

## REVIEW

View Article Online  
View Journal | View IssueCite this: *Org. Chem. Front.*, 2025, 12, 1633Remodelling molecular frameworks *via* atom-level surgery: recent advances in skeletal editing of (hetero)cyclesRubal Sharma, <sup>a,b</sup> Mitsuhiro Arisawa, <sup>b</sup> Shinobu Takizawa <sup>\*a</sup> and Mohamed S. H. Salem <sup>\*a,c</sup>

Skeletal editing is an emerging approach in synthetic chemistry that enables precise atom-level modifications within molecular cores, facilitating complex transformations and minimizing resource-intensive synthesis. This review provides a comprehensive overview of the most recent advancements in skeletal editing, with a particular focus on single atom modifications. While skeletal editing can be applied to both cyclic and acyclic compounds, this review centers on carbo- and heterocyclic systems exclusively. By integrating historical context and categorizing key developments, it highlights the major achievements in insertion, deletion, and transmutation, connecting related works and delving into mechanistic insights.

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## 1. Introduction

Modern synthetic organic chemistry has increasingly focused on the precise manipulation of molecular frameworks to enable more efficient and versatile transformations across diverse fields, including sustainable synthesis and materials science.<sup>1–3</sup> Skeletal editing, an emerging approach that allows for atom-level modifications, is garnering significant attention for its potential to remodel molecular cores with precision while reducing the need for resource-intensive *de novo*



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Mitsuhiro Arisawa

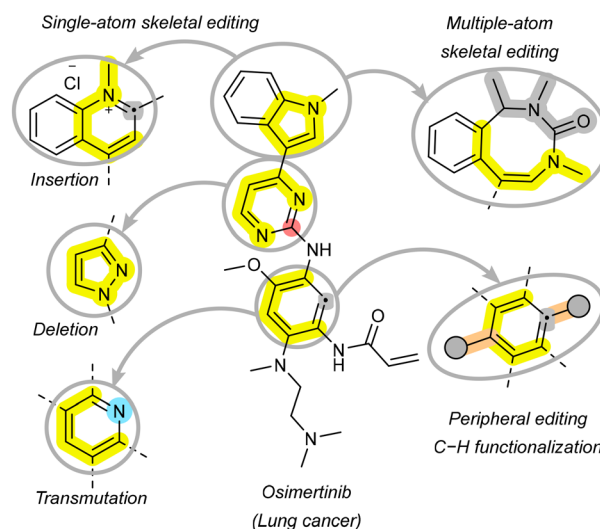
Mitsuhiro Arisawa received his Ph.D. from Graduate School of Pharmaceutical Sciences, Osaka University, Japan (Prof. Yasuyuki Kita). He joined the Faculty of Pharmaceutical Sciences at Chiba University, Japan, as an assistant professor. From 2002 to 2004, he was a visiting scholar at Harvard University, U.S.A. (Prof. Matthew D. Shair). He became an Associate Professor at Graduate School of Pharmaceutical Science, Hokkaido University, in 2005. In 2013, he moved to Graduate School of Pharmaceutical Sciences at Osaka University, an Associate Professor. He was promoted to a professor in 2019. His current research interest is organic chemistry for drug development.



synthesis.<sup>4,5</sup> By selectively inserting, deleting, or exchanging atoms within a molecule's skeleton, this technique has the potential to facilitate late-stage modifications, streamline synthetic routes, improve sustainability, and provide access to complex systems that are challenging to achieve through traditional methods (Fig. 1A).<sup>6,7</sup> In drug discovery, skeletal editing holds promise for the rapid optimization of lead compounds, potentially enhancing their potency and selectivity through efficient diversification.<sup>8–10</sup> It also introduces retrosynthetic elegance to the total synthesis of natural products, akin to widely used reactions such as cross-coupling and amide bond formation.<sup>11</sup> Beyond pharmaceuticals, skeletal editing has transformative potential in materials science, with the ability to fine-tune electronic, optical, and catalytic properties and unlock new applications in optoelectronics, energy storage, sustainable catalysis, and next-generation technologies.<sup>12–15</sup>

Historically, chemists primarily focused on modifying peripheral functional groups—referred to as “peripheral editing”—to diversify molecules without altering their core skeleton (Fig. 1A). While reactions capable of rearranging molecular cores—like the Buchner ring expansion, Baeyer–Villiger oxidation or the Ciamician–Dennstedt rearrangement, were known by the late 19<sup>th</sup> century, they were limited in scope and not widely applied to skeletal modifications until recently.<sup>16–18</sup> The rise of CRISPR gene editing in the early 2010s inspired similar tools for molecular editing, leading to the conceptualization of “skeletal editing” as a method to precisely edit molecular structures, analogous to CRISPR's role in biology.<sup>19</sup> This link is reflected in the shared terminology of “editing”, “mutations”, “transmutations”, “deletions”, and “insertions” across both fields. However, skeletal editing remains a rapidly evolving discipline without standardized terminology, leading to diverse and sometimes inconsistent terms to describe similar processes. Terms such as “skeleton”,

### A) Strategies of molecular editing



### B) Classifications of single-atom skeletal editing

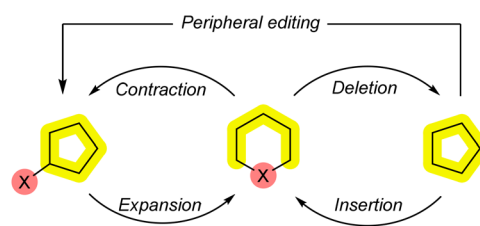


Fig. 1 Definitions and categorizations of skeletal editing.

“framework”, “scaffold”, and “core” are frequently used interchangeably to refer to molecular skeletons. Moreover, some terms are applied with varying levels of specificity, with researchers distinguishing between skeletal editing that includes



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peripheral modifications and those that do not. In these cases, terms like “deletion” and “insertion” are used to describe skeletal modifications without accompanying peripheral changes, while “contraction” and “expansion” refer to transformations that involve both skeletal and peripheral modifications (Fig. 1B).<sup>4</sup> Others, however, treat these terms as synonyms, blurring the distinction between these strategies.<sup>5,6,20,21</sup> This inconsistency underscores the need for standardization to promote clearer communication and broader adoption of skeletal editing methodologies. In 2022, Sarpong and Levin published a key review to address these ambiguities, providing clear definitions and categorizations for skeletal editing, supported by key examples.<sup>4</sup> A year later, Ball published another key review, focusing on the application of skeletal editing to the interconversion of carbo- and heteroarenes, further advancing the field’s scope and practical examples.<sup>6</sup>

Skeletal editing can be categorized based on the number of atoms involved: single-atom and multiple-atom approaches (Fig. 1A). Single-atom editing involves the insertion, deletion, or substitution of individual atoms within a molecular skeleton, enabling localized modifications. This is particularly valuable for fine-tuning properties in pharmaceuticals and sustainable materials through atom doping. Multiple-atom skeletal editing, on the other hand, involves more extensive alterations, such as the insertion, removal, or exchange of entire fragments, allowing for significant structural reshaping and the design of complex molecular architectures. While single-atom editing has garnered more attention for its potential in applications requiring precision, multiple-atom editing also features prominently, with examples like ring insertion highlighted in recent reviews.<sup>22,23</sup> Skeletal editing can include both cyclic and acyclic skeletons. In cyclic systems, the “main skeleton” refers to the central ring(s) that define the molecule’s core structure, with modifications often involving ring expansion, contraction, or rearrangement. In acyclic systems, the main skeleton is the longest chain of atoms or the central scaffold, around which modifications occur. In this review, we focus primarily on recent advances in skeletal editing of cyclic systems, particularly arenes and heteroarenes, with an emphasis on single-atom editing. While recent reviews have highlighted key developments in skeletal editing, there is still a pressing need for a comprehensive overview that links these advances to their historical context.<sup>4–6,20–22,24–26</sup> Such a review should provide a broader perspective on the evolution of skeletal editing strategies by exploring their mechanisms and the various insertive agents or catalysts used, rather than focusing on a single strategy or specific substrates. Our review addresses this gap by providing a holistic evaluation of the field, discussing key mechanisms across diverse skeletons, and consolidating recent breakthroughs during the last five years scattered across various studies. While some reviews differentiate between skeletal editing with and without peripheral modifications, we adopt a more inclusive approach. Terms like insertion and deletion are used in this review irrespective of whether peripheral modifications are involved or not.

