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Letter

Photocatalytic Palladium-Catalyzed Fluoroalkylation of Styrene Derivatives

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ABSTRACT: A visible light induced palladium-catalyzed fluoroalkylation method was developed. The Heck-type alkyl coupling reaction enables the introduction of trifluoroethyl, difluoroethyl and other fluoroalkyl fragment into styrenes under mild reaction conditions without the use of additional photosensitizers and ensures access to fluoroalkylated olefins on a broad scale.
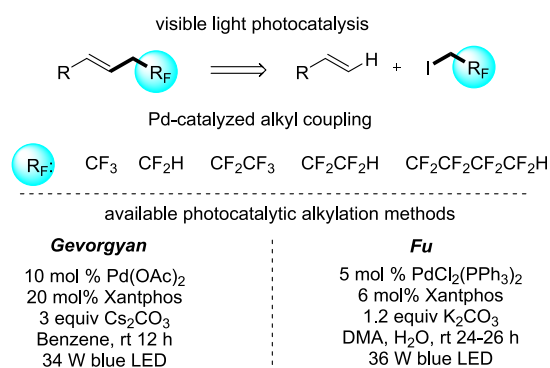

45 examples up to 86% isolated yield
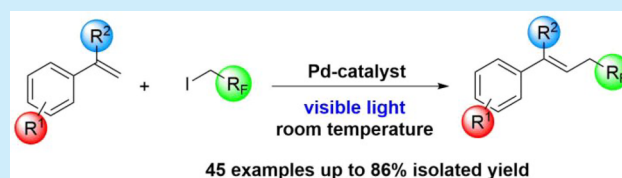
The introduction of fluorine-containing functional groups into organic molecules and drug candidates can often improve the enzymatic oxidative and thermal stability as well as increase the lipophilicity and bioavailability of molecules.[1] Therefore, in recent years the development of fluoroalkylating methods and reagents, especially trifluoromethylation[2] and trifluoroethylation,[3] has become an emerging area, including the photocatalytic transformations.[4]

Besides the fluoroalkylation of aromatic and heteroaromatic rings, the installation of short fluoroalkyl chains into terminal alkene is also important, but is a less explored transformation, which is mostly limited to perfluoroalkylation[5] and trifluoroethylation. There are several different strategies to construct the trifluoroethylated styrene structure. It can be synthesized by nucleophilic substitution from the corresponding allyl-bromide derivative,[6] oxidative trifluoromethylation,[7] classical transition metal coupling with vinyl-boronates,[8] or photocatalytic transformation[9] using the corresponding fluoroalkyl halides as coupling agents.

In continuation of our studies in the field of fluoroalkylation reactions[3a,b,10] and photocatalytic transformations,[11] we aimed to take advantage of the photo-Heck-type coupling approach to introduce more versatile fluoroalkyl groups into the styrene moiety using palladium catalysis and visible light irradiation (Scheme 1). The classical palladium catalyzed cross-coupling reaction[12] involves a well-established two-electron redox mechanism typically between the Pd(0)/Pd(II) oxidation states. However, using the original Heck reaction for the coupling of unactivated alkyl halides with aryl-alkenes is challenging because of two factors:[13] the oxidative addition step is relatively slow with low-valent transition metals, and the resulting alkylmetal species can undergo premature β-hydride elimination which leads to side products. These disadvantages can be eliminated by photoexcitation of the applied catalyst.[14] The photoexcited Pd-complexes can participate in a single-electron transfer (SET) mechanism to generate a Pd(I)-species, which allows the desired coupling to occur selectively in a photocatalytic manner. Two possible catalytic methods are

