Organic LETTERS
Letter
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Reactions of *gem*-Difluorinated Phosphonium Salts Induced by Light

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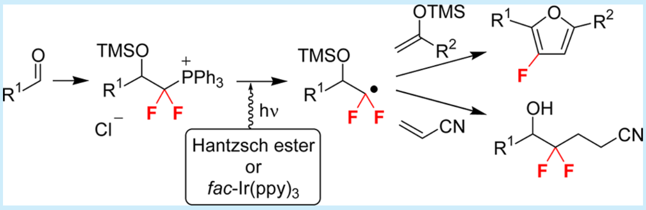
Ⓢ *Supporting Information*

ABSTRACT: *gem*-Difluorinated phosphonium salts, which are readily obtained from aldehydes and difluoromethylene phosphobetaine, can serve as a source of radicals under reductive conditions. An iridium complex or Hantzsch ester was used as a one-electron reducing agent when irradiated with visible light. The fluorinated radicals were trapped with various alkenes, leading to products either via a photoredox cycle (for the iridium catalyst) or via a hydrogen atom transfer (for the Hantzsch ester).



The importance of *gem*-difluorinated compounds for medicinal chemistry[1] has stimulated intensive studies for the synthesis of compounds of this type. Besides classic approaches based on deoxofluorination[2] and the application of building blocks,[3] the use of difluorocarbene and related reagents has recently emerged as an attractive method for the straightforward access to CF_2-substituted products.[4−7]

Visible-light-mediated reactions came to the forefront of organic chemistry during past few years.[8] The simplicity of procedures defined by the ready availability of light sources (household bulbs or cheap LED strips) in combination with novel synthetic opportunities have sparked the interest of many research groups toward this field. Frequently, the role of light is to activate a catalyst to serve as a reducing agent with respect to a substrate. Perfluorinated bromides and iodides,[9] as well as iodine(III) reagents,[10] sulfochlorides,[11] and sulfonium salts,[12] proved to be good substrates for accepting one electron with concomitant generation of fluorinated radicals. Herein, we demonstrate that *gem*-difluorinated phosphonium salts **2**, which can be generated from readily available difluoromethylene phosphabetaine (**1**),[7] can be involved in visible-light-induced generation of functionalized fluorinated radical species **3** (Scheme 1).[13]

Scheme 1. Generation of Fluorinated Radicals

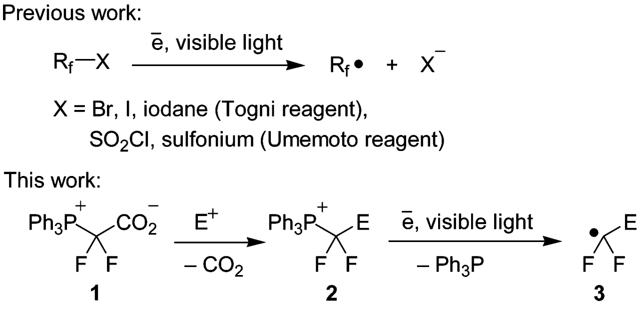
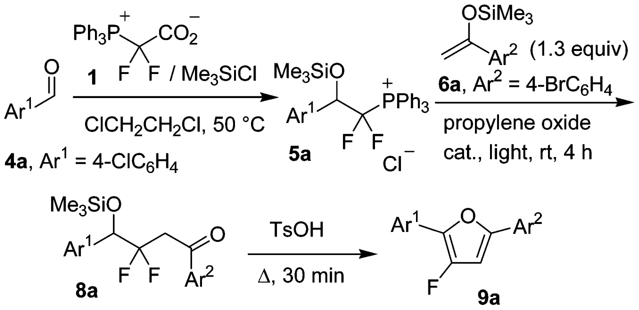


Table 1. Reaction of 4-Chlorobenzaldehyde



entry	cat. (mol %)	light	yield of **8a** (%)[a]
1	eosin Y (1)	blue LED	0
2	$Ru(bipy)_3Cl_2$ (0.5)	blue LED	0
3	$Ir(ppy)_3$ (0.5)	400 nm LED	79 (73[b])
4		400 nm LED	0
5	$Ir(ppy)_3$ (0.5)		0

