

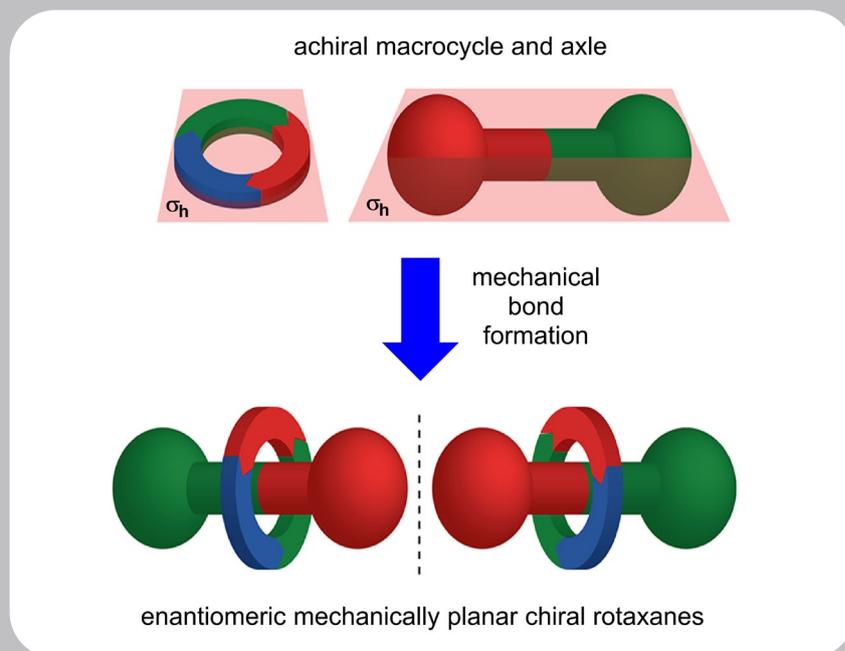
# Synform

People, Trends and Views in Chemical Synthesis

2020/08

## Synthesis of a Mechanically Planar Chiral Rotaxane Ligand for Enantioselective Catalysis

Highlighted article by A. W. Heard, S. M. Goldup



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## Dear Readers,

Exactly one year ago my Editorial for the August 2019 issue of SYNFORM was centered on the Spring American Chemical Society National Meeting & Exposition held in Orlando, FL, USA, from March 31 through April 4, 2019, which I attended sponsored by Thieme Chemistry. This year not just the ACS Meetings but almost every conference on this planet has gone virtual, including the Thieme Chemistry Editorial Board Meeting 2020 – which is better than no meeting at all, but – oh my goodness – I am missing so much the real thing... I am not saying you can't do useful stuff on videoconference – actually if it wasn't for these invaluable online tools we would have all been doomed during the lockdown – but it's only a pale mimic of an actual meeting, an ectoplasm of real life. I have never been a lover of crowds, but I cannot even explain how much I am craving a good old-style meeting with real people, in person, possibly without those life-saving – but nevertheless cumbersome – face masks... Meanwhile, I am afraid my only consolation is to look at the mask-free pictures of this issue's authors... and enjoy the great science tales they are telling, of course! Starting with the amazing molecular machines developed by S. Goldup (UK) and continuing with the informative Young Career Focus interview with S. G. Modha (India). The next article covers a new catalytic process for the efficient chlorination of (hetero)arenes published by N. Jiao (P. R. China), while the closing article explores the three-component aminomethylation of  $\alpha$ -diazo ketones developed by D. Xing and W. Hu (P. R. China).

Stay safe and enjoy your reading!!



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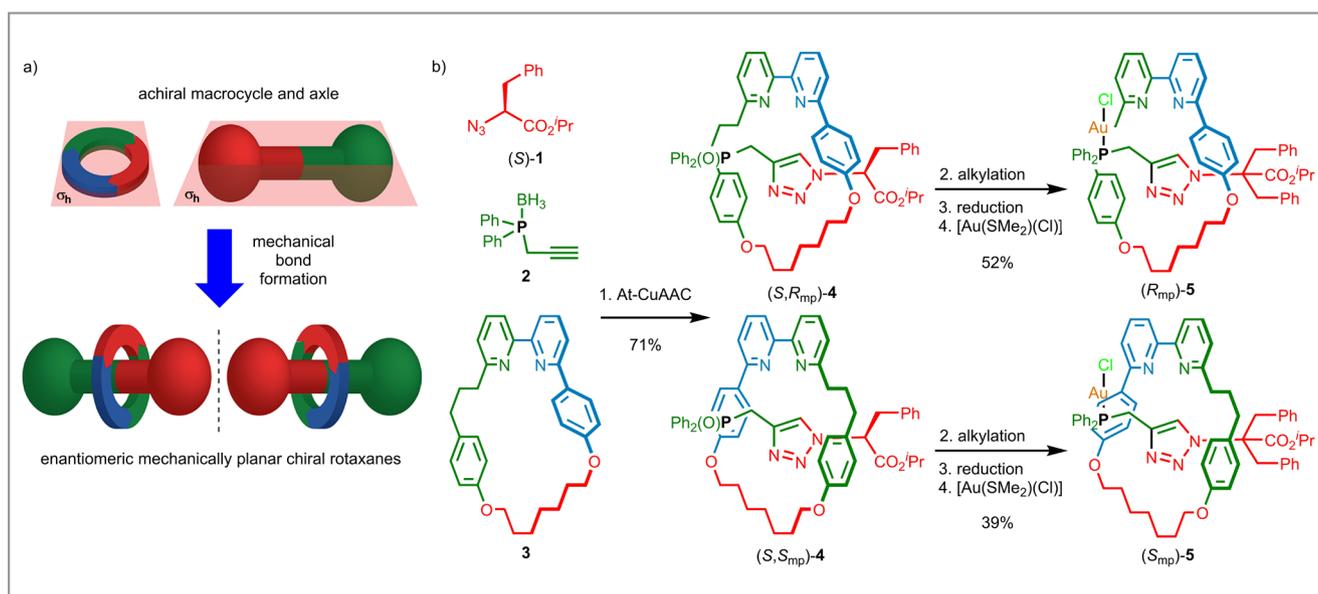
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# Synthesis of a Mechanically Planar Chiral Rotaxane Ligand for Enantioselective Catalysis

