 63.2 (*Z*), 62.9 (*E*), 55.7 (*Z*), 55.6 (*E*), 13.9 (*Z*), 13.7 (*E*).

^{19}F NMR (282 MHz, $CDCl_3$, $CFCl_3$): δ = –97.8 (br s, CF_2, *E*), –98.5 (d, J_{FH} = 11.4 Hz, CF_2, *Z*).

HRMS (EI): *m*/*z* [M^+] calcd for $C_{13}H_{13}BrF_2O_3$: 335.9996; found: 335.9991 (–1.2 ppm).

Ethyl (3*E*)- and (3*Z*)-4-Bromo-4-(2,4-difluorophenyl)-2,2-difluorobut-3-enoate (4i)

Prepared by following the general procedure from 1-ethynyl-2,4-difluorobenzene (**3i**) as a mixture of stereoisomers in an *E*/*Z* ratio of 89:11. The crude mixture was purified by column chromatography (silica gel) to give a light-yellow oil. This compound and its isomer were isolated together with an inseparable impurity; yield: 0.115 g (84%); R_f = 0.57 (pentane–Et_2O, 9:1).

IR (neat): 2988, 1769, 1658, 1502, 1296, 1144, 1073, 852 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.51–6.66 (m, 4.39 H, *E* and *Z*), 6.53 (t, $J_{H,F}$ = 11.7 Hz, 1 H, *E*), 4.39–4.21 (m, 0.67 H, *Z*), 4.11 (q, $J_{H,H}$ = 7.2 Hz, 2 H, *E*), 1.36–1.27 (m, 1.01 H, *Z*), 1.23 (t, $J_{H,H}$ = 7.2 Hz, 3 H, *E*).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 163.8 (dd, $J_{C,F}$ = 251.7, 11.6 Hz, *E*), 162.2 (t, $J_{C,F}$ = 33.6 Hz, *E*), 159.2 (dd, $J_{C,F}$ = 254.7, 12.4 Hz, *Z*), 158.8 (dd, $J_{C,F}$ = 252.5, 12.2 Hz, *E*), 132.2 (d, $J_{C,F}$ = 9.9 Hz, *Z*), 131.3 (d, $J_{C,F}$ = 10.0 Hz, *E*), 129.7 (dd, $J_{C,F}$ = 9.8, 4.5 Hz, *Z*), 128.2 (t, $J_{C,F}$ = 27.2 Hz, *E*), 124.7 (t, $J_{C,F}$ = 8.6 Hz, *E*), 121.5 (dd, $J_{C,F}$ = 15.3, 4.1 Hz, *E*), 111.6 (t, $J_{C,F}$ = 247.6 Hz, *Z*), 111.4 (dd, $J_{C,F}$ = 21.7, 3.6 Hz, *E*), 110.8 (t, $J_{C,F}$ = 249.5 Hz, *E*), 104.5 (t, $J_{C,F}$ = 25.5 Hz, *Z*), 104.3 (t, $J_{C,F}$ = 25.2 Hz, *E*), 63.4 (*E*), 63.2 (*Z*), 13.8 (*Z*), 13.7 (*E*). Some signals from the minor isomer overlapped.

^{19}F NMR (282 MHz, $CDCl_3$, $CFCl_3$): δ = –98.9 (d, J_{FH} = 11.7 Hz, CF_2, *E*), –99.0 (d, J_{FH} = 11.0 Hz, CF_2, *Z*), –106.4 (m, F, *E*), –106.5 (m, F, *Z*), –107.6 (m, F, *Z*), –107.9 (m, F, *E*).

MS (EI): *m*/*z* = 341 [$M]^+$.

Ethyl (3*E*)- and (3*Z*)-4-Bromo-2,2-difluoro-4-(3-thienyl)-but-3-enoate (4j)

Prepared by following the general procedure from 3-ethynylthiophene (**3j**) as a mixture of stereoisomers in an *E*/*Z* ratio of 68:32. The crude mixture was purified by flash chromatography (silica gel) to give a colorless oil; yield: 0.066 g (53%); R_f = 0.56 (pentane–Et_2O, 19:1).

