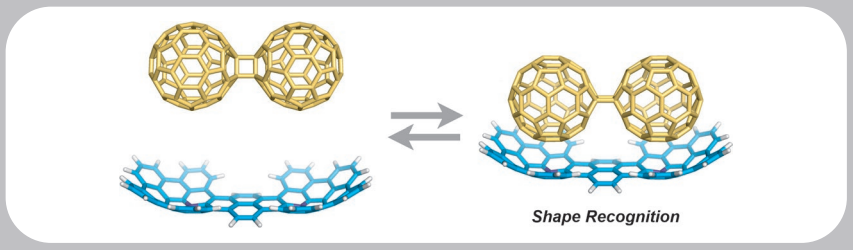
Synform

People, Trends and Views in Chemical Synthesis

2022/08

Fully Conjugated Azacorannulene Dimer as Large Diaza[80]fullerene Fragment

Highlighted article by W. Wang, F. Hanindita, Y. Hamamoto, Y. Li, S. Ito



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Thieme

Dear Readers,

The 2022 Editorial Board Meeting was held in the south of beautiful Sardinia at the end of May. It was a great opportunity to catch up in person after 3 years of disruption due to the Covid pandemic, and come up with new editorial ideas. It was also a great pleasure to congratulate and celebrate SYNLETT's Editor-in-chief Prof. Dr. Benjamin List on his recent Nobel Prize. The only letdown of an otherwise fantastic meeting was that some of us got delayed – in some cases quite severely – by missed flight connections due to bad weather or other issues, which unfortunately seem to be quite common in this summer of cancelled or disrupted flights. Despite these occasional troubles, I still believe a meeting in person is far better than a virtual one!!

This August issue of SYNFORM starts with a Young Career Focus interview with S. Liao (P. R. of China) about his professional perspectives and research interests, which currently lie predominantly at the interface of polymer chemistry and organic photocatalysis. S. Ito (Singapore) and his synthesis of a fully conjugated azacorannulene dimer as diaza[80]fullerene fragment are featured in the next Literature Coverage article, which is followed by another one having R. Shenvi (USA) and his innovative total synthesis of *Galbulimima* alkaloids as protagonists. The issue is closed by a third Literature Coverage article covering G. Liu's (P. R. of China) remarkable hydrogenation of internal alkenes, which occurs concomitantly with a remote halogenation of an alkene substituent.

Enjoy your reading!

In this issue

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Young Career Focus: Professor Saihu Liao (Fuzhou University, P. R. of China)

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 Professor Saihu Liao (Fuzhou University, P. R. of China).

Biographical Sketch

Prof. S. Liao

Saihu Liao studied chemistry at Huazhong University of Science and Technology (HUST, P. R. China), and obtained his bachelor's degree in 2005. After two years of graduate studies at the same university in Prof. Yuefa Gong's group, he moved to Germany and joined Prof. Benjamin List's group at the Max-Planck-Institut für Kohlenforschung (MPI-KOFO) in Mülheim an der Ruhr as a PhD student, where he focused on the ion-pair catalyst development based on the concept of asymmetric counteranion-directed catalysis (ACDC) and obtained his doctoral degree in organic chemistry in 2011. Then, he returned to China and joined Prof. Yong Tang's group as a research associate at the Shanghai Institute of Organic Chemistry (SIOC), Chinese Academy of Sciences, where he got to learn some chemistry about olefin polymerization. After another stay at MPI-KOFO from 2013 to 2016 as a postdoctoral researcher concentrating on new organocatalytic activation mode development, he started his independent career at Fuzhou University (P. R. China) in September 2016, where he was promoted to full professor in 2017. Now, he is also the Director of the Key Laboratory of Molecule Synthesis and Function Discovery of Fujian Province Universities. His current research interests encompass organocatalytic polymerization, photo-controlled polymerization, and sulfur radical chemistry. He was the recipient of the "Minjiang" Distinguished Professorship in 2016, was elected into the Recruitment Program of Global Experts of China in 2017, the Hundred-Talent Plan of Fujian Province in 2018, and received the Thieme Chemistry Journals Awards in 2022.

INTERVIEW

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

Prof. S. Liao The goal of our research is to develop efficient, practical, and sustainable methodologies for polymer synthesis with precise controls and functions. We are particularly interested in the development of organocatalysts, including organic photocatalysts and chiral catalysts, to achieve sequential, spatiotemporal, and stereochemical controls over different types of polymerizations. Additionally, we are also interested in the development of organic reactions involving sulfur and fluorine, targeting reagent, initiator, and monomer synthesis.

SYNFORM *When did you get interested in synthesis?*

Prof. S. Liao I was attracted by synthesis in my undergraduate course of organic chemistry and became particularly interested in the rules and mechanisms behind different reactivities. This curiosity later on led me to Prof. Yuefa Gong's physical organic chemistry course for graduate students and to choosing organic chemistry for my Master's studies. During that time, I was fascinated by the potential and versatility of organocatalysis, and luckily got the chance to pursue doctoral studies in the group of Prof. Benjamin List at the Max-Planck-Institut für Kohlenforschung (MPI-KOFO) in Germany, where I enjoyed the development of catalysts and reactions based on different concepts. I became interested in polymer synthesis when I was in Prof. Yong Tang's group, where I was impressed by the work on structural control on polyethylene through catalyst and ligand design. Later, I spent another stay in MPI-KOFO, where I finally made the decision to work on organocatalytic polymerization for my independent research.

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

Prof. S. Liao As a pivotal approach in constructing matter, organic synthesis is a fundamental science, affording the molecular basis for various research and applications. Nature does a similar thing in building up the body from elements and small molecules, at a miraculous level of precision and control. In this regard, I always expect problem- and function-oriented breakthroughs from organic synthesis to tackle those important issues that are currently challenging us.