## 2. Strategies of skeletal editing

Transformations in skeletal editing of cyclic compounds can be broadly classified into three main categories: (1) the insertion of new atom(s) into the main skeleton, leading to ring expansion; (2) the deletion of one or more atoms, resulting in ring contraction; and (3) the exchange of one or more atoms, referred to as transmutation, which alters the atom’s identity without changing the overall size of the cyclic system (Fig. 1A). Additional modifications, such as converting monocyclic systems to bicyclic systems, have also been reported.<sup>27</sup> This review will focus primarily on these three main categories, further subdividing them based on the nature of the atom(s) being inserted, deleted, or exchanged. For instance, transformations may involve the insertion or deletion of single carbon (C) or nitrogen (N) atoms, each of which can result in distinct structural and functional outcomes.

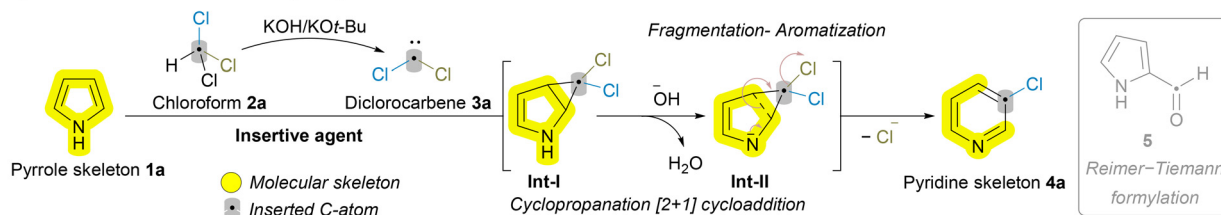
### 2.1. Ring expansion strategies through atom insertion

Atom insertion is a central strategy in skeletal editing, allowing precise incorporation of new atom(s) into cyclic structures, directly modifying molecular frameworks. Unlike traditional synthetic methods and *de novo* synthesis, which often require multiple steps, excessive reagents, and generate considerable waste, atom insertion provides a more sustainable and efficient alternative. This strategy can be classified based on the type of atom introduced; while carbon insertion is common, atoms such as nitrogen, oxygen, and boron have also been successfully inserted using various reagents.<sup>6</sup> The active species responsible for these insertions, known as insertive agents, exhibit diverse reactivity and selectivity, offering distinct advantages depending on the target transformation. In this review, we focus on the progress made with different insertive agents, exploring their ability to expand the scope of skeletal editing, overcome persistent challenges, and highlight the unique advantages each offers based on substrate and mechanism.

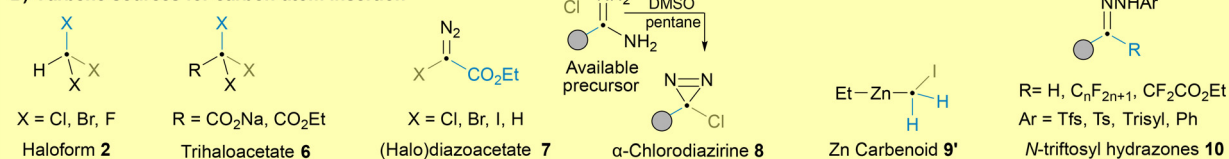
**2.1.1. Carbon atom insertion.** Carbon atom insertion is the most studied subtype of ring expansion skeletal editing strategies due to its broad applicability and rich reactivity.<sup>28</sup> While earlier examples have been reported, such as the Dowd-Beckwith rearrangement, they showed limited substrate scope, often requiring a carbonyl group in the scaffold.<sup>29,30</sup> Current research focuses on developing methods that can be applied across a broad range of substrates, utilizing diverse insertive agents. In 1881, Ciamician and Dennstedt first reported a ring expansion reaction mediated *via* carbon atom insertion using dichlorocarbene **3a** derived from chloroform **2a** as an insertive agent.<sup>17</sup> This method successfully expanded the pyrrole ring **1a** through a cyclopropanation–fragmentation–aromatization pathway (Scheme 1A). However, challenges such as competitive Reimer–Tiemann formylation **5** and the requirement for strong basic conditions limited its broader application. Despite these obstacles, this Ciamician–Dennstedt rearrangement (CD) reaction pioneered the use of various carbene sources for the ring expansion of azaheterocycles. Carbenes



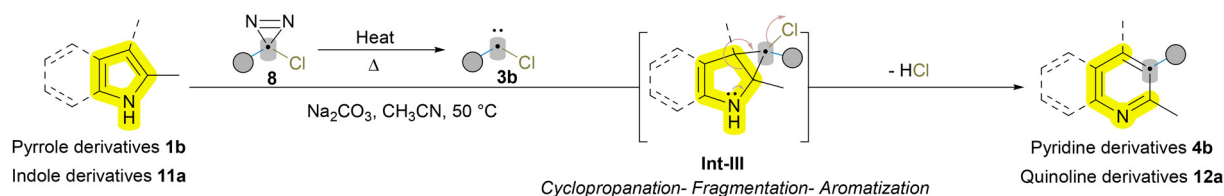
## A) Ciamician-Dennstedt reaction (1881)



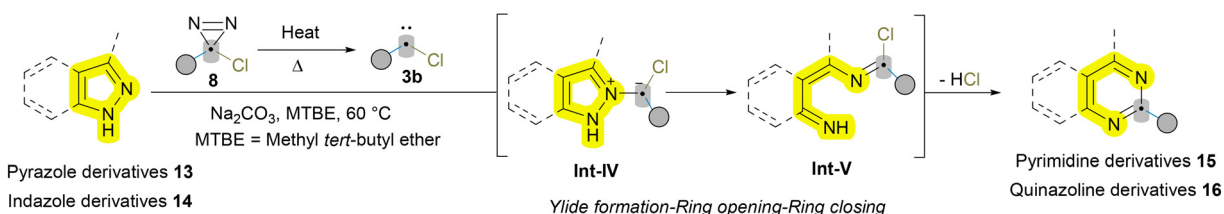
## B) Carbene sources for carbon-atom insertion



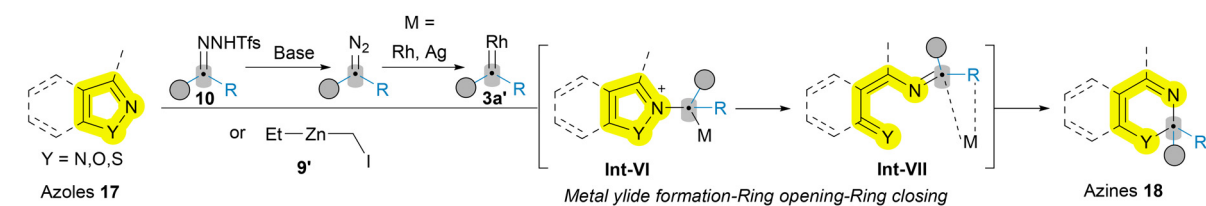
## C) Ring expansion of pyrrole and indole derivatives using α-chlorodiazirine as insertive agent (Levin 2021)



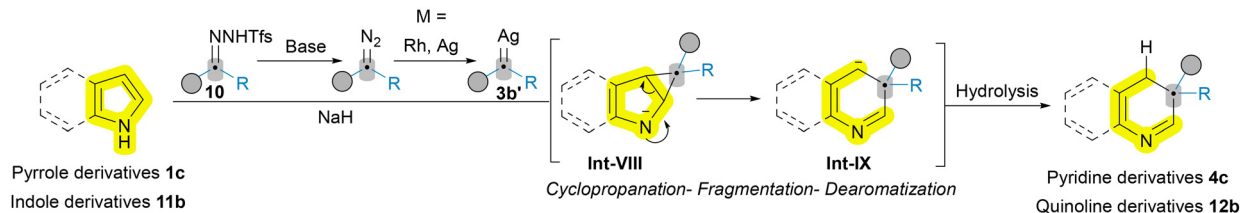
## D) Ring expansion of pyrazole and indazole derivatives using α-chlorodiazirine as insertive agent (Levin 2022)



