C(sp^3)–H Methylation Enabled by Peroxide Photosensitization and Ni-Mediated Radical Coupling

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Methylation of organic molecules is increasingly emerging as a very useful structural modification and biological profiling strategy in the rational design of bioactive compounds and drugs. In fact, a relatively subtle structural modification stemming from the introduction of a methyl group has the potential to strongly alter both pharmaco-dynamic and pharmaco-kinetic profiles of a drug candidate, as a consequence of changes in its stereo-electronic properties. According to Professor Shannon Stahl, from the University of Wisconsin-Madison (USA), methylated building blocks are a staple of medicinal chemistry library designs. "For example," explained Professor Stahl, "when an amine building-block is chosen to be included in a screening library, it is likely that various methylated analogues of that building-block will also be evaluated, if they are commercially available. The introduction of a methyl group can significantly affect the properties of the resulting drug lead. There are cases where the installation of a methyl group results in thousand-fold improvements in potency or results in defining drops in toxicity." Despite the importance of testing the outcome of introducing a methyl group at a C–H site, synthetic options are limited. Conventionally, 'magic methyl' effects are uncovered by screening methylated building blocks or by rerouting syntheses to incorporate a methyl group at an early stage. State-of-the-art protocols for C–H methylation are still encumbered by the use of directing groups or unsafe high-reactivity reagents. "My student Aris Vasilopoulos conceived a general C–H methylation strategy that features a 'radical relay' approach based on Kharasch–Sosnovsky C–H functionalization methods. These methods use a transition-metal catalyst and a peroxide-based oxidant," noted Professor Stahl.

Professor Stahl and Dr. Vasilopoulos, who led the experimental studies, began studying Kharasch–Sosnovsky-type reactions in the context of Cu-catalyzed benzylic C–H arylation using di-tert-butyl peroxide with aryl boronate esters. Aris explained, "These studies revealed a means to convert C–H into C–C bonds, but also highlighted a problem with C–H substrate conversion." He continued: "Under the 90 °C reaction temperature, low conversion of C–H substrate was observed, which led to solvent-level use of the C–H substrate, which would not be amenable to application on valuable drug-like compounds. We postulated that the tert-butoxyl radical formed from peroxide activation was competitively undergoing β-scission to form methyl radical and acetone, that was preventing efficient C–H substrate activation by hydrogen-atom transfer (HAT)." Literature studies from the 1960s by Wagner supported this hypothesis and revealed that HAT is more favorable at reduced temperatures. Other studies revealed that the peroxide could be activated at these reduced temperatures by using a photosensitizer with light. Professor Stahl noted that if the C–H substrate could be activated with limiting C–H substrate in the presence of a transition metal that can methylate the resulting intermediate, a new methylation reaction could be identified. This set of hypotheses set the stage for high-throughput experimentation efforts, led by Dr. Vasilopoulos at Merck's laboratories in Kenilworth, NJ (USA).

At Merck, Dr. Vasilopoulos screened a wide range of reaction parameters such as metal salts, ligands, photocatalysts, light sources, peroxides, acid and base additives, methyl sources, and solvents in 96-well arrays in search of an initial hit. In the first two-week Merck visit, nearly 1000 reactions were tested, but almost all of them showed no conversion of starting material. Dr. Vasilopoulos explained: "The reaction conditions that did show conversion either had 1–10% conversion to a possible methylated product or had conversion to a C–H oxygenation product (usually observed with tert-butyl hydroperoxide). One photocatalyst that showed 1–10% conversion of C–H substrate in these tests was $Ir[dF(CF_3)ppy]_2{}^{t\text{Bu}}bpyPF_6$ and, coincidentally, I found an unopened vial of 100 mg of this compound underneath my bench at UW-Madison." Testing this photocatalyst under relevant conditions with di-*tert*-butyl peroxide at UW-Madison led to a confirmed hit for 10% yield of methylation of ethylbenzene to cumene to be identified, with >50% conversion of the starting material. This reaction hit was then optimized for one substrate at Merck, using over ~2000 reactions, and then optimized in parallel for 8–12 other drug-like substrates, using over another 1000 reactions, to arrive near the final conditions published in the paper. Professor Stahl elaborated: "Mechanistic studies were then conducted to untangle the role of each reaction component as it relates to either HAT, β-scission, and/or C–C bond formation."

