Triiodide-Mediated δ-Amination of Secondary C–H Bonds

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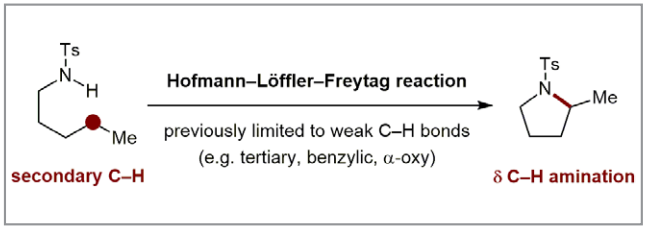
A recent article published by the group of Professor David Nagib from The Ohio State University (USA) describes a highly innovative chemical method that enables the δ-amination of secondary C–H bonds within a large range of unactivated amines bearing biologically relevant functionalities (Scheme 1).

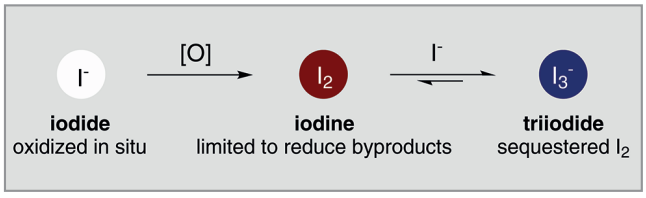
Professor Nagib explained: "This work is the first discovery from our lab that we expect will serve as the cornerstone of our entire program focused on remote C–H functionalization. As we set out to begin our research on selective C–H functionalization, we quickly realized that a general strategy for the δ-amination of secondary C–H bonds remains an unsolved problem." In fact – as explained by Professor Nagib – although the century-old Hofmann–Löffler–Freytag (HLF) reaction (Scheme 2) has been developed to solve this challenge in the context of biased amines containing weak C–H bonds (e.g. tertiary, benzylic, α-oxy), a solution does not yet exist for applying this approach to the δ-selective amination of secondary C–H bonds.

"It is understood that the requisite use of I_2 in the modified Suarez–HLF reaction limits synthetic scope and utility due to competitive byproducts associated with I_2 decomposition," said Professor Nagib. "Others have attempted to address this I_2 problem through portion-wise or sub-stoichiometric addition of I_2; however, neither approach has been able to solve the long-standing challenge for δ-amination of unbiased, secondary C–H bonds, due to the either insufficient or excessive reactivity of those methods."

Professor Nagib continued: "In this manuscript, we presented a new strategy in which I_2 is prepared in situ from NaI and rapidly trapped as a triiodide (I_3^-) species (Scheme 3). By sequestering the necessary, albeit prone to forming by-products, I_2 as I_3^-, we have demonstrated that this new triiodide strategy can solve the ongoing synthetic challenge of δ-amination of unactivated, secondary C–H bonds."

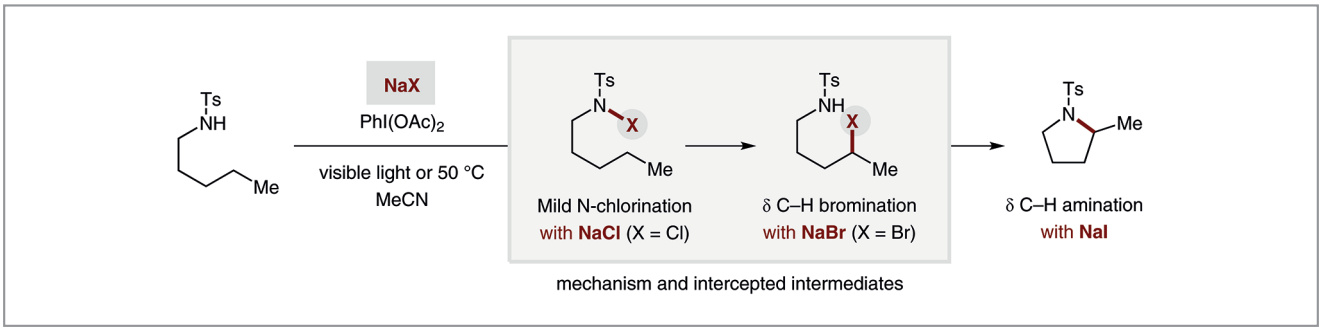


Scheme 2 The Hofmann–Löffler–Freytag (HLF) reaction



Scheme 3 The triiodide strategy enables amination of unbiased C–H bonds by sequestering I_2 as I_3^-

"At first, we had been trying to catalyze this reaction also with CuI," explained Professor Nagib. He added: "Yet, we were amused that as we added less and less catalyst (while adding more NaI salt), we still observed the same (or better) efficiency. We ultimately decided that the only thing better than 1–2% catalyst loading is 0%. And replacing it with salt, which is nearly free, is great too!"



