

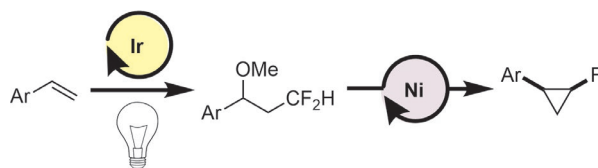
Synform

People, Trends and Views in Chemical Synthesis

2022/05

Nickel-Catalyzed Cross-Electrophile Coupling of the Difluoromethyl Group for Fluorinated Cyclopropane Synthesis

Highlighted article by E. L. Lucas, T. M. McGinnis, A. J. Castro, E. R. Jarvo



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Thieme

Dear Readers,

while excitement for the first in-person Editorial Board Meeting in three years is growing fast at Thieme Chemistry (and what a fantastic opportunity to congratulate SYNLETT Editor-in-chief Benjamin List on his Nobel Prize it will be!!), in this May issue of SYNFORM we honour the first of the two 2021 Best Paper Award winners. Professor Elizabeth Jarvo, Dr. Erika Lucas, Mr. Tristan McGinnis and Mr. Anthony Castro from the University of California-Irvine (USA), who are the recipients of the SYNLETT Best Paper Award 2021 for their article “Nickel-Catalyzed Cross-Electrophile Coupling of the Difluoromethyl Group for Fluorinated Cyclopropane Synthesis” (*Synlett* **2021**, 32, 1525), are featured in an interview that provides background information on their prize-winning research, as well as about current research activities ongoing in the group. I can anticipate that the SYNTHESIS Best Paper Award 2021 winners – Professor Ryan Gilmour and co-authors – will be featured in the June issue. The second article of this issue is a welcome interview with Professor Hongli Bao (Fujian Institute of Research on the Structure of Matter, CAS, P. R. of China), who joined the Editorial Board of SYNTHESIS in January 2022. Next in line, the first of the Literature Coverage articles deals with the stereocontrolled olefin cyclopropanation achieved by X. P. Zhang (USA) through radical differentiation of two ester groups in unsymmetrical diazomalonates. And finally, closing the issue is coverage of the recent breakthrough work published by S. Liu and X. Cheng (P. R. of China) on the insertion of ammonia into alkenes to deliver aromatic N-heterocycles.

Enjoy your reading!



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Contact

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

SYNLETT Best Paper Award 2021: Nickel-Catalyzed Cross-Electrophile Coupling of the Difluoromethyl Group for Fluorinated Cyclopropane Synthesis

Synlett **2021**, 32, 1525–1530

Background and Purpose. 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. Professor Elizabeth Jarvo, Dr. Erika Lucas, Mr. Tristan McGinnis and Mr. Anthony Castro from the University of California-Irvine, USA, are the recipients of the SYNLETT Best Paper Award 2021. In announcing this year’s winners, Benjamin List, Editor-in-Chief of *SYNLETT*, noted: “In their brilliant work, Jarvo and co-workers have invented a conceptually new approach to fluorinated cyclopropanes. It is based on a photocatalytic styrene methoxy difluoromethylation, the products of which are elegantly used in a nickel-catalyzed intramolecular cross-electrophile coupling reaction between the difluoromethyl moiety and the methyl ether. This work is highly creative and timely and an excellent example what *SYNLETT* readers can expect.” SYNFORM spoke with Professor Elizabeth Jarvo, who was happy to share some background information regarding the prize-winning paper as well as current research activities ongoing in her group.

Biographical Sketch



From left: Prof. E. Jarvo, Mr. T. McGinnis, Mr. A. Castro and Dr. E. Lucas

Elizabeth Jarvo was born in Nova Scotia, Canada. She earned her B.Sc. (Honours) from Acadia University (Canada) working in the laboratory of Michael A. Kerr and was a summer NSERC student at Concordia University (Canada) with Youla Tsantrizos. She carried out her Ph.D. studies under the direction of Scott J. Miller at Boston College (USA), and postdoctoral studies with Eric N. Jacobsen at Harvard University (USA). In 2005 she joined the faculty at the University of California, Irvine (USA) and has

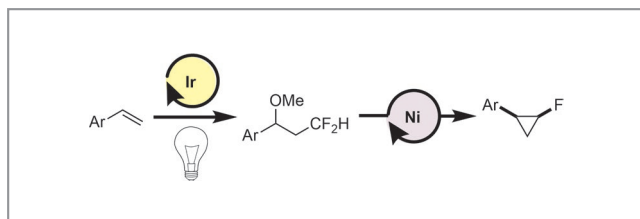
been a Full Professor since 2016. Her research program focuses on the development of new catalytic reactions including stereospecific cross-coupling and cross-electrophile coupling reactions using nickel catalysts.

