

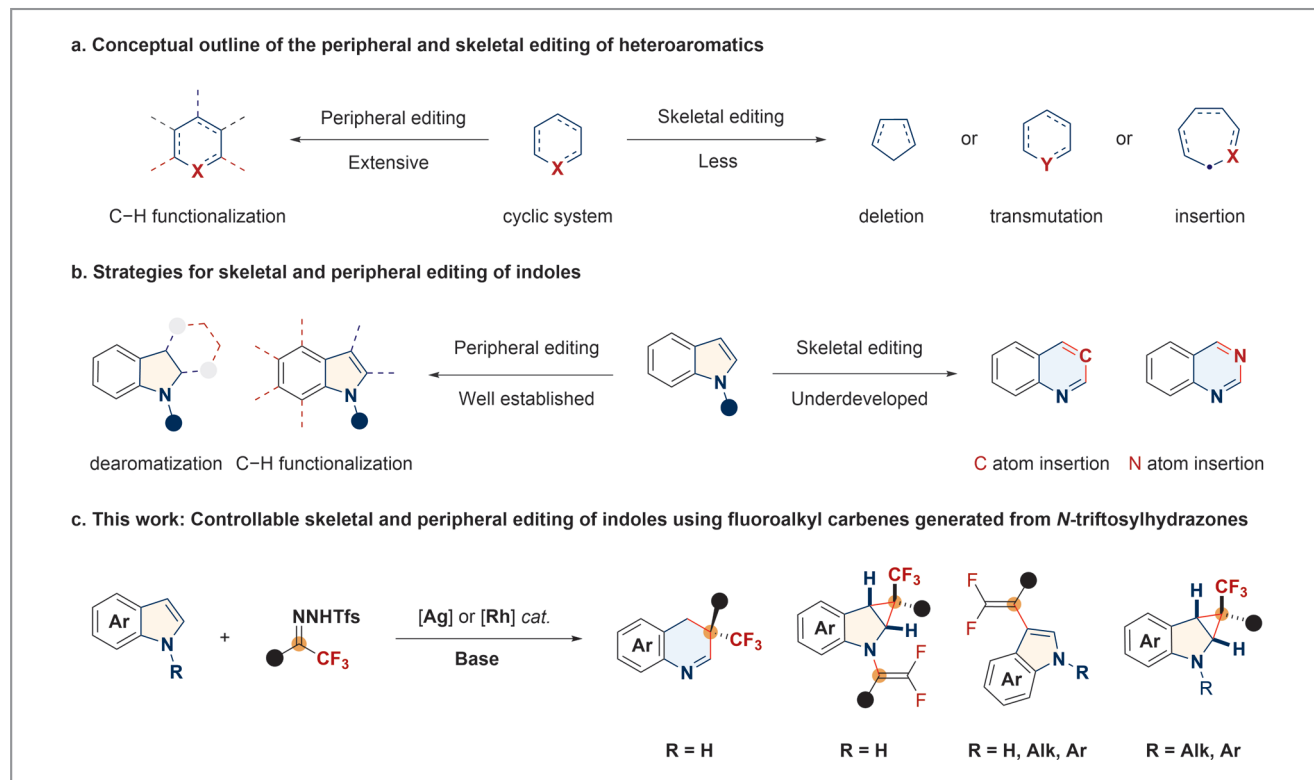
# Tunable Molecular Editing of Indoles with Fluoroalkyl Carbenes

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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 co-workers (*J. Am. Chem. Soc.* **2021**, *143*, 11337) reported a base-promoted single-carbon atom insertion into indoles to obtain

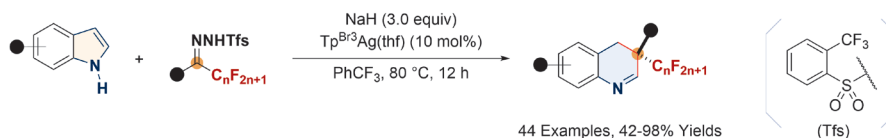
3-arylquinolines using  $\alpha$ -arylchlorodiazirines as the carbene precursors. The Morandi group (*Science* **2022**, *377*, 1104) demonstrated the skeletal editing of silyl-protected indoles to access quinazolines by trapping iodonitrene species generated from ammonium carbamate and hypervalent iodine.”