IR (neat): 2988, 1766, 1635, 1291, 1190, 1098, 684 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.67–7.66 (m, 0.46 H, *Z*), 7.51 (dd, $J_{H,F}$ = 3.0, 1.3 Hz, 1 H, *E*), 7.40–7.28 (m, 2.13 H, *E* and *Z*), 7.17 (dd, $J_{H,F}$ = 5.1, 1.3 Hz, 1 H, *E*), 6.70 (t, $J_{H,F}$ = 11.3 Hz, 0.49 H, *Z*), 6.46 (t, $J_{H,F}$ = 11.0 Hz, 1 H, *E*), 4.39 (q, $J_{H,H}$ = 7.2 Hz, 1.05 H, *Z*), 4.06 (q, $J_{H,H}$ = 7.2 Hz, 2 H, *E*), 1.38 (t, $J_{H,H}$ = 7.2 Hz, 1.59 H, *Z*), 1.21 (t, $J_{H,H}$ = 7.2 Hz, 3 H, *E*).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 162.8 (t, $J_{C,F}$ = 33.6 Hz, *Z*), 162.4 (t, $J_{C,F}$ = 34.7 Hz, *E*), 139.1 (*Z*), 136.8 (*E*), 128.1 (t, $J_{C,F}$ = 1.7 Hz, *Z*), 127.8 (t, $J_{C,F}$ = 10.5 Hz, *E*), 127.7 (t, $J_{C,F}$ = 2.8 Hz, *E*), 127.0 (*E*), 126.9 (*Z*), 126.1 (t, $J_{C,F}$ = 10.5 Hz, *Z*), 125.9 (*E*), 125.2 (*Z*), 125.0 (t, $J_{C,F}$ = 29.2 Hz, *E*), 121.2 (t, $J_{C,F}$ = 30.3 Hz, *Z*), 112.2 (t, $J_{C,F}$ = 247.0 Hz, *Z*), 111.2 (t, $J_{C,F}$ = 248.1 Hz, *E*), 63.3 (*Z*), 63.2 (*E*), 13.9 (*Z*), 13.7 (*E*).

^{19}F NMR (282 MHz, $CDCl_3$, $CFCl_3$): δ = –93.3 (d, J_{FH} = 11.0 Hz, CF_2, *E*), –97.6 (d, J_{FH} = 11.3 Hz, CF_2, *Z*).

HRMS (EI): *m*/*z* [M^+] calcd for $C_{10}H_9BrF_2O_2S$: 309.9475; found: 309.9479 (+1.3 ppm).

Ethyl (3*E*)- and (3*Z*)-4-Bromo-2,2-difluoro-4-pyridin-2-yl-but-3-enoate (4k)

Prepared by following the general procedure from 2-ethynylpyridine (**3k**) as a mixture of diastereoisomers in a *Z*/*E* ratio of 59:41. The crude mixture was purified by flash chromatography (SiO_2) to give a colorless oil. This compound and its isomer were isolated together with an inseparable impurity; yield: 0.054 g (44%); R_f = 0.46 (pentane–Et_2O, 4:1).

IR (neat): 2927, 1770, 1635, 1294, 1071, 774 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.63–8.61 (m, *Z*), 8.48–8.47 (m, 0.71 H, *E*), 7.87–7.71 (m, 3.75 H, *E* and *Z*), 7.63 (t, $J_{H,F}$ = 12.3 Hz, 1 H, *Z*), 7.34–7.30 (m, 1.50 H, *E* and *Z*), 6.63 (t, $J_{H,F}$ = 12.3 Hz, 0.73 H, *E*), 4.39 (q, $J_{H,H}$ = 7.2 Hz, 2 H, *Z*), 4.22 (q, $J_{H,H}$ = 7.2 Hz, 1.51 H, *E*), 1.37 (t, $J_{H,H}$ = 7.2 Hz, 3 H, *Z*), 1.24 (t, $J_{H,H}$ = 7.2 Hz, 3H, *E*).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 162.63 (t, $J_{C,F}$ = 33.6 Hz, *Z*), 162.55 (t, $J_{C,F}$ = 34.1 Hz, *E*), 152.7 (*Z*), 152.5 (*E*), 149.2 (*Z*), 147.5 (*E*), 137.2 (*Z*), 137.1 (*E*), 130.6 (t, $J_{C,F}$ = 9.9 Hz, *Z*), 129.9 (t, $J_{C,F}$ = 10.5 Hz, *E*), 128.4 (t, $J_{C,F}$ = 30.8 Hz, *E*), 125.6 (t, $J_{C,F}$ = 30.3 Hz, *Z*), 124.5 (*Z*), 124.1 (*E*), 124.0 (*E*), 122.7 (*Z*), 112.3 (t, $J_{C,F}$ = 247.6 Hz, *Z*), 111.6 (t, $J_{C,F}$ = 245.4 Hz, *E*), 63.3 (*Z*), 62.5 (*E*), 13.9 (*Z*), 13.8 (*E*).

