Enantioselective Synthesis of D-α-Amino Amides from Aliphatic Aldehydes

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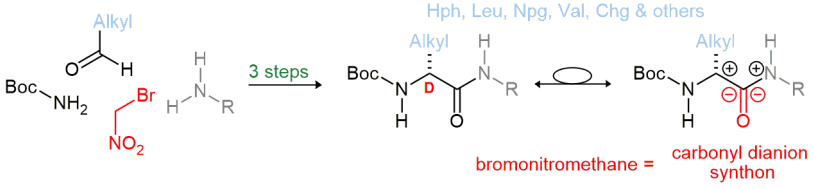
The development of a synthesis platform that provides access to any non-natural amino amide, with either configuration (L or D), in a peptide context is an overarching goal of Professor Jeffrey N. Johnston's group at Vanderbilt University (Nashville, USA). "Thinking long-term, for such a platform to be universally adopted, it needs to be based mostly on inexpensive starting materials that vary broadly in structure, provide the α-amino amide product in just a few steps, and be highly stereoselective," said Professor Johnston. "This work is a significant step in that direction, providing relatively general access to D-α-amino amides bearing alkyl side chains."

Professor Johnston continued by explaining that there are countless ways to prepare protected α-amino acids in enantio-enriched/pure form, but it's not clear that these are used very often in peptide synthesis, especially by a non-specialist. "Our goal is to simplify the homologation of a peptide chain with an unnatural amino acid without compromising the ideals of a synthetic organic chemist (1:1 stoichiometry, minimal waste generation, straightforward purification, in addition to high yield)," he said, continuing: "Our strategy is first to redirect focus from protected α-amino acids to an α-bromonitroalkane, a functional group that we've shown can serve as an acyl anion equivalent in amide synthesis (B. Shen, D. M. Makley, J. N. Johnston *Nature* **2010**, *465*, 1027). We've prepared many aryl glycine donors in this way, but we struggled to adapt our catalysis to enolizable *N*-Boc imines, the electrophile progenitors to α-alkyl α-amino amides. These electrophiles can easily convert into their non-electrophilic *N*-Boc enamide tautomers. This publication describes our use of chiral phase-transfer catalysis to solve a major part of this problem."

Palomo and co-workers developed an elegant enantioselective phase-transfer-catalyzed addition of primary nitroalkanes to *N*-Boc aldimines (*J. Am. Chem. Soc.* **2005**, *127*, 17622), and in order to dovetail this method with their synthetic plan, Professor Johnston and his co-workers simply needed bromonitromethane to substitute for nitromethane. "Certainly Palomo and co-workers merely overlooked this commercially available reagent, right?" Professor Johnston commented, ironically. He continued: "Well, when Ken – PhD student Kenneth Schwieter – first added bromonitromethane to cesium hydroxide, he quickly learned that the solid base was rather resentful of this bait-and-switch. There was significant heat generated, and the evolution of a gas concomitant with an oily material coating the CsOH. To cut a long story short," said Professor Johnston, "Ken ultimately reasoned that an *aliphatic* nitroalkane might 'temper' the solid base, producing a heterogeneous catalyst amenable to productive reaction with bromonitromethane. The protocol he developed successfully avoids the decomposition, allowing the desired reaction to occur."

According to Professor Johnston, this is the first use of bromonitromethane in an enantioselective aza-Henry reaction with enolizable imines. The chiral non-racemic alkyl β-amino-α-bromonitroalkane products are α-amino amide precursors that can be incorporated into any peptide via Umpolung Amide Synthesis (UmAS) coupling with an amine. The sequence provides homologation in only three steps from an aliphatic aldehyde. "This method for the synthesis of α-amino amides is competitive with current literature methods, and Figure 2 in the *Chem. Sci.* paper provides a comparative analysis of key methods to homologate with Boc-D-Adod," explained Professor Johnston, who concluded: "Experimentally, the biggest challenge was overcoming the incompatibility of $CsOH{\cdot}H_2O$ and bromonitromethane, which was achieved by the addition of a nitroalkane additive. Curiously, Ken also found that the presence of the nitroalkane additive led to an



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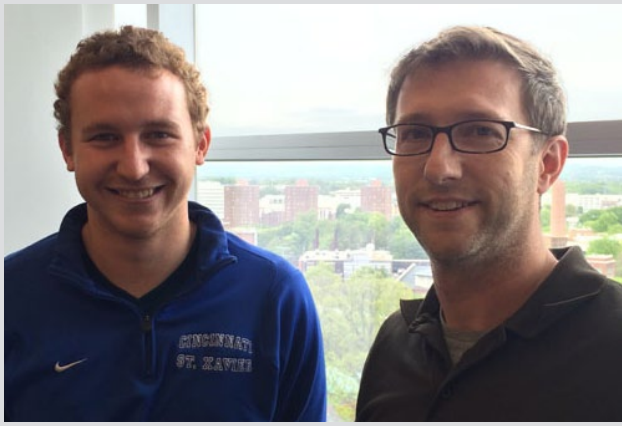
increase in enantioselection – clearly the synthetic chemist's bonus for brokering peace between CsOH and bromonitromethane!"

About the authors



From left: K. E. Schwieter, Prof. J. N. Johnston

Kenneth E. Schwieter was born and raised in Cincinnati, OH (USA). He received his B.S. degree in chemistry from Xavier University in Cincinnati in 2011. He is currently a Ph.D. student at Vanderbilt University (USA) under the mentorship of Professor Jeffrey Johnston. His research focuses on the enantioselective synthesis of α-amino amides and Umpolung Amide Synthesis (UmAS) reaction development.

Jeffrey N. Johnston received his Ph.D. in 1997 from The Ohio State University (USA), working with Professor Leo A. Paquette, and worked as an NIH Postdoctoral Fellow with David A. Evans at Harvard University (USA). In 1999, he began his independent career at Indiana University (USA), moving to Vanderbilt University (USA) in 2006 where he is currently Stevenson Professor of Chemistry. His group is focused on reaction and reagent development that realizes the synthesis chemist's ideals of efficiency and streamlined access, ultimately enabling complex molecule synthesis.

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