*Chem* 2020, 6, 994–1006

Rotaxanes are interlocked molecules in which a molecular ring is threaded onto a dumbbell-shaped axle which bears end groups too large to fit through the cavity of the ring.<sup>1</sup> Professor Steve Goldup from the University of Southampton (UK) explained: “This arrangement prevents the ring and axle from separating without a covalent bond being broken and so, even though there is no covalent bond between the ring and the axle, rotaxanes are molecular rather than supramolecular species. Rotaxanes are most famous as components of molecular machines,<sup>2</sup> which function by exploiting the controlled movement of the ring along the axle. However, there is a growing interest in how the chemical properties of rotaxanes, and other interlocked molecules, can be exploited to solve chemical problems, for example in catalysis,<sup>3</sup> sensing,<sup>4</sup> materials science<sup>5</sup> and medicinal chemistry.”<sup>6</sup> As part of a research project focused on investigating the unusual stereochemical properties of interlocked molecules, Professor Steve Goldup and postgraduate student Andrew Heard developed a rotaxane-based gold complex that carries out an enantioselective cyclopropanation reaction.

Rotaxanes have the unusual property that they can exhibit molecular chirality even if the ring and axle are achiral (Scheme 1, a).<sup>7</sup> Professor Goldup explained that this was first discussed over 50 years ago,<sup>8</sup> but until very recently it was extremely hard to make large quantities of such “mechanically planar chiral” rotaxanes as there were no methods that did not require HPLC separation of the enantiomers. In previous work, the Goldup research group took the first steps towards solving this problem by developing methods in which a covalent chiral auxiliary is included in the synthesis to allow the stereoisomers to be separated<sup>9</sup> and even direct the stereoselective formation of the mechanical bond.<sup>10</sup> Professor Goldup said: “We’ve been pushing hard to develop ways to make mechanically chiral rotaxanes for almost 10 years. In parallel, we have been investigating the use of rotaxanes as ligands in homogeneous catalysis. In this project, we brought these two ideas together to investigate whether a mechanically planar chiral rotaxane could provide a chiral environment for a gold-mediated reaction in order to generate the products enantioselectively.”

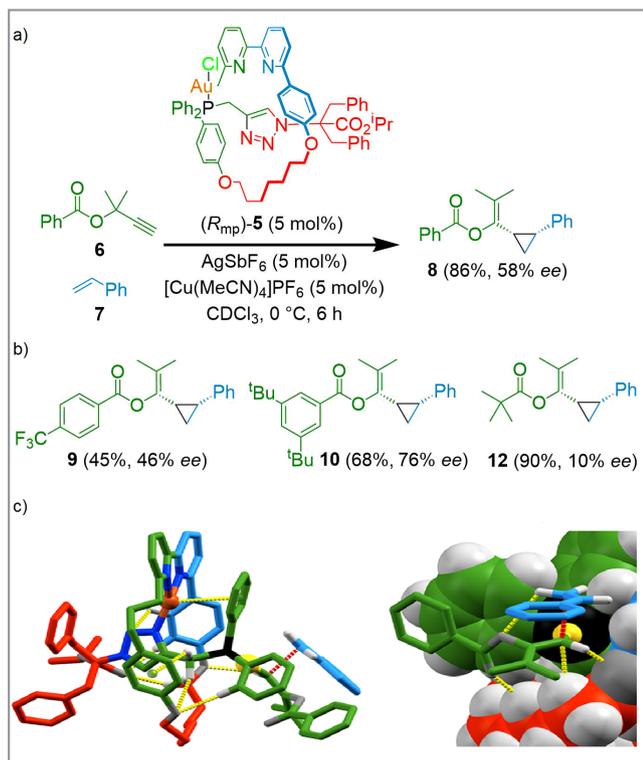


To make rotaxane-based gold complexes **5**, Andrew Heard used an active template copper-mediated alkyne–azide cycloaddition reaction (Scheme 1, b).<sup>11</sup> “In this reaction, a Cu<sup>I</sup> ion bound in the cavity of a bipyridine macrocycle (**3**) mediates the reaction of the alkyne (**2**) and azide ([S]-**1**) half-axles. Because the Cu<sup>I</sup> ion is held in the cavity of the ring, the new bonds, and thus the new axle, are formed through the ring. The key feature of the synthesis is that azide half-axle (S)-**1** is chiral and enantiopure and so the product rotaxane can be formed as two diastereomers (S,S<sub>mp</sub>)-**4** and (S,R<sub>mp</sub>)-**4** (mp refers to the mechanically planar chiral stereogenic unit) that differ only in the orientation of the ring on the axle,” said Andrew Heard, adding: “This was the hardest part of the project. Even though previous work in our group suggested one of the stereoisomers would be formed preferentially, I observed very little diastereoselectivity. Worse, the covalent stereocentre could be epimerised very easily. Ultimately, I was able to separate the diastereomers using silica gel chromatography, but I had to pre-saturate the column eluent with water to avoid epimerising the products and work quickly. It was an exciting day when I saw the HPLC analysis of my products that confirmed they were separated with excellent stereochemical purity and that my procedure was reproducible!” With the rotaxane diastereomers separated, the synthesis was completed by alkylation of the covalent stereocentre to give the separated rotaxane enantiomers, reduction of the phosphine oxide to give the gold-binding phosphine ligand, and coordination of AuCl to give pre-catalysts (R<sub>mp</sub>)-**5** and (S<sub>mp</sub>)-**5** in 98% *ee*.