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

Prof. S. Liao Inspired by Nature, and also by the Chinese philosophy of Tai Chi (Taiji) and Yin-Yang, I am particularly interested in the control of balance and equilibrium in bond formation and breakage, as well as the limitations of that control. During the time of setting up the platform for polymer chemistry study, we focused more on photo-induced radical reaction development, aiming to develop some new methods for initiator and monomer synthesis. In this regard, we developed a thioamide-type of radical thiolating agent for radical decarboxylative thiolation to free thiols (*Nat. Commun.* **2020**, *11*, 5340), which was inspired by the chain-transfer agent design in RAFT polymerizations. Further, we explored the generation and application of fluorosulfonyl radicals, which are challenging to produce due to the strong electron-withdrawing effect of the SO_2F group (*Angew. Chem. Int. Ed.* **2021**, *60*, 3956–3960; *Synlett* **2022**, *33*, 401–408). For the study of polymer chemistry, currently we are focused more on the development of organic photocatalysts, and recently introduced a catalyst design logic based on heteroatom-doping of polycyclic arenes. By following this logic, we have successfully developed both highly reducing (ODA) and oxidizing organic photocatalysts (BPS) via O– and P+ doping of anthanthrene, respectively (Figure 1). The ODA catalysts could promote the metal-free atom transfer radical polymerization (ATRP) of methacrylates at a sub-ppm level of catalyst loading (*Nat. Commun.* **2021**, *12*, 429), while BPS could achieve a strict temporal control in the cationic RAFT polymerization of vinyl ethers (*J. Am. Chem. Soc.* **2021**, *143*, 6357–6362), both by virtue of the successful establishment of an effective activation–deactivation equilibrium.

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

Prof. S. Liao Our recently published study on organocatalytic stereoselective cationic polymerization of vinyl ethers (Patent CN 113527556 A, **2021**; *Sci. China Chem.* **2022**, 65, 304–308; *J. Am. Chem. Soc.* **2022**, *144*, 679–684) is something I considered important, as it allows the synthesis of metal-free isotactic poly(vinyl ether)s with high molecular weights and melting points at low catalyst loadings. These poly(vinyl ether)s display tensile properties similar to those of commercial LDPE, but they are more adhesive to polar substrates and, importantly, they are biodegradable. This stereoselective organocatalytic polymerization system was developed based

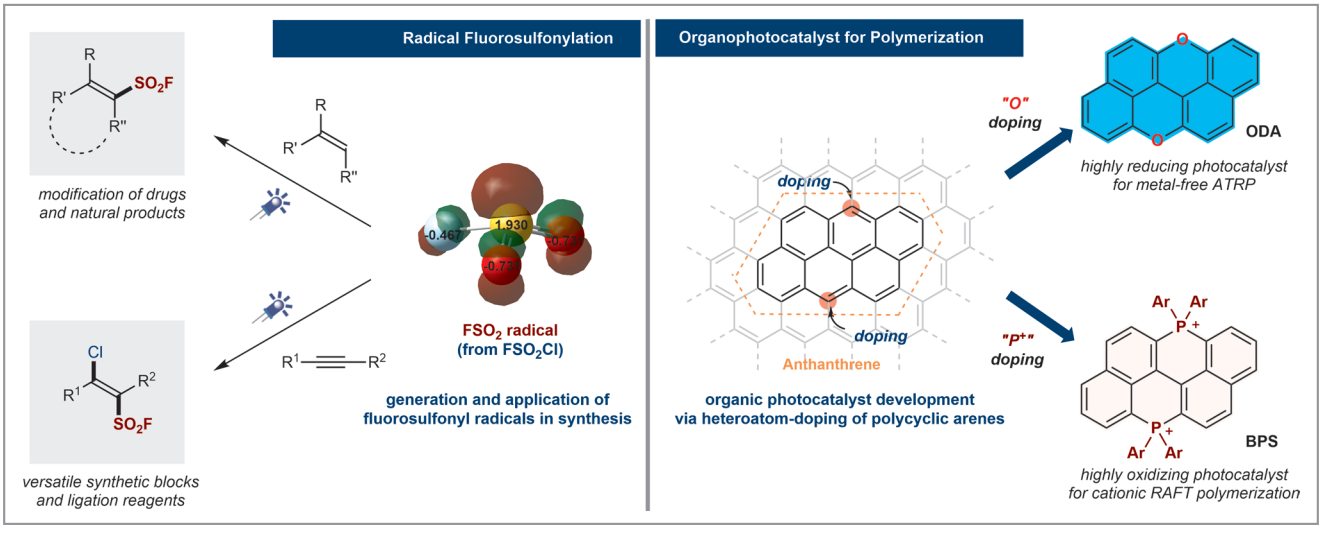

Figure 1 Radical fluorosulfonylation and the development of photoredox organocatalysts for polymerization.

on the concept of chiral counteranion mediation, which may serve as an inspiration for the development of other cationic polymerizations when seeking a tacticity control.

