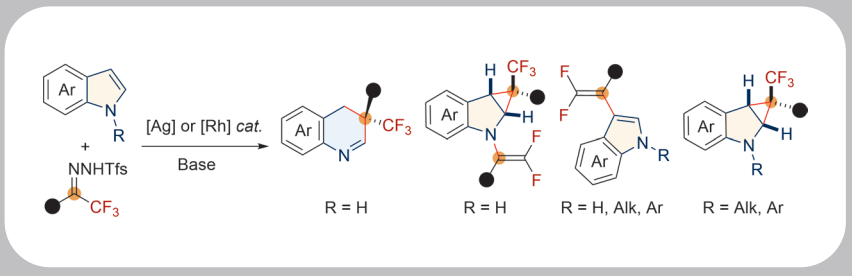
Synform

People, Trends and Views in Chemical Synthesis

2024/11

Tunable Molecular Editing of Indoles with Fluoroalkyl Carbenes

Highlighted article by S. Liu, Y. Yang, Q. Song, Z. Liu, Y. Lu, Z. Wang, P. Sivaguru, X. Bi



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Thieme

Dear Readers,

This November issue of SYNFORM starts with a report on the synthesis and characterization of donor–acceptor Stenhouse adducts, which find applications as photoswitches, recently published in *Nat. Commun.* by the group of E. Picazo (USA). The Young Career Focus interview with recent Thieme Chemistry Journals Awardee F. M. Fung (Ireland) is second up, followed by another Literature Coverage article on the stereospecific synthesis of axially stereogenic bridged biaryls using Ni-catalyzed C–O bond cleavage, as recently described in *ACS Catal*. by the group of Z.-C. Cao (P. R. of China). The final Literature Coverage article of the issue covers the molecular editing of indoles by means of fluoroalkyl carbenes developed and published in *Nat. Chem.* by the group of X. Bi (P. R. of China).

Enjoy your reading!

In this issue

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Development and Characterization of Amino Donor–Acceptor Stenhouse Adducts

Nat. Commun. **2024**, *15*, 5533

Piancatelli and related rearrangement reactions date back to as early as 1850 when Stenhouse reported the formation of a highly colored compound upon amine addition to furfural. Although the mechanism of reactivity was not fully elucidated until much later, these rearrangement reactions have provided a facile means to construct hydroxy-substituted triene or cyclopentenone adducts (Scheme 1a). The resulting scaffolds find application in the synthesis of prostanoic acids and other natural products, Stenhouse salt derivatives, and most recently, donor–acceptor Stenhouse adduct (DASA) photoswitches. The group of Professor Elias Picazo at the University of Southern California (Los Angeles, USA) initially became interested in DASA photoswitches because of their attractive photophysical features that set them apart from other molecular photoswitches. "DASAs undergo isomerization from a vividly colored triene to a colorless cyclopentenone upon absorbing low-energy light (Scheme 1b)," said Professor Picazo, adding: "This process offers a gentle method to reversibly control substantial changes in size, charge, and color."

Since their discovery a decade ago, DASAs have seen a range of structural modifications that expand their photophysical properties to absorb in the near-IR region and provide increased switching efficiencies in polar and nonpolar solvents (Scheme 1c). Professor Picazo explained: "The electronic and steric tuning at the donor, acceptor, or triene structural compartments is made possible by the modular synthesis of the photoswitch. First, furfural undergoes a Knoevenagel condensation with a carbon acid acceptor. Then, a secondary amine donor is added to the condensed product, where nucleophilic addition causes the furan to undergo dearomative ring opening, resembling an interrupted aza-Piancatelli rearrangement. This provides the hydroxy-substituted triene. However, since the Piancatelli rearrangement had only been amenable to furan substrates, this hydroxy group had remained static while all other structural compartments of the photoswitch have been modular. Given that structural modifications have been essential to photoswitch development and broader applicability, we wanted to study the photophysical effect of the triene heteroatom by synthesizing DASA derivatives with different heteroatomic substituents."

Professor Picazo explained that it had been reported previously that thiophene and pyrrole substrates failed to undergo the nucleophilic ring opening under general DASA synthesis conditions. This can be attributed to their respective aromatic stabilities of 120 kJ/mol and 89 kJ/mol in comparison to furan's stability of 66 kJ/mol. "We envisioned that the additional bonding orbital on nitrogen could be leveraged to decrease the aromatic stability of pyrrole and promote dearomative ring opening upon amine addition," remarked Professor Picazo. He continued: "We first synthesized pyrrole substrates bearing activating groups with a range of inductive character (Scheme 1d). The relative electronic deficiency of the pyrrole substrates was quantified with ^{13}C NMR by using analogous furan and thiophene substrates as markers for productive (or unproductive) ring opening. While some activating protecting groups showed reactivity, only sulfonyl-protected pyrrole was able to produce the desired amino DASA in up to 74% yield, marking the first example of a pyrrole-based interrupted aza-Piancatelli rearrangement."

After finding the optimal conditions and pyrrole substrates to produce the DASA derivatives, the group synthesized amino DASAs with varying donors and acceptors, and their hydroxy DASA counterparts. "This allowed us to study the triene heteroatom effect on photoswitching and optical properties," said Professor Picazo. He went on: "We learned that the strong electron-withdrawing nature of the sulfonamide group in comparison to hydroxyl resulted in diminished photoswitching efficiencies. Spectroscopic characterization during the irradiation period suggested that amino DASAs fail to undergo the initial *cis*-to-*trans* isomerization initiated by photoexcitation as isomeric intermediates were not observed even at low temperatures. During optical characterization, it was also found that the strong withdrawing nature of sulfonamide in amino DASAs results in a hypsochromic absorbance shift of approximately 40 nm in comparison to hydroxy DASAs. This hypsochromic shift is in contrast to the electronic contribution effect on absorbance from the other structural compartments. Conjugated donors, strong acceptors, and other triene substitutions all result in bathochromic shifts. Furthermore, amino DASAs showed decreased molar absorptivity and varying electron distribution of the triene structure." Professor Picazo concluded: "We're hoping that future studies will help us further understand the triene heteroatom's electronic and noncovalent effects on photophysical properties. In addition

