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Copper-Mediated Introduction of the $CF_2PO(OEt)_2$ Motif: Scope and Limitations

Maria V. Ivanova, Alexandre Bayle, Tatiana Besset, Xavier Pannecoucke, and Thomas Poisson*[a]

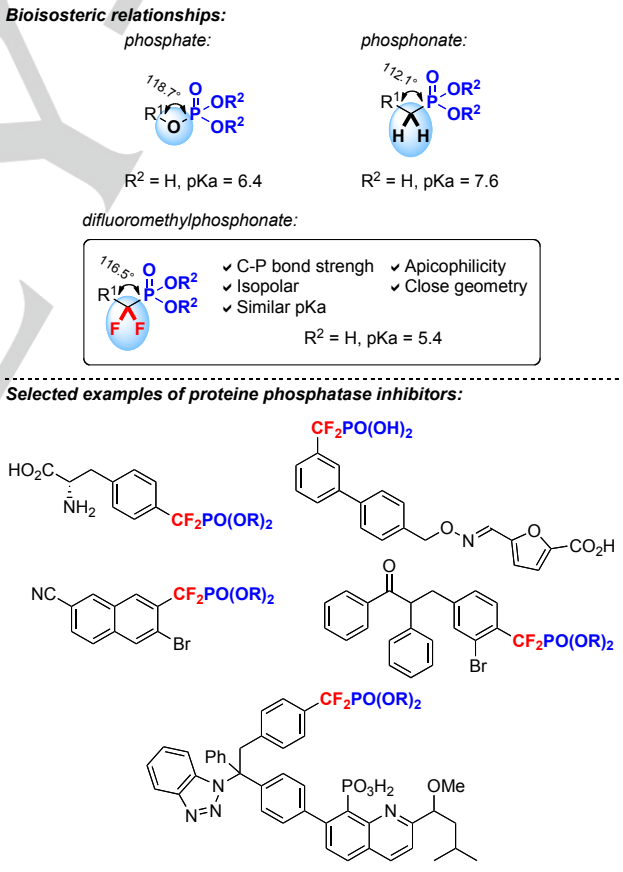
Abstract: Herein, we reported a general procedure to access $CF_2PO(OEt)_2$-containing molecules. $CuCF_2PO(OEt)_2$ reagent is accessible by a simple protocol and a broad range of substrates could be functionalized. The procedure allowed to convert aryl diazonium salts as well as aryl, heteroaryl, vinyl and alkynyl iodonium salts into the corresponding fluorinated molecules at room temperature. Mechanistic studies were performed to get a better understanding of the reaction pathway. Using similar conditions, vinyl and aryl iodides, allyl halides and benzyl bromides were also functionalized and the scope and limitations of the reaction were studied. Finally, the procedure was extended to disulfides to offer a new access to $SCF_2PO(OEt)_2$-containing molecules.

Introduction

Organofluorine chemistry is a blossoming research field mainly due to the impressive properties of the second smallest element of the periodic table: the fluorine atom.[1] The propensity of this atom to alter the physical and biological properties of a molecule gave it a pivotal role in the discovery of drugs and pharmaceuticals.[2] For instance, the appropriate introduction of a fluorine atom on a molecule might change its affinity for a biological receptor and modify its metabolic profile as well as its lipophilicity.

At last but not least, the fluorine atom or fluorinated groups are often employed as a bioisoster of important functional group.[3] As an example, the CF_2H residue is widely used to mimic an alcohol or a thiol group.[4] In that context, the difluoromethylphosphonate residue is of prime importance, since it behaves as an in vivo stable phosphate bioisoster. This paradigm, firstly proposed by Blackburn more than thirty years ago,[5] gave birth to a myriad of bioactive compounds and particularly to protein phosphatase inhibitors.[6] This interest for difluoromethylphosphonate-containing molecules arises from the in vivo stability of this phosphate surrogate. Indeed, the replacement of a labile O-P bond by a stronger C-P one hampers a possible in vivo hydrolysis. In addition, this motif presents electronic and structural similarities with the phosphate unit[7] and the difluoromethylene has a comparable apicophilicity (preference for the apical position) to an esterified oxygen.[8] All these analogies provide to the phosphorus atom of the difluoromethylphosphonate unit, a close geometry to the one of the phosphate. Furthermore, the strong electron-withdrawing character of the two fluorine atoms affords to the corresponding phosphonic acid a close pK_a to the phosphate (Scheme 1).

Taking into account the importance of difluoromethylphosphonate-containing molecules, several pathways were developed to introduce or build-up this key motif. Prior to 2010, the main approaches were quite restricted and relied on the nucleophilic fluorination of α-ketophosphonate,[9] the electrophilic α,α-fluorination of phosphonate,[10] the Michaelis-Becker or Arbuzov reactions,[11] the nucleophilic addition of difluoromethylphosphonate anion[12] and the addition of difluoromethylenephosphonyl radical or phosphonyl radical to olefin or fluorinated olefins, respectively.[13] To tackle the limitations of the above-mentionned strategies, like the use of toxic reagent or harsh conditions, a renewal of interest was observed after 2010 to develop more efficient methodologies to access $CF_2PO(OEt)_2$-containing molecules.



Scheme 1. Bioisosteric relationships and difluoromethylphosphonate-containing bioactive molecules.

[a] M. V. Ivanova, Dr. A. Bayle, Dr. T. Besset, Prof. Dr. X. Pannecoucke and Dr. T. Poisson.
Normandie Univ, INSA Rouen, UNIROUEN, CNRS, COBRA (UMR 6014), 76000 Rouen, France.
E-mail: thomas.poisson@insa-rouen.fr

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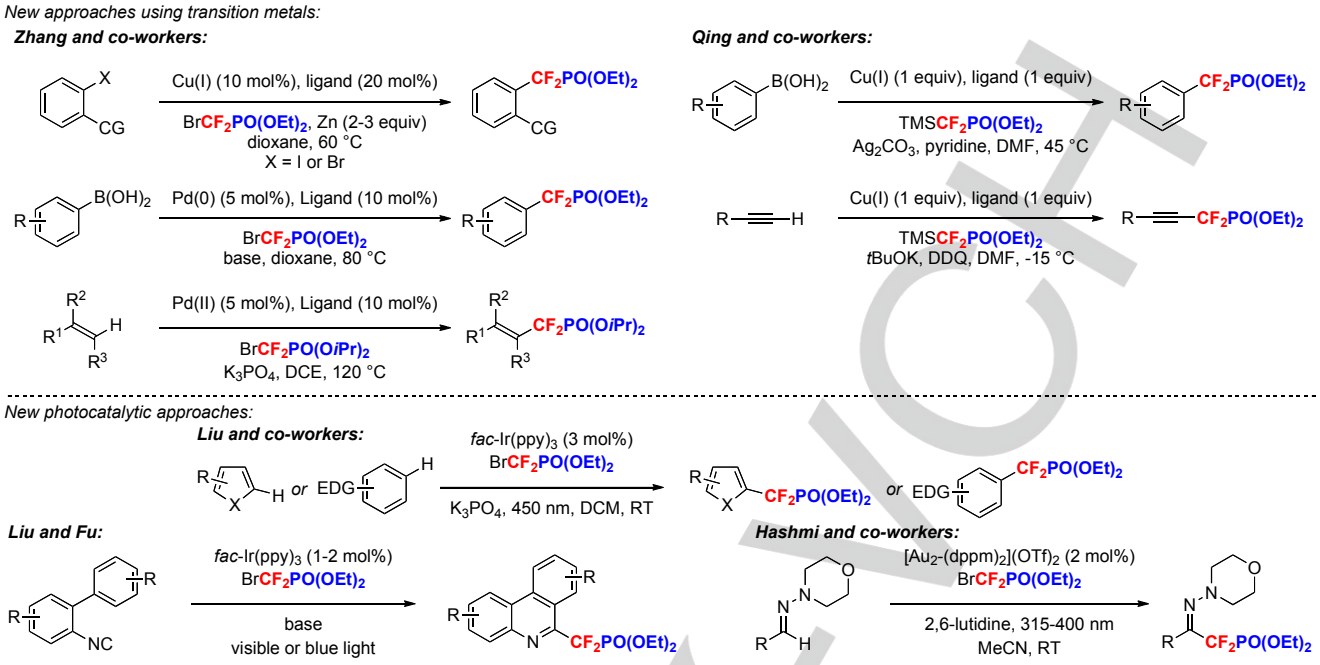
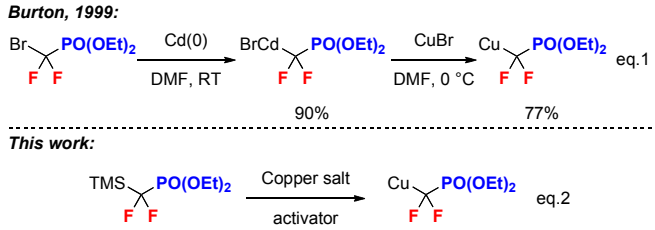


Scheme 2. State of the art. CG = coordinating group.

As part of this renewal, one should mention the impressive contributions made by the group of Zhang, regarding the development of new methodologies to introduce the $CF_2PO(OR)_2$ moiety according to metal-catalyzed cross-coupling reactions,[14] a strategy pioneered by Shibuya and co-workers in 1996.[15] Indeed, they developed accesses to aryl difluoromethylphosphonates according to copper-catalyzed Ullman-type cross-coupling reactions[14a,b] or palladium-catalyzed Suzuki cross-coupling reactions.[14c,d] In addition, an access to alkenyl difluoromethylphosphonates was reported by the same group.[14e] In parallel, the group of Qing depicted oxidative cross-coupling reactions to access either aryl or alkynyl difluoromethylphosphonates.[16] More recently, Hashmi reported the difluoromethylphosphonylation of hydrazines by using a gold-photocatalyst,[17] while the group of Liu developed a photocatalytic approach to aryl difluoromethylphosphonates and 6-difluoromethylphosphonylated phenanthridine derivatives.[18] However, despite the real advances made through these reports, it is worth to mention that all these methodologies required specific optimized conditions for each class of substrate. As part of our ongoing research program dedicated to the introduction of fluorinated building blocks,[19] we report herein a full account of our contribution toward the copper mediated synthesis of difluoromethylphosphonate-containing molecules. In that purpose and taking into consideration the synthetic limitations of the reported methodologies, we aimed at developing a general manifold to introduce the $CF_2PO(OEt)_2$ motif onto various scaffolds to broaden the current portfolio of transformations to access this important class of compounds. By designing a simple and practical way to produce the $CuCF_2PO(OEt)_2$ reagent, we described in this full paper its use toward the functionalization of various substrates: aryl diazonium salts,[20] hypervalent iodine compounds,[21] vinyl and aryl halides, allylic derivatives, benzyl halides and disulfides.

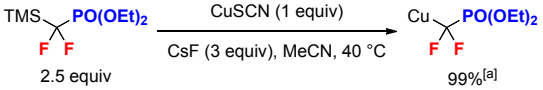
Results and Discussion

At the outset of the project we envisioned to develop a versatile reactive species that might easily enable an efficient introduction of the $CF_2PO(OEt)_2$ moiety on various classes of molecules. We focused on the formation of the $CuCF_2PO(OEt)_2$ species, since organocopper derivatives are well recognized as reactive species in a broad range of transformations.[22] In addition, copper is an attractive transition metal due to its low cost and low toxicity compared to the other metals from the block d.[22e] It is worth to mention that Burton and co-workers already reported the formation of this species.[23] However its access required the formation of the highly toxic cadmium derivatives prior to a transmetallation reaction with a copper salt (eq. 1). In order to avoid the use of cadmium, which hampered a wide application of this reagent, we turned our attention to the $TMSCF_2PO(OEt)_2$ as a precursor[24] of the corresponding copper derivative. Indeed, inspired by the work from Gooßen and co-workers,[25] we hypothesized the formation of the $CuCF_2PO(OEt)_2$ species from the TMS derivative in the presence of an activator and a copper salt (eq. 2). Note that this species was independently suspected by Zhang[14a-b] and Qing[16] to be the active species in their transformation. However no clear evidence of its involvement in the transformations was reported.



Scheme 3. Past method for the formation of $CuCF_2PO(OEt)_2$ species and present strategy.

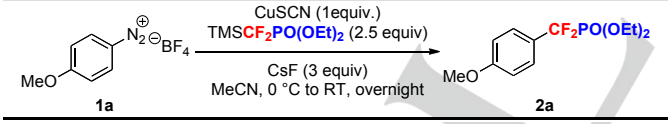
Pleasingly, after a screening of copper salts and activators, we found that 2.5 equivalents of $TMSCF_2PO(OEt)_2$ in the presence of 1 equivalent of CuSCN and CsF as an activator in MeCN at 40 °C furnished the $CuCF_2PO(OEt)_2$ species in a quantitative yield according to ^{19}F NMR (Scheme 4).



Scheme 4. Formation of $CuCF_2PO(OEt)_2$ species monitored by ^{19}F NMR. [a] Determined by ^{19}F NMR using α,α,α-trifluorotoluene as an internal standard.

As a model reaction and in order to ascertain the formation of the copper species, we decided to react the *in situ* formed $CuCF_2PO(OEt)_2$ species in the reaction with aryl diazonium salt **1a** (Table 1).[20] Indeed, due to the high reactivity of copper species with diazonium salts, we assumed that a Sandmeyer type reaction would be appropriate to demonstrate the reactivity of the $CuCF_2PO(OEt)_2$ species.

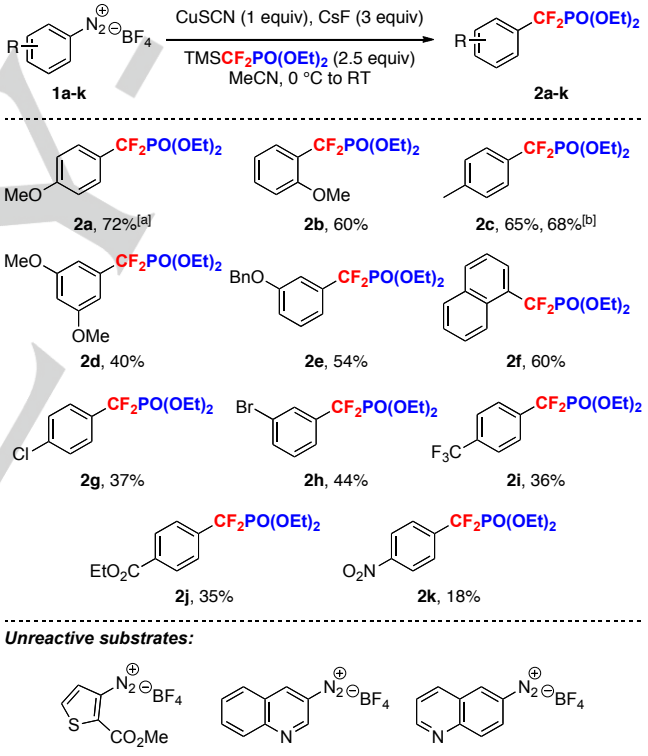
Table 1. Sandmeyer type reaction – effect of the reaction parameters.



Entry	Change from the standard conditions	Yield [%][a]
1	No change	73 (72)[b]
2	KF instead of CsF	NR
3	TMAF instead of CsF	NR
4	Cs_2CO_3 instead of CsF	23
5	CuOAc instead of CuSCN	26
6	CuI instead of CuSCN	30
7	1.5 equiv of $TMSCF_2PO(OEt)_2$	53
8	DMF instead of MeCN	24

[a] Yields were determined by ^{19}F NMR using α,α,α-trifluorotoluene as an internal standard. [b] Isolated yields. NR = no reaction.

Pleasingly, we found that the use of CuSCN as a copper source with 2.5 equiv of $TMSCF_2PO(OEt)_2$ in the presence of CsF fluoride as an activator in MeCN allowed the formation of **2a** in 73% NMR yield and 72% isolated yield. Within the optimization of the reaction, it turned out that the use of CsF was crucial since its replacement by other activators did not allow the formation of the product (entries 2 and 3) or provided it in very low yield (entry 4). The replacement of CuSCN by other copper salts was deleterious toward the formation of **2a** (entries 5 and 6), while a reduction of the amount of $TMSCF_2PO(OEt)_2$ gave the product in a lower yield (entry 7). Finally, the use of MeCN was crucial since DMF could not afford a better yield (entry 8).
Having optimized the reaction conditions regarding the formation of the $CuCF_2PO(OEt)_2$ species and its reactivity toward **1a**, we sought to extend the scope of this transformation to other aryl and heteroaryl diazonium salts (Scheme 5).[20]

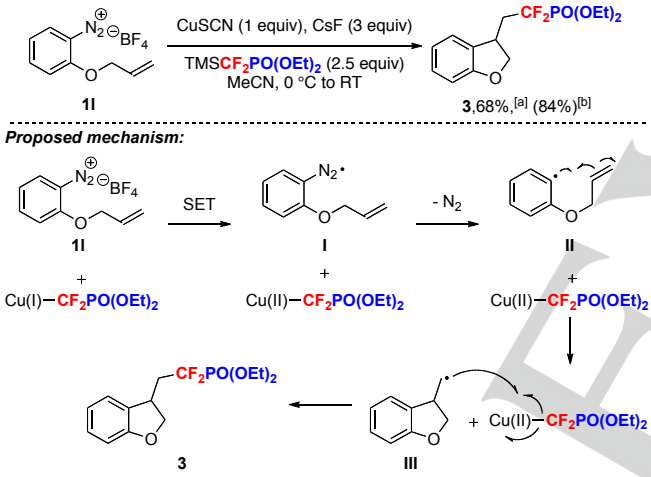


Scheme 5. Scope and limitations of the reaction of the $CuCF_2PO(OEt)_2$ species with aryl and heteroaryl diazonium salts, see ref 20. [a] The product was contaminated with 7% of $HCF_2PO(OEt)_2$. [b] Reaction was performed on a gram scale.

Aryl diazonium salts bearing an electron-donating group furnished the corresponding $CF_2PO(OEt)_2$–containing derivatives in good yields. Indeed, the presence of a methoxy substituent at the *para*- or *meta*-position gave the corresponding products **2a** and **2b** in 72% and 60%, respectively. Noteworthy, the reaction with *para*-methylphenyl diazonium salt **1c** provided

the product **2c** in 65% yield and the reaction scale was increased to the gram scale, without any loss of efficiency. The reaction was then extended to aryl diazonium salts **1d**, **1e** and **1f** furnishing the targeted fluorinated products **2d-f** in moderate to good yields. Then, the reaction was applied to diazonium salts bearing a halogen substituent, however the corresponding products **2g** and **2h** were isolated in moderate yields, 37% and 44%, respectively. The use of aryl diazonium salts, bearing electron-withdrawing group like a CF_3, an ester or a nitro substituent (**2i-k**) gave the corresponding difluoromethylphosphate derivatives in low yields, which represents a limitation of this Sandmeyer approach to introduce the $CF_2PO(OEt)_2$ motif. Disappointingly, heteroaryl diazonium salts were reluctant substrates and none of them furnished the corresponding product.

Then, to confirm that the reaction proceeded according to a classical Sandmeyer pathway involving a SET (single electron transfert),[26] a radical clock experiment using the 2-(allyloxy) diazonium salt **1l** was performed (Scheme 6).

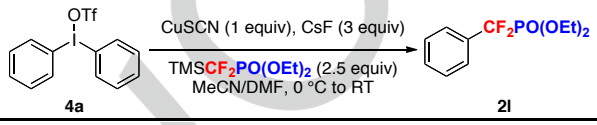


Scheme 6. Radical clock experience – proposed mechanism. [a] Isolated yield. [b] Yield was determined by ^{19}F NMR using α,α,α-trifluorotoluene as an internal standard.

Under standard conditions, the cyclized product **3** was isolated in 68% yield, which confirmed the involvement of a radical mechanism (Scheme 6). This observation was in line with the previous reports depicting a Sandmeyer type reactions.[27],[25e] Hence, the diazonium salt **1l** performed a SET with the $CuCF_2PO(OEt)_2$ reagent to provide the corresponding Cu(II) species and the radical **I**. Then, a nitrogen extrusion provided the aryl radical **II**, which underwent a radical cyclisation giving the primary radical **III**. A final reaction with the Cu(II) species furnished the cyclized product **3**.

To address the limitations of the reaction between the $CuCF_2PO(OEt)_2$ reagent and aryl diazonium salts and to extend the scope of applications of this $CuCF_2PO(OEt)_2$ reagent, we decided to investigate its reactivity toward hypervalent iodinated species.[21] Indeed, λ^3 iodanes are versatile reagents in organic synthesis, bench-stable, non toxic and easily prepared.[28] Moreover, in contrast to the diazonium salts, alkenyl and alkynyl iodonium species are stable and readily accessible. Therefore, this class of compounds might offer an access to a broader range of difluoromethylphosphonate-containing molecules. At the initial stage of this project, we studied the reaction with the commercially available diphenyl iodonium triflate **4a** as a model substrate.

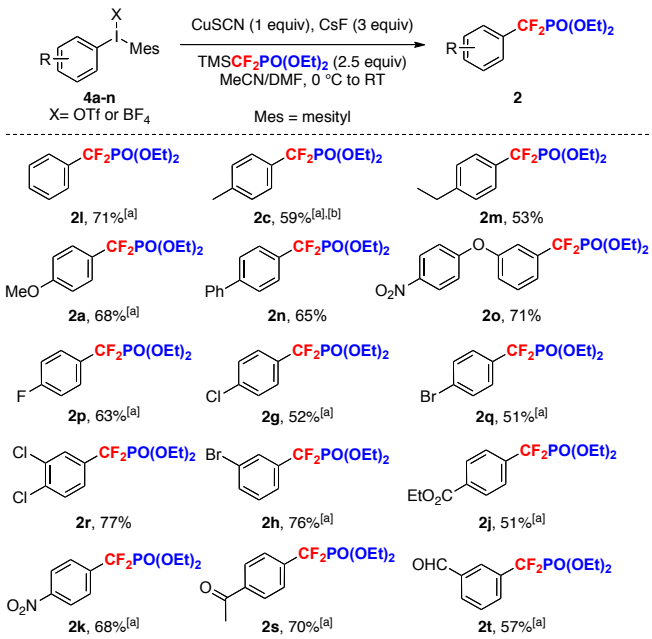
Table 2. Effect of the reaction parameters with **4a** as a reaction partner.



Entry	Change from the standard conditions	Yield [%][a]
1	None	91 (71)[b]
2	MeCN as a sole solvent	89
3	DMF as a sole solvent	35
4	CuOAc instead of CuSCN	78
5	KF instead of CsF	64
6	PhI instead of **4a**	NR

[a] Yields were determined by ^{19}F NMR using α,α,α-trifluorotoluene as an internal standard. [b] Isolated yields. NR = no reaction.

