

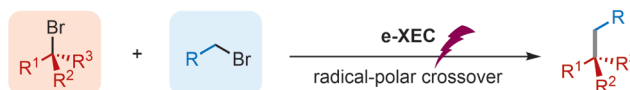
Synform

People, Trends and Views in Chemical Synthesis

2022/09

Electrochemically Driven Cross-Electrophile Coupling of Alkyl Halides

Highlighted article by W. Zhang, L. Lu, W. Zhang, Y. Wang, S. D. Ware, J. Mondragon, J. Rein, N. Strotman, D. Lehnherr, K. A. See, S. Lin



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marketing@thieme-chemistry.com

Dear Readers,

Here I am, in this torrid summer, writing this sweaty editorial, hundreds of miles away from the nearest beach. Right now, at 2 pm, the outside temperature is 37 °C in Milan. We've had virtually no rain in the past 3 or 4 months, rivers are nearly dry, grass is canary yellow, and the feeling of a looming environmental catastrophe is becoming stronger by the day. I can barely remember anything like this, with the exception of the extraordinarily hot summer of 2003, which I will never forget. We had zero snow this winter, which sadly has become the norm even where I live, nearby the Alps. I am seeing – and feeling – new and very thirsty species of mosquitos, which I suspect used to live at much southern latitudes not long ago, but seem to be very happy here now, and really fond of my blood. So, even judging from my very narrow personal experience in this summer of 2022, it is not too hard to believe that our future is not looking good, unless we drastically change the course of our selfish and short-sighted lifestyle, which is wrecking the only place where we can live. Luckily, the younger generations seem to be more sensitive towards environmental issues and will probably do less damage than us, hopefully even managing to U-turn away from the global warming cliff, although that is honestly quite hard to believe. Perhaps the best way to feel less heat is to focus on something else, so let's move on – without forgetting all the environmental gloom and doom, though. Let's switch to something way more positive then, namely the September 2022 issue of SYNFORM. The opening article is a Young Career Focus interview with A. Nowak-Król (Germany) about her goals and interests in research, which include organoboron chemistry. The next Literature Coverage article reports on a *Nature* paper stemming from a collaboration between the groups of S. Lin, K. A. See and the Merck company (USA) on a ground-breaking electrochemical approach to achieve the cross-electrophile coupling of two alkyl halides, leading to the forma-

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tion of a new C–C bond. The third article covers a novel methodology for the gold-promoted 1,2-oxyarylation and 1,2-aminoarylation of suitably functionalized alkenes, which occurs enantioselectively and with concomitant cyclization in the presence of alcohols or amines, as reported in *J. Am. Chem. Soc.* by the group of N. Patil (India). *Dulcis in fundo*, SYNFORM is proud to host another Nobel prize Laureate – Professor Benjamin List (Germany) – with his group's impressive *Nature* paper on the organocatalytic asymmetric cyanosilylation of small ketones, which took advantage of a key collaboration with the group of G.-J. Cheng (P. R. of China).

Enjoy your reading, despite the heat!!



Contact

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

Young Career Focus: Prof. Agnieszka Nowak-Król (Universität Würzburg, Germany)

Background and Purpose. SYNFORM regularly meets young up-and-coming researchers who are performing exceptionally well in the arena of organic chemistry and related fields of research, in order to introduce them to the readership. This Young Career Focus presents Prof. Agnieszka Nowak-Król (Universität Würzburg, Germany).

Biographical Sketch



Prof. A. Nowak-Król

Agnieszka Nowak-Król is a Junior Professor and an Emmy Noether group leader at the Institute of Inorganic Chemistry and the Institute for Sustainable Chemistry & Catalysis with Boron of the University of Würzburg (Germany). Agnieszka graduated with honors from the Rzeszów University of Technology in Poland. She earned her doctorate at the Polish Academy of Sciences in Warsaw (Poland) with Prof. Daniel Gryko in 2013 and continued her career as an Alexander von Humboldt postdoctoral fellow with Prof. Frank Würthner at the University of Würzburg in Germany. In 2016, she started her independent career as a group leader at the Center for Nanosystems Chemistry (Germany). In 2019, she received the Emmy Noether fellowship to establish an independent research group. In 2020, she was appointed a Junior Professor at the University of Würzburg. Agnieszka is a recipient of several awards and honors including the Thieme Chemistry Journals Award, Hector Research Career Development Award 2020, Wojciech Świątosławski Prize, and Zonta Prize. She is a member of the Societas Humboldtiana Polonorum, Soltech, and the Polish Chemical Society. Her research lies at the interface of organic, inorganic and materials chemistry. Her current activities focus on achiral and helically chiral π -conjugated organoboron compounds, boron-containing polycyclic aromatic hydrocarbons, photoswitches, helicenes containing other main group elements and their applications in organic electronics and bioimaging.

INTERVIEW

SYNFORM What is the focus of your current research activity?

Prof. A. Nowak-Król Our current research focuses on functional π -conjugated organoboron compounds, particularly chiral derivatives such as azaborole helicenes. We introduce boron, an element with unique properties, into the core structure of single helicenes, helically elongated congeners, chiral photoswitches and boron-containing polycyclic aromatic hydrocarbons including single molecules with multiple helical subunits. Once introduced, these helically chiral azaboroles form an entirely new class of compound. So, we're intensively studying their optical, chiroptical and electronic properties alongside their stability and reactivity. We're interested in the applications of these compounds as luminescent emitters in circularly polarized organic light-emitting diodes (CP-OLEDs) and bioimaging or as charge- and spin-transport materials. Since our syntheses typically proceed via highly congested intermediates, the preparation of our target molecules can be quite challenging at times. Therefore, we devote a significant amount of our time to develop effective and efficient synthetic protocols, or strategies to access these novel helicenes in the first place. In general, we apply a modular approach where the product molecules are prepared in a stepwise fashion from small achiral building blocks (Figure 1a). This is a conceptually simple and powerful approach as it offers the possibility to prepare a large variety of molecules through a simple combination of different building blocks, limited only by the accessibility of key intermediates. This drives us to develop alternative synthetic routes to the currently accepted protocols and pushes our research forward.

SYNFORM When did you get interested in synthesis?

Prof. A. Nowak-Król Shortly after I started my undergraduate studies, I joined the lab of Dr. Grażyna Groszek, a synthetic chemist working on bioactive compounds and natural products from the Technical University of Rzeszów in Poland. This was before having had any official training in practical organic chemistry. During that time I spent each weekend, winter and even summer holidays in the synthetic lab developing my own individual project. Dr. Groszek had close connections to the Institute of Organic Chemistry (IChO) of the Polish Academy of Sciences in Warsaw, one of the top organic chemistry institutes in Poland, where she herself had finished her doctoral studies. We had frequent official and unofficial visits in the lab from the IChO and other institutes, allowing for plenty of opportunities to discuss various facets of chemistry. Such a stimulating atmosphere definitely fostered my interest in synthesis. Very quickly, pursuing my PhD at IChO became a dream of mine. Initially, I planned to work on total synthesis of natural products or purely synthetic methodology, but after meeting Prof. Daniel Gryko, a member of the IChO, at the annual Meeting of the Polish Chemical Society in 2007, my perspective and plans changed. This is how I entered the field of functional dyes, while still being an undergraduate student.