“With pre-catalysts **5** in hand, Andrew then investigated whether they could be used in an Au-mediated cyclopropanation reaction first developed by Toste and co-workers (Scheme 2, a).<sup>12</sup> I’m often asked why we focused on this particular reaction. As with many things in research, it is partly by design and partly by chance,” said Professor Goldup. He continued: “It is often hard to impose stereocontrol in gold-catalysed reactions because the ligand and bound substrate are disposed at 180° to one another around the gold ion.<sup>13</sup> A number of years ago I was interested in the effect of the mechanical bond on the diastereoselectivity of Au-mediated reactions; the mechanical bond creates a very crowded three-dimensional space in which the Au<sup>I</sup> ion can be embedded and this might help solve the problem. Marzia Galli, a new PhD student in my group at the time, suggested this cyclopropanation reaction for her study because the products are formed as a mixture of *cis*- and *trans*-isomers. Because this reaction was so successful in our previous study,<sup>14</sup> we decided to investigate whether chiral rotaxane complex **5** could carry out the cyclopropanation reaction enantioselectively.” Excitingly, the first experiments with (R)-**5** led to the formation of cyclopropane **8**

in reasonable enantioselectivity and yield. “Our reaction conditions are similar to those reported by Toste and co-workers, except we include a Cu<sup>I</sup> additive which binds into the cavity of the bipyridine ring and prevents the bipyridine binding to the Au<sup>I</sup> ion and inhibiting the reaction,” explained Professor Goldup. He remarked: “We have of course checked and the Cu<sup>I</sup> salt itself is not a catalyst for the reaction!” Importantly, when the opposite hand of the complex, (S)-**5**, was used, the opposite enantiomer of **8** was formed as the major product. “That was a relief, as it reassured me that the enantioselectivity was due to the configuration of the mechanical bond rather than an adventitious chiral impurity left over from the synthesis,” said Andrew. Having demonstrated that (R)-**5** can act as an enantioselective catalyst for the reaction to produce **8**, the study was then expanded to other substrates (Scheme 2, b). Andrew Heard said: “The substrate scope didn’t tell us much more than that the catalyst is relatively general for propargylic benzoates, which is obviously nice. The high point of this part of the study was that by putting bulky substituents on the benzene ring of the substrate, we could enhance the enantioselectivity of the reaction to generate cyclopropane **10** in 76% *ee*. The low point was finding out that pivaloyl esters are not tolerated by the catalyst; these substrates gave higher enantioselectivities with Toste’s catalysts and we were hoping we would see the same but cyclopropane **12** was produced as a near-racemate. Nevertheless, comparing like-for-like, rotaxane-based complex (R)-**5** gives comparable enantioselectivity to chiral covalent catalysts reported for the same reaction.”

Goldup and Heard completed their study by carrying out computational modelling to try and provide some insight into how the structure of **5** led to the observed enantioselectivity. Professor Goldup said: “I am always very careful about how I describe this part of the study when I give lectures. Rotaxane **5** is relatively large and flexible, and this means that modelling its catalytic behaviour with a high degree of rigour is very hard and would be a significant project in its own right. The modelling we have done is very preliminary, as we make clear in the paper. It was only designed to probe the kind of interactions that may be occurring between the ligand framework and the substrate to impart stereocontrol on the reaction and provide a visual representation of how the mechanical bond can create a chiral environment for the reaction to take place within.” The modelling found that the substrate and ligand framework can interact by weak Cu–π, CH–π and C–H hydrogen bonds and that the mechanical bond can indeed create a crowded, chiral environment around the substrate (Scheme 2, c). “Given the relative simplicity of our approach, the modelling and experimental data agree remarkably well but this has to be interpreted carefully,” said Professor Goldup. “That

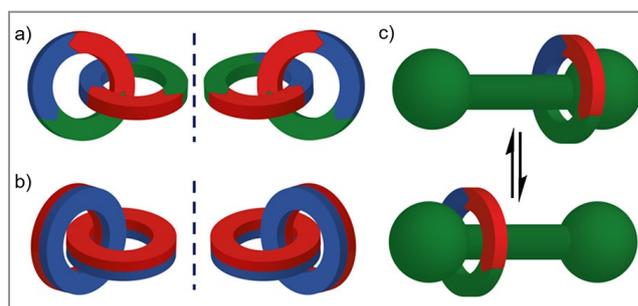


**Scheme 2** a) Enantioselective reaction of propargylic ester **6** with styrene (**7**) mediated by (R<sub>mp</sub>)-**5** to give cyclopropane **8** in 58% ee. b) Examples of substrates examined. c) Modelled (stick representation, left; spacefilling representation, right) transition state for the reaction leading to observed major enantiomer of **8** with selected intercomponent interactions highlighted.

said, our initial results suggest that modelling these kinds of complex systems is definitely possible.”

Professor Goldup and his group are excited about the future of rotaxanes and other interlocked molecules as catalysts. Andrew Heard said: “Although the synthesis was challenging in this case, our methods are improving all the time. In fact, testing them in new, challenging scenarios has driven a lot of our recent progress in this area. Now we have demonstrated that chiral mechanical bonds are useful, we are even more motivated to make functionalised systems readily available.” The Goldup group are now expanding their studies to investigate the effect of rotaxane structure on enantioselectivity in the gold-mediated cyclopropanation reaction, as well as investigating other catalytic systems. They are also looking at other applications of mechanically planar chiral rotaxanes in sensing and materials chemistry. “Mechanically planar chiral rotaxanes aren’t the only type of interlocked molecule in which the mechanical bond provides the only source of

stereochemistry,” explained Professor Goldup (Figure 1).<sup>7</sup> “Catenanes can display topological and axial chirality, and there are intriguing forms of dynamic stereochemistry that arise as a result of the motion of the two components. Although there are some interesting preliminary data,<sup>15,16</sup> along with mechanical planar chirality, the applications of these chiral molecules have yet to be investigated properly because they have been too hard to make. We have already developed ways to make topologically chiral catenanes<sup>17</sup> and are working on some of the other classes now. In conclusion, our aim is to find what mechanically chiral molecules are useful for and, in particular, what problems they can solve that are hard or impossible to solve in other ways at present.”



