An Oxazetidine Amino Acid for Chemical Protein Synthesis by Rapid, Serine-Forming Ligations

Highlighted article by I. Pusterla, J. W. Bode

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Dear Readers,

This new issue of SYNFORM could well be summarized by the score Switzerland – USA 2-2, which obviously reflects the countries of origin of the four articles that follow this Editorial. First to score was Switzerland, thanks to the elegant work of C. Mazet (Geneva University) who managed to get across the defense of a long-standing problem such as the stereochemistry control in the construction of the C(20) of steroids. But USA was not prepared to give up and the 1-1 materialized thanks to an asymmetric counter-attack of B. Borhan (Michigan State University) consisting of a stereoselective intermolecular chloro-etherification/esterification of allyl amides. But Switzerland took the lead again thanks to a stunning break down the wing of protein synthesis by J. Bode (ETH Zurich) who took advantage of a new powerful and versatile building block – an oxazetidine amino acid – for opening new routes to chemical ligation. But the resilient USA team didn’t surrender and re-equilibrated the score once again thanks to the skills of an up-and-coming materials chemist – B. Northrop (Wesleyan University) – who is the protagonist of the final interview. Man of the match? I know it might sound a bit cheesy, but that’s always you, dear readers...

Enjoy your reading!

Mattéo Zanda
Steroids are characterized by a prototypical cyclopenteno-phenanthrene ring system and a side chain attached to this polycyclic framework at C17. Driven by the distinguished biological activity differences between C20-(R) and C20-(S) isomers, the specific stereocontrolled construction of this exocyclic stereocenter is recognized as one of the most difficult challenges in the field (Review: Chem. Rev. 2014, 114, 6349). In 2010, Prof. S. Danishefsky pointed out that ‘One of the vexing problems in steroid total synthesis is that of exercising control of the configuration at C-20. The challenge is that of correlating the configuration of the presumably “freely rotating” C-20 with the resident stereochemistry of the polycyclic domain’ (J. Am. Chem. Soc. 2010, 132, 9567). The group of Professor Clément Mazet at the University of Geneva (Switzerland) has recently reported a stereospecific catalytic strategy for the perfectly stereocontrolled installation of C20, using a catalyst-directed diastereoselective isomerization of allylic alcohols.

Professor Mazet said: “The portfolio of current methods to stereoselectively construct C20 is rather limited and these strategies all come with severe limitations. In most cases, two distinct synthetic routes are needed to individually access each C20 epimer and a majority of these approaches follows long linear sequences employing stoichiometric rather than catalytic procedures.” He continued: “Repeated functional group manipulations often render these sequences lengthy and preclude rapid scale-up. Perhaps more importantly, ablation of the vicinal C17 stereocenter has been regularly practiced to facilitate stereocontrolled construction of C20 – indicating that installation of molecular complexity at one point of the molecule requires simplification on another part.”

Nominal modularity has been disclosed and almost invariably the steroidal derivatives possess a methyl substituent at C21. “As often in steroid chemistry, synthetic constraints preclude exploration of a chemical space that would match the contemporary standards for wide therapeutic investigations,” said Professor Mazet, continuing: “In order to facilitate structural diversification, at the outset of our investigations, we envisioned that an ideal strategy should be based on a common synthetic precursor and rely on the orthogonality provided by transition-metal-catalyzed cross-coupling methods.”

![Representative steroids and Mazet’s strategy](image-url)
In essence, the authors in this work developed a uniform yet modular synthetic route to access a variety of steroidal primary allylic alcohols with aryl, perfluorinated aryl, heteroaryl and alkyl substituents with perfect control of the olefin geometry. Professor Mazet said: “The development of catalytic enantioselective reactions from prochiral substrates is a recurrent challenge in modern organic synthetic chemistry. Nevertheless, the development of diastereoselective methods from advanced intermediates possessing multiple stereogenic centers where a chiral catalyst must control the absolute configuration of a given stereocenter independently of a highly complex environment certainly constitutes an even more demanding challenge.” Professor Mazet remarked: “We were pleased to achieve such high levels of diastereoselectivity in the catalyst-directed diastereoselective isomerization of steroidal allylic alcohols in both the match and mismatch situations (dr > 50:1).”

