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Reduction of SF_5CF_3 *via* iridium catalysis: radical trifluoromethylation of aromatics†

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The greenhouse gas SF_5CF_3 acts as CF_3 source for the photocatalytic trifluoromethylation of arenes on using [Ir(dtbbpy)(ppy)$_2$]PF_6 (4,4′-di-*tert*-butyl-2,2′-dipyridyl, ppy = 2-phenylpyridine) as catalyst. The trifluoromethylation of C_6D_6 in the presence of 1-octanol results in the concomitant generation of 1-fluorooctane, presumably by intermediate SF_4.

The CF_3 group plays an important role in medicinal chemistry in part due to their ability to increase the lipophilicity of compounds, and thereby enhance the rate of absorption and transport of drugs across the blood–brain barrier.[1] In 1963 Bedard *et al.* reported on the thermal homolysis of the trifluoromethyl derivatives CF_3I, CF_3Br, CF_3Cl to achieve a radical trifluoromethylation of halobenzenes.[2,3] Silver trifluoroacetate and TiO_2 as a photocatalyst were also used to form CF_3 radicals in order to synthesize trifluoromethylated aromatics.[4] Kamigata *et al*. demonstrated the trifluoromethylation of aromatics on using a ruthenium(II)phosphine complex as a catalyst and trifluormethanesulfonylchloride as CF_3 source in a thermal reaction.[5] In 2011 MacMillan *et al.* published a photocatalytic trifluoromethylation of aromatics with [Ru(phen)$_3$]Cl_2 (phen = phenanthroline) as catalyst again using F_3CSO_2Cl as a source for the trifluoromethyl group.[6] The research group of Hu *et al.* described a photochemical trifluoromethylation reaction in which an electron donor–acceptor complex between an aromatic thiophenolate anion and trifluoromethylphenylsulfone initiates a single electron transfer, and therefore the generation of CF_3 radicals.[7] In other photocatalytic trifluoromethylations of aromatics CF_3SO_2Na[8] or trifluoromethanesulfonic anhydride[9] were used as trifluoromethyl radical source. Note also that in 2009 MacMillan *et al.* reported on an enantioselective trifluoromethylation of aldehydes *via* a photoredox process coupled with organocatalysis on using the Ir redox catalyst [Ir(dtbbpy)(ppy)$_2$]PF_6 (4,4′-di-*tert*-butyl-2,2′-dipyridyl, ppy = 2-phenylpyridine). In an reductive quenching cycle CF_3I is being reduced to give a CF_3 radical.[10] Furthermore, [Ir(dtbbpy)(ppy)$_2$]PF_6 was used in a photocatalytic approach for the trifluoromethylation of alkynes.[11] Note that apart from CF_3 transfer other fluoroalkyl groups can be transferred as well *via* photocatalysis.[12]

In the last few years the activation of the greenhouse gas SF_6 and its use as fluorinating agent has been studied extensively.[13–18] Conversions are often initiated by an electron transfer to SF_6 to yield SF_6^-. The latter can either transform into a SF_5 radical and a fluoride or SF_5^- and a fluoro radical.[16,17,19] Examples for the photochemical activation of SF_6 include the application of the photocatalysts [Ru(phen)$_3$]Cl_2,[6] 4,4-dimethoxybenzophenone[15] or [Ir(dtbbpy)(ppy)$_2$]PF_6[18] The SF_6 derivative SF_5CF_3 has also a high global warming potential and a long atmospheric life-time.[20] It is assumed that SF_5CF_3 is a breakdown product of SF_6 in high-voltage equipment. The latter contains fluoropolymers which are sources for CF_3 moieties that can react with SF_5 radicals formed by high voltage discharges.[20] However, electron transfer to SF_5CF_3 can result in the generation of SF_5^- and a CF_3 radical. Thus, the formation of SF_5^- has been observed in low-energy attachment experiments by mass spectrometry.[21,22] SF_5CF_3 activation processes are rare and in solution only one example is known in the literature, to the best of our knowledge.[14]

In this contribution we report on an unprecedented trifluoromethylation of aromatic compounds by photocatalytic generation of CF_3 radicals from the greenhouse gas SF_5CF_3.

