

Directed β -C–H Amination of Alcohols via Radical Relay Chaperones

J. Am. Chem. Soc. **2017**, *139*, 10204–10207

The 1,2-hydroxyamino unit is ubiquitous in natural compounds and pharmacologically active molecules, thus representing a major synthetic target in organic chemistry. Although a number of syntheses of β -amino alcohols are available, chemists still devote considerable efforts towards developing novel strategies for improving atom economy, expanding the scope and maximizing the environmental sustainability of the methods for producing this key structural unit.

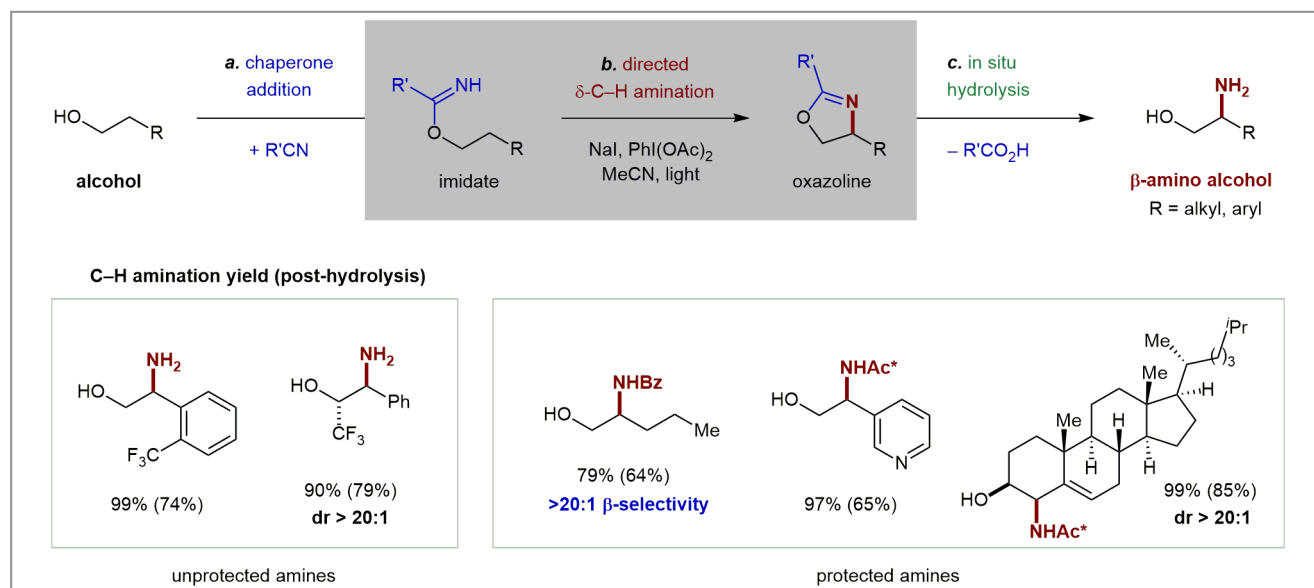
Recently, a new paper describing an innovative radical-mediated approach that enables the β -C–H amination of alcohols, which represents the first example of the ‘radical relay chaperone’ concept, was published by the group of Professor David A. Nagib at The Ohio State University (Columbus, USA). Professor Nagib explained: “Simple, traceless tethers (e.g. imidates) can be appended to ubiquitous functional motifs – such as hydroxyl groups – to enable directed C–H functionalization of a wide range of molecules, including drugs and bioactive compounds. As a proof-of-principle, we have developed a new and efficient method for the synthesis of β -amino alcohols via the regioselective C–H amination of alcohols.”

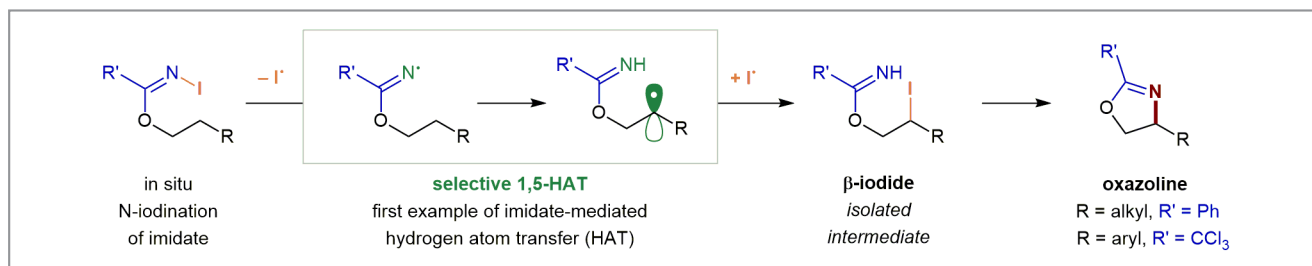
“Previously, the elegant work from the lab of Professor Du Bois (Stanford University, USA) represented the best approach for β -C–H amination of an alcohol derivative (i.e. carbamate),”

said Professor Nagib (for references see the original *JACS* article). “In a similar vein, Professors He (The University of Chicago, USA) and Lebel (University of Montréal, Canada) have reported the only other examples of this reaction, also employing Rh or Ag nitrenoids. Interestingly, for many years following these initial reports, further developments in nitrene-based C–H amination chemistry had been predominantly in the area of γ -C–H amination – as demonstrated, for example, by the important recent contributions of the Wisconsin-based group of Professor Schomaker – leaving an unmet need in the area of vicinal, β -amino alcohol synthesis,” added Professor Nagib.

