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People, Trends and Views in Chemical Synthesis

2017/06

10 Years of SYNFORM – Interview with Editor Professor Matteo Zanda (University of Aberdeen, UK)

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Thieme

Dear Readers,

In this space, you normally expect to find Matteo Zanda's Editorial. As announced in the May issue, SYNFORM is celebrating its 10th anniversary! Since its inception, Matteo Zanda has been the man behind SYNFORM, interviewing dozens of researchers and giving them the opportunity to present their research and ideas. In this issue, you have the chance to learn more about Matteo himself.

Thieme Chemistry invited Matteo Zanda to provide insight into his work for SYNFORM over the past ten years. He also talks about his research and shares his views regarding the future of chemistry in general and SYNFORM in particular.

The second article of this issue is another interview, this time with the brilliant winner of the SYNTHESIS Best Paper Award 2016, Professor Kilian Muñiz (Spain), who tells us more about his research and his award-winning article. The next article presents the elegant cyclopropane ring-opening reaction published recently in *Nat. Chem.* by I. Marek (Israel). The issue is closed by a contribution dealing with cyclopropanes, this time synthesized through a [2+1] ring formation between alkynes and diazoalkanes derived from *N*-sulfonylhydrazones, developed by X. Bi (P. R. of China).

In this issue

Please join us in congratulating Matteo Zanda, his team and all protagonists for their efforts and help since 2007! We look forward to another successful decade ahead!

Enjoy your reading!

Dr. Susanne Haak
Managing Editor Chemistry Journals
Georg Thieme Verlag KG

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

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HAPPY BIRTHDAY, SYNFORM – An Interview with SYNFORM Editor Matteo Zanda (University of Aberdeen, UK)

Ten years ago – in May 2007 – SYNFORM started as a new adventure and collaboration between Thieme Chemistry's journals department and Professor Matteo Zanda. The project was initiated in order to "serve the international chemistry community by publishing timely information about new scientific advances in organic chemistry and related fields of research," as Matteo Zanda wrote in his inaugural editorial. SYNFORM was and is meant to inform you, our readers, about facts and people from the world of chemical sciences – all this in a stimulating and thought-provoking manner. Starting with only two sections – **Inside Stories** and **SynStories** – content, format, layout, and publication frequency have been developed and changed during the last decade. In addition to pieces covering interesting articles from the current literature, nearly every issue now contains an interview with a member from the younger generation of chemists – the **Young Career Focus**. These regular sections are spiced up with **Conference Reports** and **ChemSites** (specifically presenting departments or institutions). And there are plenty more ideas for the next ten years!

On the occasion of the 10th anniversary of SYNFORM, the tables were turned for this interview: Matteo Zanda was happy to answer some questions from the Thieme Chemistry team.

Prof. M. Zanda

INTERVIEW

Thieme Chemistry *Matteo, it's been ten years since SYNFORM was launched and the first articles were published. You have been the Editor since the very beginning; looking back at all these years, what have you enjoyed most about being SYNFORM Editor?*

Prof. Matteo Zanda Honestly? It was fun all along! I wouldn't do it if it wasn't, I am a very busy academic, you know (if there was a video I would be winking at the camera at this point)? My pick, however, is being a member of the Thieme Chemistry family (because it really is like a family!) and Editorial Boards, together with all those big names of organic chemistry. I remember I was a bit scared at the first Editorial Board Meeting, sitting next to folks like Steve Ley, Dieter Enders, Paul Knochel, Peter Vollhardt and Vic Snieckus who are in all the textbooks (when they don't write them…). But they are all really nice guys, you know? Nothing to be scared about!

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Thieme Chemistry *Despite all the fun, what challenges were you confronted with during the last ten years as SYNFORM Editor and how did you respond?*

Prof. Matteo Zanda Naaahhh… no real challenges. At some point, I was struggling a bit to keep the tight editorial deadlines required for a timely monthly publication of SYNFORM because of all my other academic duties. Susanne [Haak, *editor's note*] can be tough, you know, if you are late on a deadline! But now that Alison [Sage, *editor's note*] – our fantastic editorial assistant – is with us, I am no longer struggling with deadlines. She does most of the work, you know, so I can sit back and relax! Easy life for me!

Thieme Chemistry *Now that we know that you have helping hands in the background, could you give us an overview of what your daily SYNFORM business looks like?*

Prof. Matteo Zanda I mostly work evenings and weekends for SYNFORM. The first thing is browsing the literature in depth, of course, which sometimes can be challenging owing to time constraints. I follow my instinct when it comes to selecting articles and authors for SYNFORM, if something catches my eye I simply go for it, no hesitations. I also do my best to diversify the pool of prospective authors; we don't want to feature always the same people – that would be very boring. SYNFORM has a preference for younger up-and-coming scientists, who are still trying to establish themselves in the tough world of research. I think they are the ones who deserve and need to get more visibility for their work, which is what SYNFORM does. Once a paper has been selected, I inform Alison – our super-efficient editorial assistant – who takes care of inviting the authors and liaising with them, for collecting all the necessary material, ideas, opinions, thoughts, text, photos, images, drawings. Once everything is in, Alison and I edit the article in the form of an interview. We don't do real interviews because that would be logistically challenging, plus we want the selected authors to be absolutely confident about the content of their SYNFORM article – we need to be reliable and they need to be happy with it. Once the draft is approved by the authors, all the material is sent to the Thieme Chemistry editorial office, and here is when the magical Susanne kicks in. I have been working with Susanne for more than ten years now, and believe me: she has editorial superpowers! Humans cannot be so efficient, reliable and timely. So, I am pretty sure Susanne is a mighty editorial superhuman entity, in fact – this is a little secret I am willing to share with you – she has been looking exactly the same for the last ten years, she doesn't seem to get older, and she never gets tired! Susanne is able to spot every single tiny typo in a draft. I challenge the readers to spot a typo in any of the SYNFORM articles published in these ten years: if you can do it, Thieme Chemistry may be prepared to offer you an all-inclusive two-week holiday for the whole family in a five-star hotel, first-class travel included! That's the Thieme Chemistry style! After one week of cooking of all the crude editorial material in her mysterious editorial cauldron in Stuttgart, Susanne gets back to us with the SYNFORM galley proofs, which are always super-good looking and ready to go online! Abracadabra!

Thieme Chemistry *Thank you for the compliments that we are happy to give straight back! As we all work on SYNFORM as a service to the community, what is the best feedback you have received regarding SYNFORM from authors or readers?*

Prof. Matteo Zanda Oh that's easy! It is when readers write me or tell me that they enjoy browsing/reading SYNFORM and just can't wait for the next issue to be published, to see who's featured in it. It really happens, you know? That's really rewarding for me!

Thieme Chemistry *Amazing! That is a great reward for us as well. One regular input to SYNFORM from your side is the editorials. The covered topics are always very interesting: informative or inspiring, sometimes funny, at other times critical. How do you develop the ideas?*

Prof. Matteo Zanda Thanks, I am flattered! I always pick up the first idea that springs to my mind, whatever that is. I try to avoid politics or overly 'difficult' topics in my editorials, and I always strive to be light and ironic without being (too) silly. Sometimes it works well, sometimes less, I guess. It would be very rewarding for me if our readers did recognize themselves – at least a bit – in those editorials, as I consider myself as the average academic, who is lucky enough to do this fantastic job, with all its highs and lows. What I do is really just write about my professional experience, without taking myself too seriously. If I start writing pretentious editorials, please show me the door immediately!

