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Organophotocatalysis Enables the Synthesis of *gem*-FluoroPhosphonate Alkenes

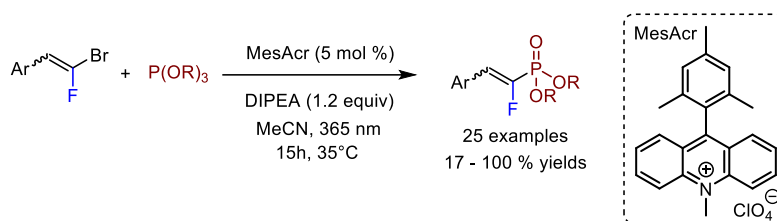
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Supporting Information Placeholder



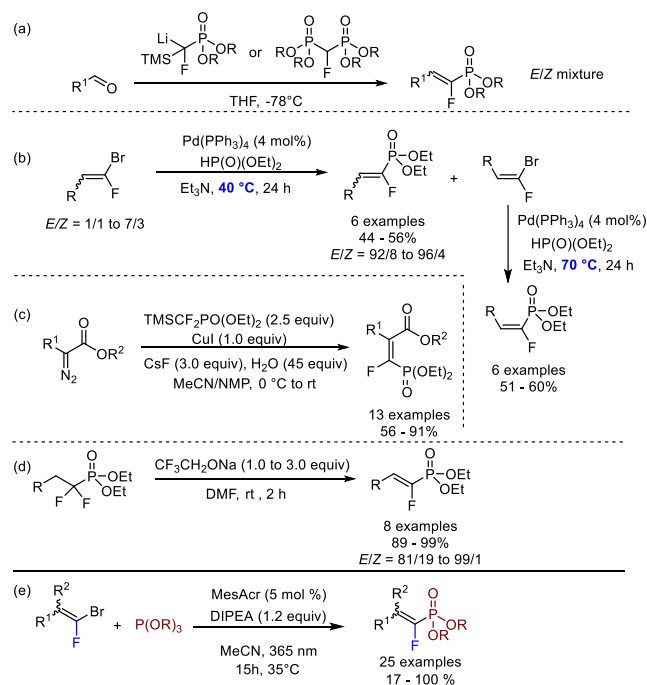
ABSTRACT: *gem*-Bromofluoroalkenes have been combined with phosphite under irradiation, in the presence of Fukuzumi's catalyst (9-mesityl-10-methylacridinium perchlorate) as organic photocatalyst, to provide valuable *gem*-fluorophosphonate derivatives, known as stable mimics of phosphates. The desired products were obtained in good to excellent yields and the reaction showed very good chemical tolerance. .

Among the organofluorinated molecules, the fluoroalkenes are recognized as a pivotal class of compounds towards the synthesis of materials,¹ bioactive compounds² or ¹⁹F NMR labeling,³ for example. Besides the recognition of the fluoroalkene moiety as a bioisostere of the peptide/amide bond,⁴ when a phosphonate is present in *gem*-position in the fluoroalkene motif, the latter became a stable phosphate mimic. Phosphate-containing biomolecules⁵ are ubiquitous in life sciences but since the phosphate moiety is sensitive to hydrolysis, stable phosphate mimics are of prime importance. Among the existing mimics, vinylphosphonate proved to be an excellent mimic of phosphate and has been already used, for example, in the design of more stable small-interfering RNA (siRNA).⁶ Since the pioneering work of Blackburn showing the potency of fluorovinylphosphonate to also act as a stable mimic of phosphate,⁷ these moieties have been used with success to enhance the metabolic stability of biomolecules.⁸

The usual general syntheses of these fluorovinylphosphonates⁹ relied on olefination reaction (Scheme 1a),^{7,10} metal-transition catalysis (Scheme 1b-c)^{9a,11} or elimination of fluoride (Scheme 1d).¹² These methods usually required the multi-step synthesis of fluorinated reagent, the use of metal-catalyst or the manipulation of hazardous compounds.

