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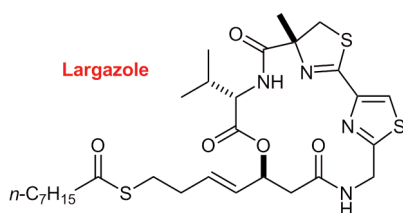
People, Trends and Views in Synthetic Organic Chemistry

2008 / 10

SYNSTORIES ■ ■ ■ ■

■ The Total Synthesis of
(-)-Cyanthiwigin F by Means
of Double Catalytic Enantio-
selective Alkylation

■ Total Synthesis of Largazole,
a Potent Histone Deacetylase
Inhibitor



■ A Concise Synthesis of
(-)-Oseltamivir (Tamiflu)

■ A Diels–Alder Approach to
Biaryls and a Novel Boroxine-
Based Suzuki Cross-Coupling
Strategy

CONTACT ++++

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Dear readers,

With more than 14,000 attendees and more than 8,000 papers presented, the 236th American Chemical Society (ACS) National Meeting and Exposition that was held on August 17–21, 2008 in Philadelphia established itself

as one of the most important events for the international chemistry community. This time, in addition to the usual highly heterogeneous nature, the attendees had also to struggle a little bit with the dispersion of the Divisions' Symposia throughout a number of different locations, not necessarily close to each other. In fact, the Convention Center could host 'just' a few Divisions, such as the Organic, the Medicinal, the Fluorine, and the Inorganic Chemistry. In spite of some logistic trouble, the ACS Philadelphia conference hosted a lot of excellent science. This issue of **SYNFORM** will try to give the flavor of the high quality organic chemistry presented in Philadelphia, publishing three **SYNSTORIES** for just as many communications presented in The City of Brotherly Love: a synthesis of the cyclic depsipeptide largazole presented by the group of Professor Jiyong Hong and co-workers (USA), a new synthesis of the antiviral (–)-oseltamivir (Tamiflu) by the group of Professor Barry Trost (USA), and a novel entry into functionalized biaryls by the group of Professor Rich Carter (USA). Last, but certainly not least, the issue is completed by a **SYNSTORY** article covering a recent breakthrough reported by the group of Professor Brian Stoltz (USA) concerning a conceptually innovative total synthesis of the marine diterpenoid (–)-cyanthiwigin F.

Enjoy your reading!

Matteo Zanda

Editor of SYNFORM

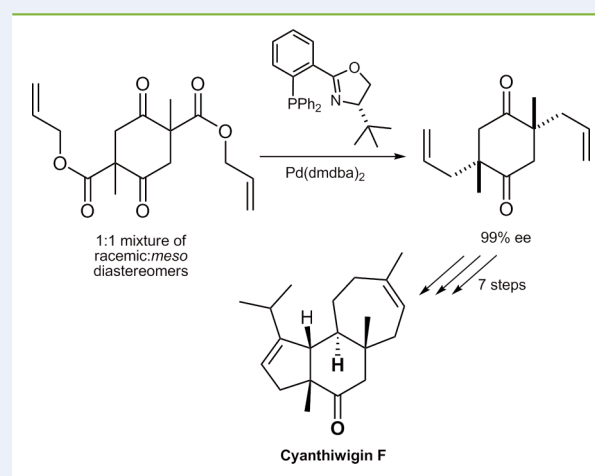
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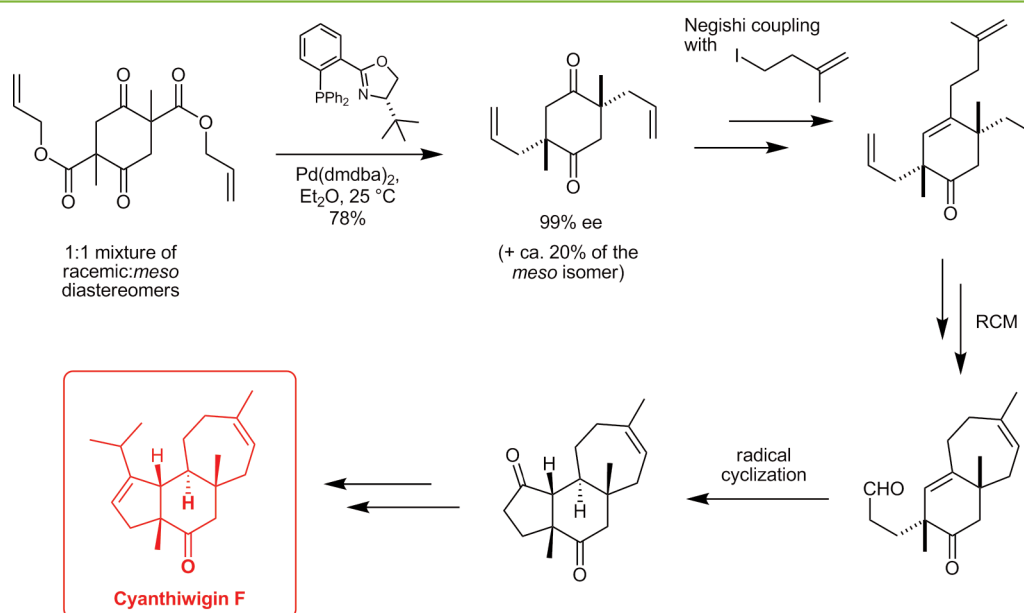
The Total Synthesis of (–)-Cyanthiwigin F by Means of Double Catalytic Enantioselective Alkylation

