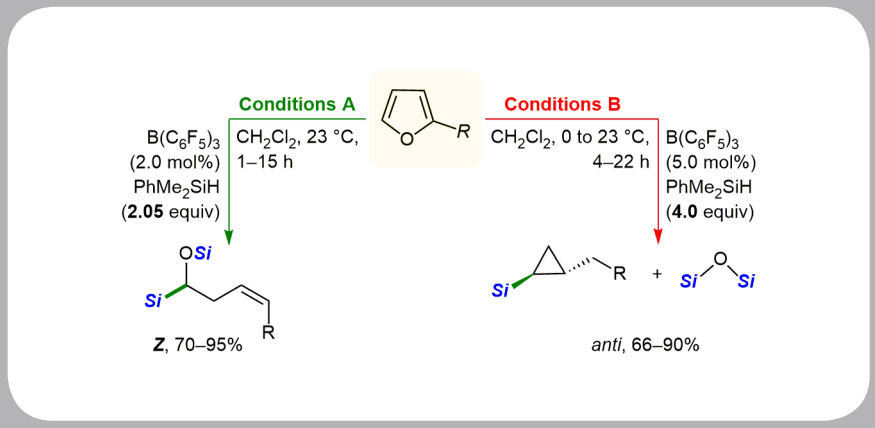
Synform

People, Trends and Views in Chemical Synthesis

2017/03

Borane-Catalyzed Ring-Opening and Ring-Closing Cascades of Furans Leading to Silicon-Functionalized Synthetic Intermediates

Highlighted article by C. K. Hazra, N. Gandhamsetty, S. Park, S. Chang



Contact
Your opinion about Synform is welcome, please correspond if you like:
marketing@thieme-chemistry.com

Thieme

Dear Readers,

Don't you have the feeling that our job of publishing research articles is becoming increasingly difficult, while editors and reviewers – regardless of the impact factor of the journal – have increasingly and unreasonably high expectations and demands? Well, I do. Medicinal and biological chemistry is an area where this issue is becoming particularly serious. Trying to publish the results of exploratory pilot work without having in vivo data (on some sort of animal model) is getting increasingly challenging even in journals that only a decade ago would let authors get away with just a handful of in vitro tests or not even that. But authors in other areas – such as synthetic methodology – are certainly not in a better situation, with editors and reviewers having all sorts of often unreasonable demands and requests to perform additional experiments, provide further data and, last but not least, a subliminal pressure to make bigger and bolder claims for attracting more readers and citations to the journal. The latter is a particularly worrying trend towards a generalized sensationalistic mood, which is nowadays widespread among publishers and reviewers. Take a look at certain 'Table of Contents' abstracts and you will immediately see what I mean... So, in order to get a paper accepted for publication, authors are increasingly pressurized to do something sensational, or make hyperbolic claims, or rush into unduly bold claims and conclusions. The good old robust, humble and cautious research work that builds solid evidence step by step, piece after piece, publication after publication, is not cool any more: you won't get far with that in the impact factors age... Am I being too pessimistic and even old-fashioned? Maybe, but this is only one aspect of a progressively deteriorating publishing and peer-review system, and in the next few editorials I'll gladly make more examples. Meanwhile I'd like to invite you to send me your thoughts and experience on the subject, by writing to synform@outlook.com.

Luckily, there is no need to make sensational claims for the chemistry presented in SYNFORM: because it is sensational! The SYNTHESIS Highlight by Y. Tanabe (Japan) kicks off this March issue, followed by a contribution on a Science article by T. P. Yoon (USA). The next article covers a *Nat. Commun.* article by S. Chang (South Korea) on a novel synthesis of silicon-substituted synthetic intermediates. The issue finale is assigned to G. Manolikakes (Germany) who is the protagonist of the Young Career Focus interview.

Enjoy your reading! And remember: we look forward to receiving your thoughts and comments!!

In this issue

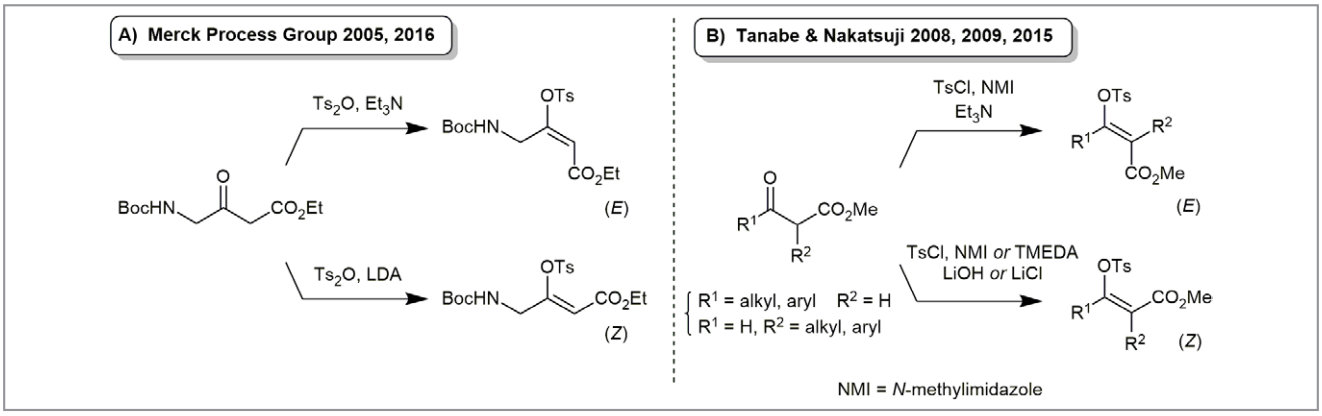
Contact
If you have any questions or wish to send feedback, please write to Matteo Zanda at: synform@outlook.com

A General and Robust Method for the Preparation of (*E*)- and (*Z*)-Stereodefined Fully Substituted Enol Tosylates: Promising Cross-Coupling Partners

Synthesis **2016**, *48*, 4072–4080

Regio- and stereocontrolled syntheses of (*E*)- and (*Z*)-stereodefined all-carbon-substituted olefins are of pivotal importance and highly challenging tasks in organic synthesis. Recent comprehensive reviews address the impressive progress in this area.[1]

Strategies based on stereoretentive cross-coupling reactions using (*E*)- and (*Z*)-stereodefined 'not fully'-substituted (R^1 *or* R^2 = H in Scheme 1) enol tosylates – which have interesting synthetic applications (see for example Figure 1) – are reliable toward this end.



Scheme 1 (*E*)- and (*Z*)-Stereocomplementary enol tosylations of 'not fully'-substituted β-keto esters