## E) Ring expansion of 1,2 heterozoles using metal carbenoids (Bi 2024)



## F) Ring expansion of indole and pyrrole derivatives using metal carbenoids (Bi 2024)



Scheme 1 Carbon atom insertion into the main skeleton of azaheterocycles leading to ring expansion.

are one of the most widely used active insertive agents in the C-atom insertion, due to their structural diversity, high reactivity, and synthetic accessibility (Scheme 1B).<sup>21</sup> In 2021, Dai and

coworkers modified the conditions of CD rearrangement during the total synthesis of pyridine-containing lycopodium alkaloids, using sodium trichloroacetate 6 as the carbene



source, which enabled the release of carbene under mild thermal conditions (70 °C), eliminating the need for a strong base.<sup>31</sup> In 2015, Bonge-Hansen employed halodiazoacetates **7** with a rhodium (Rh) catalyst to generate a Rh carbenoid, facilitating the formation of quinoline-3-carboxylates from indoles *via* the cyclopropanation–fragmentation–aromatization pathway. However, the stability of this carbene source relied on the presence of an electron-withdrawing group (acetate), limiting its general applicability. Furthermore, low yields were obtained with 2-substituted indoles, and no products were observed using *N*-*tert*-butoxycarbonyl (*N*-Boc) and *N*-methyl (*N*-Me) substrates.<sup>32</sup> In 2024, Glorius and coworkers introduced an orthogonally active atomic carbon equivalent, Cl-DADO, featuring a diazo group (carbene precursor), a chloride leaving group, and a photosensitive oxime ester designed to undergo light-induced decarboxylation, generating a radical intermediate. This versatile reagent demonstrated its utility in the skeletal editing of indole and pyrrole, enabling access to ring-expanded heterocycles that are amenable to further derivatization.<sup>33</sup>

In 2021, Levin group made a significant breakthrough by applying a novel insertive agent,  $\alpha$ -chlorodiazirine **8**, to release carbene for the efficient and selective ring expansion of pyrroles **1b** and indoles **11a** to the corresponding pyridines **4b** and quinolines **12a**, showcasing the versatility and impact of the cyclopropanation-fragmentation-aromatization mechanistic pathway (Scheme 1C).<sup>34</sup>  $\alpha$ -Chlorodiazirines **8** can be readily prepared *via* the oxidation of amidinium salts (Scheme 1B) and exhibit good results across a broad scope for 2-substituted pyrroles **1b** and indoles **11a** which was not feasible with halodiazoacetates **7**.<sup>32</sup> This method was further extended by the same group in 2022 to include pyrazoles **13** and indazoles **14** *via* N–N bond cleavage and cyclization. The method involves carbon insertion between the N–N bond through ylide formation **Int-IV**, initiated by trapping chlorocarbene **3b** at the azole N<sup>2</sup> terminus, followed by fragmentation (N–N cleavage) affording **Int-V** and cyclization (Scheme 1D).<sup>35</sup> Although  $\alpha$ -chlorodiazirine **8** demonstrated good reactivity with various monocyclic azoles (pyrroles **1b** and pyrazoles **13**) and bicyclic azoles (indoles **11a** and indazoles **14**), it was less effective for unsubstituted substrates at position 2. In these cases, the products' nitrogen lone pairs (LPs) interfere with the carbene, forming ylide intermediates and reducing the overall efficiency of the reaction.<sup>34</sup> Liam and coworkers recently reported a modified photochemically mediated protocol to overcome this limitation for pyrroles **1**, indoles **11**, and pyrazoles **13** by introducing *N*-substitution, which masks the nitrogen's lone pairs, preventing them from reacting with the carbene source.<sup>36</sup>

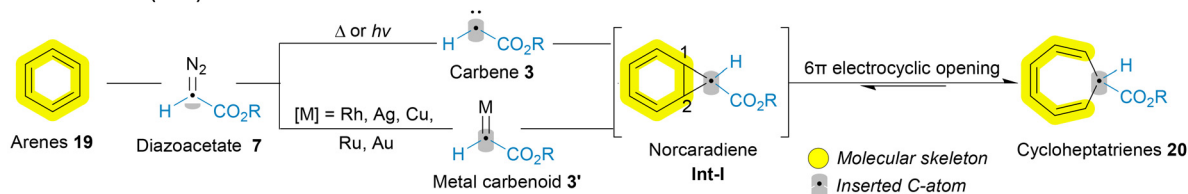
Halogenated carbene sources, such as 1,1-dibromoalkanes and bromodifluoroacetate (BrCF<sub>2</sub>COOEt) **6**, have also been employed as insertive agents for azaheterocycles' skeletal editing.<sup>37–39</sup> Metals like rhodium (Rh), silver (Ag), copper (Cu), and zinc (Zn) have been utilized as metal carbenoids in ring expansion, each following substrate-specific pathway. Recently, Bi and coworkers employed Rh- and Ag-catalyzed *N*-trifluoromethanesulfonyl (*N*-triflyl) hydrazones **10** as

carbene precursors for the dearomative ring expansion of azoles **17**,<sup>40</sup> indazoles **14**,<sup>41</sup> aziridines,<sup>42</sup> pyrroles **1**,<sup>43</sup> and indoles **11**.<sup>44,45</sup> Despite the use of similar carbene sources and metals, distinct structural features of substrates lead to different pathways.<sup>46</sup> Azoles **17**, indazoles **14** and aziridines undergo metal ylide formation, ring cleavage, and ring closing (Scheme 1E),<sup>40–42</sup> while pyrroles **1c** and indoles **11b** follow the cyclopropanation-fragmentation-dearomatization pathway (Scheme 1F).<sup>43,44</sup> In 2024, the Nakamura group reported the use of zinc carbenoids **9'** for methylene insertion into 1,2-azoles **17**, following the metal ylide formation, ring opening, and ring closing pathway (Scheme 1E).<sup>47,48</sup> These dearomative transformations elegantly yield diverse valuable products but deviate from the core concept of skeletal editing, which focuses on precise atom-level modifications while retaining the structural class of the scaffold. Transformations like those in Scheme 1E and F, though innovative, involve broader reorganization, such as converting one aromatic system to another. Other examples of metal carbenoids include the formation of spiro compounds from (benzo)isoxazoles.<sup>49,50</sup> Carbon insertion into the *in situ*-generated N-heterocyclic carbenes (NHC) to yield 3,4-dihydroquinoxalin-2(1*H*)-ones was also reported.<sup>51</sup> A few examples of ring expansion in azaheterocycles without a carbene source have been reported, such as the formation of quinolinones from oxindoles,<sup>52,53</sup> the ring expansion of pyrazolium ylides to 1,2-dihydropyrimidines,<sup>54</sup> and benzoisothiazol-3-ones to 2,3-dihydrobenzothiazin-4-ones.<sup>55</sup>