^{19}F NMR (282 MHz, $CDCl_3$, $CFCl_3$): δ = –94.6 (d, J_{FH} = 12.3 Hz, CF_2, *E*), –98.3 (d, J_{FH} = 12.3 Hz, CF_2, *Z*).

HRMS (ESI+): *m*/*z* [M + H]$^+$ calcd for $C_{11}H_{11}BrF_2NO_2$: 305.9941; found: 305.9928 (–1.3 ppm).

Ethyl (3*E*)- and (3*Z*)-4-Bromo-2,2-difluoro-5-phenylpent-3-enoate (4l)

Prepared by following the general procedure from prop-2-yn-1-ylbenzene(**3l**) as a mixture of stereoisomers in an *E*/*Z* ratio of 53:47. The crude mixture was purified by column chromatography (silica gel) to give a colorless oil; yield: 0.030 g (23%); R_f = 0.44 (pentane–Et_2O, 9:1).

IR (neat): 2965, 1769, 1663, 1261, 1091, 799 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.37–7.06 (m, 5 H, *E* and *Z*), 6.23 (t, $J_{H,F}$ = 13.2 Hz, 1 H, *E*), 6.14 (t, $J_{H,F}$ = 10.8 Hz, 0.27 H, *Z*), 4.27 (m, 2.77 H, *E* and *Z*), 3.97 (s, 2 H, *E*), 3.77 (s, 0.5 H, *Z*), 1.28 (m, 4.17 H, *E* and *Z*).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 163.2 (t, $J_{C,F}$ = 34.3 Hz, *E*), 162.7 (t, $J_{C,F}$ = 33.9 Hz, *Z*), 138.2 (t, $J_{C,F}$ = 7.1 Hz, *E*), 136.0 (*E*), 135.7 (*Z*), 134.9 (t, $J_{C,F}$ = 10.3 Hz, *Z*), 129.1 (*Z*), 128.9 (*E*), 128.8 (*Z*), 128.6 (*E*), 127.5 (*Z*), 127.2 (*E*), 124.5 (t, $J_{C,F}$ = 26.8 Hz, *E*), 123.9 (t, $J_{C,F}$ = 30.2 Hz, *Z*), 111.7 (t, $J_{C,F}$ = 245.7 Hz, *Z*), 111.5 (t, $J_{C,F}$ = 250.2 Hz, *E*), 63.6 (*E*), 63.2 (*Z*), 48.4 (*Z*), 43.1 (*E*), 13.9 (*E*), 13.8 (*Z*).

^{19}F NMR (282 MHz, $CDCl_3$, $CFCl_3$): δ = –97.5 (d, J_{FH} = 13.2 Hz, CF_2, *E*), –97.9 (d, J_{FH} = 10.8 Hz, CF_2, *Z*).

MS (EI): *m*/*z* = 320 [$M]^+$.

HRMS (EI): *m*/*z* [M – Br]$^+$ calcd for $C_{13}H_{13}F_2O_2$: 239.0884; found: 239.0886 (+1.1 ppm).

Ethyl (3*E*)- and (3*Z*)-4-Bromo-3-ethyl-2,2-difluoro-4-phenylbut-3-enoate (4m)

Prepared by following the general procedure from 1-phenylbutyne (**3m**) as a mixture of stereoisomers in an *E*/*Z* ratio of 83:17. The crude mixture was purified by column chromatography (silica gel) to give a colorless oil; yield: 0.066 g (49%); R_f = 0.71 (pentane–Et_2O, 9:1).

IR (neat): 2983, 1773, 1638, 1445, 1227, 1122, 1073, 763 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.52–7.14 (m, 6.90 H, *E* and *Z*), 4.41 (q, $J_{H,H}$ = 7.2 Hz, 0.50 H, *Z*), 3.87 (q, $J_{H,H}$ = 7.2 Hz, 2 H, *E*), 2.65 (q, $J_{H,H}$ = 7.5 Hz, 0.50 H, *E*), 2.23 (q, $J_{H,H}$ = 7.5 Hz, 2 H, *Z*), 1.41 (t, $J_{H,H}$ = 7.2 Hz, 1.76 H, *Z*), 1.24 (t, $J_{H,H}$ = 7.5 Hz, 3 H, *E*), 1.18 (t, $J_{H,H}$ = 7.2 Hz, 1.76 H, *E*), 1.06 (t, $J_{H,H}$ = 7.5 Hz, 3 H, *Z*).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 163.2 (t, $J_{C,F}$ = 33.8 Hz, *Z*), 162.8 (t, $J_{C,F}$ = 33.5 Hz, *E*), 139.8 (*Z*), 138.8 (*E*), 137.6 (t, $J_{C,F}$ = 23.9 Hz, *Z*), 136.0 (t, $J_{C,F}$ = 23.6 Hz, *E*), 131.7, 129.9 (t, $J_{C,F}$ = 8.5 Hz), 129.2 (t, $J_{C,F}$ = 1.7 Hz, *E*), 128.9 (*Z*), 128.6 (*Z*), 127.94 (*E*), 127.88 (t, $J_{C,F}$ = 1.2 Hz, *Z*), 113.6 (t, $J_{C,F}$ = 250.6 Hz, *Z*), 112.6 (t, $J_{C,F}$ = 251.0