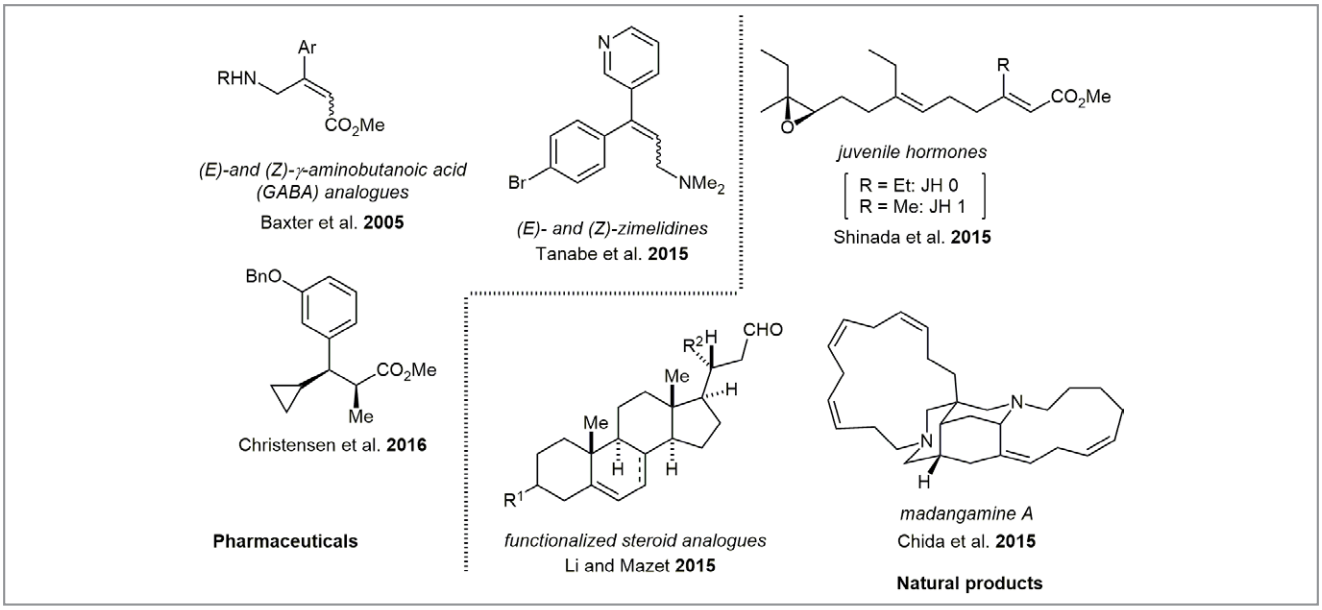
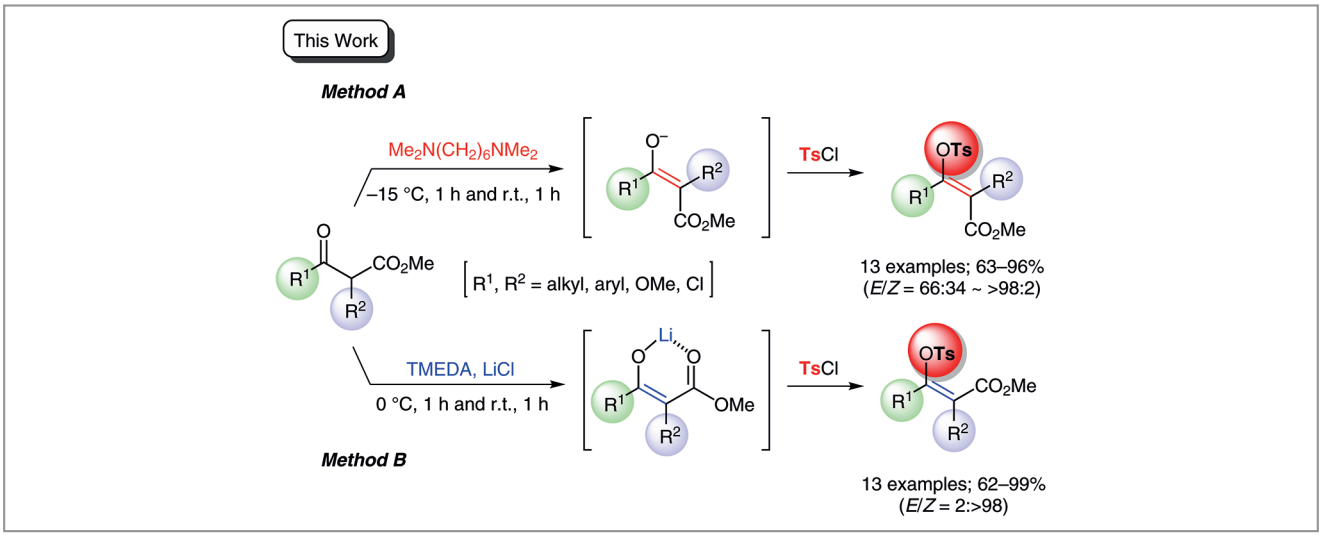
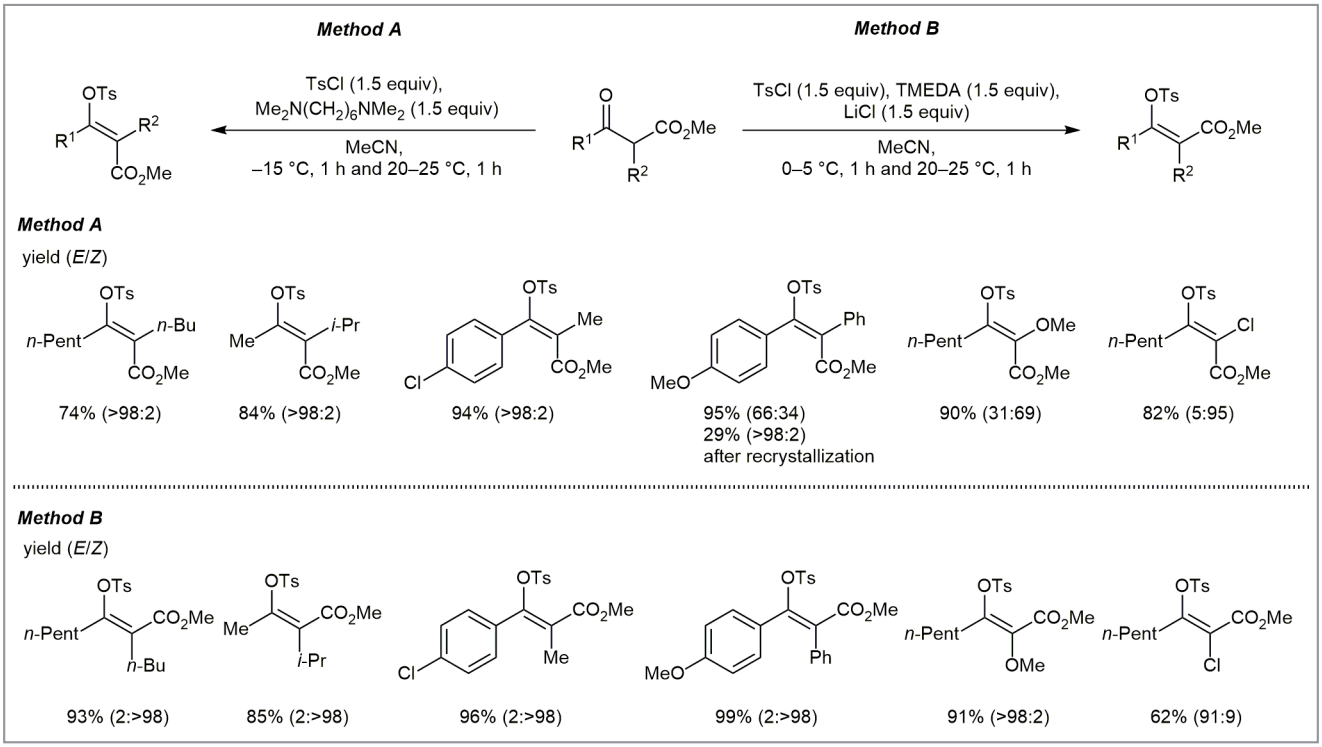


Figure 1 Synthetic applications of 'not fully'-substituted (*E*)- and (*Z*)-enol tosylates



Scheme 2 (*E*)- and (*Z*)-Stereocomplementary enol tosylations of all-carbon 'fully'-substituted β-keto esters

"For the preparation of (*E*)- and (*Z*)-enol tosylate cross-coupling partners, a group at the Merck company consistently utilizes a Ts_2O/amine system for preparing *E*-configured and Ts_2O/LiHMDS (or NaHMDS) for preparing *Z*-configured reagents (see Scheme 1),[2]" said Professor Yoo Tanabe at the Kwansei Gakuin University (Japan), "whereas in our ongoing studies we make use of the much more accessible TsCl/NMI (*N*-methylimidazole)/Et_3N (for *E*) and TsCl/NMI/LiOH (or LiCl) (for *Z*) reagents.[3]" Professor Tanabe continued: "One of our procedures will be disclosed shortly in *Organic Synthesis*



Scheme 3 Representative examples of (*E*)- and (*Z*)-stereocomplementary enol tosylations (Methods A and B)

(OS).[3d] The current privileged methodology has contributed to the successful total syntheses of some elaborated natural products and drug-related compounds, as depicted in Figure 1."

According to Professor Tanabe, the article in *Synthesis* introduces a general, cost-effective, and robust protocol for the preparation of all-carbon (fully)-substituted acyclic enol tosylate scaffolds as promising stereoretentive cross-coupling partners (R^1, R^2 = alkyl and/or aryl; Schemes 2 and 3). "Switching the reagents and conditions allows for (*E*)- and (*Z*)-stereocomplementary preparation of the corresponding enol tosylates from less reactive 'α-carbon-substituted' β-keto esters: TsCl/$Me_2N(CH_2)_6NMe_2$ was used for obtaining (*E*)-products (method A: total 13 examples; 63–96%, almost >98% *E*) and TsCl/TMEDA/LiCl for (*Z*)-products (method B: total 13 examples; 62–99%, almost >98% *Z*)," explained Professor Tanabe.

He continued: "All reactions were completed under identical optimized conditions in good to excellent yields. With regard to stereoselectivity, almost all cases produced positive and excellent results (>94:6 for method A and <2:98 for method B). Purification up to >98% de was achieved by short column chromatography or by recrystallization. As a limitation, (*E*)-selectivity using α,β-diaryl substrates is only moderate. This tendency coincides with discussions in the preceding report[3c] which ascribes it to the intrinsically more stable nature of (*Z*)-isomers. Fortuitously, these crude products could be enriched to the pure (*E*)-products (up to 98% de) by recrystallization. It should be noted that all of these stereodefined (*E*)- and (*Z*)-enol tosylates are novel compounds."

In general, these enol tosylates are relatively stable compounds that exhibit favorable reactivity for various cross-coupling reactions, thanks to recent advances in this area.

Professor Tanabe explained: "The starting α-substituted β-keto esters are readily available utilizing Ti-Claisen and base-mediated Claisen condensations between the same esters (self-type), or Ti-promoted Claisen condensations between different esters or between esters and acid chlorides (crossed-type).[4] α-Monoalkylation of parent β-keto esters is an alternative preparative method, although this is frequently accompanied by troublesome side dialkylation."

As depicted in Figure 2, a careful ^{1}H NMR monitoring experiment (–40 °C in CD_3CN) revealed that TsCl coupled with TMEDA formed a simple *N*-sulfonylammonium intermediate **IA** rather than a plausible N,N′-chelate-type intermediate **IB**. "The apparent downfield chemical shifts of the tosyl moiety in **IA** are related to the higher reactivity of the present system," remarked Professor Tanabe. He continued: "Based on the result, **IA** is likely to function as the key active species. This outcome is apparently contrary to a relevant chiral diamine-catalyzed desymmetric benzoylation of *meso*-diols with PhCOCl and related hypotheses regarding the mechanism through the corresponding N,N′-chelate-type intermediate.[5]"

A plausible mechanism for the successful emergence of (*E*)- and (*Z*)-selectivity is depicted in Scheme 4. "The (*E*)-selective reaction with highly reactive intermediate **I** proceeds via a non-chelation pathway to give (*E*)-form; $Me_2N(CH_2)_6NMe_2$ plays two different roles: that of a base reagent and also as a

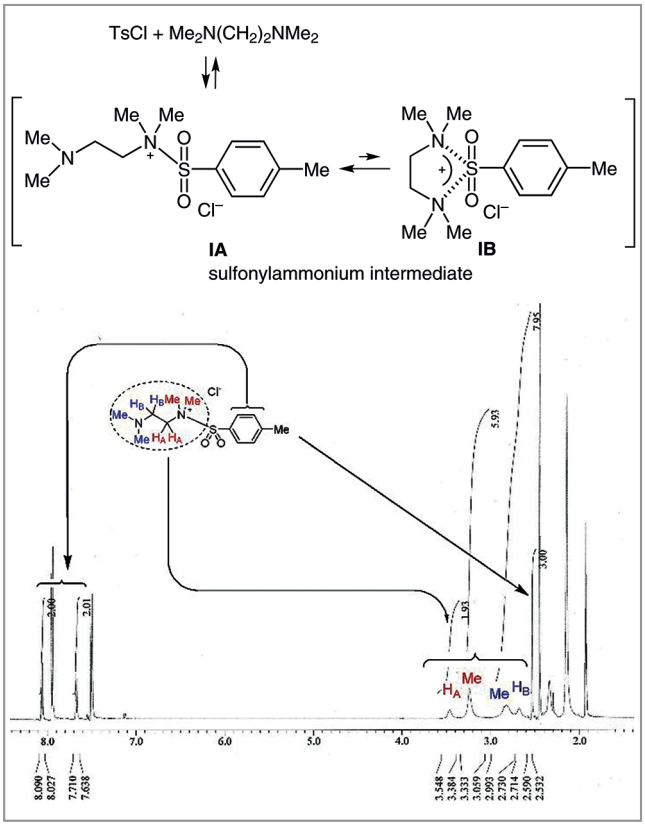
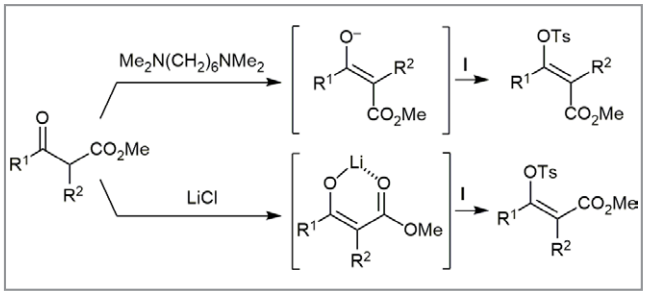


