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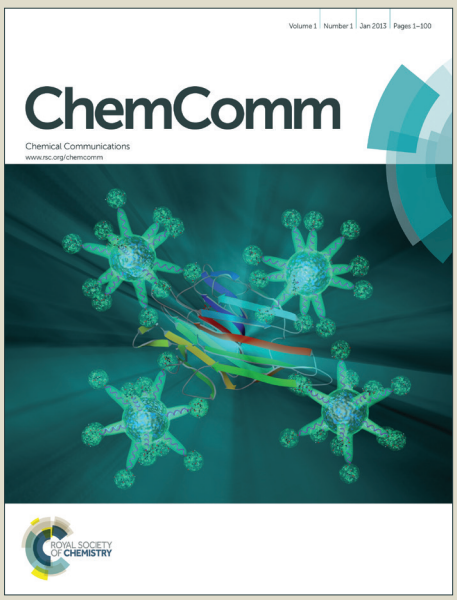

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Direct C−H Difluoromethylenephosphonation of Arenes and Heteroarenes with Bromodifluoromethyl phosphonate *via* Visible-Light Photocatalysis

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This paper reports a room temperature visible-light-driven protocol for the C−H difluoromethylenephosphonation of arenes and heteroarenes. Using a commercially available diethyl bromodifluoromethylphosphonate as a precursor of difluoromethyl radical, *fac*-Ir(ppy)$_3$ as a photosensitizer and a 3W blue LED as a light source, an array of aromatic compounds containing difluoromethylenephosphonyl group were prepared directly from the corresponding arenes and heteroarenes in excellent to moderate yields.

Aromatic molecules containing difluoromethylenephosphonyl (DFMP) group are of significant biological importance as phosphate mimics in living organisms.[1] One of the most striking and pioneering examples of the applications is the inhibition of protein tyrosine phosphatases (PTPs) with F2Pmp (Fig. 1).[2] Up to now, numerous aromatic compounds having the DFMP moieties display properties that afford them utility in biomedical studies.[3] Thus, methods for the efficient introduction of DFMP groups into benzenoid and heteroaromatic substrates are of high interest.[4] Generally, these bioactive molecules could be obtained via fluorination of the corresponding α-keto or benzylic phosphonate,[4a, 4b] and copper-mediated cross-coupling between aryl halides and metalated difluoromethylphosphonates.[4d-4h]

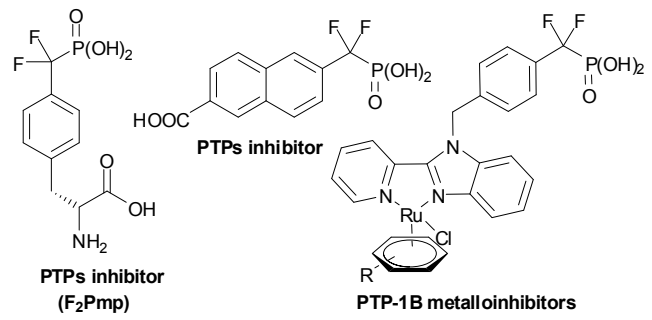
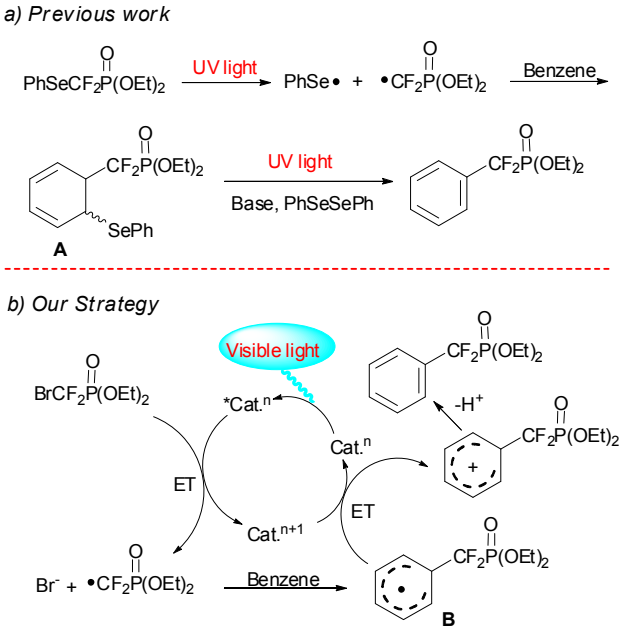


Fig. 1. Examples of biologically significant aromatic molecules containing DFMP.