We previously showed that access to (*E*)-(1-fluoro-2-arylvinyl)phosphine boranes can easily be achieved by

Scheme 1. Access to fluorovinylphosphonates



reacting diphenylphosphine borane with *gem*-bromofluoroalkenes in the presence of a base.¹³ Mechanistic studies revealed that the reaction proceeds through a radical mechanism where the *gem*-bromofluoroalkenes is reduced (SET) by the diphenylphosphine borane anion, generated *in situ*. However, given the high nucleophilicity and Lewis basicity of the phosphorus anion, the scope

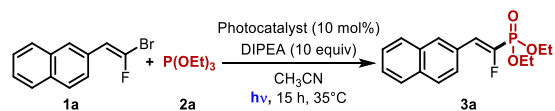
of the reaction was narrow and many functionalities were not tolerated. Based on these results, we reasoned that the single electron reduction of *gem*-bromofluoroalkenes could be accomplished by a well-selected photocatalyst under visible light irradiation. The generated fluoroalkenyl radical can then be trapped by a phosphite to yield the desired fluorovinylphosphonates under mild reaction conditions. Our working hypothesis is supported by the seminal work of König *et al.* who showed the efficiency of Rhodamine 6G to catalyze the reaction of aryl bromides with phosphite to form arylphosphonates.¹⁴ Thus, herein we reported an easy photocatalyzed free-metal access to fluorovinylphosphonates from *gem*-bromofluoroalkenes and trialkylphosphites in the presence of an organic photocatalyst under UV-light irradiation (Scheme 1e).

We started the optimization process by carrying out the reaction between the (*E*)-2-(*gem*-bromofluorovinyl)-naphthalene **1a** and triethylphosphite **2a**. Worthy of note that our previous experimental reaction conditions to synthesize (*E*)-(1-fluoro-2-arylvinyl)phosphine borane complexes¹³ totally failed, as expected, when the phosphite was used in place of the diphenylphosphine borane whereas those described by König¹⁴ gave a low but promising 6% of yield in product **3a**. Taking into account this relevant result, we decided to optimize the reaction varying the experimental conditions (Table 1). Changing the solvent for acetonitrile allowed the enhancement of the yield to 45% (Table 1, entry 1). During the course of the reaction, product **3a** was obtained alongside with two side-products in low quantities, the debrominated (*Z*)-2-(fluorovinyl)-naphthalene **4a** and the diethylphosphite **5**. Starting from *E*-substrate **1a**, the product **3a** was only obtained as the *E*-isomer without trace of the *Z*-isomer. This result is in good agreement with previous statement made by Galli *et al.*¹⁵ and later by Lodder *et al.*¹⁶ about the configurational stability of the fluorovinyl radical. Other photocatalysts were tested and the best result was obtained with the Fukuzumi's catalyst (9-mesityl-10-methylacridinium perchlorate), showcasing again the high power of acridinium species to act as efficient photocatalyst¹⁷ (Table 1, entries 2-6). Other irradiation wavelengths were studied¹⁸ and, surprisingly, the best result with MesAcr was obtained under UV irradiation at 365 nm (Table 1, entries 8-9). Other solvents were tested without increase the yield of the product **3a**.¹⁸ Using more or less triethylphosphite decreased the yield of **3a** (Table 1, entries 9-10).

Finally, we studied several combinations¹⁸ of catalyst loading and equivalent of sacrificial electron donor and using 5 mol% of organophotocatalyst with 1.2 equivalent of DIPEA proved to be as efficient as the standard conditions with 10 mol% of MesAcr and 10 equivalents of DIPEA (Table 1, entry 11). To note that DIPEA was tested among other electron donors (DBU, NEt₃...) and proved to be the better sacrificial reagent for our reaction.¹⁸

Control experiments showed that the reaction did not proceed in absence of photocatalyst or irradiation (Table 1, entries 12-13).