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Fully Conjugated Azacorannulene Dimer as Large Diaza[80]fullerene Fragment

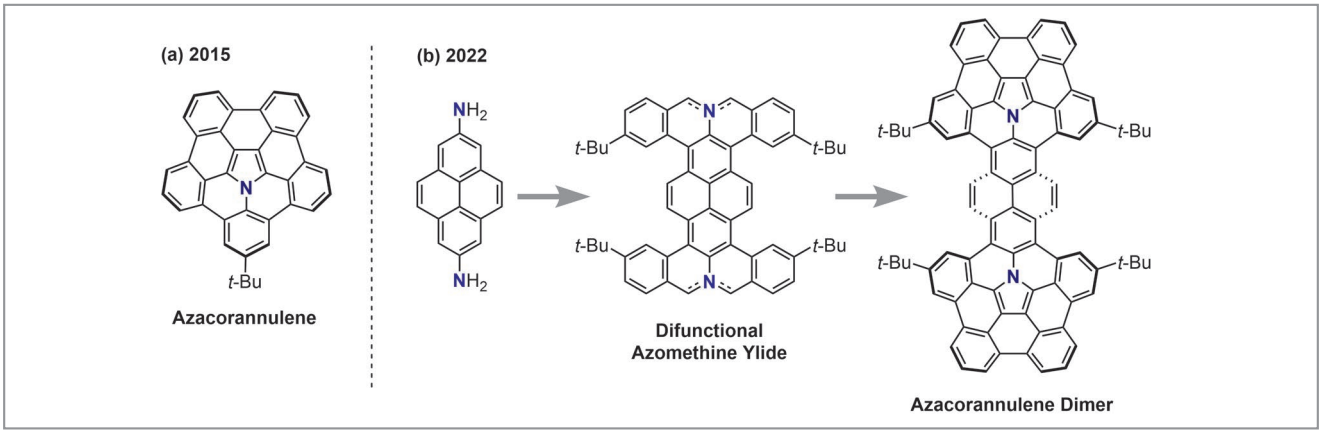
Nat. Commun. **2022**, *13*, 1498

Since their discovery in the 1980s, fullerenes have attracted much attention as a molecular form of carbon allotrope. Owing to their curved structure and rich π-electron density, fullerenes exhibit a wealth of interesting phenomena and properties and thus have been studied and tested for applications in various research fields such as electronics, catalysis, and gas storage. Fullerenes have also been an important target of bottom-up synthesis for synthetic chemists. Although the synthesis of C_{60} from small polycyclic aromatic precursors was achieved,[1] fullerenes of different shapes and sizes are still difficult to synthesize selectively. The group of Professor Shingo Ito at Nanyang Technological University (Singapore) has been studying this synthetic challenge, leading to the title paper in *Nature Communications*.

"Aside from altering the size and shape of fullerenes, introducing one or more heteroatoms into the fullerene cage can be used as an alternative approach to tune its physiochemical properties, thus changing the photochemical and electronic character of the fullerene clusters," explained Professor Ito. "However, in contrast to hydrocarbon-based fullerenes, the synthesis of heterofullerenes has been much more of a challenge. The successful example of solution-based synthesis thus far is Wudl's synthesis of $C_{59}N$.[2] Despite this, the synthesis of multiple heteroatom-embedded fullerenes has not been achieved on a macroscopic scale. There are two major challenges for this synthesis," continued Professor Ito: "Firstly, synthetic methods for heteroatom-embedded polycyclic aromatic molecules with large π-surfaces are still lacking, compared to hydrocarbon molecules consisting of only carbon and hydrogen atoms. Secondly, the 'isomeric problem', whereby introducing multiple heteroatoms into fullerene skeletal structure could generate numerous possible isomers, is a serious issue. Hence, the synthesis and isolation of a single isomer becomes much more of a challenge."

Encouraged by the above-mentioned bottom-up synthesis of C_{60},[1] researchers have shown tremendous interest in the bottom-up synthesis of multi-azafullerenes from polycyclic aromatic precursors. This synthetic approach allows for the controlled and selective introduction of nitrogen atoms into fullerenes. However, suitable synthetic protocols for nitrogen-embedded polycyclic aromatic molecules as large azafullerene fragments have not yet been developed.

Professor Ito said: "In 2015, we reported the efficient synthesis of aza-pentabenzo-corannulene (Scheme 1; left), where the key to the successful synthesis is the use of a polycyclic aromatic azomethine ylide.[3] This compound has attracted considerable attention from the community, as it represents the first example of a heteroatom-embedded corannulene. Additionally, the molecule can be regarded as a partial structure of mono-azafullerene $C_{79}N$. However, the surface area this compound covers is not large enough to be used as a precursor for azafullerene synthesis. Shinokubo et al. have reported



Scheme 1 (a) Azacorannulene reported in 2015. (b) Synthesis of azacorannulene dimer via difunctional azomethine ylide.

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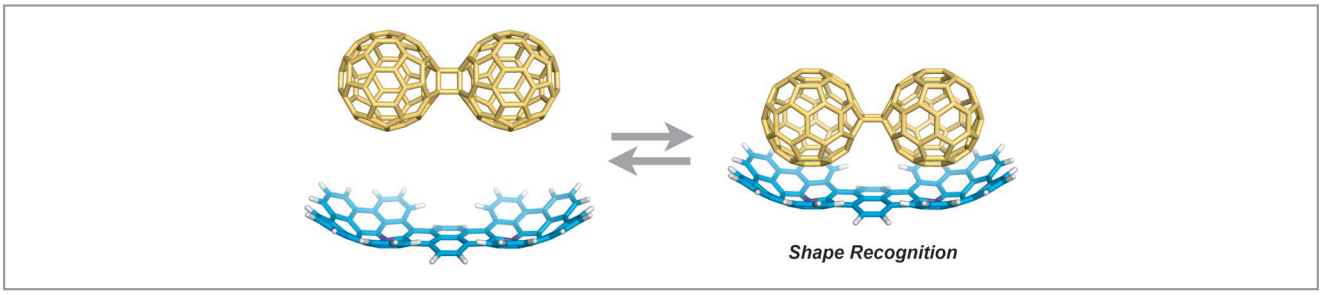

Figure 1 One of the possible modes of association between azacorannulene dimer and C_{120} determined by DFT calculations.

azacorannulene dimers linked via carbon–carbon single bonds;[4] nevertheless, molecular fragments of azafullerene with larger π-surfaces are relatively rare, due to the limited number of synthetic approaches known."

