Synthetic Methods

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Copper-Mediated Formation of Aryl, Heteroaryl, Vinyl and Alkynyl Difluoromethylphosphonates: A General Approach to Fluorinated Phosphate Mimics

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Abstract: *A general and efficient access to aryl, heteroaryl, vinyl and alkynyl difluoromethylphosphonates is described. The developed methodology using $TMSCF_2PO(OEt)_2$, iodonium salts and a copper salt provided a straightforward manifold to reach these highly relevant products. The reaction proved to be highly functional group tolerant and proceeded under mild conditions, giving the corresponding products in good to excellent yields. This method represents the first general synthetic route to this important class of fluorinated scaffolds, which are well-recognized as in vivo stable phosphate surrogates.*

Protein tyrosine phosphatase inhibitors:

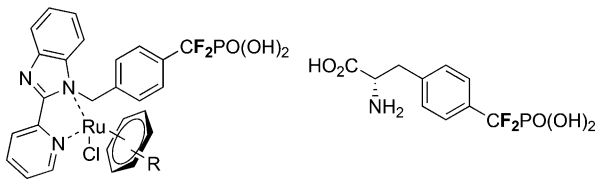

Figure 1. Biorelevant compounds bearing a difluoromethylphosphinic acid motif.

Over the last years, the demand of fluorinated molecules has impressively increased. Indeed, the unique features of the fluorine atom provide molecule-specific physical and biological properties.[1] In particular, the propensity of the fluorine atom or fluorinated groups to alter the lipophilicity, the bioavailabilty and/or the metabolic stability of a molecule afford it a pivotal role in the discovery of new pharmaceuticals.[2] Hence, the development of new methodologies to access fluorinated molecules or building blocks has fascinated the organic chemist community. While much efforts have been devoted to the introduction of the fluorine atom or the CF_3 group,[3] the introduction of functionalized difluoromethylated residues has been far less explored.[4] This statement is in sharp contrast with the high interest of the difluoromethyl motif, which can act as a remarkable bioisostere of an oxygen atom or a carbonyl group, for instance. Among these fluorinated groups, the difluoromethylphosphonate residue ($CF_2PO(OR)_2$) is extremely appealing. Indeed, the $CF_2PO(OR)_2$ group can be considered as an in vivo stable surrogate of the phosphate group. The replacement of the O–P bond by the strongest C–P bond suppresses potential metabolic hydrolysis. It is important to mention that this concept, proposed by Blackburn[5a–c] more than thirty years ago, has been used to design biologically active compounds bearing a difluoromethylphosphinic acid motif as a metabolically stable residue (Figure 1).[5d,e] In addition, the difluoromethylene residue provides to the phosphinic derivative a similar pK_a as the corresponding phosphonic acid.

These difluoromethylated phosphonate-containing molecules are usually obtained through the fluorination of the corresponding keto- or methyl-phosphonate derivatives[6] or through the introduction of the $CF_2PO(OR)_2$ residue. This latter approach mainly relied on the Cu-mediated reaction of metalated $CF_2PO(OR)_2$ derivatives with halogenated alkenes,[7a] alkynes,[7b,c] arenes bearing a coordinating group (CG),[7d–f] or aryl diazonium salts.[7g] However, no general method has emerged from these interesting reports and the depicted methodologies remained restricted to a well-defined class of substrates. Quite recently, the transition metal-catalyzed or -promoted cross-coupling reactions with boronic acids have been independently reported by Zhang[8a] and Qing.[8b] In addition to these methods, this key motif has been introduced through the copper-mediated oxidative coupling of terminal alkynes with $TMSCF_2PO(OR)_2$[9] and the addition of the difluoromethylphosphonyl radical to heteroarenes.[10] It should be noted that these methods usually required the use of moisture- and air-sensitive organometallic reagents, fine-tuned coupling partners, or harsh reaction conditions (Scheme 1). In this context, we aimed at offering a general and straightforward method to access a wide range of difluoromethylphosphonate derivatives under mild reaction conditions. For this purpose, we envisioned the Cu-mediated reaction of $TMSCF_2PO(OEt)_2$ (**1**) with various hypervalent iodine species. We hypothesized the involvement of a Cu^{III} intermediate resulting from the oxidative addition of the Cu^{I} intermediate with a λ^3 iodane as proposed by Barton and others.[11] This process utilizing inexpensive and benign copper salts as well as bench-stable and non-toxic hypervalent iodinated compounds, would afford a synthetically useful access to the highly relevant difluoromethylphosphonate derivatives. Taking benefit from the versatility of iodonium salts, this approach should offer a straightforward and robust method to synthesize a large panel of difluoromethylphos-