Nature **2008**, *453*, 1228–1231

■ Organic synthesis can be considered a science as well as an art, and sometimes the artistic aspect becomes particularly evident. One such example was recently published by the group of Professor Brian M. Stoltz, Ethel Wilson Bowles and Robert Bowles Professor of Chemistry at the California Institute of Technology, Pasadena (USA). The synthesis of the marine diterpenoid (–)-cyanthiwigin F was completed in nine synthetic steps. Of these nine reactions, seven form new carbon–carbon bonds, and four of those reactions establish more than one carbon–carbon bond in a single synthetic operation. Additionally, no protecting groups were employed. All of these facts were made possible by means of an extremely powerful double catalytic enantioselective alkylation, that represented the pivotal reaction in the synthesis.

“Our paper details the rapid synthesis of a marine natural product, cyanthiwigin F,” explained Professor Stoltz. “The main point of the manuscript, however, is not the synthesis *per se*, but the implementation of a double catalytic enantioselective reaction. This reaction builds the 1,4-bis-quaternary all-car-

bon stereocenters of the central ring of the molecule while simultaneously setting the absolute configuration critical to the synthesis in a single synthetic operation. This transformation is unique in that it uses a 1:1 mixture of racemic and *meso* starting substrates for the reaction and yet affords a highly enantioenriched product in synthetically useful dr.” In the course of the reaction, the two stereocenters of the starting material are indiscriminately ‘ablated’ and then reconstructed with high selectivity. “The process also takes advantage of a stereo-amplifying effect that has been described by Horeau and Kagan,” acknowledged Professor Stoltz. “As far as we know, there exists no similar double stereoablative, double catalytic enantioselective reaction reported in the context of natural product synthesis. The stereoablative nature of this reaction allows the use of easily scalable, non-selective chemistry in the early stages of the synthesis. Additionally, the rapid construction of the central six-membered ring of the natural product allows us to rapidly complete the natural product tricyclic scaffold.”



According to Professor Stoltz, the next critical breakthrough that occurred over the course of the synthesis was also one of the most standard reactions employed: the Negishi cross-coupling reaction to form a new sp^2 - sp^3 carbon-carbon bond. "Before attempting the Negishi coupling," said Professor Stoltz, "attempts to desymmetrize the critical diketone via formation of an enol triflate had been successful, but moving the synthesis forward beyond that point proved quite difficult." A range of transition-metal-catalyzed reactions had been investigated prior to the eventual solution published, but none of the attempted transformations provided acceptable selectivity or conversion, and none of the intermediates prepared were amenable to advancement to cyanthiwigin F. "When the Negishi reaction was at last employed, completion of the seven-membered C-ring of the molecule was easily attainable."

A second breakthrough came in the form of a radical cyclization reaction based on the work of Tomioka and coworkers published in 2005. "Multiple attempts to cyclize an acyl radical onto the six-membered ring olefin had failed," said Professor Stoltz, "so it was quite encouraging when the thiol-catalyzed conditions Tomioka reported allowed for the completion of the five-membered A-ring, and with it, the tricyclic core structure of cyanthiwigin F."