"The C–H activation reactivity allowed by photoactivation of di-*tert*-butyl peroxide is remarkably robust and tolerant of diverse functionality," said Professor Stahl, who continued:

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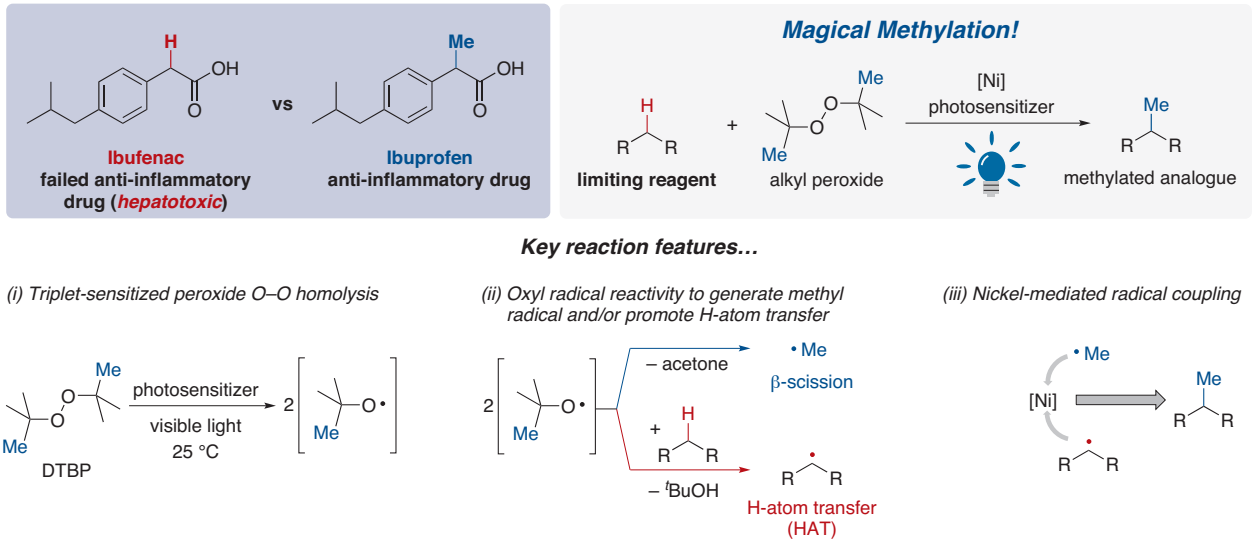

Scheme 1 The reported methylation and its key reaction features

"It is possible that this platform can be used to enable other 'radical relay' C–H functionalization reactions, such as other alkylation reactions." The identified methylation reaction conditions have been efficacious for methylation of several lead compounds. "Hopefully, it is only a matter of time before the reaction leads to identification of a 'magic methyl' effect in a bona fide drug lead," noted Professor Stahl.

Professor Stahl concluded: "Ultimately, this reaction offers a practical one-step non-directed late-stage C(sp^3)–H methylation reaction that uses all commercially available reagents. These features offer considerable advantages over other existing methods and should facilitate uptake by other researchers."

About the authors

Dr. A. Vasilopoulos

Aris Vasilopoulos was born in Nashua, NH (USA) and raised in the neighboring town of Amherst. He earned his B.S. degree in chemistry with a minor in computer science from Boston College (USA), where he also conducted three years of undergraduate research under the mentorship of Prof. Jeffery Byers. Aris then moved to the Midwest and specialized in organic chemistry at UW–Madison (USA) where he studied oxidative cross-coupling reactions in Prof. Shannon Stahl's research group. After obtaining his Ph.D. at UW–Madison, Aris joined the Advanced Chemistry Technology group at AbbVie in the greater Chicago area where he now explores and applies novel methods and techniques to medicinal chemistry programs.

Dr. S. W. Krska

Shane W. Krska was born in Deadwood, S.D. (USA). He received a B.S. in chemistry from the South Dakota School of Mines and Technology (USA) in 1992 and a Ph.D. in inorganic chemistry from the Massachusetts Institute of Technology (USA) in 1997 under the direction of Prof. Dietmar Seyferth. After conducting postdoctoral research with Professor Robert Bergman at the University of California, Berkeley (USA), he joined Merck & Co., Inc. as a senior research chemist in 1999. Dr. Krska has held positions in chemical engineering research and development, process research, and, most recently, discovery chemistry. He currently serves as distinguished scientist in the high-throughput experimentation and lead discovery capabilities group within discovery chemistry. His research interests include the development of high-throughput experimentation workflows and applications of catalysis to drug discovery and development.

Prof. S. S. Stahl

Shannon S. Stahl was born in Park Ridge, IL (USA). He obtained his B.S. degree from the University of Illinois at Urbana-Champaign (USA) in 1988 and a Ph.D. from Caltech (USA) in 1997 under the direction of Prof. John Bercaw. He was an NSF postdoctoral fellow at the Massachusetts Institute of Technology (USA) from 1997–1999, working with Prof. Stephen Lippard. He began his independent career at UW-Madison (USA) in 1999. His research group specializes in catalysis, with an emphasis on oxidation reactions, with applications to chemical synthesis, biomass conversion, and electrochemistry. Chemical synthesis efforts primarily target applications to pharmaceutical and fine chemical synthesis, and his industrial collaborations in this domain have been recognized by a US EPA Presidential Green Chemistry Challenge Award and the ACS Award in Affordable Green Chemistry.

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