Irradiation of SF_5CF_3 at a wavelength of 353 nm in C_6D_6 in the presence of 4,4′-dimethoxybenzophenone as an organic photocatalyst (Scheme 1) led to the generation of small amounts of α,α,α-trifluorotoluene-d_5. Similar, only traces of α,α,α-trifluorotoluene-d_5 were observed when 10-phenylphenothiazine (Scheme 1) was used to activate SF_5CF_3. However, irradiation of SF_5CF_3 in the presence of the photoredox catalyst [Ir(dtbbpy)(ppy)$_2$]PF_6 (Scheme 1), triethylamine and cesium carbonate with a 456 nm LED lamp for 16 h in C_6D_6 yielded α,α,α-trifluorotoluene-d_5 with a turnover number (TON) of 410 (TON are based on the concentration of the catalyst on using 1,4-difluorobenzene as internal standard) (Scheme 2). Note

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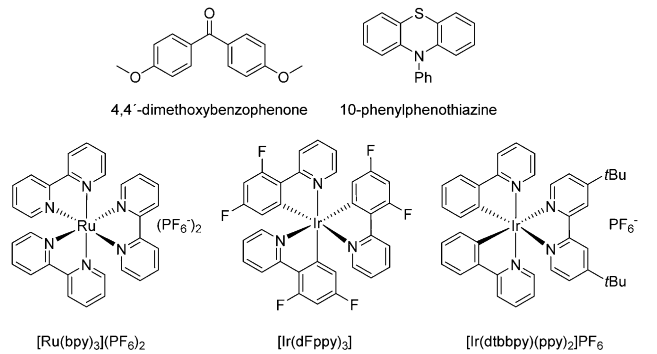
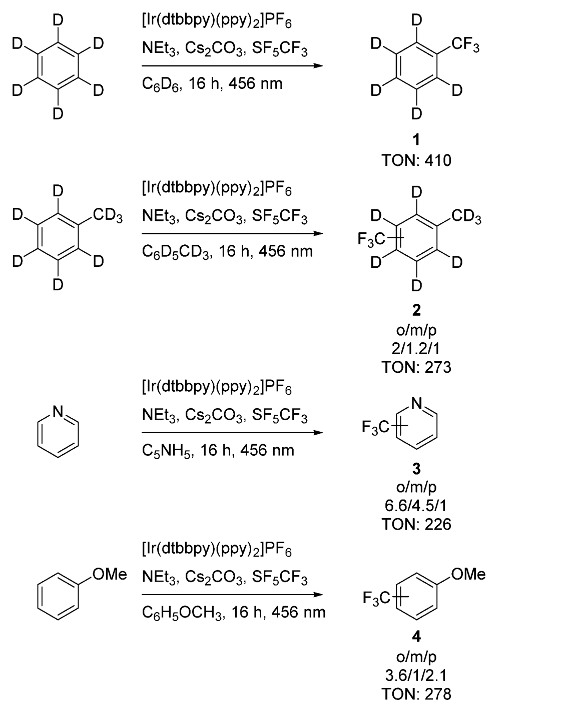


Scheme 1 Catalysts studied for the reduction of SF_5CF_3.

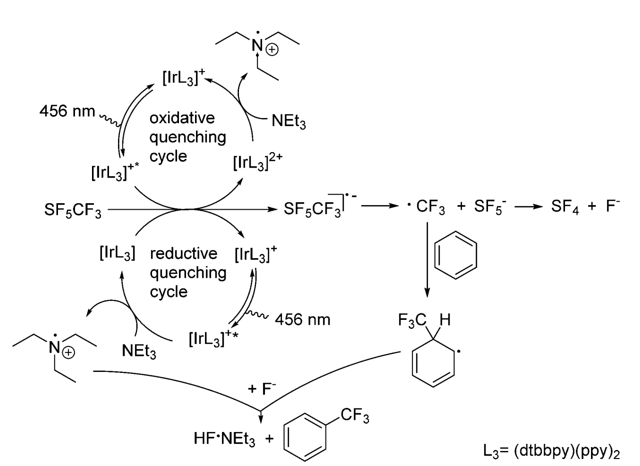
that without the presence of Et_3N the conversion does not proceed. Attempts to use K_2HPO_4 as an alternative base failed. Triethylamine and cesium carbonate in a ratio of 1 : 1 led to the highest turnover numbers. ^{19}F NMR experiments revealed the presence of DF when no Cs_2CO_3 was present. Using 4-methoxydiphenylamine and Cs_2CO_3 as bases in a ratio of 1 : 1 led to a decrease of the TON to 26. Note that with the photoredox catalyst $[Ru(bpy)_3](PF_6)_2$ or $[Ir(dFppy)_3]$ lower TONs of 28 and 46, respectively, were observed in the presence of NEt_3 and Cs_2CO_3 in a ratio of 1 : 1. Reactions with $[Ir(dtbbpy)(ppy)_2]PF_6$ as catalyst with only stoichiometric amounts of benzene in acetonitrile or dichloroethane as solvents gave α,α,α-trifluorotoluene-d_5 only in very low yield. Mainly the generation of trifluoromethane and other minor unidentified products was observed (ratio CF_3H to $PhCF_3$: 71 : 1 in acetonitrile, 52 : 1 in dichloroethane). With dichloromethane and tetrahydrofurane as solvents in the presence of stoichiometric amounts of benzene did not lead to any product formation.



