

## Visible-Light-Induced Direct $\alpha$ C–H Functionalization of Alcohols

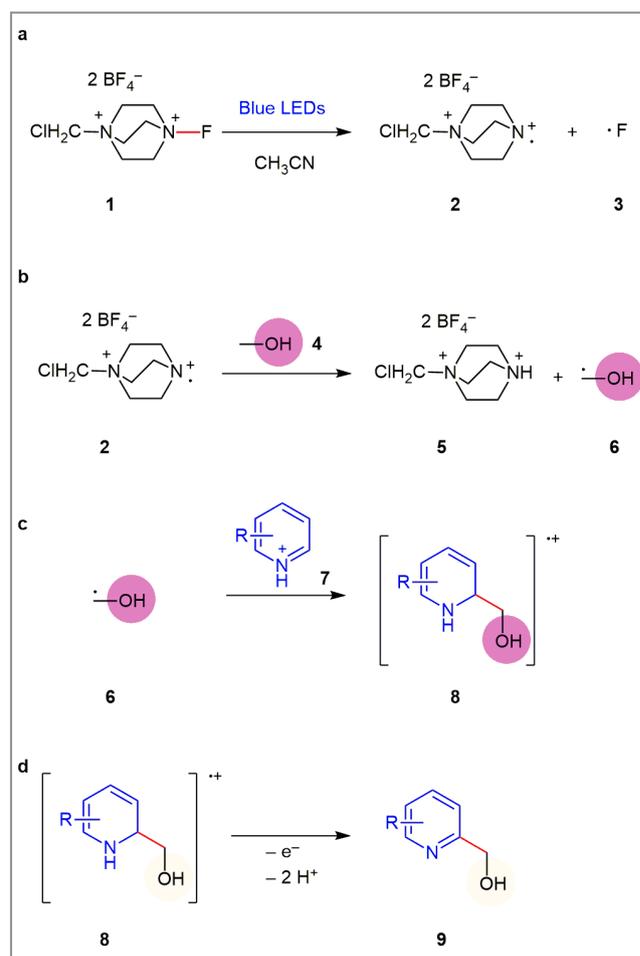
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Alcohols are ubiquitous and widely used raw starting materials with broad applications in organic chemistry, the pharmaceutical industry and chemical engineering, to name just a few. For this reason, having ready access to a broad range of alcohols through the selective  $\alpha$  C–H functionalization of alcohols would be of great significance. “The photocatalytic oxidative  $\alpha$   $sp^3$  C–H arylation of alcohols is still a challenge, especially in the presence of ethers also having  $\alpha$   $sp^3$  C–H bonds,” said Prof. Aiwen Lei, from The College of Chemistry and Molecular Sciences, Institute for Advanced Studies, Wuhan University (P. R. China). According to Professor Lei, although much attention has been paid to the oxidative  $\alpha$   $sp^3$  C–H arylation of ethers with electron-deficient heteroarenes under a photocatalytic oxidation system, it is notable that the analogous reaction of alcohols had not yet been demonstrated. “Therefore, visible-light-induced oxidative  $\alpha$   $sp^3$  C–H arylation of alcohols with electron-deficient heteroarenes to introduce an active alcoholic hydroxyl group is of great synthetic significance,” he added. Selectfluor is well known as a powerful fluorination reagent and oxidant, frequently used in combination with a metal catalyst or photocatalyst. “The N–F bond breaking of Selectfluor can be achieved by electron donation from an external reductant. Conversely, direct visible-light-induced N–F activation of Selectfluor is desirable but rarely described. We hypothesized that activated Selectfluor may exhibit different selectivity for oxidative  $sp^3$  C–H  $\alpha$ -arylation of alcohols and ethers,” said Professor Lei, whose research group recently reported that Selectfluor – under visible-light irradiation – can effectively promote the oxidative cross-coupling between alcohols and heteroarenes, without external photocatalysis, leading to the selective  $\alpha$   $sp^3$  C–H arylation of an alcohol, even in the presence of an ether.