**Figure 1** Other examples of mechanically chiral molecules include the enantiomers of: a) topologically chiral catenanes, b) axially chiral catenanes, and c) co-conformationally mechanically planar chiral rotaxanes.

*Mattias Fankle*

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### About the authors



A. Heard

**Andrew Heard** studied for his MChem under Prof. Andrew Dove at the University of Warwick (UK) and began his PhD in the Goldup group in 2017 studying applications of mechanically planar chiral molecules.



Prof. S. Goldup

**Stephen Goldup** studied for his MChem at the University of Oxford (UK), supervised by Prof. Sir Jack Baldwin and undertook his PhD at Imperial College (UK), supervised by Prof. Tony Barrett before completing his PDRA at the University of Edinburgh (UK) with Prof. David Leigh. In 2008 he began his independent career at Queen Mary, University of London (UK), first as a Leverhulme Trust Early Career Fellow and then Royal Society Fellow and Senior Lecturer. In 2014 the Goldup group moved to the University of Southampton (UK) where Steve works with an outstanding group of young scientists developing methods for the synthesis of challenging chiral interlocked molecules with catalytic, materials and sensing applications. In 2017 Steve was promoted to Professor and as of 2019 is a Royal Society Wolfson Research Fellow.

## Young Career Focus: Dr. Sachinkumar G. Modha (Uka Tarsadia University, India)

**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. Sachinkumar G. Modha (Uka Tarsadia University, India).

### Biographical Sketch



Dr. S. G. Modha

**Sachinkumar G. Modha** obtained his M.Sc. (organopharmaceutical chemistry) from Saurashtra University, Rajkot, Gujarat (India). He then worked in an organization named Oxygen Healthcare Research Pvt. Ltd. (Contract Research Organization), Ahmedabad, Gujarat (India) for 15 months. After his short stay in the group of Prof. Anamik K. Shah at Saurashtra University he went to Belgium to pursue his doctoral studies at the University of Leuven (KU Leuven) under the supervision of Prof. Erik E. Van der Eycken. After completing his PhD in 2012, he went on to work at the University of Manchester (UK) under the supervision of Prof. Michael F. Greaney as a postdoctoral research associate. In 2016, Sachin obtained the prestigious Alexander von Humboldt postdoctoral fellowship to work with Prof. Thorsten Bach at the Technical University of Munich (Germany), where his stay was extended by one year. He took up a position at Uka Tarsadia University, Bardoli, Gujarat (India) in 2019 as assistant professor.

### INTERVIEW

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

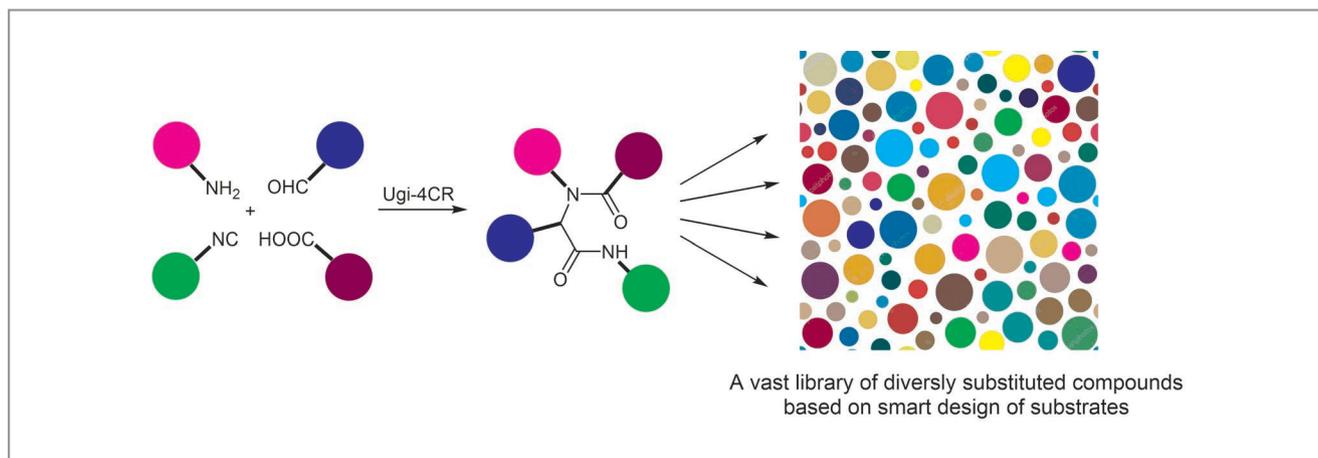
**Dr. S. G. Modha** I am fascinated by photochemistry. Harnessing the energy from electromagnetic irradiation and using it for chemical transformations that are difficult, if not impossible, to achieve otherwise, is exciting and challenging at the same time. Lots of progress has been seen in the broad field of photochemistry over the last few decades, but still many unanswered questions remain, which motivates me to contribute in this field. At the same time, I am also interested in the development of new atom-economical routes towards interesting organic molecules. In particular, I like multicomponent reactions (general concept shown in Scheme 1) and reactions at room temperature and thus some of my efforts are focused on developing new reactions towards this goal.

**SYNFORM** *When did you get interested in synthesis?*

**Dr. S. G. Modha** After completion of my postgraduate studies, I worked in a Contract Research Organization for 15 months. Different projects with reactions of scale as small as 10 mg and as big as 1.4 kg fascinated me. In particular, the idea of synthesizing a molecule which has never been synthesized before gave me goose bumps! Thus, I would say I became interested in synthesis during my work in the industry in 2006–2007.