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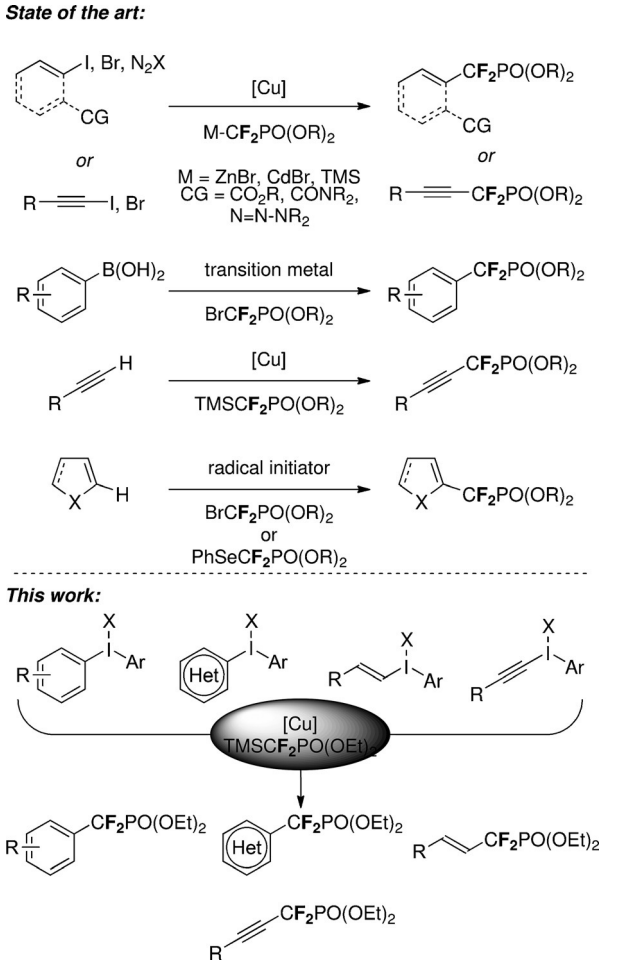
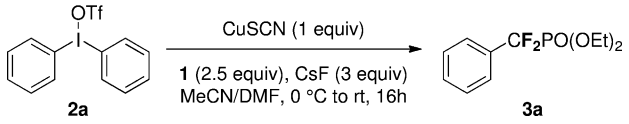


Scheme 1. Current state of the art and present strategy.

phonate compounds such as aryl, heteroaryl, vinyl and alkynyl derivatives.