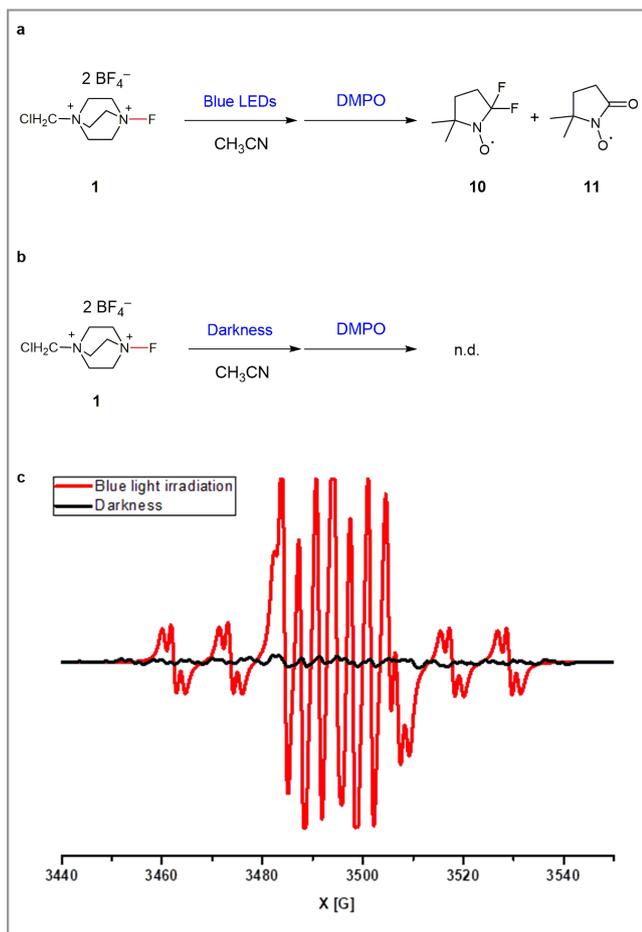
“At first, we questioned whether visible-light irradiation could induce the N–F activation of Selectfluor to directly yield the corresponding N radical cation and F radical (Scheme 1a),” said Mr. Linbin Niu, a co-author of this study. He continued: “The generated N radical cation is responsible for the fission of an  $\alpha$   $sp^3$  C–H bond of the alcohol to form the hydroxyalkyl radical (Scheme 1b). Afterwards, the electron-deficient heteroarenes – protonated by an acid – can capture the relatively nucleophilic radical and deliver the corresponding radical adducts (Scheme 1c). The oxidation and deprotonation of this radical adduct by another Selectfluor molecule would then afford the  $\alpha$ -arylated product (Scheme 1d).” Under the de-

signed oxidation conditions, the spin center shift process of the intermediate can be avoided and the carbinolic hydroxyl group is unaffected, leading to the oxidative  $\alpha$   $sp^3$  C–H functionalization of alcohols with heteroarenes.

“This assumption that the N–F activation of Selectfluor could be achieved by blue-light irradiation was subsequently confirmed by electron paramagnetic resonance (EPR) experiments,” added Mr. Niu. Two kinds of radical signals were observed, when Selectfluor in acetonitrile was irradiated by blue LEDs and when 5,5-dimethyl-1-pyrroline *N*-oxide (DMPO) was employed as a radical scavenger (Schemes 2a and 2c). Another co-author, Mr. Shengchun Wang, explained: “One of