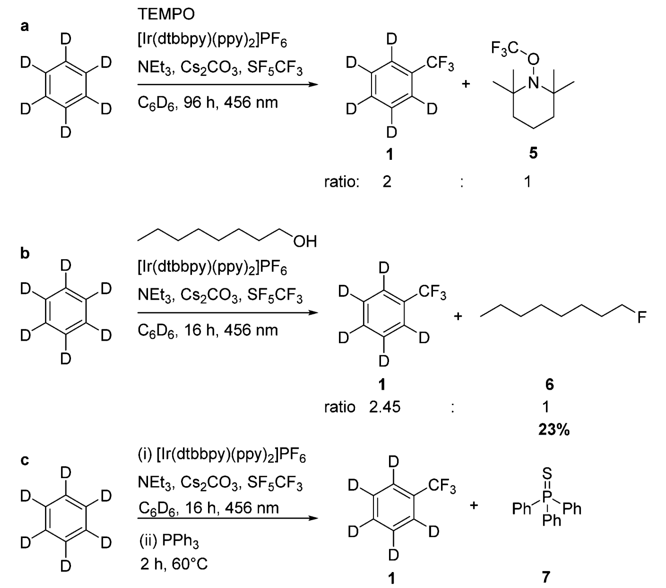
Scheme 2 Trifluoromethylation of arenes on using $[Ir(dtbbpy)(ppy)_2]PF_6$ as photoredox catalyst.

To expand the scope of the conversions, pyridine, anisole, 1,2,3,4-tetrafluorobenzene and deuterated toluene (Scheme 2) were studied towards a photochemical trifluoromethylation on using a stock solution of $[Ir(dtbbpy)(ppy)_2]PF$ as photocatalyst. All the conversions were run with the substrate as solvent. Selectivities can be explained when considering that the CF_3 radical shows an electrophilic character.[2,6] Transformations of toluene-d_8 and anisole resulted mainly in the formation of isomers with the CF_3 group in the *ortho* or *para* position. Pyridine gives mainly the *ortho*-product, but also considerable amounts of *meta*-trifluoromethylpyridine. Minor amounts of trifluoromethane were also detected. 1,2,3,4-Tetrafluorobenzene however did not show any reactivity under the standard conditions. The trifluoromethylated aromatics were characterized by their signals in the ^{19}F NMR spectra for the CF_3 groups in the *para*, *meta* or *ortho* positions as well as by GC-MS.

