THE INSIDE STORY

Chemistry in Singapore

SYNSTORIES

- Modular Syntheses of Polyene
- Natural Products via Iterative Cross-Coupling

CONTACT

Your opinion about SYNFORM is welcome, please correspond if you like: marketing@thieme-chemistry.com
Dear readers,

this new issue of SYNFORM presents an INSIDE STORY article dedicated to one of the most impressive examples of a fast-growing economy that is fully committed to the pursuit of an aggressive national research & development program: Singapore. This small country is becoming a major hub for research and education, and SYNFORM could not miss the chance to report on this sort of “paradise for scientists”. This INSIDE STORY has been possible thanks to the generous collaboration of several people in Singapore, including Dr. Christina Chai, Dr. David Chen, Dr. Steven Collier, Professor Teck-Peng Loh, and others who accepted the invitation to provide valuable information and dedicate some of their precious time to SYNFORM during my recent trip to Singapore. The Singapore model is probably difficult to export to the Western world, and there are many reasons for that. However, more long-term investments in infrastructure, research and education are needed in Europe, and even in America; Singapore may represent an important stimulus in this direction and not just a competitor in the global world market.

The issue is completed by a SYNSTORY article on a new remarkable synthetic strategy—a modular approach to polyene natural products via iterative cross-coupling—developed by the group of Professor Martin D. Burke (USA).

Stay tuned to SYNFORM!

Matteo Zanda
Editor of SYNFORM

CONTACT
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Modular Syntheses of Polyene Natural Products via Iterative Cross-Coupling

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Complex small molecules (natural products and drug-like compounds) have seemingly limitless potential to promote advances in science and medicine, but the degree to which this potential can be realized is ultimately a function of the simplicity, efficiency, and flexibility with which these types of compounds can be synthesized in the laboratory. In this regard, an inspiring benchmark can be found in the process of modern peptide synthesis in which the target molecules are made via the simple, iterative coupling of commercially available bifunctional amino acid building blocks. This process is now routinely automated and readily utilized not only by chemists, but also by biologists and physicists to promote discoveries across a wide range of disciplines.

In stark contrast, the laboratory synthesis of small molecules remains a relatively complex, arduous, and non-systematized process practiced almost exclusively by chemists with specialized background and training. A new synthesis strategy developed by the group of Professor Martin D. Burke from the Department of Chemistry, University of Illinois at Urbana-Champaign (USA) aims to dramatically change this. "Analogous to peptide synthesis," said Professor Burke, "we have discovered a way to synthesize complex small molecules using only one reaction (the Suzuki–Miyaura coupling) iteratively to bring together a collection of bifunctional haloboronic acid building blocks. Enabling this "iterative cross-coupling" approach, graduate student Eric Gillis discovered ([*J. Am. Chem. Soc.* **2007**, *129*, 6616]) that the cheap and environmentally friendly ligand N-methyliminodiacetic acid (MIDA) can reversibly attenuate the reactivity of boronic acids towards cross-coupling. Moreover," continued Professor Burke, "Eric found that this ligand can be cleaved using very mild aqueous bases (alternative approaches for controlling the reactivity of boronic acids require harsh reagents that are incompatible with complex small molecules). Eric harnessed this new methodology to complete the first total synthesis of the natural product ratanhiale, using only the Suzuki–Miyaura reaction to bring together a collection of easily synthesized, readily purified, and highly robust building blocks."

Like peptide synthesis, this simple approach is inherently modular and flexible, well-suited for combinatorial chemistry, and hopefully adaptable to automation. "This latter goal is being intensely pursued in my laboratories at this time," said Professor Burke. Moreoever, thanks to a partnership with a major international chemical company, a large collection of these types of haloboronic acid building blocks will be commercially available worldwide within the next 6–8 months.
“We hope that this will facilitate the broad utilization of these reagents. In addition, we have received strong interest from the pharmaceutical industry and one major company has already begun using this approach in their drug-discovery efforts,” he said.