Hz, *E*), 63.1 (*Z*), 62.8 (*E*), 26.8 (t, $J_{C,F}$ = 3.4 Hz, *E*), 24.7 (t, $J_{C,F}$ = 4.1 Hz, *Z*), 13.9 (*Z*), 13.8 (*Z*), 13.6 (*E*), 12.2 (*E*). Note that one carbon is overlapped.

^{19}F NMR (282 MHz, $CDCl_3$, $CFCl_3$): δ = –93.9 (s, CF_2, *E*), –99.9 (s, CF_2, *Z*).

MS (EI): *m*/*z* = 253 $[M\text{-}Br]^+$.

HRMS (EI): *m*/*z* $[M - Br]^+$ calcd for $C_{14}H_{15}F_2O_2$: 253.1040; found: 253.1042 (+0.6 ppm).

Ethyl (3*E*)- and (3*Z*)-4-Bromo-2,2-difluoro-3,4-diphenylbut-3-enoate (4n)

Prepared by following the general procedure from diphenylacetylene (**3n**) as a mixture of stereoisomers in an *E*/*Z* ratio of 75:25. The crude mixture was purified by column chromatography (silica gel) to give a colorless oil; yield: 0.056 g (36%); R_f = 0.53 (pentane–Et_2O, 9:1).

IR (neat): 2988, 1772, 1635, 1445, 1265, 1148, 1084, 715 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.60–7.32 (m, 10.72 H, *E* and *Z*), 7.23–7.05 (m, 3.52 H, *E* and *Z*), 4.45 (q, $J_{H,H}$ = 7.2 Hz, 0.67 H, *Z*), 3.90 (q, $J_{H,H}$ = 7.2 Hz, 2 H, *E*), 1.44 (t, $J_{H,H}$ = 7.2 Hz, 1.17 H, *Z*), 1.16 (t, $J_{H,H}$ = 7.2 Hz, 3 H, *E*).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 163.2 (t, $J_{C,F}$ = 33.8 Hz, *Z*), 162.7 (t, $J_{C,F}$ = 33.3 Hz, *E*), 139.4 (*Z*), 138.5 (*E*), 137.1 (*Z*), 136.6 (*E*), 135.8 (t, $J_{C,F}$ = 24.8 Hz, *E*), 134.5 (t, $J_{C,F}$ = 2.3 Hz, *Z*), 132.7 (t, $J_{C,F}$ = 6.5 Hz, *E*), 131.6 (*Z*), 130.4 (*Z*), 129.52 (*E*), 129.48 (*E*), 129.2 (*Z*), 128.9 (t, $J_{C,F}$ = 2.0 Hz, *E*), 128.62 (*E*), 128.57 (*Z*), 128.4 (*E*), 128.1 (*E*), 128.0 (*Z*), 127.9 (*Z*), 127.8 (*Z*), 112.4 (t, $J_{C,F}$ = 256.5 Hz, *Z*), 111.6 (t, $J_{C,F}$ = 253.9 Hz, *E*), 63.3 (*Z*), 63.0 (*E*), 13.9 (*Z*), 13.6 (*E*).

^{19}F NMR (282 MHz, $CDCl_3$, $CFCl_3$): δ = –91.7 (s, CF_2, *E*), –96.5 (s, CF_2, *Z*).

MS (EI): *m*/*z* = 380 $[M]^+$.

HRMS (EI): *m*/*z* $[M - Br]^+$ calcd for $C_{18}H_{15}F_2O_2$: 301.1040; found: 301.1028 (–4.0 ppm).

