

Photoredox Catalytic Activation of Trichlorofluoromethane and Addition to Styrenes

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Abstract: A new method activates CCl_3F by means of photoredox catalysis and functionalizes alkenes by the CCl_2F group. N-phenylphenothiazine is used as strongly reducing organophotocatalyst. The photoredox catalytic approach combines the productive disposal of this ozone depleting material and greenhouse gas with the synthesis of potentially useful organic

compounds, complements the concept of atom transfer radical addition, and allows for the first time direct synthetic access to the CCl_2F group as structural motif. The substrate scope is broad and the multifunctionalized class of products allows for a variety of following-up transformations.

Introduction

Fluorinated substituents play a key role in pharmaceutical chemistry^[1] and can be introduced in the meantime as late-stage functionalizations by photoredox catalysis.^[2] Among the most common fluorinated substituent is for instance the trifluoromethyl (CF_3) group, which can be introduced by photocatalytic activation of trifluoromethylsulfonyl chloride,^[3] also for vicinal difunctionalization of alkenes.^[4] However, the search for mixed halogenated functional groups, like the vicinal dichlorofluoro group, is an important but a very costly task, and usually requires multiple synthetic steps to consecutively introduce the fluorine and chlorine substituents. The high electronegativity of the fluorine substituent in the geminal position activates the chloride substituent in a unique fashion and thus enables further chemical transformations. Hence, this functional group can potentially be used in reactive drugs, that can covalently link to its target structure. The resulting chiral group is suggested to act as bioisoster for non-chiral geminal difluorides in pharmacology. Despite these advantages, this functional pattern is not widely used. We present herein a new method that allows to prepare dichlorofluoromethylated key molecules in a single step by means of photoredox catalysis.

Furthermore, we demonstrate the usefulness of these CCl_2F -functionalized compounds to access related structures in follow-up reactions. Our method complements the available photoredox catalytic atom transfer radical addition using perhalogenated methanes,^[5] like BrCCl_3 ,^[6] CF_3I ,^[7] CBr_4 ^[8] and CHCl_3 ^[9] as representative examples to CCl_3F for alkene functionalization (Figure 1).

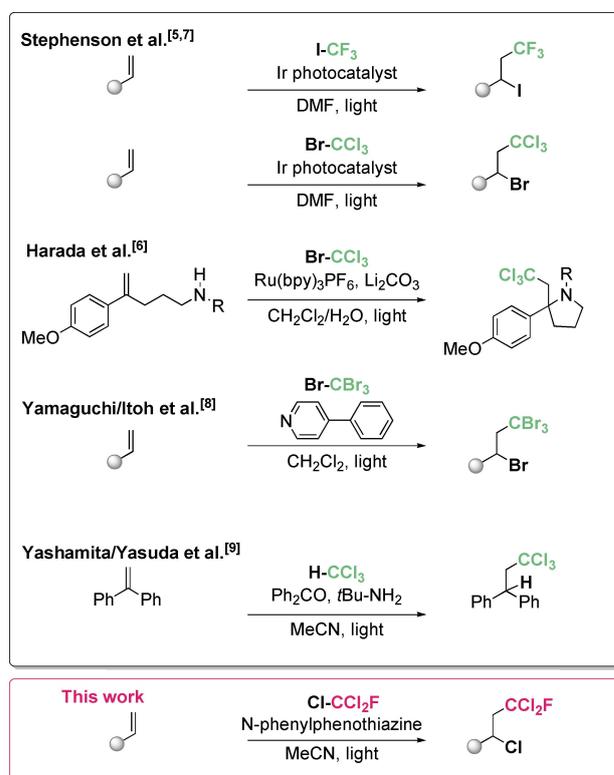


Figure 1. Recent examples for alkene functionalization by atom transfer radical addition with perhalogenated methanes, like BrCCl_3 , CF_3I , CBr_4 and CHCl_3 from the literature and the photocatalytic activation of CCl_3F in this work.