“Our radical-mediated strategy offers synthetic complementarity relative to the use of metal-nitrenes, and also offers the advantage of a broadened scope, which includes the possibility of using a range of unbiased aliphatic alcohols, as well as secondary alcohols,” explained Professor Nagib. He continued: “In this paper we included examples of many different classes of alcohols, showcasing a wide range of functional group tolerance that is an important feature of our new radical-mediated approach.”

“Importantly, we have developed a one-pot protocol in which an alcohol is rapidly converted into its β -amino analogue via in situ conversion into imidates, directed C–H amination,





Scheme 2 Mechanism of triiodide-mediated C–H amination

and hydrolysis to NH₂ group,” remarked Professor Nagib. “And we think it’s pretty cool that this entire process (alcohol to β-amino alcohol) is completed in a single afternoon!”

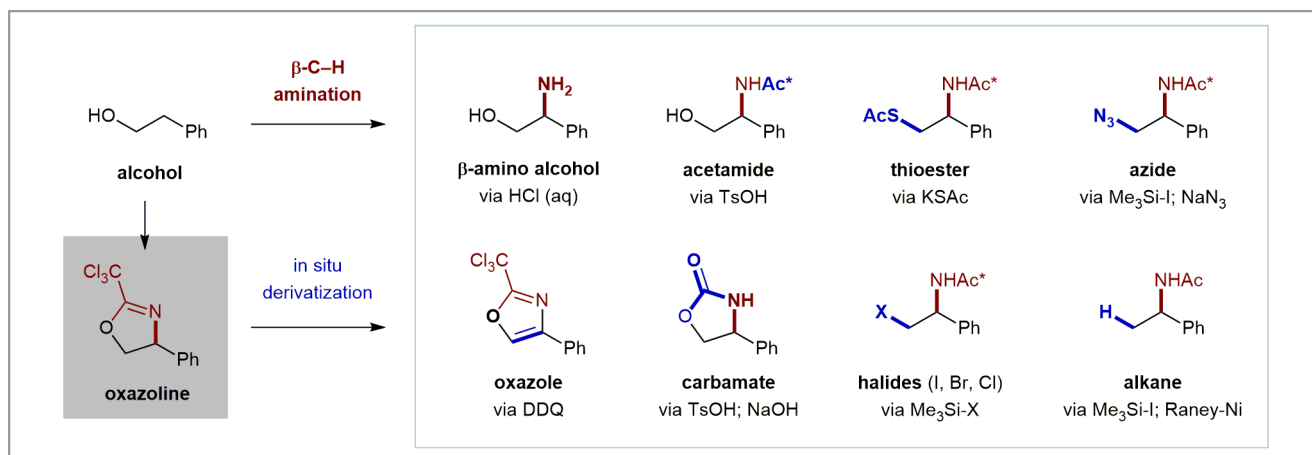
Professor Nagib revealed that after tirelessly searching for two years to find the right chaperone (and observing many radical-mediated decomposition mechanisms along the way), the group knew that they had achieved a major breakthrough as soon as they tested the imide-based scaffold, since this chaperone gave quantitative C–H amination at the first try. Professor Nagib joked: “Ethan and Kohki prefer basketball, but they were certainly dancing plenty that day!”

The trichloroimidates that the group employed in this chemistry are quite popular synthetic intermediates thanks to the Overman rearrangement. “Interestingly, in a great biographical perspective, Professor Overman describes the serendipitous discovery of his eponymous rearrangement while he was actually trying to discover a method to convert allylic alcohols into β-amino alcohols, but instead recovered allyl amines,” said Professor Nagib, who added with a smile: “We are grateful that Overman’s lab was distracted by their beautiful chemistry, allowing us to discover this C–H amination approach to access that original target.”

The group borrowed the term ‘chaperone’ from the field of biology, where it describes a protein that helps to direct the folding of other proteins. “Similarly, we thought this name provided a perfect way to describe our idea that a traceless promoter could interact with a molecule via a common motif (an alcohol in this case), initiate a radical cascade, and then be removed to leave behind a molecule with significantly more value than its precursor,” explained Professor Nagib.

