An Organometallic Route to Long Helicenes

Organocatalytic Enantioselective Cascade Michael–Michael–Wittig Reactions of Phosphorus Ylides

Radical Cyclizations of α-Bromo Aluminum Acetals

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

Do you like good food? I would guess the answer is a unanimous yes. But what is “good food”? Here I am afraid we would not have a unanimous answer, although some degree of agreement is expected in some cases. For example, most of you would recognize Italian “lasagne”, French “crepes” and Japanese “sushi” as delicious. However, it all comes down to the personal taste because some others like Scottish “haggis” or French “escargots” or Italian “trippa” which personally I don’t find particularly attractive...

Let’s take a globalized, apparently very simple food like pizza. What makes a good pizza? Have you ever tried a wood fired oven baked “pizza margherita” in a typical restaurant in the Naples area? It’s an extremely simple, yet delicious food, and what makes it really fantastic is the combination of a handful of basic ingredients: mozzarella and tomato on a fragrant layer of pizza bread, with a few basil leaves (personally I love to add a few drops of good “extra-virgin” olive oil). You don’t need many sophisticated or unusual toppings to make a fantastic pizza, just the combination of two or three simple, well-chosen and tasty ingredients. Are you hungry now? If yes, you might want to have a good pizza tonight for dinner, but let me just conclude my thought before heading to a pizzeria. Personally, I am convinced that, like a good pizza comes from simple ingredients cooked in just five minutes, a brilliant idea comes from the combination of few simple and linear thoughts which simultaneously enter your mind at the right moment and come out as a flash of genius. Simplicity is the key, for good food as well as for good ideas! And if you can resist a few more minutes before biting your well deserved pizza, you might want to have a look at this new issue of SYNFORM which is full of tasty and creative chemistry. The first SYNSTORY is about a novel enantioselective organocatalytic cyclization process developed by B.-C. Hong (Taiwan). The second SYNSTORY deals with a synthetically very useful radical cyclization reported by J. Lebreton and F. Dénès (France). Last but certainly not least, the fascinating organometallic synthesis of long helicenes reported by I. Stary (Czech Republic).

Enjoy your pizza! Pardon, your reading...

Matteo Zanda
Editor of SYNFORM
Cascade reactions are extremely attractive in terms of synthetic efficiency, particularly when they allow for the preparation of complex structures with good stereochemical control. Recently, Professor Bor-Cherng Hong and his coworkers from the National Chung Cheng University (Taiwan) have discovered a novel organocatalytic enantioselective cascade nitro-Michael–Michael–Wittig reaction involving a dynamic kinetic asymmetric transformation. This annulation reaction provides a simple and direct protocol for the stereoselective construction of trisubstituted cyclohexenecarboxylates in a multicomponent one-pot operation. “We believe that the presence of three contiguous stereocenters in the product, with an all-cis stereochemistry which is produced with high enantioselectivity, is especially noteworthy.” The researchers explain that an increase in diastereoselectivity was achieved by the first organocatalytic asymmetric conjugate addition of phosphonium ylide to nitrostyrenes with the noncovalent thiourea catalyst. The structures as well as the absolute configurations of the products were elucidated by X-ray crystal structure analysis of the appropriate derivatives.

