PHOTOREDOX-CATALYZED ALKYLATION OF HETEROAROMATIC BASES USING ETHYL ACETATE AS ALKYLATING AGENT

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The direct C-H functionalization of heteroaromatic compounds is an emerging field in modern organic synthesis. Functional group introduction through C-H activation, for instance the Minisci-reaction, needs strong oxidizing agents and high temperature.[1] Solvents having C-H bond adjacent to an oxygen (alcohol, ether or ester) can be cleaved via a hydrogen atom transfer (HAT) process, and the corresponding radical (alkyl group usually) can react with the heteroarene directly, giving benzyl alcohol derivatives. Using alcohols as coupling agents, radical-mediated elimination of H_2O via a spin-center shift (SCS) followed by a proton-coupled electron transfer (PCET) could alternatively lead to alkylated products instead of hydroxyalkylated derivatives.[2,3]

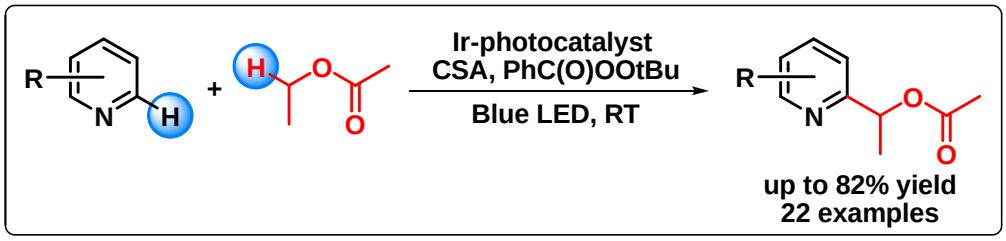

Figure 1. Photoredox $C(sp^2)$-$C(sp^3)$ cross-dehydrogenative-coupling

Our ongoing research demonstrates, that heteroaromatic rings can be alkylated in radical fashion employing EtOAc both as solvent and alkylating agent under visible-light photoredox conditions. Heterocyclic α-methyl benzyl alcohol derivatives were obtained by using catalytic amount of camphorsulfonic acid (CSA), TBBP (*tert*-butyl perbenzoate), $(Ir[dF(CF_3)ppy]_2(dtbpy))PF_6$ as photocatalyst and blue LED-light. Under the optimized conditions 22 compounds were successfully isolated on 2 mmol scale with yields up to 82%. The selected examples mainly consist of quinoline-, isoquinoline- and quinazoline derivatives possessing potential pharmacophore properties. Moreover, our model compound was synthesized on 5 g scale in a yield of 63% demonstrating the robustness of the protocol.

[1] Minisci, F.; Giordano, C.; Vismara E.; Levi; S.; Tortelli, V. *J. Am. Chem. Soc.* **1984**, *106*, 7146.

[2] Jin, J. and MacMillan, D. W. C. *Nature* **2015**, *525*, 87.

[3] Huff, C. A.; Cohen, R. D.; Dykstra, K. D.; Streckfuss, E.; DiRocco, D. A. and Krska, S. W., *J. Org. Chem.* **2016**, *81*, 6980.