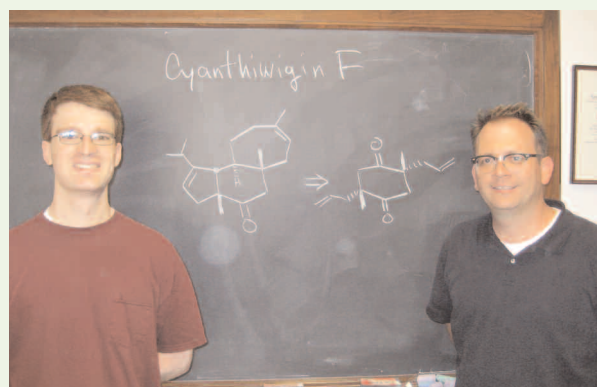
The largest surprise of the synthesis, however, was the double catalytic enantioselective alkylation reaction itself. "Despite employing a mixture of diastereomers as starting material," said Professor Stoltz, "and despite the multiple stereochemical pathways available to both allylation events, the reaction is remarkably uncomplicated to run and purify. In fact, it is arguably the easiest step in the entire synthesis!"

This work opens interesting future perspectives. Indeed, because the synthetic route employed toward cyanthiwigin F allows rapid access to a completed tricyclic cyathin core structure; adaptation of this route can in principle be used to target related natural products. "In specific, other members of the cyanthiwigin family of diterpenoid molecules can be readily prepared from late-stage intermediates along the synthetic route," confirmed Professor Stoltz.

Further developments stemming from the synthesis of the cyanthiwigin diterpenoid natural products are envisioned in terms of their potential bioactivity. "Many of the cyanthiwigin natural products display cytotoxic activity against human primary cancer cells," explained Professor Stoltz, "however, the mechanism of their activity remains an unsolved question. Additionally, a majority of the cyanthiwigin compounds remain untested. Refinement and improvement of the anti-cancer potential of the cyanthiwigin molecular framework therefore depends upon the elucidation of those functional groups and structural features responsible for biological activity." The

authors envision that the synthesis of several analogues of the parent scaffold will illustrate the impact of the various moieties upon the bioactivity of the cyanthiwigin compounds. "With this knowledge," said Professor Stoltz, "it should be possible to refine those structures and functionalities found to be the most effective anti-cancer agents. By approaching these molecules from a perspective of systematic investigation and improvement, it can be envisioned that the manipulation of these late-stage intermediate structures and synthetic derivatives of the cyanthiwigin natural products will aid in the design of novel, potent compounds for biological testing. Through collaboration with the laboratories of Professor David Horne at the City of Hope," concluded Professor Stoltz, "all of the cyanthiwigin natural products and cyanthiwigin derivatives prepared will be scrutinized for their anti-cancer activity."

Matteo Zanda



From left: J. A. Enquist, Prof. B. M. Stoltz

About the authors

John A. Enquist was born in Santa Rosa, CA, USA in 1982. He received his BA in chemistry from the University of California, San Diego (USA) in 2004, where he worked in the laboratories of Professor Yitzhak Tor. He has been a graduate student in the laboratories of Professor Brian Stoltz since 2004, where his work has focused on the total synthesis of natural product molecules. His research interests include cascade reactions, synthesis of biologically active natural products, transition-metal-catalyzed transformations, and asymmetric methodology with a focus on the formation of multiple stereocenters.

>>

Brian M. Stoltz was born in Philadelphia, Pennsylvania, USA in 1970. After spending a year at the Ludwig-Maximilians-Universität in München (Germany) he obtained his BS in Chemistry and BA in German from Indiana University of Pennsylvania (USA) in 1993. He then earned his Ph.D. in 1997 under the direction of Professor John L. Wood at Yale University (USA) specializing in synthetic organic chemistry. Following an NIH postdoctoral fellowship in the laboratories of Professor E. J. Corey at Harvard University (USA, 1998–2000), he joined the faculty at Caltech in 2000 where he is currently the Ethel Wilson Bowles and Robert Bowles Professor of Chemistry. His research focuses on the design and implementation of new synthetic strategies for the synthesis of complex molecules possessing important biological properties, in addition to the development of new synthetic methods including asymmetric catalysis and cascade processes. In addition to awards from a number of pharmaceutical companies (i.e., Abbott, Amgen, AstraZeneca,

