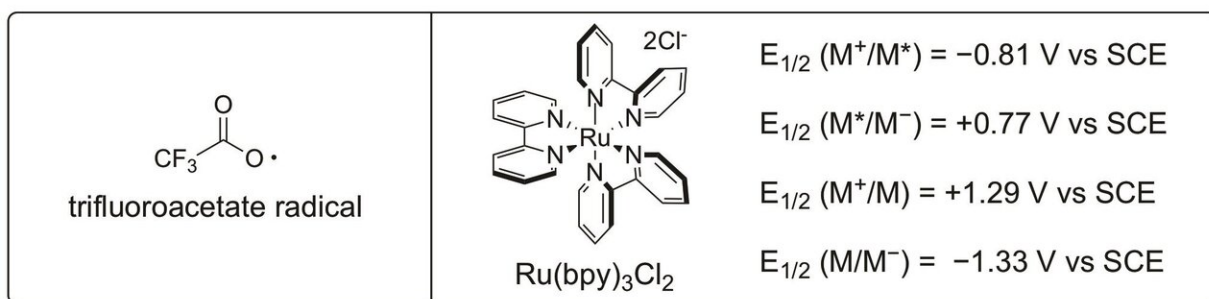
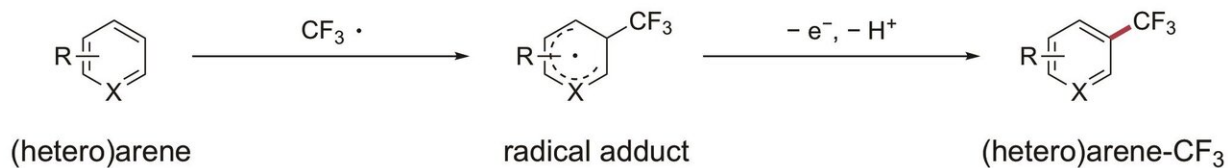
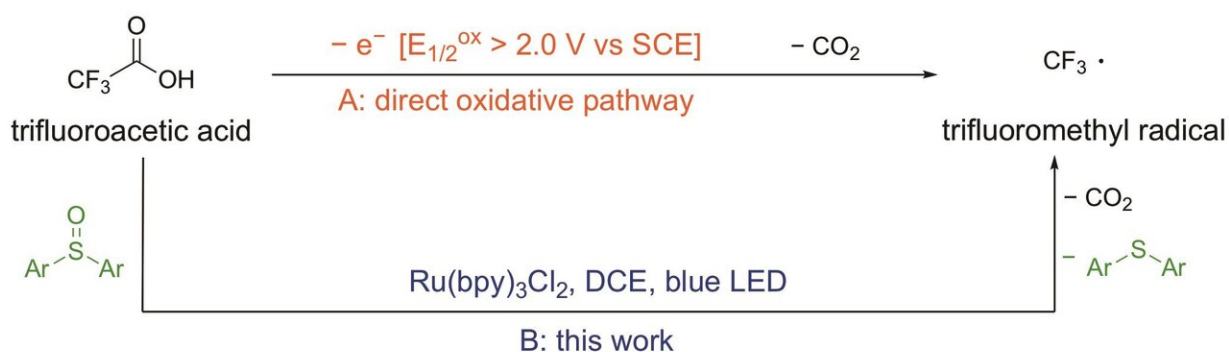


Trifluoroacetic acid acts as trifluoromethylating agent in arene C-H functionalization

August 5 2020



Trifluoromethylation, Chlorodifluoromethylation and Perfluoroalkylation of Arenes. Credit: JIN Jian

