

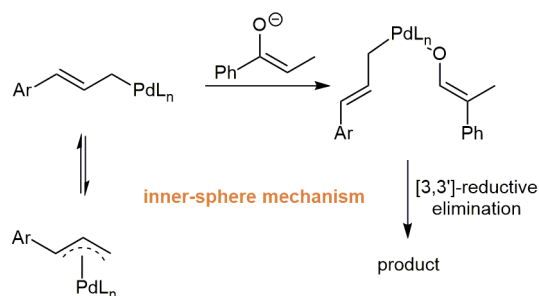
Synform

People, Trends and Views in Chemical Synthesis

2016/10

Palladium/N-Heterocyclic Carbene Catalyzed Regio- and Diastereoselective Reaction of Ketones with Allyl Reagents via Inner-Sphere Mechanism

Highlighted article by D.-C. Bai, F. Yu, W.-Y. Wang, D. Chen, H. Li, Q.-R. Liu, C.-H. Ding, B. Chen, X.-L. Hou



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Dear Readers,

Although this is the editorial of the October issue of SYNFORM, the Olympic Games are taking place right now in Rio de Janeiro. The Olympic Games always bring to my mind the famous quote of Pierre De Coubertin, founder of the International Olympic Committee: “The important thing in the Olympic Games is not to win, but to take part.” Not many in our highly competitive and success-driven world will agree with the view that participation is more important than just winning, and this includes the world of research. And this is quite unfortunate. Universities and research institutions worldwide have become obsessed with quick success. Participation without winning – namely doing research simply for the sake of increasing our knowledge and understanding of nature – is seen merely as a waste of time and, more importantly, of money. Research must lead to immediate success in the form of research funding, high impact publications and commercial returns. If you don’t get a medal – possibly a gold medal – immediately and without training, the next time you end up competing for the title of best unemployed or early-retired performer. One of the consequences of that is research doping, which – besides real cheating – can take the form of authors desperately trying to oversell what they do, using hypertrophic titles and graphical abstracts, hyperbolic trajectories of their conclusions and purely fictional prospective applications of their work. And this is becoming increasingly tolerated by reviewers and editors and even encouraged by publishers and funding agencies. I really wish we could implement a more efficient anti-doping system in research, but it’s hard to achieve that when employers, funders and governments all seem nowadays to strictly adhere to the mantra “You must win a gold medal at any cost and right now, we don’t have time for losers.” I’d honestly love to see some followers of Pierre De Coubertin as deans, principals or chairmen spending some time to nurture their staff or applicants and give them the time to come up with solid and truly high-impact results stemming from robust long-term research. But I suspect this is just an Olympic midsummer dream, and soon I’ll wake up and realize that nothing is going to change any time soon. But thanks Olympic Games and thanks Monsieur De Coubertin for this wonderful dream.

Luckily enough, our SYNFORM issue is all but a dream, it is rock-solid cutting-edge research. We kick off with an interview from the up-and-coming synthetic chemist M. Tortosa

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(Spain), who tells us about her interests and results in her career so far. The first article covers a Science paper by S. Harutyunyan (The Netherlands) describing a copper-catalyzed asymmetric alkylation of alkenyl-N-heterocycles by Grignard reagents. The second contribution reports on a *Nat. Commun.* article by X.-L. Hou (P. R. of China) on a fully stereocontrolled and conceptually novel strategy for performing the α -allylation of ketones. The honor of closing the issue is assigned to Y. Qin (P. R. of China) for another *Nat. Commun.* article describing the challenging synthesis of the complex natural product atropurpuran. I hope you will agree that all of these authors deserve a gold medal!

Enjoy your reading!



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

Young Career Focus: Dr. Mariola Tortosa (Universidad Autónoma de Madrid, Spain)

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. Mariola Tortosa (Universidad Autónoma de Madrid, Spain).

Biographical Sketch



Dr. M. Tortosa

Mariola Tortosa obtained her B.S. in chemistry from the Universidad Autónoma de Madrid (UAM, Spain) in 1999. She then joined the group of Dr. R. Fernández de la Pradilla at the Instituto de Química Orgánica General (CSIC, Madrid, Spain) to carry out her graduate work on the development of new asymmetric methods using chiral sulfoxides. In 2004, she received the Lilly Award for PhD students. In 2005, she moved to The Scripps Research Institute in Florida (USA) to work as a postdoctoral fellow with Professor William Roush. Her research in Florida was directed toward completion of the total synthesis of the antitumor agent Superstolide A using a transannular Diels–Alder strategy. In 2008, she returned to the Instituto de Química Orgánica General in Madrid as a Juan de la Cierva fellow. In 2011, she started her independent research at the Universidad Autónoma de Madrid (Spain) with a Ramón y Cajal contract. More recently, she received an ERC Starting Grant awarded by the European Research Council to work on the project ‘Design and Applications of Unconventional Borylation Reactions’. Her research interests include boron chemistry, asymmetric catalysis and the synthesis of natural products. She received the Young Investigator Award from the Royal Society of Chemistry of Spain (2014), the Young Spanish Investigator Eli Lilly Award (2014) and the Thieme Chemistry Journals Award for young professors (2015).

INTERVIEW

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

Dr. M. Tortosa Our interests range from the development of new metal-catalyzed reactions to the total synthesis of natural products. Recently, we have been focused on the chemistry of boronic esters to accomplish these goals. Inspired by unsolved problems found in the synthesis of bioactive molecules, we have searched for unconventional ways to activate boron compounds to efficiently prepare valuable synthetic intermediates.

SYNFORM *When did you get interested in synthesis?*

Dr. M. Tortosa I became interested as an undergraduate during my first course in organic chemistry. Although I enjoyed most chemistry classes, I fell in love with the power of organic synthesis to build complex molecules. I loved the idea of being able to be artistic and make molecules that could benefit society at the same time. Later on, my PhD and postdoctoral mentors played a critical role in growing and refining my interests in the field.