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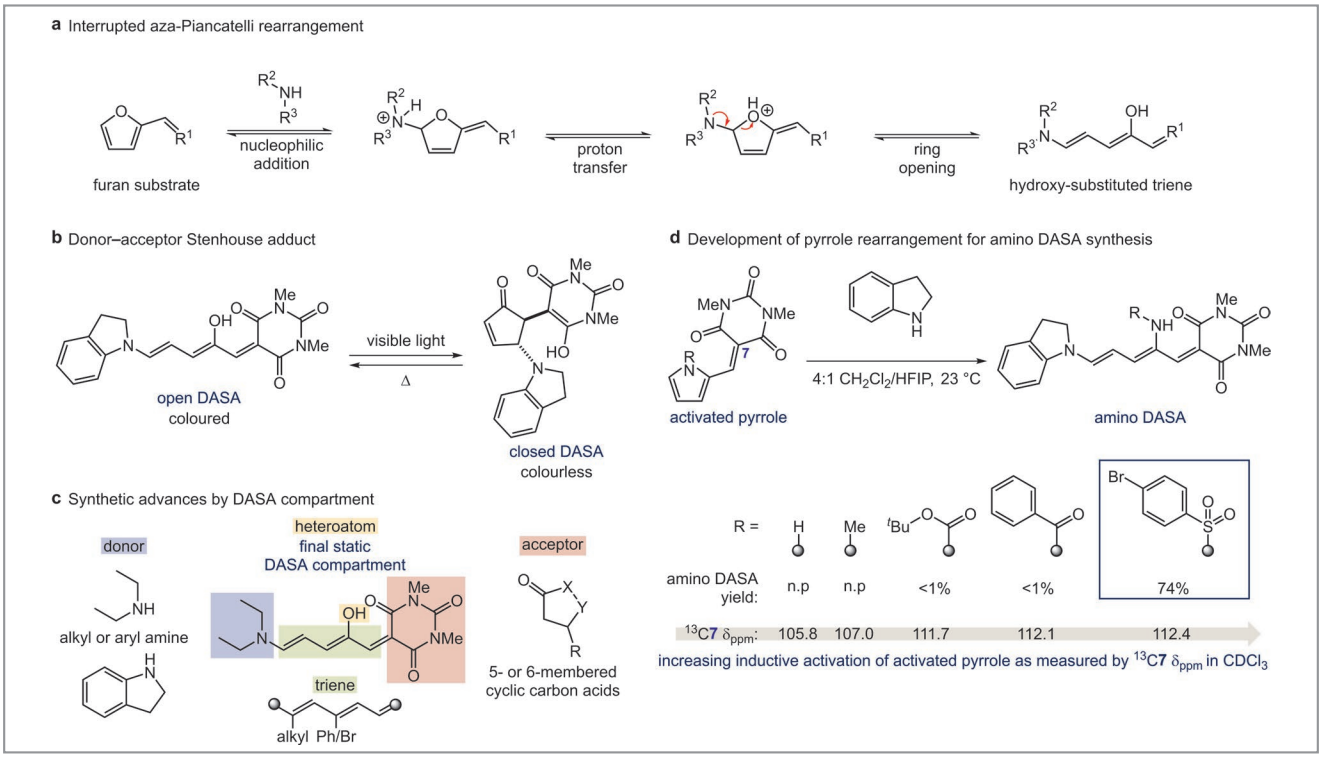

Scheme 1 The aza-Piancatelli rearrangement and development of amino donor–acceptor Stenhouse adducts

to the photoswitch studies in this report, the developed Piancatelli reactivity provided a proof-of-concept for pyrrole ring-opening, a rare transformation that may see potential in other applications."

About the authors

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Cesar Reyes received his B.S. in biochemistry and M.S. in chemistry from The University of Texas at Dallas (USA) in 2021 under the supervision of Prof. Jeremiah Gassensmith. He is currently pursuing his Ph.D. under the supervision of Prof. Elias Picazo at the University of Southern California (USA). His research focus is on the synthesis of molecules of interest and developing new reactions.

Dr. H. J. Lee

Hye Joon Lee received her Ph.D. in chemistry from University of California, Santa Barbara (USA) in 2023 under the supervision of Prof. Armen Zakarian. She is currently pursuing her postdoctoral research under the supervision of Prof. Elias Picazo at the University of Southern California (USA). Her research focus is on the synthesis of molecules of interest and reaction development.

C. Karanovic

Connie Karanovic performed summer research under the supervision of Prof. Elias Picazo at the University of Southern California (USA) as an NSF REU scholar in 2023. She is currently pursuing her B.S. in biochemistry at the University of California, Los Angeles (USA).

Prof. E. Picazo

Elias Picazo is a Professor in the Department of Chemistry at the University of Southern California (USA). He obtained his Ph.D. at the University of California, Los Angeles (USA) as an NIH predoctoral fellow under the supervision of Professor Neil Garg. Afterwards, he performed postdoctoral research in the lab of Professor Eric Jacobsen at Harvard University (USA) as an NIH K99 postdoctoral fellow. Research in the Picazo lab primarily focuses on developing and leveraging new reactivity to solve long-standing synthetic challenges. Reactivity spans transition-metal catalysis and rearrangement chemistry.

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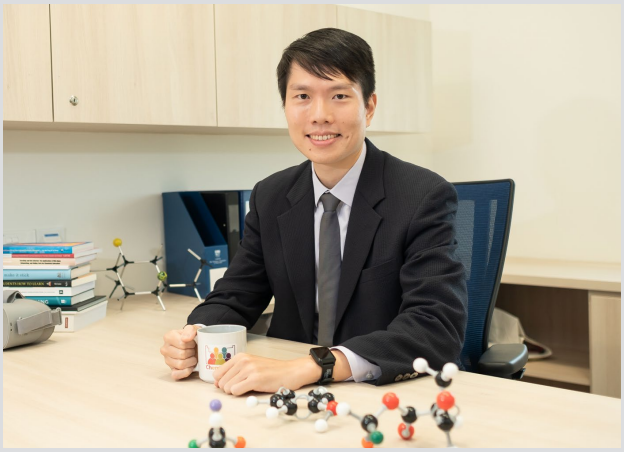
Young Career Focus: Dr. Fun Man Fung (University College Dublin, Ireland)

Background and Purpose. SYNFORM regularly meets young up-and-coming researchers who are performing exceptionally well in the arena of organic chemistry and related fields of research, in order to introduce them to the readership. This Young Career Focus presents Dr. Fun Man Fung (University College Dublin, Ireland).

Biographical Sketch



Dr. F. M. Fung

Fun Man Fung studied chemistry at the National University of Singapore (NUS), where he received his doctorate in 2020 under the supervision of Prof. Sam Li Fong Yau.

Prior to that, he received a bond-free scholarship from BASF, Germany to study for his Master of Science (Industrial Chemistry), jointly conferred by Technical University of Munich (Germany) and NUS. Before this, he earned his undergraduate Honours degree at NUS, supervised by Assoc. Prof. Lam Yulin, and received the NUS Society Gold Medal for Outstanding Achievement. Dr. Fung also earned a Certificate in Environmental, Social, and Governance (ESG) from the Singapore Management University (SMU).