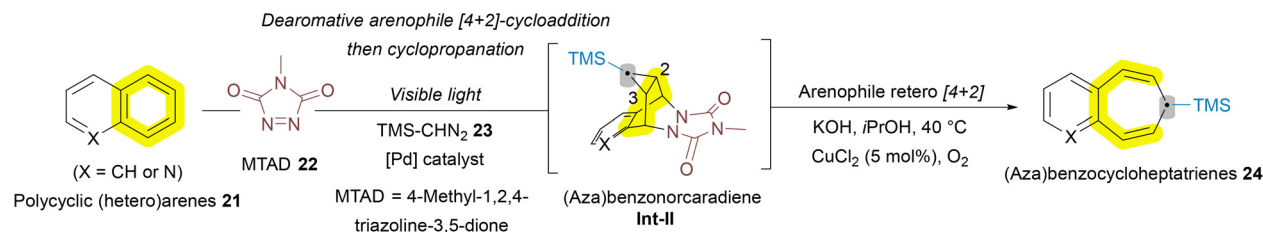
In addition to the significant progress made with carbene sources for ring expansion of azaheterocycles, arenes have also been explored for carbene-mediated skeletal editing, notably inspired by the Buchner reaction.<sup>56</sup> In 1885, the Buchner reaction was developed to enable the dearomative ring expansion of arenes **19** yielding cycloheptatrienes **20**.<sup>16</sup> This process involves the formation of norcaradiene intermediates **Int-I** *via* cyclopropanation at the 1,2-position, followed by 6 $\pi$  electrocyclic ring opening to produce cycloheptatrienes **20** (Scheme 2A).<sup>16</sup> While this reaction capitalizes on the inherent reactivity of arenes **19**, its applicability to polycyclic (hetero) arenes like naphthalenes **21** was initially limited. The Sarlah group addressed this challenge by introducing the arenophile 4-methyl-1,2,4-triazoline-3,5-dione (MTAD) **22**, which redirected cyclopropanation toward the 2,3-position when used in combination with TMS-diazomethane **23** and a palladium (Pd) catalyst (insertive agent), facilitating the formation of benzocycloheptatrienes **24** (Scheme 2B).<sup>57</sup> In 2024, the Sarpong group adopted a similar strategy to achieve the total synthesis of the natural diterpenoid harringtonolide **27** (Scheme 2C). They first converted cephanolide A **25** into the corresponding *p*-quinol methylether derivative **26** (benzenoid) following the Kita oxidative dearomatization conditions, and subsequently used diazomethane as an insertive agent to perform a ring expansion, yielding harringtonolide **27** (troponoid) through the Büchner–Curtius–Schlotterbeck reaction.<sup>58</sup> In 2024, the Jiang group developed an asymmetric rhodium/boron catalytic system for the single-atom carbon insertion of phenols with cyclopro-



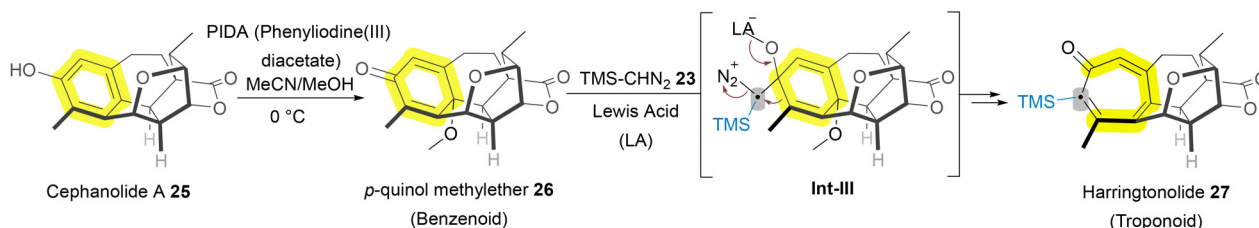
## A) Buchner reaction (1885)



## B) Ring expansion of polycyclic (hetero)arenes using TMS-diazomethane and Pd as insertive agent (Sarlah 2022)



## C) Harringtonolide synthesis using Büchner–Curtius–Schlotterbeck reaction (Paton &amp; Sarpong 2024)



Scheme 2 Carbon atom insertion into the main skeleton of arenes and polycyclic (hetero)arenes leading to ring expansion.

penes as insertive agents, synthesizing various cycloheptadienones with excellent chemo- and regioselectivity.<sup>59</sup>

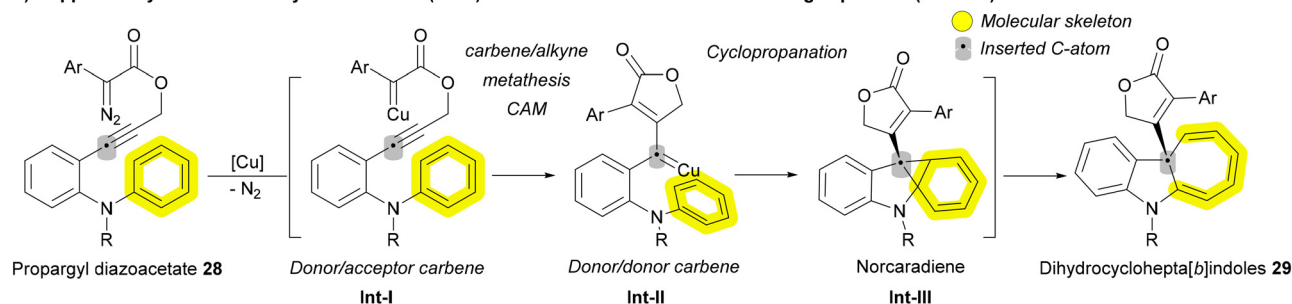
As the reaction evolved, various metal carbenoids—including silver (Ag), copper (Cu), rhodium (Rh), and ruthenium (Ru)—have been employed to enable both intra- and intermolecular asymmetric Buchner reactions. In 2019, Qiu and Xu reported a copper-catalyzed carbene/alkyne metathesis (CAM) reaction terminated with the Buchner ring expansion, yielding dihydrocyclohepta[*b*]indoles **29** (Scheme 3A). This marked the first example of the Buchner ring expansion reaction involving donor/donor-type metal carbene species.<sup>60</sup> Donor/acceptor carbenes contain one electron-donating and one electron-withdrawing group, while donor/donor carbenes feature two electron-donating groups.<sup>61</sup> Asymmetric versions of these ring-expansion reactions, have also been reported. In 2019, the Iwasa group provided an early example of an efficient enantioselective intramolecular Buchner reaction using diazoacetamides **30** (Scheme 3B). The Ru(II)–Pheox catalyst **32** demonstrated high efficiency in this transformation, achieving both high regioselectivity and enantioselectivity (up to 99% enantiomeric excess ee), yielding various  $\gamma$ -lactam fused 5,7-bicyclic-heptatriene derivatives **31a** in quantitative amounts.<sup>62</sup> Following this breakthrough, other asymmetric versions of the Buchner reaction, applying various protocols to different substrates and insertive agents, have been reported. In 2021,

Nemoto and Harada developed a diazo-free asymmetric intramolecular Buchner reaction for non-activated arenes **33**, using ynamides as a carbene source (Scheme 3C). This method enabled asymmetric ring expansion, yielding  $\gamma$ -lactam fused 5,7-bicyclic-cycloheptatrienes **31b** in the presence of a chiral phosphoric acid silver salt **34**.<sup>63</sup> In the same year, Darses and coworkers employed a similar strategy, using a dirhodium (Rh) catalyst to synthesize enantioenriched seven-membered carbocycle-containing bicyclic skeletons.<sup>64</sup> In 2022, the Zhu group reported a chiral dirhodium(II) tetracarboxylate-catalyzed enantioselective intramolecular Buchner reaction of donor/donor carbenes, leading to the synthesis of valuable chiral polycyclic products. Both aryloxy enynones and diazo compounds served as efficient carbene precursors, achieving excellent yields and outstanding enantioselectivities.<sup>65</sup>

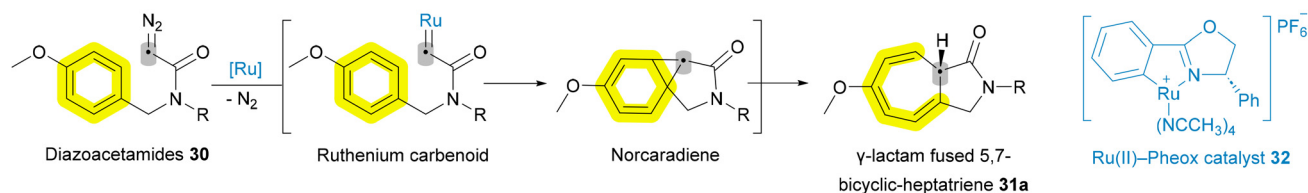
Despite all these advances in the Buchner reaction from the perspectives of sustainability, a metal-free Buchner reaction involving non-diazo compounds remains highly desirable. Addressing this need, a new strategy was introduced by Ni, Wen, and Zhang in 2022, employing hypervalent iodine [phenyliodine(III) diacetate (PIDA)] as a promoter for intramolecular Buchner reactions.<sup>66</sup> This method utilizes three-carbon-atom tethered *N*-alkoxyamides **35** as substrates. The proposed mechanism begins with the coordination of the benzamide substrate to phenyliodine(III) diacetate, forming the intermediate **Int-IV**,