Scheme 1 The new δ-amination methodology

During his undergraduate studies, Ethan Wappes' research was in the field of organic electrochemistry. "The moment Ethan realized that triiodide – a common electron mediator in batteries – was the key to solving this synthetic method, it was a very fortunate déjà vu experience!" said Professor Nagib.

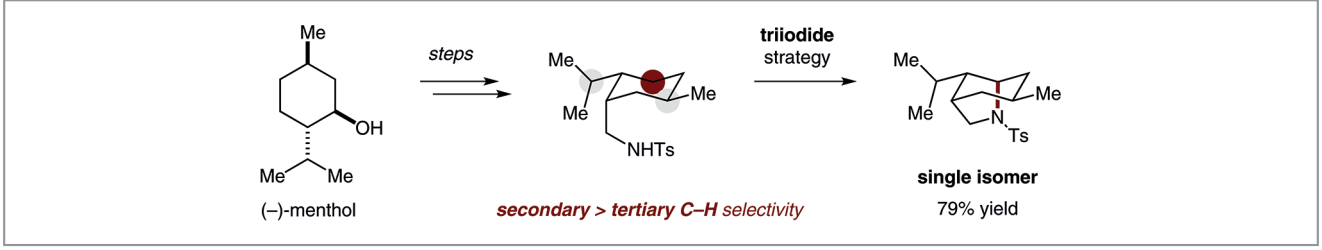
The broad impact, significance, and synthetic utility of this triiodide strategy have been demonstrated in the δ-amination of a wide range of amines containing unbiased, secondary C–H bonds (Scheme 4). "Notably, many of the pyrrolidine products that we efficiently generate through this approach have been previously inaccessible due to the limitations of the I_2-based methods," said Professor Nagib. "Furthermore, the broad tolerance of this transiently trapped I_3^- approach to biologically relevant functionality (e.g. ethers, esters, ketones, arenes, and organofluorines) suggests that this strategy will have broad applicability across many research areas at the frontiers of organic synthesis."

"Importantly, this manuscript includes significant mechanistic evidence to support the role, presence, and utility of triiodide in our hypothesized strategy," remarked Professor Nagib. "For example, UV-Vis spectroscopic evidence of this reaction confirms the presence of increasing triiodide absorption that correlates with increasing (and unprecedented) reaction efficiency in the presence of added NaI. Furthermore, sequestration of I_2 as I_3^-, which we proposed would lead to efficient product formation, is corroborated by significantly cleaner crude ^{1}H NMR spectral data that indicate a termination of the major byproduct formation pathways (Figure 1)."

He continued: "Perhaps most importantly, we have intercepted and characterized a pair of proposed intermediates by replacing the NaI starting material for NaCl or NaBr salts. These examples of interrupted mechanisms point to the mildness of this new reaction method as well as the opportunity to extend this strategy to avoiding unwanted byproducts in other polyhalide-mediated reactivity."

Professor Nagib revealed that in a private communication, Professor Richmond Sarpong of UC Berkeley (USA) has called this work a "Nice solution to an age-old problem!" Additionally, he has expressed interest "in using robust ways (like yours) in alkaloid synthesis" and even stating: "There is a total synthesis we are working on where this could come in handy."