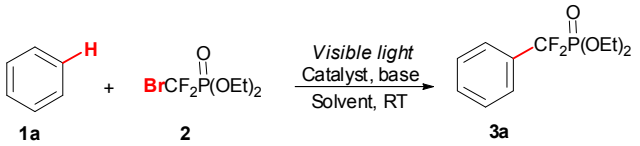
Very recently, Qing *et al.* and Zhang *et al.* have shown that aryldifluorophosphonates can be prepared from aryl boronic acids by copper-mediated oxidative coupling[4i] and palladium-catalyzed cross-coupling.[4j] These valuable protocols have proven to be efficient for the preparation of aryldifluorophosphonic acids and their derivatives. Nevertheless, the production of a large excess of wastes from reaction systems, the necessity of directing groups, as well as the requirement for prefunctionalization remain impediments of these approaches. Therefore the development of more concise and milder methods in these areas would be highly desirable from both synthetic and atom-economic points of view.



Scheme 1. Photochemical strategies for direct C−H difluoromethylenephosphonation of arenes and heteroarenes.

A potentially very promising method for constructing DFMP-substituted aromatic molecules is the direct functionalization of arenes and heteroarenes through addition of phosphonodifluoromethyl (PDFM) radicals to aromatic rings. It has been reported that PDFM radicals can be generated from the corresponding sulfanyl and selanyldifluoromethylphosphonates in the presence of tri-*n*-butyltin hydride and a catalytic amount of AIBN.[5] Later on, Fuchigami *et al.*[6] demonstrated that UV photolysis of phenylselanyldifluoromethylphosphonate releases phenylselanyl radical and PDFM radical, which can add to aromatic molecules to form intermidate A (Scheme 1). Further photolysis of A in the presence of 2,4,6-trimethylpyridine and diphenyl diselenide provides DFMP-substituted aromatic molecules in good to moderate yields. Recently, visible-light photoredox catalysis is emerging as a powerful tool to generate organic radicals.[7-9] We hypothesized that visible-light photoredox catalysis could be used to form PDFM radical under much milder conditions from readily available commercially available diethyl bromodifluoromethylphosphonate. We anticipated that the electron transfer (ET) from the excited photoredox catalyst to bromodifluoromethylphosphonate would generate PDFM radical. The PDFM radical then reacted with arene to form radical B. Further ET from radical B to the oxidized photoredox catalyst afforded the DFMP-substituted product and fulfilled the catalytic cycle (Scheme 1).