The group performed mechanistic experiments to shed insight into the underpinnings of this process, which is the first example of a 1,5-hydrogen atom transfer (HAT) initiated by an imide radical. “Our experiments indicate that the HAT event is rate-limiting with kinetic isotope effect values up to 8. Stereochemical experiments also differentiate this radical mechanism from the nitrenoid pathway,” said Professor Nagib. He continued: “For example, in this β-C–H amination, the stereochemistry is defined by the intramolecular substitution event. Knowledge of this mechanism has enabled us to develop a second-generation chaperone that promotes C–H amination of unbiased, aliphatic alcohols.”

The broad impact, significance, and synthetic utility of this chaperone strategy has been demonstrated via β-amination



Scheme 3 Access to a family of C–H aminated products via in situ derivatization (Ac* = COCCl₃)

of a wide range of alcohols containing unbiased C–H bonds, tolerating a wide range of biologically relevant functionality (e.g. ethers, esters, amines, organofluorine compounds). “Notably, the oxazoline intermediate can also be further derivatized to a family of β -amines, which have never been previously prepared from alcohols in this manner,” said Professor Nagib.

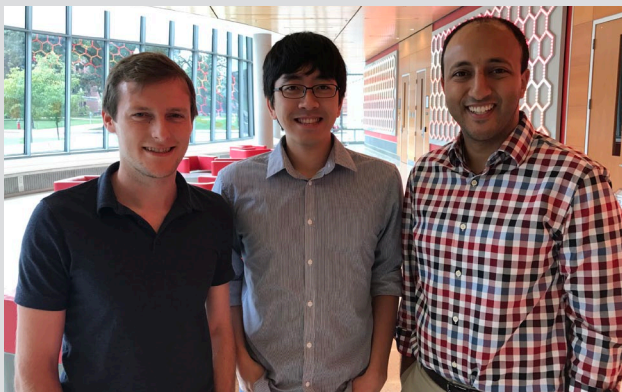
“We anticipate that due to the widespread presence of β -amino alcohols in highly valuable molecules (e.g. pharmaceuticals, natural products, and catalysts), this chemistry will be employed widely,” said Professor Nagib. He continued: “Furthermore, we expect that our lab and others’ (in both the burgeoning areas of radical chemistry and C–H functionalization) will be able to expand this strategy to develop other useful C–H functionalization reactions.”

Concerning future potential applications of the method, Professor Nagib remarked: “While presenting these findings at a recent conference, we were excited by the strong interest we heard from medicinal chemists in industry, who are interested in employing this strategy for the diversification of molecules in their drug-candidate libraries.”

He concluded: “Amines are ubiquitous in pharmaceuticals, agrochemicals, and ligand architectures; therefore, we hope that both the academic and industrial communities will take advantage of this new approach to rapidly synthesize β -amino alcohols directly from simple feedstock alcohols. We envisage that the simplicity, mildness, efficiency, and low cost of reagents featured by this strategy will enable a widespread use of radical relay chaperones for a number of synthetic applications.”

Matthew Farnish

About the authors



From left: E. Wappes, K. Nakafuku, Prof. D. Nagib

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 The Ohio State University (OSU, USA), he is a co-founder of the Nagib Lab, where he has pioneered triiodide-mediated C–H aminations, and he has been awarded an OSU Charles Waring Fellowship. He has also earned honorable mention from the National Science Foundation (NSF) Graduate Research Fellowship program, as well as a travel award from the American Chemical Society (ACS) Division of Organic Chemistry.

Kohki Nakafuku (Loveland, OH, USA) earned a B.Sc. with honors at Duke University (USA) in 2014, where he studied the kinetics and mechanism of gold-catalyzed allene racemization with

Professor Ross Widenhoefer. At OSU (USA), he is a co-founder of the Nagib Lab, where he has pioneered the development of new synthetic reactions via a radical relay chaperone strategy.

David Nagib (Philadelphia, PA, USA) earned a B.Sc. with honors at Boston College (USA) in 2006, where he studied alcohol desymmetrization via small enzyme-like catalysts with Professor Scott Miller. At Princeton University (PhD, 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), David studied C–H activation via oxidative gold mechanisms with Professor F. Dean Toste, and catalysis within metal-organic framework materials with Professor Omar Yaghi. Since 2014, David has been 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 by the American Chemical Society (PRF, 2015), National Institutes of Health (MIRA, 2016), National Science Foundation (CAREER, 2017), and the Thieme Chemistry Journals Award (2017). David was a finalist for the OSU Distinguished Undergraduate Research Mentor Award (2016), and has recently become a proud father.

Outside the lab, Ethan, Kohki, and David enjoy running local races that have beer, burgers, and brats at the finish line (but never paint-throwing!). Their other hobbies include watching college basketball, drawing hieroglyphs on papyrus, and enjoying great food, art, and music at Columbus’ many summer festivals.