Ethyl 4-Aryl-2,2-difluorobut-3-ynoates 5a–c; General Procedure

A 10 mL Schlenk flask was charged with $Cu(acac)_2$ (0.005 g, 0.02 mmol, 10 mol%), 1,10-phenanthroline (0.004 g, 0.022 mmol, 11 mol%), $Cu(OAc)_2$ (0.054 g, 1.5 equiv), NaOAc (0.034 g, 2.1 equiv), and DMF (2 mL) under air. Alkyne **3** (0.2 mmol) and $BrCF_2CO_2Et$ (5 equiv) were added, and the reactor was closed and held at 100 °C for 16 h. (**Note**: Solid alkynes were added in the Schlenk flask before the solvent.) The reactor was then cooled to r.t. and the mixture was diluted with Et_2O (15 mL) and H_2O (15 mL). The organic layer was washed successively with H_2O (2 × 20 mL) and brine (2 × 20 mL), and then the aqueous layers were combined and extracted with Et_2O (2 × 20 mL). The organic layer was dried ($MgSO_4$) and the solvent was carefully removed under vacuum (***Caution**: the products are highly volatile*). Analyses for characterization of the products were performed on a pure fraction obtained by purification by column chromatography [pentane to pentane–Et_2O (9:1)].

Ethyl 2,2-Difluoro-4-phenylbut-3-ynoate (5a)

Colorless oil; yield: 29% (^{19}F NMR); R_f = 0.19 (pentane–Et_2O, 95:5).

IR (neat): 2987, 2242, 1772, 1491, 1446, 1273, 1141, 1076 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.59–7.32 (m, 5 H), 4.42 (q, $J_{H,H}$ = 7.2 Hz, 2 H), 1.40 (t, $J_{H,H}$ = 7.2 Hz, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 161.6 (t, $J_{C,F}$ = 34.2 Hz), 132.4 (t, $J_{C,F}$ = 2.4 Hz), 130.5, 128.5, 119.3, 104.9 (t, $J_{C,F}$ = 241.1 Hz), 89.6 (t, $J_{C,F}$ = 6.3 Hz), 78.3 (t, $J_{C,F}$ = 37.7 Hz), 63.8, 13.9.

^{19}F NMR (282 MHz, $CDCl_3$, $CFCl_3$): δ = –90.0 (s).

MS (EI): *m*/*z* = 224 $[M]^+$.

HRMS (EI): *m*/*z* $[M^+]$ calcd for $C_{12}H_{10}F_2O_2$: 224.0649; found: 224.0647 (–0.7 ppm).

Ethyl 2,2-Difluoro-4-(4-(trifluoromethyl)phenyl)but-3-ynoate (5b)

Yellow oil; yield: 22% (^{19}F NMR); R_f = 0.65 (pentane–Et_2O, 95:5).

IR (neat): 2932, 1658, 1410, 1387, 1256, 1166, 1094 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.77–7.57 (m, 4 H), 4.42 (q, $J_{H,H}$ = 7.2 Hz, 2 H), 1.41 (t, $J_{H,H}$ = 7.2 Hz, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 162.2 (t, $J_{C,F}$ = 33.2 Hz), 132.70 (t, $J_{C,F}$ = 1.9 Hz), 132.67 (q, $J_{C,F}$ = 33.2 Hz), 125.5 (q, $J_{C,F}$ = 3.7 Hz), 121.7, 104.7 (t, $J_{C,F}$ = 241.8 Hz), 87.6, 80.3 (t, $J_{C,F}$ = 37.5 Hz), 64.0, 13.9. One carbon is overlapped.

^{19}F NMR (282 MHz, $CDCl_3$, $CFCl_3$): δ = –63.2 (s, CF_3), –90.6 (s).

MS (EI): *m*/*z* = 292 $[M]^+$.

HRMS (EI): *m*/*z* $[M^+]$ calcd for $C_{13}H_9F_5O_2$: 292.0523; found: 292.0518 (–1.6 ppm).

Ethyl 4-(4-Cyanophenyl)-2,2-difluorobut-3-ynoate (5c)

Yellow oil; yield: 18% (^{19}F NMR); R_f = 0.32 (pentane–Et_2O, 90:10).

IR (neat): 2993, 2234, 1718, 1658, 1596, 1276, 1178, 1142, 938 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.77–7.59 (m, 4 H), 4.42 (q, $J_{H,H}$ = 7.2 Hz, 2 H), 1.41 (t, $J_{H,H}$ = 7.2 Hz, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 132.9, 132.2, 64.1, 13.9. Only a few signals were observed.

^{19}F NMR (282 MHz, $CDCl_3$, $CFCl_3$): δ = –90.8 (s).

MS (EI): *m*/*z* = 249 $[M]^+$.