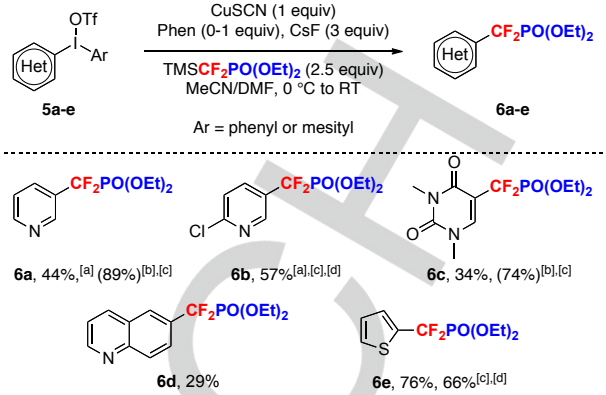
After a careful examination of the reaction parameters, we found that the use of slightly modified reaction conditions furnished the corresponding product **2l** in 71% isolated yield and 91% NMR yield. Indeed, the 1:1 mixture of MeCN/DMF was important to ensure a decent conversion into the corresponding product. The use of MeCN as a sole solvent provided **2l** in 89% yield, while DMF gave **2l** in 35% yield (entries 2 and 3). The use of other copper salts or activators furnished the product **2l** in lower yields (entries 4 and 5). A control experiment shown that phenyl iodide was unreactive under our reaction conditions. This observation assess that the reaction proceeded with the λ^3 iodane rather than with the aryl iodide that might arise from the decomposition of the hypervalent iodine species (entry 6). Having demonstrated the reactivity of the $CuCF_2PO(OEt)_2$ species toward **4a**, we sought to extend the scope of this transformation to other iodonium salts. First, various symmetric and non-symmetric diaryl iodonium salts were tested (Scheme 7).



Scheme 7. Scope of the reaction with diaryl iodonium salts. [a] See reference 21. [b] Symmetrical iodonium salt was used.

Aryl iodonium salts bearing electron-donating groups were evaluated. *para*-Alkyl substituted salts provided the corresponding difluoromethylphosphonate derivatives **2c** and **2m** in good yields. The methoxy- and phenyl-substituted iodonium salts were also compatible giving the products **2a** and **2n** in 68% and 65% isolated yields, respectively. Interestingly, substrate **4o** was reactive furnishing the biaryl ether derivative **2o** in 71% isolated yield. Then, iodonium salts bearing a halogen as a substituent were tested. Whatever, the substitution pattern, fluoride, chloride and bromide substituents were tolerated giving the corresponding products **2p**, **2g**, **2q**, **2r** and **2h** in moderate to good yields. Finally, electron-withdrawing groups like ester, nitro, ketone and even aldehyde were compatible with our reaction conditions and the corresponding fluorinated derivatives **2j**, **2k**, **2s** and **2t** were isolated in good yields. Remarkably, in the case of **2s** and **2t** no addition product on the carbonyl groups was detected in the reaction media proving the high selectivity of this transformation.

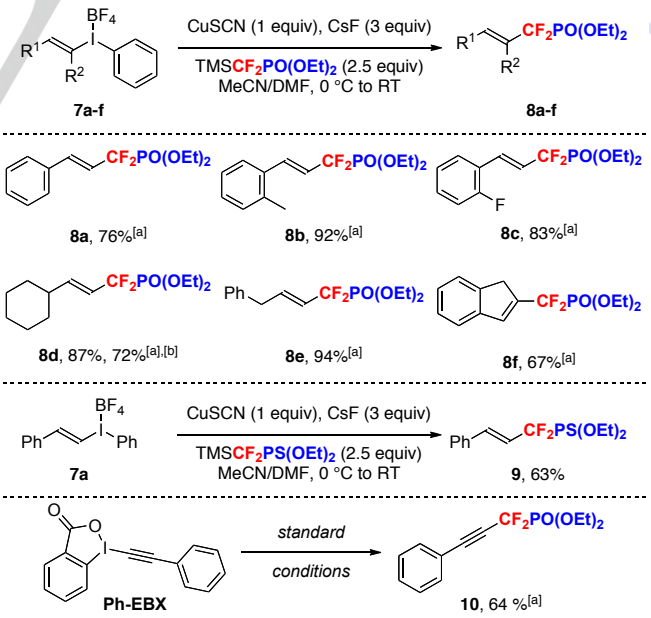
Heteroaryl derivatives are important scaffolds in agrochemical and pharmaceutical research. Hence, we then turned our attention to the synthesis of heteroaryl derivatives bearing a $CF_2PO(OEt)_2$ residue (Scheme 8).[21]



Scheme 8. Scope of the reaction with heteroaryl iodonium salts. [a] 1,10-phenanthroline (Phen) was used. [b] Yields were determined by ^{19}F NMR using α,α,α-trifluorotoluene as an internal standard. [c] See ref 21. [d] Reaction was performed on 3.4 mmol scale.

First, pyridine derivatives **6a** and **6b** were readily obtained in moderate yields. Interestingly, the *N*,*N*-dimethyl uracil derivatives **6c** was obtained in a 74% NMR yield and isolated in 34% yield, while the quinoline derivative **6d** was obtained in a poor 29% yield. Finally, the thienyl difluoromethylphosphonate **6e** was obtained in 76% yield and 66% yield on a gram scale, demonstrating the synthetic utility of the process.

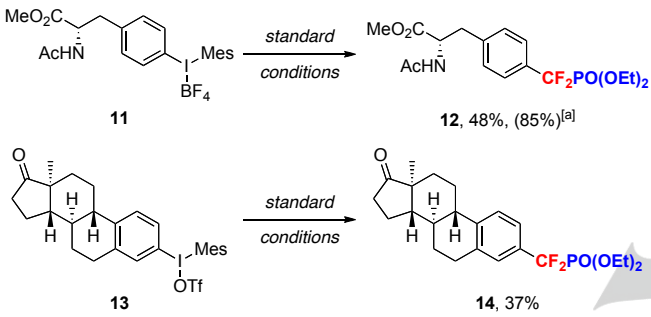
Subsequently, to further broaden the scope of our transformation we expanded this process to the synthesis of vinyl and alkynyl $CF_2PO(OEt)_2$ derivatives by using the corresponding iodonium salts (Scheme 9).



Scheme 9. Scope of the reaction with vinyl and alkynyl iodonium salts. [a] See ref 21. [b] Reaction was performed on 3.4 mmol scale.

First, iodonium salt bearing styryl substituents were tested. The salts **7a-c** provided the corresponding difluoromethylphosphonates **8a-c** in good to excellent yields. Then, alkyl-substituted olefins **8d** and **8e** were synthesized in good yields and the reaction was scaled-up to 3.4 mmol as demonstrated with **8d**. Notably, internal olefin **8f** was obtained in 67% isolated yield. In addition, this transformation was extended to the introduction of the difluoromethylphosphonothioate motif. Using a similar procedure to prepare the $CuCF_2PS(OEt)_2$ species, the reaction with vinyl iodonium salt **7a** provided the corresponding vinyl difluoromethylphosphonothioate **9** in 63% yield. Finally, by using the **Ph-EBX**,[29] alkynyl derivatives **10** was isolated in 64% yield.

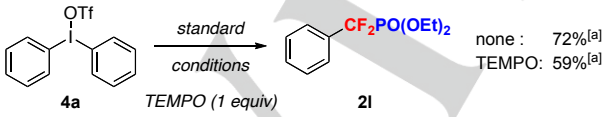
Then, to further showcase the synthetic utility of our procedure, we carried out the introduction of the $CF_2PO(OEt)_2$ motif onto biorelevant molecules (Scheme 10).



Scheme 10. Functionalization of biorelevant molecules. [a] Yields were determined by ^{19}F NMR using α,α,α-trifluorotoluene as an internal standard.

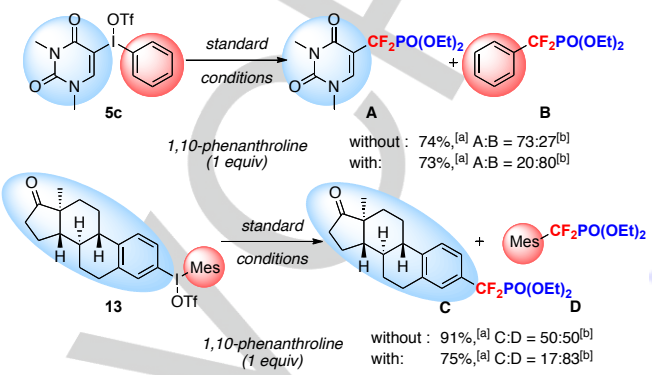
First, the iodonium salt **11** derived from iodotyrosine was used as a substrate and the corresponding difluoromethylphosphonate **12** was isolated in 48% yield. This compound is a synthetic intermediate toward the synthesis of a potent phosphatase inhibitor.[30] Then, we applied our methodology to the functionalization of the estrone derivative **13**. The iodonium salt was readily converted into the difluoromethylphosphonate **14** in a moderate 37% yield.

Intrigued by the mechanism of this transformation, mechanistic investigations were carried out.



Scheme 11. Mechanistic studies. [a] Yields were determined by ^{19}F NMR using α,α,α-trifluorotoluene as an internal standard.

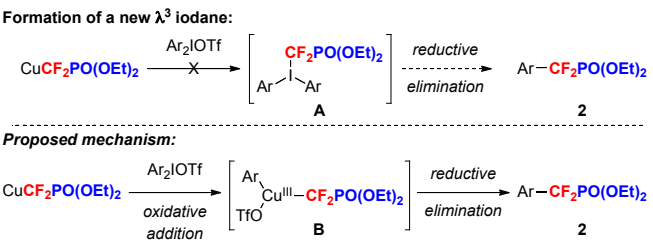
First, the reaction of **4a** with $CuCF_2PO(OEt)_2$ was performed in the presence of one equivalent of TEMPO ((2,2,6,6-tetramethylpiperidin-1-yl)oxyl) (Scheme 11). The reaction furnished the corresponding product **2l** without a significant decrease of the reaction yield. This result ruled out the intervention of a possible free radical pathway. Then, during the course of our investigations regarding the functionalization of unsymmetrical iodonium salts, an interesting impact of the addition of a ligand was observed on the selectivity of the transformation (Scheme 12).



Scheme 12. Mechanistic studies – ligand effect. [a] Yields were determined by ^{19}F NMR using α,α,α-trifluorotoluene as an internal standard. [b] Ratios were determined by ^{19}F NMR on the crude reaction mixture.

Indeed, when the reaction was carried with unsymmetrical iodonium salt **5c**, the mixture of compounds **A** and **B** was obtained in 74% yield with a 73:27 ratio. Impressively, when 1,10-phenanthroline was added to the copper species prior to the reaction with **5c**, the reaction furnished the corresponding mixture of products in 20:80 ratio and 73% yield. Similarly, with iodonium salt **13**, the impact of 1,10-phenanthroline on the selectivity of the transfer was observed. Without the addition of ligand an equimolar mixture of compounds **C** and **D** was observed, while its addition provided a 17:83 ratio.

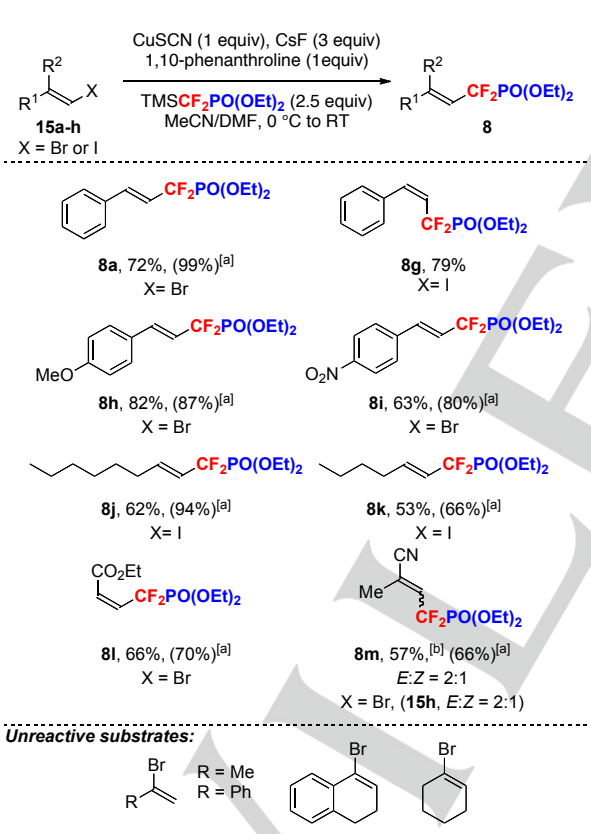
However, this significant ligand effect suggested that a copper species is involved in the reaction mechanism (Scheme 13). Therefore, the possible formation of a new λ^3 iodane **A** resulting from the replacement of the triflate by a $CF_2PO(OEt)_2$ residue can be ruled out. With this information in hand, we suggested the following reaction mechanism. First, the $CuCF_2PO(OEt)_2$ species reacted with the iodonium salt to form a putative Cu(III) species **B**. The latter underwent a reductive elimination to deliver the product **2**.[31]



Scheme 13. Proposed mechanism.

Then, we explored the reaction of the $CuCF_2PO(OEt)_2$ reagent with vinyl halides (Scheme 14). Indeed, in 1996, Shibuya and co-workers reported the reaction between $XZnCF_2PO(OEt)_2$ in the presence of a stoichiometric amount of CuBr.[15] We thought that the use of our protocol could avoid the use of Zn to prepare the corresponding fluorinated organometallic species prior the reaction.

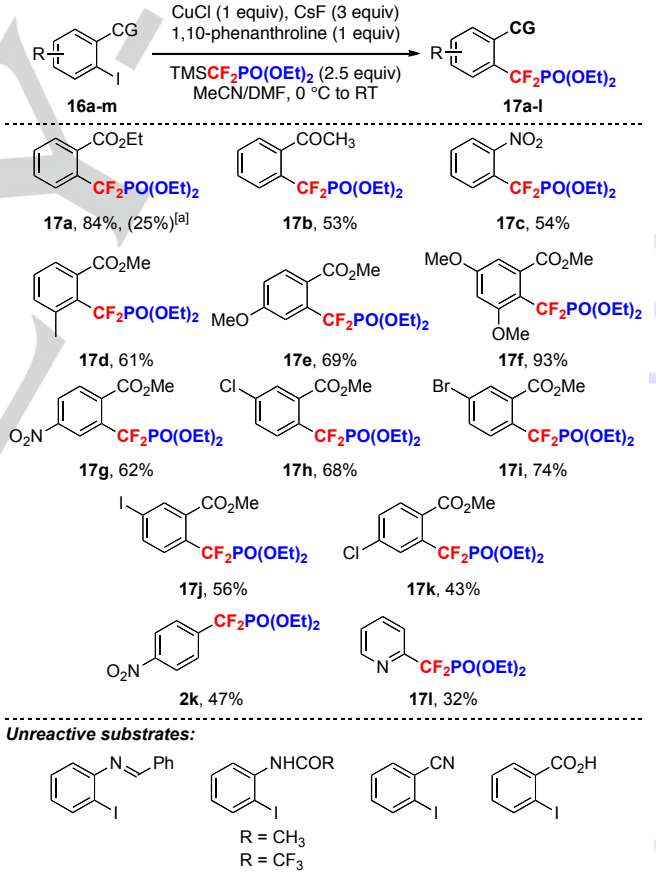
Pleasingly, by using our standard conditions along with the addition of 1,10-phenanthroline as a ligand, a broad range of vinyl halides (bromide and iodide) were readily functionalized at room temperature. First, (*E*)-β-bromostyrene **15a** was engaged under our reaction conditions providing the corresponding fluorinated product **8a** in 72% yield as a single (*E*)-isomer. When the reaction was carried out with (*Z*)-β-iodostyrene **15b**, the reaction afforded the (*Z*)-isomer **8g** in 79% isolated yield. This result proved that the reaction proceeded with the retention of the starting material geometry. Styryl derivatives bearing an electron-donating or an electron-withdrawing group were suitable substrates, as demonstrated with compounds **8h** and **8i**, which were isolated in 82% and 63% yields, respectively.



Scheme 14. Functionalization of alkenyl halides. [a] Yields were determined by ^{19}F NMR using α,α,α-trifluorotoluene as an internal standard. [b] Combined yield of the (*E*)- and (*Z*)-isomers.

Then, alkyl substituted vinyl iodides were smoothly reacted, giving the vinyl-$CF_2PO(OEt)_2$ species **8j** and **8k** in moderate to good yields (53% and 62%, respectively). Interestingly, (*Z*)-ethyl-β-bromoacrylate **15g** was reacted and provided the corresponding (*Z*)-$CF_2PO(OEt)_2$-containing olefin **8l** in 66% yield as a single diastereoisomer. This result demonstrated that the reaction conditions did not affect the stereochemistry of the starting halo olefin. Similarly, methacrylonitrile derivative **15h** (2:1 *E*/*Z* mixture) was readily functionalized and the corresponding product **8m** was isolated in 57% yield as a separable 2:1 mixture of diasteroisomers. Unfortunately, α-bromo-propene, α-bromo-styrene as well as cyclic vinyl bromide were unreactive under our reaction conditions. These examples pointed out the limitation of the reaction, which was restricted to terminal vinyl halides.

Aiming at developing a convenient method to introduce the $CF_2PO(OEt)_2$ motif, we thought that our protocol to generate the $CuCF_2PO(OEt)_2$ species might allow the Ullman cross-coupling reaction with aryl iodides bearing a coordinating group (CG) at the *ortho*-position (Scheme 15). Indeed, the group of Zhang reported the copper catalyzed Ullman cross-coupling reaction using *in situ* generated $XZnCF_2PO(OEt)_2$ on *ortho*-iodobenzoate and *ortho*-iodo- and bromo-triazene derivatives.[14a,b]

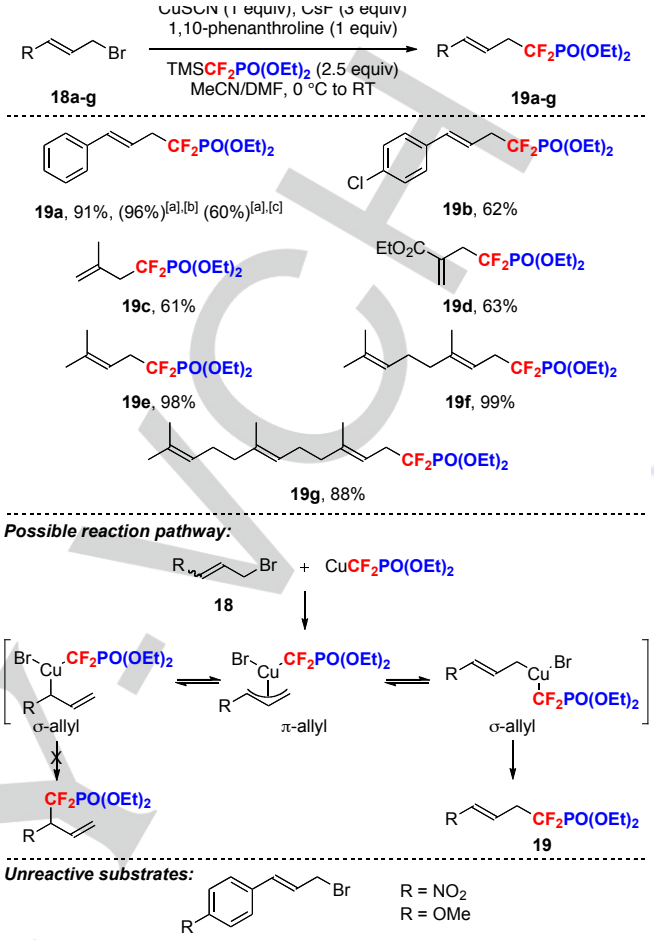


Scheme 15. Synthesis of aryl-$CF_2PO(OEt)_2$ derivatives from aryl iodides. [a] Ethyl *ortho*-bromobenzoate was used instead of **16a**. CG = coordinating group.

By replacing CuSCN by CuCl along with the addition of 1,10-phenanthroline as a ligand, the reaction with ethyl *ortho*-iodobenzoate **16a** afforded the corresponding product **17a** in

84% isolated yield (Scheme 15). Note that, the use of *ortho*-bromobenzoate instead of **16a**, allowed the formation of **17a** in a lower yield (25%). Interestingly and in contrast to the previous report on the Ullman cross-coupling reactions to introduce the $CF_2PO(OEt)_2$ motif,[14a] our transformation proceeded at room temperature. Then, the scope of the reaction was extended to other aryl iodide bearing a coordinating group at the *ortho*-position of the halide. Pleasingly, ketone and nitro groups could be a suitable coordinating group to promote this transformation since the corresponding products **17b** and **17c** were isolated in 53% and 54% yield. The reaction scope was further extended to several *ortho*-iodobenzoate derivatives. First, benzoates bearing an electron-donating group were tested. The sterically hindered substrates **16d** furnished the desired product **17d** in a decent 61% yield, while the iodobenzoates **16e** and **16f** bearing methoxy substituents were readily functionalized in 69% and 93% yields, respectively. A nitro substituent was also tolerated since the product **17g** was isolated in 62% yield. Then, *ortho*-iodobenzoate derivatives bearing a halogen substituent were evaluated. Pleasingly, chloro-, bromo- and even iodo-substituted substrates were functionalized in good yields (**17h-k**). Interestingly, in the case of **17j** no functionalization was observed at the *meta*-position, highlighting the high selectivity of this process and the importance of a coordinating group at the *ortho*-position of the halide in the Ullman cross-coupling reaction, the so-called "*ortho effect*".[32] Finally, the methodology was applied to the functionalization of *para*-nitro iodobenzene and 2-bromo-pyridine, albeit in moderate yields (47% and 32%, respectively). Noteworthy, other coordinating groups like imine, acetamide, trifluoroacetamide, as well as nitrile and carboxylic acid were inefficient under our reaction conditions.

Then, the functionalization of allyl halides was investigated to access the allyl-$CF_2PO(OEt)_2$ derivatives (Scheme 16).