Professor Jarvo has received many awards during her career: In 2005, she was awarded both the Amgen New Faculty Award and the Lilly New Faculty Award. In 2006, she received the ACS-PRF Type G award, followed by the NSF CAREER Award in 2008 and the UCI School of Physical Sciences Outstanding Contributions to Undergraduate Education Award in 2009. In 2010, she was a recipient of the Thieme Chemistry Journals Award. Other awards have followed: ACS Women in Chemistry Committee Rising Star Award (2014), Japan Society for Promotion of Science (JSPS) Fellowship (2015), UCI Chancellor’s Faculty Fellow (2017–2020), Novartis Chemistry Lectureship (2017/2018), Chemmy Award, Emory Department of Chemistry (2020), Journal of Organic Chemistry 2020 Outstanding Article of the Year and now the SYNLETT Best Paper Award 2021.

INTERVIEW

SYNFORM Could you highlight the value of your award-winning paper with respect to the state-of-the-art, as well as the potential or actual applications?

Prof. E. Jarvo We think that this chemistry will be of conceptual interest to colleagues in academia and the pharmaceutical industry. The product of the transformation is a fluorinated cyclopropane (Scheme 1), an interesting pharmacophore that has few synthetic approaches. Furthermore, the approach connects emerging methods for photocatalytic difluoromethylation of alkenes with a nickel-catalyzed cross-electrophile coupling (XEC) reaction.



Scheme 1

SYNFORM Can you explain the origin, motivations and strategy used for conducting the award-winning research?

Prof. E. Jarvo Our group previously established intramolecular XEC reactions of the strong C–F bonds of alkyl fluorides. We sought to extend this reactivity to include the difluoromethyl group, a particular challenge for multiple reasons including strength of the C–F bonds and strain associated with the reaction products.

SYNFORM What is the focus of your current research activity, both related to the award paper and in general?

Prof. E. Jarvo My laboratory is interested in the design of new catalytic reactions, particularly in the use of base metal catalysts to form challenging C–C bonds. New reaction development and improved mechanistic understanding dovetail with each other. By developing certain transformations we can better define the key features of catalysts that control reactivity, and hopefully apply this understanding in discovery of the next series of transformations.

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

Prof. E. Jarvo I think major challenges in organic synthesis continue to be issues of selectivity and sustainability. Catalysts can play a key role in addressing both of these features.

SYNFORM What does this award mean to you/your group?

Prof. E. Jarvo This award is wonderful recognition of Erika, Tristan and Anthony's creativity, passion and hard work on this project.

Editorial Board Focus: Prof. Hongli Bao (Fujian Institute of Research on the Structure of Matter, CAS, P. R. of China)

Background and Purpose. SYNFORM portraits Thieme Chemistry Editorial Board or Editorial Advisory Board members who answer several questions regarding their research interests and revealing their impressions and views on the developments in organic chemistry as a general research field. This Editorial Board Focus presents Prof. Hongli Bao (Fujian Institute of Research on the Structure of Matter, CAS, P. R. of China) who joined the Editorial Board of SYNTHESIS with effect of January 2022.

Biographical Sketch



Prof. H. Bao

Hongli Bao graduated from a joint program of the University of Science and Technology of China and the Shanghai Institute of Organic Chemistry and received her PhD in 2008, with Professor Kuiling Ding as mentor. She then moved to the USA and worked in Professor Uttam Tambar's lab in The University of Texas Southwestern Medical Center from 2009 to 2013 as a postdoctoral researcher. After four years there, she moved to Fuzhou at the end of 2013 where she is now a group leader and Professor of the Structure of Matter, at the Fujian Institute of Research, Chinese Academy of Sciences. Her research interests include radical chemistry, asymmetric catalysis, and reactions and synthesis under extremely challenging conditions.

SYNFORM *What do you think about the modern role and prospects of synthetic chemistry?*

Prof. H. Bao Synthetic chemistry is the foundation of many disciplines, including materials science, pharmacology, and the life sciences. It is fundamentally important in the further development of science and technology. Some people may think that synthetic chemistry is a tool for other scientific disciplines, but I believe synthetic chemistry could still be the engine for advances in science and technology, because it is the most creative discipline.

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

Prof. H. Bao We are exploring the boundaries of some radical reactions. Solving difficult and important problems is our interest, and we try to find answers to the questions that no one could answer previously.