Compared to other approaches, the catalytic isomerization reaction is remarkable for its mildness and high level of stereochemical predictability. “A rationale based on the con-

Scheme 2 Stereocntrolled installation of C20 in steroids; all ratios are indicated as C20-(R):C20-(S). *A catalytic amount of 2,6-di-tert-butyl-4-methylpyridine is required. † Isolated as the corresponding saturated alcohol.
formational lock of allylic alcohols around C17–C20 both in solid state and in solution has been proposed to account for the high diastereoselectivities observed,” explained Professor Mazet. A range of allylic alcohols containing electron-rich and electron-poor aryl or heteroaryl substituents are well tolerated and the stereospecific nature of the reaction provides access to the natural C20-(R) and unnatural C20-(S) configurations. Professor Mazet commented: “The scope of our method is further highlighted through structural diversification in the side chain and within the polycyclic domain of advanced and complex steroidal architectures.”

A number of challenges were encountered in this work. Professor Mazet revealed that the first challenge he and his co-worker met was the development of a short and modular synthetic route that would give access to geometrically pure (E)- and (Z)-allylic alcohols and simultaneously facilitate structural diversification. He said: “We spent half a year on this and were finally able to get straightforward access to geometrically pure steroidal (E)-enol tosylate and (Z)-enol triflate intermediates.” Professor Mazet acknowledged that the procedures independently reported by Tanabe (Org. Lett. 2008, 10, 2131) and Frantz (Org. Lett. 2008, 10, 2901) were instrumental in the successful development of this approach. High-yielding stereo-retentive Negishi cross-coupling reactions were performed from these key intermediates to enable structural diversification at C21. Professor Mazet said: “During this exercise, we were able to capitalize on some recent advances in Negishi cross-coupling reactions reported by the Buchwald group (Angew. Chem. Int. Ed. 2013, 52, 615). Once optimized, we also demonstrated that these reactions were amenable to multi-gram scales.”

Comparative analyses of the crystal structures of the model substrates chosen for establishing the method, as well as bidimensional NMR analyses, revealed the existence of a conformational lock around C17–C20 both in solid state and in solution for aryl-substituted allylic alcohols and enabled the authors to propose a rationale for the high levels of diastereoselectivity observed. Another challenge faced by the authors was that the heterocyclic-containing substrates proved particularly sensitive to traces of acid generated during the isomerization reaction – presumably upon decomposi­tion of the active iridium hydride. Professor Mazet remarked: “To circumvent this issue, we found that the use of catalytic amounts of the non-coordinating base 2,6-di-tert-butyl-4-methylpyridine (DTBMP) was beneficial to the reaction.”

Professor Mazet recalled: “We have been working on the iridium-catalyzed isomerization of allylic alcohols for about seven years. After initially identifying conditions where a hydrogenation catalyst (i.e., Crabtree catalyst; Tetrahedron Lett. 2009, 50, 4141) could be turned exclusively into an isomerization catalyst, we subsequently developed several generations of chiral iridium complexes for the enantioselective variant of this transformation (Angew. Chem. Int. Ed. 2009, 48, 5143; Chem. Commun. 2010, 46, 445; Chem. – Eur. J. 2010, 16, 12736).” He continued: “Interestingly, it is only when exploring the catalyst-directed isomerization that we have been really delineating the functional group tolerance of our method. Specifically, the compatibility with unprotected sugar moieties, 1,3-diene motifs and azides was particularly unexpected.”

Concerning the future prospects of this work, because steroids with the epimeric non-natural C20 configuration (usually C20-(S)) are much rarer but distinguish themselves by significantly superior biological activities, the group believes that their findings have the potential to greatly simplify access to epimeric structural analogues of important steroid scaffolds for applications in biological, pharmaceutical and medical sciences.