Scheme 1. Aim: Direct Fluoroalkylation of Styrene Derivatives

visible light photocatalysis

Pd-catalyzed alkyl coupling

R_F: CF₃ CF₂H CF₂CF₃ CF₂CF₂H CF₂CF₂CF₂CF₂H

available photocatalytic alkylation methods

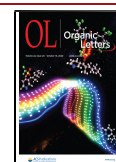| *Gevorgyan*	*Fu*
10 mol % Pd(OAc)₂	5 mol % PdCl₂(PPh₃)₂
20 mol% Xantphos	6 mol% Xantphos
3 equiv Cs₂CO₃	1.2 equiv K₂CO₃
Benzene, rt 12 h	DMA, H₂O, rt 24-26 h
34 W blue LED	36 W blue LED

available to achieve the desired functionalization with fluoroalkyl species (Scheme 1). The Gevorgyan method is based on the Pd(OAc)₂/Xantphos catalytic system, and the transformation works efficiently in benzene in the presence of Cs₂CO₃.[14e] Similarly, Fu's procedure uses the PdCl₂(PPh₃)₂/Xantphos catalyst in DMA/H₂O solvent in the presence of K₂CO₃ base.[14b] Both alkylations require blue light irradiation for appropriate excitation of the photocatalytic system.

We started our investigation with the optimization of the reaction of styrene (**1a**) and trifluoroethyl iodide (**2**) using palladium(II)−Xantphos catalyst systems. The reactions were irradiated by 440−445 nm LEDs for 18 h at 25 °C and analyzed by GC-MS. We found that the Gevorgyan-type Pd(OAc)₂−Xantphos photocoupling system[14e] works effi-

ciently in benzene in the desired trifluoroethylation and provides the expected product **3a** in complete conversion. In contrast, Fu's conditions[14b] were not suitable for the fluoroalkylation, which shows system sensitivity of the coupling partner and indicates the necessity of fine-tuning of the reaction conditions. After finding the appropriate catalytic system we aimed to fine-tune the reaction conditions to reach more suitable reaction conditions for the fluoroalkylation of styrenes. In these experiments we focused on lowering the catalyst and base loadings, and solvent selection.

We found that the catalyst loading can be lowered in the case of the trifluoroethylation, but the minimum amount of needed Pd(OAc)$_2$ catalyst for the reaction completion was 5 mol %; further reduction of the catalyst loading significantly decreased the conversion (Table 1, entries 2−6). A control

Table 1. Fine-tuning of Photocatalytic Conditions[a]

5 mol% [Pd]
10 mol% Xantphos
1.5 equiv Cs$_2$CO$_3$
benzene, blue LEDs
Ar, 25 °C, 18 h

Entry	Catalyst	Solvent	Conv.
1	10 mol % Pd(OAc)$_2$	benzene	100%[b]
2	**5 mol % Pd(OAc)$_2$**	**benzene**	**100%**
3	4 mol % Pd(OAc)$_2$	benzene	99%
4	3 mol % Pd(OAc)$_2$	benzene	89%
5	2 mol % Pd(OAc)$_2$	benzene	38%
6	1 mol % Pd(OAc)$_2$	benzene	12%
7	5 mol % Pd(OAc)$_2$	benzene	0%[c]
8	PdCl$_2$	benzene	0%
9	Pd(acac)$_2$	benzene	48%
10	Pd(TFA)$_2$	benzene	83%
11	Pd$_2$(dba)$_3$	benzene	27%
12	Pd(OAc)$_2$	water	7%
13	Pd(OAc)$_2$	acetone	40%
14	Pd(OAc)$_2$	ethyl acetate	46%
15	Pd(OAc)$_2$	THF	83%
16	Pd(OAc)$_2$	chlorobenzene	5%
17	Pd(OAc)$_2$	toluene	80%
18	Pd(OAc)$_2$	BTF	90%
19	Pd(OAc)$_2$	cyclohexane	75%

[a]Standard reaction conditions: styrene (0.2 mmol), trifluoroethyl-iodide (1.5 equiv), Cs$_2$CO$_3$ (1.5 equiv), catalyst (5 mol %), ligand (10 mol %) in 1 mL degassed benzene under Ar atmosphere, irradiated with single 10 W 440−445 nm LEDs at 25 °C. [b]3 equiv of Cs$_2$CO$_3$ were used. [c]In the dark.