“Our paper described the first example of the organocatalysis involving the Wittig reaction and Michael reactions (with the non-enolizable Wittig reagent),” explained Professor Hong. “Despite tremendous advances in the chemistry of stabilized Wittig reagents, related reactions with nitrostyrene are far less reported, and virtually received no attention for the past decades after the early observation of the decomposition (retro-Michael) of Michael adducts back to Wittig reagents and nitrostyrene (J. Org. Chem. 1968, 33, 1164; J. Org. Chem. 1973, 38, 1047). In our study, we observed certain evidence for dynamic kinetic asymmetric transformation of the stabilized Wittig reagent (phosphorus ylides) with nitroalkenes in organocatalytic transformations. Our work also culminated in an unusual stereoselective synthesis of three all-cis consecutive stereocenters in the cyclohexene derivatives,” continued Professor Hong, “which is rare because the synthesis of contiguous cis stereocenters is a persistent challenge in organic synthesis due to steric hindrance. Our paper also demonstrates an example of the combination of secondary amine and thiourea organocatalysts, which operate independently through both noncovalent and covalent catalytic mechanisms for increasing the stereoselectivity.” Professor Hong emphasizes that this work adds a new weapon to the arsenal of synthetic chemists using organocatalysis. “Organocatalysis has become the focal point in modern organic chemistry,” said Professor Hong. “Among the burgeoning organocatalytic reactions which have been explored so far, vast efforts have been devoted to enantioselective Michael reactions (conjugate addition) that take place via iminium activation or/and enamine activation. The ability to promote cascade/domino reactions by organocatalysts further expands the realm of its synthetic applications,” he continued. “The pioneering masterpiece is represented by the work of Enders et al. in 2006 (Nature 2006, 441, 861). Theoretically, by manipulating the functionaility on the mole-
cules with adequate arrangement, many different types of reactions can be achieved via multicomponent annulations. Therefore, the development of more efficient and exquisite cascade reactions is in great demand by synthetic chemists.” In terms of future perspectives and developments of this work, Professor Hong said that his group is exploring the potential of the reactions of β-alkyl-substituted nitroolefins with stabilized Wittig reagents for the synthesis of natural products. “Nitroalkenes, known as chemical chameleons for the ease of their functional group transformation, have received extensive attention in organic chemistry,” said Professor Hong. “Our new annulation reaction provides a simple and direct protocol for the stereoselective construction of highly functionalized trisubstituted cyclohexenecarboxylates in a multicomponent one-pot operation.” According to Professor Hong this process was discovered thanks to a brilliant observation by graduate student Rei-Hau Jan, one of the coauthors of the article. “Originally, the reaction was performed at low concentration (0.1 M or less) and the second step of the reaction (Michael–Wittig) was very slow; only a tiny amount of the product was observed after four to five days,” explained Professor Hong. “Without the careful observation and persistent patience of my student, the project could have been terminated in its early stage. Indeed, Rei-Hau Jan kept the reaction running for one month and observed the product in good yields with excellent stereoselectivity. The project was then re-examined and the reaction was carefully screened under various reaction conditions to reduce the reaction rate as well as to optimize the yield.” Patience is definitely a virtue for chemists!

About the authors

Bor-Cherng Hong was born in Changhua (Taiwan) in 1962. He graduated from Tunghai University (Taiwan) (BSc) in 1984 and received his MSc from National Taiwan University in 1986 (working with Professor Jim-min Fang). After the two-year mandatory military service, he went to The University of Chicago (USA) for graduate studies where he obtained his PhD degree under the guidance of Professor J. D. Winkler (1992). Immediately after graduation, he joined the group of Professor E. J. Corey as a Postdoctoral Fellow at Harvard University (USA) from January 1993 to July 1994. He was appointed as an Associate Professor at National Chung Cheng University in August 1994, established his research group, and was promoted to Full Professor in 1999. Representative awards include: Young Investigation Research Award, National Science Council (1997, 1998), Distinguished Young Scholar Research Award, Academia Sinica (1999), Distinguished Young Investigator Award from Science and Liberal-Art Foundation, National Tsing-Hua University (2000), Outstanding Young Chemist Award,

His current research interests are focused on the development of novel annulation methodologies, especially with organocatalysts, and natural products synthesis.

Rei-Hau Jan was born in Taipei (Taiwan) in 1984. After receiving his BSc from Fu Jen Catholic University (Taiwan) in 2006, he joined Professor Hong’s research group and is currently a graduate student at NCCU.