Professor Mazet concluded: “Alkyl-containing substrates are more challenging at this stage as they affect regioselectivi­ty of iridium–hydride insertion. More efforts are still needed in order to stereoselectively install C20 stereochemistry with alkyl substituents.”
About the authors

**Houhua Li** studied carbohydrate chemistry under the supervision of Professor Xinshan Ye during his B.Sc. and M.Sc. degrees at Peking University (P. R. of China). In 2009 he moved to the National Institute of Biological Sciences (NIBS) and worked with Professor Xiaoguang Lei on Lycopodium alkaloid synthesis. He joined the University of Geneva (Switzerland) in 2011 to start his graduate studies in the group of Professor Clément Mazet. His research project focuses on Ir-catalyzed selective isomerizations of allylic alcohol.

**Clément Mazet** received his Ph.D. from the University of Strasbourg (France) under the supervision of Professor L. H. Gade (2002). After postdoctoral stays with Professor A. Pfaltz (University of Basel, Switzerland, 2003–2005) and Professor E. N. Jacobsen (Harvard University, USA, 2006–2007) he joined the University of Geneva (Switzerland) to establish his independent research program. His interests include mechanistic and synthetic chemistry with particular emphasis on all aspects of selective catalysis. He recently received the Zasshikai Lectureship Award from the University of Tokyo (2012) and the Werner Prize from the Swiss Chemical Society (2013).
Highly Stereoselective, Intermolecular Haloetherification and Haloesterification of Allyl Amides


Asymmetric alkene halogenation is a powerful synthetic transformation that allows for a straightforward functionalization of readily available compounds into valuable chiral, halogenated building blocks. Although isolated reports of enantioselective variants appeared in the literature in the 1990s, the expansion of the scope and robustness of this transformation has only occurred since 2010, when the group of Professor Babak Borhan at Michigan State University (USA) published a report of a highly enantioselective chlorolactonization reaction. Since then, this research area has witnessed dramatic progress with respect to the scope of transformations and mechanistic understanding. Numerous reviews on this chemistry have already appeared in this short time (see the original *Angew. Chem. Int. Ed.* manuscript for these and other leading references).

Recently, focus has shifted to the more challenging intermolecular halofunctionalization of alkenes. Although significant progress has been made in this area, some of the most readily available nucleophiles such as water and alcohols had yet to be demonstrated as viable nucleophiles for this chemistry. Professor Borhan explained: “At the outset of this project, the aim was to develop an intermolecular haloetherification reaction with a wide substrate scope and good stereoselectivities while using readily available catalysts and reagents.” The group identified many challenges very early in the project – 1) Preventing or minimizing facile intramolecular nucleophilic capture by the pendant amide nucleophile (i.e. halocyclization) while promoting intermolecular nucleophilic capture of the intermediate by the weakly nucleophilic alcohols; 2) Addressing regioselectivity issues in substrates that do not have an intrinsic electronic bias for the site of nucleophilic capture; this latter requirement would enable the inclusion of aliphatic alkenes as compatible substrates; and 3) Discovering conditions that could be used with a variety of nucleophiles and halenium precursors with little or no modifications – this promiscuity has thus far been elusive in asymmetric alkene halogenation reactions, thereby necessitating the discovery of a unique catalyst/reagent system for different halenium source-nucleophile combinations.

Professor Borhan remarked: “The first evidence for the feasibility of an intermolecular chloroetherification reaction came (rather ironically!) while studying a halocyclization reaction (*Angew. Chem. Int. Ed.* 2011, 50, 2593).” While examining the asymmetric chlorocyclization of substrate 1 to give the dihydrooxazine 3 in CF3CH2OH (TFE), the undesired ‘TFE-incorporated’ product 2 was isolated in as high as 35% yield with moderate levels of enantioselectivity (er = 82:18) and exquisite regioselectivity (>10:1; see Scheme 1). Professor Borhan continued: “This result was encouraging to say the least, given the low nucleophilicity of TFE and no precedent for an intermolecular interception of the putative intermediate by an alcohol. Efforts were then directed towards coaxing this reaction to proceed exclusively via the intermolecular nucleophilic capture pathway by the judicious choice of reaction conditions.”