SYNFORM *What would you consider your most important scientific achievement to date and why?*

Prof. H. Bao Our most important work to date is the development of important radical reactions under extreme conditions. One way to understand the term 'free radical' is that it is a free, reactive chemical intermediate that is not easy to control. One of our goals is to control its reactivity under extremely challenging conditions, and to some extent, we have achieved this goal. A further goal is to utilize the 'freedom' of radicals to develop 'miracle reactions'. We are pursuing this goal and expect to disclose our results soon.

Mattias Farnik

INTERVIEW

SYNFORM *How do you describe the value of a product such as SYNTHESIS to the chemistry community?*

Prof. H. Bao One of my good friends said that the name of SYNTHESIS is similar to *Science* and *Nature*: pithy, powerful, and elegant. I agree with him. SYNTHESIS is one of my favorite journals, and in the last 52 years it has published so many classic organic reactions. It will continue to publish good work from this field and serve the chemistry community powerfully.

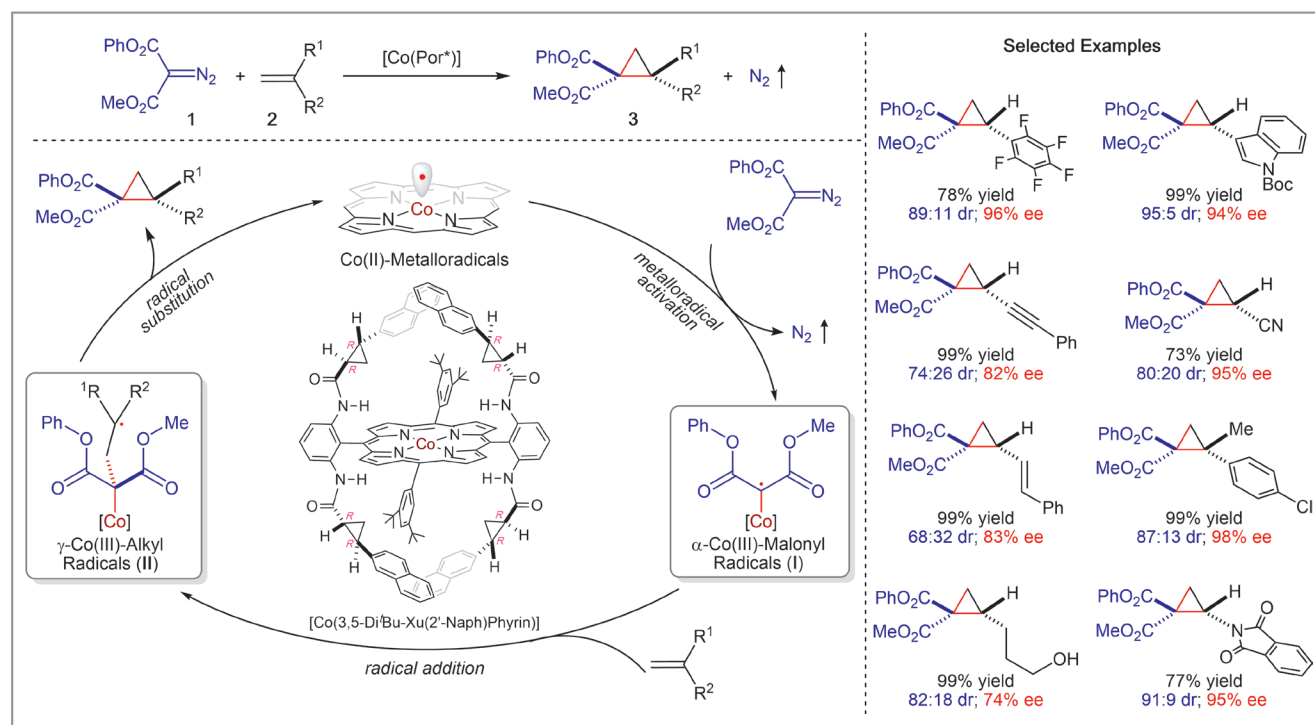
Radical Differentiation of Two Ester Groups in Unsymmetrical Diazomalonates for Highly Asymmetric Olefin Cyclopropanation