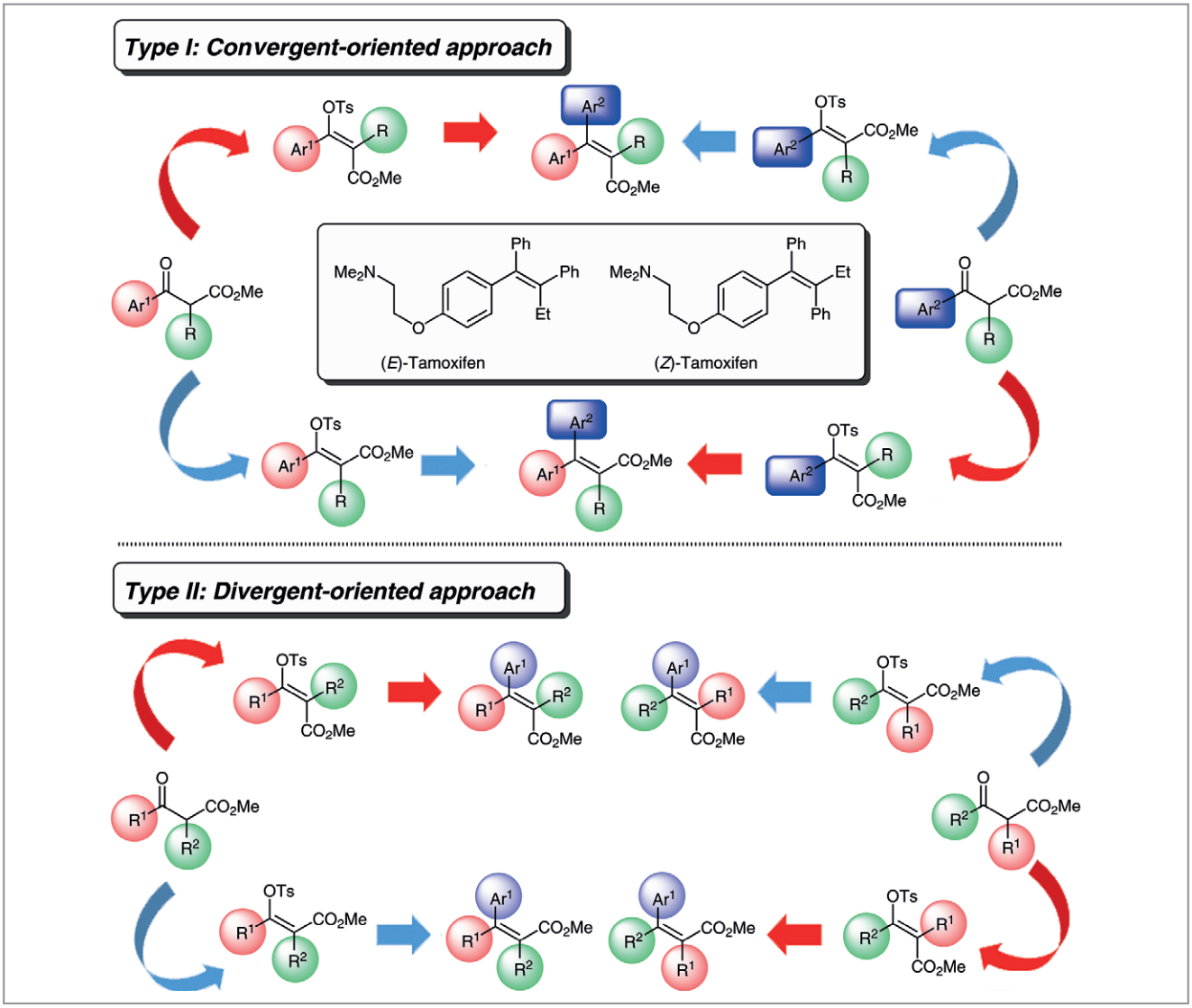
Figure 2 Formation of sulfonylammonium intermediate **IA** by ^{1}H NMR monitoring measurement at –40 °C



Scheme 4 Mechanistic investigation into the (*E*)- and (*Z*)-stereoselective enol tosylations

partner of **I** through equilibrium," explained Professor Tanabe. He continued: "$Me_2N(CH_2)_6NMe_2$ aids (*E*)-enolate formation through dipole-dipole repulsive interactions between the oxy anion and ester function. In clear contrast, the (*Z*)-selective reaction proceeds via a chelation mechanism to give (*Z*)-form; the Li cation facilitates (*Z*)-enolate formation."

Professor Tanabe and co-worker Professor Nakatsuji concluded: "The present protocol provides a useful avenue towards divergent syntheses (Type I and Type II) of various all-carbon (fully)-substituted (*E*)- and (*Z*)-stereodefined α,β-unsaturated ester scaffolds, which are distributed widely in natural products, pharmaceuticals, and supramolecules as key structural building blocks[3e] (Scheme 5). This robust and distinctive method involves stereocomplementary enol tosylations using readily available TsCl/diamine/(LiCl) reagents. High substrate generality is demonstrated in two sets (all four) of parallel and stereocomplementary synthetic pathways. Efficient parallel syntheses of zimeridine and tamoxifen were achieved utilizing subsequent highly (*E*)- and (*Z*)-stereoretentive cross-couplings (Suzuki–Miyaura, Negishi, Sonogashira, and Kochi–Fürstner)." As a final note, Professor Tanabe offered his warmest congratulations to Professor Ben L. Feringa (University of Groningen, The Netherlands) on being awarded the 2016 Nobel Prize in Chemistry.



Scheme 5 Divergent and parallel synthesis of (E)- and (Z)-α,β-unsaturated esters utilizing stereoretentive cross-couplings

About the authors

Y. Ashida

Yuichiro Ashida was born in Fukuchiyama, Kyoto (Japan) in 1989. He received his BSc degree (2012) and MSc degree (2014) from Kwansei Gakuin University (Japan) under the direction of Professor Yoo Tanabe. Presently, he is a PhD student and engages in his doctoral studies on the development of (*E*)-, (*Z*)-stereocomplementary parallel synthesis of multi-substituted α,β-unsaturated esters utilizing (*E*)-, (*Z*)-stereodefined enol tosylates and phosphonates and subsequent cross-coupling approaches, which are directed toward process chemistry.

A. Honda

Atsushi Honda was born in Hyogo (Japan) in 1992. He received his BSc degree (2015) from Kwansei Gakuin University (Japan) under the supervision of Professor Yoo Tanabe. He is currently an MSc student in the Tanabe group. His graduate research focuses on the (*E*)-, (*Z*)-stereocomplementary parallel synthesis of multi-substituted α,β-unsaturated esters and its application to (*E*)- and (*Z*)-tamoxifens.

Y. Sato

Yuka Sato was born in Shizuoka (Japan) in 1988. She received her BSc and MSc degrees from Kwansei Gakuin University (Japan) in 2011 and 2013, respectively, under the supervision of Professor Yoo Tanabe. Her research focuses on (*E*)-, (*Z*)-stereocomplementary synthesis of fully substituted α,β-unsaturated esters. She is currently working at Kansai Glico Corporation Ltd.

Prof. H. Nakatsuji

Hidefumi Nakatsuji received his BSc degree in 2005 and his PhD in 2010 from Kwansei Gakuin University (Japan) under the direction of Professor Yoo Tanabe. Dr. Nakatsuji then moved to Nagoya University (Japan, Professor Kazuaki Ishihara's group) and studied as a JSPS Postdoctoral Fellow and CREST project researcher until 2014. Next, he was promoted to Assistant Professor of the Tanabe group. His research interests are the development of chiral phosphine and phosphine oxide organocatalysts for MCR-type cyclizations and of condensation reactions for cost-effective reactions directed toward process chemistry.

Prof. Y. Tanabe

Yoo Tanabe received his BSc degree at Tokyo University (Japan) in the laboratory of Professor Kenji Mori. He received his PhD at the Tokyo Institute of Technology (Japan) under the direction of Professor Teruaki Mukaiyama on the development of practical acylation reactions. After leaving Sumitomo Chemical Co. Ltd, Dr. Tanabe moved to Kwansei Gakuin University (Japan) in 1991 as Associate Professor and was promoted to Full Professor in 1997. In 1996–1997, he studied at University of Groningen (The Netherlands) under the direction of Professors Richard M. Kellogg and Ben L. Feringa on chiral sulfur chemistry. His research focuses on the exploitation of useful synthetic reactions directed toward process chemistry, the concise synthesis of useful fine chemicals and the total synthesis of biologically active natural products.

REFERENCES

(1) Selected reviews: (a) A. B. Flynn, W. W. Ogilvie *Chem. Rev.* **2007**, *107*, 4698; (b) P. Polák, H. Váňová, D. Dvořák, T. Tobrman *Tetrahedron Lett.* **2016**, *57*, 3684.
(2) (a) J. M. Baxter, D. Steinhuebel, M. Palucki, I. W. Davies *Org. Lett.* **2005**, *7*, 215; (b) M. Christensen, A. Nolting, M. Shevlin, M. Weisel, P. E. Maligres, J. Lee, R. K. Orr, C. W. Plummer, M. T. Tudge, L.-C. Campeau, R. T. Ruck *J. Org. Chem.* **2016**, *81*, 824.
(3) (a) H. Nakatsuji, K. Ueno, T. Misaki, Y. Tanabe *Org. Lett.* **2008**, *10*, 2131; (b) H. Nakatsuji, H. Nishikado, K. Ueno, Y. Tanabe *Org. Lett.* **2009**, *11*, 4258; (c) Y. Ashida, Y. Sato, T. Suzuki, K. Ueno, K. Kai, H. Nakatsuji, Y. Tanabe *Chem. Eur. J.* **2015**, *21*, 5934; (d) Y. Ashida, H. Nakatsuji, Y. Tanabe, *Org. Synth.* under review; (e) Y. Ashida, A. Honda, Y. Sato, H. Nakatsuji, Y. Tanabe, *ChemistryOpen* **2017**, DOI: 10.1002/open.201600124.
(4) Selected examples: (a) Y. Tanabe *Bull. Chem. Soc. Jpn.* **1989**, *62*, 1917; (b) S. N. Crane, E. J. Corey, *Org. Lett.* **2001**, *3*, 1395; (c) T. Misaki, R. Nagase, K. Matsumoto, Y. Tanabe *J. Am. Chem. Soc.* **2005**, *127*, 2854; (d) R. Nagase, Y. Oguni, S. Ureshino, H. Mura, T. Misaki, Y. Tanabe *Chem. Commun.* **2013**, *49*, 7001; (e) Y. Ashida, S. Kajimoto, H. Nakatsuji, Y. Tanabe *Org. Synth.* **2016**, *93*, 286.
(5) D. Terakado, T. Oriyama *Org. Synth.* **2006**, *83*, 70.