Graduate student Bardia Soltanzadeh was able to demonstrate that numerous parameters such as the choice of the amide group, substrate concentration, solvent composition, temperature and catalyst loading could all be tweaked to promote intermolecular chloroetherification in preference to the...
halocyclization reaction. More importantly, these reaction parameters also affected the regioselectivity and enantioselectivity for the transformation. Professor Borhan explained: “Eventually, conditions were identified that gave >20:1 rr, >99:1 dr and up to >99:1 er for a variety of substrates for the chloroetherification reaction with MeOH as the nucleophilic component (see Scheme 2). Aliphatic alkenes (E-, Z- and tri-substituted alkenes) were the best substrates for this chemistry, whereas trans-styryl substrates gave lower yields due to competing halocyclization that could not be suppressed completely.”

In an effort to further showcase the generality of these conditions, other alcohols, water and carboxylic acids were evaluated as nucleophiles with both 1,3-dichloro-5,5-dimethylhydantoin (DCDMH, as the Cl source) and N-bromo-succinimide (NBS, as the Br source). All these reactions proceeded with excellent stereoselectivities (selected results are highlighted in Scheme 2).

Professor Borhan remarked: “Noteworthy is the fact that the chiral catalyst is responsible not only for the high enantioselectivities but also for the exquisite regioselectivity for reactions employing aliphatic substrates (for example, non-catalyzed reactions gave rr values of ~4:1 at best for these
substrates). These results hint at extensive pre-organization of the substrate-nucleophile-catalyst ternary complex in addition to the halogen source catalyst H-bonded complex that we have previously established (J. Am. Chem. Soc. 2010, 132, 3298).

According to Professor Borhan, the culmination of this work has addressed a well-known limitation in asymmetric alkene halogenation reactions. “Moreover, a fairly diverse substrate and nucleophile scope and the use of commercially available catalyst (DHQD2PHAL) and halogenating reagents (DCDMH or NBS) should make this chemistry readily accessible to synthetic chemists,” he said.

“Preliminary investigations also reveal intriguing nucleophile-dependent face selectivity in the alkene halogenation step. The halocyclization and the intermolecular haloetherification reactions exhibit complementary alkene face selectivity for the halonium capture despite the fact that they are formed in the same reaction! This was confirmed by derivatization studies (see Scheme 3, note the complementary absolute stereochemistry at the newly created stereocenters),” said Professor Borhan, who concluded: “These results have prompted a detailed investigation into the origins of the enantioselectivity for this class of reactions.”

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**About the authors**

**Bardia Soltanzadeh** was born in Esfahan (Iran) in 1984. He obtained his B.Sc. from Shahid Beheshti University in Iran in 2007 and his M.Sc. from Sharif University of Technology (Iran) in 2009. He is currently a PhD student at Michigan State University (USA) and his research is mainly focused on the development of the enantioselective intermolecular halofunctionalization of alkenes.

**Arvind Jaganathan** obtained his B.Sc. and M.Sc. degrees in organic chemistry (2005) from the University of Pune (India). After a short stint as a research assistant at CSIR-National Chemical Laboratory, Pune (2006), he commenced his graduate studies in Professor Borhan’s group at Michigan State University (USA) in 2007. His PhD research was primarily focused on the development of novel asymmetric alkene halogenation reactions. Arvind is currently a senior chemist at The Dow Chemical Company (USA).
Babak Borhan received his PhD in 1995 from the University of California, Davis (USA), under the joint mentorship of Professors Mark Kurth and Bruce Hammock. He then joined Professor Koji Nakanishi’s group at Columbia University (USA), focusing on research related to the isomerization events in the rhodopsin photocycle. In 1998, he started his independent career at Michigan State University (USA) and is currently a full professor in chemistry. His research spans areas of organic synthetic methodology, bioorganic chemistry, and circular dichroism spectroscopy.
The development of chemical ligation reactions has revolutionized modern chemical biology. Among these techniques, the native chemical ligation (NCL) of thioesters and N-terminal cysteines – reported by Kent and co-workers over twenty years ago (see the original Nat. Chem. article for references) – has been one of the greatest advances in protein synthesis; still, however, many synthetic targets remain out of reach. In order to identify more general and complementary protein ligation reactions, numerous groups have pursued the development of novel methods and ligation partners, including the group of Professor Jeffrey Bode at the ETH Zürich (Switzerland). Professor Bode said: “In our own effort to provide a valuable alternative, we identified the reaction between C-terminal α-keto acids and N-terminal hydroxylamines (KAHA ligation) to be robust and chemoselective.”