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

Prof. A. Nowak-Król While organic chemistry, with all its diversity, will always play a pivotal role in the development of new drugs and materials, it shouldn't be decoupled from other disciplines. Perhaps now, more than ever before, are the various branches of science so heavily interdependent. Therefore, it is essential to be open and draw as much as possible from recent achievements in engineering, physics and biology to support the progress in organic chemistry. Also, we observe a steady increase in molecular complexity; a prominent example can be seen in the design of new drugs. In an ideal scenario, this should be accompanied by an increased simplicity with regards to accessing these compounds. After all, the beauty lies in simplicity. To achieve this, we need improved synthetic strategies and new chemical reactions to shorten reaction routes, improve selectivity and avoid protecting groups, etc. I suppose computational tools may play an important role in the discovery of new chemical transformations, unexpected compound reactivity and unusual reaction sequences. Some research groups have indeed demonstrated the potential of computer-aided synthesis planning, but as always, whatever is predicted has to be experimentally verified by a well-trained synthetic chemist.

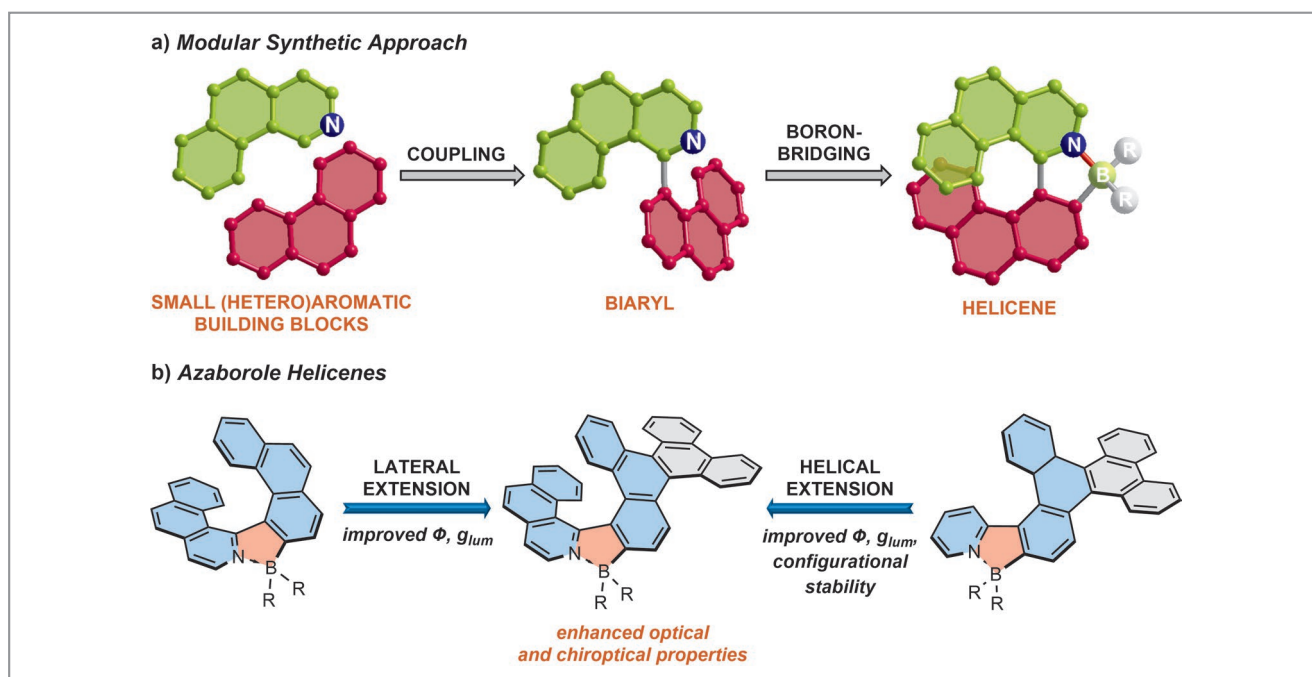


Figure 1 a) Modular synthetic approach for the synthesis of helically chiral compounds via boron-bridging. R = aryl, alkyl, halide. b) Molecular engineering of azaborole helicenes leading to improved physical and optical properties.

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

Prof. A. Nowak-Król Our research is interdisciplinary and incorporates elements of organic and inorganic chemistry, photophysical characterization with support from computational tools, and materials chemistry. Currently, our lab's major research focus is in the design, synthesis and characterization of chiral azaboroles. On one hand, we're developing new methods for the synthesis of azaboroles and the methods allowing for the stereoselective preparation of B,N-helicenes; while on the other hand, we endeavor to establish key design principles to improve their optical properties. For instance, the application of chiral compounds in CP-OLEDs requires materials that combine strong emission and large luminescence dissymmetry factors (g_{lum}), which quantify the differential emission of right- and left-handed CP light. Recently, through modification of the helicene structure, we were able to enhance both the luminescence quantum yield and the g_{lum} values (Figure 1b). The insights gained from this study will assist us in the further design of azaborole CPL emitters. Non-covalent interactions will also play a vital role in developing excellent candidates for OLEDs. In addition to finding efficient emitters, whether for applications in real-world devices or as luminescent probes, we'd also like to address important fundamental questions regarding charge and spin transport in organic semiconductors. Thus, we are actively engaged in a systematic investigation of this class of compound. Among the current efforts in our group, we are exploring helicenes containing heavier main group elements with the aim of providing a platform to develop catalytic systems for asymmetric synthesis.

Apart from *sensu stricto* scientific aims, my personal goal is to prepare highly qualified researchers in a healthy and supportive environment. I have the pleasure of working with a group of talented and motivated PhD students. It's extremely rewarding to observe their development in becoming independent researchers, responsible for their own respective projects. There is no doubt in my mind, they will be successful, whatever career path they choose.

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

Prof. A. Nowak-Król I don't look at my research in terms of scientific achievements. I think we're in a process of continuous learning. The longer we work, the greater understanding we have of the properties of our compounds, their stability and reactivity. This knowledge governs the molecu-

lar design of even better materials. At this point, I can already say, we have developed the chemistry of azaborahelicenes and established a new class of materials but there is still a lot more to be discovered. I believe that big achievements usually come in small steps and consist of little failures and victories. One needs to be patient and persistent in one's work and rely on one's critical thinking abilities. When I take a glance at my past achievements, this is exactly the approach I took to solve numerous problems.

In a more general sense, one of my most important accomplishments was pursuing my undergrad and PhD studies while being a mother. The scientific career requires high mobility and full involvement, which may be challenging when someone has established a family. Naturally, I wouldn't have achieved this without the support of my family and meeting important people on my way, like Prof. Daniel Gryko. Moving to Warsaw for my PhD studies was the first step towards the place where I am now. When I took up a postdoctoral position in the group of Prof. Frank Würthner, I already had clear plans and goals regarding my scientific career, although later, life made some adjustments.