He is the co-editor of two books: [1] 10 Things You Must Know About the International Chemistry Olympiad (IChO) and [2] Technology-Enabled Blended Learning Experiences for Chemistry Education and Outreach. He was elected to serve on the IChO steering committee for two terms (2014–2018). Since 2022, Dr. Fung has been elected Council Member of the Singapore National Institute of Chemistry (SNIC), and he represented SNIC on the IUPAC Committee on Chemistry Education as National Representative (2020–2023). Dr. Fung currently serves as a member of the Editorial Advisory Board at the *Journal of Chemical Education* (ACS Publications), and of the Early Career Advisory Board of *JACS Au*, and is Associate Editor of *Chemistry Teacher International* (IUPAC & EuChemS).

He received the 2024 Thieme Chemistry Journals Award, 2023 NUS High Inspiring Research Mentor Award, the Global Young Academy Membership (2024–2029), 2019 YSEALI Professional Fellowship and the 2021 Study of the United States Institutes (SUSI) Program Scholarship hosted at the Maureen and Mike Mansfield Center, University of Montana (USA). Dr. Fung is a member of the ASEM-DUO Wallonia-Brussels Fellowship Programme, the Asian Universities Alliance (AUA) Scholars Award Program, and the CAS Future Leaders™ Program. He is the Founding Chair of the American Chemical Society Singapore Chapter.

In 2024, he was appointed Assistant Professor at the School of Chemistry, University College Dublin, Ireland. His group currently studies how the application of learning sciences and educational technology helps learners learn better.

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INTERVIEW

SYNFORM *Which field of organic chemistry are you interested in the most and why?*

Dr. F. M. Fung Years ago, as a freshman undergraduate at the National University of Singapore Chemistry, I was exposed to all fields in the chemical sciences. But only organic chemistry hit me with the feeling of "*U Got it Bad*". I was smitten by the associations with our lives and then took many advanced classes related to organic chemistry synthesis, including spectroscopic techniques. When I started teaching at the university, my interest towards the field of chemistry education in organic chemistry piqued. If I can personify "ChemEd in Orgo Chem", I want to say to #ChemEd: "*I made you my world, have you heard?*"

SYNFORM *Following that, what is the focus of your current research activity?*

Dr. F. M. Fung It centers on discovering evidence-based strategies to learn chemistry, via several domains. First, the application of spatial reality technology in a virtual laboratory environment. Second, the construction of sustainable learning communities, and third, applied research in multimedia educational technologies (Figure 1).[1–6] These domains of research can be applied to multiple disciplines, from chemical security, to sustainable chemistry, and flow synthesis.

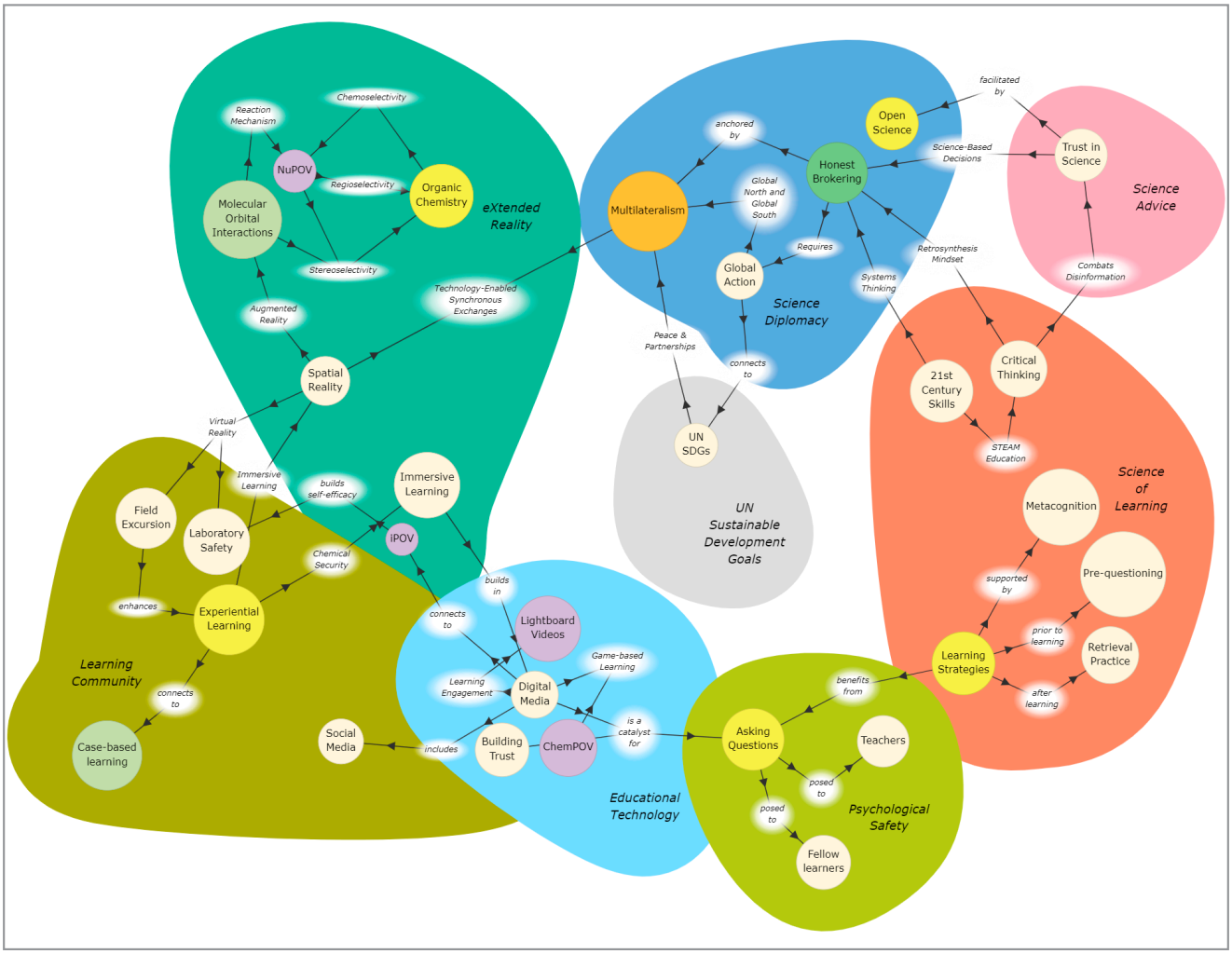

Figure 1 A Systems Thinking-inspired overview of the main research interests of F. M. Fung's research group using "SOCKit". SOCKit was developed as part of IUPAC Project 2020-014-3-050.