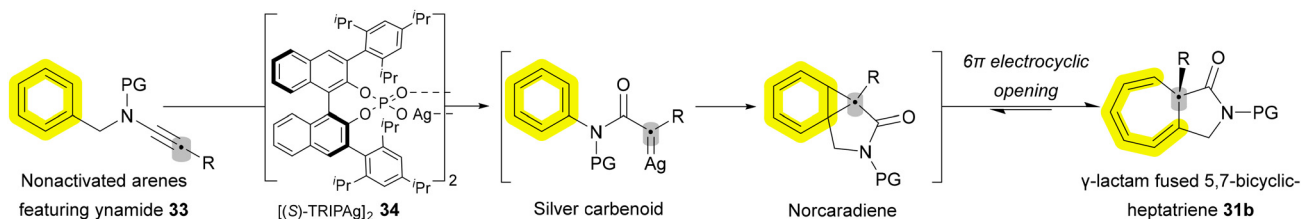
## A) Copper-catalyzed carbene/alkyne metathesis (CAM) reaction terminated with Buchner ring expansion (Xu 2019)



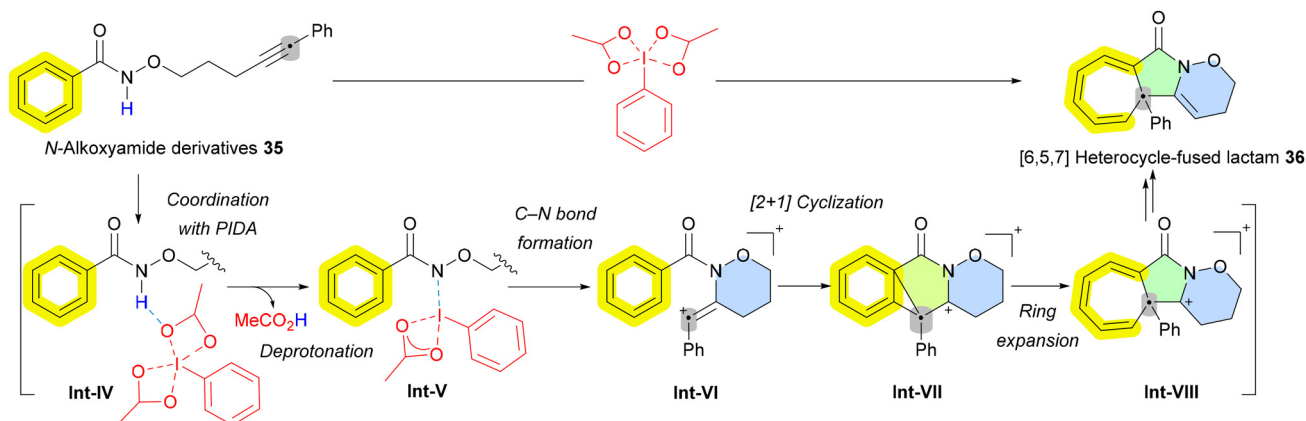
## B) Enantioselective intramolecular Buchner reaction using diazoacetamides (Iwasa &amp; Thanh 2019)



## C) Silver-catalyzed diazo free Asymmetric Intramolecular ring expansion of nonactivated arenes (Harada &amp; Nemoto 2021)



## D) Metal-free Buchner reaction involving non-diazo insertive agent employing hypervalent iodine (Zhang, Wen, and Wright 2022)



Scheme 3 Recent advances of Buchner-mediated carbon atom insertion into the main skeleton of arenes.

followed by a rapid deprotonation process that yields the slightly endergonic species **Int-V**. From **Int-V**, the release of the acetate ligand and subsequent C–N bond formation led to a stable vinyl cation, **Int-VI**. This cation induces a [2 + 1] cyclization reaction, producing a highly stabilized cationic species **Int-VII**, via a rapid process with a low energy barrier. The ring expansion then proceeds to form the seven-membered ring intermediate **Int-VIII**. Finally, a deprotonation process results in

the formation of a [6,5,7] heterocycle-fused lactam **36**, completing the reaction (Scheme 3D).<sup>66</sup> All these transformations in Scheme 3 are grounded in well-established reactivity trends, which have been studied extensively for decades. While recent advances allow them to be categorized under the broader umbrella of skeletal editing, they do not represent the forefront of the field and often deviate from the core concept of skeletal editing by converting one aromatic system into another.



In addition to various (polycyclic) arenes, other examples of (polycyclic) heteroarenes, particularly azaheterocycles, follow a sequence similar to the Buchner reaction. This typically involves a dearomative [4 + 2] cycloaddition, cyclopropanation, and subsequent electrocyclic ring opening. In 2019, Mancheño and coworkers developed a metal-free ring expansion protocol for carbon atom insertion into hydroquinolines scaffold **37** employing TMS-diazomethane (TMSCHN<sub>2</sub>) **23** as the insertive agent to afford a range of benzo[*b*]azepines **38a** (Scheme 4A). The authors proposed two possible pathways for the ring expansion. After the oxidation of **37** to the corresponding intermediate **Int-I**, nucleophilic attack of TMS-diazomethane **23** on the iminium ion generates diazo intermediate **Int-II**, which undergoes nitrogen release. This occurs through nucleophilic attack either at the olefinic carbon (3-position) or the nitrogen atom, leading to cyclopropane cationic intermediates **Int-III** or **Int-IV**, respectively. Subsequent ring opening gives rise to the 7-membered cationic intermediates **Int-V** or **Int-VI**, respectively. Finally, the release of TMS<sup>+</sup> leads to the formation of benzo[*b*]azepine **38a** (Scheme 4A).<sup>67</sup> In 2021, Beeler and coworkers introduced another approach to access mono- and polycyclic functionalized azepines **38b** through the dearomative photochemical rearrangement of aromatic *N*-ylides **40** (Scheme 4B).<sup>68</sup> That same year, the Yoo group developed an unprecedented regioselective silver(i)-catalyzed carbon atom insertion, yielding 4-substituted azepine derivatives **38c** through 1,4-dearomative addition of diazoacetates **7** (Scheme 4C).<sup>69</sup> Additionally, different azaheterocycles have been reported for carbon atom insertion using various insertive agents and different approaches, including 1,2-dihydropyridines and quinolines using gold-carbenoid as the insertive agent,<sup>70</sup> and Cu-iminium catalysis for carbon atom insertion into oxindoles affording quinolinones.<sup>53</sup> In 2024, Morandi and coworkers employed the same substrate oxindoles **42** to develop a highly efficient rare example of regiodivergent ring expansion reaction to afford both 3-substituted quinolinones **44** and 4-substituted quinolinones **45** (Scheme 4D).<sup>52</sup> They showed a successful example for the late-stage functionalization of bioactive oxindoles, such as doliracetam (drug for epilepsy) showing the potential of this method in the synthesis of quinoline derivatives and diversification of drugs.