Electrochemically Driven Cross-Electrophile Coupling of Alkyl Halides

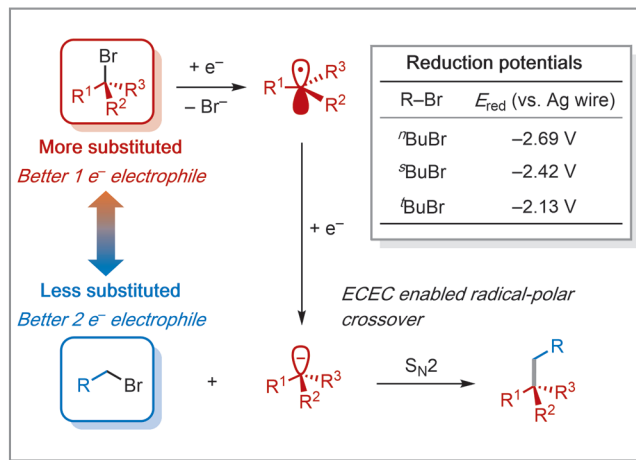
Nature **2022**, *604*, 292–297

Carbon–carbon bonds are key structural units in organic molecules. Thus, a tremendous effort has been dedicated to studying their formation. Transition-metal-catalyzed cross-coupling reactions are among the most reliable approaches for the formation of C–C bonds in organic synthesis. To avoid synthetic steps to preform organometallic reagents as well as stability and functional-group-tolerance issues that are commonly associated with these nucleophiles, cross-electrophile coupling (XEC) of organic halides has drawn substantial attention in the last decade as a methodology for achieving C–C bond formations.¹ However, despite great advances in this area, the selective XEC of two alkyl halides to construct C(sp³)-C(sp³) bonds has remained elusive.^{2,3}

Harnessing electrochemistry to solve challenging problems in organic synthesis has been an overarching goal of Professor Song Lin's research program at Cornell University (Ithaca, New York, USA). Professor Lin told SYNFORM: "In the past several years, we have advanced various electrocatalytic methods for the oxidative difunctionalization of alkenes.⁴ Recently, we turned our attention toward electroreductive chemistry. Employing electrochemical reduction of chlorosilanes and alkyl bromides, we have, for example, achieved intermolecular disilylation⁵ and carbo-functionalization of alkenes.⁶"

Inspired by the S_N2 reaction, which is commonly used to forge C(sp³)-C(sp³) bonds, the group envisioned a new approach to cross-couple two alkyl halides by exploiting their disparate electronic and steric properties (Scheme 1). "Specifically, tertiary alkyl halides preferentially undergo two consecutive single-electron reductions over less substituted primary halides to generate the corresponding carbanions, which then selectively react with primary halides owing to their smaller steric profiles," remarked Professor Lin.

Dr. Wen Zhang, the lead author of the *Nature* paper and a postdoctoral associate in the Lin laboratory, explained: "This work is innovative and significant for the following reasons: (1) The mechanism of our e-XEC process is fundamentally different from previously reported Ni-catalyzed methods as it does not require the generation of metal-alkyl intermediates, which can often lead to unselective electrophile activation or various other side reactions. (2) The e-XEC shows improved cross-coupling selectivity (vs. homocoupling) compared with known methods for C(sp³)-C(sp³) XEC. (3) Guided by cyclic voltammetry and DFT calculations, a broad scope of

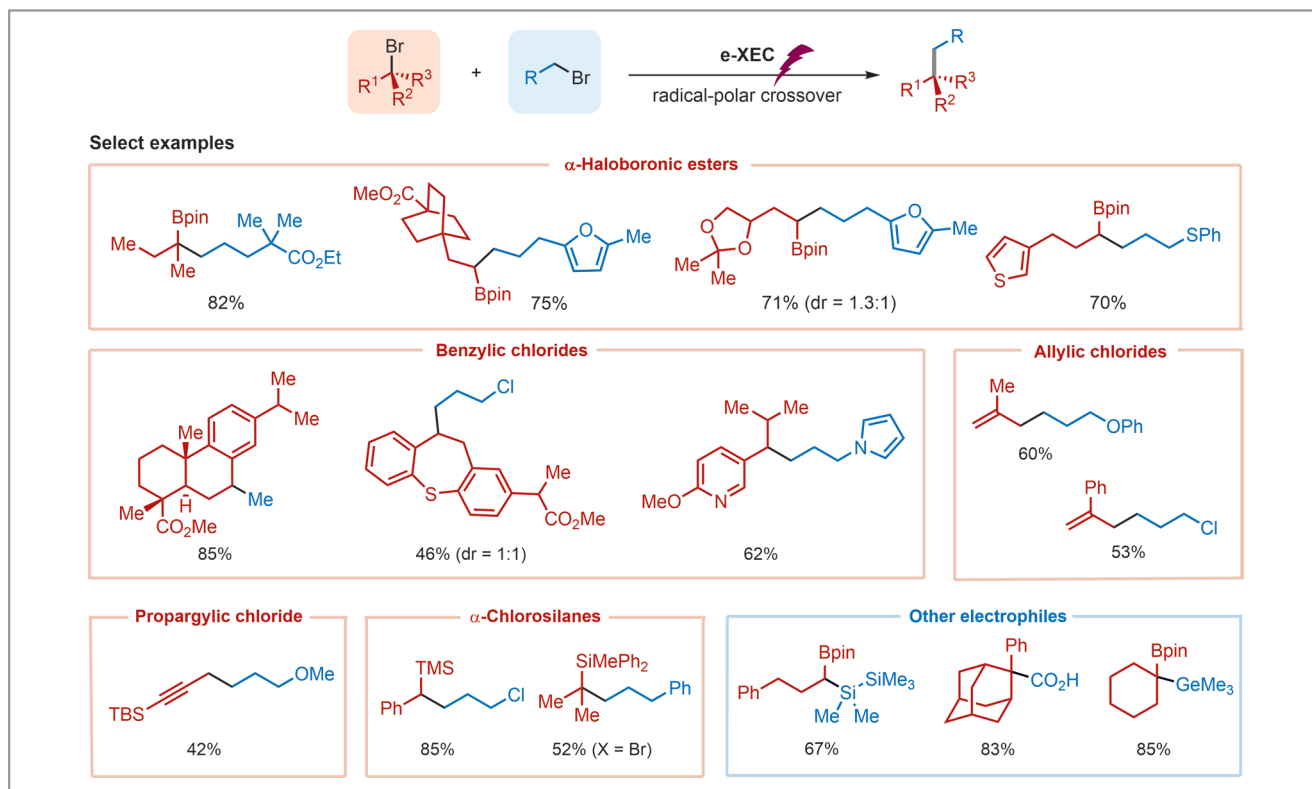


Scheme 1 Reaction design for e-XEC reaction; ECEC = electrochemical–chemical–electrochemical–chemical.

alkyl halides was shown to be compatible with the process, including α -haloboronic esters, α -halosilanes, benzylic chlorides, and allylic/propargylic halides, giving rise to a diverse panel of synthetically valuable intermediates (Scheme 2). (4) Mechanistic studies using electroanalytical and spectroscopic tools addressed issues connected to electrode passivation and informed the development of a more practical and scalable procedure."

Highlighting the future directions of the research described in this article, Professor Lin pointed out that an anion-stabilizing substituent was introduced on one of the alkyl halide electrophiles to improve reaction selectivity. "To broaden the scope of e-XEC, we will continue to explore selective reactions of two unactivated alkyl halides," said Professor Lin, continuing: "In addition, we hope to further improve the scalability of this reaction beyond laboratory scale by identifying a homogeneous reductant to replace the Mg sacrificial anode in combination with the use of a flow reactor. Besides alkyl halides, there are many other types of electrophiles that are interesting to explore using this electroreductive strategy."

The completion of this project was the result of a highly synergistic collaboration among the Lin group at Cornell, the See group at Caltech, and the Process Chemistry group at Merck. "The synthetic work carried out at Cornell benefited tremendously from the feedback and guidance from collaborators at Merck," acknowledged Professor Lin. He concluded:



Scheme 2 Selected substrate scope

“Also, the See group studied electrode passivation using electroanalytical and spectroscopic tools, and their expertise in Mg battery research brought about a simple solution to the troubling electrode fouling by using a metal-coordinating co-solvent.”