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

**Dr. S. G. Modha** Chemistry is divided into more sub-fields than ever before and thus this question is more relevant than ever. As an organic chemist I believe that the time is gone when one could just synthesize new molecules and be happy



with that. One must realize that new molecules without any applications are as good as nothing. On the other hand, if one needs organic molecules, he/she has to go to organic synthesis, and thus demand for organic chemistry is never diminishing. The ever-increasing need for new and better antibiotics to fight multi-drug resistance is one of the most pressing issues suggesting the modern role of organic synthesis to be of high importance. Under the current scenario of COVID-19, I think people and governments alike have understood the importance of science. Hopefully this unfortunate experience will make them realize that funding science should be of highest priority and if that happens then prospects of organic synthesis and science in general are brighter.

**SYNFORM** *Could you tell us more about your group's areas of research and your aims?*

**Dr. S. G. Modha** My group's area of research is mainly development of new and improved atom-economical routes under mild reaction conditions. In particular, combination of multicomponent reactions with other atom-economical and sustainable reactions is the broad theme of my group's research. My aim is to open my students towards vast possibilities that organic chemistry brings and how they can contribute to society by developing new and improved chemical reactions. As our knowledge of chemistry and science in general is expanding with each passing day, I aim towards designing alternate reaction pathways which are atom-economical and sustainable for some organic reactions that do not fit into these categories right now.

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

**Dr. S. G. Modha** Diaryliodonium reagents have been known since 1894, but there were no reports till 2015 wherein both aryls of this reagent were utilized in an organic transformation. As a post-doctoral researcher at School of Chemistry, University of Manchester (UK), I took up this challenge and successfully developed the first pathway towards atom-economical use of diaryliodonium reagents. We reported sequential C- and N-arylation of indole via copper catalysis using just one equivalent of the iodonium reagent (*J. Am. Chem. Soc.* **2015**, *137*, 1416–1419). The most interesting part of this research was that we could utilize an unsymmetrical diaryliodonium reagent and could do selective C- and N-arylation with high selectivity.

*Dr. S. G. Modha*

## DMSO-Catalyzed Late-Stage Chlorination of (Hetero)arenes

*Nat. Catal.* **2020**, *3*, 107–115

Chlorinated (hetero)arenes are widely used in organic synthesis and in pharmaceuticals. Professor Ning Jiao – an organic synthesis expert at Peking University (P. R. of China) – pointed out that Pfizer systematically screened more than 220,000 aryl derivatives and found that aromatic chlorination may change the physicochemical properties of drugs, such as  $pK_a$ , dipole moment, as well as metabolic rate, therefore improving pharmacokinetic and pharmacological properties (*Drug Metab. Lett.* **2011**, *5*, 232–242). “As the Nobel Laureate James Black stated, ‘the most fruitful basis for the discovery of a new drug is to start with an old drug’ (*Lancet* **2000**, *355*, 1022), therefore, late-stage chlorination may provide a reliable shortcut for the discovery of new drugs,” said Professor Jiao. Although some elegant chlorination reactions have been developed these protocols suffer from either the high cost of the chlorinating reagents or harsh conditions. “Therefore, the efficient and practical late-stage chlorination of bioactive molecules remains formidably challenging,” he added.

Previously, Professor Jiao’s group had developed the HX/DMSO (X = Br, I) system for late-stage aromatic bromination and iodination of bioactive molecules, in which DMSO acted as a mild oxidant (*Org. Lett.* **2015**, *17*, 2886–2889). “The mild reaction conditions and operational simplicity make this method very attractive. Since its publication, the HX/DMSO halogenation system has been widely applied in total synthesis of natural products, halogenation of heteroarenes, and modification of bioactive molecules,” remarked Professor Jiao. He continued: “After bromination and iodination, we investigated the oxidative chlorination of arenes with the HCl/DMSO system; unfortunately, the efficiency was very low because the electrode potential of  $Cl^+/Cl^-$  is higher than that of  $Br^+/Br^-$ .” The failure of this oxidative approach motivated the group to develop other strategies that could lead to a mild and efficient late-stage chlorination of arenes.