Boehringer Ingelheim, Bristol-Myers Squibb, Eli Lilly, GlaxoSmithKline, Johnson and Johnson, Merck, Novartis, Pfizer, Roche), Professor Stoltz is the recipient of the Camille and Henry Dreyfus New Faculty and Teacher-Scholar Awards, a National Science Foundation CAREER Award, the Research Corporation Research Innovation and Cottrell Scholars Awards, an A. P. Sloan Research Fellowship, an Arthur C. Cope Scholar Award from the American Chemical Society, and has received the Presidential Early Career Award in Science and Engineering (PECASE) from the White House. In 2006 he was elected a fellow of the American Association for the Advancement of Science (AAAS) and in 2008 was named a KAUST GRP Investigator. Additionally, Professor Stoltz was recognized by the Caltech Graduate Student Council with both a Classroom Teaching Award and a Mentoring Award in 2001 and by the Associated Students of the California Institute of Technology for their 30th Annual Award for Excellence in Teaching in 2006.

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Total Synthesis of Largazole, a Potent Histone Deacetylase Inhibitor

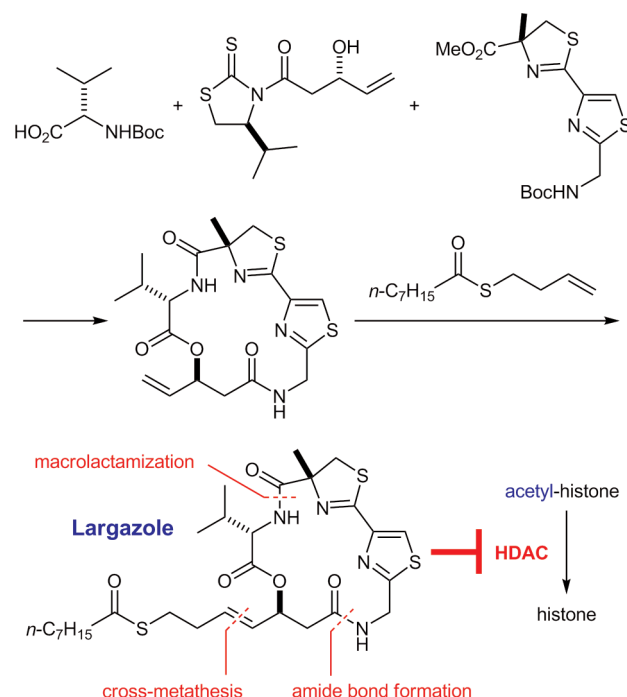
Selected Presentation from the 236th American Chemical Society National Meeting, Philadelphia (USA), August 17–21, 2008

■ Macrocyclic natural products often exhibit unique biological properties and thus are attractive candidates for drug development in many diseases. Professor Hendrik Luesch and co-workers from the University of Florida (USA) have recently reported the isolation and structural determination of largazole, a cyclic depsipeptide from a cyanobacterium of the genus *Symploca* (*J. Am. Chem. Soc.* **2008**, *130*, 1806). Largazole potently inhibited the growth of transformed mammary epithelial cells (MDA-MB-231) in the low nanomolar range and induced cytotoxicity at higher concentrations. In contrast, non-transformed mammary epithelial cells (NMuMG) were less susceptible to largazole. Similarly, transformed fibroblastic osteosarcoma cells (U2OS) were more susceptible to largazole than non-transformed fibroblasts NIH3T3. The potent biological activity and selectivity of largazole for cancer cells made largazole a highly attractive synthetic target for further investigation into the mode of action and potential as a cancer therapeutic.