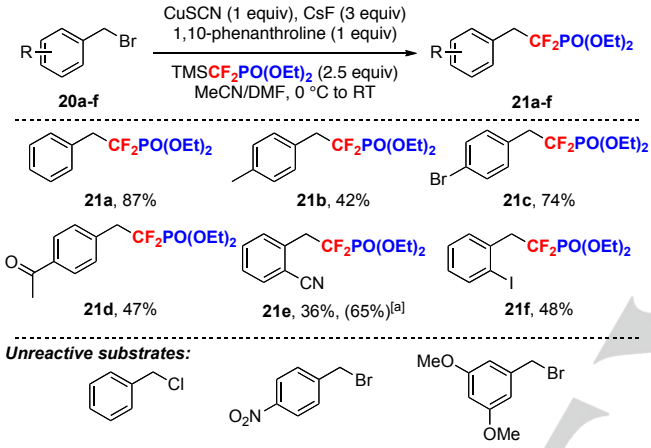


Scheme 16. Functionalization of allyl halide with the $CuCF_2PO(OEt)_2$ reagent. [a] Yields were determined by ^{19}F NMR using α,α,α-trifluorotoluene as an internal standard. [b] Cinnamyl chloride was used instead of **18a**. [c] Cinnamyl diethyl phosphate was used instead of **18a.**

First, (*E*)-cinnamyl bromide **18a** was reacted under our standard conditions affording the (*E*)-difluoromethylphosphonate **19a** in 92% NMR yield. Pleasingly, the addition of 1,10-phenanthroline as a ligand increased the reaction yield to 99% and the product **19a** was isolated in 91% yield. Notably, cinnamyl chloride and cinnamyl diethyl phosphate can also be used as starting materials, since **19a** was obtained in 96% and 60% NMR yields, respectively. Then, to study the impact of our reaction conditions on the stereochemical outcome, the reaction was carried out using (*Z*)-cinnamyl bromide. Under the standard conditions, the product with the (*E*)-configuration **19a** was isolated in 51% yield. This result was in agreement with the literature data, which suggested the involvement of a π-allylcopper(III) in allylic substitution.[33] The stereoselectivity of the reaction could be explained by the formation of the π-allyl complex followed by an isomerization step to form the σ-complex and a reductive elimination to furnish the linear product **19**. Interestingly, no trace of the branched product was detected in the reaction

mixture. Then, the reaction scope was extended to the *para*-chloro cinnamyl derivatives **19b**. Unfortunately, strong electron-donating (OMe) and electron-withdrawing (NO_2) groups at the *para*-position of the aromatic ring were not tolerated. The α-substitution did not have an impact on the reaction and the corresponding products **19c** and **19d** were isolated in good yields. Note that the presence of an ester group was tolerated. Finally, prenyl, geranyl and farnesyl bromides were readily functionalized giving the targeted difluoromethylphosphonate derivatives **19e-g** in good to excellent yields (98%, 99% and 88% respectively).

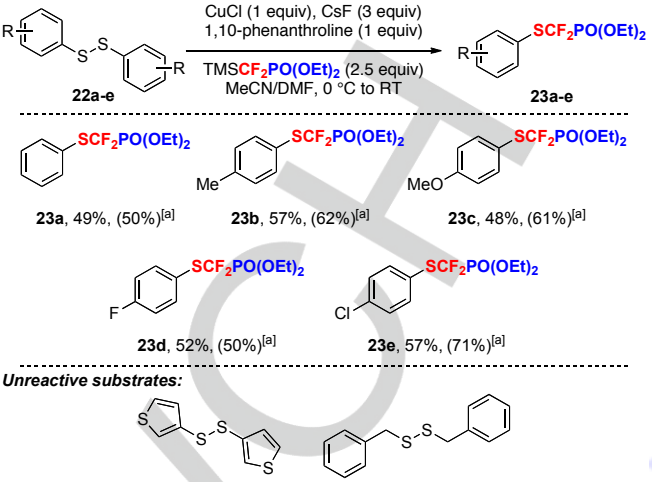
To further extend the reactivity and by analogy with the allyl derivatives, benzyl bromide derivatives were then functionalized (Scheme 17).



Scheme 17. Synthesis of benzyl $CF_2PO(OEt)_2$ derivatives. [a] Yield was determined by ^{19}F NMR using α,α,α-trifluorotoluene as an internal standard.

First, benzyl bromide **20a** was reacted under the standard conditions in the presence of 1,10-phenanthroline as a ligand and the corresponding fluorinated product **21a** was obtained in 87% isolated yield. Unfortunately, the reaction with benzyl chloride did not afford trace of the corresponding product **21a**. Then *para*-substituted benzyl bromides were reacted and the corresponding products **21b-d** were isolated in good yields. The reaction proved to be compatible with a bromide and a ketone substituent. These examples demonstrated the selectivity of the developed process. Then, *ortho*-substituted benzyl bromides were tested and the cyano and iodide substituents were tolerated giving the products **21e** and **21f** in moderate yields, 36% and 48% respectively. Note that the presence of an electron-donating group on the aromatic ring was deleterious as demonstrated with the dimethoxy substituted benzyl bromide that did not afford the corresponding $CF_2PO(OEt)_2$ derivative.

Quite recently, our group shed light on the emergent $SCF_2PO(OEt)_2$ fluorinated group.[34] Hence, we thought that the reaction between the $CuCF_2PO(OEt)_2$ species and a disulfide might offer a new synthetic access to this interesting sulfur-containing fluorinated building block (Scheme 18).[35]



Scheme 18. Reaction of the $CuCF_2PO(OEt)_2$ with disulfides. [a] Isolated yields [b] Yields were determined by ^{19}F NMR using α,α,α-trifluorotoluene as an internal standard.

First, the phenyldisulfide **22a** was used as a substrate and to our delight the corresponding $SCF_2PO(OEt)_2$ derivative **23a** was obtained in 50% NMR yield and isolated with 49% yield. Then, several disulfides were evaluated. The *para*-methyl and *para*-methoxy disulfides reacted with the $CuCF_2PO(OEt)_2$ and afforded the corresponding $SCF_2PO(OEt)_2$-containing aryls **23b** and **23c** in 57% and 48% yields, respectively. Finally, the disulfides bearing halogens at the *para*-position were also readily converted into the targeted fluorinated molecules **23d** and **23e** in moderate yields. Noteworthy, heteroaromatic disulfide and aliphatic one were unreactive and did not provide the desired fluorinated products.

Conclusions

In summary, we reported herein a full account of our investigations toward the copper-mediated introduction of the valuable phosphate bioisoster: the $CF_2PO(OEt)_2$ motif. Thanks to a straightforward procedure to prepare the $CuCF_2PO(OEt)_2$ reagent from the readily available silylated precursor a broad range of substrates were functionalized to access important fluorinated building blocks bearing this particular motif. The procedure allowed the functionalization of aryl diazonium salts, aryl, heteroaryl, vinyl and alkynyl iodoniums salts. This protocol was applied to the synthesis of biorelevant molecules. The mechanism of the transformation using iodonium salts was studied and an interesting ligand effect was observed. This study suggested the involvement of a Cu(III) species as an intermediate. Then, the methodology was extended to the functionalization of vinyl halides (bromides and iodides) and aryl iodides bearing a coordinating group at the *ortho*-position. The corresponding products were obtained in good yields and the developed methodology offered an interesting alternative to the existing methods. By using our protocol to generate the $CuCF_2PO(OEt)_2$ reagent, allyl halides and benzyl bromides were

readily converted into the corresponding fluorinated compounds at room temperature in moderate to good yields. Finally, we demonstrated that our methodology afforded an interesting pathway to access $SCF_2PO(OEt)_2$-containing molecules from disulfides. In conclusion, we developed a straightforward manifold to access a braod range of $CF_2PO(OEt)_2$-containing molecules at room temperature. We believe that this approach will be useful to synthesize important building blocks and will be applied to the synthesis of important biorelevant molecules.

Experimental Section

General: All reactions were carried out using oven dried glassware and magnetic stirring under an atmosphere of argon unless otherwise stated. Flash chromatography was performed with silica gel (0.040-0.060 nm). Reverse phase chromatography was performed on a puriFlash®215 using a puriFlash® C18HP 15μm 55G Flash column. Analytical thin layer chromatography was performed on silica gel aluminium plates with F-254 indicator and visualized by UV light (254 nm) and/or chemical staining with a $KMnO_4$ solution. ^{1}H NMR spectra were recorded on a Bruker DXP 300 at 300 MHz and a Bruker DXP 400 at 400 MHz, ^{13}C NMR spectra at 75 MHz and at 100 MHz, ^{19}F NMR spectra at 282 MHz and ^{31}P NMR at 121 MHz. Chemical shifts (δ) are quoted in parts per million (ppm) relative to the residual solvent peak for $CDCl_3$ (δ_H = 7.26 ppm; δ_C = 77.16 ppm; or relative to external $CFCl_3$: δ = 0 ppm), [D_6]acetone (δ_H = 2.05 ppm; δ_C = 29.84 ppm), CD_3OD (δ_H = 3.31 ppm; δ_C = 49.00 ppm). The following abbreviations have been used: δ (chemical shift), *J* (coupling constant), app. (apparent), br. (broad), s (singlet), d (doublet), dd (doublet of doublets), ,t (triplet), td (triplet ou doublets), tq (triplet of quadruplets) q (quartet), m (multiplet). High-resolution mass spectra (HRMS) were recorded on Waters LCT Premier, IR spectra were recorded on a PerkinElmer Spectrum 100.

Starting material synthesis:

Diethyl [difluoro(trimethylsilyl)methyl]phosphonate was synthesized according to the procedure described by O'Hagan.[24] Diazonium salts were prepared according to reported methods, see reference 25b and references cited herein. Iodonium salts, **4**, **5**, **7**, **11** and **13** were prepared according to the literature.[36]

General procedure for copper-mediated synthesis of difluoromethylphosphonates from aryl diazonium salts.

Method A:

In a glove box, a sealed tube was loaded with CuSCN (61 mg, 0.50 mmol) and CsF (228 mg, 1.50 mmol) and sealed with a rubber septum. Dry acetonitrile (1 mL) was added and the mixture was placed at 0 °C. Diethyl [(trimethylsilyl)difluoromethyl]phosphonate (325 mg, 1.25 mmol) was added and the mixture was heated at 40 °C for 1h, cooled to 0 °C and allowed to stirred at this temperature for 1 h. Unless otherwise noted, the corresponding diazonium salt (0.50 mmol) was added dropwise as a solution in acetonitrile (1 mL). The rubber septum was removed, the tube was sealed and the suspension was stirred for 16 h. The reaction mixture was diluted with diethyl ether (30 mL) and filtered through a plug of Celite®. The organic layer was washed with water (4 × 10 mL), brine (2 × 10 mL), dried over $MgSO_4$, and solvents were carefully removed. Unless otherwise noted, purification by flash chromatography on silica gel gave the pure desired product.

General procedures for the copper-mediated synthesis of difluoromethylphosphonates from iodonium salts.

Method B:

In a glove box, a tube was loaded with CuSCN (61 mg, 0.50 mmol) and CsF (228 mg, 1.50 mmol) and sealed with a rubber septum. Dry acetonitrile (1 mL) was added and the mixture was placed at 0 °C. Diethyl [(trimethylsilyl)difluoromethyl]phosphonate (neat, 325 mg, 1.25 mmol) was added and the mixture was heated at 40 °C for 1 h, cooled to 0 °C and allowed to stir at this temperature for 1 h. The corresponding iodonium salt (0.50 mmol) was added dropwise as a solution in DMF (1 mL). The rubber septum was removed, the tube was sealed and the suspension was stirred for 16 h. The reaction mixture was diluted with diethyl ether (30 mL) and filtered through a plug of Celite®. The organic layer was washed with water (4 × 25 mL), brine (25 mL), dried over $MgSO_4$, and solvents were carefully removed under vacuum. Reverse phase chromatography (H_2O/CH_3CN or MeOH, gradient: 9:1 to 0:1, rate: 1% CH_3CN or MeOH per minute) gave the product.

Method C (with 1,10-phenanthroline):

In a glove box, a tube was loaded with CuSCN (61 mg, 0.50 mmol) and CsF (228 mg, 1.50 mmol) and sealed with a rubber septum. Dry acetonitrile (1 mL) was added and the mixture was placed at 0 °C. Diethyl [(trimethylsilyl)difluoromethyl]phosphonate (neat, 325 mg, 1.25 mmol) was added and the mixture was heated at 40 °C for 1 h, cooled to 0 °C and allowed to stir at this temperature for 1 h. 1,10-Phenanthroline (90.1 mg, 1.00 mmol) was added followed by a solution of the corresponding iodonium salt (0.50 mmol) in DMF (1 mL). The rubber septum was removed, the tube was sealed and the suspension was stirred for 16 h. The reaction mixture was diluted with diethyl ether (30 mL) and filtered through a plug of Celite®. The organic layer was washed with water (4 × 25 mL), brine (25 mL), dried over $MgSO_4$, and solvents were carefully removed under vacuum. Reverse phase chromatography (H_2O/CH_3CN or MeOH, gradient: 9:1 to 0:1, rate: 1% CH_3CN or MeOH per minute) gave the product.

General procedures for the copper-mediated synthesis of difluoromethylphosphonates from vinyl halides, allyl bromides and benzyl bromides.

Method D:

In a glove box, a tube was loaded with CuSCN (61 mg, 0.50 mmol) and CsF (228 mg, 1.50 mmol) and sealed with a rubber septum. Dry acetonitrile (1 mL) was added and the mixture was placed at 0 °C. Diethyl [(trimethylsilyl)difluoromethyl]phosphonate (neat, 325 mg, 1.25 mmol) was added and the mixture was heated at 40 °C for 1 h, cooled to 0 °C and allowed to stir at this temperature for 1 h. 1,10-Phenanthroline (90.1 mg, 1.00 mmol) was added followed by a solution of the corresponding vinyl halide or allyl halide or benzyl bromide (0.50 mmol). The rubber septum was removed, the tube was sealed and the suspension was stirred for 16 h. The reaction mixture was diluted with diethyl ether (30 mL), the organic layer was washed with water (4 × 25 mL), brine (25 mL), dried over Na_2SO_4, and solvent was carefully removed under vacuum. Reverse phase chromatography (H_2O/CH_3CN, gradient: 9:1 to 0:1, rate: 1% CH_3CN per minute) gave the product.

General procedures for the copper-mediated synthesis of difluoromethylphosphonates from iodoarenes

Method E:

In a glove box, a tube was loaded with CuCl (50 mg, 0.50 mmol) and CsF (228 mg, 1.50 mmol) and sealed with a rubber septum. Dry acetonitrile (1 mL) was added and the mixture was placed at 0 °C. Diethyl [(trimethylsilyl)difluoromethyl]phosphonate (neat, 325 mg, 1.25 mmol) was added and the mixture was heated at 40 °C for 1 h, cooled to 0 °C and allowed to stir at this temperature for 1 h. 1,10-Phenanthroline (90.1 mg, 1.00 mmol) was added followed by a solution of the corresponding iodoarene (0.50 mmol). The rubber septum was removed, the tube was sealed and the suspension was stirred for 16 h. The reaction mixture was diluted with diethyl ether (30 mL), the organic layer was washed with water (4 × 25 mL), brine (25 mL), dried over Na_2SO_4, and solvent was carefully removed under vacuum. Reverse phase chromatography (H_2O/CH_3CN, gradient: 9:1 to 0:1, rate: 1% CH_3CN per minute) gave the product.

General procedures for the copper-mediated synthesis of diethyl phosphono)difluoromethylthiolated derivatives

Method F:

In a glove box, a tube was loaded with CuSCN (61 mg, 0.50 mmol) and CsF (228 mg, 1.50 mmol) and sealed with a rubber septum. Dry acetonitrile (1 mL) was added and the mixture was placed at 0 °C. Diethyl [(trimethylsilyl)difluoromethyl]phosphonate (neat, 325 mg, 1.25 mmol) was added and the mixture was heated at 40 °C for 1 h, cooled to 0 °C and allowed to stir at this temperature for 1 h. The corresponding disulfide (0.50 mmol) was added. The rubber septum was removed, the tube was sealed and the suspension was stirred for 16 h. The reaction mixture was diluted with diethyl ether (30 mL), the organic layer was washed with water (4 × 25 mL), brine (25 mL), dried over Na_2SO_4, and solvent was carefully removed under vacuum. Reverse phase chromatography (H_2O/CH_3CN, gradient: 9:1 to 0:1, rate: 1% CH_3CN per minute) gave the product.

Diethyl [(4-methoxyphenyl)difluoromethyl]phosphonate 2a. Prepared following the procedure A from 4-methoxybenzenediazonium tetrafluoroborate **1a** with 72% yield (106 mg, 0.5 mmol scale); the procedure B from di(4-methoxyphenyl)iodonium trifluoromethanesulfonate **4a** with 68% yield (100 mg, 0.5 mmol scale). Reverse phase chromatography (H_2O/MeCN). Yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.56 (d, J = 8.3 Hz, 2H), 6.94 (d, J = 8.6 Hz, 2H), 4.49-3.97 (m, 4H), 3.81 (s, 3H), 1.29 (t, J = 7.1 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 161.5 (dd, J = 3.6 and 1.7 Hz), 127.9 (td, J = 6.8 and 2.4 Hz), 124.6 (td, J = 22.7 and 14.0 Hz), 118.3 (td, J = 263.0 and 220.9 Hz), 113.9 (d, J = 1.2 Hz), 64.8 (d, J = 6.7 Hz), 55.4, 16.4 (d, J = 5.6 Hz); ^{19}F{^{1}H} NMR ($CDCl_3$, $CFCl_3$, 282 MHz) δ -107.6 (d, J = 119.7 Hz, 2F); ^{31}P{^{1}H} NMR ($CDCl_3$, 121 MHz) δ 6.6 (t, J = 119.8 Hz, 1P); IR (neat, cm^{-1}) 2985, 1614, 1515, 1250, 1011; HRMS (ESI^+) calcd for $[M+H]^+$ $C_{12}H_{18}F_2O_4P$: 295.0911, found: 295.0906 (−1.7 ppm).

Diethyl [(2-methoxyphenyl)difluoromethyl]phosphonate 2b. Prepared following the procedure A from 2-methoxybenzenediazonium tetrafluoroborate **1b**. Yield: 60% (88 mg, 0.5 mmol scale). Yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.49 (d, J = 7.8 Hz, 1H), 7.41 (app. t, J = 7.9 Hz, 1H), 6.94-7.01 (m, 2H), 4.32-4.05 (m, 4H), 3.85 (s, 3H), 1.29 (t, J = 7.1 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 157.8 (td, J = 3.3 and 2.0 Hz), 132.4 (dd, J = 3.2 and 1.6 Hz), 128.2 (td, J = 9.1 and 2.7 Hz), 120.9 (td, J = 21.7 and 13.7 Hz), 120.4 (d, J = 0.8 Hz), 118.6 (td, J = 264.1 and 219.4 Hz), 112.2 (d, J = 0.9 Hz), 64.6 (d, J = 6.7 Hz), 55.9, 16.4 (d, J = 5.8 Hz); ^{19}F{^{1}H} NMR ($CDCl_3$, $CFCl_3$, 282 MHz) δ -105.2 (d, J = 116.5 Hz, 2F); ^{31}P{^{1}H} NMR ($CDCl_3$, 121 MHz) δ 6.7 (t, J = 116.3 Hz, 1P); IR (neat, cm^{-1}) 2919, 1603, 1495, 1257, 1036, 1017; HRMS (ESI^+) calcd for $[M+H]^+$ $C_{12}H_{18}F_2O_4P$: 295.0911, found: 295.0914 (1 ppm).

Diethyl [(p-tolyl)difluoromethyl]phosphonate 2c. Prepared following the procedure A from *p*-tolyldiazonium tetrafluoroborate **1c** with 65% yield (90 mg, 0.5 mmol scale), 68% yield (680 mg, 3.6 mmol scale); the procedure B from di(4-tolyl)iodonium trifluoromethanesulfonate **4c** with 59% yield (82 mg, 0.5 mmol scale). Reverse phase chromatography (H_2O/MeCN). Yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.48 (d, J = 7.7 Hz, 2H), 7.23 (d, J = 8.0 Hz, 2H), 4.28-4.05 (m, 4H), 2.37 (s, 3H), 1.29 (t, J = 7.1 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 141.5 (dd, J = 4.1 and 2.1 Hz), 129.7 (td, J = 22.2 and 13.8 Hz), 129.2 (d, J = 1.3 Hz), 118.3 (td, J = 262.9 and 219.1 Hz), 64.8 (d, J = 6.7 Hz), 21.4, 16.4 (d, J = 5.6 Hz); ^{19}F{^{1}H} NMR ($CDCl_3$, $CFCl_3$, 282 MHz) δ -108.5 (d, J = 118.0 Hz, 2F); ^{31}P{^{1}H} NMR ($CDCl_3$, 121 MHz) δ 6.5 (t, J = 118.0 Hz, 1P); IR (neat, cm^{-1}) 2985, 1617, 1515, 1260, 1011; HRMS (ESI^+) calcd for $[M+H]^+$ $C_{12}H_{18}F_2O_3P$: 279.0962, found: 279.0957 (−1.8 ppm).

Diethyl [(3,5-dimethoxyphenyl)difluoromethyl]phosphonate 2d. Prepared following the procedure A from 3,5-dimethoxybenzenediazonium tetrafluoroborate **1d**. Reverse phase chromatography (H_2O/MeOH). Yield: 40% (65 mg, 0.5 mmol scale). Yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.74 (s, 2H), 6.53 (s, 1H), 4.27-4.07 (m, 4H), 3.79 (s, 6H), 1.31 (t, J = 7.1 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 160.8 (d, J = 1.2 Hz), 134.6 (td, J = 22.1 and 14.1 Hz), 117.9 (td, J = 263.8 and 217.8 Hz), 104.3 (td, J = 7.1 and 2.3 Hz), 103.0 (dd, J = 3.4 and 1.7 Hz), 64.9 (d, J = 6.7 Hz), 55.6, 16.4 (d, J = 5.6 Hz); ^{19}F{^{1}H} NMR ($CDCl_3$, $CFCl_3$, 282 MHz) δ -108.5 (d, J = 115.5 Hz, 2F); ^{31}P{^{1}H} NMR ($CDCl_3$, 121 MHz) δ 6.2 (t, J = 115.6 Hz, 1P); IR (neat, cm^{-1}) 2985, 1597, 1460, 1270, 1205, 1157, 1011; HRMS (ESI^+) calcd for $[M+NH_4]^+$ $C_{13}H_{23}NF_2O_5P$: 342.1282, found: 342.1274 (−2.3 ppm).

Diethyl [(3-benzyloxyphenyl)difluoromethyl]phosphonate 2e. Prepared following the procedure A from 3-benzyloxybenzenediazonium tetrafluoroborate **1e**. Reverse phase chromatography (H_2O/MeCN). Yield: 54% (100 mg, 0.5 mmol scale). Pale yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.36-7.25 (m, 5H), 7.17-7.12 (m, 3H), 6.99 (d, J = 8.1 Hz, 1H), 5.00 (s, 2H), 4.18-3.97 (m, 4H), 1.21 (t, J = 7.1 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 158.7 (d, J = 1.2 Hz), 136.6, 134.0 (td, J = 22.0 and 13.8 Hz), 129.7 (d, J = 1.2 Hz), 128.7, 128.2, 127.6, 118.8 (td, J = 6.9 and 2.3 Hz), 117.9 (td, J = 263.5 and 217.8 Hz), 112.6 (td, J = 7.1 and 2.3 Hz), 70.2, 64.9 (d, J = 6.7 Hz), 16.4 (d, J = 5.5 Hz); ^{19}F{^{1}H} NMR ($CDCl_3$, $CFCl_3$, 282 MHz) δ -108.6 (d, J = 115.7 Hz, 2F); ^{31}P{^{1}H} NMR ($CDCl_3$, 121 MHz) δ 6.3 (t, J = 115.7 Hz, 1P); IR (neat, cm^{-1}) 2985, 1587, 1442, 1268, 1012; HRMS (ESI^+) calcd for $[M+NH_4]^+$ $C_{18}H_{25}NF_2O_4P$: 388.1489, found: 388.1487 (−0.5 ppm).