The KAHA ligation with oxaproline (Opr, see Scheme 1) as hydroxylamine proved to be an excellent alternative to the NCL, and the group prepared numerous proteins with this ligation. However, Professor Bode commented that the reaction presents some drawbacks. “The primary products of the KAHA ligation with Opr are depsipeptides, and the amino acid formed at the ligation site is a non-canonical homoserine residue,” explained Professor Bode. “The reaction rate of the KAHA is suitable for the preparation of small and medium-sized proteins but may not be sufficient when moving to larger or more challenging targets where only micromolar concentrations of the reactants are present.” Through the synthesis of several proteins of up to 184 residues, the first two drawbacks were shown to be almost always negligible and sometimes even advantageous. However, the third – reaction kinetics – remains a concern for the Zürich based researchers, especially when the ligation of folded proteins or very hydrophobic segments is attempted.

In order to provide a KAHA protein ligation that both affords canonical amino acid residues and operates at a faster rate, the group sought to prepare an Fmoc-protected oxazetidine amino acid (Fmoc-Ozt-OH). Professor Bode said: “In our eyes, this compound had not only the potential to ligate giving rise to a natural amino acid (Ser), but also to react more rapidly because of the ring strain of the four-membered ring. However, this simple answer generated even more questions than the ones we were trying to address: will the oxazetidine ring be stable? Will it undergo KAHA ligation when exposed to α-keto acids? If so, will the reaction be faster? But first of all: how to prepare the oxazetidine amino acid?”

A wide palette of approaches were considered by the authors of this study, including cycloadditions, electrocyclizations, intramolecular substitution reactions, and ring contractions. “The general conclusion of these attempts was that the thermodynamic price to be paid to close the 1,2-oxazetidine ring – the one with the desired substitution pattern! – was higher than expected,” said Professor Bode. “The most pro-
mising route, intramolecular epoxide opening, proved to be a source of both excitement and disappointment,” continued Professor Bode. He explained: “Although we could successfully cyclize several substrates, we always obtained products that had the correct mass, and intriguing NMR spectra, but ultimately the wrong structure. After months of failures, we were elated to find a combination of N-protecting group and activation method that led finally to the oxazetidine ring (Scheme 2).”

Unfortunately, the benzyl substitution on the oxazetidine nitrogen atom had to be exchanged for another protecting group (ideally Fmoc) without breaking the N–O bond. This proved non-trivial, eventually requiring the use of an oxidatively cleavable amine-protecting group that necessitated careful experimentation and optimization. Professor Bode commented: “We were rewarded, however, by finding that the key cyclization proceeded in a stereospecific fashion, allowing us to prepare the oxazetidine in enantiomERIC rich form. After some protecting group manipulations and oxidation state adjustments, we arrived at our target: Fmoc-Ozt-OH (Scheme 3).”

In Fmoc-protected form, the oxazetidine proved to be stable and easy to handle – surviving even cleavage from Rink-Amide resin under strongly acidic conditions to give peptide segments bearing the Fmoc-Ozt on their N-terminus. When deprotected and exposed to α-keto acids, the ‘naked’ 1,2-oxazetidine displayed the postulated reactivity maintaining the selectivity of the KAHA ligation with Opr. “Although the unprotected oxazetidine is unstable – in marked contrast to its completely stable five-membered cousin 5-oxaproline – it can be used directly in serine-forming KAHA ligation under dilute, neutral conditions,” said Professor Bode, who concluded: “The utility of the new amino acid was shown by the three-fragment total chemical synthesis of S100A4, a protein involved in the metastasis process. This is a challenging target, made difficult by hydrophobic sequences and a tendency to aggregate. Only by performing the final ligation with the oxazetidine were we able to complete the synthesis of this target.”
About the authors

Ivano Pusterla was born in 1985 in Morbio Inferiore (Switzerland). He completed his BSc (in 2007) and MSc (2009) in chemistry at ETH Zürich (Switzerland). After an industrial internship in medicinal chemistry at Novartis Pharma AG in Basel (Switzerland) and a postgraduate stay at the University of Zürich (Switzerland), he joined the research group of Professor Jeffrey W. Bode in 2010. His PhD thesis focused on the KAHA ligation and its applications. He received his PhD in 2014 and he is currently working as an R&D chemist in bioconjugation at Lonza AG.