Thieme Chemistry *Alright. Now let's talk a bit about your research. Besides being an editor, you have held the position of Professor of Medical Technologies at the University of Aberdeen, UK, since 2009. Could you tell us more about the focus of your current research and its aims?*

Prof. Matteo Zanda My background is in synthetic organic chemistry, but I have been working at the interface with

biomedicine for many years now. Quoting my website: "My group's mission is the use of Chemistry for finding innovative solutions to translational biomedicine and imaging problems. We work side-by-side with biologists and clinicians, and we believe that Chemistry offers powerful tools for addressing unmet medical needs and we strive to support biomedical research from lab-bench-to-bedside." In a nutshell, I hope one day – possibly 50 years or more down the line – I'll look back and think: OK, it was worth it, I have done something useful with my life and my chemistry.

Thieme Chemistry *Turning to the past for a moment: you have been involved in many projects, with co-authorship of over 185 papers including eight patent applications. Looking back at your career so far, what do you consider to be your most important scientific achievement to date and why?*

Prof. Matteo Zanda I think it was the intuition that stereodefined trifluoroethylamines can behave as peptide bond bioisosteres. That concept was then picked up, used and validated by many other researchers and a few pharma companies too, which is very, very rewarding for me, as well as for my group members.

Thieme Chemistry *That's a remarkable achievement indeed, congratulations! Considering all the research that has been done in the field to date, which major problem in the world might one day be solved through medicinal chemistry?*

Prof. Matteo Zanda I hope all of them! Too ambitious? Maybe not! It will necessarily have to be a co-operation with other areas of research, such as biomedicine, engineering, materials science, but one day we'll find a solution to all the major problems currently affecting humanity. Unfortunately, some other problems will likely come to light… Clearly we have to believe in science. There are too many people around these days – also in very prominent political positions – who think that scientific evidence can be ignored – we all know who those enlightened folks are. However, I think that we, scientists, need to be better at communicating science. What's happening out there is partly our fault; we are not good enough at explaining our results and what we do. On the other hand, politicians and the general public sometimes are just not prepared to listen. This needs to change, on both sides.

Thieme Chemistry *Indeed, that's quite a fundamental problem that scientists but also publishers should be aware of. Now we would like to know more about you. When did you first become interested in chemistry?*

Prof. Matteo Zanda During secondary school. My uncle Giovanni handed me a 'Piccolo Chimico' box (a chemistry set for kids) as a birthday gift when I was 13 and that was it, I was doomed… That literally cast a spell on me; I couldn't imagine doing anything else in my life. However, when it came to deciding on a university course, I actually had a bit of hesitation, because I was very attracted by biology too. Eventually I opted for chemistry, and I never regretted that choice. My unsolicited advice to younger people? Trust your gut, do what you really like, if you are good enough you'll find your way and the perfect job for you.

Thieme Chemistry *You did your PhD in industrial chemistry. Why did you choose to focus on medicinal chemistry afterwards? What is it about bioorganic/medicinal chemistry that fascinates you?*

Prof. Matteo Zanda The truth? I never really cared about industrial chemistry, but that was the only option at Politecnico di Milano, when I finally got a chance to enroll in a PhD course. Please, don't make me comment further about the Italian academic system… I had to take industrial chemistry courses though: plants, processes and so on. With all due respect for industrial chemistry, it is not my kind of stuff…

Thieme Chemistry *Given the chance to meet any chemist (living or dead) who would it be and why?*

Prof. Matteo Zanda I would really like to meet one of those pioneers of synthetic organic chemistry, like Cannizzaro or Beckmann, and ask them: how did you manage to achieve all that without NMR and Mass Spec? Who knows what people like that would achieve with all our modern instruments and facilities…

Thieme Chemistry *That's right, all those techniques are considered as being evident nowadays. Now, we have two more personal questions. What kind of hobbies and interests do you have outside of the lab?*

Prof. Matteo Zanda I have very little time for hobbies unfortunately, but I love horror/thriller movies and I am a football (or soccer, if you like) fan, I support my city's team: Atalanta BC, which is having a great season. I also follow the Scottish

League with great interest; I go to the Pittodrie stadium whenever I can and watch The Dons (Aberdeen FC). My son Simone plays in the AFC youth academy, so – together with my wife, and sometimes my daughter too – I often embark on long car drives to follow his away matches around Scotland. That takes up most of my spare time!

Thieme Chemistry *Finally, what's one thing most people don't know about you?*

Prof. Matteo Zanda Something that my family knows very well: I am not a patient guy! Actually, I am not patient at all. I do my best to hide it, particularly when I am at work, but the consequence is that I am even less patient when I am NOT at work!

Thieme Chemistry *Getting back to SYNFORM: Are there any future projects or developments that you are currently planning? Have you any particular wishes for SYNFORM?*

Prof. Matteo Zanda Yes, definitely. Although I am not a 'social media guy' (actually I don't even have a personal Facebook or Twitter account), my plan would be to make SYNFORM more shared, more interactive, more 'social', with a more active role for the readers. This is already happening: SYNFORM started as a traditional online pdf monthly supplement to SYNLETT and SYNTHESIS, but now we have a more dynamic platform whereby articles are also published individually online on the SYNFORM website and the Thieme Chemisty Facebook page. Articles are advertised and posted on LinkedIn, and I believe this is further increasing SYNFORM's visibility. Although technically not a section of SYNFORM, we are also producing brief News articles on the top e-first articles published in SYNLETT and SYNTHESIS (and soon in SynOpen too). This concept will be implemented further, we want to be very dynamic, timely, 'social' and we really want to involve the Thieme Chemistry readership in SYNFORM – before, during and after publication. And let me take advantage of this 10th anniversary interview to invite all our readers to get in touch with us by email or through the website: please share with us your thoughts and opinions on the articles we publish and the topics we should cover in SYNFORM. Your opinions – dear readers – do matter to SYNFORM!

Thieme Chemistry *Thanks a lot for this exciting outlook! Now that we have almost come to the end of this interview, is there anything else you want to tell your readers?*

Prof. Matteo Zanda Just one thing: that being the editor of SYNFORM for these ten years has been an immense pleasure. I am looking forward to the next ten years!