Diethyl [(naphten-1-yl)difluoromethyl]phosphonate 2f. Prepared following the procedure A from naphthalene-1-diazonium tetrafluoroborate **1f**. Yield: 60% (94 mg, 0.5 mmol scale). Dark orange oil; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.45 (d, J = 8.5 Hz, 1H), 7.95 (d, J = 8.2 Hz 1H), 7.86 (d, J = 7.8 Hz, 1H), 7.81 (d, J = 7.4 Hz, 1H), 7.59-7.48 (m, 3H), 4.29-4.01 (m, 4H), 1.25 (t, J = 7.1 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 134.1 (d, J = 0.9 Hz), 132.1 (dd, J = 3.4 and 1.7 Hz), 129.9 (dd, J = 3.7 and 1.8 Hz), 128.6 (d, J = 2.5 Hz), 128.4 (td, J = 20.1 and 13.5 Hz), 126.9, 126.4 (td, J = 10.4 and 3.6 Hz), 126.3, 126.1 (td, J = 5.2 and 0.7 Hz), 124.4 (d, J = 1.7 Hz), 120.0 (td, J = 264.1 and 216.8 Hz), 64.8 (d, J = 6.8 Hz), 16.3 (d, J = 5.6 Hz); ^{19}F{^{1}H} NMR ($CDCl_3$, 282 MHz) δ -102.4 (d, J = 114.6 Hz, 2F); ^{31}P{^{1}H} NMR ($CDCl_3$, $CFCl_3$, 121 MHz) δ 6.7 (t, J = 114.7 Hz, 1P); IR (neat, cm^{-1}) 2985, 1514, 1269; 1010; HRMS (ESI^+) calcd for $[M+NH_4]^+$ $C_{15}H_{21}NF_2O_3P$: 332.1227, found: 332.1233 (1.8 ppm).

Diethyl [(4-chlorophenyl)difluoromethyl]phosphonate 2g. Prepared following the procedure A from 4-chlorobenzenediazonium tetrafluoroborate **1g** with 37% yield (55 mg, 0.5 mmol scale); the procedure B from (4-chlorophenyl)(mesityl)iodonium trifluoromethanesulfonate **4g** with 52% yield (77 mg, 0.5 mmol scale).

Reverse phase chromatography (H_2O/MeCN). Dark yellow oil; ^1H NMR (300 MHz, $CDCl_3$): δ 7.54 (d, J = 7.9 Hz, 2H), 7.42 (d, J = 8.5 Hz, 2H), 4.29-4.08 (m, 4H), 1.30 (t, J = 7.1 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 137.2 (dd, J = 4.7 and 2.4 Hz), 131.2 (td, J = 22.5 and 14.0 Hz), 128.9 (d, J = 1.3 Hz), 127.8 (td, J = 6.8 and 2.3 Hz), 117.8 (td, J = 263.5 and 218.8 Hz), 65.0 (d, J = 6.8 Hz), 16.4 (d, J = 5.5 Hz); $^{19}F\{^1H\}$ NMR ($CDCl_3$, $CFCl_3$, 282 MHz) δ -109.1 (d, J = 115.1 Hz, 2F); $^{31}P\{^1H\}$ NMR ($CDCl_3$, 121 MHz) δ 5.9 (t, J = 115.2 Hz, 1P); IR (neat, cm−1) 2986, 1602, 1492, 1270, 1256, 1012; HRMS (ESI^+) calcd for $[M+NH_4]^+$ $C_{11}H_{18}NF_2O_3PCl$: 316.0681, found: 316.0675 (−1.9 ppm).

Diethyl [(3-bromophenyl)difluoromethyl]phosphonate 2h. Prepared following the procedure A from 3-bromobenzenediazonium tetrafluoroborate **1h** with 44% yield (75 mg, 0.5 mmol scale); the procedure B from (3-bromophenyl)(mesityl)iodonium trifluoromethanesulfonate **4h** with 76% yield (129 mg, 0.5 mmol scale). Reverse phase chromatography (H_2O/MeCN). Orange oil; ^1H NMR (300 MHz, $CDCl_3$): δ 7.73 (s, 1H), 7.60 (d, J = 8.0 Hz, 1H), 7.54 (d, J = 7.7 Hz, 1H), 7.32 (app. t, J = 7.9 Hz, 1H), 4.32-4.09 (m, 4H), 1.31 (t, J = 7.1 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 134.7 (td, J = 22.3 and 13.9 Hz), 134.0 (dd, J = 3.6 and 1.7 Hz), 130.2 (d, J = 1.3 Hz), 129.4 (td, J = 7.1 and 2.4 Hz), 125.1 (td, J = 6.7 and 2.2 Hz), 117.3 (td, J = 264.1 and 218.0 Hz), 65.1 (d, J = 6.8 Hz), 16.4 (d, J = 5.5 Hz); $^{19}F\{^1H\}$ NMR ($CDCl_3$, $CFCl_3$, 282 MHz) δ -109.4 (d, J = 113.9 Hz, 2F); $^{31}P\{^1H\}$ NMR ($CDCl_3$, 121 MHz) δ 5.7 (t, J = 114.0 Hz, 1P); IR (neat, cm^{-1}) 2985, 1574, 1476, 1270, 1242, 1012; HRMS (ESI^+) calcd for $[M^{79}Br+NH_4]^+$ $C_{11}H_{18}NF_2O_3P^{79}Br$: 360.0176, found: 360.0170 (−1.7 ppm).

Diethyl [(4-{trifluoromethyl}phenyl)difluoromethyl]phosphonate 2i. Prepared following the procedure A from 4-(trifluoromethyl)benzenediazonium tetrafluoroborate **1i**. Yield: 36% (60 mg, 0.5 mmol scale). Orange oil; ^1H NMR (300 MHz, $CDCl_3$): δ 7.75-7.65 (m, 4H), 4.32-4.10 (m, 4H), 1.31 (t, J = 7.1 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 136.9-136.0 (m), 133.6-132.2 (m), 127.0 (td, J = 6.8 and 2.3 Hz), 125.6 (qd, J = 3.7 and 1.3 Hz), 120.1 (q, J = 272.7 Hz), 117.5 (td, J = 263.6 and 217.3 Hz), 65.1 (d, J = 6.8 Hz), 16.4 (d, J = 5.5 Hz); $^{19}F\{^1H\}$ NMR ($CDCl_3$, $CFCl_3$, 282 MHz) δ -63.5 (s, 3F), -109.9 (d, J = 112.8 Hz, 2F); $^{31}P\{^1H\}$ NMR ($CDCl_3$, 121 MHz) δ 5.6 (t, J = 112.8 Hz, 1P); IR (neat, cm^{-1}) 2992, 1414, 1266, 1127, 1066, 1013; HRMS (ESI^+) calcd for $[M+NH_4]^+$ $C_{12}H_{18}NF_5O_3P$: 350.0944, found: 350.0938 (−1.7 ppm).

Ethyl 4-[(diethoxyphosphoryl)difluoromethyl]benzoate 2j. Prepared following the procedure A from 4-(ethoxycarbonyl)benzenediazonium tetrafluoroborate **1j** with 35% yield (59 mg, 0.5 mmol scale); the procedure B from (((4-ethoxycarbonyl)phenyl)(mesityl)iodonium trifluoromethanesulfonate **4j** with 51% yield (86 mg, 0.5 mmol scale). Reverse phase chromatography (H_2O/MeCN). Yellow oil; ^1H NMR (300 MHz, $CDCl_3$): δ 8.11 (d, J = 8.2 Hz, 2H), 7.68 (d, J = 8.0 Hz, 2H), 4.38 (q, J = 7.1 Hz, 2H), 4.27-4.07 (m, 4H), 1.39 (t, J = 7.1 Hz, 3H), 1.30 (t, J = 7.1 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 165.8, 136.9 (td, J = 21.9 and 13.6 Hz), 132.8 (dd, J = 3.6 and 1.7 Hz), 129.7 (d, J = 1.3 Hz), 126.5 (td, J = 6.8 and 2.3 Hz), 117.8 (td, J = 263.6 and 216.9 Hz), 65.0 (d, J = 6.8 Hz), 61.5, 16.4 (d, J = 5.5 Hz), 14.4; $^{19}F\{^1H\}$ NMR ($CDCl_3$, $CFCl_3$, 282 MHz) δ -109.9 (d, J = 113.5 Hz, 2F); $^{31}P\{^1H\}$ NMR ($CDCl_3$, 121 MHz) δ 5.8 (t, J = 113.4 Hz, 1P); IR (neat, cm^{-1}) 2985, 1719, 1270, 1107, 1011; HRMS (ESI^+) calcd for $[M+NH_4]^+$ $C_{14}H_{23}NF_2O_5P$: 354.1282, found: 354.1291 (2.5 ppm).

Diethyl [(4-nitrophenyl)difluoromethyl]phosphonate 2k. Prepared following the procedure A from 4-nitrobenzenediazonium tetrafluoroborate **1k** with 18% yield (28 mg, 0.5 mmol scale); the procedure B from (4-nitrophenyl)(mesityl)iodonium trifluoromethanesulfonate **4k** with 68% yield (105 mg, 0.5 mmol scale); the procedure E from 1-iodo-4-nitrobenzene **16k** with 47% yield (72 mg, 0.5 mmol scale). Orange oil; ^1H NMR (300 MHz, $CDCl_3$): δ 8.31 (d, J = 8.6 Hz, 2H), 7.81 (d, J = 7.9 Hz, 2H), 4.32-4.13 (m, 4H), 1.33 (t, J = 7.1 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 149.5, 139.1 (td, J = 22.3 and 13.8 Hz), 127.8 (td, J = 6.7 and 2.2 Hz), 123.7 (d, J = 1.2 Hz), 117.3 (td, J = 264.3 and 216.3 Hz), 65.3 (d, J = 6.9 Hz), 16.5 (d, J = 5.4 Hz); $^{19}F\{^1H\}$ NMR ($CDCl_3$, $CFCl_3$, 282 MHz) δ -110.1 (d, J = 110.8 Hz, 2F); $^{31}P\{^1H\}$ NMR ($CDCl_3$, 121 MHz) δ 5.1 (t, J = 110.9 Hz, 1P); IR (neat, cm^{-1}) 2919, 1522, 1343, 1270, 1253, 1014; HRMS (ESI^+) calcd for $[M+NH_4]^+$ $C_{11}H_{18}N_2F_2O_5P$: 327.0921, found: 327.0920 (−0.3 ppm).

Diethyl [2-(2,3-dihydrobenzofuran-3-yl)-1,1-difluoromethyl]phosphonate 3. Prepared following the procedure A from 2-(allyloxy)benzenediazonium tetrafluoroborate **1l**. Reverse phase chromatography (H_2O/CH_3CN). Yield: 68% (109 mg, 0.5 mmol scale). Brown oil; ^1H NMR (300 MHz, $CDCl_3$): δ 7.18-7.12 (m, 2H), 6.88 (dt, J = 7.5 and 0.9 Hz, 1H), 6.80 (d, J = 7.9 Hz, 1H), 4.74 (t, J = 9.0 Hz, 1H), 4.35-4.24 (m, 5H), 3.95-3.86 (m, 1H), 2.73-2.51 (m, 1H), 2.45-2.23 (m, 1H), 1.42-1.37 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 159.7, 128.9, 128.8 124.2, 123.5 (td, J = 261.1 and 215.9 Hz), 120.8, 109.8, 64.8-64.7 (m), 38.7 (dt, J = 19.8 and 14.2 Hz), 35.5 (dt, J = 6.4 and 3.9 Hz),16.5 (d, J = 5.4 Hz), 1.15; $^{19}F\{^1H\}$ NMR ($CDCl_3$, $CFCl_3$, 282 MHz) δ −111.1 (dd, J = 298.2 and 105.4 Hz) and −113.3 (dd, J = 298.2 and 106.2 Hz); $^{31}P\{^1H\}$ NMR ($CDCl_3$, 121 MHz) δ 6.6 (t, J = 105.6 Hz, 1P); IR (neat, cm^{-1}) ν: 2986, 1599, 1483, 1462, 1269, 1230, 1162,1013, 979; HRMS (ESI^+) calcd for $[M+H]^+$ $C_{14}H_{20}F_2O_4P$: 321.1067, found: 321.1072 (1.6 ppm).

Diethyl [(phenyl)difluoromethyl]phosphonate 2l. Prepared following the procedure B from diphenyliodonium trifluoromethanesulfonate **4l**. Reverse phase chromatography (H_2O/CH_3CN). Yield: 71% (94 mg, 0.5 mmol scale). Caution: this compound is volatile. Pale yellow oil; ^1H NMR (300 MHz, CDCl3): δ 7.62 (d, J = 7.2 Hz, 2H), 7.47-7.45 (m, 3H), 4.28-4.07 (m, 4H), 1.31 (t, J = 7.1 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 132.7 (td, J = 22.0 and 13.7 Hz), 130.8 (dd, J = 3.9 and 1.9 Hz), 128.5 (d, J = 1.3 Hz), 126.3 (td, J = 6.9 and 2.4 Hz), 118.1 (td, J = 263.1 and 218.2 Hz), 64.8 (d, J = 6.7 Hz), 16.4 (d, J = 5.5 Hz); $^{19}F\{^1H\}$ NMR ($CDCl_3$, $CFCl_3$, 282 MHz) δ −109.0 (d, J = 116.3 Hz, 2F); $^{31}P\{^1H\}$ NMR ($CDCl_3$, 121 MHz) δ 6.4 (t, J = 116.3 Hz, 1P); IR (neat, cm^{-1}) ν: 2986, 2917, 1452, 1257, 1011; HRMS (EI^+) calcd for $[M]^+$ $C_{11}H_{15}F_2O_3P$: 264.0727, found: 264.0726 (−0.2 ppm).

Diethyl ((4-ethylphenyl)difluoromethyl)phosphonate 2m. Prepared following the procedure B from (4-ethylphenyl)(mesityl)iodonium trifluoromethanesulfonate **4m**. Reverse phase chromatography (H_2O/CH_3CN). Yield: 53% (78 mg, 0.5 mmol scale). Brown oil; ^1H NMR (300 MHz, $CDCl_3$): δ 7.45 (d, J = 7.2 Hz, 2H), 7.20 (d, J = 8.0 Hz, 2H), 4.20-4.00 (m, 4H), 2.61 (q, J = 7.6 Hz, 2H), 1.26-1.21 (m, 6H), 1.17 (t, J = 7.6 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 147.3 (dt, J = 2.0 Hz), 129.9 (dt, J = 22.2 and 13.6 Hz), 128.0 (d, J = 1.3 Hz), 126.3 (td, J = 7.0 and 2.4 Hz), 118.2 (td, J = 262.8 and 219.6 Hz), 64.7 (d, J = 6.7 Hz), 28.8, 16.4 (d, J = 5.7 Hz), 15.4; $^{19}F\{^1H\}$ NMR ($CDCl_3$, $CFCl_3$, 282 MHz) δ −108.3 (d, J = 118.6 Hz, 2F); $^{31}P\{^1H\}$ NMR ($CDCl_3$, 121 MHz) δ 6.6 (t, J = 118.3 Hz, 1P); IR (neat, cm^{-1}) ν: 2971, 2935, 1616, 1415, 1261, 1164, 1118, 1037, 1013, 976; HRMS (ESI^+) calcd for $[M+H]^+$ $C_{13}H_{20}F_2O_3P$: 293.1118, found: 293.1118 (0.0 ppm).

Diethyl [(1,1'-biphenyl)-4-yldifluoromethyl]phosphonate 2n. Prepared following the procedure B from [1,1'-biphenyl]-4-yl(mesityl)iodonium trifluoromethanesulfonate **4n**. Reverse phase chromatography (H_2O/CH_3CN). Yield: 65% (111 mg, 0.5 mmol scale). Brown oil; ^1H NMR (300 MHz, $CDCl_3$): δ 7.72-7.66 (m, 4H), 7.61 (d, J = 7.7 Hz, 2H), 7.46 (t, J = 7.0 Hz, 2H), 7.41-7.36 (m, 1H), 4.32-4.12 (m, 4H), 1.34 (t, J = 6.9 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 143.7 (dt, J = 2.1Hz), 140.1, 131.5 (dt, J = 22.4 and 13.4 Hz), 131.4, 129.0, 128.1, 127.4-127.3 (m), 126.8 (td, J = 6.8 and 2.1 Hz), 118.2 (td, J = 263.9 and 216.6 Hz), 64.9 (d, J = 6.8

Hz), 16.4 (d, *J* = 5.7 Hz); $^{19}F\{^1H\}$ NMR ($CDCl_3$, $CFCl_3$, 282 MHz) δ −108.8 (d, *J* = 116.6 Hz, 2F); $^{31}P\{^1H\}$ NMR ($CDCl_3$, 121 MHz) δ 6.4 (t, *J* = 116.4 Hz, 1P); IR (neat, cm^{-1}) ν: 2984, 1611, 1394, 1267, 1166, 1114, 1013, 978; HRMS (ESI^+) calcd for $[M+NH_4]^+$ $C_{17}H_{23}NF_2O_3P$: 358.1384, found: 358.1383 (-0.3 ppm).

Diethyl [(3-(4-nitrophenoxy)phenyl)difluoromethyl]phosphonate 2o. Prepared following the procedure B from mesityl(3-(4-nitrophenoxy)phenyl)iodonium trifluoromethanesulfonate **4o**. Reverse phase chromatography (H_2O/CH_3CN). Yield: 71% (142 mg, 0.5 mmol scale). Brown oil; ^1H NMR (300 MHz, $CDCl_3$): δ 8.24-8.19 (m, 2H), 7.55-7.48 (m, 2H), 7.34 (s, 1H), 7.22-7.19 (m, 1H), 7.04-7.01 (m, 2H), 4.31-4.11 (m, 4H), 1.32 (t, *J* = 7.0 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 162.7, 154.9, 143.1, 135.3 (td, *J* = 22.7 and 14.0 Hz), 130.6 (d, *J* = 1.0 Hz), 126.1, 123.1 (dt, *J* = 6.7 and 2.3 Hz), 122.7 (d, *J* = 1.9 Hz), 118.5 (dt, *J* = 6.9 and 2.1 Hz), 117.7 (dt, *J* = 264.3 and 218.6 Hz), 117.5, 65.1 (d, *J* = 6.8 Hz), 16.4 (d, *J* = 5.3 Hz); $^{19}F\{^1H\}$ NMR ($CDCl_3$, $CFCl_3$, 282 MHz) δ −109.1 (d, *J* = 114.0 Hz, 2F); $^{31}P\{^1H\}$ NMR ($CDCl_3$, 121 MHz) δ 5.8 (t, *J* = 113.8 Hz, 1P); IR (neat, cm^{-1}) ν: 2986, 2917, 1583, 1517, 1487, 1442, 1343, 1263, 1237, 1163, 1111, 1013; HRMS (ESI^+) calcd for $[M+NH_4]^+$ $C_{17}H_{22}F_2N_2O_6P$: 419.1184, found: 419.1183 (-0.2 ppm).

Diethyl [(4-fluorophenyl)difluoromethyl]phosphonate 2p. Prepared following the procedure B from (4-fluorophenyl)(mesityl)iodonium trifluoromethanesulfonate **4p**. Reverse phase chromatography (H_2O/CH_3CN). Yield: 63% (44 mg, 0.25 mmol scale). Colourless oil; ^1H NMR (300 MHz, $CDCl_3$): δ 7.64-7.59 (m, 2H), 7.16-7.11 (m, 2H), 4.29-4.09 (m, 4H), 1.31 (t, *J* = 7.1 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 164.3 (m), 128.7 (m), 117.9 (td, *J* = 263.5 and 220.1 Hz), 115.8 (dd, *J* = 22.1 and 1.2 Hz), 65.0 (d, *J* = 6.8 Hz), 16.5 (d, *J* = 5.6 Hz); $^{19}F\{^1H\}$ NMR ($CDCl_3$, $CFCl_3$, 282 MHz) δ −108.2 (d, *J* = 116.6 Hz, 2F), −109.9 (s, 1F); $^{31}P\{^1H\}$ NMR ($CDCl_3$, 121 MHz) δ 6.1 (t, *J* = 116.0 Hz, 1P); IR (neat, cm^{-1}) ν: 2921, 2852, 1609, 1513, 1463, 1256, 1022; HRMS (ESI^+) calcd for $[M+NH_4]^+$ $C_{11}H_{18}F_3NO_3P$: 300.0976, found: 300.0970 (−2 ppm). Note that despite a long acquisition time, the aromatic quaternary carbon bearing the CF_2 group is missing.

Diethyl [(4-bromophenyl)difluoromethyl]phosphonate 2q. Prepared following the procedure B from (4-bromophenyl)(mesityl)iodonium trifluoromethanesulfonate **4q**. Reverse phase chromatography (H_2O/CH_3CN). Yield: 51% (87 mg, 0.5 mmol scale). Yellow oil; ^1H NMR (300 MHz, $CDCl_3$): δ 7.59 (d, *J* = 8.4 Hz, 2H), 7.48 (d, *J* = 8.1 Hz, 2H), 4.29-4.09 (m, 4H), 1.32 (t, *J* = 7.1 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 131.8 (d, *J* = 1.3 Hz), 131.8 (td, *J* = 22.6 and 13.9 Hz), 128.0 (td, *J* = 6.8 and 2.3 Hz), 125.6 (m), 117.8 (td, *J* = 263.5 and 218.5 Hz), 65.0 (d, *J* = 6.8 Hz), 16.4 (d, *J* = 5.5 Hz); $^{19}F\{^1H\}$ NMR ($CDCl_3$, $CFCl_3$, 282 MHz) δ −109.3 (d, *J* = 114.6 Hz, 2F); $^{31}P\{^1H\}$ NMR ($CDCl_3$, 121 MHz) δ 5.8 (t, *J* = 114.9 Hz, 1P); IR (neat, cm^{-1}) ν: 2921, 2853, 1464, 1378, 1280, 1242, 1060, 1021; HRMS (ESI^+) calcd for $[M+NH_4]^+$ $C_{11}H_{18}BrF_2NO_3P$: 360.0176, found: 360.0172 (−1.1 ppm).