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Results and Discussion

Photoredox catalysis should be able to activate the greenhouse gas and potent ozone depleting molecule trichlorofluoromethane (CCl_3F , CFC-11) for the synthesis of potentially useful CCl_2F -functionalized compounds. Based on our recent results with sulfur hexafluoride photoredox catalysis using *N*-phenylphenothiazine (1) seemed to be very promising.^[10] Phenothiazines were also used by other groups as photocatalysts for strong C-halogen bond activation.^[11] The first reactions were run with α -phenyl styrene as substrate 2 (0.1 M) in neat CCl_3F . The analysis of the reaction mixture after 16 h irradiation by a 365 nm LED under strict exclusion of oxygen and water indeed showed the formation of product 4 in good yields of 55% (Table 1). Obviously, the rapid elimination of HCl in the initially formed product 3 generates the stable vinylic CCl_2F product 4. The product was identified by MS and characterized by $^1\text{H}/^{13}\text{C}/^{19}\text{F}$ NMR spectroscopy (Figure S3–S6). It shows a $^1J_{\text{CF}}$ coupling constant of 303 Hz. The ^{19}F - ^{13}C -HMBCD spectrum reveals a correlation of the methine carbon with the fluorine by $^2J_{\text{CF}} \sim 20$ Hz and $^3J_{\text{CF}} \sim 2$ Hz. This spectroscopic data is aligned with the vinylic CCl_2F product 4. Control reactions in the absence of light or catalyst 1 did not produce any product. Binary solvent mixture are beneficial for product formation. The solution of 2 (0.1 M) in mixtures of $\text{CCl}_3\text{F}:\text{MeOH} = 1:4$ and $2:1$, gave 46% and 57% of the desired product 3. Increasing the reaction temperature to 30°C together with higher substrate concentration (0.2 M) did not improve the yield. Finally, an increased catalyst concentration, either 10 mol% 1 with a 0.1 M solution of 2, or 5 mol% with a 0.05 M solution of 2, both in $\text{CCl}_3\text{F}:\text{MeCN} = 1:1$, gave nearly quantitative yields of 88% and 94%, respectively. The photoredox catalyst concentration turned out to be the most critical parameter. An increased amount of the catalyst 1 strongly decreased the yield, probably caused by overreduction of the key intermediate radical CCl_2F as previously observed in SF_5 -chemistry studies.

We propose the reaction to progress via a Giese type reaction (Figure 2). The photoexcitation of 1 initiates the electron transfer to CCl_3F that undergoes cleavage into the CCl_2F radical and the chloride anion. This photoinduced

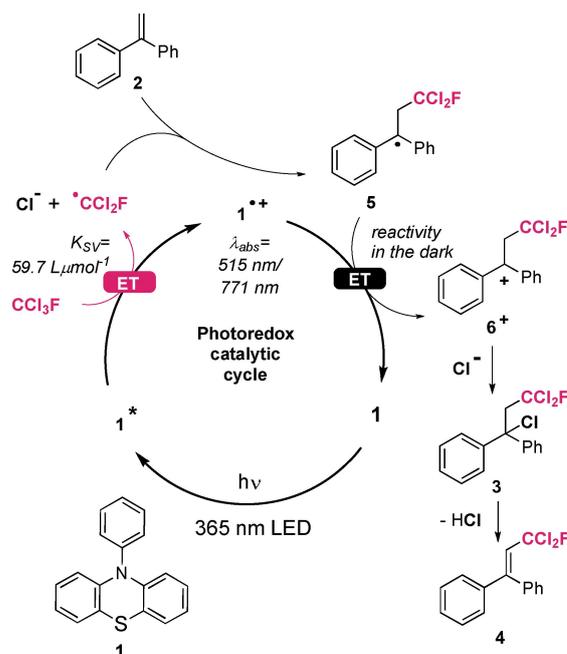


Figure 2. Proposed catalytic cycle for the chlorofluoromethylation of α -phenylstyrene (2) by *N*-phenylphenothiazine (1) as photocatalyst to the CCl_2F -products 3 and 4.

electron transfer is supported by the observed fluorescence quenching of 1 by CCl_3F with a Stern-Volmer constant of $K_{\text{SV}} = 59.7 \text{ L}\mu\text{mol}^{-1}$ (Figure S54). Furthermore, irradiation of a sample solution of 1 (200 μM) in MeCN with 3% CCl_3F for 20 s reveals the spectroscopic signature of the radical cation 1^+ with the typical absorption bands at 515 nm and 771 nm (Figure S1). The steady state concentration of the radical cation 3^+ was strongly dependent on the concentration of oxygen in the mixture. In the dark, the radical cation 1^+ was quenched by the substrate 2 and finally reached a limit at 35% of the initial radical cation concentration (Figure S2). This result indicates a thermal radical addition mechanism to the radical 5 and the quenching of the radical cation 5^+ via back electron transfer to cation 6^+ closing the photocatalytic cycle. Finally, trapping of the chloride Cl^- forms product 3 that spontaneously eliminates HCl to product 4. We did not observe significant amounts of cyclopropane being formed through the reactivity of the benzylic radical 5.^[12]