In the present study the group decided to synthesize a *fully conjugated* azacorannulene dimer (Scheme 1, right). "Towards the end, we employed a difunctional azomethine ylide derived from 2,7-diaminopyrene as a vital synthetic precursor," revealed Professor Ito. He continued: "The first primary challenge we encountered was due to the low solubility of fully conjugated difunctional azomethine ylides. At the initial trial, we synthesized the compound without any bulky substituents, but it was found to have an extremely poor solubility, thus preventing us from performing basic structural characterization. Meanwhile, a drastic improvement in its solubility was observed following the introduction of multiple *tert*-butyl groups.

Professor Ito revealed that, following the first submission of this manuscript to *Nature Communications*, the authors received several critical comments and feedback from the reviewers. "One potential drawback raised by the reviewers was regarding the lack of any practical application," said Professor Ito, continuing: "To address this issue, a reviewer suggested examining our molecule's ability to act as a host molecule for selective association with C_{120}, which motivated us to investigate its intermolecular association with fullerenes, C_{60} and C_{120}. It was discovered that our azacorannulene dimer exhibits a higher association constant with C_{120} than with C_{60}. This indicates that the boat-shaped azacorannulene dimer has superior recognition of the dumbbell-like C_{120} molecule than of the spherical C_{60} (Figure 1). Thanks to this reviewer's outstanding suggestion, we successfully managed to observe an interesting phenomenon that is difficult to achieve by other systems."

"We believe that this method provides an important step towards the selective synthesis of diazafullerenes. The utilization of difunctional azomethine ylide provides a feasible approach for the synthesis of large multi-azafullerene fragments," said Professor Ito. He concluded: "In the future, we will be trying to further extend the π-surface of this azacorannulene dimer. Our ultimate goal is to synthesize azafullerene precursors that cover 100% of the atoms of multi-azafullerenes and to succeed in the total synthesis of multi-azafullerene."

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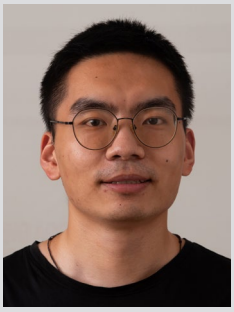
About the authors



Dr. W. Wang

Weifan Wang was born in Yancheng, Jiangsu (P. R. of China). He received both his B.S. (2014) and Ph.D. (2019) degrees in chemical process engineering of forest products from Nanjing Forestry University (P. R. of China). His studies focused on synthesis and applications of low-valent magnesium complexes. In 2020, he joined Prof. S. Ito's group at Nanyang Technological University (Singapore) for postdoctoral research on the synthesis of heteroatom-containing π-functional molecules.

F. Hanindita

Fiona Hanindita was born in Jakarta (Indonesia). She received a bachelor's degree in chemistry from Nanyang Technological University (Singapore) in 2019. She has been pursuing her Ph.D. degree under the supervision of Professor S. Ito since 2019.

Y. Hamamoto

Yosuke Hamamoto was born in Hiroshima (Japan). He received his B.Sc. (2018) and M.Sc. (2020) in chemistry from Osaka University (Japan). He is currently pursuing his Ph.D. degree at Nanyang Technological University (Singapore) under the supervision of Prof. S. Ito. He works in the field of the synthesis and investigations of π-conjugated aromatic systems.

Dr. Y. Li

Yongxin Li was born in Nanyang, Henan (P. R. of China). He received his Ph.D. degree from the Chemistry Department at National University of Singapore (Singapore) in 2003. He has worked at Division of Chemistry and Biological Chemistry, School of Physical and Mathematical Sciences, Nanyang Technological University (Singapore), as a crystallographer since 2005.

Prof. S. Ito

Shingo Ito received his B.Sc. (2003), M.Sc. (2005), and Ph.D. (2008) degrees in chemistry from The University of Tokyo (Japan) under the supervision of Professor E. Nakamura. During that time, he joined the group of Professor S. E. Denmark at University of Illinois at Urbana-Champaign (USA) and the group of Professor M. Nakamura at Kyoto University (Japan) as a predoctoral researcher. In 2008, he was appointed as Assistant Professor in the group of Professor K. Nozaki at Department of Chemistry and Biotechnology, Graduate School of Engineering, The University of Tokyo (Japan), where he was promoted to Lecturer in 2017. Since 2018, he has been Assistant Professor at Division of Chemistry and Biological Chemistry, School of Physical and Mathematical Sciences, Nanyang Technological University (Singapore). His research interests include the synthesis and applications of novel π-conjugated molecules.