Diethyl [(3,4-dichlorophenyl)difluoromethyl)]phosphonate 2r. Prepared following the procedure B from bis(3,4-dichlorophenyl)iodonium tetrafluoroborate **4r**. Reverse phase chromatography (H_2O/CH_3CN). Yield: 77% (128 mg, 0.5 mmol scale). Brown oil; ^1H NMR (300 MHz, $CDCl_3$): δ 7.68 (s, 1H), 7.53 (d, *J* = 8.5 Hz, 1H), 7.45 (dd, *J* = 8.4 and 0.6 Hz, 1H), 4.30-4.11 (m, 4H), 1.34-1.29 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 135.5 (dt, *J* = 2.3 Hz), 133.0 (d, *J* = 1.3 Hz), 132.7 (dt, *J* = 22.9 and 14.1 Hz), 130.7 (d, *J* = 1.3 Hz), 128.4 (td, *J* = 7.3 and 2.6 Hz), 125.7 (td, *J* = 7.3 and 2.6 Hz), 116.8 (td, *J* = 266.1 and 218.4 Hz), 65.0 (d, *J* = 6.9 Hz), 16.4 (d, *J* = 5.4 Hz); $^{19}F\{^1H\}$ NMR ($CDCl_3$, $CFCl_3$, 282 MHz) δ −109.4 (d, *J* = 114.0 Hz, 2F); $^{31}P\{^1H\}$ NMR ($CDCl_3$, 121 MHz) δ 5.5 (t, *J* = 113.9 Hz, 1P); IR (neat, cm^{-1}) ν: 2985, 2932, 1470, 1385, 1271, 1237, 1164, 1124, 1013, 980; HRMS (ESI^+) calcd for $[M+NH_4]^+$ $C_{11}H_{17}NCl_2F_2O_3P$: 350.0291, found: 350.0291 (0.0 ppm).

Diethyl [(4-acetylphenyl)difluoromethyl]phosphonate 2s. Prepared following the procedure B from (4-acetylphenyl)(mesityl)iodonium tetrafluoroborate **4s**. Reverse phase chromatography (H_2O/MeOH). Yield: 70% (107 mg, 0.5 mmol scale). Colourless oil; ^1H NMR (300 MHz, $CDCl_3$): δ 8.01 (d, *J* = 8.1 Hz, 2H), 7.70 (d, *J* = 7.9 Hz, 2H), 4.28-4.09 (m, 4H), 2.61 (s, 3H), 1.30 (t, *J* = 7.1 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 197.4, 138.9 (dd, *J* = 3.6 and 1.9 Hz), 137.1 (td, *J* = 21.9 and 13.6 Hz), 128.4 (d, *J* = 1.2 Hz), 126.7 (td, *J* = 6.7 and 2.2 Hz), 117.7 (td, *J* = 263.6 and 216.8 Hz), 65.0 (d, *J* = 6.8 Hz), 26.8, 16.4 (d, *J* = 5.5 Hz); $^{19}F\{^1H\}$ NMR ($CDCl_3$, $CFCl_3$, 282 MHz) δ −105.3 (d, *J* = 115.3 Hz, 2F); $^{31}P\{^1H\}$ NMR ($CDCl_3$, 121 MHz) δ 5.9 (t, *J* = 115.0 Hz, 1P); IR (neat, cm^{-1}) ν: 3670, 2988, 1689, 1613, 1407, 1264, 1011; HRMS (ESI^+) calcd for $[M+H]^+$ $C_{13}H_{18}F_2O_4P$: 307.0911, found: 307.0900 (−3.6 ppm).

Diethyl [(3-formylphenyl)difluoromethyl]phosphonate 2t. Prepared following the procedure B from (3-formylphenyl)(mesityl)iodonium tetrafluoroborate **4t**. Reverse phase chromatography (H_2O/MeOH). Yield: 57% (83 mg, 0.5 mmol scale). Colourless oil; ^1H NMR (300 MHz, $CDCl_3$): δ 10.04 (s, 1H), 8.10 (s, 1H), 7.99 (d, *J* = 7.6 Hz, 1H), 7.87 (d, *J* = 7.6 Hz, 1H), 7.62 (dd, *J* = 7.6 and 7.6 Hz, 1H), 4.29-4.10 (m, 4H), 1.30 (t, *J* = 7.1 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 191.4, 136.6 (d, *J* = 0.7 Hz), 134.1 (td, *J* = 22.6 and 14.0 Hz), 132.2 (td, *J* = 6.5 and 2.0 Hz), 131.6 (m), 129.5 (d, *J* = 0.9 Hz), 127.9 (td, *J* = 6.8 and 2.3 Hz), 117.6 (td, *J* = 263.6 and 218.0 Hz), 65.2 (d, *J* = 6.8 Hz), 16.4 (d, *J* = 5.5 Hz); $^{19}F\{^1H\}$ NMR ($CDCl_3$, $CFCl_3$, 282 MHz) δ −109.5 (d, *J* = 113.6 Hz, 2F); $^{31}P\{^1H\}$ NMR ($CDCl_3$, 121 MHz) δ 5.6 (t, *J* = 113.6 Hz, 1P); IR (neat, cm^{-1}) ν: 3676, 2988, 1720, 1611, 1394, 1250, 1212, 1014, 577; HRMS (ESI^+) calcd for $[M+H]^+$ $C_{12}H_{16}F_2O_4P$: 293.0754, found: 293.0740 (−4.8 ppm).

Diethyl [(pyridin-3-yl)difluoromethyl]phosphonate 6a. Prepared following the procedure C from (pyridin-3-yl)(mesityl)iodonium trifluoromethanesulfonate **5a**. Reverse phase chromatography (H_2O/MeOH). Yield: 44% (58 mg, 0.5 mmol scale). Caution: this compound is volatile. Yellow oil; ^1H NMR (300 MHz, $CDCl_3$): δ 8.83 (br. s, 1H), 8.73 (d, *J* = 4.7 Hz, 1H), 7.93 (d, *J* = 8.0 Hz, 1H), 7.40 (dd, *J* = 8.0 and 4.9 Hz, 1H), 4.32-4.13 (m, 4H), 1.33 (2 × t, *J* = 7.1 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 151.9 (dd, *J* = 4.0 and 2.0 Hz), 147.5 (td, *J* = 7.3 and 2.5 Hz), 134.3 (td, *J* = 6.5 and 2.0 Hz), 128.9 (td, *J* = 22.4 and 13.6 Hz), 123.2, 117.3 (td, *J* = 263.5 and 218.7 Hz), 65.1 (d, *J* = 6.9 Hz), 16.4 (d, *J* = 5.4 Hz); $^{19}F\{^1H\}$ NMR ($CDCl_3$, $CFCl_3$, 282 MHz) δ −110.4 (d, *J* = 112.8 Hz, 2F); $^{31}P\{^1H\}$ NMR ($CDCl_3$, 121 MHz) δ 5.4 (t, *J* = 112.8 Hz, 1P); IR (neat, cm^{-1}) ν: 2987, 2915, 1594, 1480, 1422, 1263, 1011; HRMS (EI^+) calcd for $[M]^+$ $C_{10}H_{14}F_2NO_3P$: 265.0679, found: 265.0684 (1.9 ppm).

Diethyl [(pyridin-3-yl)difluoromethyl]phosphonate 6b. Prepared following the procedure C from (6-chloropyridin-3-yl)(mesityl)iodonium trifluoromethanesulfonate **5b**. Reverse phase chromatography (H_2O/MeOH). Yield: 57% (85 mg, 0.5 mmol scale). Note that the product is contaminated with 10% of an unknown product. Yellow oil; ^1H NMR (300 MHz, $CDCl_3$): δ 8.61-8.59 (m, 1H), 7.92-7.87 (m, 1H), 7.45-7.42 (m, 1H), 4.34-4.16 (m, 4H), 1.31 (2 × t, *J* = 7.1 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 154.2 (dd, *J* = 4.3 and 2.2 Hz), 147.7 (td, *J* = 7.4 and 2.6 Hz), 137.1 (td, *J* = 6.1 and 1.8 Hz), 128.0 (td, *J* = 22.9 and 13.9 Hz), 124.2 (d, *J* = 1.1 Hz), 117.0 (td, *J* = 263.8 and 219.1 Hz), 65.3 (d, *J* = 6.9 Hz), 16.4 (d, *J* = 5.4 Hz); $^{19}F\{^1H\}$ NMR ($CDCl_3$, $CFCl_3$, 282 MHz) δ −110.4 (d, *J* = 111.8 Hz, 2F); $^{31}P\{^1H\}$ NMR ($CDCl_3$, 121 MHz) δ 5.0 (t, *J* = 111.7 Hz, 1P); IR (neat, cm^{-1}) ν: 2986, 2917, 1591, 1461, 1372, 1263, 1107, 1012, 575; HRMS (EI^+) calcd for $[M]^+$ $C_{10}H_{13}ClF_2NO_3P$: 299.0290, found: 299.0277 (−4.2 ppm).

Diethyl [(1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidin-5-yl)difluoromethyl]phosphonate 6c. Prepared following the procedure B from (1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidin-5-yl)(phenyl)iodonium trifluoromethane-sulfonate **5c**. Reverse phase chromatography (H_2O/MeOH). Yield: 34% (55 mg, 0.5 mmol scale). Yellow oil; ^{1}H NMR (300 MHz, CD_3OD): δ 7.94 (dd, J = 3.0 and 1.3 Hz, 1H), 4.33-4.21 (m, 4H), 3.41 (s, 3H), 3.21 (s, 3H), 1.32 (2 × t, J = 7.1 Hz, 6H); ^{13}C NMR (75 MHz, CD_3OD): δ 162.0 (m), 153.6, 147.5 (td, J = 10.7 and 3.8 Hz), 118.8 (td, J = 264.2 and 226.9 Hz), 107.0 (td, J = 22.9 and 14.9 Hz), 67.5 (d, J = 7.0 Hz), 38.6, 29.0, 17.6 (d, J = 5.6 Hz); ^{19}F{^{1}H} NMR (CD_3OD, 282 MHz) δ −107.7 (d, J = 116.7 Hz, 2F); ^{31}P{^{1}H} NMR (CD_3OD, 121 MHz) δ 5.7 (t, J = 116.7 Hz, 1P); IR (neat, cm^{-1}) ν: 2996, 1716, 1663, 1482, 1452, 1365, 1262, 1013; HRMS (ESI$^+$) calcd for [M+H]$^+$ $C_{11}H_{18}F_2N_2O_5P$: 327.0921, found: 327.0917 (−1.2 ppm).

Diethyl ((quinolin-6-yl)difluoromethyl)phosphonate 6d. Prepared following the procedure B from mesityl(quinolin-6-yl)iodonium trifluoromethanesulfonate **5d**. Reverse phase chromatography (H_2O/CH_3OH). Yield: 29% (45 mg, 0.5 mmol scale). Brown oil; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.99 (d, J = 3.2 Hz, 1H), 8.24 (d, J = 8.8 Hz, 1H), 8.18 (d, J = 9.0 Hz, 1H), 8.13 (s, 1H), 7.90 (d, J = 8.6 Hz, 1H), 7.47 (dd, J = 8.2 and 4.4 Hz, 1H), 4.30-4.10 (m, 4H), 1.31 (t, J = 7.0 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 152.2, 148.9 (d, J = 1.5 Hz), 137.1, 130.8 (dt, J = 22.1 and 13.6 Hz), 130.1 (d, J = 0.8 Hz), 127.5 (d, J = 1.2 Hz), 126.8 (td, J = 7.5 and 3.2 Hz), 126.5 (td, J = 5.9 and 1.6 Hz), 122.1, 117.8 (dt, J = 264.7 and 216.5 Hz), 65.0 (d, J = 6.8 Hz), 16.4 (d, J = 5.5 Hz); ^{19}F{^{1}H} NMR ($CDCl_3$, $CFCl_3$, 282 MHz) δ −108.7 (d, J = 114.5 Hz, 2F); ^{31}P{^{1}H} NMR ($CDCl_3$, 121 MHz) δ 6.1 (t, J = 115.0 Hz, 1P); IR (neat, cm^{-1}) ν: 2985, 2934, 1501, 1464, 1444, 1393, 1370, 1268, 1245, 1179, 1121, 1012, 979; HRMS (ESI$^+$) calcd for [M+H]$^+$ $C_{14}H_{17}F_2NO_3P$: 316.0914, found: 316.0912 (-0.6 ppm).

Diethyl [(phenyl)difluoromethyl]phosphonate 6e. Prepared following the procedure B from phenyl(thiophen-2-yl)iodonium trifluoromethanesulfonate **5e**. Reverse phase chromatography (H_2O/MeOH). Yield: 76% (103 mg, 0.5 mmol scale), 66% (606 mg, 3.4 mmol scale). Pale yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.47-7.45 (m, 2H), 7.07-7.04 (m, 1H), 4.30-4.11 (m, 4H), 1.30 (t, J = 7.1 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 133.1 (td, J = 26.3 and 17.2 Hz), 128.1 (td, J = 6.4 and 3.1 Hz), 127.9 (dd, J = 4.0 and 2.0 Hz), 126.3 (d, J = 1.0 Hz), 115.6 (td, J = 261.1 and 224.9 Hz), 64.1 (d, J = 6.7 Hz), 16.4 (d, J = 5.5 Hz); ^{19}F{^{1}H} NMR ($CDCl_3$, $CFCl_3$, 282 MHz) δ −97.4 (d, J = 114.6 Hz, 2F); ^{31}P{^{1}H} NMR ($CDCl_3$, 121 MHz) δ 5.1 (t, J = 114.6 Hz, 1P); IR (neat, cm^{-1}) ν: 2920, 2847, 1431, 1271, 1240, 1011; HRMS (EI$^+$) calcd for [M]$^+$ $C_9H_{13}F_2O_3PS$: 270.0291, found: 270.0286 (−2.0 ppm).

Diethyl [(*E*)-1,1-difluoro-3-phenylallyl]phosphonate 8a. Prepared following the procedure B from (*E*)-(2-phenylvinyl)(phenyl)iodonium tetrafluoroborate **7a** with 76% yield (110 mg, 0.5 mmol scale); the procedure D from (*E*)-(2-bromovinyl)benzene **15a** with 72% yield (104 mg, 0.5 mmol scale). Reverse phase chromatography (H_2O/MeCN). Colourless oil; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.47-7.43 (m, 2H), 7.40-7.34 (m, 3H), 7.12-7.04 (m, 1H), 6.37-6.23 (m, 1H), 4.37-4.20 (m, 4H), 1.37 (t, J = 7.1 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 137.2 (td, J = 10.7 and 6.1 Hz), 134.5 (dd, J = 3.0 and 1.5 Hz), 129.6, 128.9, 127.5 (m), 118.9 (td, J = 21.2 and 13.0 Hz), 117.6 (td, J = 259.7 and 221.1 Hz), 64.8 (d, J = 6.8 Hz), 16.5 (d, J = 5.4 Hz); ^{19}F{^{1}H} NMR ($CDCl_3$, $CFCl_3$, 282 MHz) δ −108.8 (d, J = 114.7 Hz, 2F); ^{31}P{^{1}H} NMR ($CDCl_3$, 121 MHz) δ 6.4 (t, J = 114.7 Hz, 1P); IR (neat, cm^{-1}) ν: 2985, 1652, 1580, 1497, 1451, 1266, 1180, 1012, 749, 691; HRMS (ESI$^+$) calcd for [M+NH$_4$]$^+$ $C_{13}H_{21}F_2NO_3P$: 308.1227, found: 308.1230 (1.0 ppm).

Diethyl [(*E*)-1,1-difluoro-3-(2-methylphenyl)allyl]phosphonate 8b. Prepared following the procedure B from (*E*)-(2-methylstyryl)(phenyl)iodonium tetrafluoroborate **7b**. Reverse phase chromatography (H_2O/CH_3CN). Yield: 92% (140 mg, 0.5 mmol scale). Colourless oil; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.48-7.46 (m, 1H), 7.37-7.29 (m, 1H), 7.24-7.16 (m, 3H), 6.27-6.12 (m, 1H), 4.37-4.20 (m, 4H), 2.38 (s, 3H), 1.38 (t, J = 7.1 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 136.7 (m), 135.1 (td, J = 10.7 and 6.1 Hz), 133.6 (m), 130.7, 129.4, 126.4, 126.2 (m), 120.2 (td, J = 21.1 and 12.9 Hz), 117.6 (td, J = 259.5 and 220.8 Hz), 64.8 (d, J = 6.7 Hz), 19.7, 16.5 (d, J = 5.5 Hz); ^{19}F{^{1}H} NMR ($CDCl_3$, $CFCl_3$, 282 MHz) δ −108.7 (d, J = 115.1 Hz, 2F); ^{31}P{^{1}H} NMR ($CDCl_3$, 121 MHz) δ 6.4 (t, J = 115.1 Hz, 1P); IR (neat, cm^{-1}) ν: 2985, 1650, 1486, 1393, 1266, 1013, 750, 571; HRMS (EI$^+$) calcd for [M]$^+$ $C_{14}H_{19}F_2O_3P$: 304.1040, found: 304.1053 (4.3 ppm).

Diethyl [(*E*)-1,1-difluoro-3-(2-fluorophenyl)allyl]phosphonate 8c. Prepared following the procedure B from (*E*)-(2-fluorostyryl)(phenyl)iodonium tetrafluoroborate **7c**. Reverse phase chromatography (H_2O/CH_3CN). Yield: 83% (128 mg, 0.5 mmol scale). Yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.49-7.44 (m, 1H), 7.34-7.27 (m, 1H), 7.23-7.03 (m, 3H), 6.49-6.34 (m, 1H), 4.36-4.20 (m, 4H), 1.37 (t, J = 7.1 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 161.0 (m), 131.0 (d, J = 8.7 Hz), 130.0 (m), 128.6 (m), 124.5 (d, J = 3.6 Hz), 122.4 (m), 121.6 (m), 117.4 (td, J = 259.9 and 220.3 Hz), 116.2 (d, J = 21.9 Hz), 64.9 (d, J = 6.8 Hz), 16.5 (d, J = 5.4 Hz); ^{19}F{^{1}H} NMR ($CDCl_3$, $CFCl_3$, 282 MHz) δ −109.2 (d, J = 114.4 Hz, 2F), −116 (s, 1F); ^{31}P{^{1}H} NMR ($CDCl_3$, 121 MHz) δ 6.2 (t, J = 114.4 Hz, 1P); IR (neat, cm^{-1}) ν: 2918, 1654, 1613, 1580, 1489, 1267, 1012, 755; HRMS (EI$^+$) calcd for [M]$^+$ $C_{13}H_{16}F_3O_3P$: 308.0789, found: 308.0775 (−4.6 ppm).

Diethyl [(*E*)-1,1-difluoro-3-cyclohexylallyl]phosphonate 8d. Prepared following the procedure B from (*E*)-(2-cyclohexylvinyl)(phenyl)iodonium tetrafluoroborate **7d**. Reverse phase chromatography (H_2O/CH_3CN). Yield: 87% (129 mg, 0.5 mmol scale), 72% (725 mg, 3.4 mmol scale). Colourless oil; ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.27-6.17 (m, 1H), 5.66-5.52 (m, 1H), 4.31-4.14 (m, 4H), 2.07 (app. br. s, 1H), 1.75-1.63 (m, 4H), 1.34 (t, J = 7.1 Hz, 6H), 1.25-1.04 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 145.3 (td, J = 9.7 and 5.8 Hz), 118.6 (td, J = 21.3 and 13.3 Hz), 117.3 (td, J = 258.8 and 220.2 Hz), 64.6 (d, J = 6.7 Hz), 40.2, 31.9 (m), 26.0, 25.8, 16.4 (d, J = 5.5 Hz); ^{19}F{^{1}H} NMR ($CDCl_3$, $CFCl_3$, 282 MHz) δ −108.7 (d, J = 116.2 Hz, 2F); ^{31}P{^{1}H} NMR ($CDCl_3$, 121 MHz) δ 6.4 (t, J = 116.2 Hz, 1P); IR (neat, cm^{-1}) ν: 2926, 1668, 1450, 1269, 1018, 972, 562; HRMS (ESI$^+$) calcd for [M+NH$_4$]$^+$ $C_{13}H_{27}F_2NO_3P$: 314.1697, found: 314.1687 (−3.2 ppm).

Diethyl [(*E*)-1,1-difluoro-4-phenylbut-2-en-1-yl)]phosphonate 8e. Prepared following the procedure B from (*E*)-phenyl(3-phenylprop-1-en-1-yl)-iodonium tetrafluoroborate **7e**. Reverse phase chromatography (H_2O/CH_3CN). Yield: 94% (72 mg, 0.25 mmol scale). Colourless oil; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.37-7.29 (m, 3H), 7.22 (d, J = 7.2 Hz, 2H), 6.51-6.46 (m, 1H), 5.82-5.68 (m, 1H), 4.36-4.18 (m, 4H), 3.53 (app. br. s, 2H), 1.37 (t, J = 7.1 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 138.7 (td, J = 10.2 and 5.9 Hz), 138.0 (dd, J = 2.7 and 1.3 Hz), 128.7, 128.7, 126.7, 122.2 (td, J = 21.5 and 13.2 Hz), 117.0 (td, J = 259.0 and 220.0 Hz), 64.6 (d, J = 6.7 Hz), 38.4, 16.4 (d, J = 5.5 Hz); ^{19}F{^{1}H} NMR ($CDCl_3$, $CFCl_3$, 282 MHz) δ −109.3 (d, J = 114.8 Hz, 2F); ^{31}P{^{1}H} NMR ($CDCl_3$, 121 MHz) δ 6.5 (t, J = 114.8 Hz, 1P); IR (neat, cm^{-1}) ν: 2986, 1669, 1604, 1497, 1455, 1268, 1016, 974, 700; HRMS (EI$^+$) calcd for [M]$^+$ $C_{14}H_{19}F_2O_3P$: 304.1040, found: 304.1050 (3.4 ppm).

Diethyl [(1*H*-inden-2-yl)difluoromethyl]phosphonate 8f. Prepared following the procedure B from (1*H*-inden-2-yl)(phenyl)iodonium tetrafluoroborate **7f**. Reverse phase chromatography (H_2O/MeOH). Yield: 67% (101 mg, 0.5 mmol scale). Yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.51-7.45 (m, 2H), 7.34-7.28 (m, 3H), 4.37-4.20 (m, 4H), 3.70 (br. s, 2H), 1.37 (t, J = 7.1 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 144.0, 142.8,

138.4 (m), 134.8 (td, *J* = 8.4, 5.8 Hz), 127.0, 126.7, 124.3, 122.8, 117.8 (td, *J* = 258.2, 220.7 Hz), 65.0 (d, *J* = 6.7 Hz), 38.3, 16.7 (d, *J* = 5.4 Hz); $^{19}F\{^1H\}$ NMR ($CDCl_3$, $CFCl_3$, 282 MHz) δ –105.3 (d, *J* = 115.2 Hz, 2F); $^{31}P\{^1H\}$ NMR ($CDCl_3$, 121 MHz) δ 5.9 (t, *J* = 115.3 Hz, 1P); IR (neat, cm^{-1}) ν: 2926, 1718, 1462, 1394, 1268, 1164, 1014; HRMS (ESI^+) calcd for $[M+H]^+$ $C_{14}H_{18}F_2O_3P$: 303.0962, found: 303.0948 (–4.6 ppm).