Furthermore, we investigated the substrate scope of this new photoredox catalytic transformation (Figure 3). α -methyl styrene (7) and 2-vinylnaphthalene (9) as two representatives of vinylic arenes were used as substrates and could be turned into the chlorofluoromethylated addition products 8 and 10 in reasonable yields. We found an interesting differentiation of their reactivities that further supports our mechanistic proposal. The highly activated styrenes 2 and 7 only allowed for isolation of elimination products 3 and 8 with the vinylic and allylic CCl_2F group, respectively. The primary addition products turned out to be too labile to tolerate purification under any conditions. In contrast, product 10 from the less activated vinylnaphthalene (9) was formed in 58% yield during the

Table 1. Overview of the optimization of the reaction conditions for the photoredox catalytic conversion of substrate 2 to product 3 with CCl_3F , 365 nm LED, 16 h, 20°C . For the structure of the photocatalyst 1, see Figure 2.

Line	2	1	$\text{CCl}_3\text{F}:\text{MeCN}$	Yield of 3
1	0.1 M	5 mol%	1:1	55% ^[a]
2	0.1 M	5 mol%	1:4	46%
3	0.1 M	5 mol%	2:1	57%
4	0.2 M	10 mol%	1:19	55% ^[b]
5	0.1 M	10 mol%	1:1	88%
6	0.05 M	5 mol%	1:1	94%

[a] No product 3 formed in the absence of light or the catalyst 1. [b] 30°C .

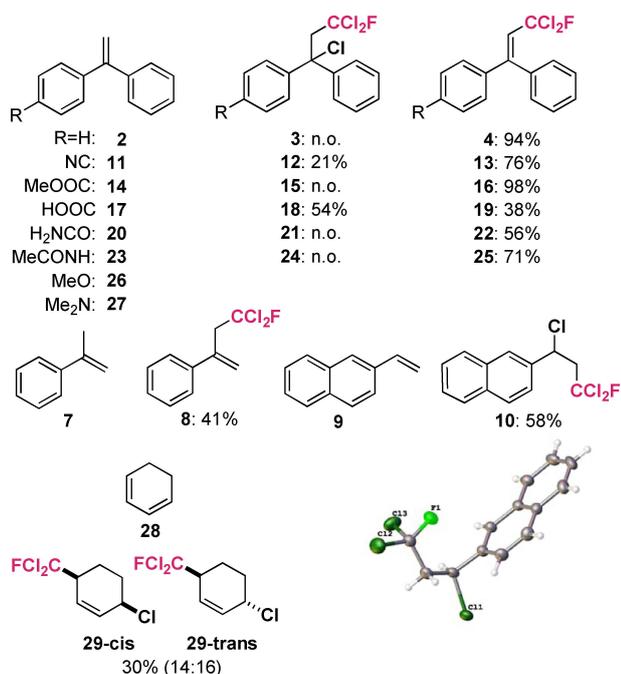


Figure 3. Product scope of the dichlorofluoromethylation of alkenes. Yields determined by ¹⁹F NMR spectroscopy. X-ray structure of **10**. Deposition Number 2235204 (for **10**) contain(s) the supplementary crystallographic data for this paper. These data are provided free of charge by the joint Cambridge Crystallographic Data Centre and Fachinformationszentrum Karlsruhe Access Structures service.

reaction and did not undergo spontaneous elimination. Derivatives of α -phenylstyrene were used to test the functional group tolerance for the substrate scope. α -Phenylstyrenes with electron-withdrawing groups in the para position, including nitril (**11**), ester (**14**), carboxylic acid (**17**) and amide (**20**) groups were converted in excellent yields into the respective products. Electron-donating groups, including methoxy (**26**) and dimethylamino (**27**) groups, were not tolerated. However, acetanilide (**23**) is a competent substrate and forms product **25** in 71% yield which shows that amino-modified substrates could in fact be converted, ensuring amide protection. Finally, 1,3-cyclohexadiene (**28**) as a representative of less activated substrates was subjected to the reaction conditions. This non-aromatic substrate yielded 30% of product **29** as a cis-trans mixture. In the ¹H-¹H-COSY, it can be observed that the CCl₂F-bearing carbon atom shows correlation to a vinylogous double bond proton, while the halogen-bearing carbon shows correlation to the corresponding second vinyl proton. Both show no cross signals to each other, indicating a 1,4 configuration of the reaction product. The connectivity was further confirmed by 1,1-ADEQUATE and is identical for both isomers. The determination of the relative configuration by NOE, on the other hand, is more difficult due to the large distance between the two protons across the ring and cannot be done with absolute certainty. However, the experiments performed allow an assignment with sufficient certainty.