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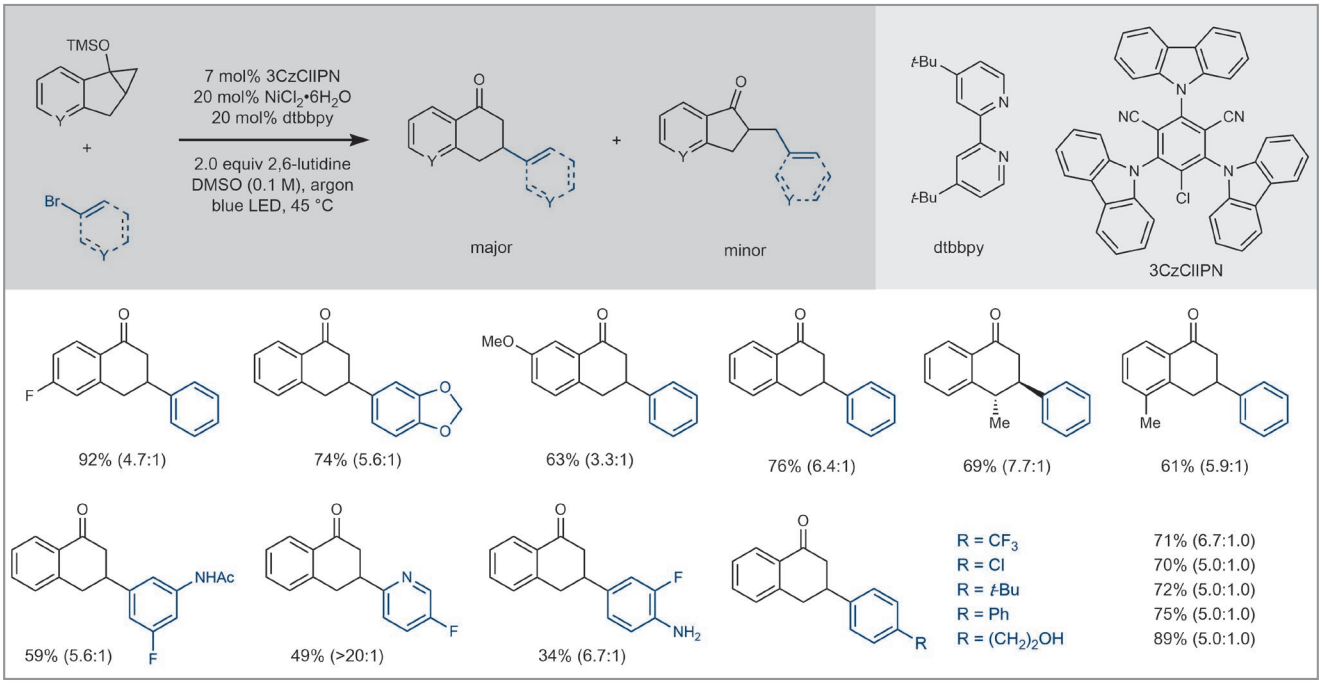
Concise Syntheses of GB22, GB13, and Himgaline by Cross-Coupling and Complete Reduction

Science **2022**, *375*, 1270–1274

Galbulimima (GB) is a genus of large, flowering tree that grows in tropical regions of eastern Asia and Oceania. GB bark finds use as an antipyretic, analgesic, and hallucinogenic by indigenous Papuans, although the alkaloid or alkaloids responsible for these responses remain unknown. The group of Professor Ryan Shenvi at Scripps Research (La Jolla, USA) has been working on this problem. Professor Shenvi explained, "Due to the poor accessibility of GB trees, low natural abundance of alkaloids, and considerable variation between bark samples, chemical synthesis may be the best way to correlate alkaloid structure to biological function." Access to class III GB alkaloids was significantly enhanced by strategic installation of methine stereocenters and a novel metallaphotoredox cross-coupling of aryl bromides and siloxycyclopropanes (Scheme 1).

Eleanor Landwehr, one of the first authors on this *Science* paper, told SYNFORM: "I joined this project during pandemic shutdowns and shiftwork, so it has been an adventure from the start. Initial photochemical conditions relied on a cooling fan and ventilated box, resulting in variation from reaction to reaction, which contributed to irreproducibility." Ms. Landwehr and author Dr. Meghan Baker worked diligently to optimize the photochemical reaction and explore its applicability to a variety of substrates. "Application to the pyridine siloxycyclopropane and aryl bromide necessary for GB alkaloid synthesis, however, resulted in low yields," said Dr. Landwehr. She continued: "It was also difficult to access large quantities of the pyridine siloxycyclopropane. I was able to simultaneously develop an alternative Suzuki/Kulinkovich route to the pyridine siloxycyclopropane with visiting student Leo Smith and optimize this cross-coupling to 57% isolated yield."

The challenging Friedel–Crafts reaction was solved by author Dr. Takuya Oguma, who found that the reaction proceeded cleanly when substrate was added to a mixture of HFIP and Et_2AlCl (Scheme 2). Ms. Landwehr explained: "In the presence of other strong Brønsted or Lewis acids, an unexpected



Scheme 1 A new *endo*-selective cyclopropane cross-coupling was developed to access attached-ring motifs that are inaccessible by enone conjugate addition.

