

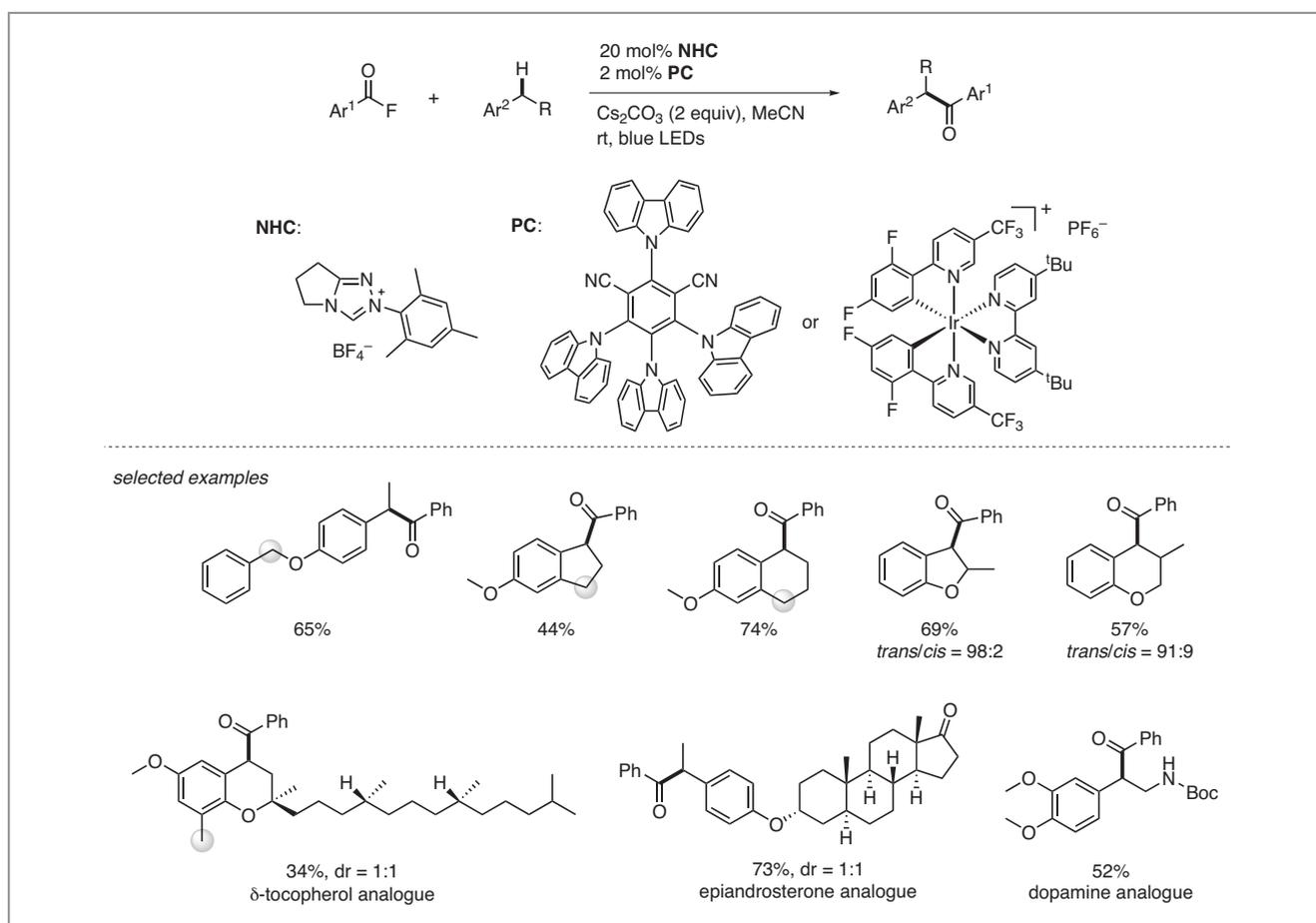
# Benzylic C–H Acylation by Cooperative NHC and Photoredox Catalysis

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The acylation of a C–H bond is a powerful and straightforward approach for the synthesis of ketones. “Acylation of arene  $sp^2$  C–H bonds, as shown in classical Friedel–Crafts reactions, is very well developed, while less progress has been achieved for  $sp^3$  C–H bond acylation,” said Professor Armino Studer of the Westfälische Wilhelms-University Münster (Germany). He further argued: “Considering that many bioactive compounds contain benzylic C–H bonds in their skeletons, acylation of such sites would be highly interesting and useful, particularly if site-selective functionalization can be achieved for substrates bearing more than one benzylic C–H bond. That

approach would ideally also allow for late-stage acylation of complex compounds, e.g. natural products, drugs or drug candidates.”

Professor Studer’s group has a long-standing interest in N-heterocyclic carbene (NHC) catalyzed radical transformations, which could offer a potential solution to the challenging issue posed by site-selective late C–H acylation. “Cross-coupling of benzylic radicals with NHC-stabilized ketyl-type radicals generated *in situ* is feasible, as realized in our recently disclosed radical alkene acyltrifluoromethylation,” said Professor Studer, explaining that: “A key consideration in achieving



**Scheme 1** Cooperative photoredox/NHC catalysis for site-selective acylation of benzylic C–H bonds

acylation of benzylic C–H bonds is to find an efficient way to generate benzylic radicals with concomitant single electron transfer (SET) reduction of acylazolium ions. Such acylazolium ions should be generated *in situ* by reaction of an acyl donor with the carbene catalyst, in a process that must be compatible with C-radical generation. Moreover, to close a redox catalysis chain, generation of the benzylic radical should be achieved via an SET-oxidation process, rendering the whole cascade a redox-neutral process.”

Following this approach, the Münster group recently demonstrated the feasibility of the acylation of benzylic C–H bonds using cooperative NHC- and photocatalysis. The generation of the benzylic radical occurs by SET-oxidation of the arene and subsequent deprotonation. “It is notable that excellent site selectivity was observed, even for systems bearing two benzylic sites. Interestingly, the bond dissociation energy of the benzylic C–H bond is not the regiochemistry-determining factor, it is the deprotonation of the arene radical cation,” said Professor Studer. He continued: “Apparently, the deprotonation approach offers an advantage over intermolecular C–H abstraction for the site-selective generation of benzylic radicals.” In order to demonstrate the potential of their strategy, late-stage benzylation of three biologically active compounds was carried out with high regioselectivities.

“Compared with other protocols for acylation of benzylic C–H bonds that proceed via metal-catalyzed or ionic pathways,<sup>2–5</sup> our method provides a mechanistically distinct process featuring radical–radical cross-coupling,” remarked Professor Studer. He concluded: “This work opens new avenues in the area of direct C–H bond acylation and asymmetric transformations are expected.”

*Mattes Tanaka*

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Prof. A. Studer

**Armido Studer** received a B.S. degree and a PhD in chemistry from ETH Zürich (Switzerland, with Prof. Dieter Seebach) in 1991 and 1995, respectively, and conducted postdoctoral research at the University of Pittsburgh (USA, with Prof. Dennis Curran) before he obtained his Habilitation at ETH Zürich in 1996. Then he moved to the Philipps-Universität Marburg (Germany), working as an associate professor (2000–2004). He has been a full professor of organic chemistry at the Westfälische Wilhelms-Universität Münster (Germany) since 2004. He is the recipient of several awards including the ERC Advanced Grant (2016) and the Pedler Award of the Royal Society of Chemistry (2019), and is an elected member of the German National Academy of Sciences ‘Leopoldina’ (2020).