HRMS (EI): *m*/*z* $[M^+]$ calcd for $C_{13}H_9F_2NO_2$: 249.0601; found: 249.0597 (–1.9 ppm).

Acknowledgment

This work has been partially supported by INSA de Rouen, Université de Rouen, CNRS, LABEX SynOrg (ANR-11-LABX-0029) and Région Haute-Normandie (CRUNCh network). M.-C.B. thanks the MESR for a doctoral fellowship. D.D. thanks the LABEX SynOrg for an undergraduate fellowship. H.-Y.X thanks the China Scholarship Council for a doctoral fellowship. The contribution of Monya Harouel (INSA Rouen) in performing preliminary experiments is gratefully acknowledged.

Supporting Information for this article is available online at http://www.thieme-connect.com/products/ejournals/journal/10.1055/s-00000084.

References

(1) These authors contributed equally.
(2) For reviews of metal-catalyzed cross-coupling reactions, see: (a) *Metal-Catalyzed Cross-Coupling Reactions*; Diederich, F.; Stang, P. J., Eds.; Wiley-VCH: Weinheim, **1998**. (b) *Cross-Coupling Reactions: A Practical Guide*; Miyaura, N., Ed.; Springer: Berlin, **2002**.
(3) (a) *Copper-Mediated Cross-Coupling Reactions*; Evano, G.; Blanchard, N., Eds.; Wiley: Hoboken, **2013**. (b) Wendlandt, A. E.; Suess, A. M.; Stahl, S. S. *Angew. Chem. Int. Ed.* **2011**, *50*, 11062. (c) Hirano, K.; Miura, M. *Chem. Commun.* **2012**, *48*, 10704.
(4) (a) Müller, K.; Faeh, C.; Diederich, F. *Science* **2007**, *317*, 1881. (b) O'Hagan, D. *Chem. Soc. Rev.* **2008**, *37*, 308.

(c) Purser, S.; Moore, P. R.; Swallow, S.; Gouverneur, V. *Chem. Soc. Rev.* **2008**, *37*, 320. (d) Jeschke, P. *ChemBioChem* **2004**, *5*, 570. (e) Böhm, H.-J.; Banner, D.; Bendels, S.; Kansy, M.; Kuhn, B.; Müller, K.; Obst-Sander, U.; Stahl, M. *ChemBioChem* **2004**, *5*, 637.

(5) For some reviews, see: (a) Besset, T.; Schneider, C.; Cahard, D. *Angew. Chem. Int. Ed.* **2012**, *51*, 5048. (b) Liu, H.; Gu, Z.; Jiang, X. *Adv. Synth. Catal.* **2013**, *355*, 617. (c) Wu, X.-F.; Neumann, H.; Beller, M. *Chem. Asian J.* **2012**, *7*, 1744. (d) Landelle, G.; Panossian, A.; Pazenok, S.; Vors, J.-P.; Leroux, F. R. *Beilstein J. Org. Chem.* **2013**, *9*, 2476..

(6) For selected examples of trifluoromethylation reactions, see: (a) Miura, M.; Feng, C.-G.; Ma, S.; Yu, J.-Q. *Org. Lett.* **2013**, *15*, 5258. (b) Wang, X.; Truesdale, L.; Yu, J.-Q. *J. Am. Chem. Soc.* **2010**, *132*, 3648. (c) Zhang, X.-G.; Dai, H.-X.; Wasa, M.; Yu, J.-Q. *J. Am. Chem. Soc.* **2012**, *134*, 11948. (d) Chu, L.; Qing, F.-L. *J. Am. Chem. Soc.* **2012**, *134*, 1298. (e) Xu, J.; Fu, Y.; Luo, D.-F.; Jiang, Y.-Y.; Xiao, B.; Liu, Z.-J.; Gong, T.-J.; Liu, L. *J. Am. Chem. Soc.* **2011**, *133*, 15300. (f) Parsons, A. T.; Buchwald, S. L. *Angew. Chem. Int. Ed.* **2011**, *50*, 9120. For selected examples of fluorination reactions, see: (g) Hull, K. L.; Anani, W. Q.; Sanford, M. S. *J. Am. Chem. Soc.* **2006**, *128*, 7134. (h) McMurtrey, K. B.; Racowski, J. M.; Sanford, M. S. *Org. Lett.* **2012**, *14*, 4094. (i) Vigalok, A. *Organometallics* **2011**, *30*, 4802. (j) Zhao, S.-B.; Becker, J. J.; Gagné, M. R. *Organometallics* **2011**, *30*, 3926. (k) Kaspi, A. W.; Goldberg, I.; Vigalok, A. *J. Am. Chem. Soc.* **2010**, *132*, 10626. (l) Chan, K. S. L.; Wasa, M.; Wang, X.; Yu, J.-Q. *Angew. Chem. Int. Ed.* **2011**, *50*, 9081. (m) Ichiishi, N.; Canty, A. J.; Yates, B. F.; Sanford, M. S. *Org. Lett.* **2013**, *15*, 5134.