Chih-Wei Tsai was born in Kinmen (Taiwan) in 1983. He received his BSc from Kaohsiung Medical University (Taiwan) in 2006. He is currently a PhD student in the Department of Chemistry and Biochemistry, NCCU, under the supervision of Professor Hong. His research interests are the development of new methodologies of asymmetric organocatalysis and their application to natural product synthesis.

Roshan Y. Nimje was born in 1977 and brought up in Mumbai (India). He received his BSc from Nagpur University (India) in 1997. Later in 1998, he moved to Amravati University (India), where he pursued his MSc (2000). He held a position of Project Assistant II at National Chemical Laboratory, Pune (India) until 2002. He has served as a Research Officer in Glenmark Pharmaceuticals, Mumbai during 2002–2004. In 2004, he went on to pursue his PhD studies at NCCU under supervision of Professor Hong and awarded his PhD degree in 2008. At present, he is a Postdoctoral Research Associate in the same group. His research interests are related to organocatalytic asymmetric synthesis.

Ju-Hsiou Liao was born in 1963. He received his BSc from National Taiwan University in 1985 and his PhD from Michigan State University (USA) under the guidance of Professor M. G. Kanatzidis in 1993. He did postdoctoral work with Professor M. G. Kanatzidis at Michigan State University (1993–1994 and 1995–1996), and with Professor Y. Piffard at the Institut des Matériaux de Nantes (France, 1994–1995). In 1996, he was appointed as an Associate Professor at NCCU, and was promoted to Full Professor in 2008. His research interests are X-ray crystallography, synthesis of solid-state materials, metal-organic frameworks and porous materials.

Gene-Hsiang Lee graduated from Chinese Culture University (Taiwan) (BSc) in chemistry, received his MSc in applied chemistry from the same university, and his PhD from National Taiwan University of Technology working on organic and polymeric materials. He is currently a senior crystallographic specialist in the X-ray Diffracton Laboratory at Instrumentation Center, National Taiwan University.
Over the last two decades, free-radical chemistry has increasingly attracted the attention of organic chemists, resulting in the development of new efficient tools to achieve functional group transformation as well as carbon–carbon and carbon–heteroatom bond formation. The methods that have come from this work have found numerous applications in organic synthesis. Recently, the group of Professor Jacques Lebreton from the University of Nantes (France) published a novel methodology based on the use of free radicals generated from α-bromo aluminum acetals, which holds remarkable potential for organic synthesis. According to his coworker Dr. Fabrice Dénès, the introduction of trialkylboranes as a source of alkyl radicals represents one of the most significant advances in this field, since it allows initiation of radical-chain processes at a very low temperature and, possibly, bond formation under tin-free conditions. “Et₃B/O₂ has become very popular as a radical initiator allowing inter- and intramolecular addition to be achieved with very high levels of diastereoselectivity and, sometimes, enantioselectivity,” he explained. “Besides this beneficial effect to the selectivity (including chemoselectivity) of radical reactions, the possibility to carry out reactions at –78 °C also offers the opportunity to extend the scope of precursors to include thermally unstable intermediates,” continued Dr. Dénès.

“As part of our program directed towards the total synthesis of macrolides from marine sources,” said Professor Lebreton, “we became interested in the preparation of polysubstituted lactol intermediates as masked linear segments of our target molecules. Recently, we reported a new approach to γ-lactols based upon the reduction of easily available α-bromo esters with DIBAL-H followed by the radical cyclization of the resulting aluminum acetals intermediate,” continued Professor Lebreton. “To the best of our knowledge, this is the first application of aluminum acetals in carbon–carbon bond formation under radical conditions.” This process proved to be successful and high-yielding with a range of representative substrates, including highly acid-sensitive precursors. “This is a significant advance compared to the classical cyclization of...
α-halo acetals (the Ueno–Stork reaction) which requires the use of either Lewis or Brønsted acidic conditions for the conversion of the cyclic acetals into the corresponding lactols,” said Dr. Dénès.