Jeffrey W. Bode studied at Trinity University in San Antonio, TX (USA). Following doctoral studies at the California Institute of Technology (USA) and ETH Zürich (Switzerland) and postdoctoral research at the Tokyo Institute of Technology (Japan), he began his independent academic career at the University of California, Santa Barbara (USA) in 2003. He moved to the University of Pennsylvania (USA) as an associate professor in 2007 and to ETH Zürich (Switzerland) as a full professor in 2010. Since 2013, he is also a Principal Investigator and Visiting Professor at the Institute of Transformative Biomolecules (WPI-ITbM) at Nagoya University (Japan).
Young Career Focus:
Professor Brian Northrop (Wesleyan University, USA)

Background and Purpose. SYNFORM regularly meets young up-and-coming researchers who are performing exceptionally well in the arena of organic chemistry and related fields of research, in order to introduce them to the readership. This Young Career Focus presents Professor Brian Northrop (Wesleyan University, USA).

INTERVIEW

SYNFORM What is the focus of your current research activity?

Prof. B. H. Northrop My research group and I are focused on developing new and efficient methods for synthesizing complex organic materials from relatively simple starting materials. Our approach takes advantage of a combination of techniques that are fundamental to both classical and contemporary physical organic chemistry, such as molecular and supramolecular self-assembly, dynamic covalent chemistry, and highly efficient ‘click’ chemistry. Our current research is focused in two predominant areas: (i) the development of selective, orthogonal thiol-Michael reactions to enable the rapid synthesis of multifunctional macromolecules; and (ii) understanding and optimizing the dynamic covalent assembly of boronic acids to allow for the de novo design of discrete, nanoporous materials.

SYNFORM When did you get interested in synthesis?

Prof. B. H. Northrop I entered college with a lot of interest in chemistry but I wasn't sure whether I wanted to major in it, partly because I had not yet had exposure to organic chemistry. Once I took organic, however, the major was a foregone conclusion. I saw organic chemistry as built upon all the foundational physical principles that I loved about general chemistry and physics but applied to the construction of molecules in a way that felt, to me, like a combination of problem-solving, art, and design. I joined a research group and loved independent research despite the fact that many (most?) of my synthetic routes failed. In fact, I enjoyed independent research more than undergraduate lab courses because many of my reactions didn’t work – often times much more can be learned from a failed reaction than a successful one. I found, as I imagine most chemists do, that the further I went in research the more questions I had and the more interesting they
became. That initial undergraduate research experience motivated me to continue in chemistry not just as my major but also as a career. Additionally, I have been very fortunate throughout my undergraduate, graduate, and postdoctoral studies to have had advisors who pushed me to think deeply and critically about my research while also being incredibly supportive.

**SYNFORM** What do you think about the modern role and prospects of organic synthesis?

**Prof. B. H. Northrop** I find it amazing to think about how far the art and science of organic synthesis has come over the past century. One can easily fall into the trap of thinking that with so much progress we are now only making incremental advances in highly specialized areas. I couldn't disagree more. One of the most incredible aspects of organic synthesis is the fact that it is boundless, limited only by our creativity, imagination, and resources (and the laws of thermodynamics). New molecules, new materials, and new synthetic methods that may previously have been considered prohibitively difficult may be discovered at any time. For example graphene, once believed unstable, can now be manufactured on an industrial scale. Similarly, recent advances in C–H functionalization have the potential to revolutionize chemical synthesis from pharmaceuticals to manufacturing to consumer goods. Furthermore, the role of organic synthesis is not limited to specialists in the area; rather it is impactful across the sciences. Research advances in biology, physics, engineering, environmental sciences, etc. are often beneficial to and help promote new developments in organic synthesis just as new synthetic developments frequently impact research in other sciences. This centrality of organic synthesis highlights the value of collaborative, cross-disciplinary research.