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

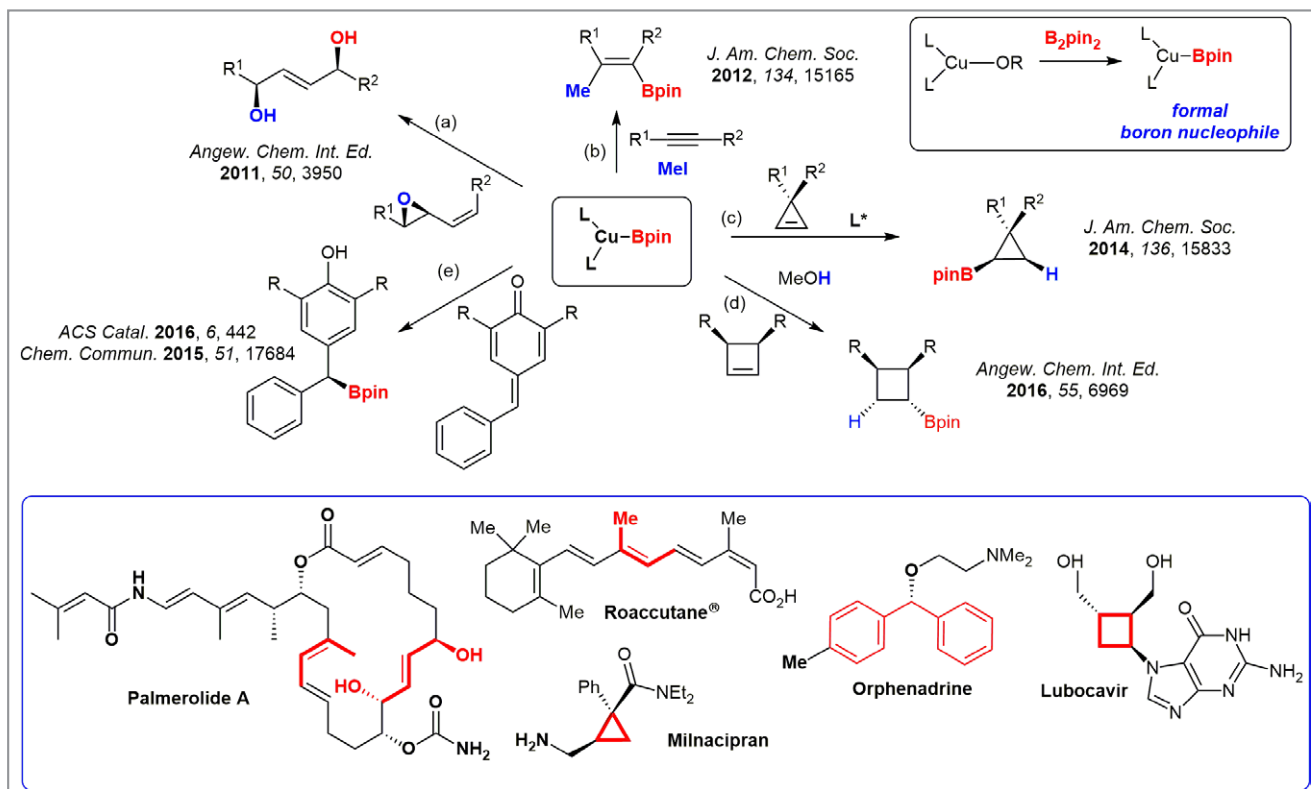
Dr. M. Tortosa Over the last 60 years there has been enormous progress in the field of synthesis. However, there is still a need to develop more efficient and more sustainable synthetic methods. One of our key commitments as organic chemists is the challenge of improving sustainability. For this goal, catalysis will continue to play an essential role to address, making reactions more selective, increasing process efficiency and reducing waste.

In a broader sense, I believe chemistry, and in particular organic chemistry, remains vital for science and society. We are increasingly witnessing a blend between scientific disciplines, and organic chemistry skills will be crucial for interdisciplinary research. For example, organic chemists will play a critical role in understanding molecular recognition and binding in drug discovery or in the use of self-assembly techniques in nanotechnology.

SYNFORM Your research group is active in the areas of metal catalysis, natural products and stereoselective synthesis. Could you tell us more about your research and its aims?

Dr. M. Tortosa As mentioned above, we have focused on the chemistry of boronic esters to accomplish these goals. Boronic esters are versatile synthetic intermediates for the preparation of a wide range of organic molecules. Traditionally, the methods for forming carbon–boron bonds have mostly been based on the electrophilic nature of boron due to its empty p-orbital. While this classical approach works very well for reactions that involve a nucleophilic partner, it necessarily limits the type of boron-containing molecules that can

be synthesized. Changing the electrophilic nature of boron, by developing methods to generate and use nucleophilic boron species, would open new ways to introduce boron atoms into organic molecules. This concept has been the driving force of my research during the first stage of my career as an independent researcher. Inspired by unsolved problems found in the synthesis of bioactive molecules, we have searched for unconventional ways to activate boron compounds to efficiently prepare valuable synthetic intermediates. One of our primary tools has been the use of catalytic amounts of copper to generate nucleophilic boron species in situ from commercially available compounds. The lower price and toxicity of copper versus other transition metals and the unique reactivity of the boryl–copper intermediates make these processes particularly attractive. We have invested particular effort in the synthesis of chiral molecules containing sp³ carbon–boron stereocenters, which are difficult to access by known methods. Using this strategy, we have successfully developed new stereoselective methods for the preparation of fragments that are present in bioactive natural products or drugs such as 1,4-diols, tri-substituted alkenes, diaryl methanes and functionalized small rings. Palmerolide A, Roaccutane®, orphenadrine, milnacipran



Scheme 1

and lubocavir are examples of bioactive molecules that have inspired the development of these synthetic methods.

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

Dr. M. Tortosa Perhaps the two projects I am most proud of are my first two publications as a corresponding author. The first project that I developed without the assistance of a single student dealt with the stereoselective synthesis of 1,4-diol fragments via a copper-catalyzed borylation reaction. These results were published in *Angew. Chem. Int. Ed.* **2011**, *50*, 3950 as a solo author publication and paved the way for my current research. I consider this project as the true starting point of my independent career. The second one dealt with the copper-catalyzed carboboration of alkynes (*J. Am. Chem. Soc.* **2012**, *134*, 15165). I think this contribution opened a new and efficient way to prepare functionalized alkenes. Both publications were crucial to apply for an ERC Starting Grant, which gave me a unique opportunity to build my own research group.



Catalytic Asymmetric Addition of Grignard Reagents to Alkenyl-Substituted Aromatic N-Heterocycles

Science **2016**, 352, 433–437

Functionalized chiral heteroarenes are common structural motifs in numerous bioactive products, pharmaceuticals, and agrochemicals. Out of the top 200 drugs by worldwide sales in 2013, more than 70 are chiral and contain heteroaromatic motifs. Currently the vast majority of chiral pharmaceuticals are produced as single enantiomers, but the syntheses often rely on non-catalytic stoichiometric methods and the use of chiral separation techniques. The difficulties in preparing these molecules as single enantiomers persist because of a lack of sufficient catalytic enantioselective transformations. Thus, efficient catalytic synthesis of pharmaceutically important chiral heteroarenes is a core objective of modern chemistry.

The group of Professor Syuzanna Harutyunyan at the Stratingh Institute for Chemistry, University of Groningen (The Netherlands) investigated the hypothesis that catalytic asymmetric C–C bond formation using conjugate addition of organometallics to conjugated alkenyl-heteroarenes would be a straightforward approach for constructing single enantiomers of chiral heteroarenes.