experiment without any irradiation indicated that the light is essential for this transformation (Table 1, entry 7). Next, we tested different Pd sources, and we demonstrated that the use of PdCl$_2$ could not result in any product; Pd$_2$(dba)$_3$ and Pd(acac)$_2$ were only moderately active in this reaction, and Pd(TFA)$_2$ performed almost as good as Pd(OAc)$_2$ (Table 1, entries 8−11). Among the tested polar solvents water, acetone and ethyl acetate were relatively ineffective (Table 1, entries 12−14), while in THF the reaction reached 83% conversion. Reactions performed in solvents similar to benzene gave versatile results: chlorobenzene was completely ineffective, while in toluene and benzotrifluoride (BTF) the coupling reaction gave 80% and 90% conversion respectively, which are good results but compared to benzene the transformation did

not reach completion. In cyclohexane alongside the desired coupling iodocyclohexane was formed as a byproduct which made this solvent unsuitable (Table 1, entry 19).

With the optimized conditions in hand first we investigated the generality of the trifluoroethylation reaction (Scheme 2).
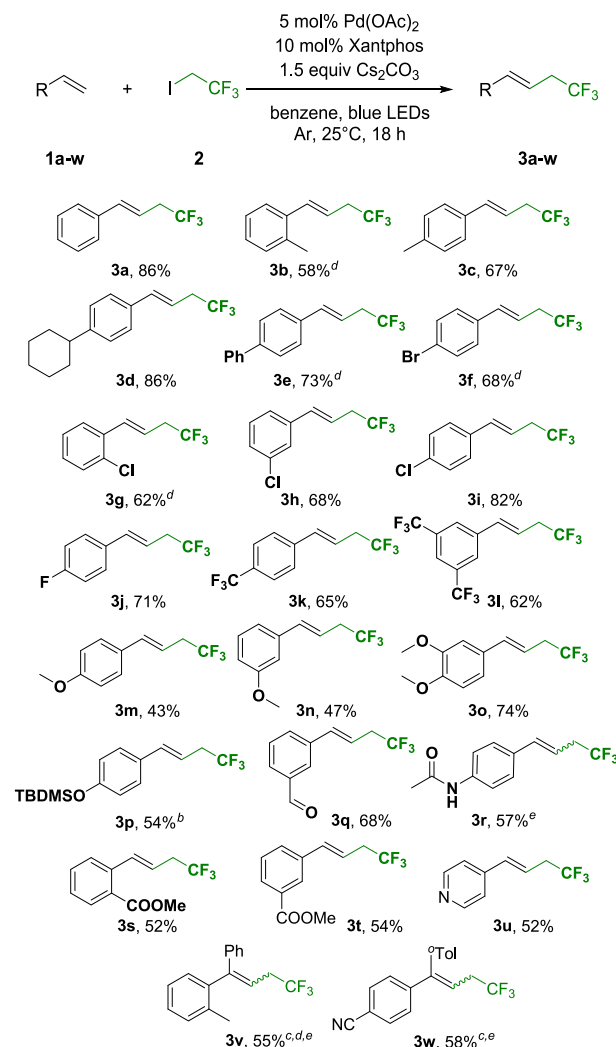
Scheme 2. Scope of Trifluorethylation

5 mol% Pd(OAc)$_2$
10 mol% Xantphos
1.5 equiv Cs$_2$CO$_3$
benzene, blue LEDs
Ar, 25°C, 18 h

3a, 86%   **3b**, 58%[d]   **3c**, 67%
3d, 86%   **3e**, 73%[d]   **3f**, 68%[d]
3g, 62%[d]   **3h**, 68%   **3i**, 82%
3j, 71%   **3k**, 65%   **3l**, 62%
3m, 43%   **3n**, 47%   **3o**, 74%
3p, 54%[b]   **3q**, 68%   **3r**, 57%[e]
3s, 52%   **3t**, 54%   **3u**, 52%
3v, 55%[c,d,e]   **3w**, 58%[c,e]

