Ketones and Aldehydes as Alkyl Radical Equivalents for C–H Functionalization of Heteroarenes

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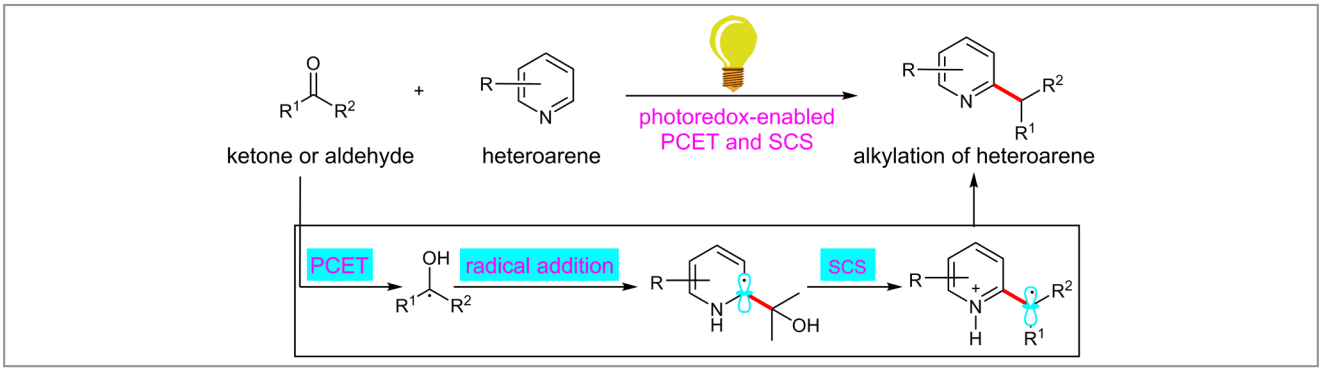
The use of aldehydes as umpolung nucleophilic reagents is a classic strategy in synthetic organic chemistry, which has complemented the use of carbonyl compounds as electrophilic partners in countless reactions with a very broad range of organometallic reagents, ylides and other nucleophiles. There have also been reports of aldehydes used as alkyl radicals, resulting from oxidative decarbonylation (for references see the original article). However, the use of aldehydes and ketones as radical equivalents in which the radical is centered on the carbonyl carbon is far less common, and the viability of such an innovative approach has been recently investigated in a paper published by the group of Professor Qingmin Wang at Nankai University (Tianjin, P. R. of China). These authors have developed a new catalytic activation mode that involves a combination of Proton Coupled Electron Transfer (PCET) and a RiboNucleotide Reductase (RNR) class I reaction to enable



Scheme 1 Proposed direct installation of alkyl groups using ketone or aldehyde under mild photoredox conditions. SCS = (3,2)-spin-center shift.

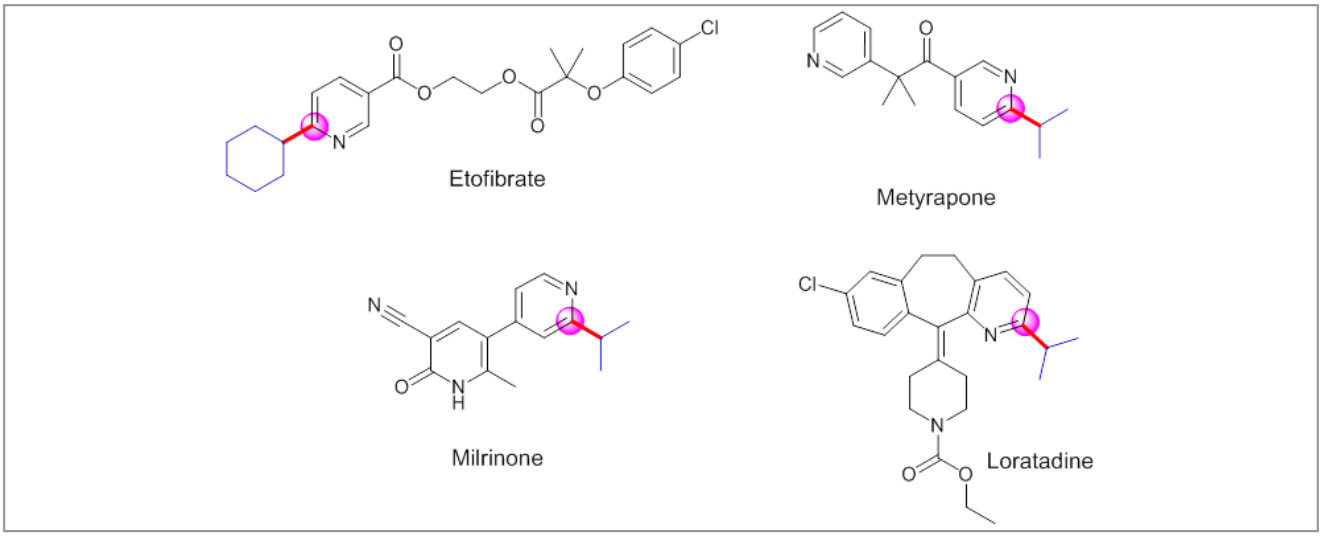


Figure 1 The new alkylation protocol for late-stage functionalization can be used to produce several complex natural products and drug molecules.

C–H alkylation of heteroarenes using ketones and aldehydes as alkyl radical sources under mild conditions, without the need for oxidants or high temperatures.

Professor Wang explained: "For the success of the transformation, we had to overcome two important challenges: first, ketones and aldehydes generally act as electrophilic alkyl groups and are difficult to couple to *N*-heteroarenes due to polarity mismatch. Second, it is difficult to get alkylation products that forge a new bond at the carbonyl carbon for aldehydes due to competing decarbonylation."

According to Professor Wang, this mild protocol represents a general use of abundant commercially available ketones and aldehydes as latent alkyl radical equivalents, which greatly expands and enriches the portfolio of reactions that can be performed with carbonyl compounds.

"We have applied this new protocol for the late-stage functionalization of several complex nitrogen-containing natural products, organic materials, small-molecule drugs, and ligands," said Professor Wang. He concluded: "We hope that this method can help the development of new drugs and new materials."

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