Table 1. Optimization of the organocatalyzed phosphonylation reaction^a



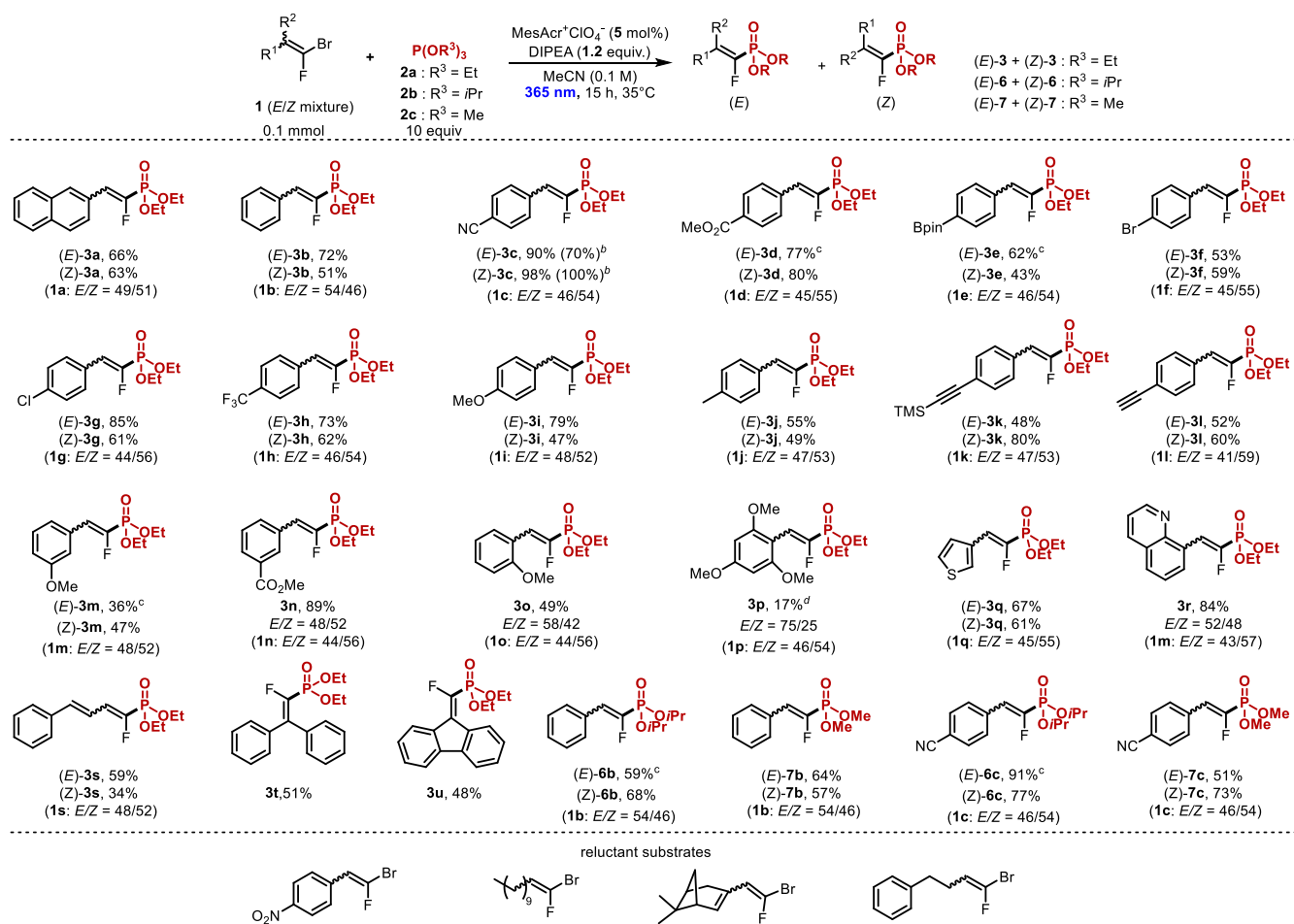
Entry	Photocatalyst	hv	NMR Yield of 3a (%)
1	Rh6G	405	45
2	Eosin Y	405	8
3	Ru(bpy) ₃	405	49
4	4CzIPN	450	nd
5	PTH	365	nd

6	MesAcr ⁺ ClO ₄ ⁻	405	58
7	MesAcr ⁺ ClO ₄ ⁻	450	31
8	MesAcr ⁺ ClO ₄ ⁻	365	65
9 ^b	MesAcr ⁺ ClO ₄ ⁻	365	46
10 ^c	MesAcr ⁺ ClO ₄ ⁻	365	55
11 ^d	MesAcr ⁺ ClO ₄ ⁻	365	63
12	-	365	traces
13	MesAcr ⁺ ClO ₄ ⁻	-	nd

^aReactions performed on 0.1 mmol scale using 10 equiv of **2a** and [**1a**] = 0.2M. ^bWith 5 equiv of P(OEt)₃. ^cWith 20 equiv of P(OEt)₃. ^dReaction performed with 5 mol% of MesAcr and 1.2 equiv of DIPEA. nd = not detected.