Mechanistically, it can be presumed that after irradiation at 456 nm a single electron transfer SET from the photocatalytic system to SF_5CF_3 leads to the $SF_5CF_3^-$ radical anion (Scheme 3). As mentioned above, the subsequent trifluoromethylation does not proceed without the presence of NEt_3 as reductant. Thus, NEt_3 can reduce the photoexcited species $[Ir(dtbbpy)(ppy)_2]^{+*}$ generated after excitation of $[Ir(dtbbpy)(ppy)_2]^+$ in a reductive quenching cycle (Scheme 3). This step is followed by the SET from the reduced $[Ir(dtbbpy)(ppy)_2]$ (E_{pc} = −1.51 V *vs.* SCE)[23,24] to SF_5CF_3. Alternatively, $[Ir(dtbbpy)(ppy)_2]^{+*}$ (E_{pc} = −0.96 V *vs.* SCE)[23,24] reduces SF_5CF_3 and the generated $[Ir(dtbbpy)(ppy)_2]^{2+}$ is then reduced by NEt_3 in an oxidative quenching cycle. Note that photocatalytic conversions of $[Ir(dtbbpy)(ppy)_2]^+$ have a tendency to proceed *via* a reductive quenching cycle.[10,25] However, the $SF_5CF_3^-$ radical anion then decomposes to give a CF_3 radical and SF_5^-.[22,26] The SF_5^- anion is not very stable and furnishes SF_4 and fluoride.[16,27] The CF_3 radical reacts then with benzene forming a cyclohexadienyl radical. The generation of the latter in trifluoromethylation reactions has been proposed by Kamigata *et al.*[5] and others.[6,9,28] Oxidation of the cyclohexadienyl



Scheme 3 Proposed mechanism for the trifluoromethylation of arenes by SF_5CF_3.



Scheme 4 Quenching of the photocatalytic trifluoromethylation with TEMPO or 1-octanol (a and b); generation of $Ph_3P = S$ after addition of PPh_3 to the reaction mixture (c).

radical by the $NEt_3^{\bullet+}$ radical cation and subsequent deprotonation of the cyclohexadienyl cation by fluoride yields the trifluoromethylated aromatic product and $NEt_3{\cdot}HF$.[2,6,9,29] Alternatively, hydrogen atom abstraction HAT from the cyclohexadienyl radical would give the intermediate Et_3NH^+, and in the presence of fluoride the same products.[23] Cesium carbonate acts as an HF scavenger. There is no indication for the formation of HD or H_2 along with an iminium ion from the NEt_3 radical. However, the observed generation of trifluoromethane in acetonitrile or dichloromethane can involve HAT from the solvent or the $NEt_3^{\bullet+}$ radical. The latter is consistent with the fact that higher NEt_3 concentrations deliver more CF_3H.

Furthermore, to confirm the intermediate formation of a CF_3 radical, TEMPO (2,2,6,6-tetramethylpiperidinyloxyl) was added to the photocatalytic trifluoromethylation reaction of C_6D_6, and indeed TEMPO inhibited the conversion (Scheme 3). However, after 96 h TEMPO-CF_3 as well as the α,α,α-trifluorotoluene-d_5 were observed in a ratio of 1 : 2. The formation of SF_4 was not observed by low temperature NMR experiments, presumably because of the presence of Cs_2CO_3. Nevertheless, when the trifluoromethylation of C_6D_6 was run in the presence of 1-octanol in the generation of 1-fluorooctane was observed, which was identified by GC-MS and ^{19}F NMR spectroscopy (Scheme 4). The experiment suggests the deoxyfluorination of the alcohol by intermediate SF_4.[30] Hence, trifluoromethylation steps can be coupled with the fluorination of an alcohol. However, under the UV irradiation SF_4 might also be further reduced yielding elemental sulfur, as it was also proposed by Nagorny *et al.* for the activation of SF_6 in the presence of the organophotocatalyst 4,4-dimethoxybenzophenone.[15] Indeed, when PPh_3 was added to the reaction mixture after the photolytic formation of $C_6D_5CF_3$, the generation of small amounts of $SPPh_3$ (7) was observed after heating the reaction mixture for two hours at 60 °C, which might be due to the presence of sulfur (Scheme 4).

In conclusion, a catalytic photoredox process for the activation of the greenhouse gas SF_5CF_3 and a concomitant trifluoromethylation of aromatics were reported. SF_5CF_3 acts as source for CF_3 radicals and at the same time SF_4 and sulfur can be furnished. The former can be used for fluorination to couple the trifluoromehylation of aromatics with a fluorination of an alcohol. Note also that iridium photocatalyzed processes were applied for the defluorination of fluorinated organic substrates,[31] which was not observed for the described transformations.

Experiments, data collection (NMR and GC-MS) and analysing the data was performed by D. Herbstritt. The manuscript was drafted by D. Herbstritt. T. Braun supervised the work, designed the project and contributed to manuscript writing.

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Conflicts of interest

There are no conflicts to declare.

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