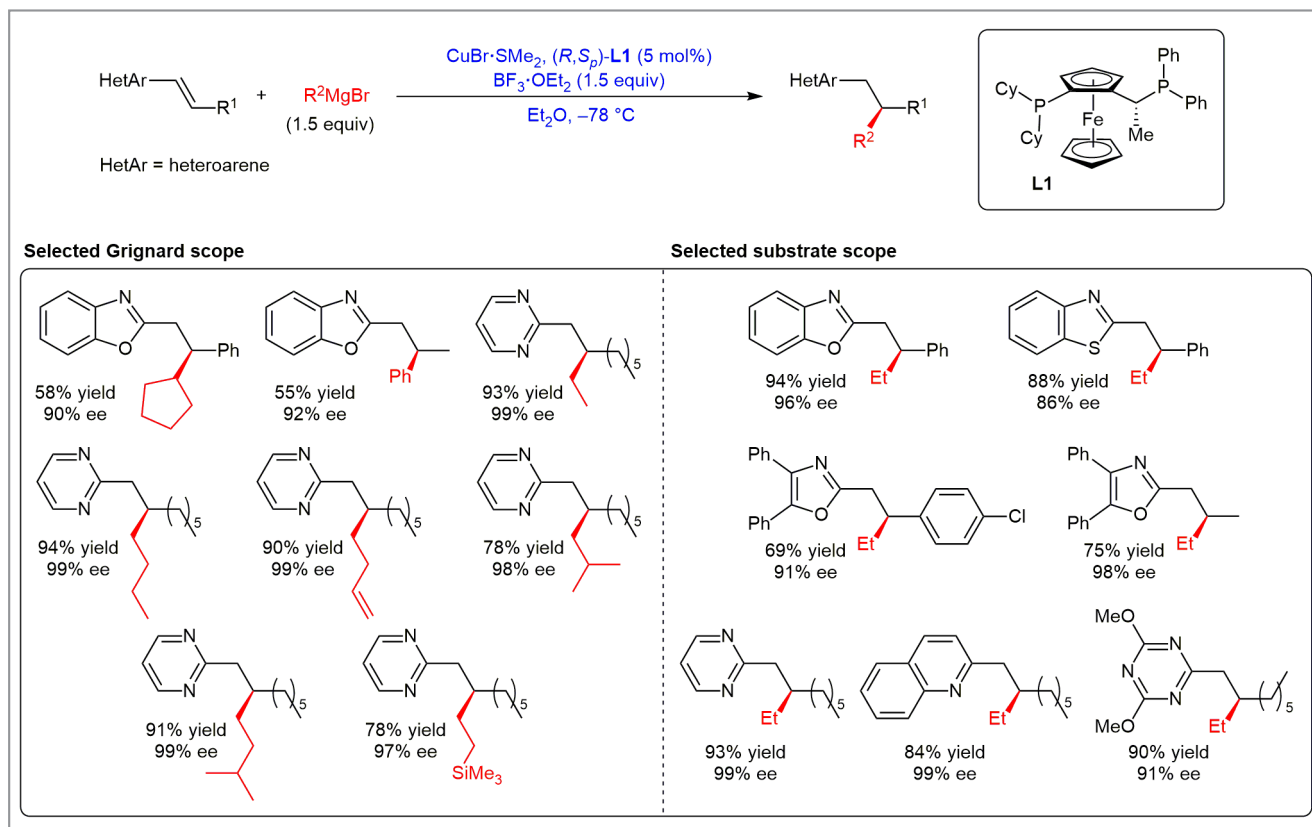
However, although numerous efficient methods exist for conjugate alkylations, arylations, alkynylations and allylations of common Michael acceptors (e.g. enones, enals or enoates), according to Professor Harutyunyan the only known examples of additions to β -substituted alkenyl-heteroarenes were reported by Lam et al. (*J. Org. Chem.* **2014**, 79, 831) and were restricted to arylations using organoboron reagents, in combination with rhodium catalysis. Professor Harutyunyan explained: “The lack of methodologies for nucleophilic additions to β -substituted alkenyl-heteroarenes is the result of the intrinsically lower reactivity of these molecules compared to common Michael acceptors. In fact, the activation provided by the heteroarene moiety of the former is weaker than that provided by the electron-withdrawing groups present in the latter.”

For several years the group's research focused on using highly reactive and readily available Grignard reagents in Cu(I)-catalyzed C–C bond forming reactions. Thus, the Harutyunyan group surmised that the high reactivity of Grignard reagents could be beneficial when considering the low reactivity of alkenyl-heteroarenes, and that chiral copper catalysis will provide the required selectivity. “The initial results obtained by postdoctoral researcher Ravindra Jumde were

not promising,” said Professor Harutyunyan. “He did not observe any product formation at different temperature ranges and decided to use more reactive organolithiums instead of Grignard reagents. Once again, the reaction outcome was unsuccessful, side products were formed and starting material was left.”

To overcome the reactivity issues associated with alkenyl-heteroarenes, Professor Harutyunyan and co-workers decided to investigate the Lewis acid ($\text{BF}_3 \cdot \text{OEt}_2$) activation of the substrates in combination with Grignard reagents. The main question was the compatibility of Grignard reagents with $\text{BF}_3 \cdot \text{OEt}_2$. Professor Harutyunyan said: “From our previous studies on Grignard addition to acyl silanes we were aware that for a short time at low temperature these two reagents are compatible. The Lewis acid was used in our previous research to avoid the reduction of ketones, which is an important side reaction. We were extremely pleased to see the conjugate addition product for the first time when using the Lewis acid/Grignard reagent/Cu/phosphine reaction system applied to alkenyl-heteroarenes.” At this point PhD student Francesco Lanza and, later, bachelor's student Marieke Veenstra joined the project. The team was capable of achieving alkylation of unreactive alkenyl-heteroarenes to the corresponding chiral N-containing aromatic heterocycles. Professor Harutyunyan revealed that after months of optimization studies they developed a methodology: an operationally simple, chemoselective and highly enantioselective conjugate addition reaction that utilizes readily available and cost-efficient reagents and catalysts. “As is evident from the experimental data, the stereoselectivities are extremely high, reaching 99% in many cases,” said Professor Harutyunyan. “Remarkably, a variety of heterocyclic motifs can be employed in this reaction successfully and the system also tolerates various types of Grignard reagents, including linear, branched, functionalized as well as aryl analogues.”

Professor Harutyunyan remarked: “The key to this success was our ability to combine several critical elements: 1) enhancing the reactivity of alkenyl-heteroarenes via Lewis acid activation, 2) harnessing the high reactivity of readily available and atom-efficient Grignard reagents, and 3) using a chiral copper complex as the catalytically active structure. Furthermore, our experiments on catalyst loading and recovery,



Scheme 1 Copper-catalyzed addition of Grignard reagents to alkenyl-heteroarenes: selected Grignard reagents and heteroarene-substrate scope

also on preparative scale, demonstrate that the method is very promising for large-scale applications.” She continued: “What is also remarkable is that this reaction system tolerates various solvents such as toluene, dichloromethane, ether and MTBE, as well as different chiral ligands, which can be used in combination with copper catalysis. This flexibility of both solvent and chiral ligand is quite important for further applications. The current drawback of the method – which we still need to address – is the low temperature (–78 to –50 °C) required for compatibility of Grignard reagents and Lewis acid.”