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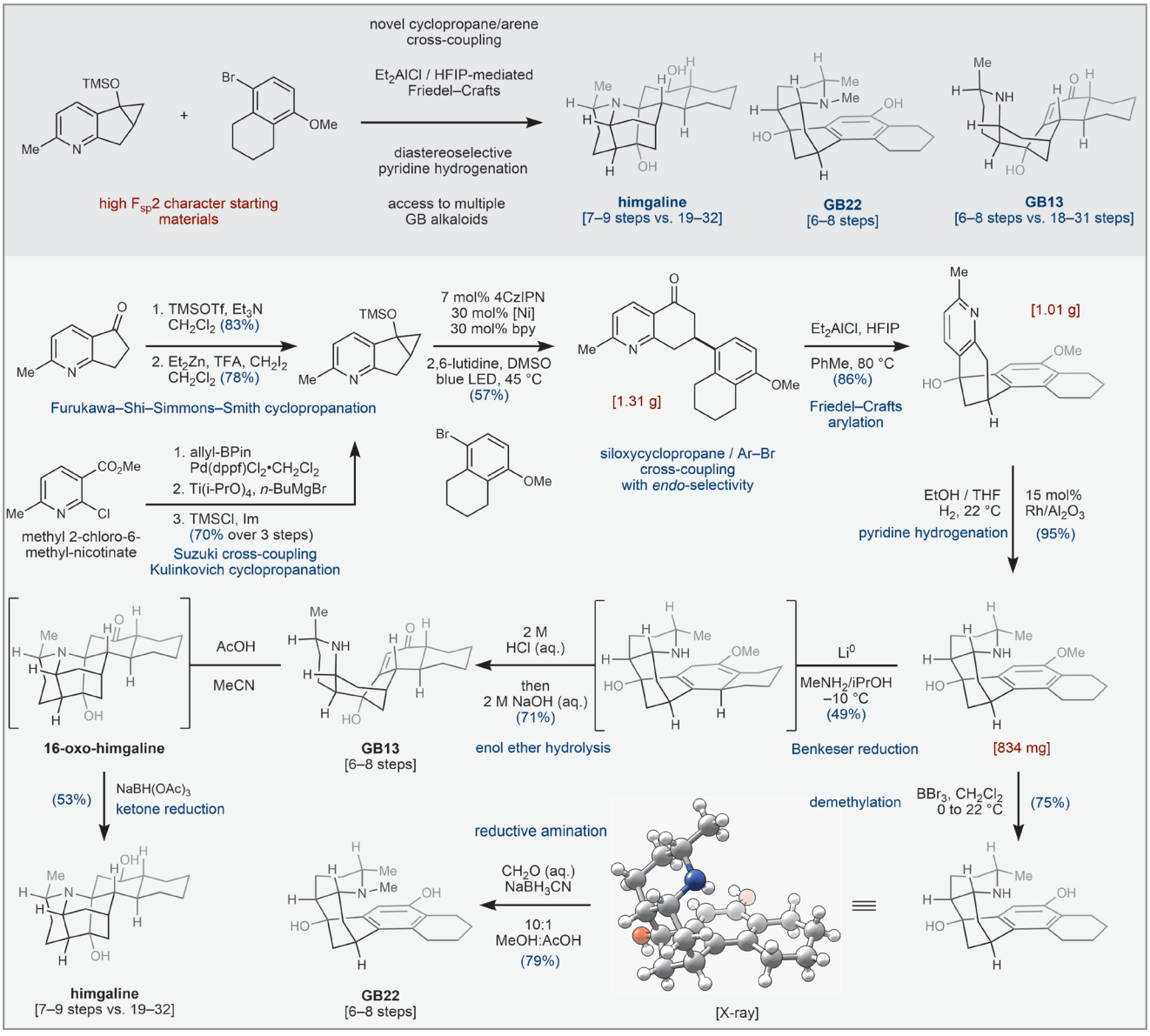
retro-Friedel–Crafts reaction cleaved our hard-won attached-ring bond."

On the cusp of her thesis defense, Meghan Baker discovered that methylamine solvent enabled efficient arene reduction, beyond the trace quantities observed with other conditions. "Prior to this observation, we could not decide whether to publish the substrate scope and GB22 or to add GB13 and himgaline to the same manuscript," remarked Ms. Landwehr. She continued: "Her contribution compelled us to include these more complex natural products. Ryan was so excited by the discovery that he joined us in lab for a few days and even made some of our first crude mixtures of GB13 and himgaline. For the first months of optimization, we were able to use an old lecture bottle of methylamine. This became a game of chicken between yield and residual gas: we feared for the day that this US Drug Enforcement Administration (DEA)-regulated substance would run out and we would be stuck. The day finally came when, in the middle of a Benkeser reduction, the lecture bottle petered out. That day we were forced to jury-rig a system to free-base an old container of methyl-



Scheme 2 Aromatic building blocks can be advanced to high fraction sp^3 *Galbulimima* (GB) alkaloids through a sequence of simple stereoselective reductions.

amine hydrochloride with NaOH, pass the gas through a drying tube and condense it into the reaction vessel."

This slow setup significantly impeded optimization. So, the discovery that a Birch variant reported by Koide *et al.* efficiently reduced the same arene was a great relief. Ms. Landwehr said: "I remember vividly my lab mate Nathan Dao running up to me and saying, "Did you see the Birch reduction in *Science* today?" and within 30 minutes the first LC showed mostly our desired product."

Acid hydrolysis of the enol ether followed by basification with sodium hydroxide yielded GB13 with only small amounts of the minor diastereomer. Ms. Landwehr said: "Stereoselectivity may arise from conversion into 16-oxo-himgaline upon treatment with acid, followed by equilibration to the lowest energy configuration."

Professor Shenvi concluded: "If targets are chosen carefully, total synthesis can be an irreplaceable and enabling science. Preliminary data already indicates that high-affinity biomolecular targets for class III alkaloids are found among human neuronal receptors. We expect other alkaloids from the bark of *Galbulimima* to yield a trove of new leads for therapeutic development."

About the authors

Top row, left to right: M. A. Baker, Prof. R. A. Shenvi, E. M. Landwehr; Bottom row, left to right: T. Kawajiri, T. Oguma

Meghan A. Baker received her B.S. in biochemistry from the University of Texas at Austin (USA) in 2016 and completed her Ph.D. in the lab of Professor Ryan Shenvi at Scripps Research (USA) in 2021. She is now a Senior Scientist in Discovery Process Chemistry at Merck in South San Francisco (USA).

Ryan A. Shenvi earned his PhD in 2008 as an NDSEG predoctoral fellow with Professor Phil Baran at the Scripps Research Institute (USA). After NIH-funded postdoctoral studies with E. J. Corey at Harvard University (USA), Ryan returned to Scripps to start his own research group. His laboratory develops new chemistry to navigate natural product space and interfaces synthesis design with structural biology.

Eleanor M. Landwehr earned her B.S. in chemical engineering from UW-Madison (USA) in 2020 where she conducted research in the lab of Jennifer Schomaker. She is currently a second-year student in the Skaggs Graduate School of Chemical and Biological Sciences at Scripps Research (USA).