With the optimized reaction conditions in hand, *i.e.* 1.2 equiv of DIPEA, 10 equiv of phosphite, 5 mol% of MesAcr in acetonitrile under 365 nm irradiation, we studied the scope of the reaction (Scheme 2). Nevertheless, as we were interested to get *E*- and *Z*-isomers of the fluorovinylphosphonate, we decided to study the scope of the reaction on a *E/Z* mixture of *gem*-bromofluoroalkenes. *E/Z* ratio of the products **3** in the crude of the reaction was always corresponding to the *E/Z* mixture of *gem*-bromofluoroalkenes **1** introduced in the reaction media, excepted for ortho-substituted substrates **1** for which the ratio is modified in favor of the more stable *E* isomer, probably due to steric hindrance. Fortunately, it was possible to separate *E*- and *Z*-isomers of product **3** most of the time, so the yields indicated in the scheme 2 correspond to isolated yields of each isomer, based on the amount of each isomer in the *E/Z* mixture of substrate **1**. Unsubstituted naphthyl and phenyl products **3a** and **3b** were obtained in good yields. The presence of *para*-cyano-substituent on the phenyl ring allowed to get the product **3c** in quantitative yield. This substrate was then used to scale up the reaction and a global yield of 86% of (*E*- and (*Z*)-**3c** was obtained starting from 1 mmol of **1c**. Other products bearing a valuable *para*-substituent for post-functionalization, such as an ester moiety (**3d**), a pinacolborane (**3e**), a bromine (**3f**) or a chlorine atom (**3g**) were also obtained in moderate to very good yields (43-85%). It should be noted that in our conditions, no side-product from photo-Arbuzov reaction between phosphite and aryl bromide occurred.¹⁴ The presence of electron-withdrawing or electron-donating group on the aromatic moiety was well tolerated and products with trifluoromethyl (**3h**), methoxy (**3i**) or methyl group (**3j**) in *para*-position were obtained in fair to good yields (47-79%).

Scheme 2. Scope of the reaction.^a



^aReaction conditions: **1** (0.1 mmol), **2a** (1 mmol), DIPEA (0.12 mmol), MesAc (5 mol%) in acetonitrile (1 mL) at 35 °C for 15 h. Isolated yields. ^bOne mmol scale. ^ccontaminated with a small amount of *Z*-isomer. ^dinseparable mixture of **3p**/phosphorous side-products in 1:1 ratio.²⁰

Products bearing a substituted (**3k**) or unsubstituted alkyne (**3l**) at *para*-position were also obtained in good yields. Substituent in *meta*-position, whatever their electronic nature, were also well tolerated furnishing the corresponding products **3m** in fair yield and **3n** in very good yield (89%), albeit as an inseparable *E/Z* mixture for the latter. The presence of a methoxy group in *ortho*-position did not prevent the reaction and the mono-substituted compound **3o** was produced in moderate 49% yield. Nevertheless, the polysubstituted product **3p** was only produced in low 17% yield, probably due to steric hindrance, as a mixture with other phosphorous-containing side-products. The reaction can also be carried out with success in the presence of heterocycle yielding a thiophene (**3q**) or quinoline (**3r**) derivatives in 64% and 84% global yields, respectively. Finally, the reaction could also be applied to conjugated alkene or tetrasubstituted *gem*-bromofluoroalkenes giving the corresponding products **3s**, **3t** and **3u**, in moderate yields. Other trialkylphosphites could also be used in the reaction. Tri(*iso*-propyl)phosphite **2b** as well as trimethylphosphite **2c** gave good to excellent yields in corresponding products **6** and **7**, respectively. Some *gem*-bromofluoroalkenes substrates proved to be reluctant such as the *para*-nitrophenyl or alkyl derivatives.

Control experiments were conducted to get more insights into the reaction mechanism. The light on/ light off experiments confirmed that the light is crucial to trigger the reaction.¹⁸ The addition of 2,2,6,6-tetramethylpiperidine 1-oxyl (TEMPO) as radical inhibitor began to