Enantioselective Photochemistry through Lewis Acid Catalyzed Triplet Energy Transfer

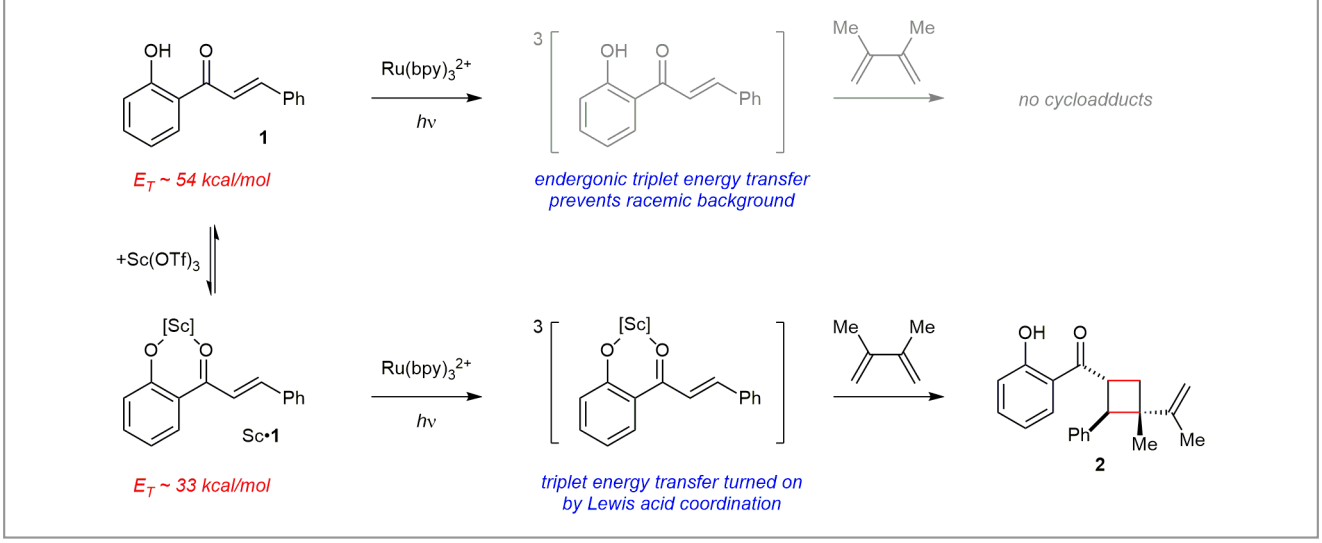
Science **2016**, *354*, 1391–1395

Carbonyl photochemistry is prominent in many of the most important reactions in photochemical synthesis. It has been known for many decades that the photochemical properties of carbonyl compounds can be modulated by Lewis acid catalysts. Professor Tehshik P. Yoon of the University of Wisconsin–Madison (USA) explained: "In the 1980s, Fred Lewis showed that the coordination of enones to oxophilic Lewis acids such as BF_3 and $EtAlCl_2$ could completely change the energetics of their singlet excited states.[1] This phenomenon can result in changes to the UV absorption spectra of coordinated enones and in an increased efficiency of subsequent photocycloaddition reactions. Recently, Thorsten Bach's laboratory has exploited these effects to design highly enantioselective photocycloaddition reactions using chiral Lewis acids".[2]

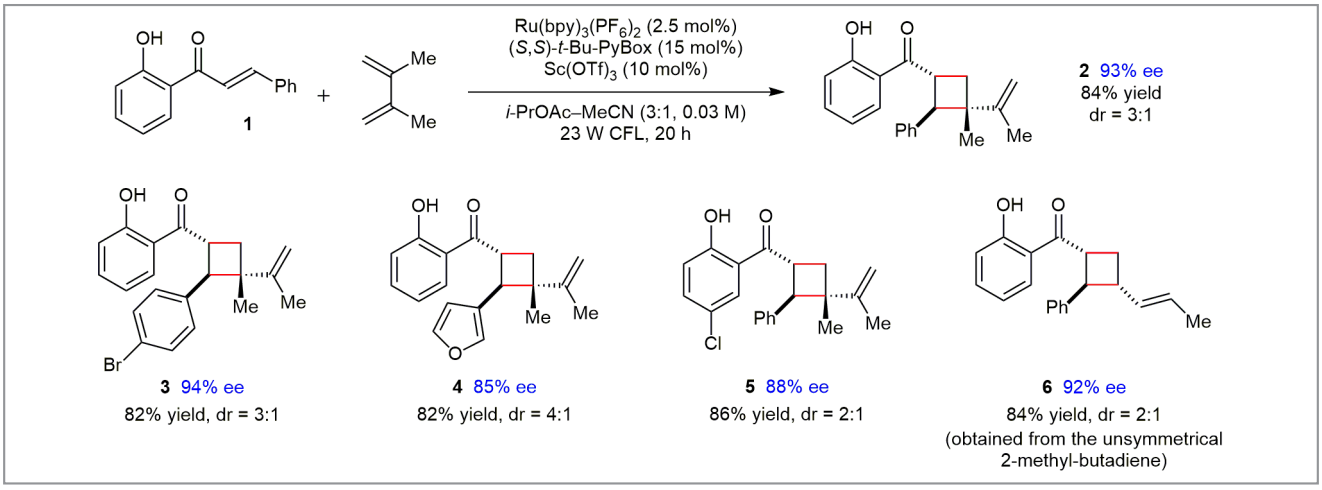
The group of Professor Yoon has also been working in this area and the central discovery reported in their recent *Science* paper is that Lewis acids can have a similarly large impact on the triplet excited states of enones. Professor Yoon said: "We found that the coordination of $Sc(OTf)_3$ to 2′-hydroxychalcone **1** results in a surprisingly large decrease in the energy of its first excited triplet state. When **1** is irradiated in the presence of $Sc(OTf)_3$ and $Ru(bpy)_3^{2+}$, triplet energy transfer is thermodynamically feasible from photoexcited $Ru^*(bpy)_3^{2+}$ only to the Lewis acid coordinated assembly, and not to the free chalcone (Scheme 1)."

This result opens up the possibility of chiral Lewis acid catalysis of triplet sensitization. "When a chiral pybox $Sc(OTf)_3$ complex is used in combination with $Ru(bpy)_3^{2+}$, we are able to synthesize highly enantioenriched cyclobutanes using relatively low concentrations of both co-catalysts," said Professor Yoon (Scheme 2). He continued: "A large part of this investigation involved the optimization of this system and an exploration of the variety of chalcones and dienes that participate in the reaction."

Professor Yoon explained: "We think that this strategy for asymmetric catalysis is important for a few different reasons. First, this is another example of highly enantioselective photochemistry using tandem photocatalysis, a topic that my laboratory has been interested in for several years.[3] We think that one of the major benefits of using a separate enantiocontrolling catalyst, that is chemically distinct from the photochemically active moiety, is that the structure of the chiral controller can be optimized extensively without significantly altering the photochemical behavior of the photocatalyst." He continued: "In addition, the transformation we have discovered is an example of a triplet photosensitization reac-



Scheme 1 Conceptual scheme for Lewis acid catalyzed triplet energy transfer



Scheme 2 Enantioselective catalytic triplet sensitization reactions

tion. One advantage of photosensitized reactions over direct photochemical reactions is that the reactive triplet state can be accessed without first passing through a singlet excited state. The reactivity of enones in their singlet excited states can be substantially different from those in their triplet states – for instance, the regiochemical outcomes can differ, and the quantum yields of singlet and triplet photoreactions can be quite different, particularly in intermolecular reactions where the shorter lifetimes of singlet states can be especially problematic. By bypassing the singlet state and directly accessing the organic triplet, we were able to focus on optimizing the chemistry of the triplet state photoreaction without having to worry about any negative impacts on the singlet photochemistry."

Professor Yoon revealed that their initial observation of this reactivity was accidental. "We were investigating whether photoredox activation of the hydroxychalcone substrates might lead to Diels–Alder cycloaddition reactions, along the lines of what Porco had reported a few years ago using chemical redox catalysts,[4]" explained Professor Yoon. He continued: "In our first few experiments, although we did observe some formation of the [4+2] cycloadducts that Porco described, the main products of these reactions were these unexpected cyclobutanes described in our *Science* paper. I was, frankly, a little irritated at first. I had planned to apply the Diels–Alder reaction to a total synthesis project, for which the [2+2] products were not at all useful. Moreover, I really did not understand how these cyclobutanes were forming. I kept proposing possible trivial explanations, and Travis (i.e. Dr. Travis R. Blum, first author of the article, then Ph.D. student) kept running control experiments to disprove my hypotheses."

Professor Yoon remarked: "There have only been a few other times in my career to date when a morass of confusing empirical data has suddenly resolved into a clear and coherent picture. It's a delightful feeling, especially when the conclusion is more interesting than the problem we were originally attempting to solve. After making multiple observations that seemed inconsistent with photoredox activation, the ultimate inescapable conclusion that emerged was that we were observing Lewis acid catalyzed triplet energy transfer. We were excited by this realization because this mechanism seemed to really represent a fundamentally new physical effect that had not previously been characterized. As much work as it was to complete the synthesis and characterization work for this paper, we spent just as much effort convincing ourselves that the mechanistic picture we were proposing was reasonable. We ended up needing to collaborate with Desiree Bates, a computational chemist in our department, to learn to estimate the energies of organic excited states using DFT computations. We also had to go outside of our department to find a spectrometer capable of detecting the weak, low-energy emission that we think is arising from the low-energy triplet states that we are accessing."