Although it is certainly true that small molecules have tremendous structural diversity and do not so obviously lend themselves to this type of unified synthesis strategy, according to Professor Burke “it is interesting to note that most natural products are in fact biosynthesized via the iterative coupling of bifunctional building blocks (polyketides from acetate and/or propionate units, polyterpenes from isoprene building blocks, etc.). This is similar in many ways to the biosyntheses of their peptide, oligonucleotide, and oligosaccharide counterparts. In addition,” noted Professor Burke, “most drug-like small molecules are comprised of different combinations of aryl, heteroaryl, and related types of units. Thus, there are certain types of ‘building blocks’ that appear over and over again in small molecules, and we feel that this inherent modularity can be harnessed to great effect.”

A specific example of this can be found in the most recent communication from the Burke group which is subject of this SYNSFORUM. “In this paper, post-doctoral fellow Suk joong Lee, graduate student Kaitlyn Gray, and undergraduate student James Pack disclosed their discovery that this iterative cross-coupling strategy can be applied to the synthesis of the notoriously challenging ‘polyene’ natural products,” he said. “As we highlight in this article, polyenes represent an extremely broad and useful class of complex small molecules and the same ‘haloalkenylboronic acid’ building blocks could in theory be useful for making a wide variety of these types of compounds.” However, polyenylboronic acids are notoriously unstable, which thus far has precluded their general utilization. “Overcoming this limitation,” said Professor Burke, “we discovered a collection of bifunctional haloalkenyl MIDA boronates which are strikingly stable to purification and storage, and remarkably selective to a wide range of cross-coupling reactions. This stability is maintained in the resulting polyenyl MIDA-boronate ester intermediates — which is perhaps the most striking result from this work. For example,” he continued, “we found that several of the corresponding boronic acids are so unstable that they cannot even be isolated, yet the MIDA boronates can be purified with silica gel chromatography and stored indefinitely as crystalline solids. In fact, some of these reagents have been stored on the bench-top under air for nearly two years now without any appreciable decomposition.”

Thus, according to Professor Burke, the two things that make these polyene building blocks special are “first, their theoretical capacity for limitless iterative coupling (as opposed to more traditional ‘lynchpin’ reagents which only enable two coupling steps), and second, the striking stability of these reagents and the intermediate polyenylMIDA-boronate esters, which is critical to their successful utilization. We demonstrate this utility with efficient syntheses of all-trans-retinal, β-lipohapedic acid, and half of the amphotericin B macrocyclic skeleton. To the best of our knowledge,” he said, “the latter represents the longest polyene ever synthesized using the Suzuki–Miyaura reaction. In this paper we also describe the first triply metal selective (Zn vs. Sn and B) cross-coupling reaction, the first selective cross-coupling with a differentially ligated diboron reagent, and the first cross-couplings between polyenylchlorides and vinylboronic acids.”

“We hope that these types of building blocks and methods will dramatically improve the way in which many natural products and other small molecules are synthesized in the laboratory,” concluded Professor Burke. “In the long term, we are very optimistic that this iterative cross-coupling strategy can help make the process of complex small molecule synthesis as simple as possible.”
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THE INSIDE STORY

An Interview with Sir Jack Baldwin

SYNSTORIES

Proline-Catalyzed Mannich Reactions of Acetaldehyde (Focus on an article from the current literature)

An Enantioselective Organocatalytic Oxidative Dearomatization Strategy (Focus on an article from the current literature)

Chiral Bronsted Acid Catalyzed Asymmetric Baeyer-Villiger Reaction (Focus on an article from the current literature)

FURTHER HIGHLIGHTS

SYNTHESIS

Review on: Electrophilic Iodination of Organic Compounds Using Elemental Iodine or Iodides (by S. Stavber et al.)

SYNLETT

Account on: 1,7-Electrocyclizations of Azomethine Ylides – Scope and Synthetic Aspects (by M. Nygres et al.)

SYNFACCTS

Synfact of the Month in category “Polymer-Supported Synthesis”: Suzuki-Miyaura Coupling Reaction Using Palladium Nanoparticles Immobilized on SPB

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