Following this initial discovery, the group now aims to take it to the next level and develop methylations as well as to generate quaternary stereocenters. Professor Harutyunyan concluded: “These are real challenges for such unreactive substrates that we have to address in the near future. Also from the mechanistic point of view, we suspect that the reaction follows a common pathway established for Cu(I)-catalyzed additions of organometallics. However, the role of Lewis acid, besides the activation of heteroarene substrates, is not clear yet and remains to be investigated.”

Matthew Farnish

About the authors



Prof. S. R. Harutyunyan

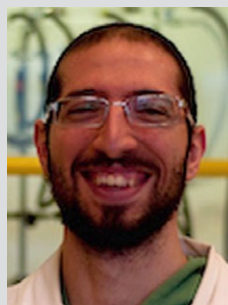
Syuzanna R. Harutyunyan received her Master's degree in chemistry from Yerevan State University (Armenia). In 1999 she moved to Moscow (Russia) to undertake PhD studies under the supervision of Professor Yuri N. Belokon. During her PhD, Syuzanna developed new strategies for enantioselective synthesis of amino acids under phase-transfer conditions. In 2002 she spent several months as a visiting scientist in Warsaw (Poland), working with Professor Karol Grela on developing highly reactive alternatives to the well-known Grubbs catalysts. In 2003 Syuzanna joined the research group of Professor Ben L. Feringa at the University of Groningen (The Netherlands) as a post-doctoral research fellow and worked in asymmetric catalysis. In 2007 she joined the Process & Development department at Janssen Pharmaceutica (Belgium). Her research focused on the development of new RCM metathesis catalysts for application in the industrial-scale synthesis of a new anti-HCV drug. In 2010 Syuzanna was appointed as a tenure-track Assistant Professor at the University of Groningen and subsequently started her independent research career. In 2013 Syuzanna was tenured and promoted to Associate Professor at the University of Groningen. Her research activities include organic synthesis, organometallic reactions, catalysis, autocatalysis and enantioselective transformations.



Dr. R. P. Jumde

Ravindra P. Jumde was born and raised in the small town of Achalpur in the Maharashtra region of India. He obtained his MSc in 2005 from S.G.B. Amravati University (MS, India). He worked as a project assistant at National Chemical Laboratory, Pune (India) from 2006 to 2008. In January 2009 he won a 'Galileo Galilei PhD fellowship' at University of Pisa (Italy), where he worked in the group of Professor Dario Pini and Dr. Alessandro Mandoli on 'supported chiral ligands and organocatalysts for enantioselective transformations.' After obtaining his PhD in January 2012, he won a post-doctoral grant from ISTM-CNR (Italy) to work in the same group on 'the development of novel catalytic asymmetric reactions' (intramolecular cyclization), and 'study of asymmetric transformations in flow, micro and mini flow devices.' In September 2013 he moved to Milan (Italy)

at ISTM-CNR to work with Dr. Claudio Evangelisti on the preparation of metal nanoparticles by MVS technique and their use in different metal-catalyzed reactions in continuous flow. Since January 2015 he has been working at the University of Groningen (The Netherlands) in the group of Professor Syuzanna R. Harutyunyan. His main scientific interests are asymmetric catalysis, new reaction methodology development, and mechanistic investigations.



F. Lanza

Francesco Lanza was born in Messina (Italy) in 1987. In 2010 he received his B.S. degree from the Università degli Studi di Messina. In the same year he moved to Bologna (Italy) to attend the Master's course in chemistry at the Alma Mater Studiorum – Università di Bologna where he obtained his M.S. degree in chemistry under the supervision of Professor Marco Lombardo in 2012. Since 2013 he has been working at the University of Groningen (The Netherlands) in Professor Syuzanna R. Harutyunyan's research group. He is currently working on copper-catalyzed addition of organometallic reagent to heteroaromatic frameworks.



M. J. Veenstra

Marieke J. Veenstra was born and raised in Kropswolde in the province of Groningen (The Netherlands). She obtained her B.Sc. in chemistry from the University of Groningen in 2015. During her Bachelor's project she worked in the group of Professor Syuzanna R. Harutyunyan on copper-catalyzed asymmetric addition to alkenyl-substituted aromatic N-heterocycles.

Palladium/N-Heterocyclic Carbene Catalyzed Regio- and Diastereoselective Reaction of Ketones with Allyl Reagents via Inner-Sphere Mechanism

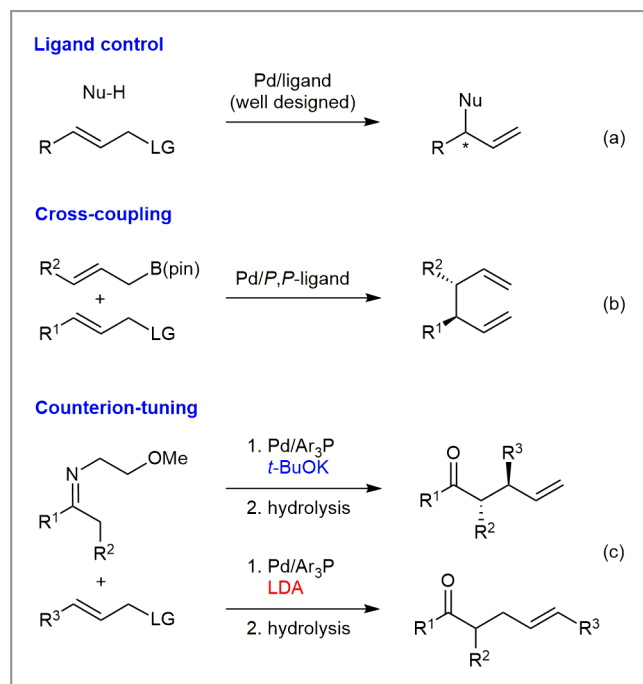
Nat. Commun. 2016, 7, 11806

As one of the most important transition-metal-catalyzed reactions, Pd-catalyzed allylic alkylation, usually proceeding via attack of nucleophiles on the carbon of π -allyl Pd complexes (outer-sphere mechanism), is a powerful tool for C–C bond and C–X bond formations. The adjacent two stereocenters are also constructed stereoselectively for both cyclic and acyclic compounds.¹ Many different types of allyl reagents can be used in the reaction; however, control of the regioselectivity to afford branched allylic alkylated products from monosubstituted allyl reagents is still an important issue that has not been fully solved. To date several strategies have been developed to tackle the problem, such as ligand-control and cross-coupling strategies, which show their high efficiency (Scheme 1, a,b).^{2a–d} However, efficient but simple protocols are still much in demand for the control of regioselectivity of