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

Dr. F. M. Fung First, organic chemistry is LIFE and it is a salient topic to teach enthusiastic learners! For instance, the relationships in organic chemistry are a close resemblance to life: such as nucleophile–electrophile, reducing agent–oxidising agent, suprafacial–antarafacial attacks, and many more. Some people call it the Yin–Yang or "Molecular Courtship". Second, the philosophy in *Retrosynthetic Thinking*, strategizing about the possible synthons from the target molecule, could be taught to anyone who wishes to learn about the "Learning how to think like a human". Third, collaboration in organic chemistry research can be a channel for science diplomacy between countries, and the importance of international scientific collaborations cannot be emphasized enough – it was evident during the pandemic.

SYNFORM *What difficulties are there for young upcoming chemists in your field? Do you have any tips?*

Dr. F. M. Fung Managing mental health is ostensibly a challenge for a number of people, and that is an important issue to address for chemists, both young and established. It might probably affect young upcoming chemists more as they are at the beginning of their research journey.

Pro tip: Learn to get things done, and sustain the love for learning, for learning endures all times.

SYNFORM *Could you tell us something about yourself outside the lab, such as your hobbies or extra-work interests?*

Dr. F. M. Fung I enjoy volunteering for causes I believe in, such as serving on the IUPAC Global Women's Breakfast project and IUPAC Committee on Chemistry Education. I am a supporter of *Science Diplomacy* and *Youth Empowerment*, and therefore I founded the ACS Chapter in Singapore with several like-minded leaders. As an alumnus of the YSEALI program, I serve as a mentor for students from the Institute of Technical Education (ITE), Singapore. As a proud TUM alumnus, I act as a mentor for the TUM mentoring program for a researcher based in Stuttgart, Germany.

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

Dr. F. M. Fung I believe that scientific achievement is only possible with a team of good people through concerted efforts in mentorship and youth empowerment in science. I vividly remember when I led the Singapore Delegation as Head Mentor at the 46th International Chemistry Olympiad 2014 held in Hanoi, Vietnam. Our representative attained the top position (1st Gold), a first-ever for Singapore, and still the best achievement to date since 1965. The mentors from the various countries kept in touch, and 10 years after, we still meet up and discuss about science, collaborations, and mentorship!

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Axially Chiral Bridged Biaryls by Ni-Catalyzed Kinetic Asymmetric C–O Bond Cleavage

ACS Catal. **2024**, *14*, 8176–8183

Axially chiral bridged biaryl scaffolds, which represent an important subset of axial chirality in organic chemistry, have been acknowledged as a fundamental structural motif in many natural products, biologically active molecules, chiral ligands, and catalysts. Moreover, the unique torsional angle and electronic properties of this scaffold have greatly facilitated its widespread utilization in optoelectronic materials. "Enhancing the potential of catalytic methodologies for the enantioselective synthesis of axially chiral bridged biaryls is a significant objective within the realms of organic chemistry and medicinal chemistry, as well as materials science," said Professor Zhi-Chao Cao at the Anhui Agricultural University (P. R. of China). He further elaborated: "Although the conventional approach of central-to-axial chirality relay has been well-established, it only allows for the construction of targets containing additional stereogenic centers in the bridge. Alternative methods, such as asymmetric aryl–aryl coupling and desymmetrization, have been preliminarily explored; nevertheless, the scope of viable substrates has been limited (selected reviews: *Chem. Commun.* **2022**, *58*, 11031–11044; *Sci. Sin. Chim.* **2023**, *53*, 402–409) (Scheme 1A)."

Over the past decades, catalytic kinetic resolution has been extensively explored for the construction of enantioenriched compounds, due to its ability to attain significantly high levels of enantiopurity by simply adjusting the conversion ratio. "In this context, a variety of approaches such as asymmetric deprotection, asymmetric protection of X–H bonds (where X = N, O), asymmetric C–H functionalization, and asymmetric hydrogen-transfer reduction have been developed for the creation and control of axial chirality (selected reviews: *Adv. Synth. Catal.* **2011**, *353*, 1613–1666; *Chem. Eur. J.* **2015**, *21*, 11644–11657) (Scheme 1B)," said Professor Cao. He continued: "Despite an early example of kinetic resolution of axially chiral bridged biaryl being documented through chiral oxazaborolidine-mediated Corey–Bakshi–Shibata reduction, this is a noncatalytic process (*Tetrahedron: Asymmetry* **1997**, *8*, 4121–4126)."

In furtherance of their previous endeavors regarding the asymmetric cleavage of unactivated C–O bonds (review: *ChemCatChem* **2024**, *16*, e202301566), the recent title article in *ACS Catalysis* from the group of Professor Cao describes a method for the production of axially chiral bridged biaryl compounds by integrating catalytic kinetic resolution with asymmetric activation of aromatic C–O bonds (Scheme 1C). "The described method offers a pathway to a diverse array of valuable dibenzodioxepine compounds utilizing substrates exhibiting both symmetric and asymmetric substitution patterns (Schemes 1D and 1E)," said Professor Cao, adding: "Moreover, versatile post-functionalization was carried out, resulting in the assembly of many functionally important molecules. This catalytic kinetic resolution process was executed using a nickel catalyst under mild reaction conditions in the presence of a new chiral N-heterocyclic carbene ligand." He continued: "This work represents the first catalytic kinetic resolution achieved through the asymmetric cleavage of an unactivated aromatic C–O bond."

In collaboration with Professor Gen Luo at the Anhui University (P. R. of China), DFT calculations were also conducted to elucidate the reaction mechanism (Figure 1). "The reaction proceeds through a mono-ligand pathway, which is significantly different from the previously reported bis-ligand pathway," said Professor Luo. He further explained: "The rate-determining step of the reaction is the C–O oxidative addition, which proceeds via a Ni/Mg bimetallic cooperative mechanism. Thanks to the significant barrier difference in the C–O oxidative addition between the two enantiomers, we can achieve kinetic resolution of dibenzodioxepines."

Professor Cao concluded by examining future perspectives of this work: "By merging the power of catalytic kinetic resolution with asymmetric C–O bond activation, we have established a new platform for assembling an axially chiral bridged biaryl scaffold with high efficiency, which could potentially expedite the synthesis of many pharmaceutically relevant molecules and optical materials. Moreover, owing to the prevalence of the unactivated C–O bond in both natural and synthetic worlds, this strategy will offer a promising platform for the preparation of enantiopure oxygen-containing compounds from readily available building blocks."