From a different perspective, Professor Yoon pointed out that the control of stereochemistry in photochemical reactions has long been recognized as a difficult problem. He said: "Some of the earliest attempts to control the enantioselectivity of photochemical reactions date back to the1930s,[5] but for a long time, there was a persistent belief that the reactivity of highly photoexcited molecules was simply too uncontrollable to ever be amenable to asymmetric catalysis in any general way. This belief has only been disproven within the last de-

cade or so.[6] Therefore we think any new strategy for enantioselective catalysis of photochemical reactions remains interesting, particularly when they involve excited state organic intermediates."

"I'm proud of this paper, and I'm even more proud of the way that the story came together. This was a project that we might have missed entirely had Travis not been curious about a set of anomalous results. We learned a lot about characterizing and investigating the properties of excited states," said Professor Yoon. He concluded: "The next steps will be to develop applications for this reactivity, which is something we are actively pursuing at the moment. We are also curious to know how general this phenomenon is. If we can show that the triplet-lowering effect of Lewis acids on carbonyl compounds is general and not in some way specific to this class of 2-hydroxychalcone substrates, I think we might have a really robust way to control the stereochemistry of excited-state organic photoreactions."

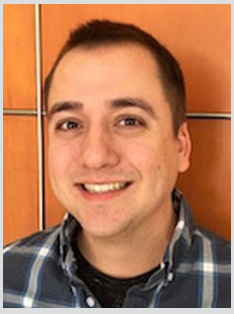
REFERENCES

(1) (a) F. D. Lewis, D. K. Howard, J. D. Oxman *J. Am. Chem. Soc.* **1983**, *105*, 3344; (b) F. D. Lewis, S. V. Barancyk *J. Am. Chem. Soc.* **1989**, *111*, 8653.
(2) (a) H. Guo, E. Herdtweck, T. Bach *Angew. Chem. Int. Ed.* **2010**, *49*, 7782. (b) R. Brimioulle, T. Bach *Science* **2013**, *342*, 840.
(3) (a) Y. P. Yoon *Acc. Chem. Rev.* **2016**, *49*, 2307; (b) J. Du, K. L. Skubi, D. M. Schultz, T. P. Yoon *Science* **2014**, *344*, 392.
(4) (a) H. Cong, D. Ledbetter, G. T. Rowe, J. P. Caradonna, J. A. Porco Jr. *J. Am. Chem. Soc.* **2008**, *130*, 9214; (b) H. Cong, C. F. Becker, S. J. Elliott, M. W. Grinstaff, J. P. Porco Jr. *J. Am. Chem. Soc.* **2010**, *132*, 7514.
(5) W. Kuhn, E. Knopf *Naturwissenschaften* **1930**, *18*, 183.
(6) R. Brimioulle, D. Lenhart, M. M. Maturi, T. Bach *Angew. Chem. Int. Ed.* **2015**, *54*, 3872.

About the authors

Dr. T. Blum

Travis Blum attended Hobart and William Smith Colleges (USA), and obtained his Bachelor's degree in 2010 after studying the total synthesis of bioactive marine depsipeptides. He then moved to the University of Wisconsin–Madison (USA), where he was awarded an NIH Chemical Biology Interface Training Grant and studied both electron-transfer and energy-transfer photocatalysis during his doctoral work under Professor Tehshik P. Yoon. He received his Ph.D. in 2016, and is currently a postdoctoral fellow at Harvard University (USA) in the laboratory of Professor David Liu.



Dr. Z. Miller

Zach Miller completed his undergraduate studies in chemistry at Wittenberg University (USA), during which time he was awarded an NSF REU that was carried out at Syracuse University (USA) under the direction of Professor Donald Dittmer. In 2015, he completed his Ph.D. studies at the University of Michigan (USA) under the guidance of Professor John Montgomery where he focused on organometallic catalysis.

Dr. D. Bates

Desiree Bates received her B.S. from Winona State University (USA) in 2006 and her Ph.D. in theoretical and computational chemistry from Mississippi State (USA) with Professor Gregory Tschumper in 2011. As the computational chemistry leader in the chemistry department's computer center at UW–Madison (USA), where she has served since 2011, she collaborates with students and research groups at a variety of levels on how to employ computational approaches to aid their research.

Dr. I. Guzei

Ilia Guzei obtained his Ph.D. in chemistry at Wayne State University (USA) in 1996 based on his work with pyrazolato complexes of transition metals and crystallographic studies. After a postdoctoral stay at University of Delaware (USA) and a brief appointment at Iowa State University (USA), Ilia became Director of Crystallography at the Chemistry Department of University of Wisconsin (USA) in 2000. At UW–Madison he received an Excellence Early Career Award in 2009, Chancellor's Award for Excellence in Research in 2013, and was promoted to Distinguished Scientist in 2015.

Prof. T. P. Yoon

Tehshik Yoon was born in 1975 in Montreal (Canada) and was raised in Blacksburg, VA (USA). He received his A.B. from Harvard University (USA), where he performed undergraduate research with Professor David Evans, and his M.S. from Caltech (USA), where he studied with Professor Erick Carreira. He was the first Ph.D. student of Professor David MacMillan, first at Berkeley (USA) and then Caltech (USA), and completed postdoctoral studies with Professor Eric Jacobsen at Harvard University (USA). Since 2005, Tehshik has served on the faculty at the University of Wisconsin–Madison (USA). He was promoted to Associate Professor in 2011 and to Professor in 2013.

Borane-Catalyzed Ring-Opening and Ring-Closing Cascades of Furans Leading to Silicon-Functionalized Synthetic Intermediates

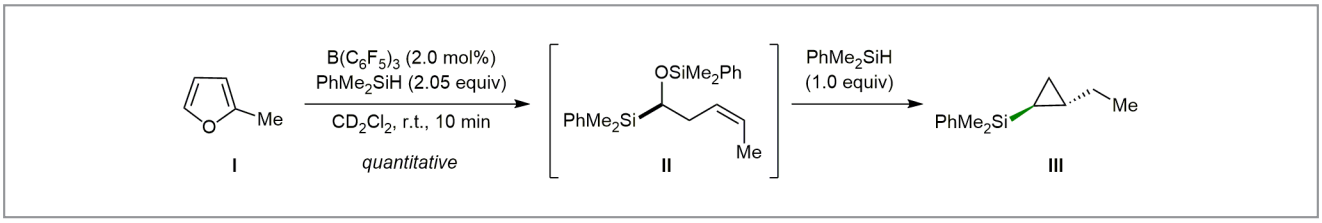
Nat. Commun. **2016**, *7*, 13431

A number of transition-metal complexes are known to efficiently catalyze hydrosilylation of unsaturated functionalities including C=O, C=N and C=C bonds, largely via inner- or outer-sphere pathways. Representatively, a series of platinum-based hydrosilylation catalysts (e.g. Karstedt's catalyst) display powerful and selective catalytic performance, especially in hydrosilylation of alkenes, thus enabling large-scale synthesis of various alkyl silanes in industry. However, most of the presently available hydrosilylation processes rely on the use of expensive transition metals (Rh, Ir, Pt, or Pd). In this regard, certain Lewis acids such as $B(C_6F_5)_3$ have drawn significant attention as catalysts due to their practical merits. In 1996, the Piers group first reported the $B(C_6F_5)_3$-catalyzed hydrosilylation of aromatic aldehydes, ketones, and esters (for references see the original *Nat. Commun.* article). Since then, the $B(C_6F_5)_3$ catalyst system has been shown to be effective not only for hydrosilylation of unsaturated functionalities but also for reductive sp^3-C–X bond cleavage (X = O, S, or halides) using hydrosilanes. The Park and Chang group from the Institute for Basic Science and KAIST (Daejeon, South Korea) recently reported the $B(C_6F_5)_3$-catalyzed dearomative silylative reduction of quinolines and pyridines leading to (partially) saturated azacyclic products having sp^3-C–Si bonds *beta* to the nitrogen atom. Subsequently, they also showed that α,β-unsaturated nitriles and esters can undergo a selective silylative reduction.