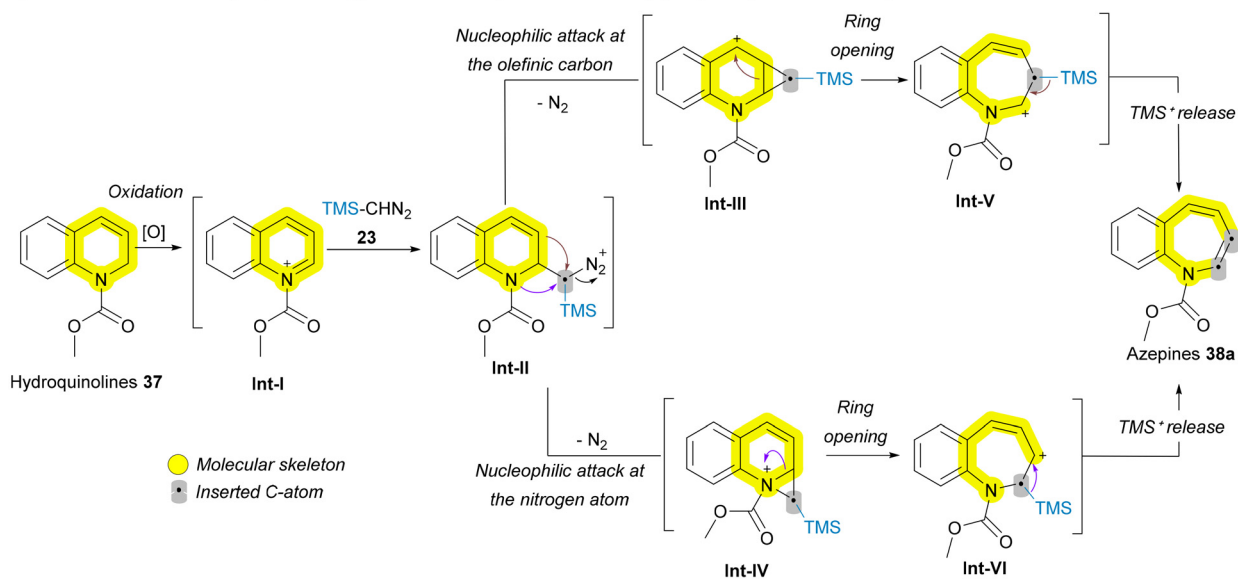
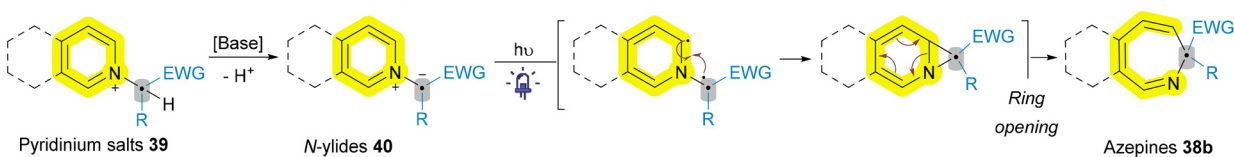
In 2022, Arnold group, the pioneers of directed evolution to engineer enzymes, reported a landmark example of enantioselective single-carbon atom insertion into aziridines **46** to afford azetidines **47** as a new-to-nature activity of engineered “carbene transferase” enzymes. The iron carbenoid insertive agent could be trapped by nucleophilic aziridine forming aziridinium ylides **Int-I**, which could undergo intramolecular [1,2]-Stevens rearrangement liberating the desired product **47** (Scheme 5A).<sup>71</sup> This pioneering achievement opens the door to bio-catalyzed skeletal editing, enabling unprecedented efficiency and stereocontrol in chemical transformations. Gutierrez and Glorius developed a photoredox-catalyzed ring expansion strategy to efficiently insert functionalized carbon atoms into indenenes. The process leverages  $\alpha$ -iodonium diazo compounds as masked carbyne equivalents, alongside photo-

redox catalysis, to achieve carbon insertion under mild conditions.<sup>72</sup> Beside all these single atom insertions, some recent reports of multiple atom insertion have been introduced,<sup>73,74</sup> including the work of Clayden of the asymmetric deprotonation of *N*-benzyl urea derivatives of nitrogen heterocycles **48** leads to enantioselective insertion of the benzylic substituent into an aromatic C–N bond *via* chiral lithium (Scheme 5B).<sup>75</sup> Not only azaheterocycles are the heteroarenes that have been reported for the carbon atom insertion, but also other heterocycles for example oxetane and thietane heterocycles have been reported to undergo photo-mediated carbon atom insertion employing diazoacetates **7** as an insertive agent to afford tetrahydrofuran and thiolane heterocycles.<sup>76</sup>

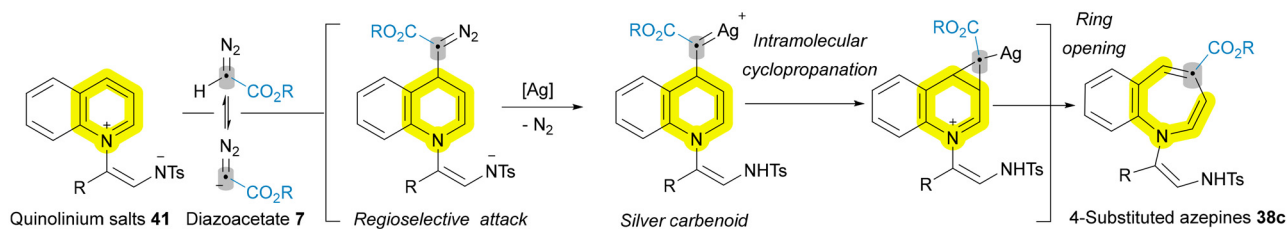
**2.1.2. Nitrogen atom insertion.** Nitrogen atom insertion into cyclic frameworks is one of the key strategies in synthetic organic chemistry, driven largely by its significant role in drug discovery. Almost 82% of FDA-approved drugs during the last decade between 2013 and 2023 feature at least one nitrogen-containing heterocycle.<sup>77</sup> Hence, nitrogen atom insertion is particularly valuable in medicinal chemistry, where it enables the diversification of molecular libraries and facilitates more nuanced structure–activity relationship studies with minimal effort. While classical nitrogen insertion methodologies such as the Beckmann rearrangement (1886) and Schmidt reaction (1924) successfully converted carbonyl compounds into lactams, their broader application has been hindered by the harsh conditions and limited regioselectivity, restricting their utility across a diverse range of substrates.<sup>78,79</sup> Recent advancements have focused on developing more versatile, functionally tolerant, and stereoselective protocols.<sup>80</sup> A notable example is the Aza-Baeyer–Villiger rearrangement reported by Wahl and colleagues.<sup>81</sup> This approach introduces nitrogen atoms into cyclic frameworks **50a** through a Criegee-type intermediate **Int-I**, utilizing amino diphenylphosphinates **51** as a readily available nitrogen source (Scheme 6A). In addition to its practicality, the method qualifies for late-stage diversification, as showcased by the synthesis of Rolipram and its *N*-alkylated analogs.<sup>81</sup> The same group investigated similar oxidative rearrangement strategy, applying it to prochiral cyclobutanones **50b** to achieve stereocontrol in the formation of a diverse range of  $\gamma$ -lactams **52b**, including those featuring challenging quaternary stereocenters.<sup>82</sup> By employing a bifunctional amine source **53**, featuring leaving group and a chiral auxiliary (Scheme 6B), this approach facilitates the generation of a hemiaminal intermediate **Int-II** from the cyclobutanone substrate **50b**. The subsequent elimination of the leaving group, guided by the chiral auxiliary, orchestrates the regioselective migration of the C–C bond, leading to the desymmetrization and enantioselective formation of  $\gamma$ -lactams **52b**. Notably, this method provides access to pharmacologically relevant molecules, such as pregabalin, baclofen, and brivaracetam, underscoring its broad applicability and utility in drug synthesis. In 2024, Huang group developed an efficient photoredox-catalyzed nitrogen insertion strategy to access multi-substituted isoquinolines from indanones-derived oxime esters. Their mechanistic investigations revealed that ring-opening of



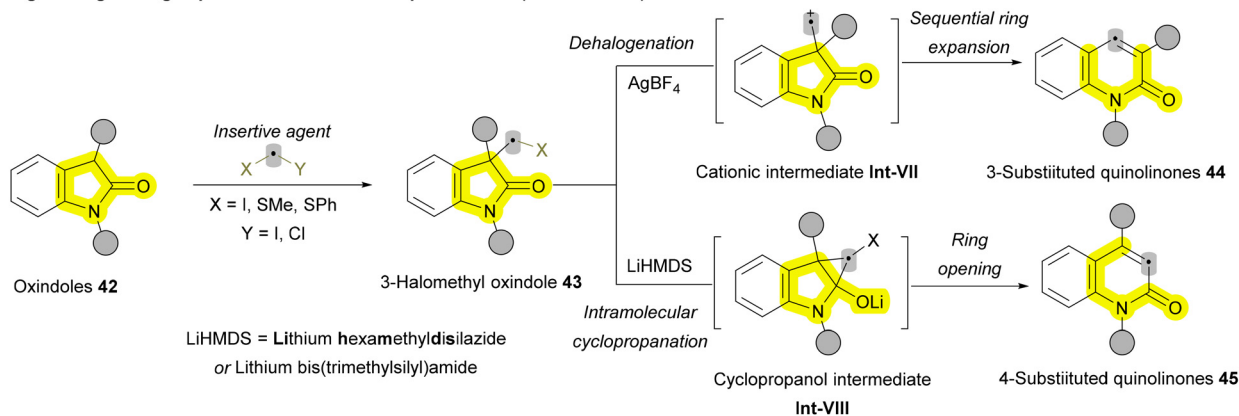
## A) Metal-free oxidative ring-expansion approach for the synthesis of benzo[b]azepines (Mancheño 2019)