Thieme Chemistry *Thank you very much for this interview! We are very excited to continue our successful cooperation in the same great spirit as always! We wish you all the best for the future, and look forward to hearing about further developments in your laboratories.*

SYNTHESIS Best Paper Award 2016: Enantioselective Vicinal Diacetoxylation of Alkenes under Chiral Iodine(III) Catalysis

Synthesis **2016**, *48*, 2367–2376

Background. Thieme Chemistry and the Editors of SYNTHESIS and SYNLETT present the 'SYNTHESIS/SYNLETT Best Paper Awards'. These annual awards honor the authors of the best original research papers in each of the journals, considering their immediate impact on the field of chemical synthesis.
Kilian Muñiz and Thorsten H. Wöste from the Catalan Institution for Research and Advanced Studies and The Barcelona Institute of Science and Technology (Spain) are the recipients of the SYNTHESIS Best Paper Award 2016. The authors are recognized for their work on the enantioselective vicinal diacetoxylation of alkenes under chiral iodine(III) catalysis. Paul Knochel, Editor-in-Chief of SYNTHESIS, commented: "The development of new catalytic asymmetric synthesis of chiral molecules is especially important for pharmaceutical and fine chemistry in general. Kilian Muñiz and Thorsten Wöste have reported a very mild method for converting styrene and a range of related functionalized styrene derivatives into the corresponding vicinal diacetoxy derivatives with excellent enantioselectivities (up to 96% ee). The reactions proceed via a hypervalent iodine(III) catalytic species generated in situ. This enantioselective method is not only important by itself, but the results reported in this SYNTHESIS Best Paper 2016 will be very instructive for the future development of similar hypervalent iodine catalyzed difunctionalizations of alkenes. This work will be of interest both for synthetic applications as well as for the comprehension of iodine(I/III)-catalyzed enantioselective addition."
SYNFORM talked to Kilian Muñiz who was happy to share some background information regarding the prize-winning paper as well as current research activities ongoing in his group.

Biographical Sketch

Prof. Dr. K. Muñiz

Kilian Muñiz was born in 1970 in Hildesheim (Germany). He studied chemistry at the Universities of Hannover (Germany) and Oviedo (Spain) and at Imperial College, London (UK), and received a Doctorate in Chemistry from the RWTH Aachen (Germany) in 1998 working with Professor Carsten Bolm. He was a postdoctoral associate with Professor Ryoji Noyori at Nagoya University (Japan) in 1999/2000. He started his independent research in 2001 at Bonn University (Germany), before accepting a full professorship at Strasbourg University (France). He was elected as a junior member to the Institut Universitaire de France in 2008. Kilian Muñiz moved to his present position at ICIQ in Tarragona (Spain) in 2009. Since 2010 he has also been an ICREA research professor. His research throughout the past decade has dealt with the development of new processes in the area of amination chemistry, in particular with the oxidative diamination of alkenes.

Outside the laboratory, he spends time on modern (European) literature and arts, and enjoys good food and wine.

INTERVIEW

SYNFORM *Could you highlight the value of your award-winning paper with respect to the state-of-the-art, potential or actual applications, and explain the origin, motivations and strategy used for conducting the research?*

Prof. Dr. K. Muñiz The 1,2-diol unit is a concurrent motif in numerous small molecules with biological, pharmaceutical and medicinal impact. One of the most appropriate approaches to their synthesis consists of a single-step oxidative transformation of alkenes as widely available starting materials. If conducted in an asymmetric fashion, such a reaction builds defined three-dimensional architectures from flat sources. The dominating process is the area that still belongs to osmium catalysis with chiral alkaloid ligands, which was pioneered by K. Barry Sharpless and recognized with a share in the 2001 Nobel Prize. The idea of exploring chiral non-racemic iodine(III) reagents to achieve vicinal dioxygenation of alkenes was initially conceived by Thomas Wirth in pioneering studies from the 1990s and extended by Morifumi Fujita. We initially became interested in these types of reagents within our work on the related 1,2-diamination of alkenes and suddenly found ourselves involved in the question of how to pursue asymmetric reactions catalytic in iodine(III). Together with Kazuaki Ishihara we have explored the working mode of related catalysts and identified supramolecular hydrogen bonding as a powerful tool for the design of aryliodine(III) catalysts (Figure 1).

The results reported in the SYNTHESIS paper are based on a postdoctoral stay of Thorsten Wöste, who joined my laboratory after a Doctorate with Professor Martin Oestreich. He was able to develop well-balanced conditions that use electrophilic fluorine reagents for the selective oxidation of the iodine center and to prevent any possible achiral background reaction. Our publication also devotes some effort to understanding the underlying mechanistic pathways that are involved in the diacetoxylation reaction. Knowledge of competing pathways is obviously very important, when one aims to develop new transformations or to improve existing ones. In the present case, we identified three different pathways that are involved in the formation of the final diacetoxylation product – luckily they all provide the same major enantiomer!

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

Prof. Dr. K. Muñiz My group focuses on oxidative amination reactions in general and vicinal diamination reactions in particular. If there is a challenge in amination, I am interested! I find C–N bond-forming events a stimulating field of research, since, unlike many other organic transformations, there is no real precedent in Nature. Traditionally, we have worked a lot on transition-metal catalysis, particularly high-oxidation-state palladium catalysts. Recently, we have explored the redox properties of iodine compounds which provide catalysts of unique economic and ecological appeal. In combination with other concepts such as photochemistry, this field currently widens into an exciting playground. Among my favorites of our recent accomplishments is an iodine-catalyzed intramolecular C–H amination initiated by light that forms pyrrolidines (Figure 2). This is the first realization of a catalytic version of the famous Hofmann–Löffler reaction, more than a century after its general development.

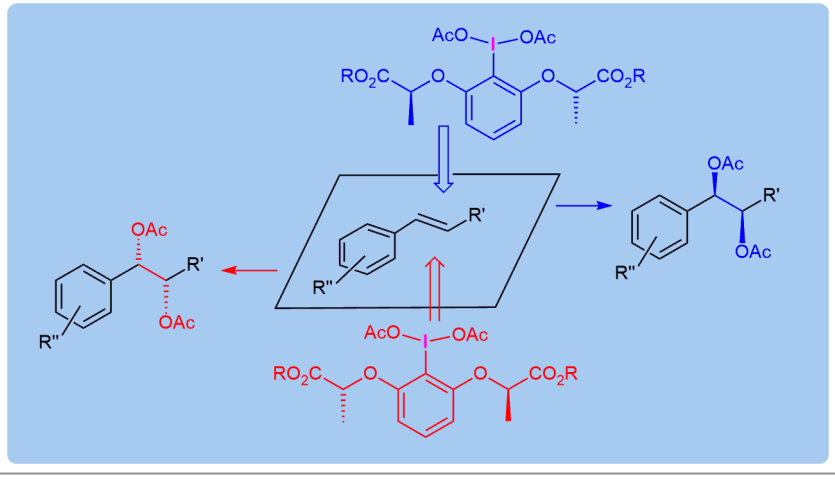

Figure 1

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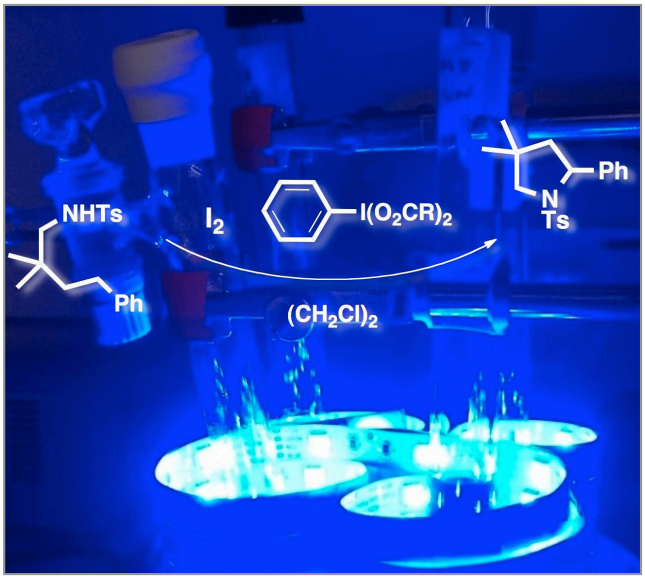