Chem Catal. **2022**, *2*, 330–344

Metal-catalyzed asymmetric cyclopropanation of alkenes with diazomalonates offers a potentially attractive approach for the construction of 1,1-cyclopropane diesters – a class of valuable three-membered carbocycles that serve as important building blocks for organic synthesis – with effective control of stereoselectivity. Due to the inherent stereocontrol challenge associated with two similar electron-withdrawing ester groups, the existing catalytic systems involving electrophilic metalcarbene intermediates have shown limited substrate scope and have been hampered by low enantioselectivity.¹ One conceptually different strategy for asymmetric cyclopropanation with unsymmetrical diazomalonates has recently been reported by the research group of Professor X. Peter Zhang at Boston College (Chestnut Hill, MA, USA). Professor Zhang and co-workers have demonstrated that Co(II) complexes of porphyrins [Co(Por)], as stable 15e-metalloradicals with well-defined open-shell d⁷ electronic structure, are

capable of homolytic activation of diazo compounds and organic azides, generating α -Co(III)-alkyl radicals and α -Co(III)-aminyl radicals, respectively, as kinetically competent catalytic intermediates for stereoselective radical processes. “In the past two decades, Co(II)-based metalloradical catalysis (MRC) has been successfully applied for the development of various types of stereoselective radical transformations, including olefin cyclopropanation,² olefin aziridination,³ C–H alkylation,⁴ and C–H amination⁵ as well as radical cascade⁶ reactions,” said Professor Zhang.

As a new synthetic application of Co(II)-MRC, Professor Zhang and co-workers have shown in this featured paper the development of Co(II)-catalyzed asymmetric cyclopropanation of alkenes with unsymmetrical diazomalonates. “Both excellent reactivity and selectivity have been achieved for this challenging cyclopropanation reaction through the fine-tuning of the D₂-symmetric chiral amidoporphyrin, to adopt



Scheme 1 Co(II)-based metalloradical catalysis for highly stereoselective olefin cyclopropanation with unsymmetrical diazomalonates

suitable environments that can govern the stereochemical course of the catalytic process (Scheme 1),” said Professor Zhang, who continued: “We have found that [Co(3,5-Di^tBu-Xu(2'-Naph)Phyrin)] is a highly effective catalyst for asymmetric cyclopropanation of various alkenes with methyl phenyl diazomalonate (MPDM). The multiple noncovalent attractive interactions between the catalyst and the substrates, both diazomalonate and alkene, help to differentiate the two similar ester groups and deliver the products in a highly stereoselective fashion.” He added: “We have shown that the Co(II)-based metalloradical system can smoothly activate unsymmetrical methyl phenyl diazomalonate even at room temperature, with effective differentiation of the two ester groups to cyclopropanate wide-ranging alkenes, affording 1,1-cyclopropane diesters bearing two contiguous stereogenic centers in high yields, with excellent control of both diastereo- and enantioselectivity.”

To support the hypothesis of an underlying stepwise radical pathway for the Co(II)-based catalytic process, Professor Zhang and co-workers performed combined computational and experimental studies, that provided multiple lines of convincing evidence. “The DFT calculations also revealed the existence of multiple H-bonding and π -stacking interactions in transition states involved with the cyclopropanation reaction. In addition to the rigidification of conformations, these noncovalent attractive interactions can cooperatively lower the activation barriers of the transition states, which may enhance catalytic reactivity and improve stereoselectivities of the cyclopropanation,” remarked Professor Zhang. Several stereospecific transformations from the resulting enantioenriched 1,1-cyclopropane diesters were demonstrated in this work, which the authors believe will find useful synthetic applications for the construction of other chiral organic molecules. Professor Zhang concluded: “This new catalytic system, which offers a streamlined entry to chiral 1,1-cyclopropane diesters, has solved one of the long-standing challenges in the field of asymmetric cyclopropanation. It once again showcases the power and potential of MRC in addressing challenging problems in organic synthesis through a fundamentally different approach.”

Matthew Fenske

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About the authors



Prof. X. P. Zhang

X. Peter Zhang received his Ph.D. from the University of Pennsylvania (USA) in 1996 under the direction of Prof. Bradford Wayland. He then undertook postdoctoral work at the Massachusetts Institute of Technology (USA) as a National Institutes of Health (NIH, USA) Postdoctoral Fellow during the period of 1996–2001, first with Prof. Stephen Lippard and then with Prof. Stephen Buchwald. Dr. Zhang began his independent career as assistant professor of chemistry at the University of Tennessee (USA) in 2001. He moved to the University of South Florida (USA) as associate professor of chemistry in 2006 and was promoted to professor in 2010. In 2015, Dr. Zhang joined Boston College (USA) as professor of chemistry. The research program of his laboratory has been focused on the formulation of metalloradical catalysis (MRC) as a conceptually new strategy to guide the development of general approaches for effectively controlling reactivity and selectivity of radical processes.