(*E*)-(diethoxy-λ^4-sulfanylidene)(1,1-difluoro-3-phenylallyl)phosphane 9. Prepared following the procedure B from *(E)*-phenyl(styryl)iodonium tetrafluoroborate **7a** and *O*,*O*-diethyl (difluoro(trimethylsilyl)methyl)phosphonothioate. Reverse phase chromatography (H_2O/CH_3CN). Yield: 63% (48 mg, 0.25 mmol scale). Yellow oil; ^1H NMR (300 MHz, $CDCl_3$): δ 7.48-7.45 (m, 2H), 7.41-7.36 (m, 3H), 7.08 (dq, *J* = 16.3 and 2.9 Hz, 1H), 6.40-6.26 (m, 1H), 4.32-4.21 (m, 4H), 1.35 (t, *J* = 7.1 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 137.1 (td, *J* = 10.4 and 6.5 Hz), 134.7 (d, *J* = 1.4 Hz), 129.6, 128.9, 127.6 (d, *J* = 1.0 Hz), 118.6 (td, *J* = 21.6 and 14.2 Hz), 118.4 (td, *J* = 264.6 and 183.9 Hz), 64.8 (d, *J* = 6.7 Hz), 16.3 (d, *J* = 6.2 Hz); $^{19}F\{^1H\}$ NMR ($CDCl_3$, $CFCl_3$, 282 MHz) δ –109.5 (d, *J* = 120.6 Hz, 2F); $^{31}P\{^1H\}$ NMR ($CDCl_3$, 121 MHz) δ 75.3 (t, *J* = 120.8 Hz, 1P); IR (neat, cm^{-1}) ν: 2983, 2927, 1651, 1474, 1452, 1390, 1298, 1274, 1181, 1013, 961, 855; HRMS (ESI^+) calcd for $[M+H]^+$ $C_{13}H_{18}F_2SO_2P$: 307.07332, found: 307.07202 (-4.22 ppm).

Diethyl [1,1-difluoro-3-phenyl-2-propyn-1-yl]phosphonate 10. Prepared following the procedure B from 1-(phenylethynyl)-1,2-benziodoxol-3(1*H*)-one. Reverse phase chromatography (H_2O/CH_3CN). Yield: 64% (92 mg, 0.5 mmol scale). Yellow oil; ^1H NMR (300 MHz, $CDCl_3$): δ 7.54-7.51 (m, 2H), 7.43-7.33 (m, 3H), 4.40-4.30 (m, 4H), 1.40 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 132.4 (td, *J* = 2.7 and 1.8 Hz), 130.6, 128.7, 119.6 (td, *J* = 3.3 and 1.9 Hz), 109.6 (td, *J* = 253.2 and 229.6 Hz), 91.7 (dd, *J* = 14.2 and 7.4 Hz), 78.5 (td, *J* = 33.6 and 17.2 Hz), 65.6 (d, *J* = 6.6 Hz), 16.5 (d, *J* = 5.5 Hz); $^{19}F\{^1H\}$ NMR ($CDCl_3$, $CFCl_3$, 282 MHz) δ –96.8 (d, *J* = 107.8 Hz, 2F); $^{31}P\{^1H\}$ NMR ($CDCl_3$, 121 MHz) δ 3.42 (t, *J* = 108.1 Hz); IR (neat, cm^{-1}) ν: 2987, 2236, 1490, 1446, 1273, 1114, 1030, 757; HRMS (EI^+) calcd for $[M]^+$ $C_{13}H_{15}F_2O_3P$: 288.0727, found: 288.0731 (1.4 ppm).

Diethyl[((*S*)4-{2-acetamido-3-methoxy-3-oxopropyl}phenyl)difluoromethyl]phosphonate 12. Prepared following the procedure B from (*S*)-(4-(2-acetamido-3-methoxy-3-oxopropyl)phenyl)(mesityl)iodonium tetrafluoroborate **11**. Reverse phase chromatography (H_2O/CH_3CN). Yield: 48% (39 mg, 0.2 mmol scale). Colourless oil; ^1H NMR (300 MHz, $CDCl_3$): δ 7.53 (d, *J* = 7.4 Hz, 2H), 7.18 (d, *J* = 8.0 Hz, 2H), 6.07 (d, *J* = 7.7 Hz, 1H), 4.92-4.85 (m, 1H), 4.27-4.04 (m, 4H), 3.71 (s, 3H), 3.23-3.07 (m, 2H), 1.98 (s, 3H), 1.32-1.27 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 171.9, 169.8, 139.2 (dd, *J* = 3.9 and 1.9 Hz), 131.6 (td, *J* = 22.3 and 13.9 Hz), 129.5 (d, *J* = 1.2 Hz), 126.6 (td, *J* = 6.7 and 2.3 Hz), 118.1 (td, *J* = 262.9 and 218.3 Hz), 64.9 (d, *J* = 6.6 Hz), 53.1, 52.5, 37.8, 23.2, 16.4 (d, *J* = 5.5 Hz); $^{19}F\{^1H\}$ NMR ($CDCl_3$, $CFCl_3$, 282 MHz) δ –108.8 (d, *J* = 116.2 Hz, 2F); $^{31}P\{^1H\}$ NMR ($CDCl_3$, 121 MHz) δ 6.2 (t, *J* = 116.1 Hz, 1P); IR (neat, cm^{-1}) ν: 3290, 3026, 2924, 2852, 1744, 1660, 1542, 1493, 1452, 1373, 1260, 1123, 1017, 696; HRMS (ESI^+) calcd for $[M+H]^+$ $C_{17}H_{25}F_2NO_6P$: 408.1388, found: 408.1384 (–1.0 ppm).

Diethyl [((estronyl)difluoromethyl]phosphonate 14. Prepared following the procedure B from mesityl(estronyl)iodonium tetrafluoroborate **13**. Reverse phase chromatography (H_2O/CH_3CN). Yield: 37% (82 mg, 0.5 mmol scale). Yellow oil; ^1H NMR (300 MHz, $CDCl_3$): δ 7.36 (s, 2H), 7.34 (s, 1H), 4.30-4.10 (m, 4H), 2.97-2.93 (m, 2H), 2.55-2.28 (m, 3H), 2.18-1.95 (m, 4H), 1.67-1.42 (m, 6H), 1.33 (m, 6H), 0.91 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 220.7, 142.8 (d, *J* = 2.0 Hz), 136.9 (d, *J* = 1.4 Hz), 130.0 (dt, *J* = 22.2 and 13.6 Hz), 126.8 (dt, *J* = 6.7 and 2.5 Hz), 125.6 (d, *J* = 1.1 Hz), 123.5 (dt, *J* = 6.9 and 2.3 Hz), 118.5 (dt, *J* = 265.4 and 218.4 Hz), 64.8 (d, *J* = 6.7 Hz), 50.6, 48.0, 44.5, 37.9, 35.9, 31.6, 29.5, 26.4, 25.7, 21.7, 16.4 (d, *J* = 5.6 Hz), 13.9; $^{19}F\{^1H\}$ NMR ($CDCl_3$, $CFCl_3$, 282 MHz) δ –108.4 (d, *J* = 117.9 Hz, 2F); $^{31}P\{^1H\}$ NMR ($CDCl_3$, 121 MHz) δ 6.5 (t, *J* = 117.8 Hz, 1P); IR (neat, cm^{-1}) ν: 2933, 1737, 1259, 1123, 1015, 910, 727; HRMS (ESI^+) calcd for $[M+NH_4]^+$ $C_{23}H_{35}NF_2O_4P$: 458.2272, found: 458.2279 (1.5 ppm).

Diethyl [(*Z*)-1,1-difluoro-3-phenylallyl]phosphonate 8g. Prepared following the procedure D from (*Z*)-(2-iodovinyl)benzene **15g**. Reverse phase chromatography (H_2O/CH_3CN). Yield: 79% (115 mg, 0.5 mmol scale). Colourless oil; ^1H NMR (300 MHz, $CDCl_3$): δ 7.46 (d, *J* = 8.0 Hz, 2H), 7.35-7.28 (m, 3H), 6.93 (dt, *J* = 12.9 and 3.1 Hz, 1H), 5.84-5.67 (m, 1H), 4.29-4.16 (m, 4H), 1.32 (t, *J* = 7.1 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 139.1 (q, *J* = 6.6 Hz), 134.8 (d *J* = 1.4 Hz), 129.3 (dt, *J* = 3.9 and 1.2 Hz), 128.5, 127.9, 120.1 (td, *J* = 20.9 and 13.6 Hz), 117.6 (td, *J* = 260.7 and 220.5 Hz), 64.8 (d, *J* = 6.5 Hz), 16.4 (d, *J* = 5.3 Hz); $^{19}F\{^1H\}$ NMR ($CDCl_3$, $CFCl_3$, 282 MHz) δ –104.4 (d, *J* = 111.6 Hz, 2F); $^{31}P\{^1H\}$ NMR ($CDCl_3$, 121 MHz) δ 6.7 (t, *J* = 111.4 Hz, 1P); IR (neat, cm^{-1}) ν: 2985, 2916, 1645, 1495, 1446, 1393, 1269, 1196, 1139, 1093, 1011, 977; HRMS (ESI^+) calcd for $[M+NH_4]^+$ $C_{13}H_{21}NF_2O_3P$: 308.1227, found: 308.1215 (-3.9 ppm).

Diethyl (*E*)-(1,1-difluoro-3-(4-methoxyphenyl)allyl)phosphonate 8h. Prepared following the procedure D from (*E*)-1-(2-bromovinyl)-4-methoxybenzene **15h**. Reverse phase chromatography (H_2O/CH_3CN). Yield: 82% (131 mg, 0.5 mmol scale). Brown oil; ^1H NMR (300 MHz, $CDCl_3$): δ 7.40 (d, *J* = 8.4 Hz, 2H), 7.01 (d, *J* = 14.5 Hz, 1H), 6.88 (d, *J* = 8.4 Hz, 2H), 6.16 (app. qt, 1H), 4.32-4.23 (m, 4H), 3.82 (s, 3H), 1.37 (t, *J* = 7.1 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 160.8, 136.6 (td, *J* = 10.8 and 6.2 Hz), 129.0 (d, *J* = 0.9 Hz), 127.1 (d, *J* = 1.6 Hz), 118.0 (td, *J* = 257.3 and 222.2 Hz), 116.3 (td, *J* = 21.3 and 13.2 Hz), 114.3, 64.8 (d, *J* = 6.7 Hz), 55.5, 16.6 (d, *J* = 5.6 Hz); $^{19}F\{^1H\}$ NMR ($CDCl_3$, $CFCl_3$, 282 MHz) δ –108.3 (d, *J* = 116.4 Hz, 2F); $^{31}P\{^1H\}$ NMR ($CDCl_3$, 121 MHz) δ 6.5 (t, *J* = 116.6 Hz, 1P); IR (neat, cm^{-1}) ν: 2963, 1652, 1606, 1514, 1252, 1172, 1098, 1013, 972, 791; HRMS (ESI^+) calcd for $[M+NH_4]^+$ $C_{14}H_{23}NF_2O_4P$: 338.1333, found: 338.1341 (2.4 ppm).

Diethyl (*E*)-(1,1-difluoro-3-(4-nitrophenyl)allyl)phosphonate 8i. Prepared following the procedure D from (*E*)-1-(2-bromovinyl)-4-nitrobenzene **15i**. Reverse phase chromatography (H_2O/CH_3CN). Yield: 63% (106 mg, 0.5 mmol scale). Brown oil; ^1H NMR (300 MHz, $CDCl_3$): δ 8.19 (d, *J* = 8.6 Hz, 2H), 7.63 (d, *J* = 8.3 Hz, 2H), 6.98 (d, *J* = 12.8 Hz, 1H), 6.01-5.85 (m, 1H), 4.36-4.18 (m, 4H), 1.37 (t, *J* = 7.1 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 147.5, 141.5, 136.5 (q, *J* = 6.9 Hz), 129.9 (dt, *J* = 3.8 and 1.3 Hz), 123.4 (dt, *J* = 21.3 and 13.4 Hz), 123.2, 117.2 (td, *J* = 260.1 and 216.9 Hz), 65.0 (d, *J* = 6.9 Hz), 16.4 (d, *J* = 5.4 Hz); $^{19}F\{^1H\}$ NMR ($CDCl_3$, $CFCl_3$, 282 MHz) δ –105.4 (d, *J* = 109.2 Hz, 2F); $^{31}P\{^1H\}$ NMR ($CDCl_3$, 121 MHz) δ 6.0 (t, *J* = 109.2 Hz, 1P); IR (neat, cm^{-1}) ν: 2987, 2916, 1598, 1519, 1344, 1268, 1140, 1091, 1011, 857; HRMS (ESI^+) calcd for $[M+NH_4]^+$ $C_{13}H_{20}F_2N_2O_5P$: 353.1078, found: 353.1081 (0.8 ppm).

Diethyl (*E*)-(1,1-difluoronon-2-en-1-yl)phosphonate 8j. Prepared following the procedure D from (*E*)-1-iodooct-1-ene **15j**. Reverse phase chromatography (H_2O/CH_3CN). Yield: 62% (93 mg, 0.5 mmol scale). Colourless oil; ^1H NMR (300 MHz, $CDCl_3$): δ 6.34-6.21 (m, 1H), 5.72-5.57 (m, 1H), 4.30-4.18 (m, 4H), 2.13 (s, 2H), 1.44-1.26 (m, 14 H), 0.87 (app. t, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 140.4 (td, *J* = 10.2 and 6.0 Hz), 120.7 (td, *J* = 21.2 and 13.1 Hz), 116.9 (td, *J* = 259.3 and 220.6 Hz), 64.6 (d, *J* = 6.9 Hz), 32.2, 31.7, 28.8, 28.3 (d, *J* = 1.5 Hz), 22.6, 16.5 (d, *J* = 5.6 Hz), 14.1;$^{19}F\{^1H\}$ NMR ($CDCl_3$, $CFCl_3$, 282 MHz) δ –108.6 (d, *J* = 115.7 Hz, 2F); $^{31}P\{^1H\}$ NMR ($CDCl_3$, 121 MHz) δ 6.8 (t, *J* = 116.0 Hz, 1P); IR (neat, cm^{-1}) ν: 2930, 2859, 1270, 1189, 1165, 1100, 1019, 969; HRMS (ESI^+) calcd for $[M+H]^+$ $C_{13}H_{26}F_2O_3P$: 299.1588, found: 299.1589 (0.3 ppm).

Diethyl (*E*)-(1,1-difluorohept-2-en-1-yl)phosphonate 8k. Prepared following the procedure D from (*E*)-1-iodohex-1-ene **15k**. Reverse phase chromatography (H_2O/CH_3CN). Yield: 53% (72 mg, 0.5 mmol scale). Colourless oil; ^1H NMR (300 MHz, $CDCl_3$): δ 6.35-6.22 (m, 1H), 5.73-5.57 (m, 1H), 4.31-4.18 (m, 4H), 2.15 (s, 2H), 1.42-1.29 (m, 10H), 0.89 (t, J = 7.3 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 140.4 (td, J = 10.2 and 5.9 Hz), 120.8 (td, J = 21.2 and 13.2 Hz), 117.2 (td, J = 258.4 and 220.2 Hz), 64.5 (d, J = 6.6 Hz), 31.9, 30.4 (d, J = 1.5 Hz), 22.2, 16.5 (d, J = 5.5 Hz), 13.9; $^{19}F\{^1H\}$ NMR ($CDCl_3$, $CFCl_3$, 282 MHz) δ −108.6 (d, J = 115.4 Hz, 2F); $^{31}P\{^1H\}$ NMR ($CDCl_3$, 121 MHz) δ 6.8 (t, J = 115.4 Hz, 1P); IR (neat, cm^{-1}) ν: 2960, 2933, 2875, 1671, 1269, 1187, 1165, 1099, 1016, 974; HRMS (ESI^+) calcd for $[M+H]^+$ $C_{11}H_{22}F_2O_3P$: 271.1275, found: 271.1268 (-2.6 ppm).

Ethyl (*Z*)-4-(diethoxyphosphoryl)-4,4-difluorobut-2-enoate 8l. Prepared following the procedure D from ethyl (*Z*)-3-bromoacrylate **15l**. Reverse phase chromatography (H_2O/CH_3CN). Yield: 66% (95 mg, 0.5 mmol scale). Brown oil; ^1H NMR (300 MHz, $CDCl_3$): δ 6.24 (app. dd, 1H), 5.96 (app. ddt, 1H), 4.33-4.18 (m, 6H), 1.36 (t, J = 7.2 Hz, 6H), 1.28 (t, J = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 164.8 (d, J = 1.3 Hz), 128.6 (dd, J = 13.8 and 7.1 Hz), 127.5 (dt, J = 22.1 and 14.0 Hz), 116.4 (td, J = 262.5 and 217.0 Hz), 65.1 (d, J = 6.7 Hz), 61.4, 16.4 (d, J = 5.6 Hz), 14.1; $^{19}F\{^1H\}$ NMR ($CDCl_3$, $CFCl_3$, 282 MHz) δ −108.5 (d, J = 107.1 Hz, 2F); $^{31}P\{^1H\}$ NMR ($CDCl_3$, 121 MHz) δ 5.1 (t, J = 107.9 Hz, 1P); IR (neat, cm^{-1}) ν: 2987, 2919, 1736, 1658, 1446, 1396, 1270, 1212, 1149, 1095, 1010, 868, 795; HRMS (ESI^+) calcd for $[M+H]^+C_{10}H_{18}F_2O_5P$: 287.0860, found: 287.0854 (-2.1 ppm).

Diethyl (*E*)-(3-cyano-1,1-difluorobut-2-en-1-yl)phosphonate 8m. Prepared following the procedure D from 3-bromo-2-methylacrylonitrile (*E*/*Z*=1/0.7) **15m**. Reverse phase chromatography (H_2O/CH_3CN). Yield: 38% (48 mg, 0.5 mmol scale). Colourless oil; ^1H NMR (300 MHz, $CDCl_3$): δ 6.34-6.22 (m, 1H), 4.35-4.25 (m, 4H), 2.18-2.14 (m, 3H), 1.42-1.37 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 135.1 (dt, J = 23.6 and 12.7 Hz), 120.9 (dt, J = 7.6 Hz), 118.7-118.6 (m), 116.4 (td, J = 261.6 and 217.7 Hz), 65.3 (d, J = 7.1 Hz), 17.2-17.1 (m), 16.5 (d, J = 5.5 Hz);$^{19}F\{^1H\}$ NMR ($CDCl_3$, $CFCl_3$, 282 MHz) δ −107.9 (d, J = 107.5 Hz, 2F); $^{31}P\{^1H\}$ NMR ($CDCl_3$, 121 MHz) δ 5.2 (t, J = 107.2 Hz, 1P); IR (neat, cm^{-1}) ν: 2923, 1272, 1171, 1107, 1011, 950; HRMS (ESI^+) calcd for $[M+NH_4]^+$ $C_9H_{18}F_2N_2O_3P$: 271.1023, found: 271.1026 (1.1 ppm).

Diethyl (*Z*)-(3-cyano-1,1-difluorobut-2-en-1-yl)phosphonate 8m. Prepared following the general procedure D from 3-bromo-2-methylacrylonitrile (*E*/*Z*=1/0.7) **15m**. Reverse phase chromatography (H_2O/CH_3CN). Yield: 19% (24 mg, 0.5 mmol scale). Colourless oil; ^1H NMR (300 MHz, $CDCl_3$): δ 6.27-6.17 (m, 1H), 4.41-4.20 (m, 4H), 2.16-2.12 (m, 3H), 1.42-1.38 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 134.7 (dt, J = 22.5 and 12.6 Hz), 117.5-117.3 (m), 115.7-115.6 (m), 115.3 (td, J = 262.4 and 218.5 Hz), 65.7 (d, J = 7.0 Hz), 22.5, 16.5 (d, J = 5.6 Hz); $^{19}F\{^1H\}$ NMR ($CDCl_3$, $CFCl_3$, 282 MHz) δ −109.8 (d, J = 107.9 Hz, 2F); $^{31}P\{^1H\}$ NMR ($CDCl_3$, 121 MHz) δ 4.3 (t, J = 107.7 Hz, 1P); IR (neat, cm^{-1}) ν: 2918, 2848, 1264, 1189, 1165, 1016; HRMS (ESI^+) calcd for $[M+H]^+$ $C_9H_{15}F_2NO_3P$: 254.0758, found: 254.0770 (4.7 ppm).

Ethyl 2-[(diethoxyphosphoryl)difluoromethyl]benzoate 17a. Prepared following the procedure E from ethyl 2-iodobenzoate **16a**. Reverse phase chromatography (H_2O/CH_3CN). Yield: 84% (141 mg, 0.5 mmol scale). Brown oil; ^1H NMR (300 MHz, $CDCl_3$): δ 7.75-7.73 (m, 1H), 7.51-7.49 (m, 3H), 4.39-4.32 (m, 2H), 4.25-4.11 (m, 4H), 1.35 (t, J = 7.1Hz, 3H), 1.37-1.27 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 168.5, 132.6 (q, J = 3.7 Hz), 130.7 (d, J = 1.6 Hz), 130.0 (d, J = 1.4 Hz), 129.9 (dt, J = 21.7 and 15.2 Hz), 128.7 (dd, J = 7.5 and 1.4 Hz), 128.6, 118.2 (td, J = 265.5 and 215.8 Hz), 64.9 (d, J = 6.7 Hz), 61.9, 16.4 (d, J = 5.5 Hz), 14.1; $^{19}F\{^1H\}$ NMR ($CDCl_3$, $CFCl_3$, 282 MHz) δ −102.0 (d, J = 112.1 Hz, 2F); $^{31}P\{^1H\}$ NMR ($CDCl_3$, 121 MHz) δ 5.8 (t, J = 112.6 Hz, 1P); IR (neat, cm^{-1}) ν: 2984, 2920, 2852, 1732, 1445, 1392, 1368, 1263, 1141, 1095, 1012, 940, 761; HRMS (ESI^+) calcd for $[M+H]^+$ $C_{14}H_{20}F_2O_5P$: 337.1016, found: 337.1022 (1.8 ppm).

Diethyl [(2-acetylphenyl)difluoromethyl]phosphonate 17b. Prepared following the procedure E from ethyl 1-(2-iodophenyl)ethan-1-one **16b**. Reverse phase chromatography (H_2O/CH_3CN). Yield: 53% (81 mg, 0.5 mmol scale). Brown oil; ^1H NMR (300 MHz, $CDCl_3$): δ 7.73 (d, J = 6.7 Hz, 1H), 7.55-7.47 (m, 2H), 7.26 (t, J = 5.9 Hz, 1H), 4.32-4.14 (m, 4H), 2.58 (s, 3H), 1.34 (t, J = 7.1 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 204.0, 141.6 (q, J = 3.4 Hz), 131.0 (d, J = 1.6 Hz), 129.2 (d, J = 1.6 Hz), 128.6 (dt, J = 7.3 and 1.2 Hz), 128.3 (dt, J = 21.7 and 15.2 Hz), 126.0, 118.6 (td J = 265.1 and 216.8 Hz), 65.1 (d, J = 6.9 Hz), 31.7 (t, J = 3.4 Hz), 16.4 (d J = 5.5 Hz); $^{19}F\{^1H\}$ NMR ($CDCl_3$, $CFCl_3$, 282 MHz) δ −101.2 (d, J = 112.7 Hz, 2F); $^{31}P\{^1H\}$ NMR ($CDCl_3$, 121 MHz) δ 5.5 (t, J = 112.9 Hz, 1P); IR (neat, cm^{-1}) ν: 2986, 2917, 1706, 1268, 1248, 1120, 1032, 1011, 939, 766; HRMS (ESI^+) calcd for $[M+H]^+$ $C_{13}H_{18}F_2O_4P$: 307.0911, found: 307.0909 (-0.7 ppm).