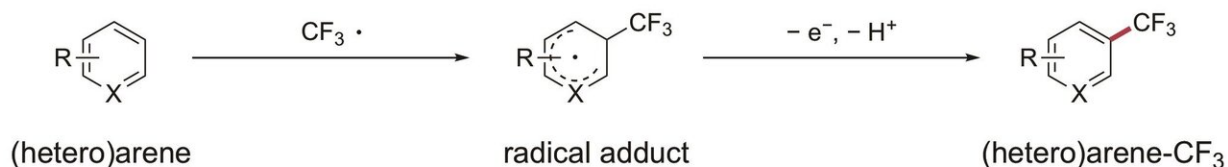
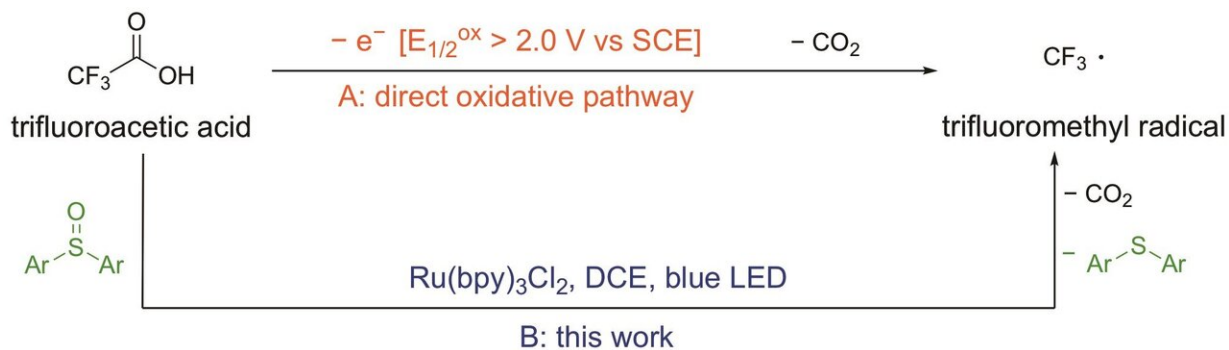
Researchers at the Shanghai Institute of Organic Chemistry of the Chinese Academy of Sciences have developed a catalytic system that directly installs the trifluoromethyl group onto arenes. The new reaction uses simple and abundant trifluoroacetic acid as the trifluoromethylating agent, and offers a milder alternative to the existing strategies.

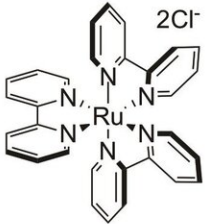
Published on August 5 in the journal *Cell Reports Physical Science*, the reported transformation is the first to successfully use trifluoroacetic and related acids as trifluoromethyl, chlorodifluoromethyl, and perfluoroalkyl radical sources with [visible light](#) irradiation.

Fluorinated drugs have better membrane permeability and increased bioavailability compared with their non-fluorinated analogs because of the changes in the physical and chemical properties. Trifluoromethyl group is one of the privileged moieties in modern drug discovery.

Among the top 200 small molecule pharmaceuticals by [retail sales](#) in 2018, there were 15 drugs containing at least one trifluoromethyl group, mostly (80%) on their aryl or heteroaryl scaffolds. Therefore, simple methodologies for the incorporation of trifluoromethyl group into arenes and heteroarenes are highly desirable.

Trifluoroacetic [acid](#) (TFA) is among the most attractive trifluoromethylation reagents with respect of its low prices, ease of handling, and availability in large quantities. However, because of its exceedingly high oxidation potential, [harsh conditions](#) are required for the direct oxidation of TFA to the trifluoroacetate radical, which after prompt CO₂ extrusion affords the desired CF₃ radical.



<chem>FC(F)(F)C(=O)[O]</chem> trifluoroacetate radical	 Ru(bpy) ₃ Cl ₂	$E_{1/2} (M^+/M^*) = -0.81 \text{ V vs SCE}$ $E_{1/2} (M^*/M^-) = +0.77 \text{ V vs SCE}$ $E_{1/2} (M^+/M) = +1.29 \text{ V vs SCE}$ $E_{1/2} (M/M^-) = -1.33 \text{ V vs SCE}$
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Working Hypothesis for the Trifluoromethylation. Credit: JIN Jian

The combination of photoredox catalysis and a diaryl sulfoxide provides a platform for the facile generation of CF₃ radical from trifluoroacetic acid under mild conditions. The resultant CF₃ radical would then add to the (hetero) arene substrate, followed by an oxidative re-aromatization process to afford the trifluoromethylated (hetero) arene product.

This protocol is applicable for chlorodifluoromethylation and perfluoroalkylation as well. And a diverse array of arenes and heteroarenes were successfully transformed into valued fluoroalkylated compounds.

"We anticipate this visible light-promoted C-H fluoroalkylation method will find broad application," said Professor Jin Jian who led the project.

This work was supported by the Natural Science Foundation of Shanghai, the Shanghai Institute of Organic Chemistry of the Chinese Academy of Sciences.

More information: Dehang Yin et al. Photoredox Catalytic Trifluoromethylation and Perfluoroalkylation of Arenes Using Trifluoroacetic and Related Carboxylic Acids, *Cell Reports Physical Science* (2020). [DOI: 10.1016/j.xcrp.2020.100141](https://doi.org/10.1016/j.xcrp.2020.100141)

Provided by Chinese Academy of Sciences

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