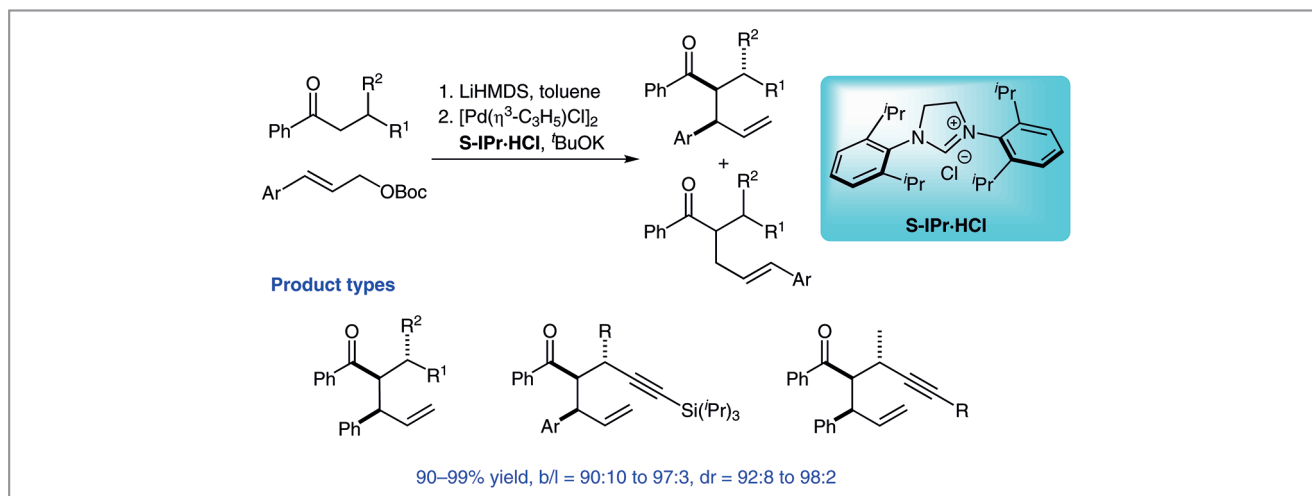
the reaction with monosubstituted allyl reagents. The work of Professor Xue-Long Hou from the Shanghai Institute of Organic Chemistry (P. R. of China) on regioselectivity tuning by action of counterions of bases in the reaction of imines and allyl reagents under Pd catalysis with phosphines as ligands is one such example (Scheme 1, c).^{2e}

Recently, an efficient and practical procedure was developed by Professor Hou and his colleagues. Professor Hou remarked: “We found that, with N-heterocyclic carbene (NHC) **S-IPr** as ligand, branched products were produced in high regioselectivity in the reaction of ketones with monosubstituted allyl substrates under Pd catalysis. A wide range of ketones and allyl reagents are suitable (Scheme 2).” Lower regioselectivity was observed with *N,N'*-phenyl or -trimethylphenyl-substituted NHCs, while linear products were afforded as the major component with phosphine as ligand despite of either Li⁺ or K⁺ as the counterion of the base. Professor Hou explained: “Like phosphine, NHCs are also strong σ -donors, but their stereochemistry is totally different in coordination chemistry. The substituents on the NHC nitrogen are toward the metal atom but those on phosphine are far away from the metal when they coordinate with it. This might be the reason for the observed regioselectivity of the reaction using NHC and phosphine as ligands.” In addition to its unusual regioselectivity, the reaction exhibits another useful characteristic. “Acyclic ketones with three contiguous stereocenters were produced in excellent diastereoselectivity if β -substituted ketones were the pre-nucleophile,” said Professor Hou. He continued: “Because of the easy availability of optically active β -substituted ketones, this methodology affords simple access to optically active acyclic ketones with three contiguous stereocenters, which should be useful in organic synthesis. We have shown some useful applications of the methodology in the *Nat. Commun.* paper (Scheme 3), and the reaction can also proceed on gram scale without loss of efficiency and stereoselectivity.”

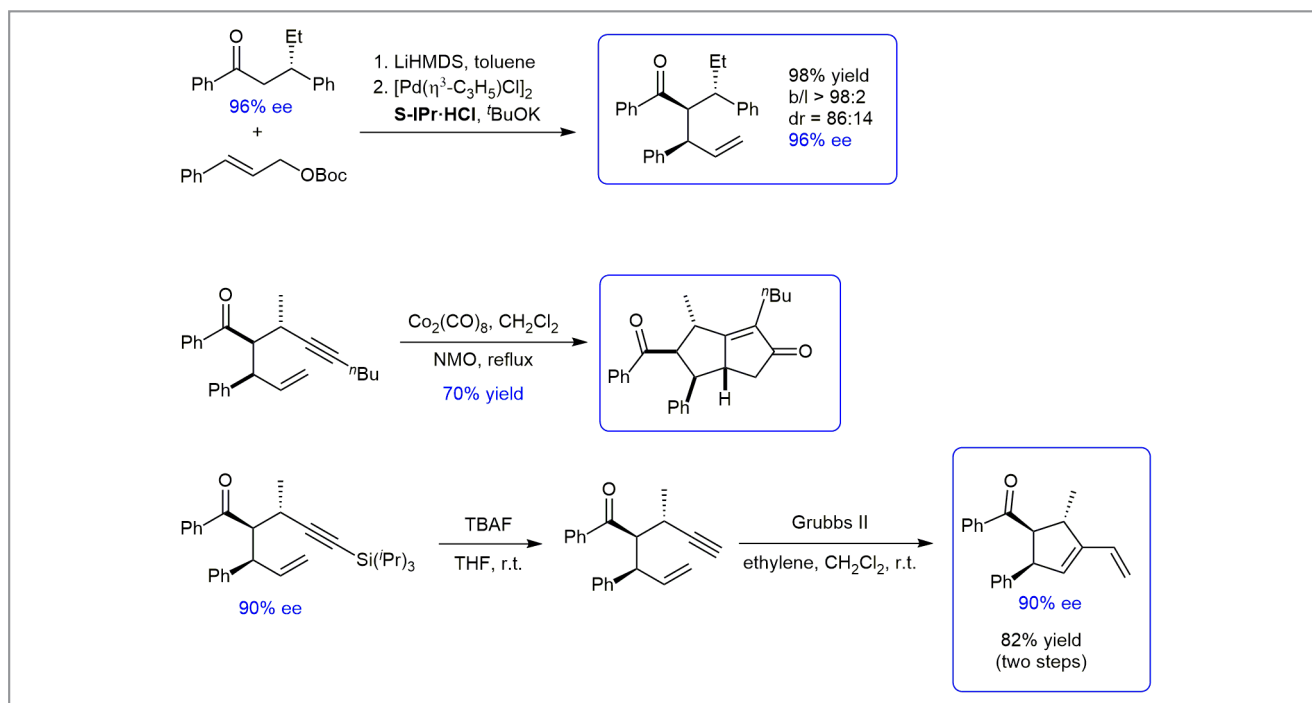
In collaboration with Dr. Bo Chen, a theoretical chemist at Cornell University (USA), transition states of the reaction were proposed to explain why *anti*-products were afforded predominantly in the reaction of ketones without substituents at the β -position, but *syn*-products were the major products