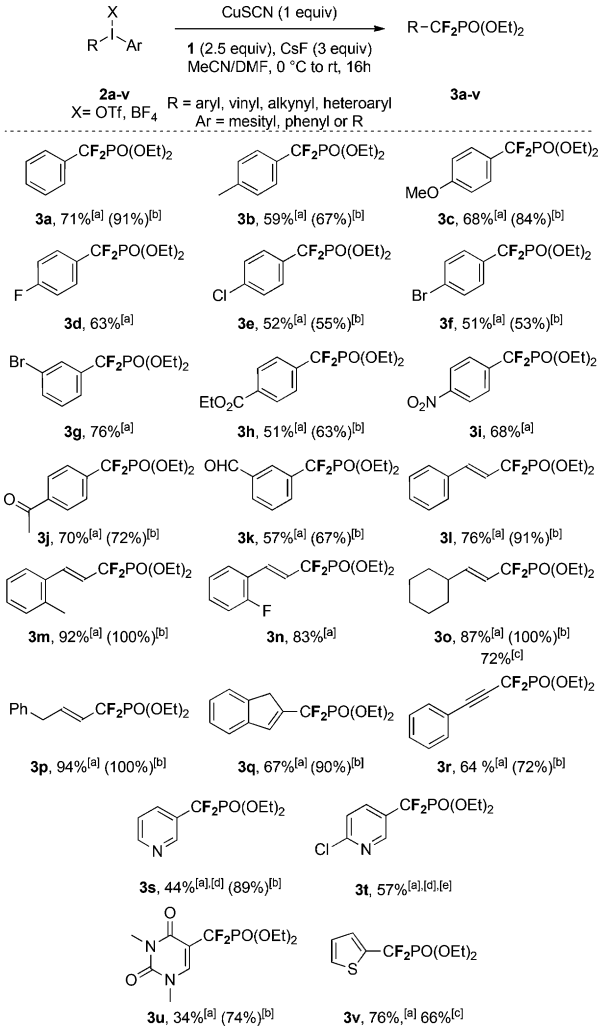
At the outset of the project, diphenyliodonium triflate **2a** was used as a model substrate. We first generated the $CuCF_2PO(OEt)_2$ species from $TMSCF_2PO(OEt)_2$ (**1**) in the presence of a copper salt and a Lewis base to promote the transmetalation, which was reacted with the diphenyliodonium salt **2a**. After careful screening of the reaction conditions we obtained the expected compound **3a** in 91% NMR yield and 71% isolated yield (Table 1, entry 1). Note that the replacement of CuSCN by CuOAc or CuI furnished lower yields (entries 2 and 3). The use of MeCN/DMF mixture as solvent was found crucial (entries 4 and 5) and a survey of Lewis bases confirmed the key role of CsF over other activators to promote the Si–Cu transmetalation (entry 6). Unfortunately, all our attempts to decrease the stoichiometry of **1** failed, resulting in lower conversion to **3a** (entry 7). A set of control experiments confirmed the importance of the presence of CsF and, most importantly, when the reaction was carried out in the presence of phenyl iodide instead of **2a**, no reaction took place (entries 8 and 9). This last result highlighted the prime importance of **2a** as a coupling partner.

Table 1: Addition of $CuCF_2PO(OEt)_2$ to the aryl iodonium **2a**.



Entry	Variation from standard conditions	Yield [%][a]
1	none	91 (71)[b]
2	CuOAc instead of CuSCN	78
3	CuI instead of CuSCN	45
4	MeCN as sole solvent	89
5	DMF as sole solvent	35
6	KF instead of CsF	64
7	1.5 equiv of $TMSCF_2PO(OEt)_2$	28
8	without CsF	0
9	PhI instead of **2a**	0

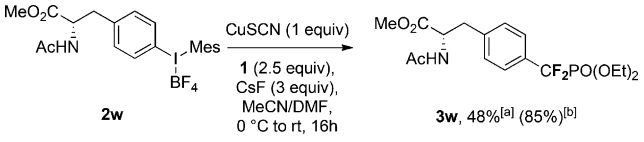
[a] Yields determined by ^{19}F NMR spectroscopy using α,α,α-trifluorotoluene as internal standard. [b] Yield of isolated products.



Scheme 2. Scope of the reaction (0.25–0.5 mmol scale). [a] Yield of isolated products. [b] NMR yields determined by using α,α,α-trifluorotoluene as internal standard. [c] Reactions performed on 3.4 mmol scale. [d] 1,10-phenanthroline (1 equiv) was added. [e] Contaminated with 10% of an unknown product.