Matthew Farnok

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About the authors

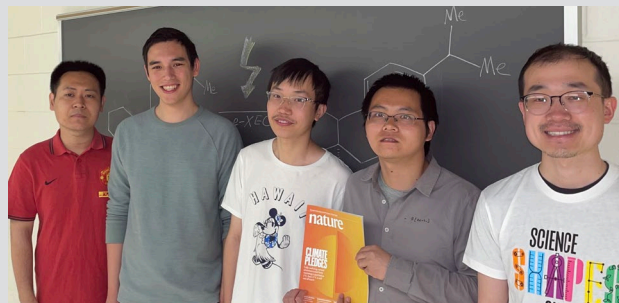


From left: W. Zhang, Prof. K. See and S. Ware

Wendy Zhang was born and raised in Changchun (P. R. of China). She completed her B.S. and M.S. at The College of William and Mary (USA) under Professor William McNamara in iron polypyridyl catalyst for photocatalytic hydrogen evolution. She later joined Professor Kimberley See's lab at Caltech (USA), focusing on improving the performance of Mg sacrificial anodes for organic electrosynthesis.

Kimberly See is an Assistant Professor of Chemistry in the Division of Chemistry and Chemical Engineering at Caltech (USA). She was born and raised in Colorado and received her B.S. in chemistry from the Colorado School of Mines (USA). Kim pursued her Ph.D. in chemistry at the University of California, Santa Barbara (USA) where she worked with Profs. Ram Seshadri and Galen Stucky. Kim was awarded the St. Elmo Brady Future Faculty Postdoctoral Fellowship at the University of Illinois at Urbana-Champaign (USA) and worked with Prof. Andrew Gewirth in the Department of Chemistry. Now, her group at Caltech studies the electrochemistry of Earth abundant, inexpensive materials with a focus on next-generation energy storage.

Skylar Ware was born and raised in Cincinnati, OH (USA). She completed her B.S. at The Ohio State University in 2018, where she conducted undergraduate research with Professor Robert Baker in electrochemical CO₂ reduction. In autumn 2018, she joined Professor Kim See's research group as a graduate student at Caltech (USA). Her research focuses on electrolyte development for electrocatalysis and energy storage devices.



From left: Dr. Y. Wang, J. Rein, L. Lu, Dr. W. Zhang and Prof. S. Lin

Yi Wang was born in Zhejiang (P. R. of China). He received his B.S. degrees in chemistry and economics from Peking University (P. R. of China). Then, he pursued graduate studies under the supervision of Professor Zhi-Xiang Yu at Peking University. His doctoral research was focused on mechanistic studies of catalytic reactions and carbon-to-carbon proton transfers. In September 2021, he joined the Lin research group at Cornell University (USA) as a postdoctoral associate. His current research is focused on developing and understanding electrochemical reactions.

Jonas Rein was born in Dudweiler (Germany) in 1999 and grew up in Mainz (Germany). He received his B.Sc. degree in 2019 from the Johannes-Gutenberg University in Mainz (Germany) working under the supervision of Prof. Waldvogel on electrochemical C–H functionalizations. Since then, he has been with Prof. Lin's group at Cornell University (USA) for his Ph.D. studies focusing on the development of high-throughput experimentation for electrochemistry and novel scaffolds for asymmetric organocatalysis.

Lingxiang Lu was born and raised in P. R. of China. He received his B.S. degree in chemistry from Wuhan University under the supervision of Prof. Hexiang Deng and Fusheng Ke, working on metal–organic frameworks and lithium sulfur batteries. In 2017, he joined Prof. Song Lin's research group at Cornell (USA) for Ph.D. studies on electrosynthesis. He is currently working on developing electroreductive transformations for organic synthesis.

Wen Zhang was born and raised in Anhui (P. R. of China). He obtained his B.S. from Sichuan University (P. R. of China) in 2013. Then, he pursued graduate studies under the guidance of Prof. Guosheng Liu at Shanghai Institute of Organic Chemistry (SIOC), Chinese Academy of Sciences (P. R. of China). His doctoral research was focused on asymmetric C–H bond functional-

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zation via copper-catalyzed radical relay. In December 2018, he started his postdoctoral studies with Prof. Song Lin at Cornell University (USA) where his research is focused on the development of novel electrochemical methods for organic synthesis.

Song Lin was born and raised in Tianjin (P. R. of China). After earning his B.S. from Peking University (P. R. of China) in 2008, he pursued graduate studies at Harvard University (USA) working under the direction of Prof. Eric Jacobsen. His doctoral research was focused on the development and mechanistic understanding of enantioselective organocatalysis. He then carried out postdoctoral studies with Prof. Chris Chang at UC Berkeley (USA) on electrocatalytic reduction of CO₂ using covalent organic frameworks. In the summer of 2016, Prof. Song Lin joined the Cornell faculty (USA). His research focuses on the discovery of new catalytic strategies for organic synthesis using fundamental principles of electrochemistry and radical chemistry.



J. Mondragon

Wolczanski, working with strained molecules to generate novel alkylidenes.



Dr. N. Strotman

Over the last 15 years, Neil has leveraged his

skills in physical organic chemistry and catalysis in the enabling technologies space and has gained experience in process development, plant scale implementation, project leadership, PAT, and flow chemistry. In his free time, Neil enjoys hiking, woodworking, and traveling with his family.



Dr. D. Lehnerr

Dan Lehnerr received his B.Sc. from the University of Victoria (Canada). He pursued his graduate studies under the mentorship of Prof. Rik Tykwinski (Chemistry) and Prof. Frank Hegmann (Physics) developing organic materials for optoelectronic applications. He carried out postdoctoral research at Harvard University (USA) with Prof. Eric Jacobsen focused on organocatalysis and reaction mechanism elucidation, and subsequently at Cornell

University (USA) with Prof. William Dichtel researching nanographenes and ortho-arylene-based foldamers. In 2016 he joined the Catalysis Group within Process Research and Development at Merck & Co., Inc. in Rahway, NJ (USA). His research interests are at the intersection of reaction discovery, physical organic chemistry, computational chemistry, and new capabilities to enable the development of medicines.

Enantioselective Au(I)/Au(III) Redox Catalysis Enabled by Chiral (P,N)-Ligands

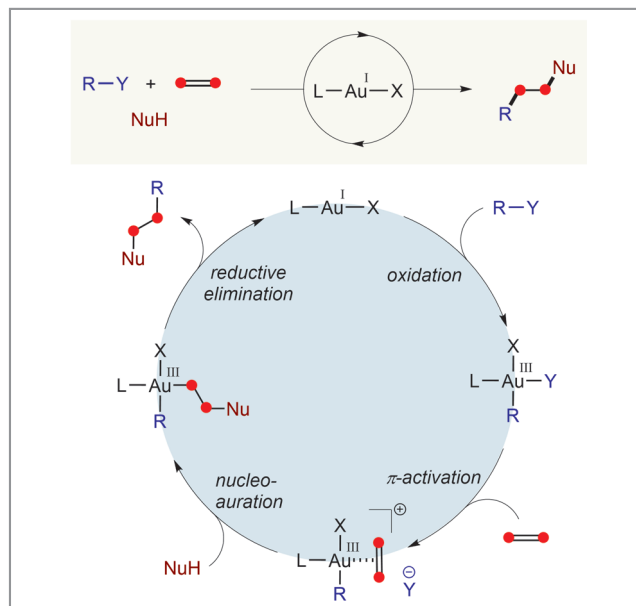
J. Am. Chem. Soc. **2022**, *144*, 7089–7095

In the past decade, Au(I)/Au(III) redox catalysis has emerged as a new technique, opening up avenues for the cross-coupling and 1,2-difunctionalization reactions of C–C multiple bonds that were previously inaccessible with Au(I) or Au(III) catalysis. However, the enantioselective version of Au(I)/Au(III) redox catalysis remained elusive until recently, when the research group of Dr. Nitin Patil (Indian Institute of Science Education and Research Bhopal, India) developed new hemilabile chiral (P,N)-ligands (ChetPhos) to realize the first example of enantioselective Au(I)/Au(III) redox catalysis.