Scheme 1 Some strategies in Pd-catalyzed allylic alkylation reaction using monosubstituted allyl reagents



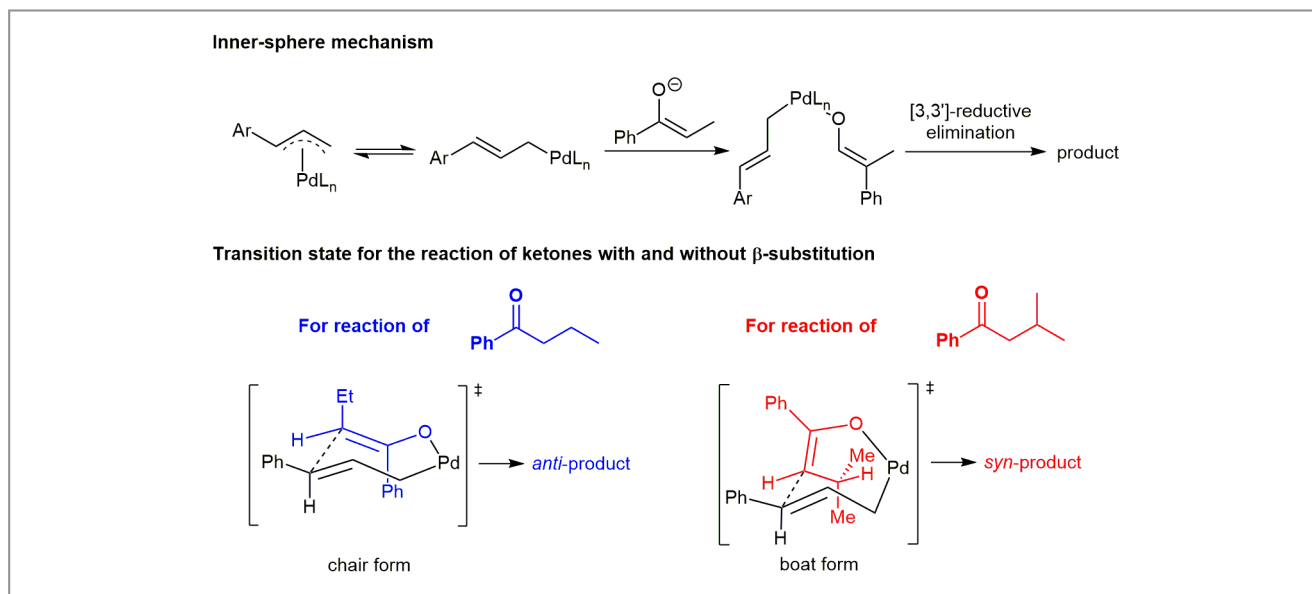
Scheme 2 Pd/NHC-catalyzed allylic alkylation of ketones with monosubstituted allyl reagents



Scheme 3 Application of the methodology – some examples

for those using ketones with substituents at the β -position. Professor Hou said: “Mechanistic investigations by experiments using optically active deuterium-labeled allyl reagent and *cis*-disubstituted cyclohexene, as well as DFT calculations, revealed that the reaction proceeds via an inner-sphere mechanism, that is, through nucleophile attack on Pd followed by C–C bond-forming [3,3]-reductive elimination.”

According to Professor Hou and colleagues, these results demonstrate that, as NHCs are easily synthesized and also commercially available, Pd/NHC should be a simple and effective catalyst system to realize high regio- and diastereoselectivities in the reaction of ketones and monosubstituted allyl reagents,^{1–3} affording products with two or three contiguous stereocenters in excellent diastereoselectivity. “Because both



Scheme 4 Proposed transition state and reaction mechanism

ketones and allyl reagents are easily available and the experimental protocol of the reaction is simple, this methodology should be useful in organic synthesis. More importantly, the results reveal that the reaction of 'hard' nucleophiles with allyl reagents under Pd catalysis, occurring in the intermolecular way through an inner-sphere mechanism, represents a new reaction mode," said Professor Hou. He concluded: "There is much room to modify the structures of allyl reagents and nucleophiles to afford a variety of molecules with multiple stereocenters, which should further expand the scope of this method."

Mattes Fenske

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About the authors



Prof. X.-L. Hou

Xue-Long Hou graduated from Shanghai First Medical College (P. R. of China) in 1978. After working there for two years, he entered the Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences (SIOC, P. R. of China) and obtained his Ph.D. in 1986 under the mentorship of Professors Wei Yuan Huang of SIOC and Henry N. C. Wong of the Chinese University of Hong Kong. Then, he did postdoctoral research with Professor Emanuel Vogel for about two years as Alexander von Humboldt Research Fellow at Cologne University (Germany). He returned to SIOC in 1989 and was promoted to full professor in 1997. His research interests are the design of chiral ligands and their applications in asymmetric catalysis as well as the development of efficient catalyst systems in organic synthesis.



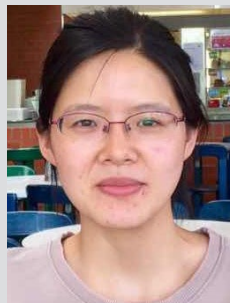
Dr. D.-C. Bai

Da-Chang Bai obtained his B.S. degree in 2009 from Zhengzhou University (P. R. of China) and his Ph.D. in 2014 from Shanghai Institute of Organic Chemistry (P. R. of China) with Professor Xue-Long Hou. After working in Professor Hou's lab as research assistant for one year, he joined Professor Rong Shi Li's group at the University of Nebraska Medical Center (USA) as a postdoctoral research fellow. His research interests involve organometallic chemistry, synthetic organic chemistry and medicinal chemistry.



F. Yu

Feile Yu, born in Hunan Province (P. R. of China), received his B.S. degree from Shenzhen University of China (P. R. of China) in 2013 and then became a graduate student under the supervision of Professor Xue-Long Hou at Shanghai Institute of Organic Chemistry (P. R. of China). His main research interests are the development of transition-metal-catalyzed synthetic methodologies.



W.-Y. Wang

Wan-Ying Wang obtained her B.S. degree in 2011 from An-Hui Normal University (P. R. of China) and then became a graduate student of Professor Xue Long Hou at Shanghai Institute of Organic Chemistry (P. R. of China). Since October 2015 she has been a Ph.D. student of Dr. Tanja Gulder at Technische Universität München (Germany). Her main research interest is the development of new organometallic-catalyzed methodologies.