Table 1. Optimization of reaction conditions

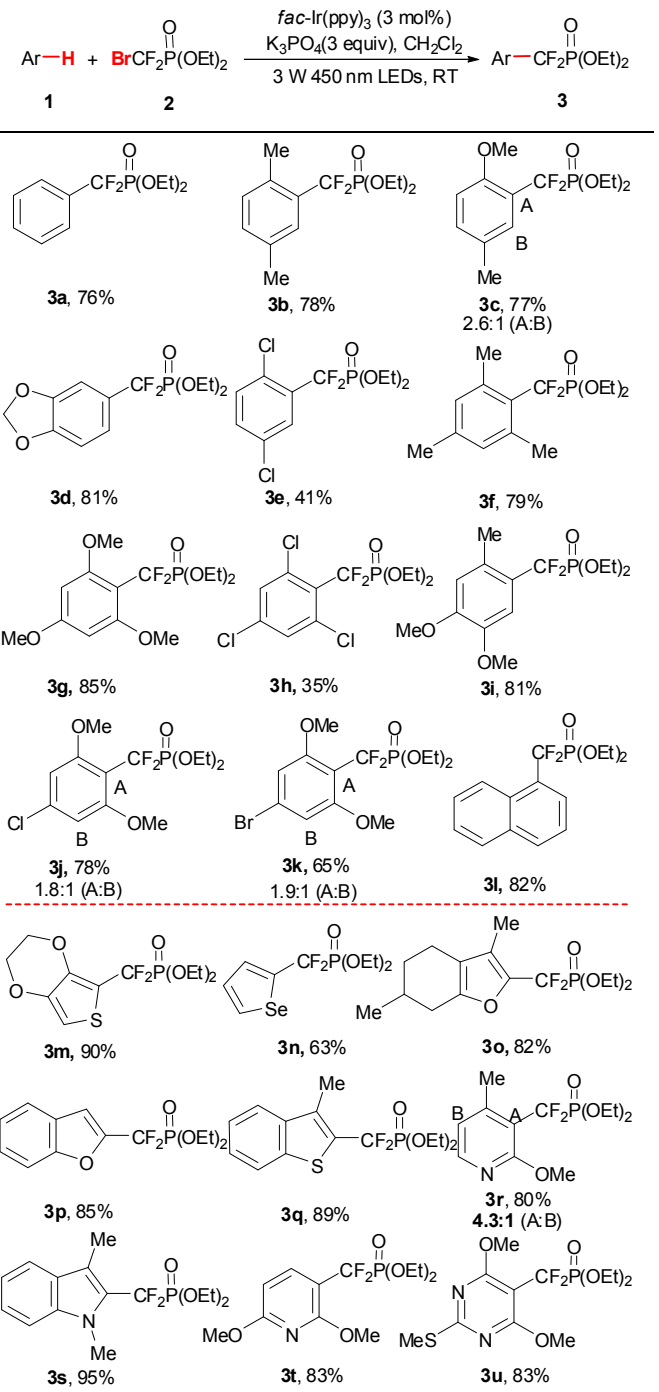


1a **2** **3a**

Entry [a]	Solvent	Base	Catalyst	Yield (%) [b]
1	CH_3CN	KOAc	$Ir(ppy)_3$	15
2	DMF	KOAc	$Ir(ppy)_3$	42
3	DMSO	KOAc	$Ir(ppy)_3$	47
4	MeOH	KOAc	$Ir(ppy)_3$	0
5	CH_2Cl_2	KOAc	$Ir(ppy)_3$	65
6	CH_2Cl_2	NaOAc	$Ir(ppy)_3$	51
7	**CH_2Cl_2**	**K_3PO_4**	$Ir(ppy)_3$	**81(76[c])**
8	CH_2Cl_2	t-BuOK	$Ir(ppy)_3$	0
9	CH_2Cl_2	K_2CO_3	$Ir(ppy)_3$	55
10	CH_2Cl_2	CS_2CO_3	$Ir(ppy)_3$	74
11	CH_2Cl_2	CsF	$Ir(ppy)_3$	21
12	CH_2Cl_2	K_3PO_4	$Ir(dtbbpy(ppy)_2PF_6$	0
13	CH_2Cl_2	K_3PO_4	$Ru(bpy)_3Cl_2$	0
14	CH_2Cl_2	K_3PO_4	$Ru(phen)_3Cl_2$	0
15[d]	CH_2Cl_2	K_3PO_4	$Ir(ppy)_3$	86
16[e]	CH_2Cl_2	K_3PO_4	$Ir(ppy)_3$	37
17	CH_2Cl_2	K_3PO_4	-	N.R.
18[f]	CH_2Cl_2	K_3PO_4	$Ir(ppy)_3$	N.R.

[a] Reaction conditions: **1a** (2.0 mmol, 10 equiv), **2** (0.2 mmol, 1.0 equiv), base (0.6 mmol, 3.0 equiv), and photocatalyst (0.006 mmol, 3.0 mol%) in dry solvent (2.0 mL) was irradiated with a 3 W blue LED for 36 h. [b] Determined by ^{19}F NMR using fluorobenzene as internal standard. [c] Yield of isolated product. [d] 20 equiv **1a** was used. [e] 5 equiv **1a** was used. [f] No irradiation. DMF = *N,N*- dimethylformamide, DMSO = dimethylsulfoxide.

Table 2. Scope of the difluoromethylenephosphonation

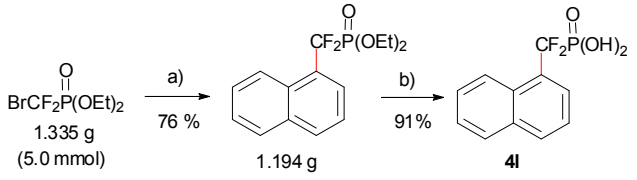


[a] Reaction conditions: **1** (2.0 mmol,10 equiv), **2** (0.2 mmol, 1.0 equiv), K_3PO_4 (0.6 mmol, 3.0 equiv), and *fac*-$Ir(ppy)_3$ (0.006 mmol, 3.0 mol%) in dry CH_2Cl_2 (2.0 mL) was irradiated with a 3 W blue LED for 36 h at RT. [b] Isolated yield.