According to Dr. Patil, homogeneous gold catalysis originated with the ability of gold, commonly stereotyped as a tunable soft π -acid, to activate C–C multiple bonds towards intra- or intermolecular attack by nucleophiles. “These reactions are thought to involve the formation of an organo-gold intermediate first, which upon nucleophilic attack generally undergoes protodemetalation to deliver new carbon–carbon or carbon–heteroatom bonds,” explained Dr. Patil. He continued: “On the other hand, the identification of new reactivity based on Au(I)/Au(III) redox catalysis is challenging due to the fact that gold(I), unlike its isoelectronic counterpart Pd(0), doesn’t change its oxidation state during the catalytic cycle. This apparent reluctance to engage in redox activity is commonly attributed to the comparatively high redox potential of the Au(I)/Au(III) couple ($E^0 = +1.41$ V) in contrast to that of the Pd(0)/Pd(II) one ($E^0 = +0.92$ V).” Dr. Patil acknowledged that in the past decade, significant research efforts have been devoted to overcoming issues connected to the high redox potential of the Au(I)/Au(III) couple, facilitating gold-catalyzed 1,2-difunctionalization reactions involving cross-coupling reactivity (Scheme 1).¹

“In general, the available methods to access the Au(I)/Au(III) catalytic cycle are as follows: (1) external oxidant-aided approach;² (2) merged gold/photoredox catalysis approach;^{3,4} (3) utilizing an ethynylbenziodoxolone⁵ – a dual-role agent which acts as an oxidant and an alkyne surrogate; (4) ligand-enabled approach,” said Dr. Patil.^{6–9} “However, a report on the enantioselective version of Au(I)/Au(III) redox catalysis was lacking in the literature.”

Dr. Patil added that the main challenge in realising enantioselective Au(I)/Au(III) redox catalysis is to tackle the typical geometrical restrictions and distinct coordination behavior of



Scheme 1 1,2-Difunctionalization of alkenes under Au(I)/Au(III) redox catalysis

Au(I) and Au(III) species. “Au(I) complexes are generally dicoordinated and linear; while Au(III) complexes prefer tetracoordinated square-planar geometry,” he explained. “Therefore, in order to achieve enantioselective Au(I)/Au(III) redox catalysis, it is necessary to control four coordination sites of an *in situ* generated Au(III) intermediate by a single modulatory ligand (L) present in LAuX. Further, the linear geometry favored by Au(I) complexes prevents the use of chiral bidentate ligands, which are required to impart structural rigidity to the *in situ* generated Au(III) complexes.”

In order to address these issues and to realize enantioselective Au(I)/Au(III) redox catalysis, Dr. Patil’s group developed a new class of hemilabile chiral (P,N)-ligands (Figure 1) based on the following assumptions: 1) the soft phosphorus center of the ligand should coordinate with the soft Au(I) species to form a linear LAuX complex, while the hard nitrogen center should coordinate with the *in situ* generated high-valent Au(III) species; 2) the phosphorus center must bear the bulky alkyl groups in order to push the Au(I) center towards nitrogen, which is necessary to expedite the oxidative addition

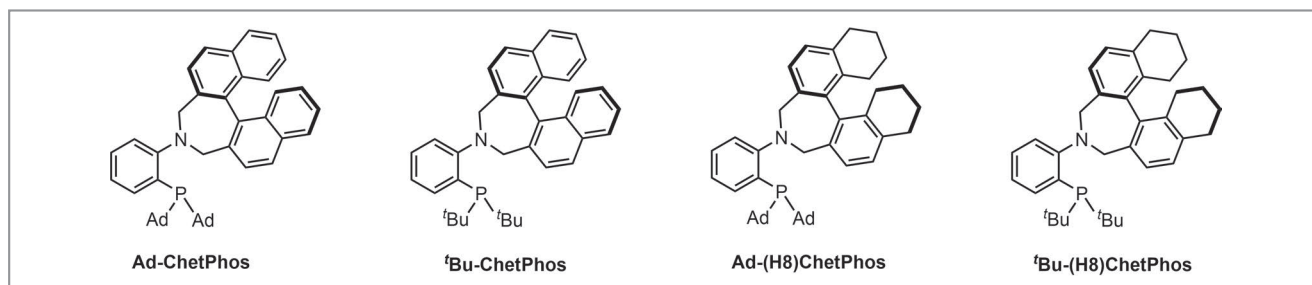
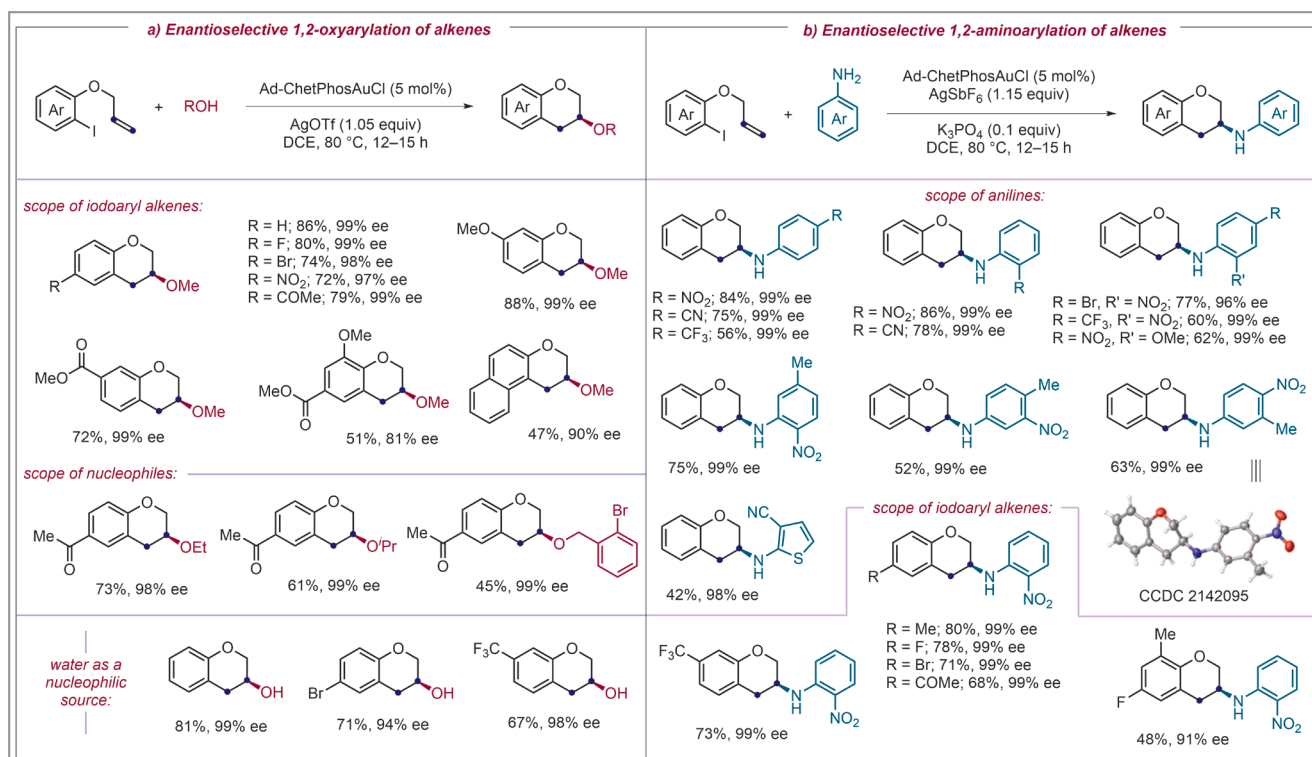