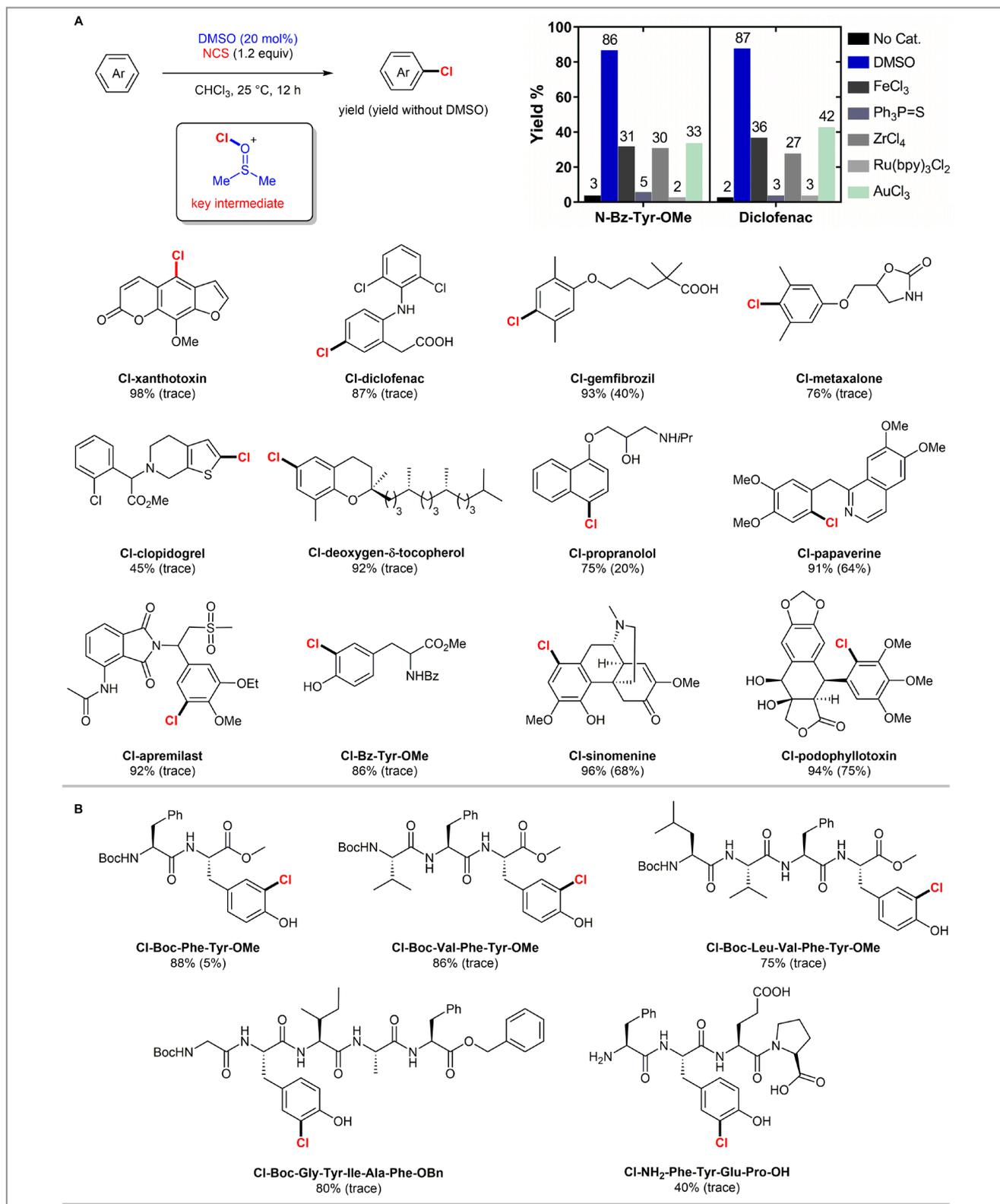
During the study of aromatic bromination with HBr/DMSO, Professor Jiao’s group found that the reaction rate increased if there was a slight excess of DMSO relative to HBr. “Since HBr is oxidized to bromonium ion *in situ*, we speculated that a suitable amount of DMSO may promote the halogenation. We reasoned that if that was actually the case, DMSO may be used as a Lewis base to catalyze the challenging chlorination,” explained Professor Jiao. With the goal of proving this hypothesis, the group tested the chlorination of arenes with commercially available NCS as the chlorine source. “At the beginning of this study, the chlorination was performed

with DMSO as the solvent,” Professor Jiao said. “Unfortunately, only trace amounts of chlorination product were detected. Surprisingly, the chlorination of xanthotoxin, a natural product extracted from *Ammi majus* plant, afforded the product in 90% yield with 20 mol% of DMSO as the catalyst. Then, we achieved the late-stage chlorination of drugs and natural products (Scheme 1, A).” Gratifyingly, the group found that many functional groups, including –OH and –NH<sub>2</sub>, could be perfectly tolerated in this system. These experiments indicated that the reactivity of NCS was strongly improved by DMSO, which made the chlorination possible. Moreover, the newly discovered DMSO catalysis was compared to some other reported Lewis acid and Lewis base promoted catalytic approaches. “For the chlorination of single amino acid N-Bz-Tyr-OMe and approved drug diclofenac, low efficiencies were obtained with other catalysts including Ph<sub>3</sub>P=S, FeCl<sub>3</sub>, ZrCl<sub>4</sub>, AuCl<sub>3</sub> and Ru(bpy)<sub>3</sub>Cl<sub>2</sub>, respectively,” noted Professor Jiao. He continued: “Conversely, these experiments revealed that DMSO catalysis featured high efficiency and good functional-group tolerance. In addition, this DMSO/NCS chlorination system performed very well on a multi-gram scale. Naproxen, gemfibrozil, and indole substrates were chlorinated in high yields, which shows great potential for industrial applications (up to 54.5 g).”

Professor Jiao noted that chemical modification of peptides or proteins has emerged as an invaluable tool in biochemistry (*Chem. Rev.* **2015**, *115*, 2174–2195). “Tyrosine is essential in proteins and many peptide drugs such as alarelin and oxytocin,” he explained. “Importantly, a series of structurally diverse peptides with tyrosine residue could also be chlorinated efficiently by this novel DMSO catalytic protocol (Scheme 1, B). It is noteworthy that most of the chlorination reactions did not perform well in the absence of DMSO.” This chemistry provides a practical synthetic protocol and shows great potential in biological applications, as well as in drug discovery and development, which also opens an avenue for further exploration and utilization of DMSO in organic synthesis.

Professor Jiao concluded: “An efficient late-stage chlorination of complex natural products, drugs, and peptides has been developed by our group. The very common and humble DMSO was disclosed as an efficient Lewis base catalyst. The strong polarization of DMSO makes the activation of chlorination possible, thus enabling the chlorination process. Accordingly, our mechanistic studies revealed that the active DMSO-Cl<sup>+</sup> was the key intermediate of this protocol.”

*Matteo Fanello*



**Scheme 1** (A) Selected examples of DMSO-catalyzed late-stage chlorination. (B) Late-stage chlorination of peptides.

## About the authors



From left: S. Song, W. Wang, J. Wei, Y. Zhu, X. Shi, X. Zhang, N. Jiao

**Song Song** was born in Jiangsu, P. R. of China, in 1985. He received his B.Sc. degree in chemistry from Nankai University (P. R. of China) in 2007. He received his Ph.D. under the supervision of Prof. Qi-Lin Zhou at Nankai University in 2012 and then continued to work as a research assistant. His research area was asymmetric hydrogenation of unsaturated carboxylic acids. In 2013, he conducted his postdoc with Prof. Ning Jiao at Peking University (P. R. of China). From 2015, he worked at School of Pharmaceutical Sciences in Peking University, and from 2018 to the present, he has been an assistant professor. His research interests mainly focus on development of green methodologies for halogenation and thiolation.