B) Photochemical rearrangement of aromatic *N*-ylides for the synthesis of benzo[b]azepines (Beeler 2021)

## C) Regioselective 1,4-dearomative addition of diazoacetates to activated heteroarenes (Yoo 2021)



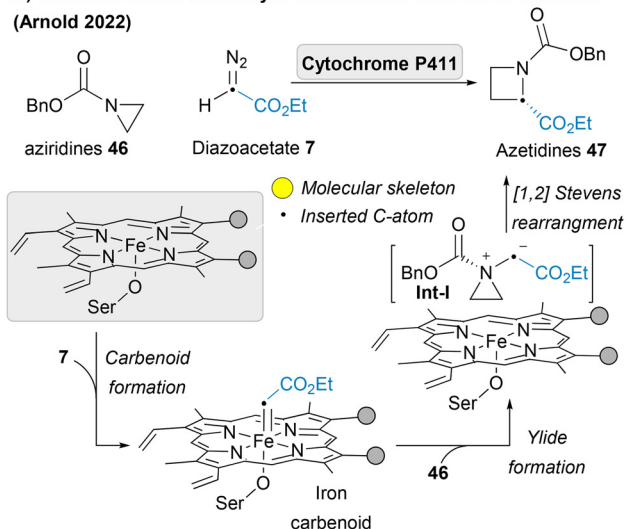
## D) Regiodivergent ring-expansion of oxindoles to quinolinones (Morandi 2024)



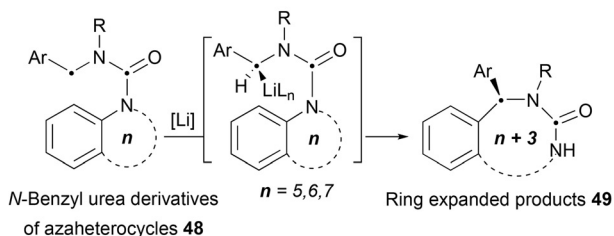
Scheme 4 Recent advances of carbon atom insertion into the main skeleton of quinolinium and pyridinium salts and oxindoles.



### A) Enantioselective biocatalytic carbon atom insertion of aziridines (Arnold 2022)



### B) Enantioselective 3-atoms insertion via chiral lithium (Clayden 2024)

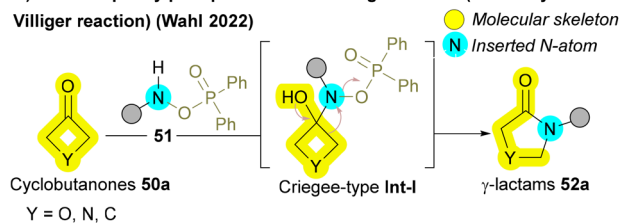


**Scheme 5** Enantioselective biocatalytic carbon atom insertion and multiple atom insertion.

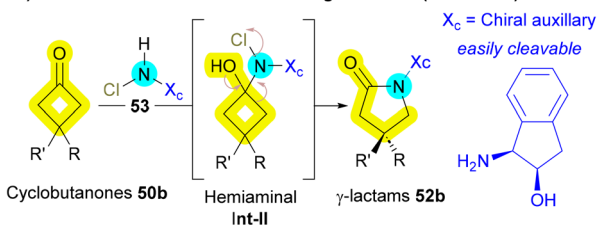
oxime esters yielded thioesters, the key intermediates for the synthesis of isoquinolines upon nitrogen insertion from amines.<sup>83</sup> In 2024, Sarpong and coworkers introduced a two-step protocol for single nitrogen insertion into hydrocarbon frameworks, bypassing strain-release mechanisms. The first step employs site-selective benzylic oxidation to install ketones or aldehydes as traceless directing groups. The second step uses C–C reductive amination of these carbonyl compounds, targeting the C–C  $\sigma$ -bond to produce tertiary amines with a borane catalyst and hydroxylamine as the nitrogen source. Their method enables late-stage nitrogen insertion, facilitates the divergent synthesis of isomeric amines from a single precursor, and allows nitrogen translocation within cyclic systems *via* a deletion/insertion sequence, expediting chemical space exploration.<sup>84</sup>

In addition to classical carbonyl-containing substrates, other non-carbonyl substrates have also been explored for nitrogen insertion. *O*-Sulfonylhydroxylamines 55 have emerged as highly efficient nitrogen sources for the ring expansion of cyclic alcohols and cyclic alkanes 54, as demonstrated by Wahl *et al.*<sup>85</sup> and Zhang *et al.*,<sup>86</sup> respectively. These methodologies typically proceed through the formation of a carbocation intermediate **Int-III**, which subsequently transforms into an iminium ion **Int-V**. Upon reduction, this intermediate **Int-V** affords the desired ring expanded product 38 (Scheme 6C).<sup>86</sup>

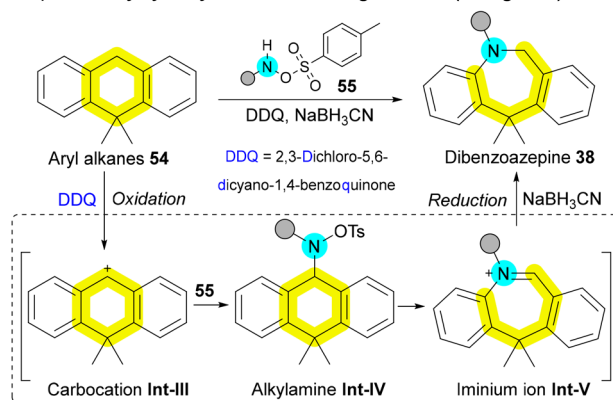
### A) Amino diphenylphosphinates as a nitrogen source (Aza-Baeyer Villiger reaction) (Wahl 2022)



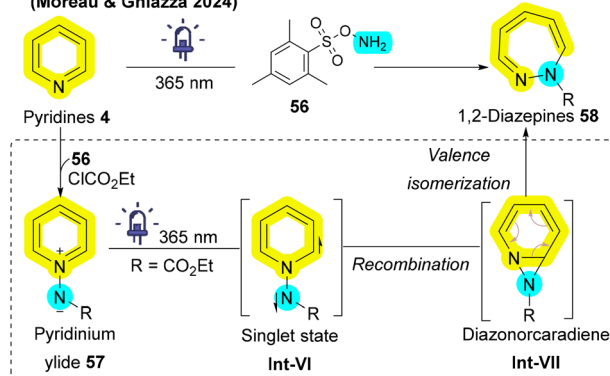
### B) Bi-functionalized amine as a nitrogen source (Wahl 2021)



### C) *O*-Sulfonylhydroxylamines as a nitrogen source (Zhang 2024)



### D) Photochemical nitrogen insertion using MSH as a nitrogen source (Moreau & Ghiazza 2024)



**Scheme 6** Nitrogen atom insertion employing amine derivatives as insertive agents.

In 2024, Ghiazza and Moreau unveiled an innovative landmark photochemical approach that utilizes *O*-(mesitylsulfonyl) hydroxylamine (MSH) 56 to induce the ring expansion of pyridines 4 into 1,2-diazepines 58. This skeletal transformation is driven by the *in situ* formation of 1-aminopyridinium ylides 57, which are then excited to their singlet state **Int-VI** upon UV irradiation. Subsequently, they undergo rearrangement into diazonorcaradienes **Int-VII**, followed by sequential fragmenta-



tion and dearomatization, ultimately yielding the 1,2-diazepine scaffold **58** (Scheme 6D).<sup>87</sup> These pioneering methodologies not only demonstrate the utility of *O*-sulfonylhydroxylamines **55** and **56** as nitrogen sources but also significantly broaden the substrate scope for nitrogen insertion reactions, highlighting its potential in skeletal editing strategies and representing the forefront of the field.