Figure 1 Newly developed chiral (P,N)-ligands

process by allowing nitrogen coordination; 3) the chelation of (P,N)-ligand with *in situ* generated Au(III) species should offer the desired structural rigidity required for efficient enantio-induction; 4) the greater *trans*-influence of phosphorus in a square-planar Au(III) intermediate should allow the precise positioning of substrate in the C_2 -symmetric chiral environment present around the nitrogen center. These ligands were named as ChetPhos and their successful implementation in developing the first enantioselective 1,2-heteroarylation of alkenes under Au(I)/Au(III) redox catalysis was described in the title article.

“Gold(I) complexes of the newly developed ligands were used as catalysts to achieve enantioselective 1,2-oxyarylation and 1,2-aminoarylation of alkenes,” said Dr. Patil. He continued: “Among all the tested catalysts, Ad-ChetPhos ligated gold(I) complex showed superior performance for the 1,2-oxyarylation and 1,2-aminoarylation of alkenes. The method turned out to be fairly general, delivering 3-oxychromans and 3-aminochromans in good yields and excellent enantiomeric excess (Scheme 2).”

Dr. Manoj V. Mane performed DFT calculations in order to understand the enantio-induction model (Figure 2). The



Scheme 2 1,2-Oxyarylation and 1,2-aminoarylation of alkenes

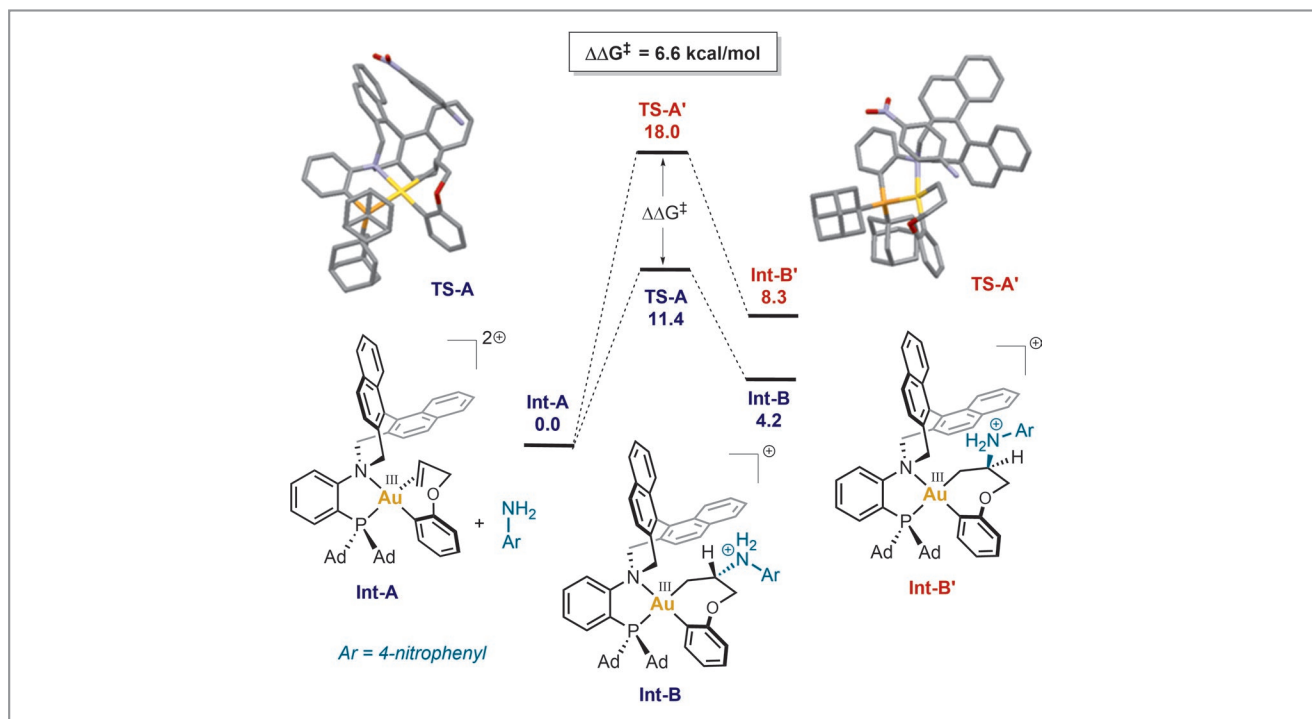


Figure 2 DFT calculations for enantio-determining step. Free energy values are at M06(SMD-dichloroethane)/Au(SDD)//TZVP//BP86/SDD(Au)/SVP level of theory.

studies revealed that the *Si*-face attack of a nucleophile (**TS-A**) has a barrier of 11.4 kcal/mol; while the *Re*-face attack (**TS-A'**) demands 18.0 kcal/mol. Dr. Patil explained: “The ChetPhos ligands provided a powerful enantio-discrimination (energy difference between **TS-A'** and **TS-A**: 6.6 kcal/mol), which resulted in excellent enantioselectivities.”

Dr. Patil concluded: “We have developed the first example of enantioselective Au(I)/Au(III) redox catalysis, enabled by the newly designed hemilabile chiral (P,N)-ligands – ChetPhos. The potential of this concept is demonstrated in gold-catalyzed 1,2-oxyarylation and 1,2-aminoarylation of alkenes leading to medically important 3-oxy- and 3-aminochromans with high yields and enantioselectivities. This concept of ligand-enabled enantioselective Au(I)/Au(III) redox catalysis should be applicable to a vast number of cross-coupling reactions and alkene difunctionalization reactions.”

Anasthasios

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About the authors



C. C. Chintawar

Chetan C. Chintawar is currently carrying out his doctoral studies at IISER Bhopal (India) in the laboratory of Dr. Nitin T. Patil. He was born in 1993 in Nanded (Maharashtra), India. He completed his Master's (2015) in organic chemistry from the Department of Chemistry, SGB Amravati University (India). His research interests include the development of novel methodologies for difunctionalization reactions of C–C multiple bonds under gold catalysis.



V. W. Bhojare

Vivek W. Bhojare was born in 1994 in Amravati, Maharashtra (India). He completed his Master's (2016) in organic chemistry from the Department of Chemistry, Sant Gadge Baba Amravati University, Amravati (India). Thereafter in 2017, he joined Dr. Nitin T. Patil's research group for his doctoral studies. His research interests include the development of new transformations based on oxidative gold catalysis.



Dr. M. V. Mane

Manoj V. Mane was born in Manevadi in Maharashtra, Beed District (India). He received his Ph.D. in theoretical and computational chemistry under the supervision of Prof. Kumar Vanka at CSIR-National Chemical Laboratory, Pune (India) in 2016. He held a postdoctoral position in the Department of Chemistry at the Korea Advanced Institute of Science and Technology (South Korea) with Prof. Mu-Hyun Baik. Afterward, in July 2019, he moved to King Abdullah University of Science and Technology (Saudi Arabia) as postdoctoral fellow to work with Prof. Luigi Cavallo. He is focusing on the use of computational methods to analyze and understand the mechanism of organometallic and homogeneous catalysis reactions.