[a]Standard reaction conditions: substrate (0.5 mmol), trifluoroethyl iodide (1.5 equiv), Cs$_2$CO$_3$ (1.5 equiv), Pd(OAc)$_2$ (5 mol %), and Xantphos (10 mol %) was used in 2.5 mL degassed benzene under an Ar atmosphere, irradiated with single 10 W 440−445 nm LEDs at 25 °C. [b]The reaction time was 24 h. [c]10 mol % catalyst, 20 mol % Xantphos and 3 equiv. base were used. [d]Average of two reactions. [e]E/Z ratio **3r** 13:1; **3v** 3:1; **3w**: 33:1.

The transformation proceeded smoothly with styrene derivatives with electron-withdrawing and electron-donating groups as well, regardless of their position on the aromatic ring. We synthesized different alkyl (**3b**, **3c**, **3d**) and aryl (**3e**) derivatives in good yields, and the reaction worked efficiently with halogenated styrenes (**3f−j**) and methoxy derivatives (**3m**, **3n**, **3o**) as well. The silyl protected phenol functional group is also tolerated under the reaction conditions, and product **3p** was isolated in 54% yield after a 24 h reaction time. Aldehyde (**3q**), amide (**3r**) and ester (**3s**, **3t**) derivatives were also prepared successfully from the corresponding styrene. In

this series the pyridine derivative (**3u**) was also obtained in 52% yield. On the other hand, 1,1-diphenylethylene derivatives proved to be less reactive in this transformation. Therefore, increased catalyst and base loadings were necessary to accomplish the desired coupling. We managed to synthesize the **3v** and **3w** derivatives in 55% and 58% yields, respectively.

Next, we broadened the scope of the photocatalytic fluoroalkylation method with versatile fluoroalkyl iodides (Scheme 3). We found that 1,1-difluoro-2-iodoethane is also capable of participating in the coupling reaction.

Scheme 3. Scope of Different Fluoroalkyl Iodides[a]
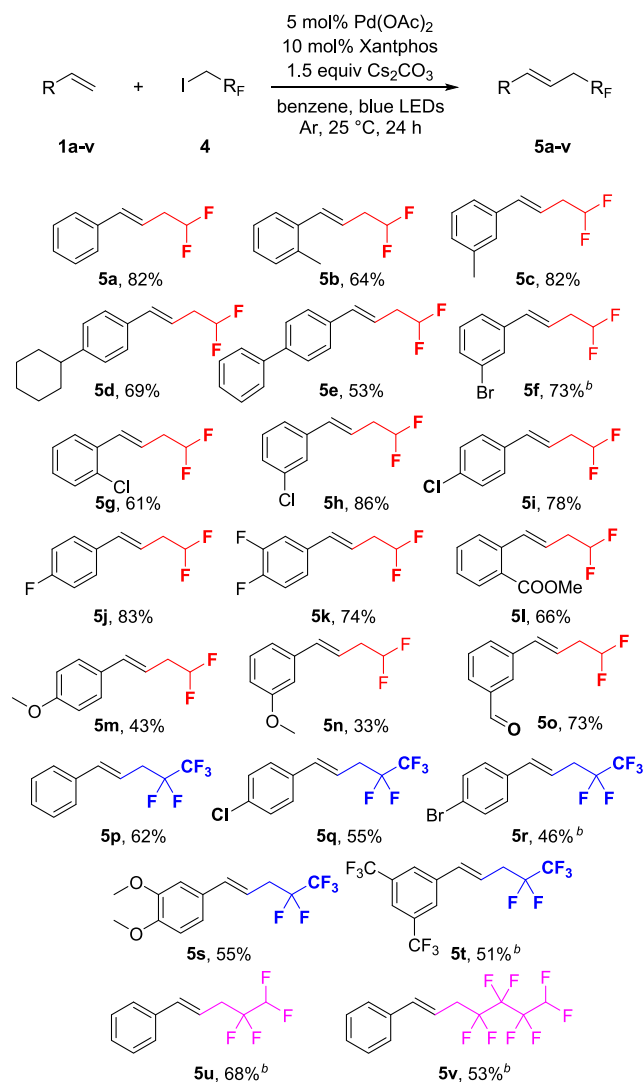
[a]Standard reaction conditions: substrate (0.5 mmol), fluoroalkyl iodide (1.5 equiv), Cs$_2$CO$_3$ (1.5 equiv), Pd(OAc)$_2$ (5 mol %), Xantphos (10 mol %) was used in 2.5 mL degassed benzene under Ar atmosphere, irradiated with single 10 W 440−445 nm LEDs at 25 °C. [b]Average of two reactions.