(7) Surapanich, N.; Kuhakarn, C.; Pohmakotr, M.; Reutrakul, V. *Eur. J. Org. Chem.* **2012**, 5943.

(8) For a preliminary communication from our group regarding the direct introduction of the CF_2CO_2Et moiety, see: Belhomme, M.-C.; Poisson, T.; Pannecoucke, X. *Org. Lett.* **2013**, *15*, 3428.

(9) (a) Murakami, S.; Ishii, H.; Tajima, T.; Fuchigami, T. *Tetrahedron* **2006**, *62*, 3761. For a photocatalytic approach, see: (b) Wallentin, C.-J.; Nguyen, J. D.; Finkbeiner, P.; Stephenson, C. R. J. *J. Am. Chem. Soc.* **2012**, *134*, 8875. (c) Jiang, H.; Huang, C.; Guo, J.; Zeng, C.; Zhang, Y.; Yu, S. *Chem. Eur. J.* **2012**, *18*, 15158.

(10) (a) Taguchi, T.; Kitagawa, O.; Morikawa, T.; Nishiwaki, T.; Uehara, H.; Endo, H.; Kobayashi, Y. *Tetrahedron* **1986**, *27*, 6103. (b) Ashwood, M. S.; Cottrell, I. F.; Cowden, C. J.; Wallace, D. J.; Davies, A. J.; Kennedy, D. J.; Dolling, U. H. *Tetrahedron Lett.* **2002**, *43*, 9271.

(11) (a) Qi, Q.; Shen, Q.; Lu, L. *J. Am. Chem. Soc.* **2012**, *134*, 6548. (b) Schwaebe, M. K.; McCarthy, J. R.; Whitten, J. P. *Tetrahedron Lett.* **2000**, *41*, 791. (c) Feng, Z.; Min, Q.-Q.; Xiao, Y.-L.; Zhang, B.; Zhang, X. *Angew. Chem. Int. Ed.* **2014**, *53*, 1669.

(12) (a) Poisson, T.; Belhomme, M.-C.; Pannecoucke, X. *J. Org. Chem.* **2012**, *77*, 9277. (b) Lemonnier, G.; Poisson, T.; Couve-Bonnaire, S.; Pannecoucke, X. *Tetrahedron Lett.* **2013**, *54*, 2821. (c) Lemonnier, G.; Poisson, T.; Couve-Bonnaire, S.; Jubault, P.; Pannecoucke, X. *Eur. J. Org. Chem.* **2013**, 3278. (d) Ferrary, T.; David, E.; Milanole, G.; Besset, T.; Jubault, P.; Pannecoucke, X. *Org. Lett.* **2013**, *15*, 5598.

(13) Besset, T.; Cahard, D.; Pannecoucke, X. *J. Org. Chem.* **2014**, *79*, 413.

(14) Others radical inhibitors or radical scavengers such as butylated hydroxytoluene (TBHT), benzoquinone, or diphenylethene had no effect on the outcome of the reaction.

(15) For a review, see: (a) Casitas, A.; Ribas, X. *Chem. Sci.* **2013**, *4*, 2301. (b) Phipps, R. J.; Gaunt, M. J. *Science* **2009**, *323*, 1593. (c) Phipps, R. J.; McMurray, L.; Ritter, S.; Duong, H. A.; Gaunt, M. J. *J. Am. Chem. Soc.* **2012**, *134*, 10773. (d) Chen, B.; Hou, X.-L.; Li, Y.-X.; Wu, Y.-D. *J. Am. Chem. Soc.* **2011**, *133*, 7668. (e) Barton, D. H. R.; Finet, J.-P.; Khamsi, J. *Tetrahedron Lett.* **1988**, *29*, 1115. (f) Gigant, N.; Chausset-Boissarie, L.; Belhomme, M.-C.; Poisson, T.; Pannecoucke, X.; Gillaizeau, I. *Org. Lett.* **2013**, *15*, 278. For selected examples involving a well-defined Cu(III) species, see: (g) Casitas, A.; King, A. E.; Parella, T.; Costas, M.; Stahl, S. S.; Ribas, X. *Chem. Sci.* **2010**, *1*, 326. (h) Huffman, L. M.; Casitas, A.; Font, M.; Canta, M.; Costas, M.; Ribas, X.; Stahl, S. S. *Chem. Eur. J.* **2011**, *17*, 10643. (i) Casitas, A.; Canta, M.; Solà, M.; Costas, M.; Ribas, X. *J. Am. Chem. Soc.* **2011**, *133*, 19386.