Dr. N. Patil

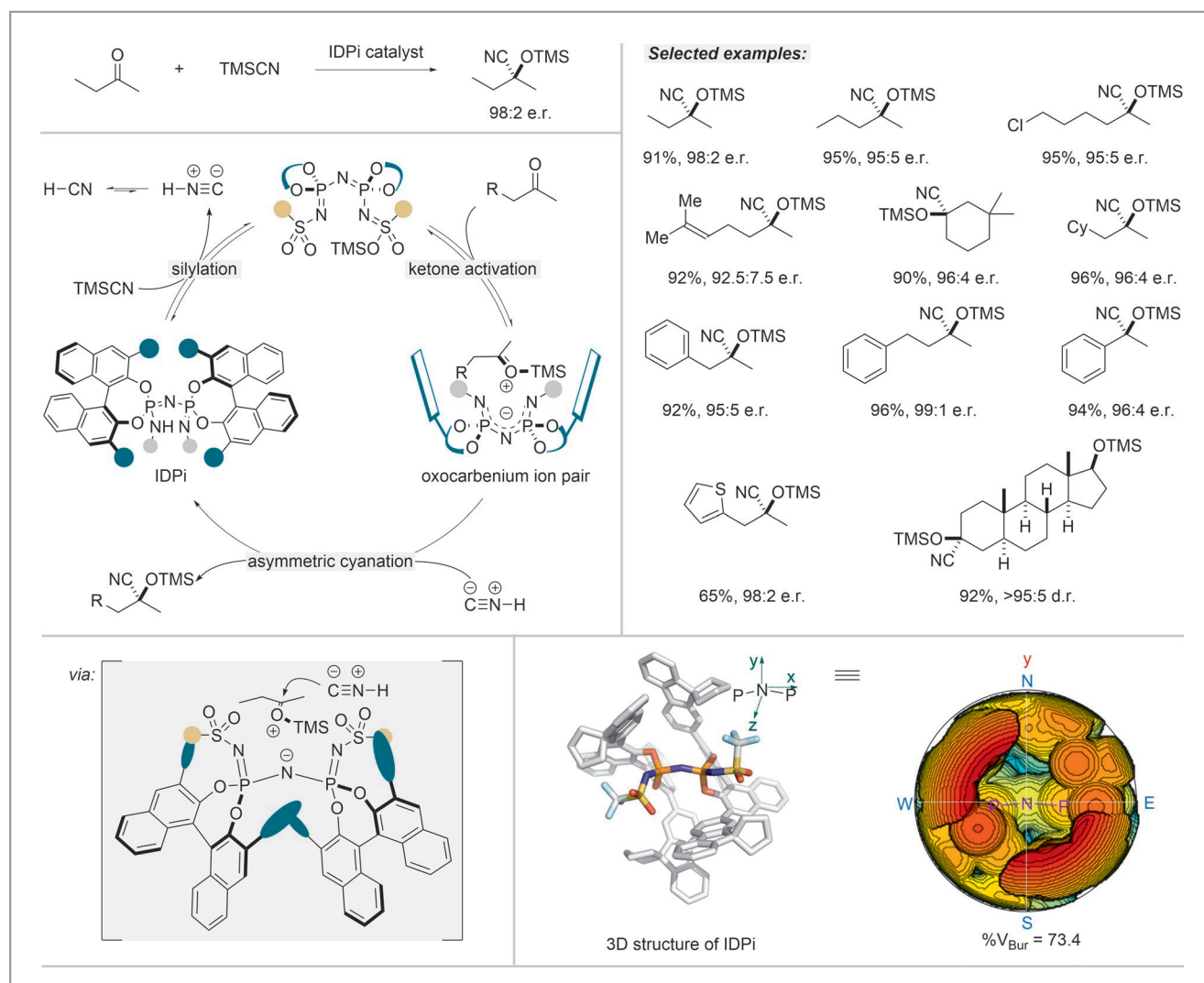
Nitin Patil completed his doctoral studies from the University of Pune (India) in 2002 under the supervision of Prof. Dilip D. Dhavale. Subsequently, he joined Professor Christoph Schneider's group as a postdoctoral fellow at the University of Goettingen (Germany). In November 2002, he moved to Tohoku University (Japan), as a JSPS postdoctoral fellow to work with Prof. Yoshinori Yamamoto, where he was later appointed as an Assistant Professor. In June 2006, he joined Prof. K. C. Nicolaou's laboratory at ICES (Singapore), and later at The Scripps Research Institute (USA). He began his independent career in September 2008 at CSIR-IICT, Hyderabad (India), and subsequently moved to CSIR-NCL, Pune (India), in August 2013. Since July 2017, he has been an Associate Professor at the Department of Chemistry, IISER Bhopal (India).

Organocatalytic Stereoselective Cyanosilylation of Small Ketones

Nature **2022**, *605*, 84–89

The asymmetric cyanosilylation of carbonyl compounds is a highly versatile approach to build C–C bonds, enabling access to silyl-cyanohydrins, which are important building blocks with wide applications in the pharmaceutical and chemical industry. In past decades, the enantioselective cyanosilylation reaction has been thoroughly studied and many fascinating methodologies have been established.¹ Nevertheless, the enantiofacial discrimination of dialkyl ketones is difficult

to control with chiral catalysts, due to the limited steric and electronic differences of the two substituents, and constitutes a long-standing challenge in organic synthesis. In particular, asymmetric reactions involving 2-butanone, which carries a methyl and an ethyl group on the carbonyl group, typically can only be catalyzed by enzymes following the ‘lock-and-key principle’. Recently, the research group of Professor Benjamin List at the Max-Planck-Institute für Kohlenforschung (Germa-



ny) has designed and employed a sterically confined organic superacidic imidodiphosphorimidate (IDPi) catalyst to successfully accomplish the asymmetric cyanosilylation of 2-butanone with an enantiomeric ratio of 98:2 (Scheme 1). “This particular reaction has already been studied with various catalysts, including engineered enzymes, metal complexes, and organocatalysts, which all proved to be competent catalysts, albeit furnishing the desired product with insufficient selectivity,” said Professor List.

“In the past five years, IDPi-based catalysis has been employed to solve challenging problems in the field of asymmetric catalysis, such as activation of inert olefins,² single aldolizations of acetaldehyde enolates,³ transformation of a non-classical carbocation,⁴ and organocatalytic reactions with (sub)ppm-level catalyst loading.⁵ While addressing these synthetic challenges, we are also keen to seek better ways to differentiate extremely challenging enantiofaces, including those of 2-butanone. Here we were encouraged from previous results on Diels–Alder reaction and intramolecular Friedel–Crafts reaction involving the differentiation of methyl and ethyl groups,^{6,7}” said Professor List.

To probe the mechanism of this new synthetic application of IDPi catalysis, the authors of the title *Nature* article first performed the reaction under the catalysis of a less acidic chiral disulfonimide (DSI) catalyst. The reaction exclusively provided the corresponding silyl enol ether, and no silylcyanohydrin was detected. “This result suggests the decisive role of strong acidity in the chemoselectivity of this reaction,” explained the first author Dr. Hui Zhou, who continued: “We performed NMR studies and captured the formation of silyl enol ethers in the initial stage of the reaction. Subsequently, a key control experiment between the silyl enol ether and in situ generated (iso)hydrocyanic acid further confirmed the surprising existence of the enol silane under the reaction conditions.”