Further investigation focused on the reactivity of the functionalized geminal dichlorofluorides as potential precursors for chlorofluorinated compounds (Figure 4). Firstly, we applied

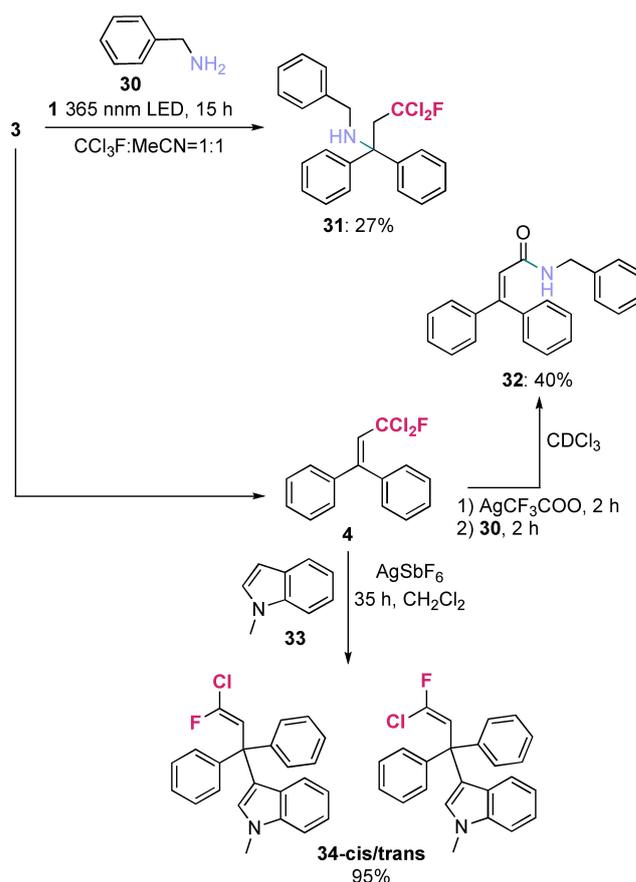


Figure 4. Following up chemistry with the CCl₂F-product **4**.

benzylamine (**30**) to substitute one of the chlorine atoms in compound **4**. Similar reactions were recently reported by Paquin to get geminal chlorofluoroamines.^[13] Unfortunately, this highly unstable compound could not be isolated but its formation was confirmed by ¹⁹F NMR spectroscopy (Figure S52, 53). **4** was reacted with bench-grade solvent in the presence of silver salt. ¹⁹F NMR-spectroscopic investigations revealed the rise of the doublet of a putative hydroxyfluorochloromethyl intermediate ($\delta_{19F} = -55\ ppm$, $^3J_{FH} = 14.2\ Hz$) after partial hydrolysis decomposing over prolonged storage under generation of the stable acylfluoride resonating at $\delta_{19F} = 42\ ppm$ in due course. This intermediated could be trapped by the addition of benzylamine (**30**) forming the corresponding amide **32** in 40% yield. In contrast, the photocatalytic conversion of **3** in the presence of benzylamine (**30**) gave the regioisomeric product **31** in 47% yield. Secondly, we tried to activate the substrates in the presence of silver hexafluoroantimonate (1.00 equiv.) in the presence of the strong nucleophile 1-methylindene (**33**, 5.00 equiv.) to investigate the Friedel-Crafts type reaction. The geminal chlorofluoroalkenes **34** were formed as mixture of the two isomers in a ration of 3:1 (trans:cis) in a yield of 95%

Conclusions

We developed a method that activates CCl_2F by means of photoredox catalysis and functionalizes alkenes by transfer of the CCl_2F group. N-phenylphenothiazine is used as strongly reducing organophotocatalyst. Our method combines the productive disposal of this ozone depleting material with the synthesis of potentially useful CCl_2F -organic compounds. The photoredox catalytic approach complements the concept of atom transfer radical addition and allows for the first time direct access to this sensitive structural motif. The substrate scope is broad and the multifunctionalized class of products allows for a variety of following-up transformations.

Experimental Section

All experimental details are described in the Supporting Information.

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Conflict of Interest

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available in the supplementary material of this article.

Keywords: Photochemistry · phenothiazine · styrene · photocatalysis · UV light

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RESEARCH ARTICLES



One pot, one step, just light on: The new photoredox catalytic method combines the disposal of CCl_3F as potent greenhouse gas with the

formation of fluorinated organic compounds as new synthetic building blocks.

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