Professor Nagib concluded: "We anticipate that due to the prevalence of pyrrolidines in pharmaceuticals (fifth most common heterocycle in US FDA approved drugs) this chemistry



Scheme 4 One of the synthetic applications of the new method

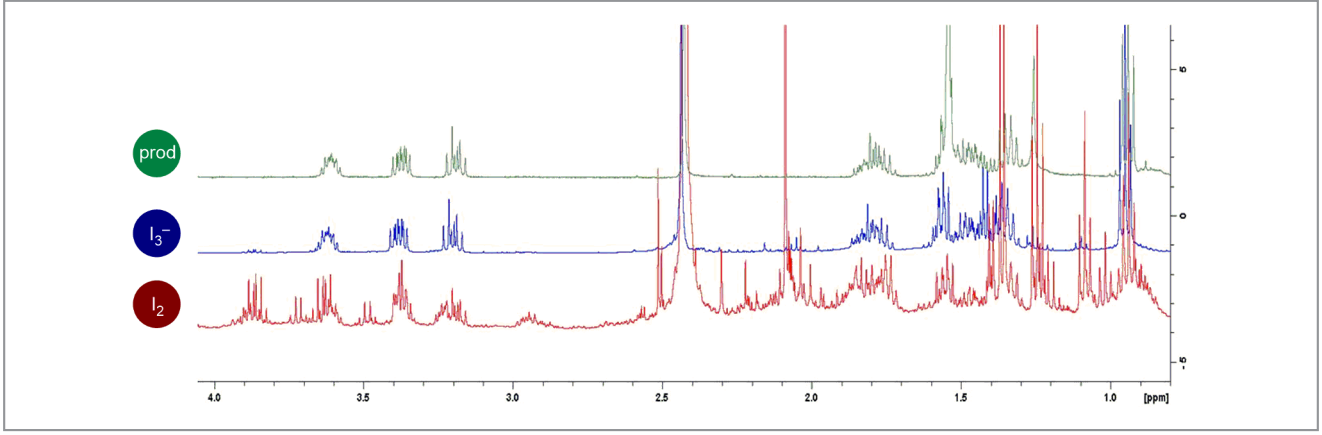


Figure 1 ^{1}H NMR analysis of new I_3^- strategy vs I_2 reaction applied to the synthesis of *N*-tosyl-2-*n*-propyl-pyrrolidine

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will be particularly valuable for chemists in both industrial sectors (e.g. medicinal chemistry) as well as in the academic community (especially in the field of C–H functionalization). We hope that many people will use our simple, new method for derivatizing their secondary C–H bonds."

About the authors

From left: S. Fosu, Prof. D. Nagib, E. Wappes

Ethan Wappes (Fort Wayne, IN, USA) earned a B.Sc. with honors at Indiana University (USA) in 2014, where he studied electrochemical ring-expansions with Professor Dennis Peters. At Ohio State University (OSU, USA), he has been awarded a Charles Waring fellowship (OSU) and honorable mention by the National Science Foundation (NSF) Graduate Research Fellowship program.

Stacy Fosu (Macomb, IL, USA) earned a B.Sc. at the University of Illinois at Urbana-Champaign (USA) in 2011 and her M.Sc. from Illinois State University (USA) in 2014, where she synthesized novel benziporphyrins with Professor Timothy Lash. At OSU (USA), she has been awarded a Chemistry-Biology Interface Program fellowship and is a Howard Hughes Medical Institute (HHMI) Gilliam Fellow.

Trevor Chopko (Akron, OH, USA) earned a B.Sc. with honors at The Ohio State University (USA) in 2016, where he developed radical-mediated C–H functionalizations with Professor David Nagib and was a fellow of the OSU Honors & Scholars Center. He is currently an intern in the Translational Imaging division of Merck & Co.

David Nagib (Philadelphia, PA, USA) earned a B.Sc. with honors at Boston College (USA) (Scholar of the College, 2006), while desymmetrizing alcohols via de novo peptide catalysts with Professor Scott Miller. At Princeton University (USA) (Ph.D., 2011), he developed new trifluoromethylation reactions via photoredox catalysis with Professor David MacMillan. As an NIH Postdoctoral Scholar at the University of California, Berkeley (USA, 2014), David studied C–H activation via oxidative gold mechanisms with Professor F. Dean Toste, and catalysis in post-synthetically modified metal-organic framework materials with Professor Omar Yaghi. David is an Assistant Professor in the Department of Chemistry and Biochemistry at The Ohio State University (USA), where his team's research on radical-mediated C–H functionalization has been recognized with a 2015 Doctoral New Investigator Award by the American Chemical Society Petroleum Research Foundation (ACS PRF) and a 2016 Outstanding Investigator Award by the National Institutes of Health (NIH MIRA).

When not working alongside their awesome labmates, Ethan, Stacy, Trevor, and David enjoy running, reading, baking, building miniature pyramids, and exploring Columbus' great food, art, and music scenes.

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