inhibit the reaction above 2 equivalents and totally inhibited the reaction when 10 equivalents were added. This result could be explained because the triethylphosphite is also a radical trapping agent, and the same quantity of TEMPO compared to the triethylphosphite is necessary to totally quench the reaction.¹⁸ Nevertheless, we were unable to detect a TEMPO-adduct in the reaction media. When trapping agent 2,6-di-*tert*-butyl-4-methylphenol (BHT) was added in the reaction media in absence of triethylphosphite **2a**, the major compound formed was the debrominated (*Z*)-2-(fluorovinyl)-naphthalene **4a**.¹⁸ The measured quantum yield supports a radical chain mechanism ($\phi = 3.02$).¹⁸ Then, considering the ability of MesAc to emit upon excitation at 365 nm, this organophotocatalyst was submitted to Stern–Volmer quenching experiments.¹⁸ Whereas no interaction occurred between the MesAc* and the phosphite or between the MesAc* and the *gem*-bromofluoroalkene **1**, a direct interaction occurred between the excited state of MesAc and the DIPEA (Figure 1). So, based on our preliminary mechanistic experiments and on previous work, we propose the mechanism depicted in Scheme 3. It starts with the excitation of Mes-Acr at 365 nm to generate the highly oxidative state (Mes-Acr)* that interacts with DIPEA to generate the corresponding aminium radical cation. At this stage, two scenarios might be considered: (i) the formation of α -aminoalkyl radical that may promote the homolytic activation of carbon-bromine bond as previously demonstrated by Leonori and

coworkers for alkyl- and aryl-halides,¹⁹ or (ii) single electron reduction of our *gem*-bromofluoroalkenes by the reduced form of the catalyst (Mes-Acr[•]). As shown in Table 1, Leonori's conditions for the generation of α -aminoalkyl radicals, *i.e.* 4CzIPN as a photocatalyst and DIPEA, were not compatible with our reaction as only by-products were detected at the end of the reaction. This indicates that halogen atom transfer mechanism (XAT) is probably not involved in our reaction. The second possibility (ii) is also unlikely thermodynamically ($\Delta G^\circ = +23.1$ kcal/mol) based on the redox potentials of **1** ($E^\circ = -1.59$ V/SCE) and Mes-Acr[•]/Mes-Acr ($E^\circ = -0.57$ V/SCE), respectively. At this stage, the only reasonable possibility we retain is the excitation of the acridine radical with a second photon to generate a highly reductive state (Mes-Acr^{••}) that can cleave the C-Br bond of **1** to form the fluorovinyl radical. The latter is subsequently trapped with the phosphite to form a phosphoranyl radical that undergoes a rapid β -scission to yield the desired adduct **3**.¹⁸ Worthy of note that the ability of the acridine radical to act as photoreducing species was recently reported by Nicewicz and also by Gianetti for structurally related radical species,²⁰ although different from the simple Fukuzumi's catalyst we used. Nevertheless, the two-photon mechanism should be proved and the quantum yield supporting a radical chain mechanism has also to be explained that is why we are currently working of these mechanistic aspects and our results will be reported in due course. In summary, we developed an efficient synthesis of fluorovinylphosphonates by photocatalysis under metal-free mild conditions. The reaction proved to be highly tolerant and can be applied to the formation of products substituted by relevant moieties for post-functionalization, such as a cyano, a boronic pinacol ester or halogen atoms. While the reaction is not efficient for alkyl substrates, the reaction proved to be very efficient for aromatic and heteroaromatic *gem*-bromofluoroalkenes. Conjugated alkenes as well as tetrasubstituted alkenes are also suitable substrates for the reaction. Most of the products could be isolated in both *E*- and *Z*-configuration. To confirm our mechanistic hypotheses, more experiments are required and currently under investigation.

ASSOCIATED CONTENT

Data Availability Statement

The data underlying this study are available in the published article and its online supplementary material.

Supporting Information

The Supporting Information is available free of charge at <https://pubs.acs.org/doi/> Reaction optimization, experimental procedures, characterization data, copies of ¹H, ¹³C, ¹⁹F and ³¹P NMR spectra (PDF)

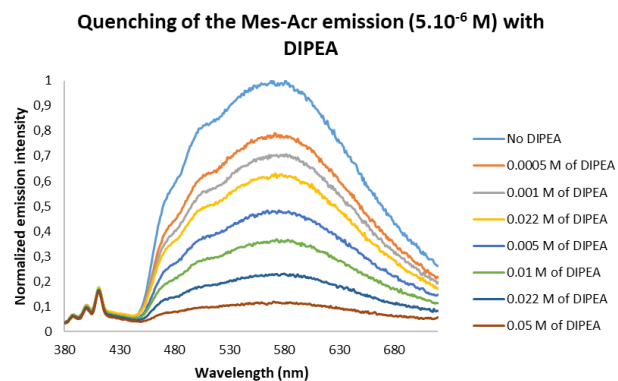


Figure 1. Stern-Volmer quenching experiments

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Notes

The authors declare no competing financial interest.

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