“This very mild approach to γ-lactols allows solving the problem of chemoselectivity encountered for the hydrolysis of cyclic acetals obtained by cyclization of α-halo acetals and we expect our methodology to be embraced by many synthetic chemists in the field of total synthesis,” they concluded.

REFERENCES


About the authors

Fabrice Dénès was born in Paris (France) in 1975. After undergraduate studies at the University Pierre et Marie Curie (Paris VI) he received his PhD in 2002 under the supervision of Professors J.-F. Normant and F. Chemla. From September 2002 to February 2005, he worked as a Postdoctoral Associate in the group of Professor P. Renaud at the University of Bern (Switzerland). In 2005, he moved to the University of Nantes (France) where he was appointed Assistant Professor in the group of Professor J. Lebreton and Dr. A. Guingant. His research interests include the development of synthetic methods based on organometallic or radical reactions, as well as the synthesis of natural products and/or analogues possessing a biological activity.

Jacques Lebreton was born in Guérande (France) in 1960. He received his PhD (1986) from the University of Paris XI-Orsay under the supervision of Professor Eric Brown. In 1986, he began his first postdoctoral fellowship with Professor James A. Marshall at the University of South Carolina (USA), and then a second with Professor Robert E. Ireland at the University of Virginia (USA). He joined the laboratories of CIBA-GEIGY (Novartis) in Basel (Switzerland) in 1990, where he worked in the group of Dr. Alain De Mesmaeker in the field of antisense. In 1994, he joined the CNRS and in 1998, he was promoted to Professor at the University of Nantes (France). Most of his recent work focuses on the synthesis of bioactive molecules for biological application purposes in the field of HIV, central nervous system diseases, cancer and drug delivery, through academic and industrial collaborations. His research efforts also include the synthesis of labeled molecules in order to study biological processes.

Anne Boussonnière was born in Saint-Nazaire (France) in 1984. She graduated from the University of Nantes (France) with a Master’s degree in organic and medicinal chemistry. As an undergraduate, she did an internship in the pharmaceutical chemistry department at the Sanofi-Aventis research center in Vitry-sur-Seine (France). She is currently pursuing her PhD at the University of Nantes under the supervision of Professor J. Lebreton and Dr. F. Dénès. Her research is focused on the use of aluminum acetals in radical chemistry.
In the realm of organic chemistry there are numerous fascinating structures, and unquestionably helicenes are among them. For over five decades, these chiral screw-like molecules consisting of all-ortho-fused benzene rings have attracted significant attention but they were predominantly considered fascinating stereochemical curiosities rather than useful organic materials. Nowadays, the situation is different. A race for finding new intriguing helicene applications has recently started hand in hand with remarkable advances in their synthesis. “That is not surprising as more complex molecules become generally more fashionable and, therefore, attractive utilizations of helicenes in enantioselective catalysis and technology-oriented science can be envisaged,” said Dr. Ivo Starý from the Academy of Sciences of the Czech Republic in Prague. Recently the group of Dr. Starý reported an organometallic route to helicenes that is particularly attractive for the synthesis of long helicenes.

“Nowadays, chemists have an ample toolbox of synthetic methods to create helicene structures comprising five to seven benzene rings but attempts at synthesizing long helicenes having over ten fused cycles are very rare,” said Dr. Starý. “That indicates serious difficulties connected with the preparation of long helicenes.”

Following the golden rule of total synthesis to increase the molecular complexity as late as possible, Dr. Starý and coworkers decided to construct the skeleton of the benchmark [11]helicene derivative practically at the end of its synthesis by simultaneously closing six carbocycles. “To pursue this multiple operation, we took advantage of the reliability and robustness of transition-metal-catalyzed alkyne cycloisomerization, whose effectiveness in the helicene synthesis we had already demonstrated,” he explained. Dr. Starý said that several lessons were learned from the synthesis of [11]helicene and its heterocyclic congeners. “The formation of helicene scaffolds by alkyne cycloisomerization is a rather smooth process in contrast to the assembly of required alkyne precursors. Furthermore, handling helical aromatics is easy since they are usually perfectly soluble and stable. These attributes, in fact,
are not common for many large planar aromatic counterparts whose synthesis and utilizations have often to fight with the insolubility of such systems,” he said.