>>



Dr. J. Wang

Jingyi Wang received her Ph.D. in organic chemistry at Boston College (USA) in 2021 under the supervision of Professor X. Peter Zhang, where she carried out research work on developing new synthetic methodologies to construct biologically valuable molecules. She also applied electron paramagnetic resonance (EPR) to investigate the radical intermediates involved in Co(II)-based metalloradical catalysis. Currently, she is a senior scientist at GlaxoSmithKline (Cambridge, Massachusetts, USA) working on the development of novel solid-phase DNA encoded libraries as highly efficient functional drug screening platforms.



J. Xie

Jingjing Xie is currently a graduate student at Boston College (USA) in the group of Professor X. Peter Zhang, where she has carried out research work focusing on the application of 1,4-hydrogen atom abstraction as a key step for synthetic methodology development to construct biologically valuable molecules via Co(II)-based metalloradical catalysis. Before her graduate studies at Boston College, she received her M.S. degree in analytical chemistry from the University of Massachusetts Dartmouth (USA). Jingjing will join Amgen as a medicinal chemist after completing her graduate studies at Boston College.



W-C. C. Lee

Wan-Chen Cindy Lee is currently a graduate student at Boston College (USA) in the group of Professor X. Peter Zhang, where her research projects focus on the development of enantioselective radical reactions for stereoselective organic synthesis via metalloradical catalysis. She has also engaged with mechanistic studies on catalytic radical processes. Before her graduate studies at Boston College, she completed her M.S. degree in organic chemistry from the University of San Francisco (USA) in 2017 under the supervision of Prof. Jie Jack Li.



Dr. D-S. Wang

Duo-Sheng Wang received his Ph.D. in chemistry from Dalian Institute of Chemical Physics, Chinese Academy of Sciences (P. R. of China). Currently, he is a senior research associate in the group of Professor X. Peter Zhang at Boston College (USA), where his research interest is focused on developing methodologies for radical cycloaddition to construct cyclic scaffolds via metalloradical catalysis. He is also involved with the use of DFT calculations to elucidate mechanisms of catalytic radical reactions.

Insertion of Ammonia into Alkenes To Build Aromatic N-Heterocycles

Nat. Commun. **2022**, *13*, 425

Ammonia is one of the most-produced industrial chemicals, with a value of 144 million metric tons in 2020 (Figure 1). In addition to its use in fertilizers (~90% of the worldwide production), ammonia can also be utilized as a nitrogen source to build nitrogen-containing compounds.¹ “There is a series of advantages when using ammonia as a nitrogen source. It has an 82% mass-rate nitrogen incorporation and is reactive enough as a nucleophile. It is easy to store, transport, handle, and separate. On the other hand, there are several challenges in pursuing applications of ammonia in organic synthesis,” said Dr. Shuai Liu, from Nanjing University (P. R. of China), continuing: “First, the N–H bond in ammonia has a bond-dissociation energy of 107 kJ/mol, leading to a high barrier for direct cleavage by the catalyst. Second, ammonia is a strong ligand for diverse metal species, requiring demanding conditions for catalytic processes. Third, the resulting amine product could be more reactive than ammonia itself, posing additional difficulty in the control of chemoselectivity.” With this background, Dr. Shuai Liu and Professor Xu Cheng (also from Nanjing University, P. R. of China) recently reported their study on the direct insertion of ammonia into alkenes to build aromatic N-heterocycles with electricity as the driving force.