**Xinyao Li** was born in Zhejiang, P. R. of China, in 1988. He studied organic chemistry under the supervision of Prof. Jiayi Xu during his B.Sc. and M.Sc. at Beijing University of Chemical Technology (P. R. of China). He received his Ph.D. under the supervision of Prof. Ning Jiao at School of Pharmaceutical Sciences in Peking University (P. R. of China) in 2016 and then continued to work as a research assistant. In 2017, he was awarded a Humboldt Research Fellowship and conducted his postdoc with Prof. Thorsten Bach at the Technical University of Munich (Germany). His research interests mainly lie in transition-metal catalysis, radical chemistry, enantioselective photochemistry and DFT calculations for mechanistic studies.

**Weijin Wang** was born in Yunnan, P. R. of China, in 1998. He is currently a fourth-year undergraduate student at School of Pharmaceutical Sciences, Peking University (P. R. of China). Under the supervision of Prof. Ning Jiao, his research interests focus on developing green and efficient halogenation methodologies.

**Jialiang Wei** was born in Hebei province, P. R. of China. He received his B.Sc. in macromolecular materials and engineering in 2016 from Sun Yat-sen University (P. R. of China). From 2013 to 2016, he was a member of the national “Top-Notch Undergraduate Program for Pure Science” under the supervision of Prof. Xiaodan Zhao doing research on organoselenium/sulfur catalysis. Currently, he is a Ph.D. candidate in Prof. Ning Jiao’s group in Peking University (P. R. of China). His current research interests focus on the design and synthesis of novel and efficient catalysts for aerobic oxidation.

**Yiqun Zhang** was born in Tianjin, P. R. of China, in 1993. He studied aerobic oxidative dehydrogenative coupling under the supervision of Prof. Ning Jiao and Prof. Song Song during his B.Sc. and M.Sc. at Peking University (P. R. of China). In 2018, he moved to the Chinese University of Hong Kong (P. R. of China) and worked as a Ph.D. candidate under the supervision of Prof. Qian Miao. Now his research interest is covalent and non-covalent organic network construction based on negatively curved nanographene.

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**Xiaomeng Shi** received her Bachelor’s degree in chemistry from Peking University (P. R. of China) in 2004. Then she went to Boston College in Boston, MA, USA and graduated with a PhD from Prof. Mary Roberts’ lab in the field of mass spectrometry and protein science. After graduation, Xiaomeng worked in Northeastern University, Barnett Institute for Chemical & Biological Analysis (USA) as a postdoctoral research associate with Prof. John Engen. After two years of work experience in Tsinghua University (P. R. of China), Xiaomeng now is working as an associate research fellow in the State Key Laboratory of Natural and Biomimetic Drugs, Peking University. Her major research

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**Xiaohui Zhang** was born in Henan, P. R. of China, in 1990. He studied analytical chemistry under the supervision of Prof. Xinxiang Zhang during his BSc and PhD at Peking University (P. R. of China), mainly researching on capillary electrophoresis and tumor metabolism. Since 2018, he has been technologist-in-charge at State Key Laboratory of Natural and Biomimetic Drugs at Peking University. He is responsible for the daily operation of the mass spectrometry platform and protein sample analysis.

**Ning Jiao** was born in Shandong, P. R. of China, in 1976. He received his B.Sc. degree at Shandong University (P. R. of Chi-

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## Enantioselective Three-Component Aminomethylation of $\alpha$ -Diazo Ketones with Alcohols and 1,3,5-Triazines

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$\beta$ -Amino carbonyl moieties are versatile synthetic building blocks that can be employed toward a wide variety of natural products and biologically active compounds. As an important research branch of the Mannich reaction, the aminomethylation reaction of ketones or aldehydes represents an efficient protocol for accessing  $\beta$ -amino carbonyl compounds. "Recent years have witnessed the application of a variety of aminomethylation reagents to the enantioselective variant of the reaction; however, asymmetric induction of these transformations is dominated by the use of chiral catalysts to activate the nucleophiles, i.e. chiral amines or Lewis acids with chiral ligands," said Professor Dong Xing from East China Normal University (P. R. of China), adding: "While this nucleophile-based activating strategy was feasible and showed good enantiocontrol, the nucleophiles were limited to inherently activated substrates such as unmodified ketones or 1,3-dicarbonyl compounds, thus the scope and application of this type of transformation were also significantly limited (Scheme 1, a)."

The groups of Professor Xing and Professor Wenhao Hu (Sun Yat-sen University, P. R. of China) have a long-standing common research interest in carbene-involved enantioselective multicomponent reactions (MCRs) via cooperative catalysis. "As part of our ongoing research, we designed the rhodium(II)/chiral phosphoric acid (CPA) co-catalysed three-component reaction of  $\alpha$ -diazo ketone, alcohol and 1,3,5-triaryl-1,3,5-triazine, with the hope that an electrophile activation strategy would be established (Scheme 1, b)," said Professor Hu, continuing: "However, due to the instability and low concentration properties of the formaldimine species generated in situ from 1,3,5-triazine, it remains uncertain whether such an electrophile activation mode is workable."