**Scheme 1** The designed reaction pathways



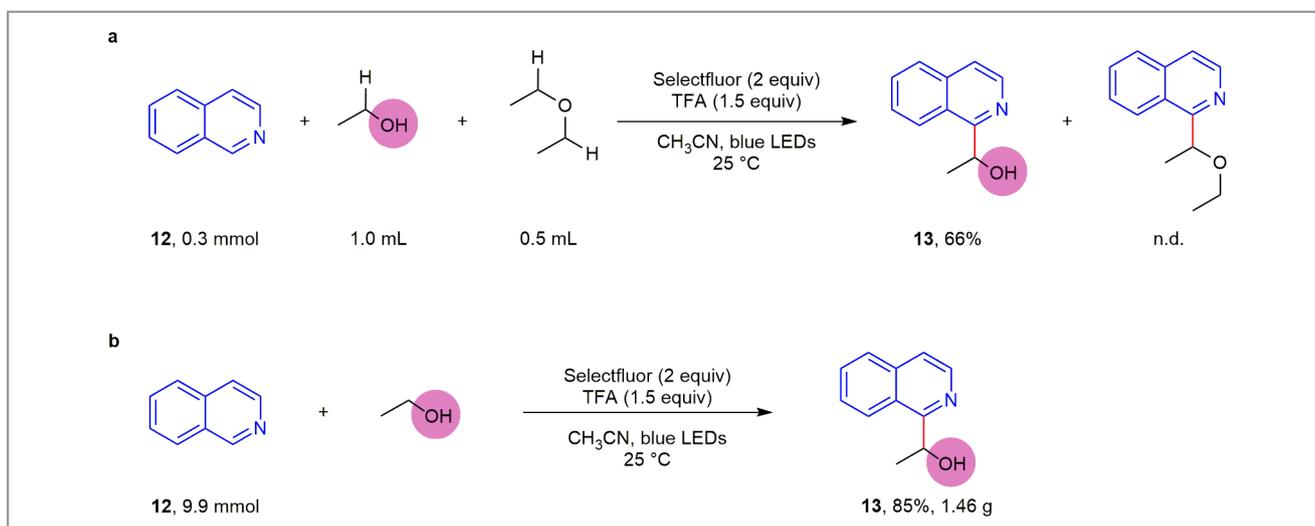
**Scheme 2** The electron paramagnetic resonance (EPR) experiments

the radicals, **10**, was confirmed as the radical adduct between two fluorine radicals and DMPO, while the other one, **11**, resulted from the oxidation of DMPO, where the ratio of **10**:**11** is 3:8.” In contrast, the team did not detect the radical adduct between two fluorine radicals and DMPO under darkness (Schemes 2b and 2c).

“It is significant that the single selectivity and good yield for the oxidative  $\alpha$   $sp^3$  C–H arylation of alcohols in the presence of an  $sp^3$  C–H of an ether were observed (Scheme 3a),” said Mr. Niu, continuing: “The gram-scale experiment carried out by Jiamei Liu demonstrates the potential utility of this protocol (Scheme 3b).”

“In summary,” said Prof. Lei, “we have developed a visible-light-induced oxidative  $\alpha$   $sp^3$  C–H arylation of alcohols with heteroarenes, which is promoted by Selectfluor under blue LED irradiation. What is essential for this protocol is the N–F activation of Selectfluor achieved by blue-light irradiation. These observed reactivities may have significant implications for further chemical transformations.”

*Matters female*



**Scheme 3** Investigation and application of this protocol. (a) Intermolecular competition experiment. (b) Gram-scale synthesis experiment.

## About the authors



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**Linbin Niu** was born and grew up in Zhengzhou, Henan Province (P. R. of China). He received his B. S. degree from Zhengzhou University (P. R. of China) in 2015 before moving to Wuhan University (P. R. of China) to further his studies in organic chemistry, directed by Prof. Aiwen Lei. Now, he is a PhD student and his research interests are photocatalysis, electrocatalysis, and nanocatalysis.



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Prof. A. Lei

**Aiwen Lei** graduated from Huaibei Normal University (P. R. of China) in 1995 and obtained his PhD at the Shanghai Institute of Organic Chemistry, Chinese Academy of Science (P. R. of China) in 2000, directed by Prof. Xiyan Lu. He worked as a post-doctoral fellow in the Department of Chemistry at Pennsylvania State University (USA), with Prof. Xumu Zhang from 2000 to 2003. Then he joined the group of Prof. James P. Collman at Stanford University (USA) working as a research associate for two years. Finally, he joined Wuhan University (P. R. of China) as a professor in 2005. His research interests are organic synthesis methodology, physical organic chemistry, electrocatalysis, photocatalysis, nanocatalysis and biomimetic catalysis.



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