Takuya Oguma is an associate director at Shionogi & Co. Ltd. He earned his PhD in 2014 at Kyushu University (Japan), where he explored iron-catalyzed asymmetric oxidation with Dr. Tsutomu Katsuki. He joined the research group of R. A. Shenvi at Scripps Research (USA) as a visiting scientist and developed methodology and total synthesis (2018–2019). He is currently focusing on CNS drug discovery at Shionogi (Japan).

Takahiro Kawajiri received his B.S. (2016) and Ph.D. (2020) in the lab of Professor Hironao Sajiki at Gifu Pharmaceutical University (Japan). He joined the lab of Professor Ryan Shenvi at Scripps Research (USA) in 2018 as a visiting student. He is currently a process chemist at Shionogi (Japan).

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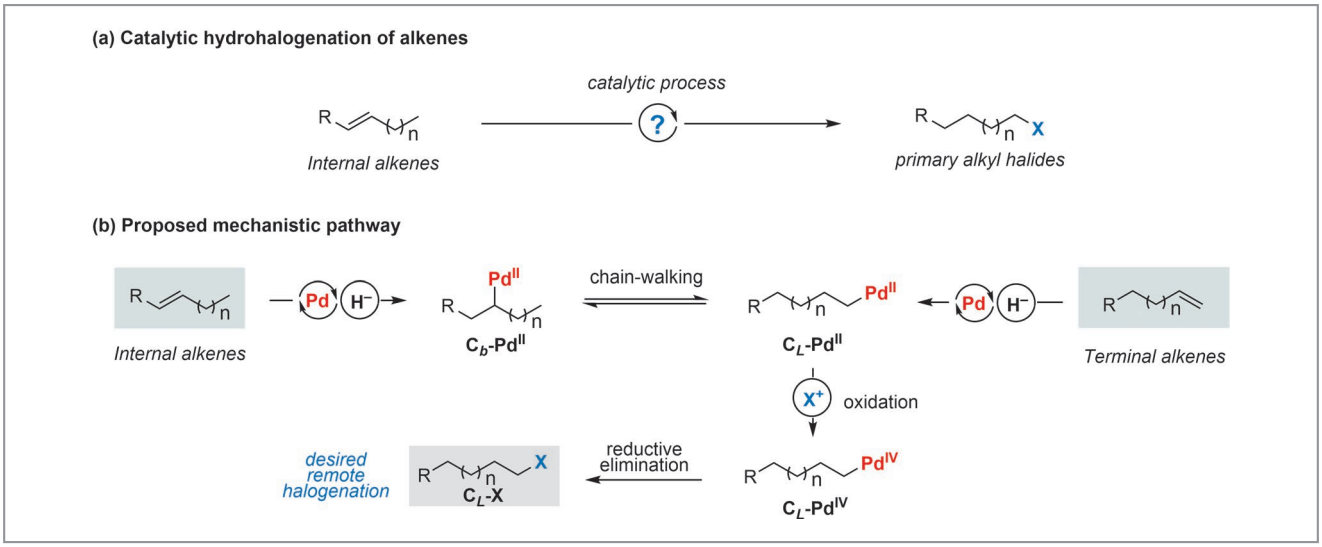
Catalytic Remote Hydrohalogenation of Internal Alkenes

Nat. Chem. **2022**, *14*, 425–432

Primary alkyl halogens have wide applications in academic and industrial chemical research as a result of their excellent reactivity toward various organic transformations. In terms of access to this key class of compounds, catalytic halogenation of feedstock olefins is most attractive but highly challenging.[1] Alternatively, the halogenation of alkenes generally provides branched alkyl halides, but there is a lack of methods to prepare linear alkyl halides directly from terminal alkenes, let alone from internal alkenes and mixtures of alkene isomers. Very recently, a remote oxidative halogenation of alkenes under palladium catalysis was reported by the research group of Professor Guosheng Liu at Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences (Shanghai, P. R. of China), who demonstrated that both terminal and internal alkenes can be regioselectively converted into primary alkyl halides with high efficiency (Scheme 1a). "Remote hydrofunctionalizations of internal alkenes under reductive or redox neutral reaction conditions have been extensively investigated in recent decades. Meanwhile, remote oxidation reactions, such as oxidative halogenation and oxygenation reactions, are of great interest but have not been documented to date," said Professor Liu. The first author, Dr. Xiang Li, remarked: "Research interests in our group focused on oxidative functionalization of unactivated alkenes. Recently, we reported a palladium-catalyzed enantioselective diacetoxylation[2] and oxycarbonylation[3] of terminal alkenes with high regio- and enantioselectivity, wherein the simplest alkenes, such as propylene and butene, performed very well. Notably, these reactions were enabled by introducing substituents into a pyridyl-oxazoline (Pyox) ligand at the C6 of pyridine, prompting us to survey the formal anti-Markovnikov hydrochlorination of terminal alkenes and remote hydrochlorinations of internal alkenes."