This attracted our interest because the difluoromethyl moiety is a well-studied motif in medicinal chemistry. The difluoromethyl group is isosteric and isopolar with the −OH and −SH groups and can behave as a H-donor as well.[15] The preparation of difluoroethylated styrene derivatives is performed only through the functionalization of allylic halides

with difluorocarbene sources,[16] and direct difluoroethylation of terminal alkene is unprecedented.

Applying the previously used reaction conditions, we found that the coupling of 1,1-difluoro-2-iodoethane with styrene requires a 24 h reaction time to reach completion, and we could isolate the corresponding difluoroethylated styrene product (**5a**) in 82% yield. With the slightly modified procedure, 12 additional derivatives were prepared to explore the scope of the photocatalyzed coupling reaction. This transformation also possesses good functional group tolerance, and alkyl (**5b, 5c, 5d**), aryl (**5e**), halogen (**5f−k**), ester (**5l**), methoxy (**5m, 5n**), and aldehyde (**5o**) derivatives were successfully synthesized.

Increasing further the versatility of the fluoroalkyl part we utilized 1H,1H-pentafluoropropyl iodide as a coupling partner, and we obtained the corresponding coupling products under the standard reaction conditions. In this case the pentafluoropropylated derivatives (**5p−t**) were isolated in 46−62% yield. Additionally, two other fluoralkyl iodides were also tested in this transformation, 1,1,2,2-tetrafluoro-3-iodopropane and 1H,1H,5H-octafluoropentyl iodide, and successfully gave the desired coupled products (**5u, 5v**) in 68% and 53% yield, respectively, which demonstrates that longer fluorous chains are also applicable in this palladium-catalyzed photochemical transformation.

Results of the radical quenching and light on−off experiments[17] support that the fluoroalkylation reaction follows the general mechanism of the palladium-catalyzed alkylations.[14] The Xantphos−Pd(0) complex can be excited with blue light (440−460 nm), and then this Pd species reacts with fluoroalkyl iodide in the SET reaction, supposedly generating a Xantphos−Pd(I)−I and fluoroalkyl radical pair (the latter was trapped with TEMPO to prove its presence),[17] which are in close proximity. Alkene reacts with this palladium(I) intermediate through insertion or radical addition, and then a β-hydrogen radical elimination could form the coupled styrene product and the common H−Pd(II)−I. This latter species undergoes base-assisted reductive elimination to produce Xantphos−Pd(0), ready for the next catalytic cycle.

In conclusion we developed a visible light driven palladium-catalyzed Heck-type coupling between styrenes and fluoroalkyl iodides at room temperature, which enables the introduction of versatile fluoroalkyl chains into terminal alkene functionality. A series of styrene derivatives were subjected to the present reaction conditions and formed the corresponding fluoroalkyl derivatives in good yields. In our synthetic studies five different fluoroalkyl iodides were successfully utilized. This method offers an efficient disconnection to incorporate fluorine-containing functional groups into styrene derivatives, which could serve as a useful derivatization method to obtain fluoroalkenylated compounds.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c03043.

General information, synthesis procedures, characterizations of products (^{1}H, ^{13}C, ^{19}F NMR, IR, HRMS), and spectra (PDF)

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

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(17) For details, see Supporting Information.