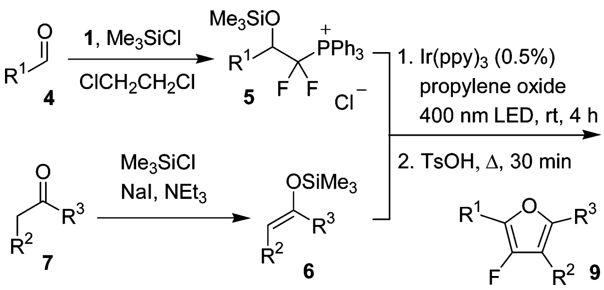
[a]Determined by ^{19}F NMR of reaction mixtures with 4-fluorotoluene as an internal standard. [b]Isolated yield of **9a**.

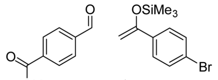
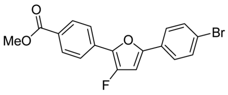
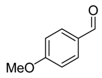
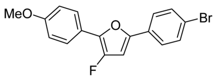
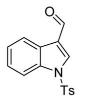
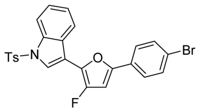
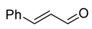
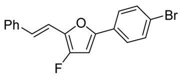
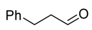
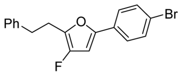
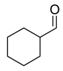
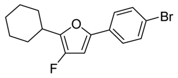
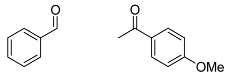
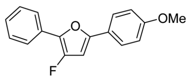
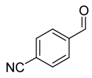
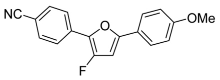
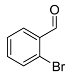
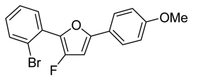
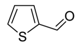
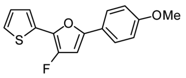
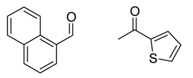
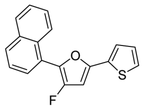
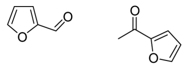
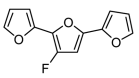
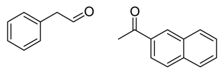
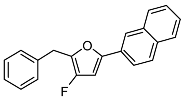
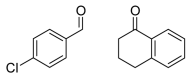
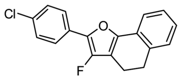
Phosphonium salt **5a**, generated from 4-chlorobenzaldehyde (**4a**), phosphobetaine **1**, and chlorosilane,[7] was selected as a model substrate, and its reaction with silyl enol ether **6a** derived from 4-bromoacetophenone (**7a**) was evaluated (Table 1). Reactions were performed in the presence of propylene oxide (2 equiv) to remove chlorosilane. The reaction mixture containing a photocatalyst was irradiated using an LED strip. With the sodium salt of eosin Y and $Ru(bipy)_3Cl_2$, starting salt **5a** remained unaffected. There was no reaction without light or

Received: January 13, 2016

DOI: 10.1021/acs.orglett.6b00117
Org. Lett. XXXX, XXX, XXX−XXX

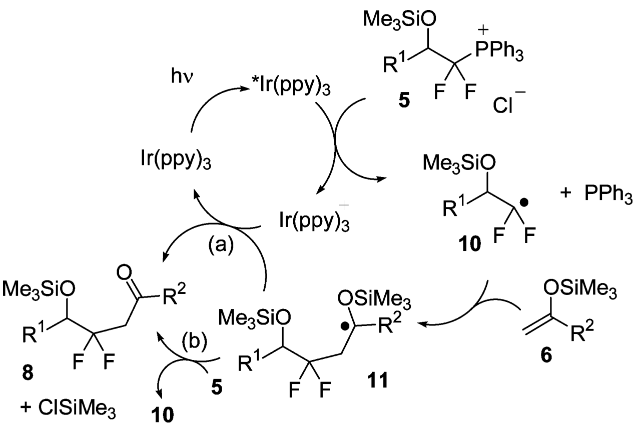
Table 2. Synthesis of Furans 9[a]