D. Chen

Di Chen was born in Hunan Province of China (P. R. of China) and received her B.S. degree from Hunan University (P. R. of China) in 2005. From 2005 to 2007 she was a research assistant at Shenzhen Feiyang Industrial Co. Ltd. (P. R. of China). Since 2007 she has been part of the group of Professor Xue-Long Hou at Shanghai Institute of Organic Chemistry (P. R. of China) as a chemical analyst.



H. Li

Hao Li obtained his B.S. degree in 2011 from Anhui Normal University (P. R. of China) and then became a research assistant in Professor Xue-Long Hou's group. In August 2013 he was admitted to the co-cultivation program of Shanghai University and the Shanghai Institute of Organic Chemistry (P. R. of China) and earned his M.S. degree under Professors Xue-Long Hou and Bing Xu. His research involves synthetic organic chemistry, organometallic chemistry and silicon chemistry.

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Q.-R. Liu

Qing-Rong Liu was born in Guangxi Province (P. R. of China) and received her M.S. degree from Guangxi Normal University (P. R. of China) in 2015. She now works as an assistant researcher in Professor Xue-Long Hou's group at the Shanghai Institute of Organic Chemistry (P. R. of China).



Prof. C.-H. Ding

Chang-Hua Ding received his Ph.D. under the guidance of Professor Xue-Long Hou in 2005 at the Shanghai Institute of Organic Chemistry (P. R. of China). From 2005–2007 he was a postdoctoral fellow in the group of Professor Junzo Otera at Okayama University of Science (Japan). He moved to Professor Keiji Maruoka's group at Kyoto University (Japan) working there as a research associate from 2007 to 2009. He has been an associate professor in the group of Professor Xue-Long Hou at the Shanghai Institute of Organic Chemistry (P. R. of China) since 2009. His research interests focus on the development of asymmetric catalytic transformations and their application in organic synthesis.



Dr. B. Chen

Bo Chen was born and grew up in Chongqing (P. R. of China). He obtained his B.S. degree at University of Science & Technology Beijing (P. R. of China) in 2006. He received his Ph.D. in organic chemistry at Shanghai Institute of Organic Chemistry (P. R. of China) in 2011 under the direction of Professors Yun-Dong Wu and Yu-Xue Li. He did his first postdoctoral research with Professor Weston Thatcher Borden at the University of North Texas (USA) from 2012 to 2014. He is now a postdoctoral research associate at Cornell University (USA), working with Professor Roald Hoffmann. He works in the area of computational organic chemistry, in close collaboration with experimentalists. His research interests include (a) mechanisms of organic/organometallic reactions, in solution or solid state, under ambient (1 atm) or high pressures (up to 200,000 atm), and (b) the chemistry of diradicals, carbenes, and nanothreads.

Total Synthesis of (±)-Atropurpuran

Nat. Commun. **2016**, *7*, 12183

Plants of the genera *Aconitum* and *Delphinium* are widely distributed in the northern hemisphere and many of them have been employed in folk medicine to treat pain, rheumatism and neurological disorders. These species provide various groups of diterpenoid alkaloids possessing polycyclic and complex structures and a range of intriguing bioactivities. Professor Yong Qin's group at Sichuan University (P. R. of China) began to study the total synthesis of atropurpuran in the summer of 2009. Professor Qin explained the origins of their interest: "Professor Feng-Peng Wang (from the same department) is a respected colleague and globally well-known phytochemist who has consistently and extensively investigated the chemistry and biology of diterpenoid alkaloids for over 30 years (*Nat. Prod. Rep.* **2010**, *27*, 529–570). In 2006, Professor Wang's group isolated a pentacyclic diterpenoid named atropurpuran from *Aconitum hemsleyanum* var. *atropurpureum*; however, this was not published until 2009 after they successfully obtained X-ray crystallographic data to fully verify its cage-like and congested architecture. This compound was considered a biosynthetic precursor of related diterpenoid alkaloids (e.g., arcutine and arcutinine). In view of its interesting structure and unexplored bioactivity, atropurpuran seemed likely to be a research focus for synthetic chemists (see the original paper for references)."

Professor Qin continued: "It was in the summer of 2009 during a chat with Professor Wang that he speculated whether I could conquer the two molecules: atropurpuran and aconitine. That was the starting point of this synthetic adventure." The first version of the synthetic endeavor towards atropurpuran relied on the original biosynthetic pathway proposed by Professor Wang and was mainly carried out by PhD student Huan Chen. "In this context, we synthesized two intermediates (**A** and **B**) employing different organocatalytic Michael ad-

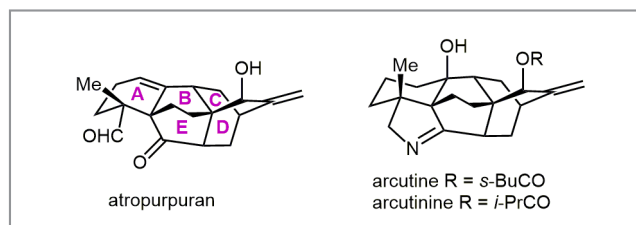


Figure 1

dition reactions as key steps, respectively," said Professor Qin. "Unfortunately, neither compound is suitable to be advanced to the target since their preparation suffers from tedious synthetic steps and low efficiency."

After an extremely challenging five-year effort, the turning point for the project came in March 2014 when the group designed a different synthetic route, finally leading to success. Professor Qin remarked: "Another two researchers became the main force of the new strategy: Jing Gong, another PhD student under my supervision, and Dr. Xiao-Yu Liu, a former PhD student of Professor Wang, who joined my group as an associate professor. As expected, a tandem oxidative dearomatization/intramolecular Diels–Alder cycloaddition reaction took place smoothly to afford compound **C** in decagram quantities, which we considered to be a cornerstone for the whole synthesis. We actually did not have much trouble before we started to assemble the final ring (ring B) of the target molecule." Unfortunately, various conditions for the ketyl-olefin cyclization of intermediate **D** to form ring B proved unsuccessful. By carefully checking the reaction transition state, the authors believed that a bulky group at C20 would not only interrupt the undesired intramolecular H-bonding but also force ring E to adopt a boat conformation, thus favoring the spati-