Figure 2

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

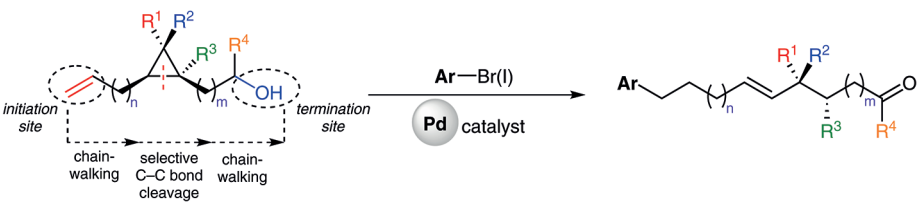
Prof. Dr. K. Muñiz First, a dynamic research group brings together people from many different countries to work closely together. I cannot envision any better place than Europe for doing so. I am a strong advocate of European unification and (organic) chemistry should be instrumental in promoting the benefits of this idea within the next generation of chemists. Then, organic chemistry is a timeless art and will continue to stand out for its creativity. Developing new and unexpected reactions has always been at the heart of organic chemistry. I would hope this never changes since it is one of the most exciting features of our science! To plan and execute the unknown transformation and to arrive at the target molecule is very stimulating and at the heart of any curiosity-driven research, which ultimately is what academic work has always been about. Obviously, the rules have changed a little bit over time and modern society's demands rightly require that creative organic synthesis embraces sustainability. Homogeneous molecular iodine catalysis, with its inherent economic and ecological benefits, is obviously a perfect match!

A Unique Palladium-Catalyzed Heck Arylation as a Remote Trigger for Cyclopropane-Selective Ring Opening

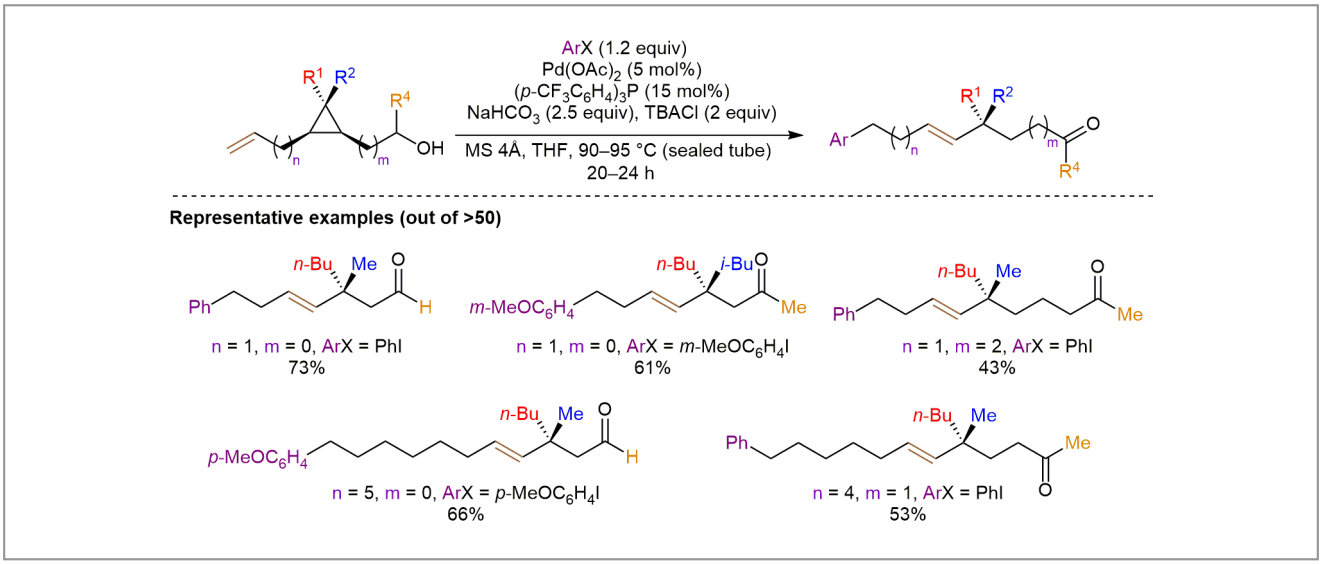
Nat. Commun. **2017**, *8*, 14200

The concept of remote functionalization, originally coined by Breslow in 1972,[1] relates to the selective functionalization at a site away from the site of a functional group. Following this pioneering work, an impressive body of work has been reported for the remote functionalization of non-reactive molecules in the gas phase.[2] However, after these reports, the field became rather dormant, most probably due to the synthetic difficulties encountered, until the last few years when there has been a resurgence of interest in this approach. It is now considered as one of the hottest topics in synthetic organic chemistry thanks to the contributions of worldwide leading research groups.[3] Initially, the research group of Professor Ilan Marek (Technion – Israel Institute of Technology, Haifa, Israel) had developed the remote functionalization of hydrocarbon chains by merging two cutting-edge methods, namely the allylic C–H bond activation and C–C bond cleavage of ω-ene cyclopropanes.[4] "Although particularly straightforward if one wants to distantly control positioned acyclic quaternary and tertiary stereocenters, this approach required stoichiometric amounts of zirconocene derivatives,[5]" explained Professor Marek, who continued: "We wanted to design a new system where the remote functionalization could be performed catalytically, but all our attempts to develop the zirconium-catalyzed remote functionalization of hydrocarbons failed." Although very disappointing, these repetitive failures led Jeffrey Bruffaerts, Alexandre Vasseur and Sukhdev Singh, all co-workers in Professor Marek's research group, to envisage alternative catalytic processes that would allow these highly regarded but complex remote functionalization transformations to occur. "Since secondary sp^3 organo-palladium species readily undergo β-H elimination and re-addition, as proved by the synthetically relevant work of Baudoin,[6] Mazet,[7] and Kochi,[8] my co-workers were expecting that the Heck arylation reaction could potentially trigger a chain-walking mechanism and selective ring-opening reaction," recalled Professor Marek. Indeed, early work dating back to the mid-1970s mentioned that the arylation of homoallylic alcohols led to the migration of palladium converting alcohols into ketones.[9] "The power of this approach was beautifully illustrated when enantiomerically enriched stereocenters were created on ω-alkenol by the research groups of Sigman[10] and Correia and Pflatz,[11]" said Professor Marek. So, would the palladium-catalyzed Heck reaction triggering a Pd walk and selective ring opening of substituted cyclopropyl carbinols potentially be a powerful approach? "If such a transformation was possible, the clear advantage of this strategy would reside in the rather easy diastereo- and enantioselective preparation of polysubstituted cyclopropanes that would be translated into acyclic stereocenters after unfolding of the three-membered ring (Scheme 1)," was Professor Marek's answer.