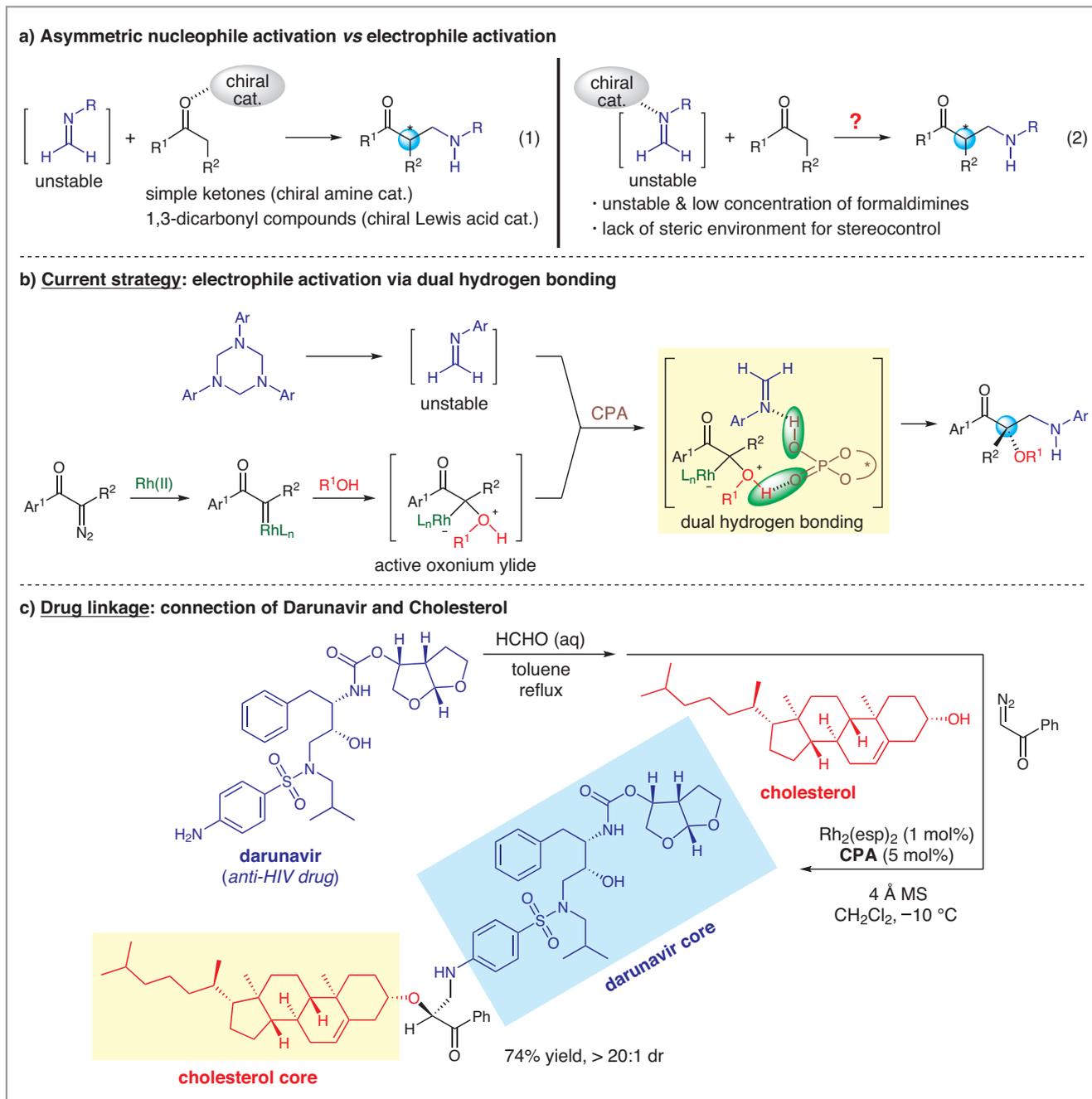
At the very beginning of their exploration, tremendous efforts were made to modify the reaction conditions with different  $\alpha$ -carbonyl diazo compounds as the carbene precursor. "It finally turned out that the structure of the diazo compound has a significant impact on the outcome of the reaction," explained Professor Xing. He added: "We continually noticed that the structure of both the CPA and the rhodium(II) catalyst are both responsible for the stereoselective control of this transformation."

With the established optimized reaction conditions, a wide range of alcohols, including simple aliphatic alcohols,

allylic alcohol, propargyl alcohol, complex natural alcohols, and even water could all be applied to this three-component aminomethylation. "It is also impressive that this method can be used for the efficient linkage of two complicated drug candidates (Scheme 1, c)," said Professor Xing.

Professor Hu concluded: "This work offers an efficient electrophile-based asymmetric activation for aminomethylation with unstable formaldimine species. Further efforts to apply this protocol to the trapping of other types of active intermediates are ongoing in our labs."





**Scheme 1** The electrophile-based asymmetric aminomethylation and its drug linkage application.

## About the authors



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**Wenhao Hu** received a B.S. in chemistry from Sichuan University (P. R. of China, 1987), M.S. from Chengdu Institute of Organic Chemistry, Chinese Academy of Sciences (P. R. of China, 1990), and Ph.D. from Hong Kong Polytechnic University (P. R. of China) with Professor Albert S. C. Chan (1998). He became a postdoctoral fellow at the University of Arizona (USA) with Professor Michael P. Doyle. In 2002–2006, he worked as a

medicinal chemist at Genesoft in South San Francisco (USA) and a process chemist at Bristol-Myers Squibb in New Jersey (USA). In 2006 he joined East China Normal University (P. R. of China) as a professor of Chemistry, and the head of Shanghai Engineering Research Center of Molecular Therapeutics and New Drug Development. In 2016, he moved to Sun Yat-sen University (P. R. of China) as the head of School of Pharmaceutical Science. He received National Natural Science Funds for Distinguished Young Scholar (2011). His research interests include synthetic methodology, MCRs, and medicinal and process chemistry.



Prof. D. Xing

**Dong Xing** received his B.S. and M.S. degrees from East China Normal University (P. R. of China, 2003) and his Ph.D. from the University of Hong Kong (P. R. of China) with Professor Dan Yang in 2011. He then joined the School of Chemistry and Molecular Engineering at East China Normal University as an assistant professor and Chenhui Scholar. He was then promoted to associate professor in 2015. In 2016, he began his postdoctoral

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## Coming soon

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