Diethyl [(2-nitrophenyl)difluoromethyl]phosphonate 17c. Prepared following the procedure E from ethyl 1-iodo-2-nitrobenzene **16c**. Reverse phase chromatography (H_2O/CH_3CN). Yield: 54% (83 mg, 0.5 mmol scale). Brown oil; ^1H NMR (300 MHz, $CDCl_3$): δ 7.82-7.81 (m, 1H), 7.63-7.61 (m, 3H), 4.35-4.17 (m, 4H), 1.34 (t, J = 7.0 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 148.8, 132.1 (d, J = 1.4 Hz), 131.4 (d, J = 1.1 Hz), 129.9 (td, J = 7.7 and 1.4 Hz), 125.4 (dt, J = 22.8 and 15.9 Hz), 124.0, 117.2 (td J = 266.7 and 216.9 Hz), 65.5 (d, J = 7.1 Hz), 16.4 (d, J = 5.4 Hz); $^{19}F\{^1H\}$ NMR ($CDCl_3$, $CFCl_3$, 282 MHz) δ −103.4 (d, J = 108.8 Hz, 2F); $^{31}P\{^1H\}$ NMR ($CDCl_3$, 121 MHz) δ 4.4 (t, J = 108.6 Hz, 1P); IR (neat, cm^{-1}) ν: 2988, 1541, 1370, 1270, 1036, 1012, 939; HRMS (ESI^+) calcd for $[M+H]^+$ $C_{11}H_{15}F_2NO_5P$: 310.0656, found: 310.0665 (2.9 ppm).

Methyl 2-[(diethoxyphosphoryl)difluoromethyl]-3-methylbenzoate 17d. Prepared following the procedure E from methyl 2-iodo-3-methylbenzoate **16d**. Reverse phase chromatography (H_2O/CH_3CN). Yield: 61% (103 mg, 0.5 mmol scale). Yellow oil; ^1H NMR (300 MHz, $CDCl_3$): δ 7.37-7.29 (m, 2H), 7.21 (d, J = 6.7 Hz, 1H), 4.27-4.06 (m, 4H), 3.86 (s, 3H), 2.62 (t, J = 2.8 Hz, 3H), 1.31-1.26 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.0, 139.3 (td, J = 3.9 and 1.4 Hz), 134.0 (d, J = 1.4 Hz), 133.7 (dt, J = 5.6 and 3.0 Hz), 130.3 (d, J = 1.2 Hz), 128.5 (dt, J = 20.5 and 15.2 Hz), 125.9, 119.6 (td, J = 267.6 and 213.7 Hz), 64.8 (d, J = 6.7 Hz), 52.7, 21.6 (t, J = 4.3 Hz), 16.4 (d, J = 5.5 Hz); $^{19}F\{^1H\}$ NMR ($CDCl_3$, $CFCl_3$, 282 MHz) δ −98.1 (d, J = 112.5 Hz, 2F); $^{31}P\{^1H\}$ NMR ($CDCl_3$, 121 MHz) δ 6.6 (t, J = 112.3 Hz, 1P); IR (neat, cm^{-1}) ν: 2953, 1735, 1587, 1435, 1392, 1370, 1290, 1269, 1147, 1061, 1011, 976; HRMS (ESI^+) calcd for $[M+NH_4]^+$ $C_{14}H_{23}NF_2O_5P$: 354.1282, found: 354.1286 (1.1 ppm).

Methyl 2-[(diethoxyphosphoryl)difluoromethyl]-4-methoxybenzoate 17e. Prepared following the procedure E from methyl 2-iodo-4-methoxybenzoate **16e**. Reverse phase chromatography (H_2O/CH_3CN). Yield: 69% (122 mg, 0.5 mmol scale). Brown oil; ^1H NMR (300 MHz, $CDCl_3$): δ 7.54 (d, J = 8.7 Hz, 1H), 7.23 (s, 1H), 6.98 (ddd, J = 8.5 and 1.6 and 0.9 Hz, 1H), 4.27-4.12 (m, 4H), 3.85 (s, 3H), 3.83 (s, 3H), 1.32-1.27 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 168.3, 160.9, 132.8 (dt, J = 21.7 and 15.5 Hz), 131.3, 124.1 (dt, J = 3.4 Hz), 117.9 (td, J = 265.1 and 215.0 Hz), 115.9 (d, J = 1.5 Hz), 113.9 (td, J = 8.6 and 1.6 Hz), 64.9 (d, J = 6.8 Hz), 55.7, 52.6, 16.4 (d, J = 5.7 Hz); $^{19}F\{^1H\}$ NMR ($CDCl_3$, $CFCl_3$, 282 MHz) δ −101.1 (d, J = 111.7 Hz, 2F); $^{31}P\{^1H\}$ NMR ($CDCl_3$, 121 MHz) δ 6.1 (t, J = 111.1 Hz, 1P); IR (neat, cm^{-1}) ν: 2986, 1733, 1609, 1576, 1505, 1435, 1268, 1130, 1209, 1130, 1097, 1013, 985; HRMS (EI^+) calcd for $[M]^+$ $C_{14}H_{19}F_2O_6P$: 352.08873, found: 352.08840 (-0.95 ppm).

Methyl 2-[(diethoxyphosphoryl)difluoromethyl]-3,5-dimethoxybenzoate 17f. Prepared following the procedure E from methyl 2-iodo-3,5-dimethoxybenzoate **16f**. Reverse phase chromatography (H_2O/CH_3CN). Yield: 93% (178 mg, 0.5 mmol scale). Brown oil; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.17 (s, 1H), 6.98 (s, 1H), 4.26-4.02 (m, 4H), 3.87 (s, 3H), 3.86 (s, 3H), 3.82 (s, 3H), 1.29-1.24 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 168.5, 150.1 (d, J = 1.2 Hz), 150.0 (d, J = 1.2 Hz), 124.9 (q, J = 3.9 Hz), 123.7-122.7 (m), 117.9 (td, J = 264.6 and 219.1 Hz), 111.6, 110.9 (td, J = 7.8 and 1.1 Hz), 64.9 (d, J = 7.2 Hz), 56.2, 56.1, 52.7, 16.4 (d, J = 5.5 Hz); ^{19}F{^{1}H} NMR ($CDCl_3$, $CFCl_3$, 282 MHz) δ −100.7 (d, J = 114.2 Hz, 2F); ^{31}P{^{1}H} NMR ($CDCl_3$, 121 MHz) δ 6.2 (t, J = 114.2 Hz, 1P); IR (neat, cm^{-1}) ν: 2941, 2852, 1733, 1605, 1525, 1464, 1435, 1356, 1271, 1205, 1165, 1129, 1090, 1007, 974; HRMS (ESI$^+$) calcd for $[M+H]^+$ $C_{15}H_{22}F_2O_7P$: 383.1071, found: 383.1081 (2.6 ppm).

Methyl 2-[(diethoxyphosphoryl)difluoromethyl]-4-nitrobenzoate 17g. Prepared following the procedure E from methyl 2-iodo-4-nitrobenzoate **16g**. Reverse phase chromatography (H_2O/CH_3CN). Yield: 62% (114 mg, 0.5 mmol scale). Yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.56 (s, 1H), 8.35 (dd, J = 8.5 and 1.2 Hz, 1H), 7.70 (d, J = 8.5 Hz, 1H), 4.33-4.20 (m, 4H), 3.94 (s, 3H), 1.35 (t, J = 7.2, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 166.9, 148.5, 137.6 (q, J = 3.3 Hz), 132.7 (td, J = 23.1 and 15.5 Hz), 130.2, 125.5 (d, J = 1.4 Hz), 124.0 (dt, J = 7.9 and 1.3 Hz), 117.4 (td, J = 266.2 and 218.1 Hz), 64.4 (d, J = 6.9 Hz), 53.3, 16.4 (d, J = 5.6 Hz); ^{19}F{^{1}H} NMR ($CDCl_3$, $CFCl_3$, 282 MHz) δ −103.3 (d, J = 109.1 Hz, 2F); ^{31}P{^{1}H} NMR ($CDCl_3$, 121 MHz) δ 4.7 (t, J = 108.8 Hz, 1P); IR (neat, cm^{-1}) ν: 2988, 1740, 1614, 1592, 1532, 1436, 1352, 1278, 1259, 1089, 1012, 951; HRMS (ESI$^+$) calcd for $[M+H]^+$ $C_{13}H_{17}NF_2O_7P$: 368.0711, found: 368.0713 (0.5 ppm).

Methyl 5-chloro-2-[(diethoxyphosphoryl)difluoromethyl]benzoate 17h. Prepared following the procedure E from methyl 5-chloro-2-iodobenzoate **16h**. Reverse phase chromatography (H_2O/CH_3CN). Yield: 68% (121 mg, 0.5 mmol scale). Brown oil; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.70-7.66 (m, 1H), 7.50-7.48 (m, 2H), 4.29-4.10 (m, 4H), 3.88 (s, 3H), 1.33-1.28 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 167.3, 137.1 (q, J = 1.9 Hz), 133.7 (q, J = 3.7 Hz), 130.4 (d, J = 1.4 Hz), 130.1 (td, J = 7.8 and 1.4 Hz), 128.8, 128.7 (td, J = 22.4 and 15.4 Hz), 117.8 (td, J = 265.5 and 216.7 Hz), 65.0 (d, J = 6.8 Hz), 52.9, 16.3 (d, J = 5.5 Hz); ^{19}F{^{1}H} NMR ($CDCl_3$, $CFCl_3$, 282 MHz) δ −102.4 (d, J = 110.8 Hz, 2F); ^{31}P{^{1}H} NMR ($CDCl_3$, 121 MHz) δ 5.4 (t, J = 111.1 Hz, 1P); IR (neat, cm^{-1}) ν: 2988, 1741, 1596, 1569, 1436, 1393, 1293, 1263, 1152, 1118, 1090, 1014, 968; HRMS (ESI$^+$) calcd for $[M+NH_4]^+$ $C_{13}H_{20}NClF_2O_5P$: 374.0736, found: 374.0738 (0.5 ppm).

Methyl 5-bromo-2-[(diethoxyphosphoryl)difluoromethyl]benzoate 17i. Prepared following the procedure E from methyl 5-bromo-2-iodobenzoate **16i**. Reverse phase chromatography (H_2O/CH_3CN). Yield: 74% (149 mg, 0.5 mmol scale). Brown oil; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.66-7.58 (m, 3H), 4.27-4.12 (m, 4H), 3.88 (s, 3H), 1.33-1.28 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 167.3, 133.8 (q, J = 3.6 Hz), 133.4 (d, J = 1.4 Hz), 131.7, 130.3 (td, J = 7.6 and 1.3 Hz), 129.4 (dt, J = 22.1 and 15.4 Hz), 125.3 (dt, J = 1.9 Hz), 117.7 (td, J = 265.4 and 216.4 Hz), 65.1 (d, J = 6.9 Hz), 53.0, 16.4 (d, J = 5.5 Hz); ^{19}F{^{1}H} NMR ($CDCl_3$, $CFCl_3$, 282 MHz) δ −102.6 (d, J = 110.8 Hz, 2F); ^{31}P{^{1}H} NMR ($CDCl_3$, 121 MHz) δ 5.3 (t, J = 111.0 Hz, 1P); IR (neat, cm^{-1}) ν: 2989, 2954, 1740, 1591, 1566, 1436, 1390, 1291, 1260, 1153, 1124, 1102, 1012, 965, 938; HRMS (ESI$^+$) calcd for $[M+NH_4]^+$ $C_{13}H_{20}NBrF_2O_5P$: 420.0210, found: 420.0225 (3.6 ppm).

Methyl 2-[(diethoxyphosphoryl)difluoromethyl]-5-iodobenzoate 17j. Prepared following the procedure E from methyl 2,5-diiodobenzoate **16j**. Reverse phase chromatography (H_2O/CH_3CN). Yield: 56% (125 mg, 0.5 mmol scale). Brown oil; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.87 (d, J = 7.9 Hz, 2H), 7.46 (d, J = 8.2 Hz, 1H), 4.25-4.11 (m, 4H), 3.89 (s, 3H), 1.34-1.29 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 167.1, 139.3 (d, J = 1.4 Hz), 137.5, 133.5 (q, J = 3.6 Hz), 130.1 (dt, J = 6.4 and 1.6 Hz), 129.9 (dt, J = 22.2 and 15.4 Hz), 118.1 (td, J = 264.5 and 216.0 Hz), 97.0 (dt, J = 2.2 Hz), 65.1 (d, J = 6.9 Hz), 53.0, 16.4 (d, J = 5.4 Hz); ^{19}F{^{1}H} NMR ($CDCl_3$, $CFCl_3$, 282 MHz) δ −102.9 (d, J = 111.4 Hz, 2F); ^{31}P{^{1}H} NMR ($CDCl_3$, 121 MHz) δ 5.3 (t, J = 111.0 Hz, 1P); IR (neat, cm^{-1}) ν: 2918, 1738, 1585, 1562, 1436, 1393, 1289, 1259, 1155, 1125, 1098, 1039, 1013, 965, 938; HRMS (ESI$^+$) calcd for $[M+NH_4]^+$ $C_{13}H_{20}NF_2IO_5P$: 466.0092, found: 466.0103 (2.4 ppm).

Methyl 4-chloro-2-[(diethoxyphosphoryl)difluoromethyl]benzoate 17k. Prepared following the procedure E from methyl 4-chloro-2-iodobenzoate **16k**. Reverse phase chromatography (H_2O/CH_3CN). Yield: 43% (76 mg, 0.5 mmol scale). Brown oil; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.62 (s, 1H), 7.54 (dd, J = 8.3 and 1.9 Hz, 1H), 7.49 (d, J = 8.3 Hz, 1H), 4.43-4.24 (m, 4H), 3.88 (s, 3H), 1.41-1.36 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 167.8, 136.6 (d, J = 1.5 Hz), 132.6 (dt, J = 22.1 and 15.3 Hz), 130.9 (d, J = 1.5 Hz), 130.6-130.4 (m), 130.4, 128.7 (td, J = 8.3 and 1.4 Hz), 117.5 (td, J = 266.0 and 216.1 Hz), 65.2 (d, J = 6.7 Hz), 52.9, 16.4 (d, J = 5.7 Hz); ^{19}F{^{1}H} NMR ($CDCl_3$, $CFCl_3$, 282 MHz) δ −102.3 (d, J = 110.2 Hz, 2F); ^{31}P{^{1}H} NMR ($CDCl_3$, 121 MHz) δ 5.4 (t, J = 110.7 Hz, 1P); IR (neat, cm^{-1}) ν: 2988, 1738, 1596, 1435, 1393, 1290, 1261, 1224, 1112, 1013, 983; HRMS (ESI$^+$) calcd for $[M+H]^+$ $C_{13}H_{17}ClF_2O_5P$: 357.0470, found: 357.0458 (-3.4 ppm).

Diethyl [(pyridin-2-yl)difluoromethyl]phosphonate 17l. Prepared following the procedure E from 2-bromopyridine **16l**. Reverse phase chromatography (H_2O/CH_3CN). Yield: 32% (43 mg, 0.5 mmol scale). Brown oil; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.68 (d, J = 4.3 Hz, 1H), 7.81 (t, J = 8.1 Hz, 1H), 7.68 (d, J = 8.3 Hz, 1H), 7.39 (t, J = 6.3 Hz, 1H), 4.32-4.25 (m, 4H), 1.33 (t, J = 7.1 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 151.7 (dt, J = 23.8 and 14.4 Hz), 149.6, 137.2, 125.4 (d, J = 1.4 Hz), 121.8 (app dt), 116.5 (td, J = 264.1 and 216.8 Hz), 65.0 (d, J = 6.6 Hz), 16.4 (d, J = 5.6 Hz); ^{19}F{^{1}H} NMR ($CDCl_3$, $CFCl_3$, 282 MHz) δ −111.0 (d, J = 108.8 Hz, 2F); ^{31}P{^{1}H} NMR ($CDCl_3$, 121 MHz) δ 5.5 (t, J = 108.8 Hz, 1P); IR (neat, cm^{-1}) ν: 3505, 2987, 1589, 1437, 1370, 1266, 1132, 1101, 1012, 944; HRMS (ESI$^+$) calcd for $[M+H]^+C_{10}H_{15}NO_3F_2P$: 266.0758, found: 266.0764 (2.3 ppm).

Diethyl (*E*)-(1,1-difluoro-4-phenylbut-3-en-1-yl)phosphonate 19a Prepared following the procedure F from (*E*)-(3-bromoprop-1-en-1-yl)benzene **18a** with 91% yield (139 mg, 0.5 mmol scale); the procedure F from (*Z*)-(3-bromoprop-1-en-1-yl)benzene with 51% yield (76 mg, 0.5 mmol scale). Reverse phase chromatography (H_2O/CH_3CN). Colourless oil; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.39 (d, J = 7.6 Hz, 2H), 7.32 (t, J = 7.5 Hz, 2H), 7.28-7.25 (m, 1H), 6.60 (d, J = 16.4 Hz, 1H), 6.21 (dt, J = 15.8 and 7.1 Hz, 1H), 4.33-4.23 (m, 4H), 3.10-2.92 (m, 2H), 1.37 (t, J = 7.1 Hz 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 136.6, 136.0, 128.6, 127.8, 126.3, 119.7 (td, J = 262.6 and 213.8 Hz), 118.3 (dt, J = 11.0 and 5.7 Hz), 64.4 (d, J = 6.4 Hz), 38.0 (td, J = 21.1 and 16.3 Hz), 16.3 (d, J = 5.6 Hz); ^{19}F{^{1}H} NMR ($CDCl_3$, $CFCl_3$, 282 MHz) δ −110.7 (d, J = 107.9 Hz, 2F); ^{31}P{^{1}H} NMR ($CDCl_3$, 121 MHz) δ 6.9 (t, J = 107.5 Hz, 1P); IR (neat, cm^{-1}) ν: 2985, 1497, 1268, 1163, 1014, 957, 745; HRMS (ESI$^+$) calcd for $[M+Na]^+$ $C_{14}H_{19}F_2O_3NaP$: 327.0938, found: 327.0936 (-0.6 ppm).

Diethyl (*E*)-(4-(4-chlorophenyl)-1,1-difluorobut-3-en-1-yl)phosphonate 19b. Prepared following the procedure F from (*E*)-1-(3-bromoprop-1-en-1-yl)-4-chlorobenzene **18b**. Reverse phase chromatography (H_2O/CH_3CN). Yield: 62% (105 mg, 0.5 mmol scale). Brown oil; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.22 (app. t, 4H), 6.46 (d, J = 15.7 Hz, 1H), 6.11 (dt, J = 15.9 and 7.1 Hz, 1H), 4.24-4.15 (m, 4H), 3.00-2.83 (m, 2H), 1.29 (t, J = 7.3 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ

135.2, 134.9, 133.5, 128.8, 127.7, 119.9 (td, *J* = 261.0 and 215.2 Hz), 119.0 (q, *J* = 5.7 Hz), 64.5 (d, *J* = 6.6 Hz), 38.1 (dt, *J* = 21.4 and 15.6 Hz), 16.4 (d, *J* = 5.5 Hz); $^{19}F\{^1H\}$ NMR ($CDCl_3$, $CFCl_3$, 282 MHz) δ −111.2 (d, *J* = 107.9 Hz, 2F); $^{31}P\{^1H\}$ NMR ($CDCl_3$, 121 MHz) δ 6.8 (t, *J* = 107.4 Hz, 1P); IR (neat, cm^{-1}) ν: 2992, 2915, 1491, 1456, 1266, 1093, 1011, 967, 794; HRMS (ESI^+) calcd for $[M+NH_4]^+$ $C_{14}H_{22}ClNF_2O_3P$: 358.0964, found: 358.0966 (0.6 ppm).

Diethyl (1,1-difluoro-3-methylbut-3-en-1-yl)phosphonate 19c. Prepared following the procedure F from 3-bromo-2-methylprop-1-ene **18c**. Reverse phase chromatography (H_2O/CH_3CN). Yield: 61% (74 mg, 0.5 mmol scale). Brown oil; ^1H NMR (300 MHz, $CDCl_3$): δ 5.02 (s, 1H), 4.92 (s, 1H), 4.30-4.21 (m, 4H), 2.77 (td, *J* = 20.3 and 4.9 Hz, 2H), 1.84 (s, 3H), 1.37 (t, *J* = 7.2 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 135.9 (dt, *J* = 3.3Hz), 119.9 (td, *J* = 262.2 and 216.1 Hz), 117.9, 64.5 (d, *J* = 6.7 Hz), 41.7 (dt, *J* = 20.7 and 14.8 Hz), 23.7, 16.5 (d, *J* = 5.5 Hz); $^{19}F\{^1H\}$ NMR ($CDCl_3$, $CFCl_3$, 282 MHz) δ −111.1 (d, *J* = 107.8 Hz, 2F); $^{31}P\{^1H\}$ NMR ($CDCl_3$, 121 MHz) δ 7.0 (t, *J* = 108.1 Hz, 1P); IR (neat, cm^{-1}) ν: 2986, 1652, 1446, 1394, 1269, 1164, 1099, 1014, 977; HRMS (ESI^+) calcd for $[M+NH_4]^+C_9H_{21}F_2O_3PN$: 260.1227, found: 260.1227 (0.0 ppm).

Ethyl 4-(diethoxyphosphoryl)-4,4-difluoro-2-methylenebutanoate 19d. Prepared following the procedure F from ethyl 2-(bromomethyl)acrylate **18d**. Reverse phase chromatography (H_2O/CH_3CN). Yield: 63% (95 mg, 0.5 mmol scale). Colourless oil; ^1H NMR (300 MHz, $CDCl_3$): δ 6.44 (s, 1H), 5.85 (s, 1H), 4.28-4.20 (m, 6H), 3.14 (dt, *J* = 19.7 and 3.8 Hz, 2H), 1.37 (dt, *J* = 7.1 and 1.8 Hz, 6H), 1.29 (dt, *J* = 7.1 and 1.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 166.3, 131.3, 130.9 (dt, *J* = 3.6 Hz), 119.2 (td, *J* = 262.6 and 217.7 Hz), 64.7 (d, *J* = 6.7 Hz), 61.3, 35.1 (td, *J* = 20.8 and 15.7 Hz), 16.5 (d, *J* = 5.6 Hz), 14.2; $^{19}F\{^1H\}$ NMR ($CDCl_3$, $CFCl_3$, 282 MHz) δ −112.3 (d, *J* = 106.8 Hz, 2F); $^{31}P\{^1H\}$ NMR ($CDCl_3$, 121 MHz) δ 6.5 (t, *J* = 107.6 Hz, 1P); IR (neat, cm^{-1}) ν: 2985, 1718, 1635, 1273, 1155, 1012, 799; HRMS (ESI^+) calcd for $[M+Na]^+$ $C_{11}H_{19}F_2O_5NaP$: 323.0836, found: 323.0834 (-0.6 ppm).