We started our investigation by exploring the reaction of benzene and diethyl bromodifluoromethylphosphonate **2** in various photochemical conditions. It was encouraging to see that the reaction of benzene with **2** in a CH_3CN solution containing *fac*-

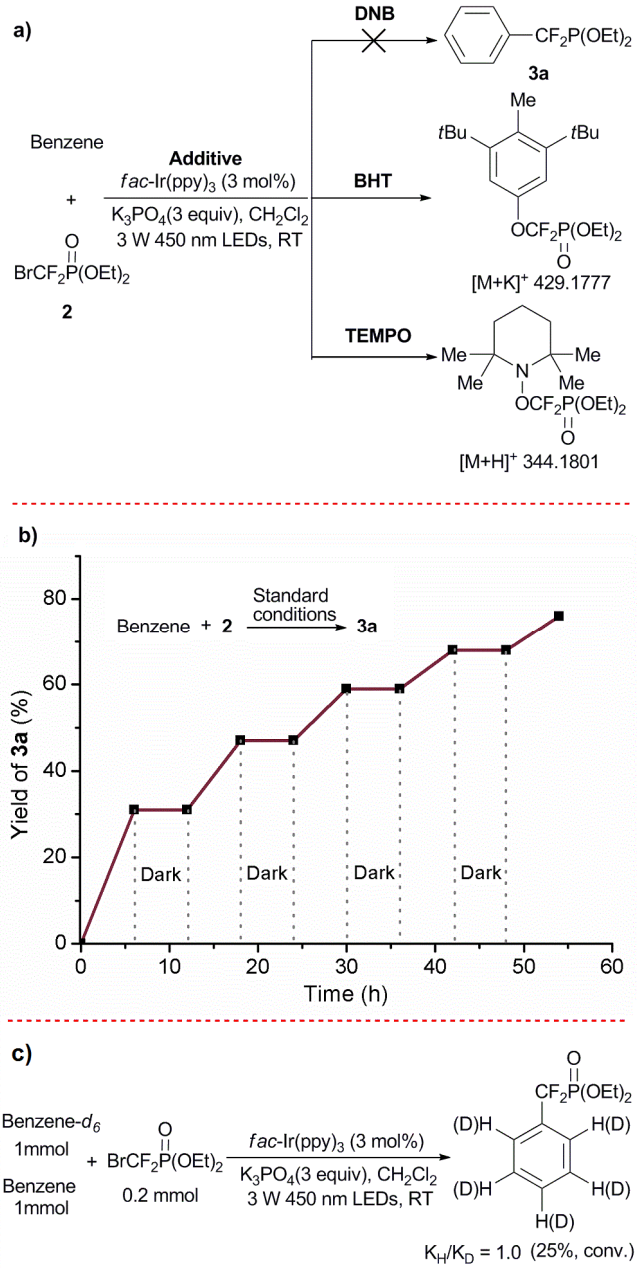
$Ir(ppy)_3$ as a photocatalyst and potassium acetate (KOAc) as a base provided the aimed product **3a** in 15% yield after 36 h of irradiation (blue LEDs, λ =450 nm) at room temperature (Table 1, entry 1). Several solvents such as DMF, DMSO and CH_2Cl_2 were applied to this reaction to replace CH_3CN (Table 1, entries 2-5), and CH_2Cl_2 was chosen as the ideal organic solvent for the reaction. Other different bases including NaOAc, K_3PO_4, t-BuOK, K_2CO_3, Cs_2CO_3, and CsF were then tested (Table 1, entries 6-11), it was glad to see that the yield of **3a** was improved to 81% in the presence of K_3PO_4. Next, several typical Ru- and Ir-photocatalysts were studied for their efficiency (Table 1, entries 12-14). Disappointingly, the reaction did not work in any of these catalyst except *fac*-$Ir(ppy)_3$. In addition, enhancing the amount of benzene slightly increased the yield of **3a** (Table 1, entry 15), and the attempt to reduce the amount of benzene caused a significantly decreased yield (Table 1, entry 16). Moreover, control experiments established the importance of both visible light and the photocatalyst, as no desired reaction was observed in the absence of light and *fac*-$Ir(ppy)_3$.