"Using the simplest diastereomerically pure model substrates, the modified Larock's experimental conditions proved to be the most efficient protocol to provide the acyclic products in good yields and selectivities as unique (*E*)-isomers (Scheme 2)," said Professor Marek. The scope of the reaction is very broad, as could be seen in the original paper, and summarized by the few representative examples described below. "Aryl iodide (as well as aryl bromide) as a coupling partner possessing a functional group, such as an electron-donating or electron-withdrawing group – including an interesting methyl ketone moiety – react similarly with the starting substrates. Various substitution patterns on the quaternary stereocenter



Scheme 1

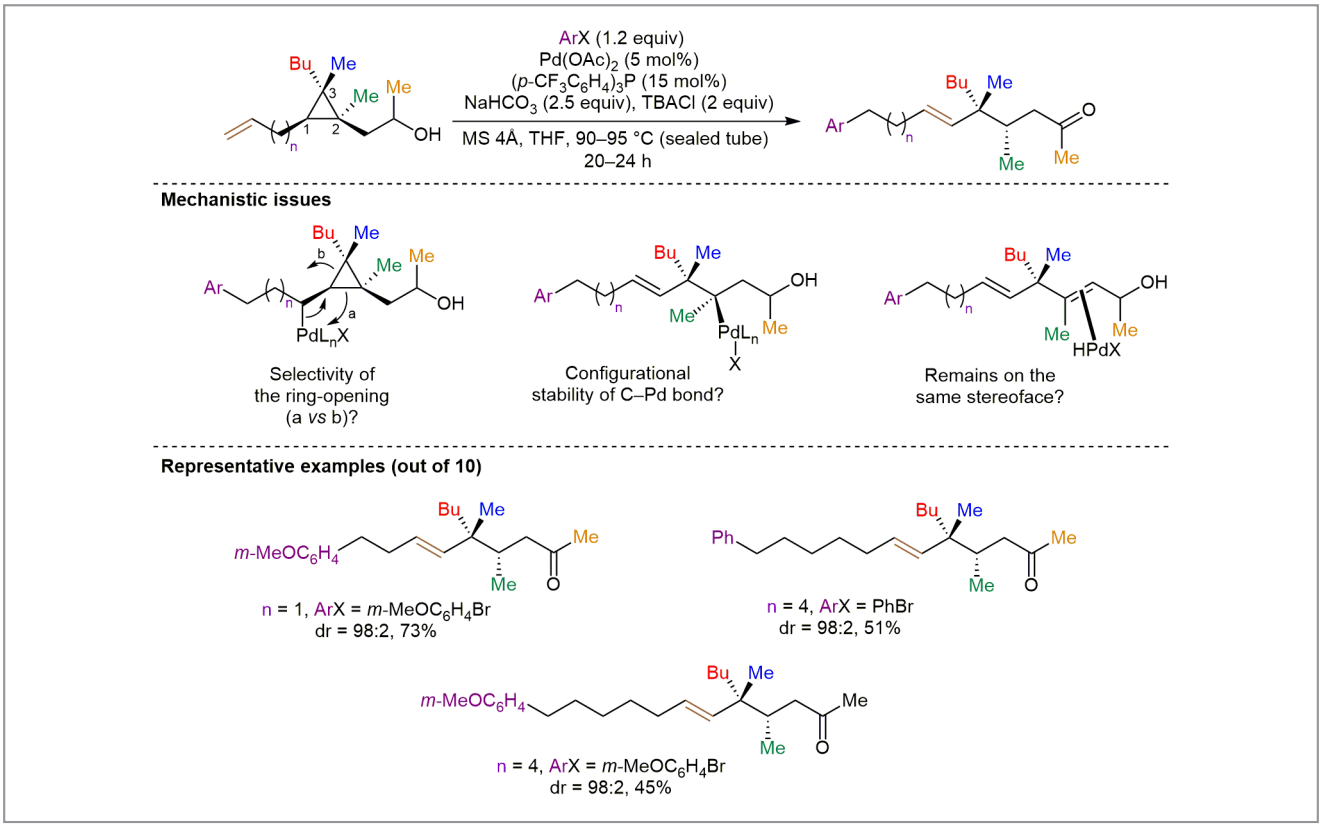


Scheme 2

(R^1 and R^2) and secondary alcohol derivatives also underwent similar transformations to provide the corresponding ketones. Even more interesting is that the chain-length variation does not actually alter the efficiency of this combined transformation (n = 4, m = 2, Scheme 2)," explained Professor Marek.

The next level of complexity that was investigated by Professor Marek's research group concerned the unfolding of 1,2,2,3,3-pentasubstituted cyclopropanes as illustrated in Scheme 3. "In this case, not only might the selectivity of the C–C bond cleavage be difficult to control (both C1–C2 and C1–C3 bonds have the same substitution level), but also the ring opening would lead to a species containing a stereogenic C-center palladium species and the issue of its configurational stability needed to be considered (Scheme 3)," he explained. "Moreover, when the Pd walk proceeds further through the *syn*-β-H elimination, a planar olefin is formed and the chirality can only be preserved if the Pd species does not disengage from the olefin and re-adds on the same stereoface. Gratifyingly, my outstanding team was able to show that the products resulting from the remote arylation of ω-alkenyl cyclopropyl alcohols were obtained in satisfactory yields as a single set of diastereoisomers (dr = 98:02), suggesting that the Pd does not disengage during the process and migrates on the same stereoface,[12]" said Professor Marek. He continued: "These results open vast perspectives for the metal walk all over carbon skeletons possessing stereogenic centers."

"It is now clear that the remote functionalization by metal walk opens new perspectives in organic synthesis and many more organic chemists will embrace this concept and benefit from all the advantages and opportunities it has to offer. In conclusion," Professor Marek said, "it has been a real privilege to be associated with such talented co-workers and without their inspiration, dedicated work and input, none of this would have seen the light of day."



Scheme 3

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Jeffrey Bruffaerts was born in Brussels (Belgium) in 1990. He graduated from the Université Catholique de Louvain (Belgium) where he was awarded a BSc (2011) and an MSc (2013), during which he worked under the supervision of Professor Olivier Riant. Since then, he has joined the laboratory of Professor Ilan Marek at the Technion – Israel Institute of Technology (Israel) for his doctoral studies. His PhD thesis is focusing on the development of novel remote functionalization based synthetic methodologies, mostly applied to hydrocarbons.

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Alexandre Vasseur was born in Revin (France) in 1982. He studied chemistry at the University of Reims Champagne-Ardenne (France). He completed his PhD studies in 2012 on Pd-catalyzed dehydrogenative Heck reactions of heteroarenes with electron-rich and/or hindered alkenes under the supervision of Dr. Jean Le Bras. He then joined the group of Professor Ilan Marek at Technion – Israel Institute of Technology (Israel) and worked on transition-metal-assisted remote functionalization of alkenes. In 2015, he moved to the Ecole Centrale de Marseille (France) where he is currently working on the synthesis of secondary phosphine oxide–palladium complexes and their applications in organic synthesis as a Teaching and Research Temporary Attaché (ATER) in the research group of Professor Alexandre Martinez, Dr. Laurent Giordano and Dr. Didier Nuel.

