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Jeffrey studied chemistry and philosophy at Trinity University in San Antonio, Texas, where he worked in the research group of Prof. Michael P. Doyle. After PhD studies at the the California Institute of Technology and ETH Zürich with Prof. Erick M. Carreira, he spent two years in Japan as a JSPS postdoctoral fellow with Prof. Keisuke Suzuki at the Tokyo Institute of Technology. In 2003, he began his independent career in US, at UC-Santa Barbara and then the University of Pennsylvania. In 2010, he moved to the Swiss Federal Institute of Technology (ETH) in Zürich, Switzerland, as a full Professor in the Laboratory of Organic Chemistry. Since 2013, he is also a Principal Investigator at the Institute of Transformative bio-Molecules at Nagoya University, where the Bode Group has a satellite laboratory.

Since starting his academic career, Jeffrey's research and teaching have been recognized by numerous awards including an Arthur C. Cope Scholar Award (2008), and and Elias J. Corey Award for Outstanding Original Contribution in Organic Synthesis by a Young Investigator (2011). He has also served as Chair of the Editorial Board for *Organic and Biomolecular Chemistry* (2011–2014) and is currently an Executive Editor for *Encyclopedia of Reagents for Organic Synthesis* and co-Editor-in-Chief of *Helvetica Chimica Acta*.

Research

Overview

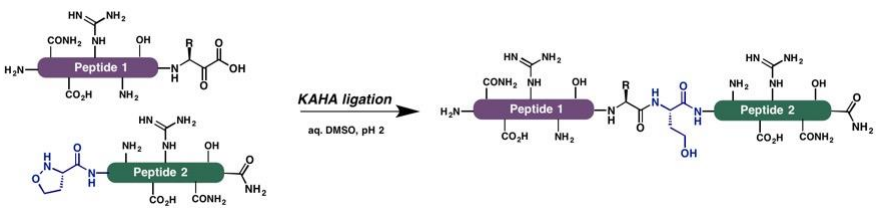
The goal of our research group is the synthesis of molecules and conjugates that are currently outside the reach of conventional synthetic methods. Preparing molecules such as proteins, glycopeptides, sequence and length-controlled polymers, and covalent conjugates of these large structures (mw >5,000) requires a new generation of chemical reactions. Most importantly, bond forming reactions that operate under aqueous conditions in the presence of unprotected functional groups with fast reaction rates are needed if chemists will ever be able to synthesize structures with the complexity and functional properties commonly found in biological systems.

The Bode Group also seeks new methods to generate structural and functional complexity in small organic molecules. For example, we have pioneered facile approaches to chiral saturated N-heterocycles, as exemplified by our SnAP Reagents. All of our efforts are supported by the development of fundamentally new organic reactions including catalytic processes, new cross-coupling methodologies, and chemical ligation reactions.

These ambitions are currently manifested in multiple projects across many scientific disciplines. While all members practice synthetic organic chemistry, our labs also include molecular and cellular biology, peptide synthesis, materials science, physical organic chemistry, hardware and software development, and extensive analytical and chromatographic facilities.

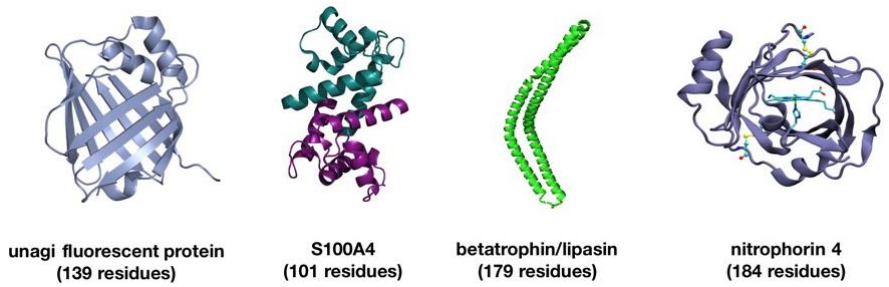
Protein synthesis with the ketoacid-hydroxylamine (KAHA) ligation

The ability to chemically synthesize biologically active proteins in a controlled fashion is one of the greatest achievements of synthetic chemistry in the last 20 years. As part of these efforts, our group reported the α-ketoacid–hydroxylamine (KAHA) ligation as a chemoselective coupling of large, unprotected peptide segments. The KAHA ligation employs C-terminal peptide α-ketoacids (KAs) and N-terminal peptide hydroxylamines (HAs), which react chemoselectively to form amides or esters. This reaction proceeds in aqueous media without reagents or catalysts.



