Organic synthesis, Drug development, Photocatalysis

Metal-free photocatalytic systems for trifluoromethylation and oxygenation of aromatic compounds

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Abstract

9-(4-Chloro-2,6-xylyl)-10-methylacridinium has been shown to generate long-lived photoelectron transfer states with high oxidizing and reducing power upon photoirradiation. By using this molecule as a photoredox catalyst, efficient trifluoromethylation of aromatic compounds was successfully achieved under metal-free, room temperature, and visible light irradiation.

Background & Results

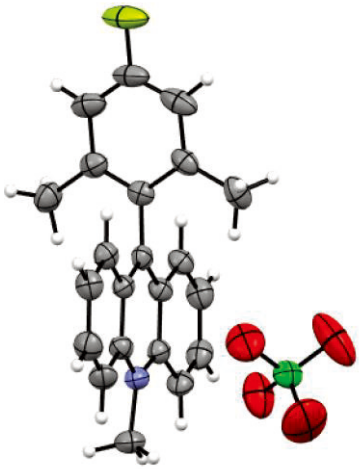
It is widely known that molecules to which fluorine substituents are introduced generally exhibit very high biological activity, which has led to the synthesis of compounds containing fluoromethyl groups, especially trifluoromethyl groups, attracting the attention of many researchers. Such compounds are in particularly high demand in the life science field, including drug discovery, because they play important roles in the fields of pharmaceuticals and agrochemicals. However, despite their importance, metal catalysts have conventionally been considered essential for the reaction that directly converts the C-H bond of aromatic compounds and introduces a trifluoromethyl group. Therefore, similar reactions using metal-free catalyst systems have not been reported.

On the other hand, metal catalysts have a high environmental impact, and their use is often restricted, especially in the production of pharmaceuticals, because residual metal impurities in the products can be problematic. For this reason, a metal-free catalyst system was sought. Photocatalytic reactions using light have attracted attention here. Photocatalysis uses light as an energy source to promote chemical reactions, and unlike conventional reactions that rely on heat or chemical reagents, photocatalysis is characterized by its clean and energy efficiency.

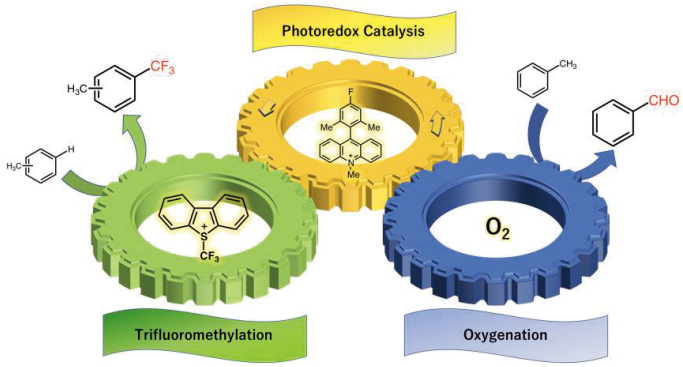
In this technology, 9-(4-chloro-2,6-xylyl)-10-methylacridinium (Acr^+-XylCl), which exhibits high oxidizing and reducing power and generates long-lived electron-transfer state when irradiated with visible light, was used as a photocatalyst. This photocatalyst is superior in its ability to effectively activate the C-H bonds of aromatic compounds by visible light excitation and to directly introduce trifluoromethyl groups. This makes it possible to achieve trifluoromethylation reactions in metal-free catalyst systems. It is also clear that the catalyst can be used for highly efficient and selective oxygenation of toluenes to benzaldehydes by electron-transfer oxidation.

Significance of the research and Future perspective

New reaction techniques based on photoredox catalysts offer great potential for improving sustainability in chemical synthesis. In our study, we have developed a metal-free catalytic system, which enables efficient activation of C-H bonds of aromatic compounds and direct introduction of trifluoromethyl groups without the use of conventional metal catalysts. Furthermore, by utilizing the strong oxidative power of photocatalysts, they have succeeded in a reaction that oxygenates simple compounds such as toluene and converts them into valuable compounds such as benzaldehyde. This oxygenation reaction can use oxygen or air as an oxidant, making it a safe and energy-efficient process that does not require conventional peroxides or high oxidants. Although regulations on metal residues are strict in pharmaceutical development, this technology is expected to be an effective method because it is metal-free.



A photoredox catalyst: 9-(4-chloro-2,6-xylyl)-10-methylacridinium (Acr^+-XylCl) perchlorate



Photoredox catalytic systems for trifluoromethylation and oxygenation

Patent Japanese Patent No. 5470623, No. 5213142

Treatise Ohkubo, Kei et al. 9-(4-Halo-2,6-xylyl)-10-methylacridinium ion as an effective photoredox catalyst for oxygenation and trifluoromethylation of toluene derivatives. ACS Catalysis. 2024, 14, 2671-2684. doi: 10.1021/acscatal.3c06111

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