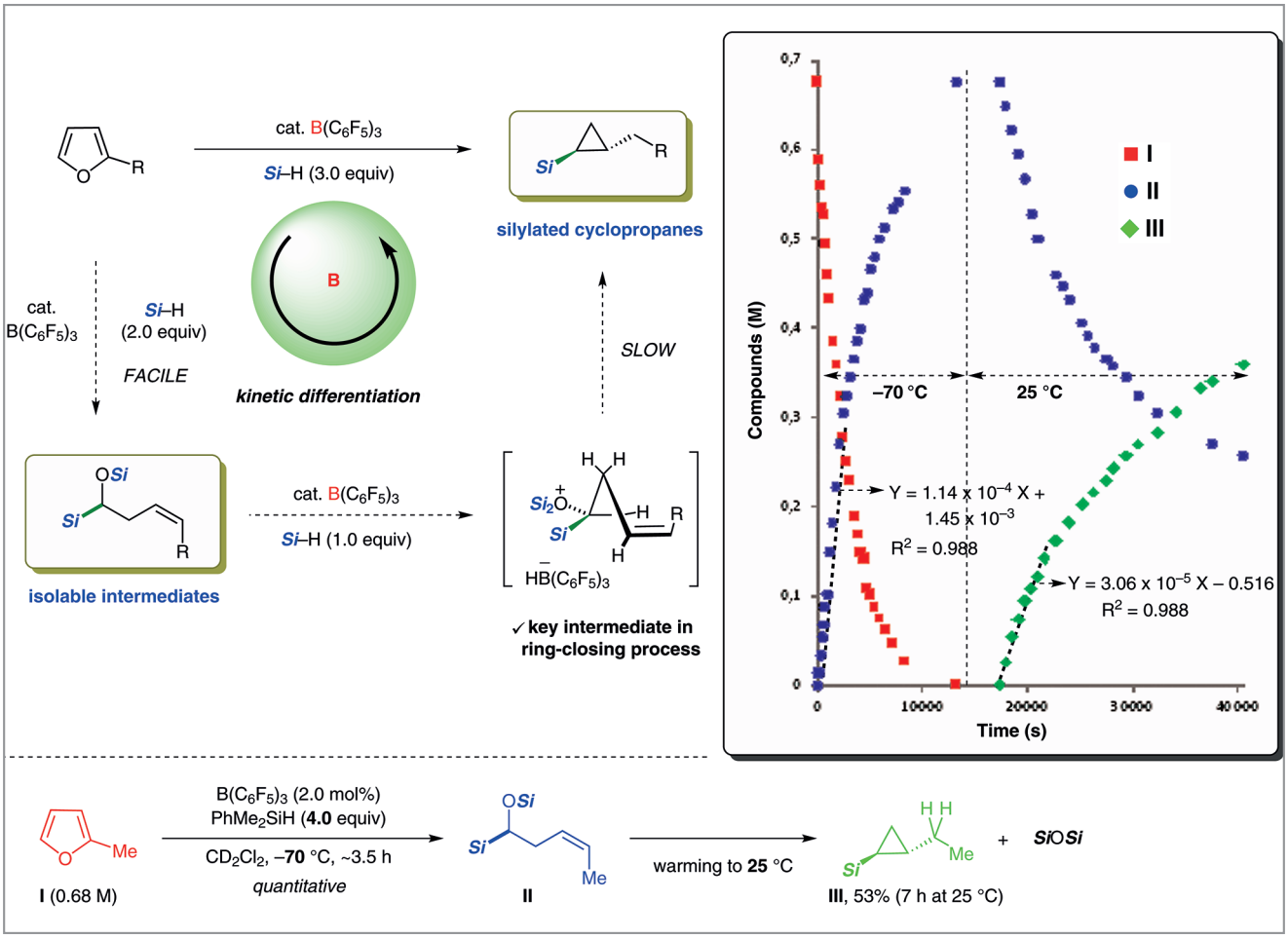
Continuing their efforts along these lines, Professor Chang and co-workers turned their attention to furans, one of the representative biomass-derived chemicals, mainly due to the fact that furans are predicted to undergo reductive cleavage serving as various types of carbon sources. The Chang group envisioned that $B(C_6F_5)_3$ would be capable of catalyzing a hydrosilylative transformation of furans. Professor Chang said: "The unique reactivity of $B(C_6F_5)_3$/hydrosilane toward the sp^3-C–O and sp^2-C=C bonds initially made us curious about which products could be generated from furans under the $B(C_6F_5)_3$-mediated hydrosilylation conditions." In a preliminary reaction, 2-methylfuran (**I**) was subjected to the $B(C_6F_5)_3$-catalytic conditions to reveal that **I** underwent ring-opening with $PhMe_2SiH$, leading to the corresponding alkenyl silyl ether bearing an sp^3-C–Si bond *alpha* to the oxygen atom (**II**). Interestingly, the double bond in the product was determined to be exclusively *Z*. "Such an unprecedented ring-opening product with excellent chemo-, regio-, and stereoselectivities under mild metal-free conditions is considered to be exceptional, and it also caught our attention with regard to the mechanistic pathway," remarked Professor Chang. Through a set of optimization studies, the authors found that as little as 2.0 mol% of $B(C_6F_5)_3$ with 2.05 equivalents of $PhMe_2SiH$ allowed for quantitative silylative ring opening of **I** at room temperature within ten minutes (Scheme 1).

"More interestingly, when one more equivalent of $PhMe_2SiH$ was added into the reaction mixture, we observed an exothermic reaction with a new product formation," said Professor Chang. He continued: "The structure of this new compound was identified to be a silylated cyclopropane (**III**) with exclusive *anti*-diastereoselectivity with the formation of a stoichiometric amount of disiloxane by-product."

To gain mechanistic insights, the Chang group conducted an NMR study in a reaction of 2-methylfuran (**I**) with $PhMe_2SiH$ (4.0 equiv, Scheme 2). "Low-temperature NMR monitoring was a useful analytical technique especially for a rapid cascade transformation as in this case," remarked Professor Chang. He continued: "The reaction was observed to proceed smoothly at –70 °C leading to (*Z*)-α-silyloxy alkenyl



Scheme 1 $B(C_6F_5)_3$-catalyzed silylative ring-opening and ring-closing cascade of 2-methylfuran (I)



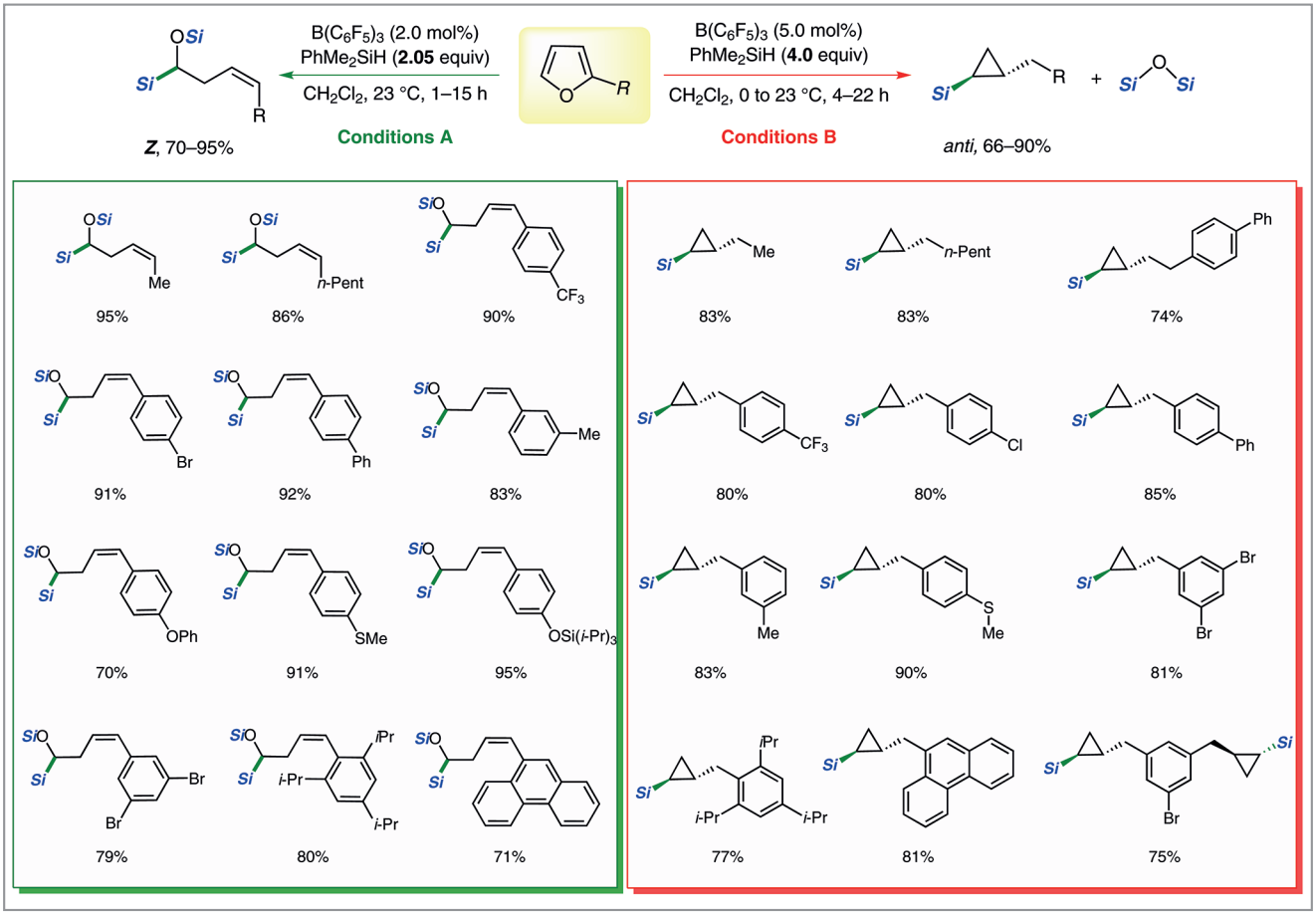
Scheme 2 Borane-catalyzed ring-opening and ring-closing cascade of furans giving rise to synthetically valuable silicon compounds with ^{1}H NMR monitoring of this process (Si = $SiMe_2Ph$)

silane (**II**) quantitatively over 3.5 hours. Upon further warming to room temperature, the in situ generated intermediate **II** was converted into the corresponding silylated cyclopropane (**III**). These results clearly indicated that the ring-opening and ring-closing cascade of 2-methylfuran (**I**) proceeded under perfect kinetic differentiation."

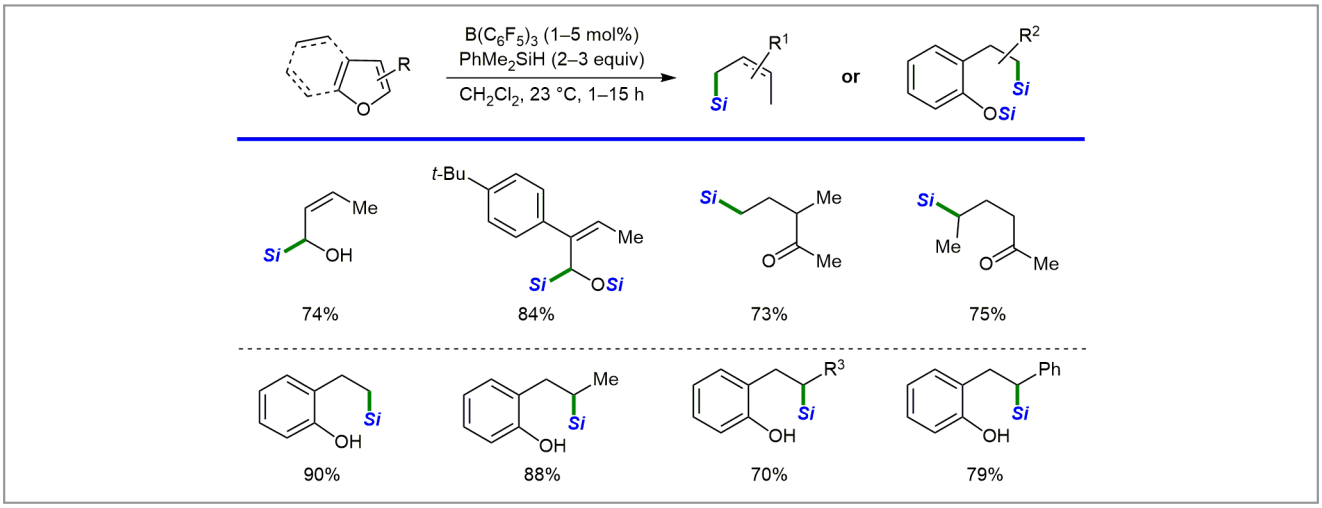
With this mechanistic depiction, Chang and co-workers explored the substrate scope (Scheme 3). Professor Chang said: "We were pleased to see that a variety of 2-substituted furans were transformed into a single product of α-silyloxy-(*Z*)-homoallylsilanes in high yields under standard conditions with excellent stereoselectivity (*Z*/*E* > 99:1, Scheme 3; Conditions A)." Professor Chang also said: "In agreement with the kinetic behavior observed in the low-temperature NMR study, a range of 2-substituted furans were smoothly converted into *anti*-2-alkylcyclopropyl silanes at room temperature in good to high yields irrespective of their electronic and steric variations when $PhMe_2SiH$ (4.0 equiv) was used in the presence of $B(C_6F_5)_3$ (5.0 mol%) catalyst (>99% *anti*-selectivity, Scheme 3; Conditions B)."