Dr. S. Singh

Sukhdev Singh was born in Sirsa, Haryana (India) in 1980. After completing his MSc in chemistry from Delhi University (India), he spent six months in Jubilant Chemsys Limited (India), a leading CRO industry situated in Noida (Uttar Pradesh). Meanwhile, he qualified in the national eligibility examination and was awarded a Junior Research Fellowship from UGC India. He then joined the research group of Professor Ashok K. Prasad at Delhi University (India) for his PhD thesis and worked in the area of heterocyclic chemistry. Part of his PhD thesis work was completed at Paris Descartes University (France) under the supervision of Professor Hamid in the area of synthesis of fluorinated amino acids. He was awarded his PhD in 2012. He joined the group of Professor Ilan Marek at the Technion – Israel Institute of Technology (Israel) in 2013 as a postdoctoral fellow and his research work is mainly focused on remote functionalization and transition-metal-mediated selective cyclopropane ring opening.

Prof. I. Marek

Ilan Marek was born in Haifa (Israel), educated in France, and received his PhD in 1988 from the University Pierre et Marie Curie, Paris (France) under the guidance of Professor J. F. Normant. In 1989, he was a postdoctoral fellow in Louvain-la-Neuve (Belgium) with Professor L. Ghosez and obtained a research position at the CNRS in France in 1990. After obtaining his Habilitation in Organic Chemistry, he moved to the Technion – Israel Institute of Technology (Israel) at the end of 1997 where he currently holds a Full Professor position. Since 2005, he holds the *Sir Michael and Lady Sobell Academic Chair*. He has received many awards for academic excellence and for teaching. He is a member of the advisory board of several journals and serves as Senior Editor of the Patai series. He is concerned with the design and development of new and efficient stereo- and enantioselective strategies for the synthesis of important complex molecular structures. He is particularly interested in developing carbon–carbon bond-forming as well as carbon–carbon bond-activation processes that create multiple stereocenters efficiently in a single-pot operation. Understanding of reaction mechanisms gives insight into the origins of chemo- and stereoselectivity, and governs optimization towards the most efficient and general protocols for his methodologies. His vision is that we should provide an answer to challenging synthetic problems but it has to be coupled with unique efficiency and elegance.

Decomposition of *N*-Sulfonylhydrazones to Diazoalkanes Goes to Room Temperature and Application to [2+1] Cyclopropenation with Alkynes

Chem. Eur. J. **2017**, *23*, 4756–4760

It is well known that diazo compounds are outstanding building blocks in organic synthesis. Since their discovery over 100 years ago, these reagents have been frequently employed in a variety of processes, starting from homologation reactions to metal-catalyzed C–H insertions. However, due to their toxic and explosive nature, direct use of diazo compounds in many of these chemically interesting reactions and their utilization in large-scale production has been very difficult. To avoid these difficulties, chemists have developed a range of diazo surrogates as an alternative diazo source in numerous organic transformations. Thus, the organic chemistry community has devoted a lot of effort and interest in developing efficient protocols where these reagents could be generated in situ. To date, *N*-tosylhydrazones have proved to be some of the most useful diazo surrogates, because of their rapidly expanding repertoires of organic transformations. However, high dissociation temperature (≥70 °C) remains an inherent drawback of *N*-tosylhydrazones, and severely limits their use in synthetic areas where low reaction temperatures are generally employed, such as reactions of highly strained small rings, asymmetric and natural product synthesis. Great efforts have been devoted towards solving this challenging issue, but room-temperature decomposable *N*-sulfonylhydrazones remain unknown thus far.

Recently, this challenging issue has been addressed by the research group of Professor Xihe Bi at the Northeast Normal University (P. R. of China), who discovered for the first time the room-temperature decomposable property of *N*-nosylhydrazones. "We initially investigated the NaH-promoted dissociation of *N*-nosylhydrazone **1a** and *N*-tosylhydrazone **1a**′ at 25 °C and observed that the former smoothly released 4-chlorophenyl diazomethane, whereas the latter remained

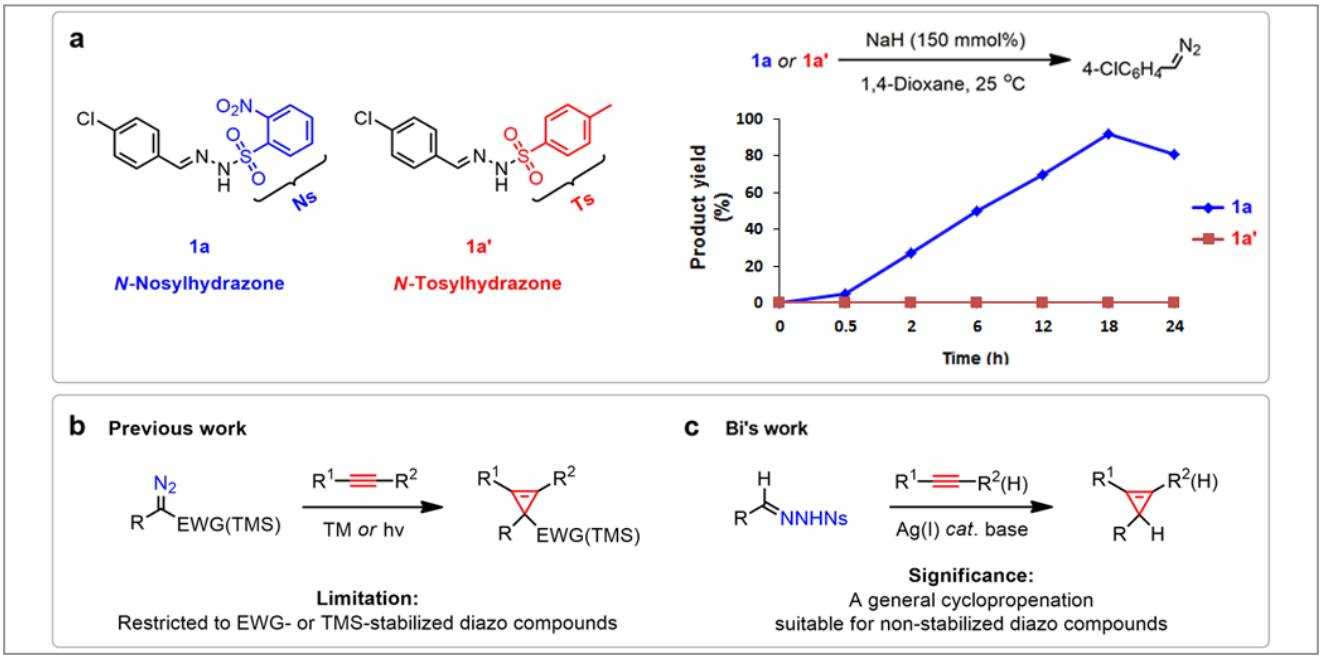
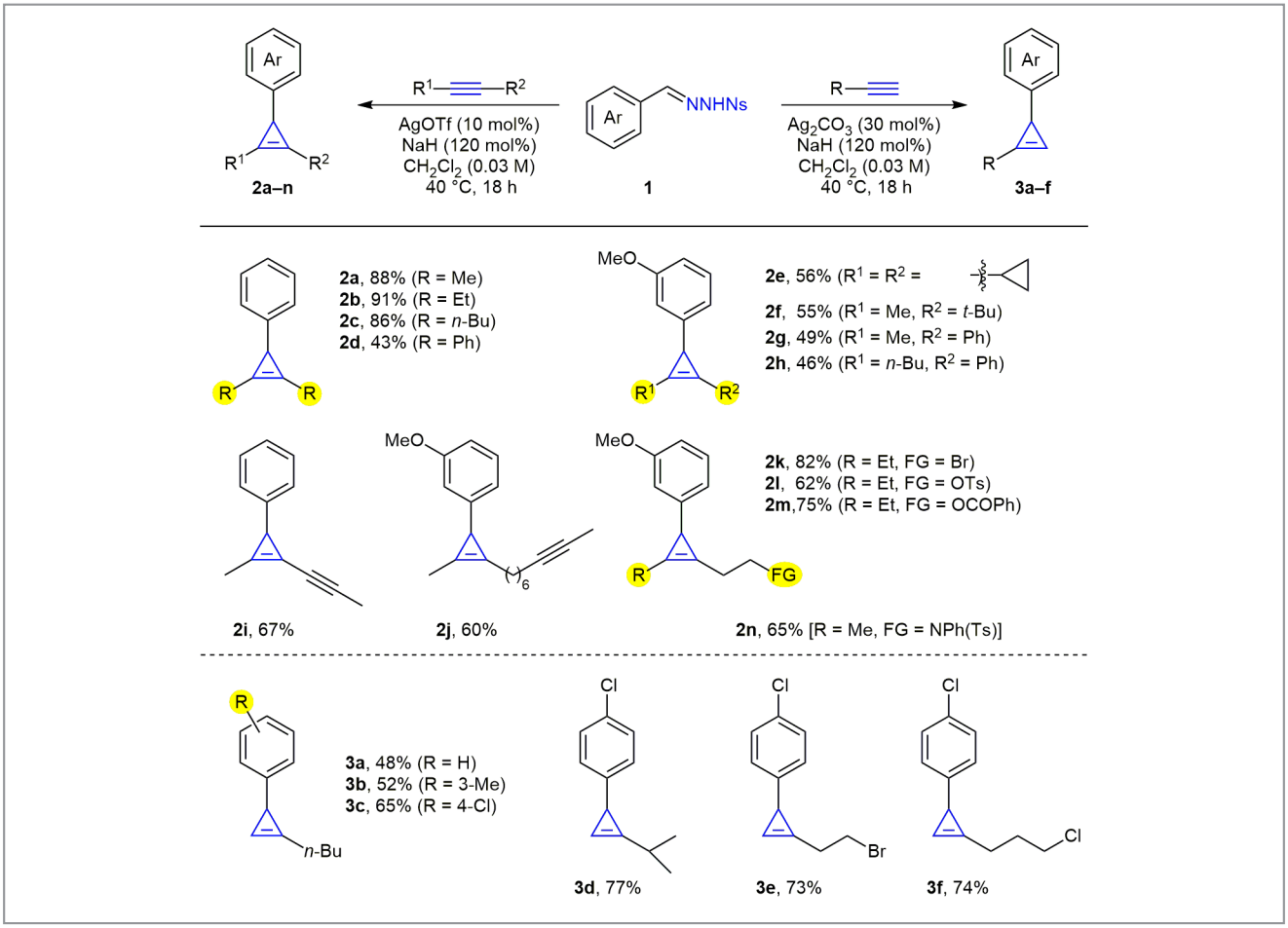