Recently, Professor Jiyong Hong and co-workers from Duke University, Durham (USA) joined forces with the Luesch group and accomplished a concise and convergent synthesis of largazole (8 steps, 19% overall yield from the known synthetic intermediate) based on a macrocyclization reaction for formation of the 16-membered depsipeptide core followed by an olefin cross-metathesis reaction for installation of the thioester (*J. Am. Chem. Soc.* **2008**, *130*, 8455). They also prepared and evaluated the key analogues of largazole to reveal that histone deacetylases (HDACs) are the molecular targets and the thiol group is the pharmacophore of the natural product. “Histone deacetylation is an epigenetic mechanism that regulates gene transcription,” explained Professor Hong, “including genes that control proliferation, which can lead to silencing of tumor suppressor genes. HDAC inhibition is a validated approach for cancer therapy and an active area of pharmaceutical drug discovery research. The FDA recently approved suberoylanilide hydroxamic acid (SAHA) for the treatment of cutaneous T-cell lymphoma. HDAC inhibition could indeed explain the phenotype induced by largazole, including selectivity for transformed cells.”

Following the initial report, Professor Hong, Professor Luesch and co-workers generated and biologically evaluated a

series of analogues with modifications to the side chain or 16-membered macrocycle to characterize largazole's structural requirements for HDAC inhibitory and antiproliferative activities (*Org. Lett.* **2008**, *10*, 4021). “Structure–activity relationship of the analogues suggested that the four-atom linker between the macrocycle and octanoyl group in the side chain and the (*S*)-configuration at the C17 position are critical to repression of HDAC activity,” said Professor Hong. “However, the valine residue in the macrocycle can be replaced with alanine without drastic loss of activity. Further biological studies with largazole,” he concluded, “including metabolic stability in serum and pharmacokinetics, are currently underway to assess the chemotherapeutic potential of largazole.” This work was brilliantly presented at the ACS Meeting in Philadelphia by Professor Hong's graduate student Yongcheng Ying.



The impressive interest in largazole and its derivatives is further demonstrated by the fact that several groups are currently working on it, for example, Professor Craig J. Forsyth and his coworker Bo Wang from Ohio State University, Columbus (USA), who presented another synthetic approach to largazole in the same session of the ACS Meeting in Philadelphia, and the group of Professor Robert M. Williams

from Colorado State University, Fort Collins (USA), that recently published a further total synthesis of largazole (*J. Am. Chem. Soc.* **2008**, *130*, 11219). For additional syntheses of largazole and derivatives see: *Org. Lett.* **2008**, *10*, 3595; *Org. Lett.* **2008**, *10*, 3907; *Angew. Chem. Int. Ed.* **2008**, *47*, 6483. ■

Matteo Zanda



From left: H. Kim, S. Byeon, Y. Ying, Prof. J. Hong

About the authors

Yongcheng Ying received his B.Sc. degree from the University of Science and Technology of China (Anhui, P. R. of China) in 2004. Currently, he is a graduate student of the chemistry department at Duke University (USA) under the supervision of Professor Jiyong Hong. His graduate research interests include natural product synthesis and study of mode of action.

Jiyong Hong received his B.Sc. and M.Sc. degrees from Seoul National University (South Korea). He obtained his Ph.D. degree from The Scripps Research Institute (USA) under the guidance of Professor Dale L. Boger and was a postdoctoral research associate at The Scripps Research Institute (USA) with Professor Peter G. Schultz. He then joined Duke University as an Assistant Professor of Chemistry in 2005. His research interest focuses on using chemical tools to understand the signaling pathways underlying cell and developmental biology.



From left: K. Taori, Prof. H. Luesch, Y. Liu

Hendrik Luesch received his *Diplom* in Chemistry at the University of Siegen (Germany) in 1997. He attended the University of Hawaii at Manoa to study marine natural products chemistry and obtained his Ph.D. in chemistry under the supervision of Professor Richard E. Moore in 2002. He then undertook three years of postdoctoral studies as an Irving S. Sigal Fellow at The Scripps Research Institute under the guidance of Professor Peter G. Schultz in the area of functional genomics. In 2005 he joined the faculty of the Department of Medicinal Chemistry at the University of Florida (USA) where he combines his interest in marine natural products chemistry with systems biology approaches for the discovery and characterization of potential drugs and molecular drug targets.