Diethyl (1,1-difluoro-4-methylpent-3-en-1-yl)phosphonate 19e. Prepared following the procedure F from 1-bromo-3-methylbut-2-ene **18e**. Reverse phase chromatography (H_2O/CH_3CN). Yield: 98% (126 mg, 0.5 mmol scale). Brown oil; ^1H NMR (300 MHz, $CDCl_3$): δ 5.18 (dt, *J* = 7.3 and 1.2 Hz, 1H), 4.28-4.18 (m, 4H), 2.82-2.67 (m, 2H), 1.73 (s, 3H), 1.63 (s, 3H), 1.34 (t, *J* = 7.3 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 138.1, 120.7 (td, *J* = 261.2 and 214.9 Hz), 112.6 (dt, *J* = 5.5 and 5.3 Hz), 64.3 (d, *J* = 6.7 Hz), 33.2 (dt, *J* = 21.2 and 15.4 Hz), 25.9, 18.1, 16.4 (d, *J* = 5.5 Hz); $^{19}F\{^1H\}$ NMR ($CDCl_3$, $CFCl_3$, 282 MHz) δ −111.4 (d, *J* = 108.7 Hz, 2F); $^{31}P\{^1H\}$ NMR ($CDCl_3$, 121 MHz) δ 7.4 (t, *J* = 109.1 Hz, 1P); IR (neat, cm^{-1}) ν: 2985, 2917, 1444, 1393, 1261, 1162, 1091, 1014, 977; HRMS (ESI^+) calcd for $[M+H]^+C_{10}H_{20}F_2O_3P$: 257.1118, found: 257.1107 (-4.3 ppm).

Diethyl [(*E*)-1,1-difluoro-4,8-dimethylnona-3,7-dien-1-yl]phosphonate 19f. Prepared following the procedure F from geranyl bromide **19f**. Reverse phase chromatography (H_2O/CH_3CN). Yield: 99% (161 mg, 0.5 mmol scale). Colourless oil; ^1H NMR (300 MHz, $CDCl_3$): δ 5.18 (t, *J* = 6.4 Hz, 1H), 5.04 (s, 1H), 4.26-4.17 (m, 4H), 2.82-2.69 (m, 2H), 2.00 (s, 4H), 1.71 (d, *J* = 4.2 Hz, 1H), 1.62 (d, *J* = 6.7 Hz, 5H), 1.55 (s, 3H), 1.33 (t, *J* = 7.1 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 141.7, 124.1, 131.8, 120.2 (td, *J* = 260.0 and 214.7 Hz), 112.3 (q, *J* = 5.6 Hz), 64.4 (d, *J* = 6.7 Hz), 39.9, 33.2 (dt, *J* = 20.7 and 15.4 Hz), 26.6, 26.4, 25.8, 17.8, 16.5 (d, *J* = 5.7 Hz); $^{19}F\{^1H\}$ NMR ($CDCl_3$, $CFCl_3$, 282 MHz) δ −111.5 (d, *J* = 109.3 Hz, 2F); $^{31}P\{^1H\}$ NMR ($CDCl_3$, 121 MHz) δ 7.4 (t, *J* = 109.3 Hz, 1P); IR (neat, cm^{-1}) ν: 2982, 2916, 1444, 1371, 1262, 1162, 1016, 977; HRMS (ESI^+) calcd for $[M+Na]^+$ $C_{15}H_{27}F_2O_3NaP$: 347.1564, found: 347.1566 (0.6 ppm).

Diethyl [(3*E*,7*E*)-1,1-difluoro-4,8,12-trimethyltrideca-3,7,11-trien-1-yl]phosphonate 19g. Prepared following the procedure F from farnesyl bromide **18g**. Reverse phase chromatography (H_2O/CH_3CN). Yield: 88% (172 mg, 0.5 mmol scale). Colourless oil; ^1H NMR (300 MHz, $CDCl_3$): δ 5.22-5.18 (m, 1H), 5.08-5.06 (m, 2H), 4.28-4.18 (m, 4H), 2.84-2.71 (m, 2H), 2.05-1.94 (m, 8H), 1.74-1.57 (m, 12H), 1.35 (t, *J* = 7.1 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 141.6 (d, *J* = 3.4 Hz), 135.4 (d, *J* = 9.5 Hz), 131.5 (d, *J* = 21.8 Hz), 124.6, 124.3 (d, *J* = 4.6 Hz), 123.8, 120.5 (td, *J* = 260.1 and 215.6 Hz), 112.2 (ddt, *J* = 9.0 and 1.6 Hz), 64.4 (d, *J* = 6.7 Hz), 40.2, 39.8 (d, *J* = 7.9 Hz), 33.0 (dt, *J* = 20.9 and 14.8 Hz), 32.0 (app. d), 26.8-26.6 (app dt), 26.4-26.3 (app dt), 25.7 (d, *J* = 2.2 Hz), 17.7 (d, *J* = 3.9 Hz), 16.5 (d, *J* = 5.7 Hz); $^{19}F\{^1H\}$ NMR ($CDCl_3$, $CFCl_3$, 282 MHz) δ −111.5 (d, *J* = 109.3 Hz, 2F); $^{31}P\{^1H\}$ NMR ($CDCl_3$, 121 MHz) δ 7.4 (t, *J* = 109.3 Hz, 1P); IR (neat, cm^{-1}) ν: 2968, 2916, 1444, 1375, 1269, 1162, 1016, 977, 899 HRMS (ESI^+) calcd for $[M+Na]^+$ $C_{20}H_{35}F_2O_3$ NaP: 415.2190, found: 415.2193 (0.7 ppm).

Diethyl [1,1-difluoro-2-phenylethyl]phosphonate 21a. Prepared following the procedure G from benzyl bromide **20a**. Reverse phase chromatography (H_2O/CH_3CN). Yield: 87% (121 mg, 0.5 mmol scale). Brown oil; ^1H NMR (300 MHz, $CDCl_3$): δ 7.31 (s, 5 H), 4.25-4.11 (m, 4H), 3.44-3.29 (td, *J* = 20.2 and 5.8 Hz, 2H), 1.30 (t, *J* = 7.1 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 131.0, 130.9-130.7 (m), 128.4, 127.7, 119.5 (td, *J* = 262.6 and 213.3 Hz), 64.5 (d, *J* = 7.1 Hz), 40.3 (dt, *J* = 21.4 and 15.9 Hz) 16.4 (d, *J* = 5.6 Hz); $^{19}F\{^1H\}$ NMR ($CDCl_3$, $CFCl_3$, 282 MHz) δ −111.1 (d, *J* = 107.6 Hz, 2F); $^{31}P\{^1H\}$ NMR ($CDCl_3$, 121 MHz) δ 6.9 (t, *J* = 107.5 Hz, 1P); IR (neat, cm^{-1}) ν: 2985, 1497, 1456, 1269, 1164, 1081, 1028, 977, 886; HRMS (ESI^+) calcd for $[M+NH_4]^+$ $C_{12}H_{21}NF_2O_3P$: 296.1227, found: 296.1224 (-1.0 ppm).

Diethyl (1,1-difluoro-2-(p-tolyl)ethyl)phosphonate 21b. Prepared following the procedure G from 1-(bromomethyl)-4-methylbenzene **20b**. Reverse phase chromatography (H_2O/CH_3CN). Yield: 42% (61 mg, 0.5 mmol scale). Brown oil; ^1H NMR (300 MHz, $CDCl_3$): δ 7.20 (d, *J* = 7.7 Hz, 2H), 7.14 (d, *J* = 7.7 Hz, 2H), 4.29-4.10 (m, 4H), 3.40-3.25 (td, *J* = 20.0 and 5.3 Hz, 2H), 2.33 (s, 3H), 1.31 (t, *J* = 7.1 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 137.4, 130.9, 129.1, 127.6 (dt, *J* = 6.3 and 3.9 Hz), 119.7 (td, *J* = 261.1 and 215.0 Hz), 64.5 (d, *J* = 6.9 Hz), 39.8 (dt, *J* = 20.8 and 15.4 Hz), 21.2, 16.4 (d, *J* = 5.6 Hz); $^{19}F\{^1H\}$ NMR ($CDCl_3$, $CFCl_3$, 282 MHz) δ −111.3 (d, *J* = 107.4 Hz, 2F); $^{31}P\{^1H\}$ NMR ($CDCl_3$, 121 MHz) δ 7.1 (t, *J* = 107.5 Hz, 1P); IR (neat, cm^{-1}) ν: 2985, 2932, 1516, 1269, 1165, 1033, 1012, 978, 769; HRMS (ESI^+) calcd for $[M+H]^+$ $C_{13}H_{20}F_2O_3P$: 293.1118, found: 293.1114 (-1.4 ppm).

Diethyl (2-(4-bromophenyl)-1,1-difluoroethyl)phosphonate 21c. Prepared following the procedure G from 1-bromo-4-(bromomethyl)benzene. **20c** Reverse phase chromatography (H_2O/CH_3CN). Yield: 74% (132 mg, 0.5 mmol scale). Brown oil; ^1H NMR (300 MHz, $CDCl_3$): δ 7.43 (d, *J* = 8.3 Hz, 2H), 7.16 (d, *J* = 8.2 Hz, 2H), 4.24-4.13 (m, 4H), 3.37-3.23 (td, *J* = 19.5 and 5.3 Hz, 2H), 1.30 (t, *J* = 7.3 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 132.6, 131.5, 129.8 (dt, *J* = 6.4 and 3.9 Hz), 121.9, 119.1 (td, *J* = 261.4 and 214.6 Hz), 64.6 (d, *J* = 6.9 Hz), 39.7 (dt, *J* = 21.0 and 15.3 Hz), 16.3 (d, *J* = 5.6 Hz); $^{19}F\{^1H\}$ NMR ($CDCl_3$, $CFCl_3$, 282 MHz) δ −111.4 (d, *J* = 106.0 Hz, 2F); $^{31}P\{^1H\}$ NMR ($CDCl_3$, 121 MHz) δ 6.6 (t, *J* = 106.1 Hz, 1P); IR (neat, cm^{-1}) ν: 2985, 2915, 1490, 1268, 1164, 1032, 1011, 979; HRMS (ESI^+) calcd for $[M+NH_4]^+$ $C_{12}H_{20}BrNF_2O_3P$: 374.0332, found: 374.0319 (-3.5 ppm).

Diethyl (2-(4-acetylphenyl)-1,1-difluoroethyl)phosphonate 21d. Prepared following the procedure G from 1-(4-(bromomethyl)phenyl)ethan-1-one **20d**. Reverse phase chromatography (H_2O/CH_3CN). Yield: 47% (75 mg, 0.5 mmol scale). Brown oil; ^1H NMR (300 MHz, $CDCl_3$): δ 7.94-7.90 (app. dt, 2H), 7.41 (d, *J* = 8.3 Hz, 2H), 4.30-4.12 (m, 4H), 3.50-3.35 (td, *J* = 19.6 and 5.3 Hz, 2H), 2.59 (s, 3H),

1.32 (t, *J* = 7.2 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 197.9, 136.6, 136.3 (dt, *J* = 6.4 and 3.7 Hz), 131.3, 128.4, 119.2 (td, *J* = 262.1 and 215.7 Hz), 64.7 (d, *J* = 6.9 Hz), 40.2 (dt, *J* = 21.0 and 15.5 Hz), 26.8, 16.4 (d, *J* = 5.6 Hz); ^{19}F{^{1}H} NMR ($CDCl_3$, $CFCl_3$, 282 MHz) δ –111.2 (d, *J* = 106.3 Hz, 2F); ^{31}P{^{1}H} NMR ($CDCl_3$, 121 MHz) δ 6.6 (t, *J* = 106.5 Hz, 1P); IR (neat, cm^{-1}) ν: 2986, 1683, 1610, 1360, 1267, 1165, 1089, 1033, 1011, 979, 957; HRMS (ESI^+) calcd for $[M+NH_4]^+$ $C_{14}H_{23}NF_2O_4P$: 338.1333, found: 338.1333 (0.0 ppm).

Diethyl (2-(2-cyanophenyl)-1,1-difluoroethyl)phosphonate 21e. Prepared following the procedure G from 2-(bromomethyl)benzonitrile **20e**. Reverse phase chromatography (H_2O/CH_3CN). Yield: 36% (55 mg, 0.5 mmol scale). Brown oil; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.68 (d, *J* = 7.7 Hz, 1H), 7.57 (t, *J* = 7.4 Hz, 1H), 7.49 (d, *J* = 7.4 Hz, 1H), 7.42 (t, *J* = 7.3 Hz, 1H), 4.34-4.24 (m, 4H), 3.69-3.55 (app. t, 2H), 1.37 (t, *J* = 7.2 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 134.5 (dt, *J* = 7.5 and 2.9 Hz), 133.1, 132.7, 132.3, 128.5, 118.5 (td, *J* = 262.0 and 214.4 Hz), 117.8, 114.9, 65.0 (d, *J* = 6.8 Hz), 38.4 (dt, *J* = 20.9 and 15.9 Hz), 16.5 (d, *J* = 5.5 Hz); ^{19}F{^{1}H} NMR ($CDCl_3$, $CFCl_3$, 282 MHz) δ –111.6 (d, *J* = 104.9 Hz, 2F); ^{31}P{^{1}H} NMR ($CDCl_3$, 121 MHz) δ 5.9 (t, *J* = 104.5 Hz, 1P); IR (neat, cm^{-1}) ν: 2987, 2228, 1270, 1163, 1028, 1010, 762; HRMS (ESI^+) calcd for $[M+NH_4]^+$ $C_{13}H_{20}F_2N_2O_3P$: 321.1180, found: 321.1191 (3.4 ppm).

Diethyl (1,1-difluoro-2-(2-iodophenyl)ethyl)phosphonate 21f. Prepared following the procedure G from (1-(bromomethyl))-2-iodobenzene **20f**. Reverse phase chromatography (H_2O/CH_3CN). Yield: 48% (97 mg, 0.5 mmol scale). Brown oil; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.88 (d, *J* = 7.9 Hz, 1H), 7.39 (d, *J* = 7.5 Hz, 1H), 7.32 (t, *J* = 7.5 Hz, 1H), 6.98 (t, *J* = 7.5 Hz, 1H), 4.35-4.26 (m, 4H), 3.63 (t, *J* = 19.9 Hz, 2H), 1.39 (t, *J* = 7.0 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 139.9, 134.7 (dt, *J* = 8.4 and 2.5 Hz), 132.0, 129.5, 128.3, 119.2 (td, *J* = 261.7 and 214.9 Hz), 102.5, 64.8 (d, *J* = 6.7 Hz), 43.7 (dt, *J* = 20.1 and 16.1 Hz), 16.6 (d, *J* = 5.6 Hz); ^{19}F{^{1}H} NMR ($CDCl_3$, $CFCl_3$, 282 MHz) δ –111.6 (d, *J* = 106.1 Hz, 2F); ^{31}P{^{1}H} NMR ($CDCl_3$, 121 MHz) δ 6.6 (t, *J* = 106.4 Hz, 1P); IR (neat, cm^{-1}) ν: 2984, 1474, 1438, 1267, 1163, 1030, 1008, 741; HRMS (ESI^+) calcd for $[M+NH_4]^+$ $C_{12}H_{20}INF_2O_3P$: 422.0194, found: 422.0186 (-1.9 ppm).

Diethyl [(phenylthio)difluoromethyl]phosphonate 23a. Prepared following the procedure H from 1,2-diphenyldisulfide **22a**. Reverse phase chromatography (H_2O/CH_3CN). Yield: 49% (72 mg, 0.5 mmol scale). Brown oil; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.65-7.63 (m, 2H), 7.48-7.35 (m, 3H), 4.36-4.23 (m, 4H), 1.40-1.35 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 137.0, 130.5, 129.2, 124.7 (td, *J* = 299.7 and 217.2 Hz), 124.4 (m), 65.4 (d, *J* = 6.6 Hz), 16.4 (d, *J* = 5.6 Hz); ^{19}F{^{1}H} NMR ($CDCl_3$, $CFCl_3$, 282 MHz) δ –84.6 (d, *J* = 100.7 Hz, 2F); ^{31}P{^{1}H} NMR ($CDCl_3$, 121 MHz) δ 4.0 (t, *J* = 100.9 Hz, 1P); IR (neat, cm^{-1}) ν: 2986, 2933, 1488, 1476, 1442, 1394, 1273, 1162, 1115, 1011, 982, 910; HRMS (ESI^+) calcd for $[M+NH_4]^+$ $C_{11}H_{19}NF_2O_3PS$: 314.0791, found: 314.0787 (- 1.3 ppm).

Diethyl [((4-methylphenyl)thio)difluoromethyl]phosphonate 23b. Prepared following the procedure H from 1,2-bis(4-methylphenyl)disulfide **22b**. Reverse phase chromatography (H_2O/CH_3CN). Yield: 57% (88 mg, 0.5 mmol scale). Brown oil; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.51 (d, *J* = 8.0 Hz, 2H), 7.19 (d, *J* = 7.9 Hz, 2H), 4.35-4.23 (m, 4H), 2.36 (s, 3H), 1.39-1.34 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 140.9, 137.0, 130.0, 130.4-130.0 (m), 124.5 (td, *J* = 300.6 and 215.4 Hz), 65.4 (d, *J* = 6.5 Hz), 21.4, 16.4 (d, *J* = 5.7 Hz); ^{19}F{^{1}H} NMR ($CDCl_3$, $CFCl_3$, 282 MHz) δ –84.9 (d, *J* = 101.1 Hz, 2F); ^{31}P{^{1}H} NMR ($CDCl_3$, 121 MHz) δ 4.1 (t, *J* = 101.4 Hz, 1P); IR (neat, cm^{-1}) ν: 2986, 2926, 1493, 1445, 1395, 1371, 1273, 1164, 1116, 1014, 981, 911; HRMS (ESI^+) calcd for $[M+H]^+$ $C_{12}H_{18}F_2O_3PS$: 311.0682, found: 311.0683 (0.3 ppm).

Diethyl (difluoro((4-methoxyphenyl)thio)methyl]phosphonate 23c. Prepared following the procedure H from 1,2-bis(4-methoxyphenyl)disulfide **22c**. Reverse phase chromatography (H_2O/CH_3CN). Yield: 48% (78 mg, 0.5 mmol scale). Brown oil; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.57-7.52 (m, 2H), 6.93-6.88 (m, 2H), 4.35-4.23 (m, 4H), 3.81 (s, 3H), 1.40-1.35 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 161.7, 138.9, 124.6 (td, *J* = 266.6 and 216.3 Hz), 115.2-115.1 (m), 114.8, 65.4 (d, *J* = 6.6 Hz), 55.5, 16.4 (d, *J* = 5.7 Hz); ^{19}F{^{1}H} NMR ($CDCl_3$, $CFCl_3$, 282 MHz) δ –85.4 (d, *J* = 101.3 Hz, 2F); ^{31}P{^{1}H} NMR ($CDCl_3$, 121 MHz) δ 4.2 (t, *J* = 101.3 Hz, 1P); IR (neat, cm^{-1}) ν: 2987, 1591, 1495, 1464, 1394, 1274, 1250, 1175, 1164, 1115, 1015, 981; HRMS (ESI^+) calcd for $[M+H]^+$ $C_{12}H_{18}F_2O_4PS$: 327.0631, found: 327.0634 (0.9 ppm).

Diethyl [((4-fluorophenyl)thio)difluoromethyl]phosphonate 23d. Prepared following the procedure H from 1,2-bis(4-fluorophenyl)disulfide **22d**. Reverse phase chromatography (H_2O/CH_3CN). Yield: 52% (82 mg, 0.5 mmol scale). Brown oil; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.64-7.59 (m, 2H), 7.11-7.02 (m, 2H), 4.35-4.20 (m, 4H), 1.39-1.35 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 164.3 (d, *J* = 250.6 Hz), 139.2 (d, *J* = 8.8 Hz), 124.7 (td, *J* = 297.1 and 219.0 Hz), 119.7-119.5 (m), 116.5 (d, *J* = 22.0 Hz), 65.5 (d, *J* = 6.6 Hz), 16.4 (d, *J* = 5.7 Hz); ^{19}F{^{1}H} NMR ($CDCl_3$, $CFCl_3$, 282 MHz) δ –85.2 (d, *J* = 101.0 Hz, 2F) and -110.2 (s,1F); ^{31}P{^{1}H} NMR ($CDCl_3$, 121 MHz) δ 3.8 (t, *J* = 101.4 Hz, 1P); IR (neat, cm^{-1}) ν: 2987, 2918, 1590, 1491, 1397, 1371, 1273, 1225, 1159, 1118, 1010, 913; HRMS (ESI^+) calcd for $[M+NH_4]^+$ $C_{11}H_{18}NF_3O_3PS$: 332.0697, found: 332.0696 (- 0.3 ppm).

Diethyl [((4-chlorophenyl)thio)difluoromethyl]phosphonate 23e. Prepared following the procedure H from 1,2-bis(4-chlorophenyl)disulfide **22e**. Reverse phase chromatography (H_2O/CH_3CN). Yield: 57% (94 mg, 0.5 mmol scale). Brown oil; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.56 (m, 2H), 7.36 (m, 2H), 4.38-4.23 (m, 4H), 1.39-1.35 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 138.2, 137.2, 129.5, 124.6 (td, *J* = 298.6 and 219.7 Hz), 122.8 (td, *J* = 4.4 and 2.9 Hz), 65.5 (d, *J* = 6.5 Hz), 16.4 (d, *J* = 5.6 Hz); ^{19}F{^{1}H} NMR ($CDCl_3$, $CFCl_3$, 282 MHz) δ –84.9 (d, *J* = 100.1 Hz, 2F); ^{31}P{^{1}H} NMR ($CDCl_3$, 121 MHz) δ 3.7 (t, *J* = 100.1 Hz, 1P); IR (neat, cm^{-1}) ν: 2986, 2934, 1574, 1477, 1391, 1274, 1163, 1118, 1092, 1010, 910; HRMS (ESI^+) calcd for $[M+NH_4]^+$ $C_{11}H_{18}NClF_2O_3PS$: 348.0402, found: 348.0414 (3.4 ppm).

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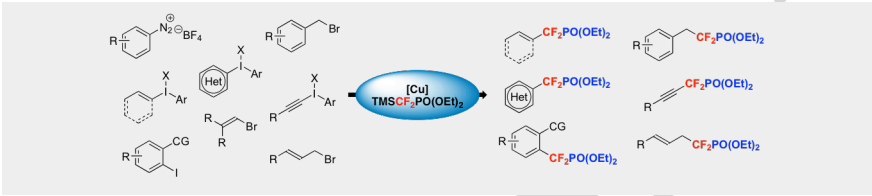

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