Dr. Starý acknowledged that Dr. Petr Sehnal was a key person who synthesized \([11]\)helicene and related structures during his PhD studies at the IOCB AS CR (Institute of Organic Chemistry & Biochemistry, Academy of Sciences of the Czech Republic) in Prague. “He developed bases of the multi-cycloisomerization strategy which we now strive to extend to the synthesis of even longer aromatic screws. \([11]\)Helicene might serve as a unique short conductive bridge in molecular electronics applications that are now under investigation in collaboration with the Krakow STM group headed by physicist Marek Szymonski,” concluded Dr. Starý.

**About the authors**

**Irena G. Stará** was born in Prague (Czech Republic). She received her MSc degree from Charles University, Prague in 1988 (under the guidance of Professor P. Kočovský) and her PhD from the Academy of Sciences of the Czech Republic in 1993 (under the guidance of Dr. J. Závada DSc.). From 1993 to 1994 she was a Postdoctoral Fellow at the University of Geneva (Switzerland) with Professor W. Oppolzer and from 2000 to 2001 a Research Assistant at the University of Glasgow (UK) with Professor P. Kočovský. In 2008 she was a Visiting Professor at the University of Bourgogne (France). Currently she is a senior scientist and project leader at the IOCB AS CR in Prague. Her current research interests are the development of new synthetic methodologies for the preparation of novel aromatic systems, enantioselective catalysis and the application of emerging technologies to organic synthesis.

**Ivo Starý** was born in Prague (Czech Republic) in 1961. He received his MSc degree from Charles University, Prague in 1984 and PhD from the Czechoslovak Academy of Sciences in 1990 (both under the guidance of Professor Pavel Kočovský). From 1993 to 1994 he was a Postdoctoral Fellow at the University of Geneva with Professor E. P. Kündig and from 2000 to 2001 a Research Assistant at University of Glasgow with Professor Pavel Kočovský. He obtained a research position at the IOCB AS CR in Prague in 1990 where he currently holds a senior research team leader position. He received the first Bader Award (1994) and Thieme Chemistry Journal Award (2004). Since 2005 he is a member of the International Advisory Board of the European Journal of Organic Chemistry. He leads courses on reaction mechanisms at Charles University, Prague. His current research interests are organic synthesis, organometallic chemistry, catalysis and molecular electronics. He is an active musician playing viola.
Petr Sehnal was born in Turnov (Czech Republic) in 1979. He received his PhD from Charles University in 2006 (he performed his research under the guidance of Dr. I. Starý at the Institute of Organic Chemistry & Biochemistry, Academy of Sciences of the Czech Republic, Prague). He is currently a Postdoctoral Fellow in the group of Professor I. Fairlamb at the University of York (UK).

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Jiří Mišek was born in Klatovy (Czech Republic) in 1979. He received his PhD from Charles University in 2007 (he performed his research under the guidance of Dr. I. Starý at the IOCB AS CR in Prague). He is currently a Postdoctoral Fellow in the group of Professor S. Matile at University of Geneva.

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Marek Szymonski, Professor at Jagiellonian University, Krakow (Poland), is currently head of the Department of Physics of Nanostructures and Nanotechnology, Institute of Physics and coordinator of the NANOSAM Centre, both in Krakow. Recently, he served as a Dean of the Faculty of Physics, Astronomy and Applied Computer Science of the Jagiellonian University. He specializes in surface science research with a particular emphasis on desorption processes stimulated by electronic excitation and the characterization of compound semiconductor surfaces.

Ivana Cisařová is head of the Centre for Molecular and Crystal Structures, Department of Inorganic Chemistry, Charles University, Prague. She is an expert in X-ray crystallography of small molecules.
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