Subsequently, Professor Chang and co-workers found that the present $B(C_6F_5)_3$ catalysis was applicable for the silylative ring opening of additional furan derivatives, providing the corresponding silylated products in good yields (Scheme 4). "It is notable that the chemoselectivity was altered depending on the position of substituents on the furan substrates, thus delivering a range of various ring-opening products," remarked Professor Chang.

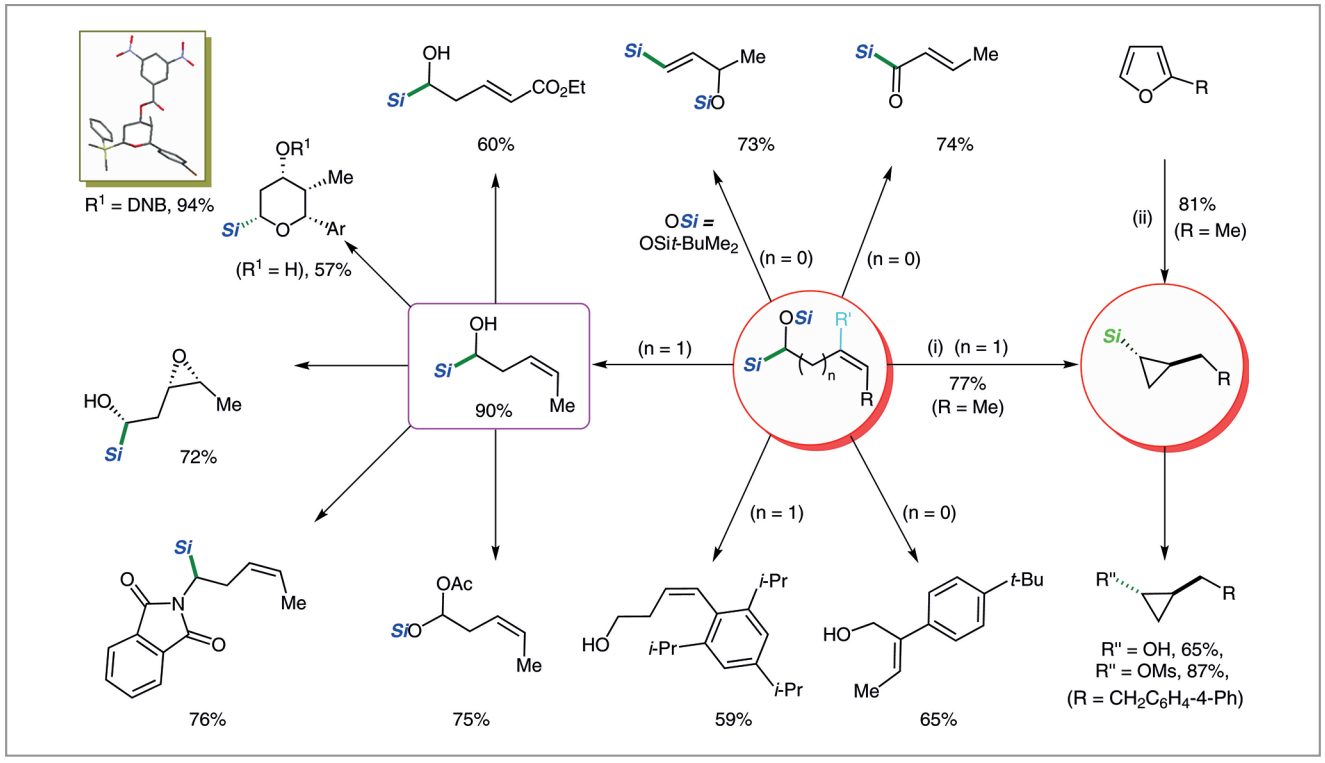
In addition, Professor Chang and co-workers demonstrated the synthetic utility of two types of products obtained through the present $B(C_6F_5)_3$-catalyzed hydrosilylation cascade of furans (Scheme 5). Professor Chang explained: "The



Scheme 3 $B(C_6F_5)_3$-catalyzed cascade silylative transformation of furans (*Si* = $SiMe_2Ph$)



Scheme 4 $B(C_6F_5)_3$-catalyzed silylative ring opening of alkyl furans and benzofurans (*Si* = $SiMe_2Ph$, R^3 = 4-TIPSO-C_6H_4, TIPS = triisopropylsilyl)



Scheme 5 Enrichment and elaboration of products (*Si* = $SiMe_2Ph$, *Si* = $SiPh_2H/SiMe_2Ph$)

obtained products of α-silyloxy homoallylsilanes and *anti*-2-alkylcyclopropyl silanes possess synthetic building units which are readily transformed into other synthetically valuable functional groups. Therefore, the synthetic utility of the present method could be potentially broad in synthetic and medicinal chemistry."

"In conclusion, chemodivergent catalytic transformations of furans have been developed to furnish synthetically valuable silicon-functionalized products, α-silyloxy-(*Z*)-alkenyl silanes and *anti*-cyclopropyl silanes with excellent diastereoselectivity," said Professor Chang. He also noted: "The mechanistic pathway of this cascade reaction was well elucidated by a series of mechanistic experiments." Finally, he commented: "The present procedure showcases an example of biomass conversion to provide synthetically valuable chemicals under extremely mild and convenient conditions without requiring transition-metal species."

About the authors

Dr. C. K. Hazra

Chinmoy Kumar Hazra is currently working as a postdoctoral scientist under Professor Sukbok Chang at the Institute for Basic Science (IBS) (South Korea). He obtained his Ph.D. from the Westfälische Wilhelms-Universität Münster (Germany) in 2013 (Professor Martin Oestreich) and his M.S. degree in chemistry from the Indian Institute of Technology Bombay (India) in 2010. He also stayed at the University of Strasbourg (France) for a postdoctoral experience with Professor Françoise Colobert. His research interests include the development of metal-free catalysis with mechanistic understanding and synthetic applications.

Dr. N. Gandhamsetty

Narasimhulu Gandhamsetty was born in 1980 and raised in Sathupalli (Kadapa, India). He obtained his Ph.D. at the Indian Institute of Chemical Technology (India) under Professor Jhillu S. Yadav in 2014. Currently, he is working as a postdoctoral scientist under Professor Sukbok Chang at the Institute for Basic Science (IBS) (South Korea). He received an 'outstanding research award' from IBS in 2016. His research interests are the development of new synthetic methods, silylative reductions, and organocatalytic methodologies for general applications in synthetic organic chemistry.

Dr. S. Park

Sehoon Park was born in Seoul (South Korea) in 1977 and received his Ph.D. (2008) in chemistry from the Tokyo Institute of Technology (Japan) under Professor Kohtaro Osakada, where he received a Monbukagakusho scholarship (2004–2008). He then joined the University of North Carolina at Chapel Hill (USA) as a postdoctoral fellow (Professor Maurice Brookhart, 2009–2012). In 2013, he joined Professor Chang's group at the Institute for Basic Science (IBS) (South Korea), where he is a senior research fellow. He was a recipient of the outstanding research award in 2014. Currently, he is also an Adjunct Professor at the Korea University of Science and Technology. His research interests are synthetic and mechanistic organometallic chemistry as well as synthetic methodology in catalysis.

Prof. S. Chang

Sukbok Chang is Director at the Center for Catalytic Hydrocarbon Functionalizations in a program of the Institute for Basic Science (IBS) (South Korea) and also Professor at the Korea Advanced Institute of Science & Technology (KAIST). In 1996, he earned his Ph.D. at Harvard University (USA) under Professor Eric N. Jacobsen. After postdoctoral work at Caltech (USA) with Professor Robert H. Grubbs, he joined Ewha Womans University in Seoul (South Korea) as an Assistant Professor in 1998, and moved to KAIST in 2002. His research interests include the development and mechanistic understanding of metal-catalyzed organic transformations.

Young Career Focus: Dr. Georg Manolikakes (Goethe-Universität Frankfurt, Germany)

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 Dr. Georg Manolikakes (Goethe-Universität Frankfurt, Germany).

Biographical Sketch

Dr. G. Manolikakes

Georg Manolikakes was born and raised in Ebersberg (Germany). He studied chemistry at the Ludwig-Maximilians-Universität München (Germany). He received his Diploma (2005) and PhD (2009) from the same university under the guidance of Professor Paul Knochel in the field of functionalized organometallics. In 2009, Georg joined the group of Professor Phil S. Baran at the Scripps Research Institute in La Jolla, CA (USA) as a postdoctoral fellow, where he worked on the total synthesis of cortistatin A, a marine natural product. Since October 2010 Georg is an independent research group leader at the Goethe-Universität Frankfurt (Germany). His research interests focus on the development of new methods for the synthesis of biologically relevant molecules with particular emphasis on multicomponent reactions. His work has been recognized by a number of awards and fellowships, among them the Thieme Chemistry Journals Award (2016), the Dr. Otto-Röhm Memorial Foundation Award (2016), an Exploration Grant from the Boehringer Ingelheim Foundation (2016) and a Liebig Fellowship from the Fonds der Chemischen Industrie (2011).

INTERVIEW

SYNFORM *What is the focus of your current research activity?*

Dr. G. Manolikakes The central theme in my research group is the development of new, efficient and highly modular methods for the construction of complex organic molecules from relatively simple starting materials. Our fundamental approach can be considered as a functional group based approach. We start with the identification of specific functional groups or structural motifs, which are prevalent in biologically active compounds. Then we look for novel, more efficient, sustainable or perhaps still undiscovered methods for the construction of these substructures. Our current research can be divided into two major areas: (i) the development of sulfur dioxide based three-component reactions for the synthesis of sulfones and sulfonamides; and (ii) new methods for the sustainable and stereoselective construction of amines and α-amino acids.