With the proposed mechanism (Scheme 1b), the engineered Pyox ligand **L3** with a hydroxyl group was demonstrated as an efficient ligand to carry out palladium-catalyzed hydrochlorination of both terminal and internal alkenes with excellent chemo- and regioselectivity, where the commonly used *N*-chlorosuccinimide (NCS) was employed as an electrophilic chlorine source and $^{i}Pr_3SiH$ as a compatible hydrogen source (Scheme 2a). "Compared to ligands **L1** and **L2**, the excellent performance of **L3** revealed that both the alkyl substituent in the pyridyl residue and the OH group in the oxazoline ring were essential for the reaction, where the former could promote the fast palladium migration, and the latter could accelerate the oxidative chlorination of C_L–Pd^{II}(**L3**) by NCS, owing to the hydrogen-bonding between OH group in **L3** and the oxygen atom of NCS (Scheme 2a)," said Professor



Scheme 1 Palladium-catalyzed hydrohalogenation of alkenes

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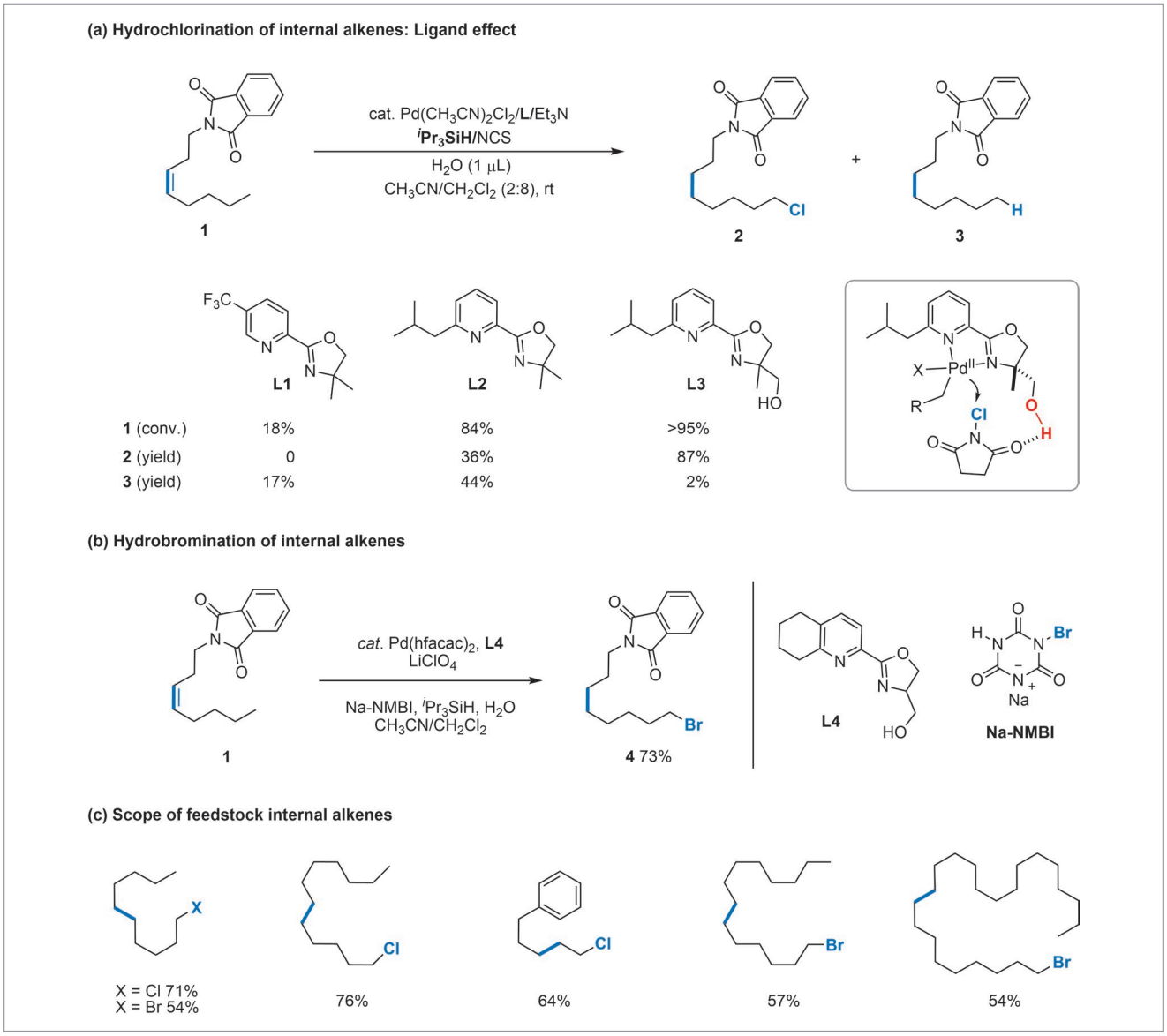
Liu. "Notably, the amount of water is vital for the reaction's reproducibility, which could activate hydrosilane to promote PdH species formation. Moreover, addition of a trace of NEt_3 acted as a labile ligand to suppress the side oxygenation and amination reactions," he added.

"Inspired by the results of the chlorination process, we made further great efforts on the hydrobromination of alkenes; however, the difficulty encountered in this endeavor was beyond our expectation," said Professor Liu. In fact, under similar reaction conditions, a series of commonly used electrophilic bromination reagents turned out to be incompatible with silanes. The reactions failed to deliver hydrobromination product **4**, affording debromination products instead. After numerous failures, the group finally found that the mild brominating reagent Na-NMBI efficiently afforded the linear hydrobromination product **4** (Scheme 2b). "The optimized reaction conditions have broad substrate scope in terms of alkenes, in which also the simplest internal alkenes give linear alkyl halides in good yields with exquisite site-selectivity. The catalytic system is also good for the mixture of alkene isomers



Scheme 2 Remote hydrohalogenation of internal alkenes

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generated from dehydrogenation of alkanes, providing a window to investigate the high-value utilization of inexpensive alkane substrates," said Professor Liu.

Professor Liu concluded: "This new catalytic system provides an easy access to primary alkyl halogens in moderate to excellent yields, with exquisite site-selectivity and good functional group tolerance under very mild conditions. A rationally designed Pyox ligand played a critical role in the reaction efficiency and selectivity. This ligand-promoted chain migration paves the way for the palladium-catalyzed selective functionalization of internal alkenes."

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