(16) We cannot exclude the possibility that the reductive elimination precedes the proton abstraction.

(17) (a) Suero, M. G.; Bayle, E. D.; Collins, B. S. L.; Gaunt, M. J. *J. Am. Chem. Soc.* **2013**, *135*, 5332. (b) Walkinshaw, A. J.; Xu, W.; Suero, M. G.; Gaunt, M. J. *J. Am. Chem. Soc.* **2013**, *135*, 12532.

(18) For selected examples, see: (a) Egami, H.; Shimizu, R.; Sodeoka, M. *Tetrahedron Lett.* **2012**, *53*, 5503. (b) Janson, P. G.; Ghoneim, I.; Ilchenko, N. O.; Szabó, K. J. *Org. Lett.* **2012**, *14*, 2882. (c) Mizuta, S.; Verhoog, S.; Engle, K. M.; Khotavivattana, T.; O'Duill, M.; Wheelhouse, K.; Rassias, G.; Médebielle, M.; Gouverneur, V. *J. Am. Chem. Soc.* **2013**, *135*, 2505. (d) Wang, X.-P.; Lin, J.-H.; Zhang, C.-P.; Xiao, J.-C.; Zheng, X. *Beilstein J. Org. Chem.* **2013**, *9*, 2635.

(19) Fanga, X.; Yanga, X.; Mao, S.; Wanga, Z.; Chena, G.; Wu, F. *Tetrahedron* **2007**, *63*, 10684.

(20) No improvement was observed under an inert atmosphere.

(21) For selected examples, see: (a) Chu, L.; Qing, F.-L. *J. Am. Chem. Soc.* **2010**, *132*, 7262. (b) Liu, C.; Ma, H.; Nie, J.; Ma, J. *Chin. J. Chem.* **2012**, *30*, 47. (c) Baert, F.; Colomb, J.; Billard, T. *Angew. Chem. Int. Ed.* **2012**, *51*, 10382. (d) Alazet, S.; Zimmer, L.; Billard, T. *Angew. Chem. Int. Ed.* **2013**, *52*, 10814. (e) Chen, C.; Chu, L.; Qing, F.-L. *J. Am. Chem. Soc.* **2012**, *1324*, 12454.

(22) For some example of applications, see: (a) Fustero, S.; Fernández, B.; Bello, P.; del Pozo, C.; Arimitsu, S.; Hammond, G. B. *Org. Lett.* **2007**, *9*, 4251. (b) Arimitsu, S.; Fernández, B.; Bello, P.; del Pozo, C.; Fustero, S.; Hammond, G. B. *J. Org. Chem.* **2008**, *73*, 2656. (c) Kizirian, J.-C.; Aiguabella, N.; Pesquer, A.; Fustero, S.; Bello, P.; Verdaguer, X.; Riera, A. *Org. Lett.* **2010**, *12*, 5620.

(23) CF_2Br_2 is banned under the *Montreal Protocol*, see: http://ozone.unep.org/Publications/MP_Handbook/Section_1.1_The_Montreal_Protocol/ (accessed May 5, 2014).

(24) The crucial roles of $Cu(OAc)_2$ and of carboxylate as a ligand in several transformations have been previously reported. For a review, see: (a) Ackermann, L. *Chem. Rev.* **2011**, *111*, 1315. (b) For selected examples, see references 6a and 6b.

(25) When the reaction was carried out with three equivalents of NaOAc in the absence of any other additive, no alkyne **5a** was formed, and 33% of alkene (*E*)-**4a** was detected.

(26) A substantial amount of a product resulting from homocoupling of alkyne **3** was obtained.

(27) When a mixture of 68:32 mixture of alkenes (*E*)- and (*Z*)-**4a** was treated under the standard conditions, only traces of **5a** were detected by ^{19}F NMR spectroscopy.

(28) Bucher, C.; Gilmour, R. *Angew. Chem. Int. Ed.* **2010**, *49*, 8724.

(29) Leonelli, F.; Capuzzi, M.; Calcagno, V.; Passacantilli, P.; Piancatelli, G. *Eur. J. Org. Chem.* **2005**, 2671.