**SYNFORM** Your research group is active in the areas of organic synthesis and organic materials. Can you tell us more about your research and its aims?

**Prof. B. H. Northrop** Our research in the area of thiol-Michael ‘click’ reactions focuses on understanding and optimizing the selective addition of a given thiol to a given Michael
acceptor. While thiol-Michael reactions typically proceed in high to quantitative yields with great tolerance of different functional groups and solvents, mixtures of several thiols and/or Michael acceptors (i.e., ternary or quaternary reactions) generally lead to mixtures of thioether products. My group is using a combination of computational modeling and experimental test reactions to screen myriad combinations of reaction conditions to elucidate the fundamental influences that solvent, initiator, and thiol and Michael acceptor functionality play on the energetics, kinetics, and selectivity of thiol-Michael reactions. To date we, and others in this area, have found several means of achieving complete selectivity in mixtures of thiols and Michael acceptors (Scheme 1A). Most recently, students in my group have developed reaction conditions that promote the pairwise addition of two different thiols to two different Michael acceptors within quaternary reactions. My group then takes advantage of these selective thiol-Michael reactions to prepare complex macromolecules such as multifunctional polymers, layered dendrimers, and mechanically interlocked polymers.

My group is also investigating the self-assembly of boronic acids, both with themselves and with aromatic donors such as catechol and o-phenylenediamine derivatives. We have, for example, synthesized a variety of polycyclic aromatic bis(catechol) derivatives that, when combined with aryl diboronic acids, dynamically assemble into nanoporous covalent organic polygons (Scheme 1B). These boronate ester polygons can be considered discrete analogues of ‘infinitely’ periodic covalent organic frameworks (COFs). Our aim is to use these solution-processable covalent organic polygons to better understand the assembly mechanisms and structure-function relationships of insoluble COFs. We are also using synthesis and theoretical modeling to investigate the influence of extended conjugation on the electronic properties of oligomers and polymers of boronate ester and diazaborole assemblies.

**SYNFORM** *What is your most important scientific achievement to date and why?*

**Prof. B. H. Northrop** Currently, I think the greatest impact of my group’s research is more a matter of approach than a specific result. By this I mean that we approach research projects working across each of the ‘three M’s’ of chemistry: making, modeling, and measuring. This complementary blend of synthesis, analysis, and theory provides my group with a deep, fundamental understanding of the chemical reactions and processes we are interested in. From this understanding comes the ability to develop and control everything from chemical reactivity to supramolecular assembly in a rational manner. Examples of this multipronged approach include our investigation of the mechanism and selectivity of thiol-maleimide reactions (*Polym. Chem.* **2015**, *6*, 3415) and our elucidation of the vibrational properties of boronic acid derived assemblies (*Chem. Mater.* **2014**, *26*, 3781). It is my hope that our approach to research and our initial published work have laid a solid foundation for a variety of more important scientific achievements in the future.
Halides with Arylboronic Acids
Rhodium-Catalyzed Asymmetric Allylic Arylation of Racemic Anti-Markovnikov Hydroamination of Homoallylic Amines -Sulfonyl Hydrazones
Diastereoselective Addition of Grignard Reagents to α-Epoxy N-Sulfonyl Hydrazones
Anti-Markovnikov Hydroamination of Homoallylic Amines
Rhodium-Catalyzed Asymmetric Allylic Aylation of Racemic Halides with Arylboronic Acids

Further highlights

**Synthesis**
Review: Cobalt-Catalysed Bond Formation Reactions
(by P. Röse, G. Hilt)

**Synlett**
Thieme–IUPAC Prize Account: Our Path to Less Toxic Amphoterics
(by M. D. Burke and co-workers)

**Synfacts**
Synfact of the Month in category “Metal-Catalysed Asymmetric Synthesis and Stereoselective Reactions”: Azides and Nitriles in Palladium-Catalysed Decarboxylative Allylation

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