By developing new building blocks and chemical reactions, we can now easily prepare large peptide segments (40+ residues) bearing the necessary reaction partners – C-terminal peptide α-ketoacids and N-terminal peptide hydroxylamines – by standard

Fmoc-SPPS. Along with innovative, orthogonal protecting group strategies, we can easily iterate segment ligations for the synthesis of protein targets up to about 200 residues. Recent examples of proteins prepared with the KAHA ligation include Pup, CspA, UFM1, SUMO2, SUMO3, S100A4, Nitrophorin 4 and betatrophin(lipasin).



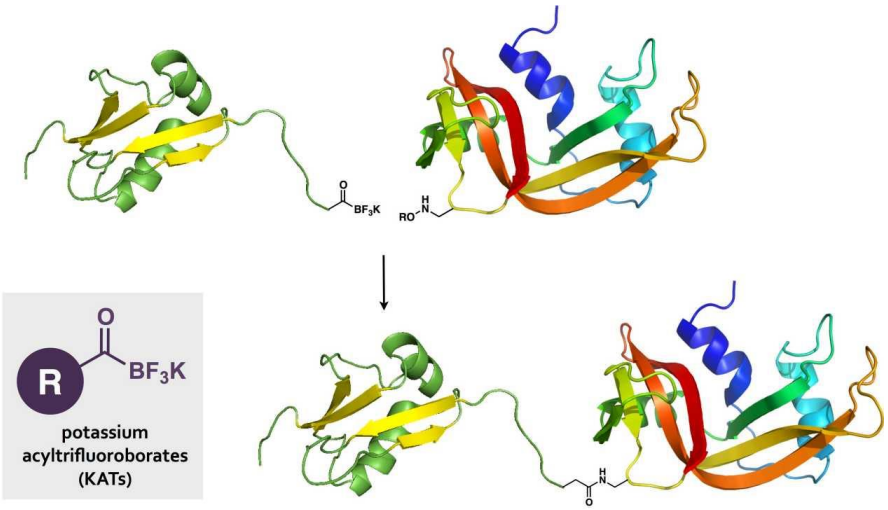
unagi fluorescent protein (139 residues) | S100A4 (101 residues) | betatrophin/lipasin (179 residues) | nitrophorin 4 (184 residues)

Our ability to prepare synthetic proteins with any kind of unnatural amino acids, post-translational modification, fluorescent tag, or synthetic handle forms the basis of our increasing efforts in chemical biology and the synthesis of synthetic proteins of therapeutic interest.

Acylboronates for amide-forming bioconjugation

A major limitation of many chemoselective reactions – including our own KAHA ligation – is relatively slow reaction rate. This prevents the conjugation of large molecules under the dilute (1 mM or less) concentrations suitable for their solubilization and handling. An ideal ligation reaction for synthetic applications such as protein–protein conjugation would employ stable, easily introduced functional groups and proceed under aqueous conditions at room temperature with a second order rate of 10 M^{-1} s^{-1} or faster. [104]

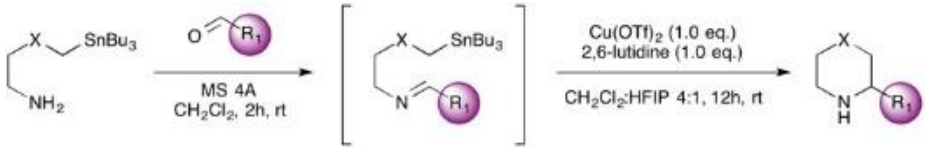
To meet this challenge, we have identified potassium acyltrifluoroborates (KATs) as unique, stable functional groups that undergo rapid amide-forming ligations with hydroxylamines. [67,90] These ligations proceed in aqueous media, in the presence of fully unprotected functional groups, with rate constants up to 100 M^{-1} s^{-1}, depending on the structure of the KAT and reaction pH. We have established several new methods for the synthesis of KATs and other acylboronates and their incorporation into peptides, polymers, proteins, and small molecules, including N-heterocycles.