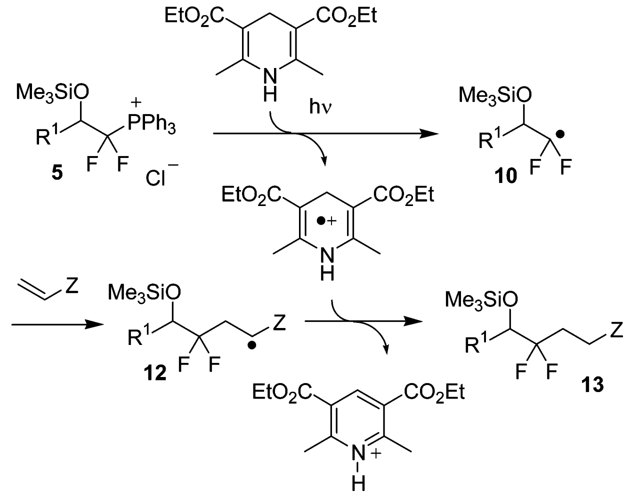
entry	substrates	product		yield (%)[b]
1	 **6a**		**9b**	82
2			**9c**	75
3			**9d**	68
4[c]			**9e**	53
5[c]			**9f**	55
6			**9g**	50
7			**9h**	93
8			**9i**	92
9			**9j**	98
10			**9k**	85
11[c]			**9l**	68
12[c]			**9m**	64
13			**9n**	50
14			**9o**	54

[a] Aldehyde **4** (1 equiv), **1** (1.2 equiv), Me_3SiCl (1.5 equiv), **6a** (1.3 equiv) or **7** (1.5 equiv), $Ir(ppy)_3$ (0.5 mol %), propylene oxide (2 equiv), TsOH (1 equiv). [b] Isolated yield. [c] Irradiation time was 12 h.

Scheme 2. Proposed Photoredox Mechanism



Scheme 3. Reaction of Hantzsch Ester



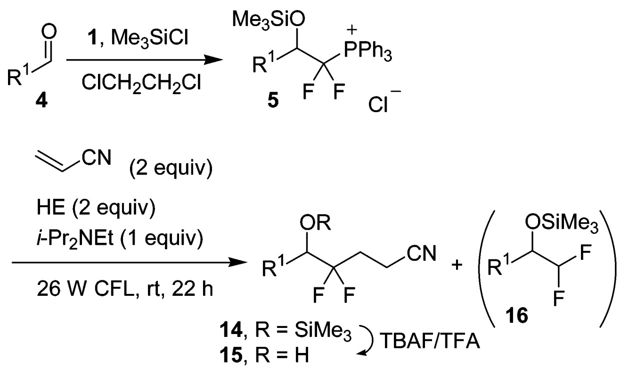
photocatalyst. With the iridium catalyst, *fac*-$Ir(ppy)_3$, primary product **8a** was formed in 79% yield (entry 3). However, attempts to purify ketone **8a** or the corresponding desilylated alcohol by column chromatography were unsuccessful—upon elution, the gradual formation of furan **9a** was noted. Accordingly, the reaction mixture was treated with toluenesulfonic acid at reflux for 30 min to effect cyclization, and furan **9a** was isolated in 73% yield.

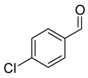
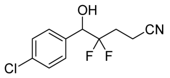
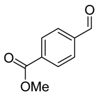
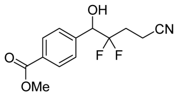
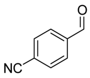
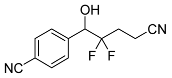
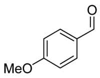
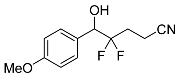
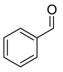
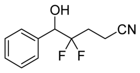
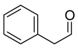
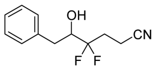
Under the optimized conditions, a series of aldehydes were reacted with silyl enol ethers **6** derived from ketones **7** (Table 2). However, preparation of analytically pure silyl enolates **6** requires distillation, which requires gram-scale experiments. Therefore, we employed a more practical millimole scale procedure for the synthesis of enolates **6** involving silylation of ketones **7** with the $Me_3SiCl/NaI/NEt_3$ system, followed by non-aqueous workup. The crude enolates **6** had >95% purity and were used for reactions with salts **5** without further purification.