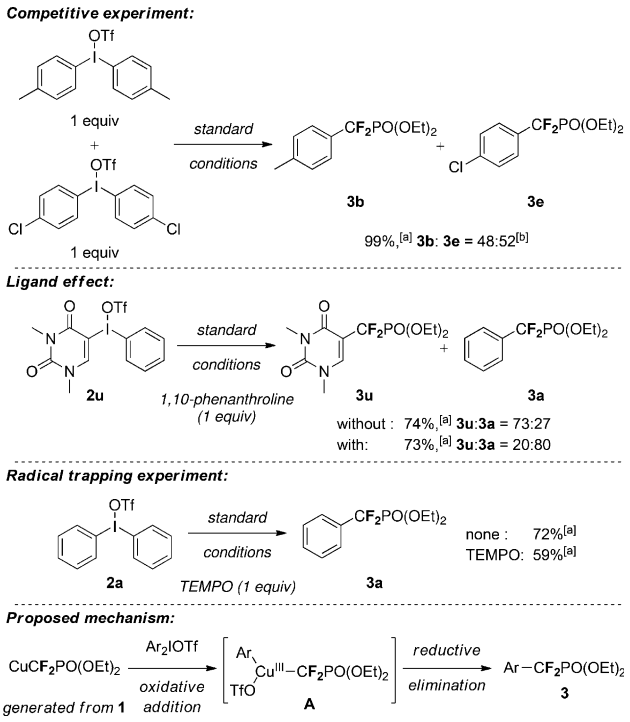
Having established the optimized reaction conditions, we sought to extend the scope of the reaction to aryl, vinyl, alkynyl and heteroaryl iodonium salts (Scheme 2). First, the *para*-tolyl-substituted iodonium salt **2b** was coupled with the $CF_2PO(OEt)_2$ moiety under standard conditions and the corresponding difluoromethylated phosphonate **3b** was obtained in good yield. Electron-donating substituents (e.g. OMe) were suitable as **3c** was isolated in good yield (68%). The reaction proved to be tolerant toward *para*- and *meta*-halide-substituted iodonium salts. Indeed, iodonium salts with fluorine, chlorine, and bromine as substituents afforded the corresponding phosphonates **3d**–**g** in good yields. Ester and nitro groups were also well tolerated and the corresponding difluoromethylated phosphonates **3h** and **3i**, respectively, were isolated in good yields. To our delight, iodonium salts **2j** and **2k** reacted readily to afford the corresponding products **3j** and **3k** without any trace of products resulting from the addition of the difluoromethylphosphonate residue on the ketone or aldehyde. These two examples highlight the functional group tolerance of the process.[12] We then turned our attention to the alkenyl iodonium salts **2l**–**q**. Aryl- and alkyl-substituted alkenes reacted smoothly to give the corresponding products **3l**–**p** in excellent yields (76–94%), while the cyclic alkene **3q** was isolated in a slightly lower yield (67%). To demonstrate the synthetic utility of our process, we performed a reaction on a larger scale with iodonium **2o** and the corresponding product **3o** was isolated in 72% yield. In addition, the reaction proved to be effective with alkynyl derivative **2r**, providing the difluoromethylphosphonate **3r** in moderate 64% yield. Due to the prime importance of fluorinated heterocycles in the search for pharmaceuticals and agrochemicals, the design of a straightforward method to introduce the $CF_2PO(OR)_2$ moiety on these privileged scaffolds is a matter of importance. Hence, we tested pyridine, uracil and thiophene iodonium salts **2s**–**v**. Pyridine derivatives **3s** and **3t** were isolated in good yields of 44% and 57%, respectively. Interestingly, the uracil iodonium salt **2u** was also suitable, offering an efficient synthetic pathway to the uracil difluoromethylphosphonate **3u** in 34% yield. Finally, the thiophene derivative **3v** was isolated in a good 76% yield and a larger scale reaction afforded **3v** in 66% isolated yield showcasing the versatility of the method.

Subsequently, we chose to apply our methodology to a more complex structure to highlight the synthetic utility of our approach (Scheme 3). We tested our reaction conditions on the amino acid based iodonium salt **2w**. Pleasingly, the amino acid part was readily transferred and the corresponding difluoromethylated phosphonate **3w** was isolated in 48% yield, thus providing a straightforward access to the corresponding phosphatase inhibitor precursor.[5d]



Scheme 3. Application of the methodology to biologically relevant products. [a] Yield of isolated products. [b] NMR yield determined by using α,α,α-trifluorotoluene as internal standard.