A Concise Synthesis of (–)-Oseltamivir (Tamiflu)

Selected Presentation from the 236th American Chemical Society National Meeting, Philadelphia (USA),

August 17–21, 2008

■ The constant threat of avian influenza outbreaks generates a large demand for the current anti-flu drug Tamiflu [(–)-Oseltamivir Phosphate]. The current industrial preparation route starts from naturally occurring (–)-Shikimic acid, whose source is limited. Therefore, developing alternative routes starting from easily accessible simple starting materials is desirable. Multiple research groups have contributed to the total synthesis of the drug. However, all reported syntheses involve more than 12 steps and many of them require the use of hazardous azides as reagents (for a recent review, see: M. Shibasaki, M. Kanai *Eur. J. Org. Chem.* **2008**, 1839).

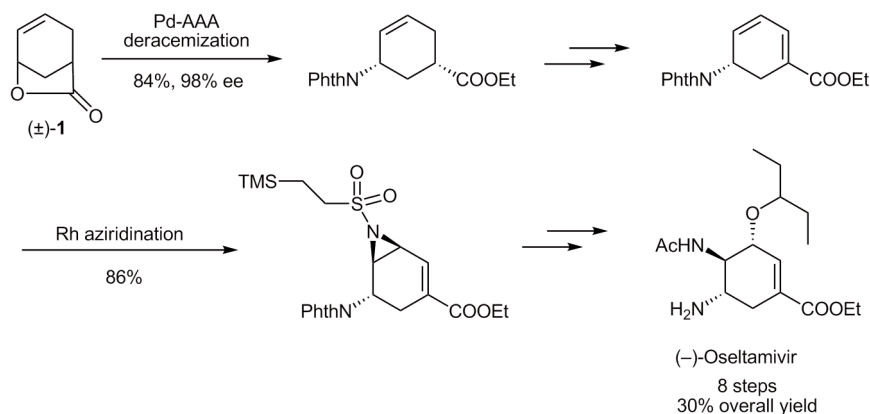
At the recent ACS Conference in Philadelphia, Ting Zhang, a graduate student in the group of Professor Barry M. Trost from Stanford University (USA), effectively presented a novel synthetic approach to (–)-Oseltamivir [see also: *Angew. Chem. Int. Ed.* **2008**, 47, 3759; *Synfacts* **2008**, 895 (Synfact of the Month)] that could represent a significant step forward in terms of synthetic efficiency.

“Our synthetic route, featuring a novel palladium-catalyzed deracemization reaction with a unique nitrogen nucleophile and an unprecedented rhodium-catalyzed chemo-, regio-, stereoselective direct aziridination reaction of a conjugated diene,” explained Ting Zhang, “produces (–)-Oseltamivir in eight steps with 30% overall yield, and hence, is the shortest and most efficient synthesis to date. With further process opti-

mization, we believe that our synthesis can potentially serve as a valuable alternative for the commercial production of Tamiflu.”

“Many others and we,” she continued, “have demonstrated that the palladium-catalyzed asymmetric allylic alkylation (Pd-AAA) reactions are powerful tools for the asymmetric synthesis of complex bioactive molecules. At the outset of the synthesis, we envisioned that a Pd-AAA reaction with lactone **1** using a suitable nitrogen nucleophile should allow the asymmetric installation of one of the requisite nitrogen functionalities, from which the stereochemistry of the rest of the molecule can derive. However, a commonly used nitrogen nucleophile such as phthalimide failed to give any products.” The problem was successfully solved by considering possible sources of the lack of reactivity. Indeed, trapping of the resulting carboxylate group with a TMS group, thereby minimizing charge-charge repulsion, led to the successful coupling of the two reactants. “This is in contrast to the reaction of lactone **1** with carbon nucleophiles,” said Ting Zhang, “where the trapping with TMS is not necessary. The demonstrated effect of the TMS group with a nitrogen nucleophile certainly opens a door for the future development of AAA reactions.”

Although other synthetic routes to Tamiflu have also used aziridination reactions to install one of the nitrogen groups, direct and selective aziridination on conjugated electron-defi-