Professor Gui-Juan Cheng and co-workers at the Chinese University of Hong Kong (China) performed DFT calculations to support the experimental observations. “Results of structural analysis showed that the IDPi catalyst has a confined structure with a buried volume of up to 73.4%, and its central skeleton and substituents form a narrow chiral pocket, which efficiently differentiates the transition state structures. Our calculations suggest that varying the substituents of the catalyst can influence the shape, size, embedded volume and steric hindrance, thereby providing enzyme-like pockets to specifically recognize different types of substrates such as aliphatic ketones and aromatic ketones,” explained Professor Cheng.

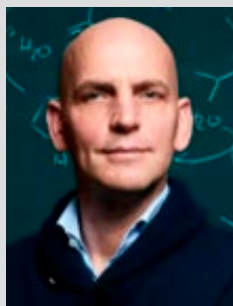
Based on the experimental, NMR and theoretical results, the authors proposed a plausible mechanism as follows: 1.

a silylium-based active catalyst is generated from the reaction of the pre-catalyst IDPi and TMSiCN with the release of isohydrocyanic acid; 2. activation of the ketone leads to the formation of an oxycarbonium ion pair intermediate; 3. addition of isohydrocyanic acid furnishes the target product and regenerates the catalyst. “We hope that our research will stimulate further research on confinement control in selective catalysis,” concluded Professor List.

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About the authors



Prof. B. List

Benjamin List was born in 1968 in Frankfurt, Germany. He graduated from Freie University Berlin (Germany) in 1993 and received his Ph.D. (1997) from the University of Frankfurt (Germany). After postdoctoral studies (1997–1998) as a Feodor Lynen Fellow of the Alexander von Humboldt foundation at The Scripps Research Institute (USA), he became a Tenure Track Assistant Professor there in January 1999. Subsequently, he developed the first proline-catalyzed asymmetric intermolecular aldol-, Mannich-, Michael-, and α -amination reactions. In 2003 he moved to the Max-Planck-Institut für Kohlenforschung (Germany), where he has been a director since 2005. From 2012 until 2014 he was the managing director of the institute. He has served as an honorary professor at the University of Cologne (Germany) since 2004, and as a specially appointed professor at Hokkaido University (Japan) since 2020. His research interests are new catalysis concepts and chemical synthesis in general. He has pioneered and contributed several concepts including aminocatalysis, enamine catalysis, and asymmetric counteranion-directed catalysis (ACDC). His accomplishments have been recognized by several awards including the Otto Bayer Prize (2012), the Mukaiyama Award (2013), the Cope Scholar Award (2014), the Gottfried Wilhelm Leibniz Prize (2016), member of the German National Academy of Sciences Leopoldina (2018), Nobel Prize in Chemistry (2021), and Herbert C. Brown Award (2022).



Dr. H. Zhou

Hui Zhou was born in Ezhou city, Hubei (P. R. of China). She obtained her Ph.D. in 2016 from Lanzhou Institute of Chemical Physics (LICP), Chinese Academy of Sciences (CAS, China) under the supervision of Prof. Gaoxi Jiang and Prof. Chungu Xia. After a short time staying in Prof. Xin Cui's lab as a postdoctoral fellow at Mississippi State University (USA), she moved to the Max-Planck-Institut für Kohlenforschung (Mülheim an der Ruhr, Germany) and worked as a postdoctoral fellow under the supervision of Prof. Benjamin List. Currently her research focuses on asymmetric organocatalysis. She has received prizes such as the Ph.D. National Scholarship (2015, Ministry of Education of China), and a Post-doctoral Fellowship (2017, Max-Planck Society).



Prof. G. J. Cheng

Gui-Juan Cheng received her Ph.D. from Peking University (P. R. of China) in 2015 under the supervision of Prof. Yun-Dong Wu and Prof. Xinhao Zhang. She then worked in Prof. Walter Thiel's research group at Max-Planck-Institut für Kohlenforschung (Germany) as a postdoctoral fellow. Dr. Cheng began her independent career as an assistant professor at the Chinese University of Hong Kong (Shenzhen, P. R. of China) in 2018. The research program of her laboratory has been focused on mechanistic studies of organic and enzymatic reactions and the mechanism-based development of organic and biocatalytic reactions.



Dr. Y. Zhou

Yu Zhou obtained his Ph.D. in chemistry at The Hong Kong University of Science and Technology (HKUST, P. R. of China) in 2018 under the supervision of Professor Zhenyang Lin. During that time, he carried out computational studies on the reaction mechanism of transition-metal catalysts, especially copper catalysts. Currently, he is the associate research fellow at the Chinese University of Hong Kong, Shenzhen (CUHKSZ, P. R. of China). His research interest is focused on theoretical studies of electronic structures and reaction mechanisms of organocatalysts and metalloenzymes.



Dr. H.-Y. Bae

Han-Yong Bae was born in the Republic of Korea. He received his Ph.D. from Sungkyunkwan University (2015, SKKU, Korea), conducting studies on biomimetic Brønsted base catalyzed asymmetric organocatalysis under the supervision of Professor Choong Eui Song. After completing his graduate studies, he moved to Germany and pursued postdoctoral research with Professor Benjamin List at the Max-Planck-Institut für Kohlenforschung. He developed a new highly active silylium Lewis acid mediated organocatalytic asymmetric Mukaiyama aldol reaction (approaching sub-ppm-level asymmetric organocatalysis). In 2019, Han-Yong was appointed as an Assistant Professor at

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Ulsan National Institute of Science and Technology (UNIST, Korea), and shortly thereafter, moved to SKKU as an Assistant Professor (tenure track). His current research interests are exploiting fundamental homogeneous catalysis as a tool for further multidisciplinary and practical applications in the synthesis of biologically relevant molecules, materials science, and biological science.



Dr. M. Leutzsch

Markus Leutzsch received his M.Sc. in chemistry from Leipzig University (Germany) in 2011. He then moved to the Max-Planck-Institut für Kohlenforschung (Mülheim an der Ruhr, Germany) to pursue his doctoral studies in the group of Prof. Benjamin List and the in-house NMR department under the guidance of Dr. Christophe Farés. Thereafter he moved to the University of Cambridge (UK) to work as postdoctoral research associate in the Magnetic Resonance Research Centre

lead by Prof. Dame L. F. Gladden, Prof. M. D. Mantle and Prof. A. J. Sederman. He then moved back to the Max-Planck-Institut für Kohlenforschung (Germany) in late 2018 as a senior NMR research scientist. His current research interests include mechanistic investigations of a broad range of catalytic reactions and the spectroscopic characterization of NMR-active transition-metal nuclei.



Y. Li

Yihang Li is currently a graduate student at Max-Planck-Institut für Kohlenforschung (Mülheim an der Ruhr, Germany) in the group of Professor Benjamin List, where his research projects focus on the development of chiral confine super-base catalysts for enantioselective reactions. He is also involved with studies on super-acid catalysis. Before his graduate studies at Max-Planck-Institut für Kohlenforschung, he completed his M.S. in organic chemistry from the Nankai University (P. R. of China) in 2017 under the supervision of Prof. Pingping Tang.

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— Literature Coverage

Highly Sterically Hindered Peptide Bond Formation between α, α -Disubstituted α -Amino Acids and *N*-Alkyl Cysteines Using α, α -Disubstituted α -Amidonitrile

— Literature Coverage

A Selenide Catalyst for the Activation of Alkenes through $Se^{\sigma\pi}$ Bonding

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