SYNFORM *When did you get interested in synthesis?*

Dr. G. Manolikakes My interest in chemistry started in high school. In the last two years of high school I had the opportunity to spend some time in the school lab and conduct my first own, very small but still independent research project. In the course of this project I became fascinated by the combination of theoretical knowledge and practical application of this knowledge in an experiment as well as the reverse process, the generation of new knowledge through well-planned and well-executed experiments. During my chemistry studies I got more and more interested in organic synthesis, its creative power to build very complex molecules and the underlying logic based solely on molecular reactivity. To date I am thrilled by the fact that we can purposefully design and synthesize so far unknown molecules with distinct properties starting from

© Georg Thieme Verlag Stuttgart • New York – Synform **2017/03**, A53–A55 • Published online: February 15, 2017 • DOI: 10.1055/s-0036-1590075

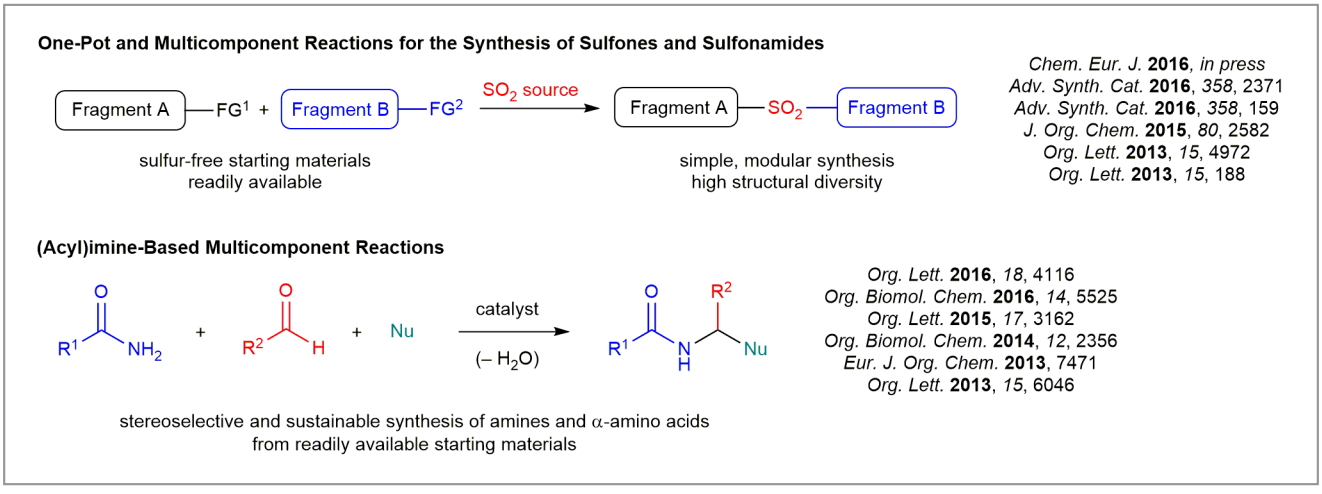
some sketches on a plain paper (or on an empty space in a conference program or a paper tissue).

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

Dr. G. Manolikakes Although organic synthesis has seen tremendous developments over the last 100 years, its main purpose is still the same: the synthesis of organic compounds for all aspects of human life. We should always keep in mind that we as synthetic chemists are creative scientists with the unique ability to interconvert simple matter into molecules that matter for humanity. I believe that organic synthesis today is facing two major challenges (or rather opportunities): how we synthesize molecules and the synthesis of new molecules for new applications. The development and implementation of more sustainable processes and the utilization of renewable raw materials should (and will) be a major focus in modern organic synthesis. At the same time, we have to use our ability to create new molecules with new functions to meet the ever-changing needs of society. The second task can only be addressed in collaborative projects with other scientists from all other disciplines, such as biology, physics or medicine. Synthetic chemists and their knowledge of how to design and control function at the molecular level are central to these multidisciplinary research projects.

SYNFORM *Your research group is active in the area of organic synthesis, especially using organometallic reagents. Could you tell us more about your research and its aims?*

Dr. G. Manolikakes Our main focus is the developments of new methods for the efficient and modular synthesis of specific substructures and not a certain type of methodology. Anything or rather any method goes, as long as we reach our fundamental goals. However, we rarely meet our final objectives in one step. In general, this is an iterative process. Our recent developments of one-pot reactions for the synthesis of sulfones with sulfur dioxide as key building block are a good example. We started indeed with organometallic reagents, partially due to my strong background in this area. But after the establishment of certain reactivity profiles, we moved on to incorporate the direct functionalization of C–H bonds in order to develop more sustainable approaches. And we will continue to devise more efficient methods until we reach our final goal, a completely sustainable and highly modular synthesis of sulfones and sulfonamides. In the same manner we could develop new methods either for a sustainable or for a stereoselective synthesis of amines and α-amino acids. Now we have to merge both developments to reach a green and stereoselective synthesis. In addition, we are starting to explore the application of our methods for the preparation of molecules with distinct properties for multidisciplinary research projects in medicine and materials science. My co-workers and I are very happy to see that some of our compounds show very promising biological activities.



Scheme 1 Overview of research projects in the Manolikakes group

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

Dr. G. Manolikakes Given that I still stand at the beginning of my career, I hope my most significant achievements still lie in the future. Nonetheless, I believe that with our contributions in the fields of sulfur dioxide chemistry and amine synthesis, many of them highlighted in *Synfacts* or *Org. Process Res. Dev.*, we are well on track towards our ultimate goal, universal tools for the sustainable synthesis of complex molecules containing either a sulfonyl or an amine moiety. However, we are only at the beginning of this process. My biggest hope is that one day at least one of my methods will be used for the synthesis of a molecule that will benefit society as a whole.

Coming soon

Literature Coverage

Metal-Free Enantioselective Oxidative Arylation of Alkenes: Hypervalent-Iodine-Promoted Oxidative C–C Bond Formation

Literature Coverage

Expeditious Diastereoselective Synthesis of Elaborated Ketones via Remote Csp³–H Functionalization

Literature Coverage

Pyridine-Catalyzed Radical Borylation of Aryl Halides

Further highlights

Synthesis **Review: Syntheses of Biologically Active 2-Aryl-cyclopropylamines**
(by J. Yamaguchi and co-workers)

Synlett **Account: 3-Acyltetramic Acids: A Decades-Long Approach to a Fascinating Natural Product Family**
(by M. Petermichl and R. Schobert)

Synfacts **Synfact of the Month in category "Synthesis of Natural Products and Potential Drugs": Syntheses of Sarcandrolide J and Shizukaol D**

For current SYNFORM articles, please visit www.thieme-chemistry.com
SYNFORM issue 2017/04 is available from March 17, 2017
at www.thieme-connect.com/ejournals

Editor
Matteo Zanda, NRP Chair in Medical Technologies, Institute of Medical Sciences, University of Aberdeen, Foresterhill, Aberdeen, AB25 2ZD, UK
and
C.N.R. – Istituto di Chimica del Riconoscimento Molecolare
Via Mancinelli, 7, 20131 Milano, Italy
Editorial Assistant: Alison M. Sage
synform@outlook.com; fax: +39 02 23993080

Editorial Office
- Managing Editor: Susanne Haak, susanne.haak@thieme.de, phone: +49 711 8931 786
- Scientific Editor: Michael Binanzer, michael.binanzer@thieme.de, phone: +49 711 8931 768
- Scientific Editor: Stefanie Baumann, stefanie.baumann@thieme.de, phone: +49 711 8931 776
- Scientific Editor: Selena Boothroyd, selena.boothroyd@thieme.de
- Assistant Scientific Editor: Kathrin Ulbrich, kathrin.ulbrich@thieme.de, phone: +49 711 8931 785
- Senior Production Editor: Thomas Loop, thomas.loop@thieme.de, phone: +49 711 8931 778
- Production Editor: Thorsten Schön, thorsten.schoen@thieme.de, phone: +49 711 8931 781
- Editorial Assistant: Sabine Heller, sabine.heller@thieme.de, phone: +49 711 8931 744
- Senior Marketing Manager: Julia Stötzner, julia.stoetzner@thieme.de, phone: +49 711 8931 771
- Postal Address: Chemistry Journals, Editorial Office, Georg Thieme Verlag KG, Rüdigerstraße 14, 70469 Stuttgart, Germany,
- Homepage: www.thieme-chemistry.com

Publication Information
Synform will be published 12 times in 2017 by Georg Thieme Verlag KG, Rüdigerstraße 14, 70469 Stuttgart, Germany, and is an additional online service for Synthesis, Synlett and Synfacts.

Publication Policy
Product names which are in fact registered trademarks may not have been specifically designated as such in every case. Thus, in those cases where a product has been referred to by its registered trademark it cannot be concluded that the name used is public domain. The same applies as regards patents or registered designs.

Ordering Information for Print Subscriptions to Synthesis, Synlett and Synfacts
The Americas: Thieme Publishers New York, Thieme Medical Publishers, Inc., 333 Seventh Avenue, New York, NY 10001, USA.
Via e-mail: customerservice@thieme.com
Via website: www.thieme-chemistry.com
Phone: +1 212 760 0888; Fax: +1 212 947 1112
Order toll-free within the USA: +1 800 782 3488

Europe, Africa, Asia, and Australia: Thieme Publishers Stuttgart, Georg Thieme Verlag KG, Rüdigerstraße 14, 70469 Stuttgart, Germany.
Via e-mail: customerservice@thieme.de
Via website: www.thieme-chemistry.com
Phone: +49 711 8931 421; Fax: +49 711 8931 410

Current list prices are available through www.thieme-chemistry.com.

Online Access
The online versions of Synform as well Synthesis, Synlett, Synfacts and SynOpen are available through www.thiemeconnect.com/products/ejournals/journals) where it is also possible to register for a free trial account. For information on multi-site licenses and pricing for corporate customers as well as backfiles, please contact our regional offices:

The Americas: esales@thieme.com, phone: +1 212 584 4695
Europe, Africa, Asia, and Australia: eproducts@thieme.de, phone: +49 711 8931 407
India: eproducts@thieme.in, phone +91 120 45 56 600
Japan: brhosoya@poplar.ocn.ne.jp, phone +81 3 3358 0692

Manuscript Submission to Synthesis, Synlett, and SynOpen
Manuscript submissions will be processed exclusively online via http://mc.manuscriptcentral.com/synthesis, http://mc.manuscriptcentral.com/synlett and http://mc.manuscriptcentral.com/synopen, respectively. Please consult the Instructions for Authors before compiling a new manuscript. The current version and the Word template for manuscript preparation are available for download at www.thieme-chemistry.com.