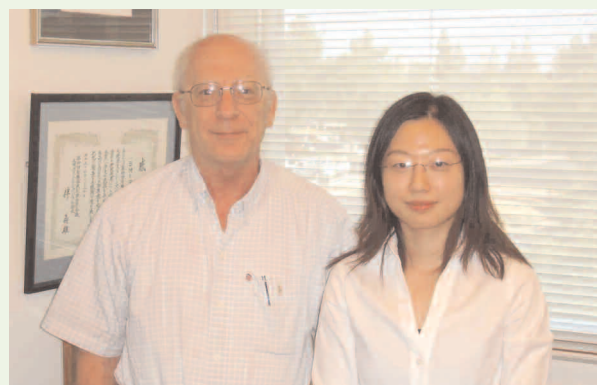


cient dienes has not been reported until this work. “The chemo- and regioselectivity of the aziridination and the stability of the formed vinyl aziridine are the biggest challenges,” said Ting Zhang. “This step took us six months to optimize. Dr. Kiran Guthikonda and David Zalatan from Professor Justin Du Bois’ research group shared with us some insights on the rhodium-catalyzed aziridination reaction and on the most current findings of newly developed rhodium complexes. They were very kind to share some of their precious catalysts with us. The application of the rhodium catalyst essentially solved the half-year puzzle of the selective aziridination reaction.”

The use of explosive azide reagent is also a drawback in some of the synthetic routes published. “We used phthalimide and 2-(trimethylsilyl)ethanesulfonamide as nitrogen sources and thus avoided the use of azide in our synthesis without compromising on reactivity or selectivity,” Zhang confirmed.

“All reagents used in our synthesis are available from commercial sources. Lactone **1** can potentially be accessed in ton-scale quantities easily. We believe,” she concluded, “that if some day in the future a new synthesis of Tamiflu has to be developed to meet the global anti-influenza need, our synthetic route, after further industrial optimization, can serve as a valuable candidate.” ■

Matteo Zanda



From left: Prof. B. M. Trost, T. Zhang

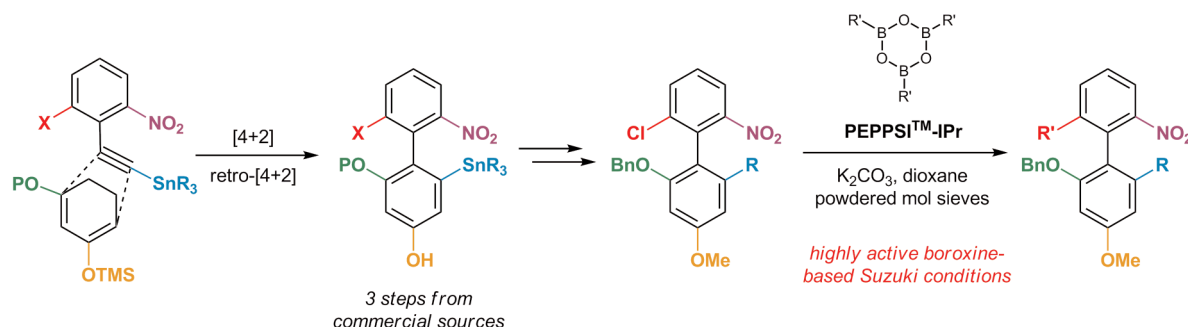
About the authors

Barry M. Trost was born in Philadelphia, Pennsylvania (USA) in 1941. He received his BA degree from the University of Pennsylvania in 1962 and three years later (1965) obtained his Ph.D. degree in Chemistry from the Massachusetts Institute of Technology. He directly moved to the University of Wisconsin where he was promoted to Professor of Chemistry in 1969 and subsequently became the Vilas Research Professor in 1982. He joined the faculty at Stanford University as Professor of Chemistry in 1987 and became Tamaki Professor of Humanities and Sciences in 1990.

Ting Zhang received her B.Sc. degree in chemistry from Nankai University (Japan) in 2004 and then matriculated at Stanford University. She is currently a fifth-year graduate student in Professor Trost’s research group. Her research includes palladium-catalyzed asymmetric transformations in combination with other transition metal catalysis and their applications in complex molecule syntheses.

A Diels–Alder Approach to Biaryls and a Novel Boroxine-Based Suzuki Cross-Coupling Strategy

Selected Presentation from the 236th American Chemical Society National Meeting, Philadelphia (USA), August 17–21, 2008



■ Biaryls represent a privileged structure in a number of fields, such as catalysis, materials science, nanotechnology, natural substances and biomedical chemistry. It is therefore not surprising that the synthesis of this stereogenic structural element continues to be the object of intensive research efforts.