Aromatic and heteroaromatic aldehydes usually gave good yields of furans **9**. Importantly, enolizable aldehydes also gave products, though in slightly reduced yields (Table 2, entries 5, 6, and 13). Unfortunately, reaction of silyl enol ether derived from cyclohexanone with salt **5a** did not give product, and salt **5a** remained unconsumed. The reason for this phenomenon is not clear at present.

Concerning the mechanism, we speculate that the photocatalytic cycle starts with single electron reduction of

Table 3. Reactions of Salts **5** with Acrylonitrile



entry	aldehyde	product		yield of **15** (%)[a]
1			**15a**	79
2			**15b**	88
3			**15c**	79
4			**15d**	68
5			**15e**	75
6			**15f**	73

[a]Isolated yield.

phosphonium salt **5**, generating radical **10** together with triphenylphosphine. Addition of the fluorinated radical to the electron-rich double bond provides radical species **11**, which is oxidized by the iridium complex, affording primary product **8** (path a). Alternatively, intermediate **11** may be directly oxidized by starting salt **5**, leading to a chain process (path b).

Inspired by the opportunity for the generation of radical **10**, we were interested in evaluating its reactivity with electron-deficient alkenes. However, for these alkenes, the photoredox cycle shown in Scheme 2 is not applicable because after addition of radical **10** at the C═C bond, a new radical would not be amenable to oxidation. Therefore, the latter radical should be trapped by another stoichiometric reagent.

According to literature data,[14,16] Hantzsch ester (HE) can serve as a reducing agent when irradiated with visible light, while its radical cation, as well as HE itself, can behave as a source of hydrogen. Correspondingly, the mechanistic scenario for the reaction of phosphonium salts **5** with electron-deficient alkenes is shown in Scheme 3.

When salt **5a** (R^1 = 4-ClC_6H_4) was reacted with acrylonitrile and HE under irradiation with a conventional CFL bulb, silyl ether **14a** was formed in about 30% yield (determined by ^{19}F NMR of the reaction mixture) along with oligomeric material.[15] We proposed that formation of oligomers is associated with inefficient trapping of radical **12**, which prefers to react with another molecule of acrylonitrile. Rewardingly, the addition of 1 equiv of Hünig's base as a source of hydrogen[16] led to an increase in yield of compound **14a** up to 79%. However, compound **16a** was also observed in about 10% yield, evidently formed by hydrogen atom transfer to fluorinated radical **10**.[17] Increasing the amount of Hünig's base neither increased the yield nor affected the ratio of **14**/**16**.

A series of aldehydes were involved in reaction with phosphobetaine **1** and subsequent coupling with acrylonitrile (Table 3). Typically, good yields of products **15** were observed for aromatic substrates. Phenylacetic aldehyde also worked well (entry 6). At the same time, in reactions of cinnamaldehyde and hydrocinnamaldehyde, no products were formed.

In summary, the cleavage of the carbon−phosphorus bond in difluorinated phosphonium salts by means of light-induced reducing agents with the generation of a radical species was described. The *gem*-difluorinated radical may interact either with electron-rich or with electron-poor alkenes under photoredox or hydrogen atom transfer conditions, respectively.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b00117.

Experimental procedures, compound characterization data, and copies of NMR spectra for all compounds (PDF)

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work was supported by the Russian Science Foundation (Project 14-13-00034).

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(16) In a control experiment performed in the dark, salt **5a** remained unconsumed (^{19}F NMR control). Therefore, light is needed for the reaction to proceed.

(17) Performing the reaction using LED 400 gave an increased amount of byproduct **16a**.

DOI: 10.1021/acs.orglett.6b00117
Org. Lett. XXXX, XXX, XXX−XXX