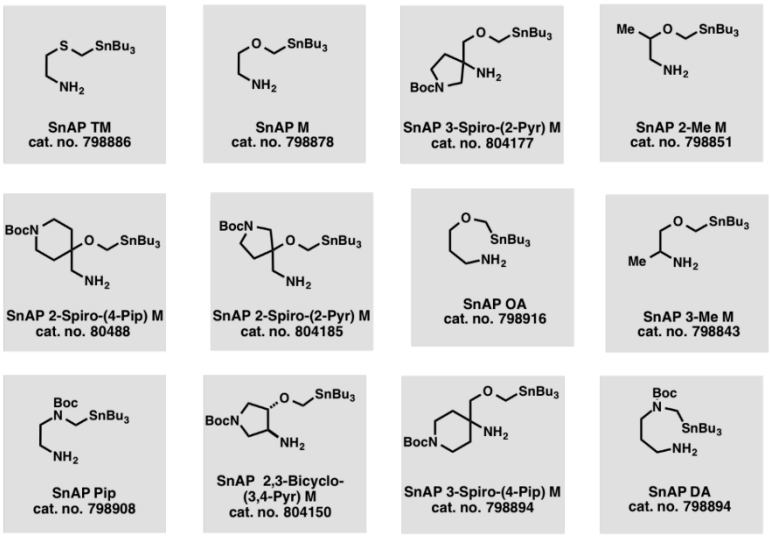
This conjugation reaction provides a new approach to the synthesis of complex molecules such as protein-protein, protein-polymer, and protein–small molecule conjugates. The KAT ligation also serves as an ideal reaction for the formation of hydrogels. We are currently studying the application of KATs within fields such as protein chemistry and material science, emphasizing the versatility of these molecules and the opportunity for even greater breakthroughs yet to come.

N-heterocycle synthesis with SnAP chemistry

Saturated N-heterocyclic building blocks are of growing importance in modern small molecule pharmaceuticals, but their synthesis often requires long, inflexible routes or difficult to remove N-protecting groups. In order to establish a cross-coupling approach to C-substituted, N-unprotected morpholines, piperazines, thiomorpholines, diazepanes, and other compounds, including bicyclic and spirocyclic N-heterocycles, we have developed SnAP Reagents for the one-step synthesis of these compounds from aldehydes and ketones.



SnAP Reagents are an ever-expanding class of reagents, which are now available for the convenient one-step synthesis of medium-ring (6-9 membered) saturated N-heterocycles, including bicyclic and spirocyclic structures. They are easy to use, work with a wide variety of aldehydes and ketones – including heteroaromatics, and provide predictable access to some of the most valuable structures in modern drug development. Thanks to the support of an ERC Proof of Concept Grant, many of the SnAP Reagents are now commercially available from Sigma-Aldrich.

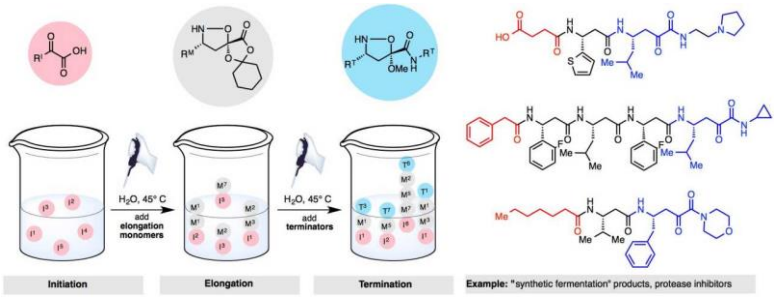


More recently, we have developed catalytic variants and established that the mechanism involves a radical pathway. [112] Based on these findings, we are developing new reagent classes using different precursors, such as silicon and halogen based reagents.

Synthetic Fermentation

The beauty of microbially produced natural products is that complex, stereochemically rich, biologically active molecules can be grown in aqueous media without organic solvents, reagents, or toxic byproducts.

Inspired by microbial fermentation, we have developed "synthetic fermentation," a technique where small molecule building blocks can be coupled together in aqueous media, with no organisms, enzymes or reagents, to furnish unprotected organic molecules. These "cultures" can be used directly in biological assays. Thousands of molecules can be "grown" in aqueous media in a few hours using nothing more than a pipette and a multi-well plate.



Our best implementation produces β-peptide oligomers using variants of our KAHA and KAT ligation, As a proof-of-concept, this technique has already been used to identify an inhibitor of hepatitis C virus NS3/4A protease with a half-maximum inhibitory concentration of 1.0 μM. Work is currently ongoing on further therapeutic applications, such as the discovery of new antibiotics, as well as broadening the scope

of the technique through product diversification and expansion of the building block library.

Secret, high-risk projects

Our lab always maintains a culture of innovation and risk-taking. Students are often involved with innovative projects either to develop entirely new chemistry or to use the discoveries we have made in unconventional ways. Current examples include new syntheses and applications of hydrogels, novel macrocycles, catalysis, automated organic chemistry, chemical sensing, and new applications of photochemistry. Creative ideas and ambitious students are always welcome!