A conceptually new approach to the synthesis of biaryls and their subsequent functionalization was reported at the 236th ACS National Meeting in Philadelphia by graduate student Johanna Perkins and Professor Rich Carter from the Department of Chemistry, Oregon State University (USA).

“This presentation illustrated our efforts towards applying our Diels–Alder approach to biaryls (DAB) to the synthesis and functionalization of tetra-*ortho*-substituted biaryl templates,” explained Johanna Perkins. “We employed an efficient cycloaddition–cycloreversion reaction that generated a wide variety of biaryls rapidly in as few as three steps from commercially available starting materials. We went on to demonstrate that we can further functionalize these biaryl templates through a variety of Suzuki, Heck and Stille coupling reactions, as well as additional functional group manipulations.”

The authors have also developed a practical crystallization protocol of separating the enantiomers of axial chiral biaryls through the use of a menthol carbamate. “These templates should have considerable utility in the development of novel ligands for transitional metal catalysis and organocatalysis,” Perkins said. “Towards this goal, we also reported our early progress towards the development of novel, chiral anilino alcohol biaryl ligands for use in asymmetric aldol reactions.

Future work will include optimization of our novel ligand systems and their application to a range of asymmetric transformations. We also will continue to push the boundaries of our DAB strategy through the construction of novel and highly functionalized biaryl compounds.”

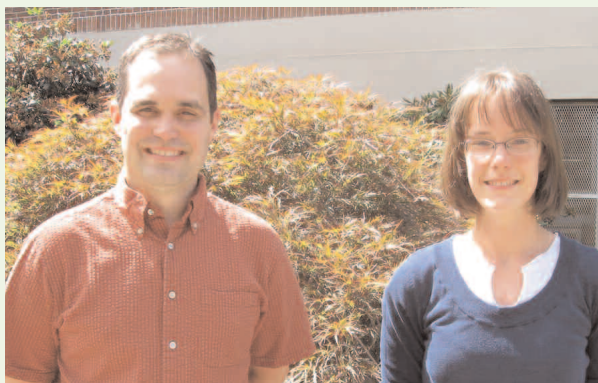
Additionally, the authors disclosed their ability to couple a sterically encumbered aryl chloride with a wide range of functional groups through the use of a novel boroxine-based Suzuki coupling. “To our knowledge, the powerful coupling capabilities of boroxines under anhydrous conditions have not been explored by the scientific community,” Perkins confirmed. “We believe that these coupling conditions should prove a valuable tool in the synthetic chemists’ arsenal for accomplishing challenging Suzuki couplings,” she concluded. ■

Matteo Zanda

About the authors

Johanna Perkins earned her B.S. Degree in Chemistry from St. Edward's University in Austin, TX (USA). She is currently a fifth year Ph.D. candidate at Oregon State University where she acts as a research assistant in the group of Professor Rich Carter.

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From left: Prof. R. Carter, J. Perkins

Rich Carter is Associate Professor at the Department of Chemistry, Oregon State University (USA). Professor Carter's research focuses on the synthesis of complex natural products and the development of novel protocols for accessing challenging structural motifs in organic chemistry. Professor Carter earned his B.S. Degree in Chemistry from Gettysburg College in Gettysburg, PA (USA) and a Ph.D. in Chemistry from the University of Texas at Austin (USA) under the supervision of Professor Philip D. Magnus.

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■ An Expedient Asymmetric Synthesis of Platencin

(Focus on an article from the current literature)■ Direct and Stereospecific Synthesis of Allenes via Reduction of Propargylic Alcohols with $\text{Cp}_2\text{Zr}(\text{H})\text{Cl}$ *(Focus on an article from the current literature)*

■ Second-Generation Difluorinated Cyclooctynes for Copper-Free Click Chemistry

(Focus on an article from the current literature)

FURTHER HIGHLIGHTS + + + +

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Review on: Cobalt-Catalysed Carbon–Carbon Bond Formation Reactions

(by G. Hilt et al.)

SYNLETT

Account on: Zwitterionic Iodonium Compounds: Useful Tools in Organic Synthesis

(by E. Malamidou-Xenikaki, S. Spyroudis)

SYNFACTS

Synfact of the Month in category “Metal-Mediated Synthesis”:

[Dehydrohalogenation of Alkyl Halides with Complementary Regioselectivity](#)

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