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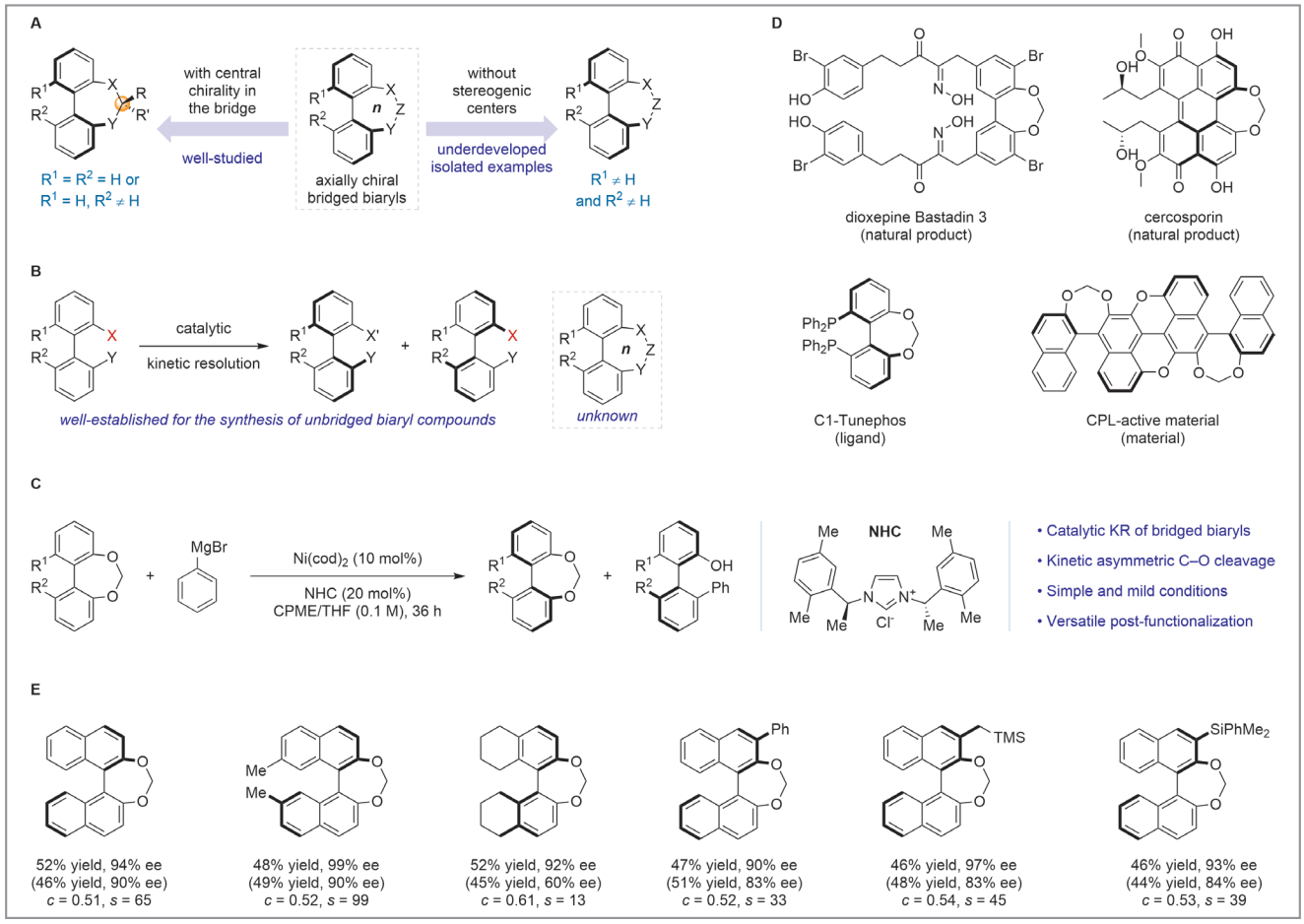


Scheme 1 The catalytic asymmetric synthesis of axially chiral bridged biaryls. **A**. Established methods for the catalytic asymmetric synthesis of axially chiral bridged biaryls. **B**. Construction of axial chirality through catalytic kinetic resolution. **C**. The catalytic kinetic resolution of axially chiral bridged biaryls via asymmetric C–O bond cleavage. **D**. Selected examples of molecules containing dibenzodioxepine units. **E**. Selected examples of products; yield and ee are given first for unreacted starting material, figures in parentheses that follow are for arylation product.