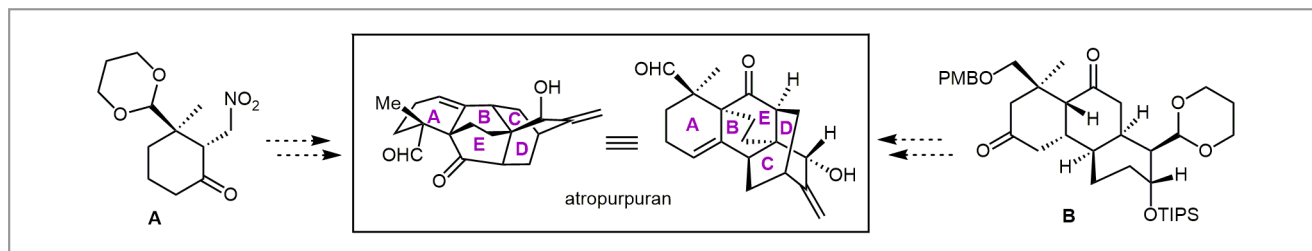
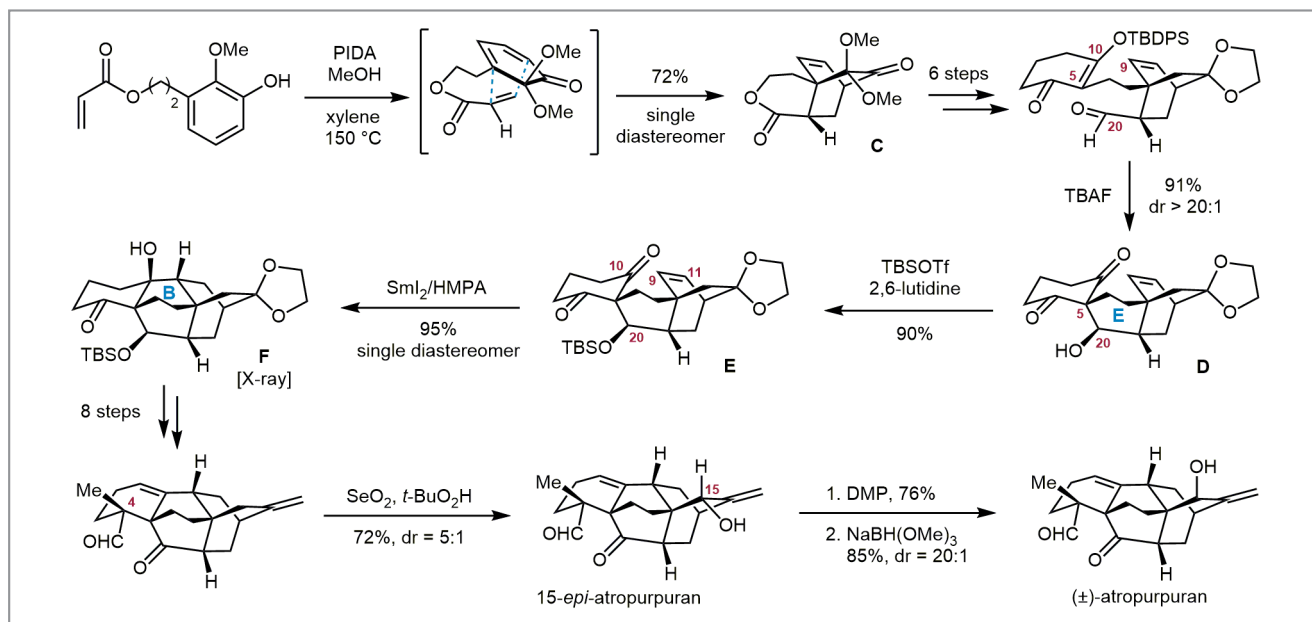


Figure 2



Scheme 1

al proximity between C10 ketyl with C9^{9,11} and enabling the cyclization (see the original paper for details). As a result, by installing a bulky *tert*-butyldimethylsilyl (TBS) group on C20 alcohol, Professor Qin and co-workers were able to reach the atropurpuran core (intermediate **F**) from **E** via a ketyl-olefin cyclization in an efficient manner.

“The endgame of our synthesis was more challenging than we anticipated, with some simple reactions failing to work, probably because of the rigid nature of the core structure,” said Professor Qin. “To our delight, after extensive experimentation, we ultimately figured out a sequence to atropurpuran. Of note, a chemoselective and stereoselective reduction was achieved to install the requisite hydroxyl group at C15 of the target natural product in the last step of the synthesis.”

“We believe this is an interesting story on natural product research where a natural product was isolated and synthesized through a *de novo* route in the same department, which we are very proud of,” said Professor Qin, who concluded: “In the long run, development of an entry to optically pure atropurpuran and arcutinine, as well as exploration of their biological profiles would be desirable. Additionally, the accomplishment of this work sheds light on the importance of strategic rational design which would greatly facilitate total synthesis of such three-dimensionally complex and cage-like molecules.”

Matthew Farnish

About the authors



J. Gong

Jing Gong was born in Sichuan (P. R. of China). He received his B.Sc. degree in chemistry at Sichuan University (P. R. of China) in 2013. In the same year he joined the group of Professor Yong Qin at Sichuan University to pursue his Ph.D. degree. His research focuses on the total synthesis of complex natural products.



Dr. H. Chen

Huan Chen was born and raised in Chengdu of Sichuan Province (P. R. of China). He obtained his B.Sc. degree in pharmacy from Sichuan University (P. R. of China) in 2009. He then began his doctoral research in Professor Yong Qin's group, working on the total synthesis of atropurpuran. In 2006, he received his Ph.D. degree in chemistry of medicinal natural products from Sichuan University.

>>



Prof. X.-Y. Liu

His research interests include target- and diversity-oriented synthesis based on complex natural products, especially various groups of diterpenoid alkaloids and related diterpenes.

Xiao-Yu Liu received his Ph.D. degree in 2012 under the supervision of Professor Feng-Peng Wang at Sichuan University (P. R. of China). After conducting postdoctoral research in the group of Professor David Y.-K. Chen at Seoul National University (Korea), he joined the faculty of Sichuan University in 2014 working with Professor Yong Qin. His research interests



Prof. Y. Qin

associate at the University of Vermont (USA). Then he moved to San Diego (USA) and worked as a research scientist at Triad Therapeutics Inc. In 2003, he joined the faculty of West China School of Pharmacy, Sichuan University (P. R. of China) as a full professor. Since 2011, he is an adjunct professor at the Innovative Drug Research Centre, Chongqing University. His research has been focused on the total synthesis of bioactive natural products and medicinal chemistry.

Yong Qin received his B.Sc. degree from Yunnan University (P. R. of China) in 1989 and his Ph.D. from the Institute of Chemistry, Chinese Academy of Sciences (P. R. of China) in 1995. From June 1995 to August 1996, he worked at the Chengdu Institute of Organic Chemistry (P. R. of China) as an assistant and associate professor. From August 1996 to August 2000, he worked with Professor Martin E. Kuehne as a postdoctoral

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 Rüdigerstraße 14, 70469 Stuttgart, Germany,
 ■ Homepage: www.thieme-chemistry.com

Publication Information

Synform will be published 12 times in 2016 by Georg Thieme Verlag KG, Rüdigerstraße 14, 70469 Stuttgart, Germany, and is an additional online service for Synthesis, Synlett and Synfacts.

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