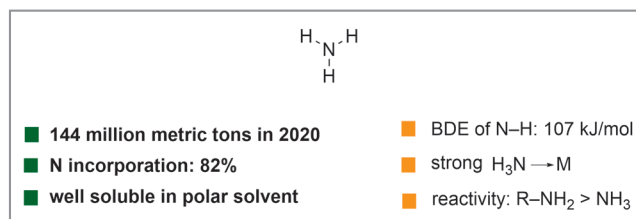
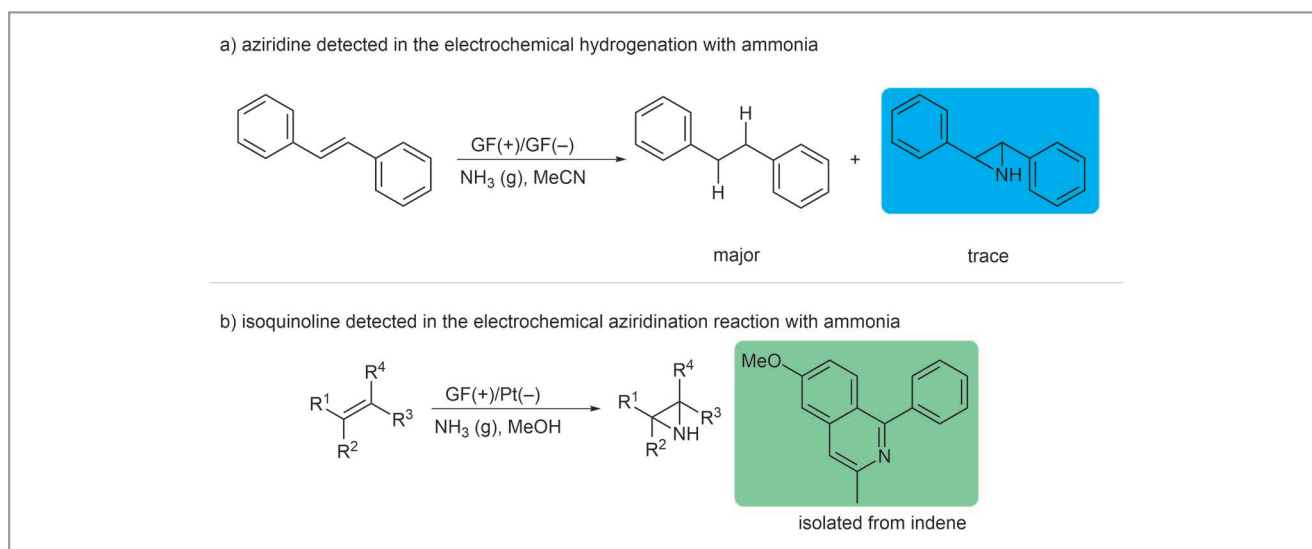


Figure 1 The factors of ammonia

This work is rooted in a previous research campaign where ammonia was employed as a hydrogen source: in 2019, Dr. Li and Professor Cheng reported the electrochemical hydrogenation of unsaturated functional groups with ammonia (Scheme 1a).² In that work, when stilbene was subjected to hydrogenation, a very small amount of aziridine product was detected. This finding led to a work on the aziridination of tetra-, tri-, and disubstituted alkenes using ammonia as a nitrogen source by Dr. Liu, Professor Cheng, and Professor Yong Liang (Scheme 1b).³ “It should be noted that during the preparation of that manuscript, Professor Timothy Noël and co-workers published their research on electrochemical



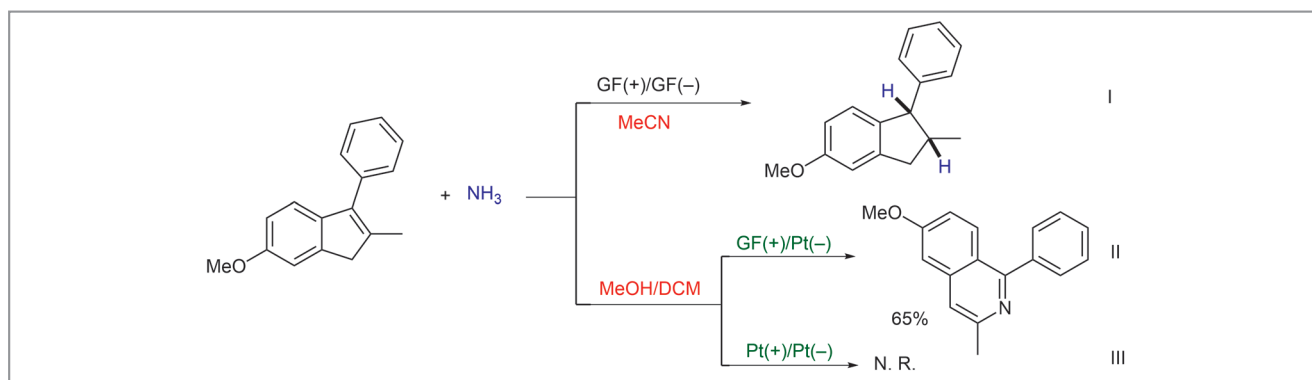
Scheme 1 The initial findings leading to the synthesis of isoquinoline with ammonia

aziridination using primary amines and ammonia,⁴ acknowledged Professor Cheng. “In our work, an unexpected product was found with a substrate having an indene substituent. After extensive characterization of this new compound, we confirmed that an isoquinoline was generated,” he added.