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

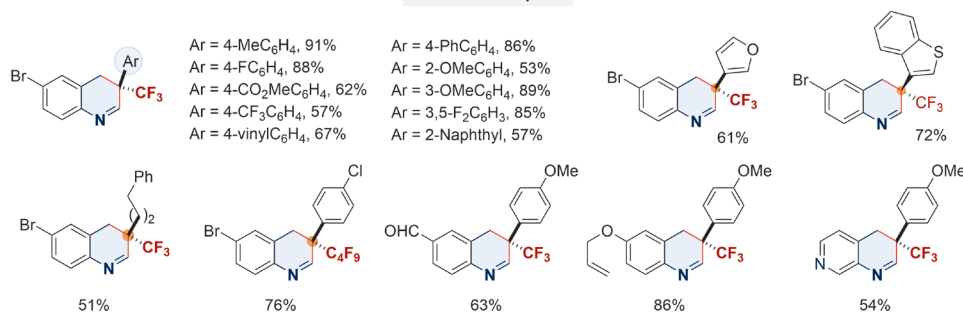
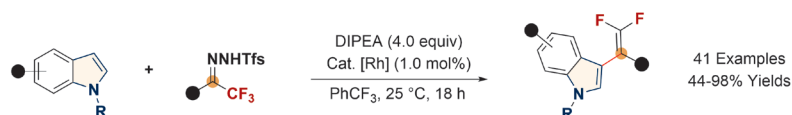


**Scheme 1** Possibilities of skeletal and peripheral editing of indoles

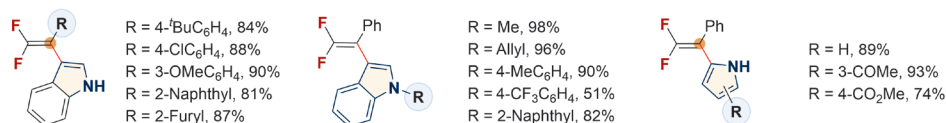
## a. Skeletal editing



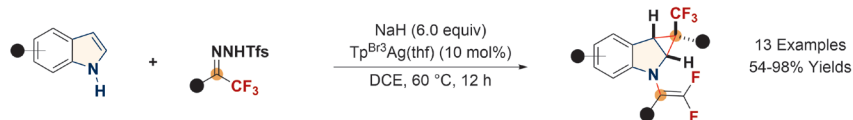
## Selected Examples

b. C3-H *gem*-difluoroolefination

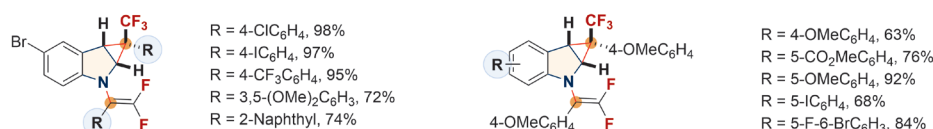
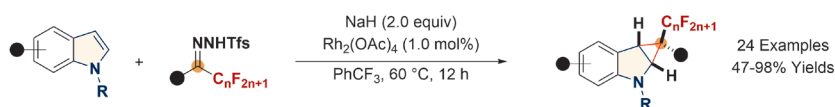
## Selected Examples



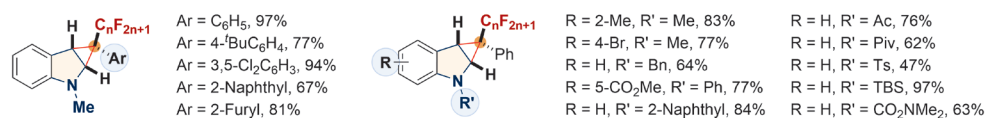
## c. Dearomative cyclopropanation



## Selected Examples

d. Tandem cyclopropanation and N1-H *gem*-difluoroolefination

## Selected Examples

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

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*-triflylhydrazones 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*-triflylhydrazones (1.0 equiv) and NaH (3.0 equiv) under the catalysis of  $\text{Tp}^{\text{Br}_3}\text{Ag}(\text{thf})$  (10 mol%) (where  $\text{Tp}^{\text{Br}_3}$  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 raputimonindole 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*-triflylhydrazones 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*-triflylhydrazones in the presence of a  $\text{Tp}^{\text{Br}_3}\text{Ag}$ -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*-triflylhydrazones catalyzed by the  $\text{Rh}(\text{OAc})_2$ -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  $\text{Tp}^{\text{Br}_3}\text{Ag}$ -NaH catalytic system enables 2,3-cyclopropanation to form cyclopropane over  $\beta$ -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.”

Mattias Farnok

## About the authors



**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*-triflylhydrazones in molecular editing.

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Q. Song



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Dr. P. Sivaguru



**Zhaohong Liu** received a Ph.D. in organic chemistry under the supervision of Professor Xihe Bi at Northeast Normal University (P. R. of China) in 2018 and then joined the Department of Chemistry at the same university as an Associate Professor. His research interests concern carbene chemistry.

Prof. Z. Liu



**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.

Prof. X. Bi