With optimized conditions in hand, we examined the substrate scope of this visible-light-driven direct difluoromethylene phosphonation by reacting structurally and electronically diverse arenes and heteroarenes with diethyl bromodifluoromethylphosphonate **2** (Table 2). A broad array of substituted benzenes can be efficiently react with **2** to generate corresponding DFMP-substituted derivatives in good to moderate yields (Table 2, **3a**-**3k**). In general, arenes bearing electron-withdrawing substituents afforded lower yields than those with electron-donor groups. The site selectivity of these reactions is consistent with that anticipated for a radical aromatic substitution pathway.[7a, 8e] For example, with the arenes bearing different substituents, the corresponding products were formed as a mixture of regioisomers (Table 2, **3c**, **3j**, **3k**). The DFMP groups prefer to locate in the position where there is greater electron density, indicating the PDFM radical is electrophilic. Further exploration of the substrate scope was carried out by reacting bromodifluoromethylphosphonate **2** with heteroarenes. As shown in table 2, thiophene, selenophene, furan, benzofuran, benzothiophene, indole, pyridine and pyrimidine substrates were compatible with this new difluoroacetamidation approach (**3m**–**3u**, 63–95% yield). Because these heteroarenes are valuable motifs in biological and medical chemistry, the present method is expected to be useful for synthesis of bioactive heteroarenes containing DFMP moieties.



Scheme 2. Gram-scale synthesis of PTPs inhibitor **4l**. Reaction condition: a) naphthalene (50 mmol), K_3PO_4 (15 mmol), *fac*-$Ir(ppy)_3$ (0.015 mmol), CH_2Cl_2 (50 mL), irradiated with blue LEDs for 36 h. b) ⅰ) TMSBr (7.0 mmol), CH_2Cl_2 (20 mL), RT, 20 h; ⅱ) MeOH-H_2O (13:1, v/v) 20 mL, RT, 2 h.

The importance and utility of this method is further illustrated by its application synthesis PTPs inhibitor **4l** [4a, 4b] on a gram scale. As shown in Scheme 2, the photoreactions of bromodifluoromethyl phosphonate **2** (5.0 mmol) with naphthalene (50 mmol) in the presence of *fac*-$Ir(ppy)_3$ and K_3PO_4 afforded α-DFMP-substituted naphthalene **3l** in 76 % isolated yield. Further hydrolysis of phosphonate esters **3l** using bromotrimethylsilane (TMSBr) produced the desired PTPs inhibitor **4l** in excellent yield.



Scheme 3. Mechanism investigation

A series of experiments were performed to certify the mechanism of this transformation (Scheme 3). Addition of 2 equiv of 1,4-dinitrobenzene (DNB), an ET scavenger to the reaction mixture of benzene and **2** under the standard condition

fully suppressed the formation of **3a**, indicating the reaction takes place though the ET from the excited *fac*-Ir(ppy)$_3$ to **2**. Further evidence for the ET procedure is supported by electrochemical study. Compound **2** shows an irreversible reduction event at -0.84 V (vs. SCE in CH_3CN). Because the potential for *fac*-Ir(ppy)$_3$*→fac-Ir(ppy)$_3^{+\bullet}$ couple is -1.73 V (vs SCE, in CH_3CN), [9] The ET from the excited state of *fac*-Ir(ppy)$_3$ to **2** is exothermic. When radical inhibitors such as BHT and TEMPO were introduced into the photocatalytic system, no target product was detected. To our delight, the adducts of the two radical inhibitors with DFMP were detected by ESI-HRMS, thus providing straightforward evidence of a PDFM radical formation. In addition to the trapping investigations, an off/on light profile over time was carried out. It was observed that this production of **3a** requires continuous irradiation of visible light (Scheme 3, b). The result indicates that radical chain propagation is not the major reaction pathway. To understand rate-determining step for the photoreaction, the reaction of a 1:1 mixture of benzene and benzene-d_6 with **2** was performed under the standard condition. The intermolecular KIE was found to be 1.0 after 25% conversion, indicating that the C-H bond fission of benzene is not rate-determining in the photoredox catalytic cycle.

In conclusion, we have described the first visible-light-driven difluoromethylenephosphonation of arenes and heteroarenes. By employing inexpensive and commercial availably diethyl bromodifluoromethylphosphonates as the PDFM radical precursors and *fac*-Ir(ppy)$_3$ as the photocatalyst, we have successfully realized the preparation of DFMP substituted aromatic molecules directly from the corresponding arenes. The reaction proceeds at room temperature with a commercial blue LED as a light source, providing a mild, concise and attractive alternative to the previously developed methods.[4] Further investigations to apply this new protocol to more complex molecules are underway in our laboratory.

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Notes and references

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† Electronic Supplementary Information (ESI) available: Experimental procedures, characterization data, and copies of NMR spectra. See DOI: 10.1039/c000000x/

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