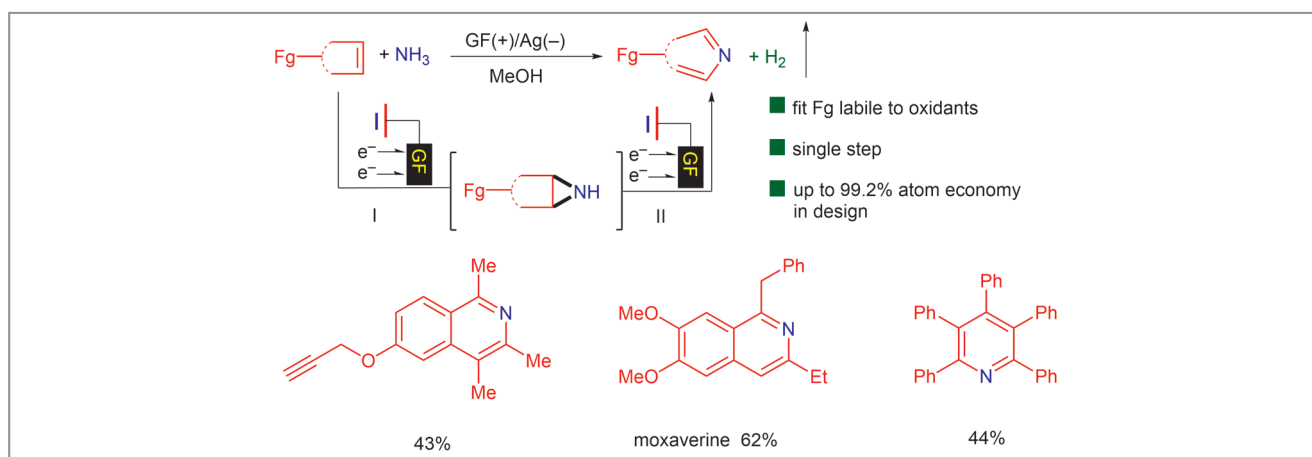
This result inspired the authors to study the potential of ammonia in the electrochemical reaction to build aromatic N-heterocycles. “We reasoned that this would be the most economical and convenient way to make aromatic N-heterocycles, since hydrogen would be the only by-product,” Prof. Cheng said, continuing: “Reported protocols for the preparation of aromatic N-heterocycles adopt the condensation of a nitrogen source with a pre-oxidized substrate.” Dr. Liu carried out an extensive screening of conditions and found that a graphite felt (GF) anode and MeOH are essential for this conversion. “When other solvents were applied, we always observed that the hydrogenation of the substrate was the predominant reaction (Scheme 2, I),” said Dr. Liu. He continued: “Instead, MeOH

was able to inhibit the hydrogenation pathway (Scheme 2, II). If a Pt anode was used rather than graphite felt, the decomposition of MeOH readily took place (Scheme 2, III). This was the common reaction in fuel cell.”

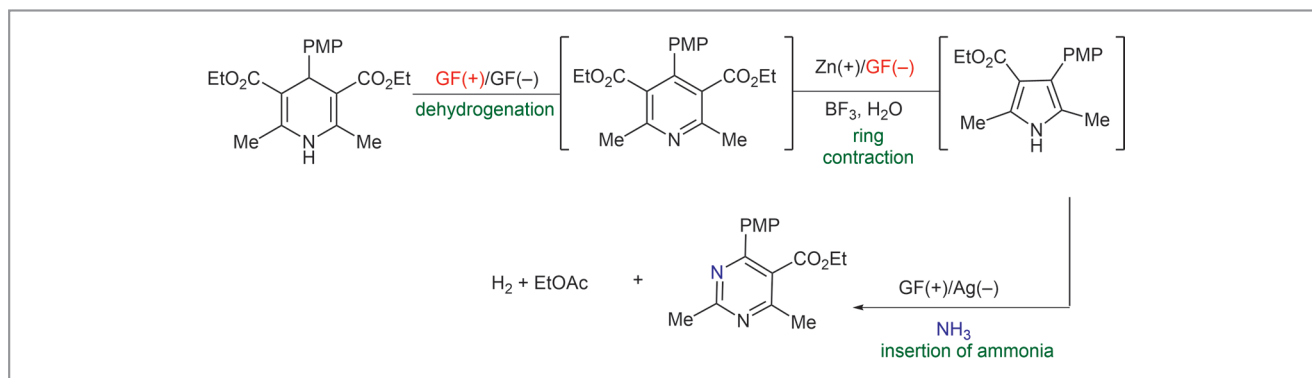
Subsequently, Dr. Liu started to explore the substrate scope of this transformation. A series of substituted indenenes were prepared and subjected to the electrochemical insertion of ammonia, affording the corresponding isoquinolines and pyridines (Scheme 3). “The reaction works well with indene-bearing substituents – like phenyl and alkyl – at specific position,” said Dr. Liu, “especially for the substituents able to stabilize the positive charge.” Dr. Liu further explained: “The activation of alkene at the anode would be one key stage of the overall transformation, which would give the cationic radical.” Therefore, careful analysis of the reaction mixture showed that an aziridine was the intermediate. Dr. Liu remarked: “This aziridine is quite unstable, as it would decompose even in the –20 °C freezer upon standing for a couple of