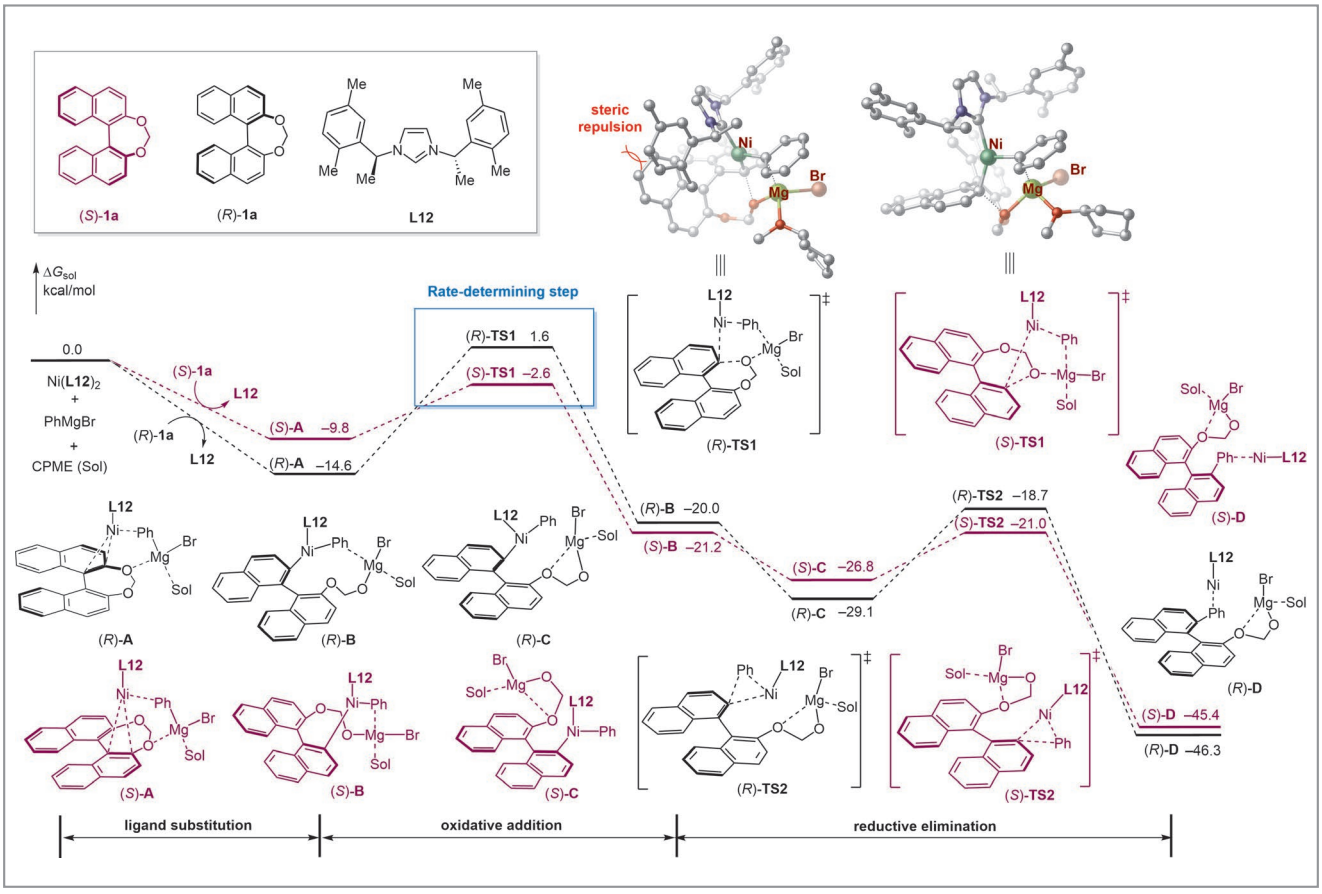
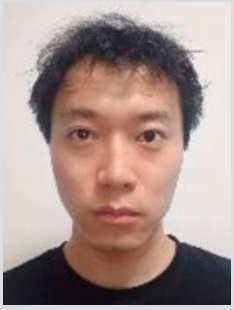


Figure 1 Computed energy profile of the Ni(cod)$_2$/**L12**-catalyzed kinetic asymmetric C–O bond cleavage

About the authors



Y. Fang

Yijun Fang received his B.Sc. and M.Sc. from Anhui Agricultural University (P. R. of China). He then joined Professor Zhi-Chao Cao's group at the same university as a Ph.D. candidate in 2022. His research interests are mainly focused on metal-catalyzed asymmetric cleavage of aromatic C–O bonds.

J. Hu

Jiameng Hu received her B.Sc. in chemistry from Anqing Normal University (P. R. of China) in 2022. She is currently pursuing her M.Sc. degree at Anhui University (P. R. of China) under the supervision of Prof. Gen Luo, focusing on computational analysis of rare-earth-metal-catalyzed [3+2] annulation and transition-metal-catalyzed asymmetric coupling reactions.

T. Sun

Tingting Sun received her B.Sc. from Wannan Medical College (P. R. of China) and M.Sc. from Anhui Agricultural University (P. R. of China). She then joined Professor Zhi-Chao Cao's group at the same university as a Ph.D. candidate in 2021. Her research interests are mainly focused on atroposelective synthesis.

Y. Zhou

Yu Zhou received his B.Sc. in chemistry from Hefei Normal University (P. R. of China) in 2020. He then completed his M.Sc. degree in 2023 at Anhui University (P. R. of China) under the supervision of Prof. Gen Luo. His research interests are mainly focused on theoretical studies of rare-earth/transition-metal-catalyzed reactions, including C–H functionalization and asymmetric C–O cleavage.

Prof. G. Luo

Gen Luo is a Professor at Anhui University (P. R. of China). He received his B.Sc. from Anhui Normal University (P. R. of China) and Ph.D. from Dalian University of Technology (P. R. of China) under the supervision of Prof. Yi Luo. During his Ph.D. studies, he served as a joint-training Ph.D. candidate at RIKEN (Japan) with Prof. Zhaomin Hou (Feb 2014–Feb 2015). In August 2016, he rejoined the group of Prof. Zhaomin Hou at RIKEN as a postdoctoral fellow. At the end of 2017, he returned to Dalian University of Technology as an associate professor and was promoted to full professor in 2019 at Anhui University. His current work is focused on gaining mechanistic understanding of homogeneous organometallic reactions by employing computational chemistry, especially for computational rare-earth organometallic chemistry.

Prof. Z-C. Cao

Zhi-Chao Cao is a Professor in the Department of Chemistry and Pesticides at Anhui Agricultural University (P. R. of China). He obtained his Ph.D. with Professor Zhang-Jie Shi at Peking University (P. R. of China), then he carried out postdoctoral studies at Caltech (USA) with Professor Gregory C. Fu and at the University of North Carolina–Chapel Hill (USA) with Professor Wei You. Research in the Cao group focuses on asymmetric catalysis and cross-coupling.