Figure 1 Comparison discovery of *N*-nosylhydrazones as room-temperature diazo surrogates, and cyclopropenation with alkynes; a: of the base-promoted dissociation of *N*-nosylhydrazones and *N*-tosylhydrazones at 25 °C, b,c: cyclopropenation of alkynes with diazo compounds

intact (Figure 1a)," said Professor Bi. "The significance of this discovery was demonstrated by overcoming the long-standing challenge in cyclopropene chemistry of non-stabilized diazo compounds not being suitable partners in the cyclopropenation of alkynes (Figure 1b,c)."

The reaction scope is quite broad (Scheme 1). "All the internal alkynes that we tested underwent the cyclopropenation with *N*-nosylhydrazones to afford the corresponding cyclopropenes (**2a–n**) with useful efficiencies (43–91% yield)," added Professor Bi. He continued: "A remarkable steric hindrance effect of alkyne substrates on the cyclopropenation reaction was observed. For example, the linear alkynes generally gave high yields (**2a–c**, 86–91%), whereas those with branched chains or a bulky phenyl ring led to gradually decreased product yields (**2d–h**, 43–56%). Notably, the most bulky 1,2-diphenylethyne also proved to be reactive, albeit with AgOTFA as catalyst. Diverse functionalities, including alkynyl, halogen, ester, and amino groups, were well tolerated, thus affording a range of functionalized cyclopropenes (**2i–n**, 60–82%)." The tolerance of the bromo group in the presence of a halophilic silver catalyst was especially noteworthy. Furthermore, under slightly modified conditions (Ag_2CO_3 as catalyst, highly diluted reaction solution), terminal alkynes also proved to be suitable reaction partners in this silver-catalyzed protocol, and afforded a group of difficult to synthesize 1-alkyl-3-arylcyclopropenes in good yields (**3a–f**, 48–77%).

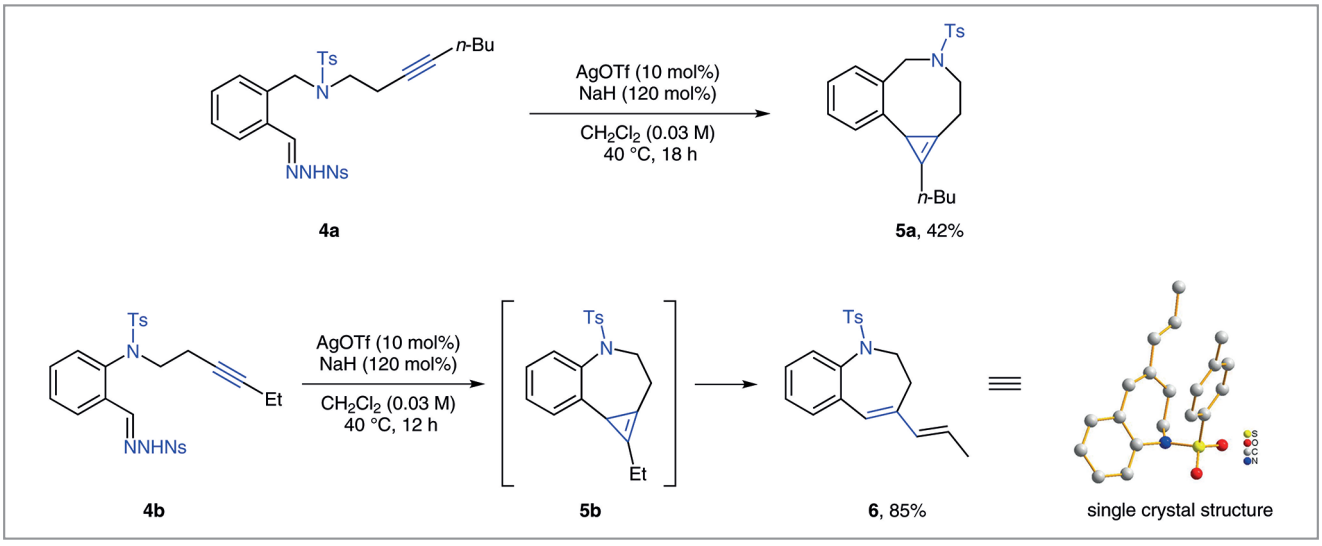
Subsequently, Bi and co-workers applied this silver-catalyzed protocol to the synthesis and isolation of more strained cyclopropenes that are otherwise difficult to obtain by other methods. As shown in Scheme 2, they eventually isolated the eight-member-fused cyclopropene **5a** in moderate yield (42%) starting from *N*-nosylhydrazone **4a**, in a diluted solution (0.03 M). In contrast, the reaction of substrate **4b**, which has one less carbon atom in the side-chain, progressed beyond the step of