Scheme 2 Key factors regulating the chemoselectivity



Scheme 3 Reaction pathway and typical products



Scheme 4 Electrochemical approach to “edit” N-heterocycles

days, but without producing an isoquinoline.” Professor Cheng and Dr. Liu drafted a plausible reaction pathway in which the cyclic alkene is activated by anode oxidation and converts into an aziridine intermediate by trapping with ammonia (Scheme 3, I). “The next round of oxidation at the anode is the other key step of the process, driving the rearrangement of aziridine to isoquinoline (Scheme 3, II); cathode of Pt, Ag, and graphite felt could evolve hydrogen to balance the charge,” said Dr. Liu.

Next, an idea evolved into a plan (Scheme 4). “We reckoned we could now edit the heterocycles by using electricity, utilizing the Hantzsch ester as a starting material,” explained Professor Cheng and Dr. Liu. With this plan, Dr. Liu prepared the substituted Hantzsch ester and started exploring the electrochemical tandem reaction. “At first, the Hantzsch ester was converted into pyridine via a two-electron oxidation, then switching the electrode resulted in a rearrangement of pyridine to pyrrole,⁵ and finally insertion of ammonia into the pyrrole gave a pyrimidine with an unexplored substitution pattern,” said Dr. Liu, adding: “There is no need to isolate the intermediate.”

Professor Cheng concluded, “This article showed the potential of an electrochemical protocol capable of facilitating the introduction of ammonia into molecules, while giving an important clue on future reaction design.”

Matthew Farnok

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About the authors

*Dr. S. Liu*

Chemical Engineering at Xuzhou University of Technology (P. R. of China) as a lecturer. His studies focus on electrochemical heterocyclic synthesis.

Shuai Liu was born in 1993 in Jiangsu Province (P. R. of China). He received his Bachelor's degree from Jiangsu Normal University (P. R. of China) in 2015, and his Master's degree from the same university in 2018 under the supervision of Prof. Shu-Jiang Tu and Prof. Bo Jiang. He obtained his doctoral degree from Nanjing University (P. R. of China) in 2021 under the supervision of Prof. Xu Cheng. Currently, he is at the School of Materials and

*Prof. Dr. X. Cheng*

Austin (USA) as a postdoc in Prof. Dionicio Siegel's group for natural product synthesis. After this, he spent two years in Prof. Arun K. Ghosh's group at Purdue University (USA) as a postdoc for natural product synthesis and medicinal chemistry. In 2012, he joined the School of Chemistry and Chemical Engineering at Nanjing University (P. R. of China) as an associate professor and was promoted to professor in 2018. Currently, electrochemical synthesis is the focus of his group.

Xu Cheng was born in Tianjin (P. R. of China) and received his B.S. degree from Nankai University (P. R. of China) in 2000. In 2005, he received his Ph.D. from Nankai University in the group of Prof. Qin-Lin Zhou. Then he moved to the Max-Planck-Institut für Kohlenforschung, Mülheim an der Ruhr (Germany) and joined Prof. Benjamin List's group as a postdoc studying enantioselective organocatalysis. In 2009, he moved to the University of Texas at

Coming soon

Literature Coverage

A Photoredox-Catalyzed Approach for Formal Hydride Abstraction To Enable C_{sp^3} -H Functionalization with Nucleophilic Partners (F, C, O, N, and Br/Cl)

Literature Coverage

Remote Steric Control for Undirected *meta*-Selective C-H Activation of Arenes

Literature Coverage

Enantioselective Cu(I)-Catalyzed Borylative Cyclization of Enone-Tethered Cyclohexadienones and Mechanistic Insights

Further highlights

Synthesis Review: **Biocatalytic One-Carbon Transfer – A Review**

(by M. Müller and co-workers)

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Synfacts Synfact of the Month in category “Synthesis of Natural Products and Potential Drugs”: **Synthesis of Four Kopsane Alkaloids**

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