To gain insight in the reaction mechanism, we first studied the reaction competition between an electron-donating substituted aryl iodonium salt and an electron-withdrawing substituted one (Scheme 4). The reaction carried out in the presence of di-*para*-tolyl iodonium salt and the di-*para*-chlorophenyl iodonium salt did not reveal a significant selectivity for one of these substrates. In addition, we studied the influence of the addition of a ligand with the iodonium salt **2u**. Impressively, the addition of 1,10-phenanthroline changed drastically the selectivity of the reaction. Without ligand the uracyl ring was preferentially transferred, while the addition of 1,10-phenanthroline reversed this selectivity favoring the formation of **3a**.[13] This intriguing result clearly highlights the involvement of the copper species in the reaction mechanism. Therefore, we can rule out the possible formation of a potential λ^3-iodane ($Ar_2ICF_2PO(OEt_2)$) in the course of the reaction.[14]

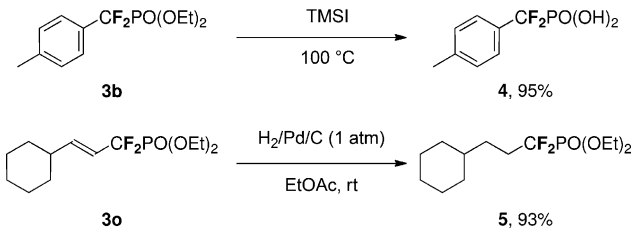


Scheme 4. Mechanistic studies and proposed mechanism. [a] NMR yields determined by using α,α,α-trifluorotoluene as internal standard. [b] Ratio determined by ^{19}F NMR spectroscopy.

If a new λ^3-iodane were involved as reaction intermediate, the copper species should not have any influence on the reaction outcome. In addition, the reaction performed in the presence of TEMPO ((2,2,6,6-tetramethylpiperidin-1-yl)oxyl) as radical inhibitor did not afford a significant drop of the reactivity. This result precludes the involvement of a free-radical pathway. Taking into account these data, we propose the following mechanism to explain the reaction outcome (Scheme 4). The copper species generated from **1** performs an oxidative addition reaction with the iodonium salt to provide the Cu^{III} species **A**. The latter undergoes

a reductive elimination to deliver the difluoromethylphosphonate **3**.

To highlight the versatility of the difluoromethylphosphonate compounds **3**, some key transformations were carried out (Scheme 5). First, the difluoromethylphosphonate **3b** was readily converted to the difluoromethylphosphinic acid derivative **4** in 95% yield. Second, the alkenyl difluoromethylphosphonate **3o** was smoothly reduced offering hence an efficient pathway to the otherwise difficult to access alkyl derivative **5** in 93% yield.



Scheme 5. Synthetically useful transformations of the products.

In conclusion, we reported here the first general method to access (hetero)aryl, vinyl and alkynyl difluoromethylphosphonate derivatives by reacting $TMSCF_2PO(OEt)_2$ with various iodonium salts in the presence of a copper salt. The corresponding products were obtained in good to excellent yields under mild conditions. The developed methodology proved to be highly functional group tolerant and was applied to a broad range of substrates including biologically relevant molecules. This approach opens a new avenue to the synthesis of phosphate mimics. Mechanistic studies supported a mechanism involving a Cu^{III} intermediate. Finally, the synthetic utility of the difluoromethylated phosphonates was demonstrated.

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[12] Note that the use of unsymmetrical diaryl iodonium salts resulted in a mixture of products with no selectivity. Thus the use of a bulky mesitylene residue is of prime importance.

[13] When 1,10-phenanthroline was added to the competitive reaction between both iodonium salts a slight enhancement of the selectivity towards the formation of **3e** was observed (**3b**:**3e** = 41:59) accompanied by a decrease of the reaction yield to 73%.
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