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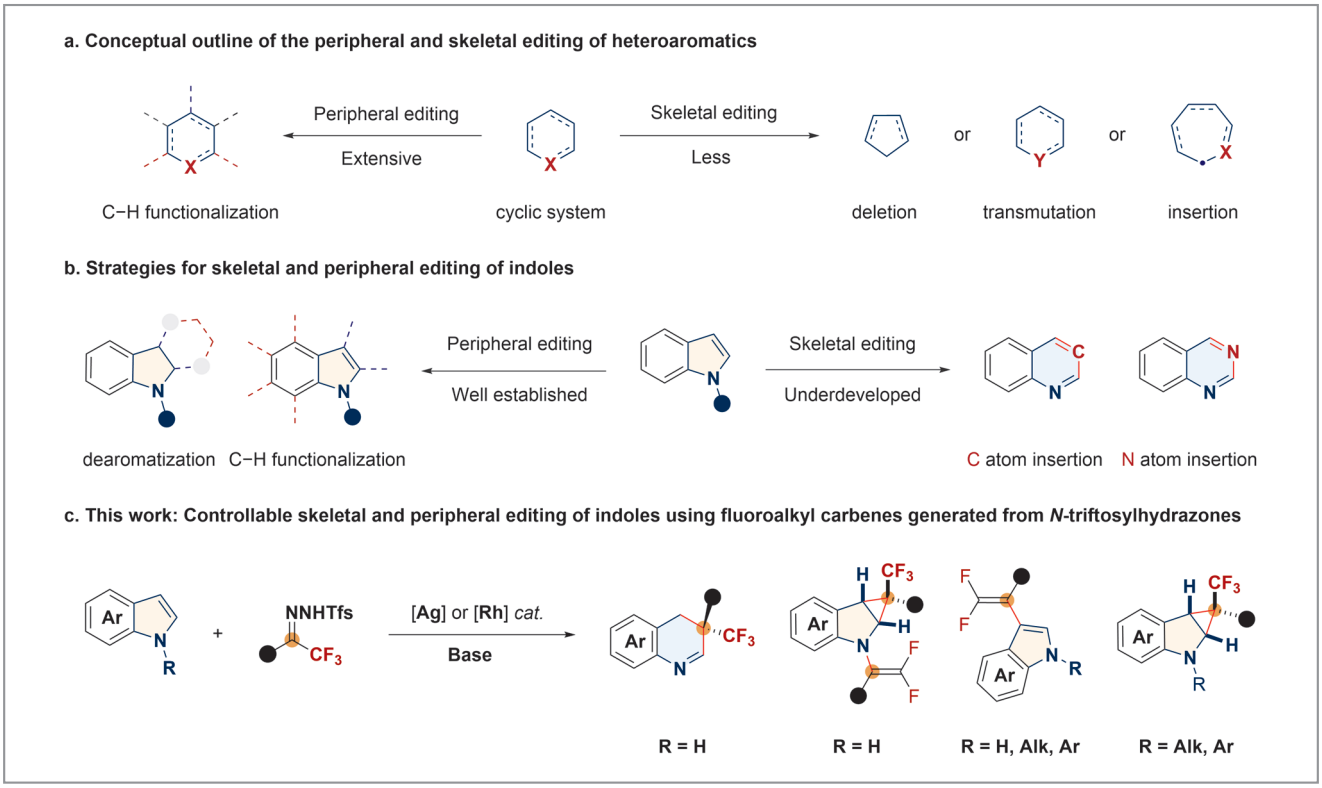
Tunable Molecular Editing of Indoles with Fluoroalkyl Carbenes

Nat. Chem. **2024**, *16*, 988–997

The rapid generation of molecular complexity through peripheral and skeletal editing of simple starting materials is an important goal of modern chemical synthesis (Scheme 1a). Indoles are prominent in many therapeutics and bioactive natural products and are abundant in numerous medicinal and agrochemical libraries. Hence, the direct editing of indoles to access new chemical space, higher potency, and improved compound stability or drug-like properties is a central focus of current organic and medicinal chemistry research. "However, existing molecular editing reactions of indoles, such as dearomative cyclization/cycloaddition or C–H functionalization, have mainly focused on the functionalization of the periphery of indoles, leaving the underlying core skeleton intact (Scheme 1b)," said Professor Xihe Bi, from Northeast Normal University (P. R. of China). He added: "Recently, Levin and coworkers (*J. Am. Chem. Soc.* **2021**, *143*, 11337) reported a base-promoted single-carbon atom insertion into indoles to obtain 3-arylquinolines using α-arylchlorodiazirines as the carbene precursors. The Morandi group (*Science* **2022**, *377*, 1104) demonstrated the skeletal editing of silyl-protected indoles to access quinazolines by trapping iodonitrene species generated from ammonium carbamate and hypervalent iodine."

According to Professor Bi, despite these impressive advances, existing peripheral and skeletal editing typically rely on different strategies and starting materials. Hence, Professor Bi's and Dr. Zhaohong Liu's groups (both at Northeast Normal University) envisioned that a controllable editing process that could edit both the core skeleton and the periphery of the indole scaffold with a common reagent would increase the chemical space around this leading pharmacophore. "As drug discovery programs seek more complicated chemical spaces, fluoroalkyl groups with spatial vectors and a quaternary carbon center will become more appealing if synthetic methodologies allow their utilization. Specifically, the direct insertion



Scheme 1 Possibilities of skeletal and peripheral editing of indoles

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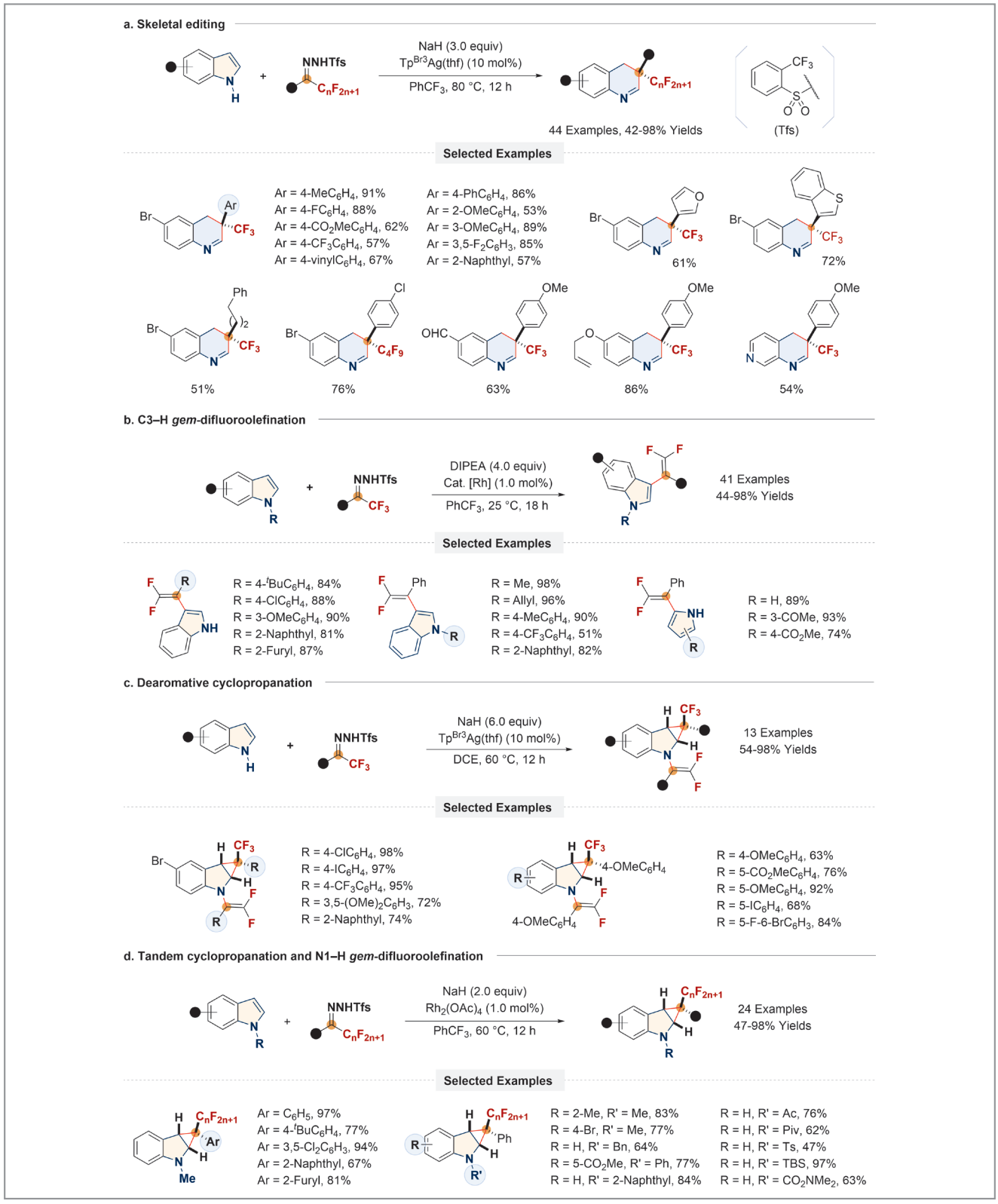