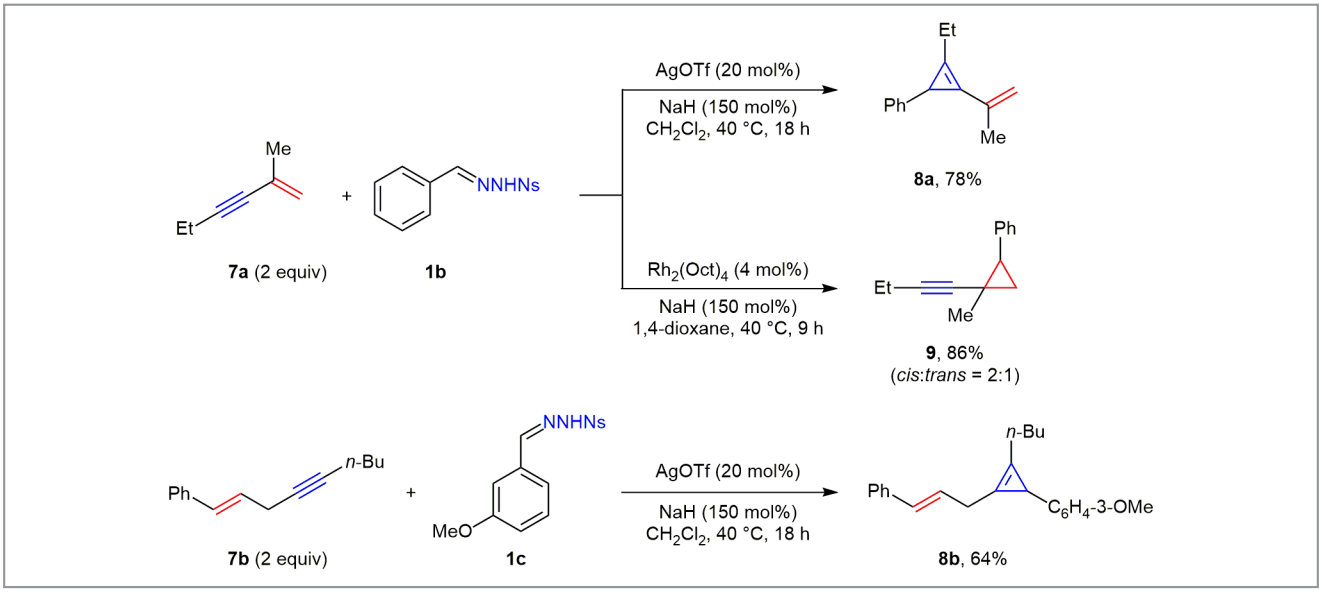
Scheme 1 Reaction scope

forming fused cyclopropene **5b**, giving the pharmacologically interesting benzo[*b*]azepine **6** in 85% yield by a regioselective ring-opening reaction. The structure of **6** was confirmed by X-ray crystallographic analysis.

"Interestingly, we found that the present silver-catalyzed protocol was applicable for the chemoselective cyclopropenation of enyne systems **7a** and **7b** with *N*-nosylhydrazones, thus providing the corresponding cyclopropenes **8a** and **8b** in good yields," said Professor Bi. However, the same reaction was carried out with rhodium catalysts, affording the alkynyl cyclopropanes **9** in 86% yield as a 2:1 mixture of *cis* and *trans* isomers. "Normally, silver catalysts do not favor the cyclopropenation selectivity in an enyne system, as reported by Davies and co-workers, who observed complete cyclopropanation of enyne **7a** with α-diazocarbonyl compounds under silver catalysis," said Professor Bi, who remarked: "These results clearly indicate the difference in the reactivity between *N*-nosylhydrazone and α-diazocarbonyl compounds. It is noteworthy



Scheme 2 Intramolecular reaction

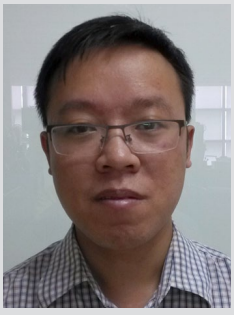


Scheme 3 Switchable chemoselectivity of cyclopropenation vs cyclopropanation

that the chemoselectivity, i.e. cylopropenation vs cyclopropanation, of the enyne system can be altered by choosing the appropriate diazo species and metal catalysts."

Finally, Professor Bi concluded: "*N*-Nosylhydrazones have been found for the first time as a room-temperature-decomposable diazo surrogate, and its synthetic application was demonstrated in the cyclopropenation of alkynes with donor-diazo compounds by silver catalysis. We have no doubt that this *N*-nosylhydrazone strategy will have a broad impact across diazo chemistry, especially for applications in asymmetric synthesis."

About the authors



Z. Liu

Zhaohong Liu received his B.S. degree from Sichuan University (P. R. of China) in 2006. In the same year, he joined Asymchem Laboratories Co., Ltd. as a synthetic chemist. Since 2012, he has been a graduate student in Professor Xihe Bi's group at Northeast Normal University (P. R. of China). His research interest concerns silver-catalyzed transfer reactions of carbene.

Q. Li

Qiangqiang Li was born in Shanxi (P. R. of China) in 1990, and received his B.S. degree in chemistry from Datong University (P. R. of China) in 2014. He then joined the Bi group at the Northeast Normal University (P. R. of China) as a Master's student. His research interest concerns silver-catalyzed transfer reactions of carbenes.

Dr. P. Liao

Peiqiu Liao received her B.S. degree in 2001 from Wuhan University (P. R. of China). In 2008, she received her Ph.D. from Changchun Institute of Applied Chemistry, Chinese Academy of Science (P. R. of China). Then, she joined the Bi group at Northeast Normal University (P. R. of China) as an Engineer in 2008 and became a Senior Engineer in 2012. Her current research interest concerns transition-metal-catalyzed annulation reactions.

Prof. X. Bi

Xihe Bi obtained his Ph.D. in 2006 from Northeast Normal University (P. R. of China). He then joined the group of Professor Michael Famulok at University of Bonn (Germany) as an Alexander von Humboldt Research Fellow. At the end of 2008, he started his independent research at Northeast Normal University. Professor Bi's research team mainly focuses on silver catalysis in organic synthesis. He has received honors and awards including the Young Scholar of the Changjiang Scholars Program of China (2016), the NSFC Foundation for Excellent Young Scientist (2015), the Thieme Chemistry Journals Award (2014), and the Alexander von Humboldt Research Fellowship (2006).

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