Scheme 2 Tunable skeletal and peripheral editing of indoles using fluoroalkyl *N*-triftosylhydrazones

of a fluoroalkyl group into the core skeleton of azaarenes to construct a quaternary stereocenter is highly challenging," stated Professor Bi.

Recently, Bi's and Liu's groups developed strategically distinct skeletal and peripheral editing reactions of indoles by trapping electrophilic fluoroalkyl carbenes derived in situ from fluoroalkyl *N*-triftosylhydrazones in a controllable manner (Scheme 1c). "During the discovery phase, we prioritized the synthetic practicality, feasibility, versatility, operational simplicity, and bench stability of the reagent," explained Professor Bi. He continued: "These divergent transformations enabled access to four different types of quinoline- and indole-based bicyclic and tricyclic compounds with bio-isosteric trifluoromethyl and/or *gem*-difluorovinyl groups that are widely recognized as privileged pharmacophores. This protocol widens the path to achieve fluorine-based molecular complexity by selective modification of the core and periphery of five-membered azaarenes, employing simple reagents and controllable catalytic conditions."

Professor Bi's group found that the treatment of indole (3.0 equiv) scaffold with fluoroalkyl *N*-triftosylhydrazones (1.0 equiv) and NaH (3.0 equiv) under the catalysis of $Tp^{Br3}Ag(thf)$ (10 mol%) (where Tp^{Br3} denotes tris(3,4,5-tribromopyrazolyl) borate and thf denotes tetrahydrofuran) at 80 °C in trifluorotoluene for 12 hours produced the target ring-expansion products bearing a trifluoromethylated quaternary center in high yields (Scheme 2a). Professor Bi told SYNFORM: "What particularly stands out about this protocol is its convenience and scope, with almost 44 derivatives achieved in yields of up to 90%. The developed protocol was even suitable for the late-stage modification of complex bioactive molecules such as verticillatine B and raputimonoindole B." Professor Bi's group also extended the applicability of this skeletal editing protocol to synthesize tetrahydroquinoline-bearing trifluoromethyl quaternary carbon centers through a tandem one-carbon insertion and reduction sequence in a one-pot, two-step manner.

Professor Bi and Dr. Liu's group remarked that a series of peripherally functionalized indole derivatives have also been synthesized by changing the reaction conditions or stoichiometry of reacting partners (Scheme 2b): "For example, the rhodium-catalyzed reaction between indole and fluoroalkyl *N*-triftosylhydrazones using DIPEA as the base at 25 °C, produced the C3 *gem*-difluoroolefination products in moderate to good yields," said Professor Bi. The treatment of indole with excess fluoroalkyl *N*-triftosylhydrazones in the presence of a $Tp^{Br3}Ag$–NaH catalytic system provided the tandem cyclopropanation and N1 *gem*-difluoroolefination products (Scheme 2d). They finally achieved the dearomative cyclopropanation of *N*-substituted indoles using fluoroalkyl *N*-triftosylhydrazones catalyzed by the $Rh(OAc)_2$-NaH system (Scheme 2c).

Professor Bi said to SYNFORM: "The proposed mechanism for the skeletal editing of indoles involves a dearomative cyclopropanation followed by ring opening to give the ring expansion product. A control experiment suggests that NaH is critical for the ring-opening of cyclopropane, as no ring expansion product was observed in its absence. According to DFT calculations, the $Tp^{Br3}Ag$–NaH catalytic system enables 2,3-cyclopropanation to form cyclopropane over β-F elimination, which then undergoes tandem hydrogen abstraction, reversible ring opening, and water-assisted protonation to afford ring expansion products."

Professor Bi concluded by examining the future perspectives of this work: "By harnessing an appropriate transition metal and base, we have provided a controllable molecular editing approach for the assembly of the molecular complexity of indoles, which could potentially expedite the synthesis of diverse 2,3-dihydroquinoline and indole scaffolds bearing a trifluoroalkylated quaternary center," he said, adding: "Given the abundance of indoles in bioactive molecules and natural products, the developed method holds an even greater promise for the construction of complex target molecules by avoiding the multistep synthesis. Additionally," remarked Professor Bi "this logical fluoroalkyl carbene insertion strategy would be advantageous for controlled editing of heteroaromatics and drug molecules, which should be intriguing in drug development."

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Shaopeng Liu graduated from the Capital Normal University (P. R. of China) in 2020, and then entered the Organic Chemistry major of Northeast Normal University (P. R. of China) to study for a Ph.D. in Professor Xihe Bi's research group, mainly engaged in the reactivity research of *N*-triftosylhydrazones in molecular editing.

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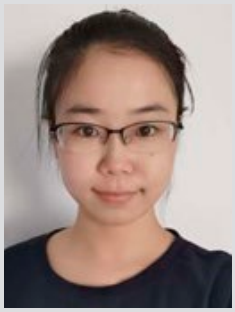

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Prof. X. Bi

Xihe Bi started his independent research as an Associate Professor at Northeast Normal University (P. R. of China) at the end of 2008 and was promoted to Full Professor in 2013. Prof. Bi's group research has concentrated mainly on silver catalysis and *N*-sulfonyl hydrazone-based carbene chemistry. He has received several honors and awards, including the Alexander von Humboldt Research Fellowship, the NSFC Foundation for Excellent Young Scientist, the Thieme Chemistry Journals Award, the Fellow of the Royal Society of Chemistry, and the Newton Advanced Fellowship.

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