Another promising insertive agent for N-atom insertion reactions is the nitrene.<sup>88</sup> Early investigations into the chemistry of nitrenes were initiated by Huisgen, Doering, Beach and Cotter, which laid the foundation for subsequent research in this area.<sup>89–91</sup> Aryl nitrenes have been successfully employed as reactive intermediates to facilitate the synthesis of azepines from corresponding aryl azides **59a** which can generate the corresponding nitrenes **Int-I** *via* thermal decomposition, photochemical activation, or heavy atom tunneling.<sup>91–96</sup> Once formed, aryl nitrenes **Int-I** can undergo aziridination, producing aziridine **Int-VI** or azirine **Int-III** intermediates that subsequently undergo oxidative ring opening to yield azacycloheptatetraenes **60**. These scaffolds can further convert to the corresponding azepines **38d** upon nucleophilic addition (Scheme 7A).<sup>92</sup> While this approach yields diverse and valuable skeletons, it sometimes involves converting aromatic rings into non-aromatic analogues and *vice versa*, which falls short of achieving the optimal goal of atom-level modifications. Wei group expanded the utility of azides as nitrogen sources by employing transition metals such as cobalt and rhodium to mitigate the undesired C–H insertions that are common in traditional nitrene ring expansion reactions.<sup>97,98</sup> In 2023, Wei group demonstrated a transformation involving biaryls with peripheral carbamoyl azides **61** that are activated by a rhodium catalyst, allowing direct insertion into the C–C bonds of arene rings to generate fused azepine products **38e** (Scheme 7B). Although this transformation is particularly challenging, the employment of a paddlewheel dirhodium complex, Rh<sub>2</sub>(esp)<sub>2</sub>, effectively inhibited the unwanted competing C–H amination pathway.<sup>98</sup> In addition to azide derivatives **59a** and **61**, Ji and Wei's groups have explored the incorporation of TMSN<sub>3</sub> as an insertive agent in conjunction with metal catalysts for a variety of substrates, including cycloalkenes **62**,<sup>97</sup> indoles,<sup>99</sup> and arenols (more details in section 2.3.1),<sup>100</sup> to facilitate nitrogen atom insertion *via* nitrene intermediates. For example, in reactions involving cobalt, azido radicals generated from TMSN<sub>3</sub> by a radical chain reaction selectively attack cycloalkenes **62** to produce carbon radicals **Int-VII**, which subsequently yield aziridine radicals **Int-IX**. Through consecutive oxidative ring opening and dehydrogenation, the corresponding pyridine derivatives **4** are formed (Scheme 7C).<sup>97</sup> In the case of indoles, a domino reaction occurs that generates azido radicals, leading to diazidation and the formation of quinazolin-4-amine derivatives.<sup>99</sup> Conversely, for arenols, dearomatization followed by aryl migration, afforded the corresponding benzazepine derivatives.<sup>100</sup> In 2024, Wang and Luan employed AgOTf as a catalyst and PhI = NTs as insertive agent to induce nitrogen atom insertion of arenols affording azepinone.<sup>101</sup> Iron has been utilized as a catalyst by Yu's group to

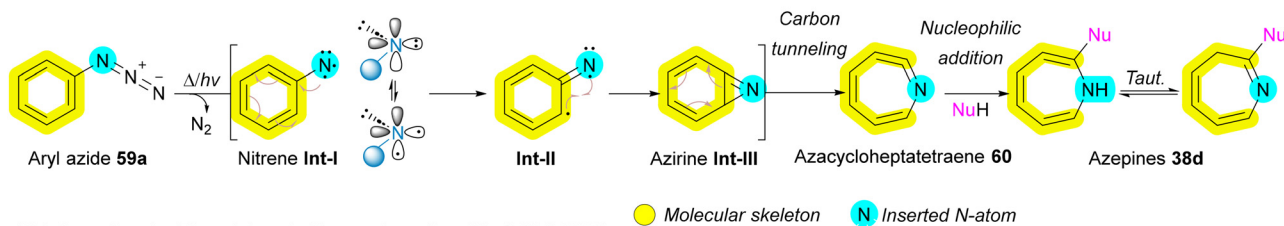
convert  $\alpha$ -azidyl phenyl ketones into enamides through nitrogen insertion.<sup>102</sup>

In 2023, a metal-free photochemical approach for the intramolecular nitrogen insertion has been reported by Tian, Ariafard and Hashmi, involving a cascade reaction that generates nitrene intermediates **Int-XI**, aziridination, and subsequent water addition to obtain desired azepinone derivatives **63** (Scheme 7D).<sup>103</sup> In 2022, Leonori and his group have explored nitroarenes **64**, an unprecedented stable and commercially accessible substrate, to synthesize azepines **38g** and azepanes **65** using blue light as an energy source. In this process, nitroarenes **64** are converted to singlet nitrenes **Int-XV** in the presence of blue light, facilitating azirine **Int-XVI** formation at C=C bonds followed by a 6 $\pi$ -electrocyclic ring opening, ultimately producing azepines **38g**. These azepines **38g** can subsequently undergo hydrogenolysis to yield azepanes **65** (Scheme 7E).<sup>104</sup>

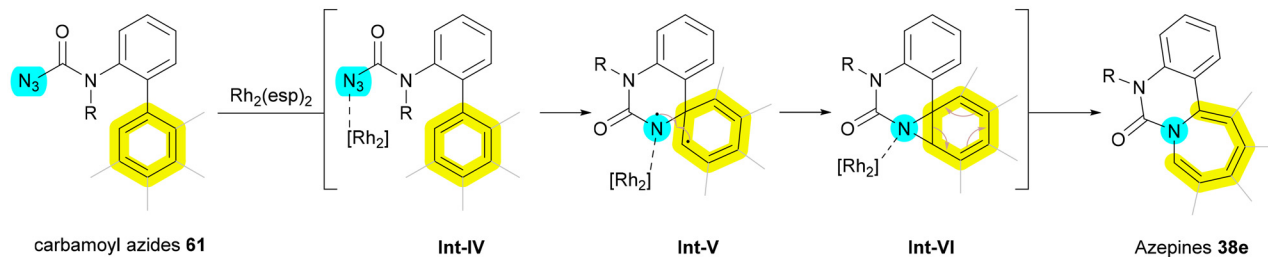
Recently, several innovative methods have been developed to transform indoles **11** and pyrroles **1** into their nitrogen-extended counterparts, including quinazolines **16** and pyrimidines **15**. A key example dates back to 1987 when Kumar utilized *N*-acetoxyaminophthalimide **66**, generated *via* the oxidation of *N*-amino phthalimide with lead(IV) acetate Pb(OAc)<sub>4</sub>, as an insertive agent. The reaction followed a pathway including the formation of aziridine **Int-I**, followed by subsequent ring expansion (Scheme 8A).<sup>105</sup> Building on similar principles, the Morandi group later introduced a pioneering strategy for nitrogen insertion into *N*-protected indoles **11b**, enabling access to N,N-heterocycles such as quinazolines **16b** and quinoxalines **68**, depending on the substitution pattern of the indoles **11b**. This reaction exhibits a broad substrate scope, tolerating various functional groups, and thus enabling the biosoteric diversification of natural products and pharmaceutical agents.<sup>106</sup> In 2024, the Alcarazo group applied the same strategy to obtain indoles from cycloalkene substrates, further expanding the versatility of nitrogen insertion chemistry.<sup>107</sup> Morandi group's strategy employed iodonitrenes **67**, generated *in situ* from hypervalent iodine and ammonium carbamate (NH<sub>4</sub>CO<sub>2</sub>NH<sub>2</sub>), as highly reactive electrophilic aminating agents. This innovative chemistry not only opened the gate for numerous future developments but also provided elegant solutions to several persistent challenges in nitrogen insertion and amination reactions. The reaction proceeds through the formation of a cationic azirine **Int-III** and aziridine **Int-IV** intermediates, followed by the elimination of iodobenzene to afford the desired quinoxaline **68** or quinazoline **16b** (Scheme 8B). The use of silyl protecting group (TBS) of indole **11b** is critical to avoid side interactions between the nucleophilic nitrogen of the indole **11b** and the electrophilic iodonitrene **67**, forming an unstable isodiazene intermediate **Int-V** that can degrade the carbon skeleton.<sup>106</sup> Hence, the requirement for a protecting group, coupled with its inefficiency in converting pyrroles to pyrimidines, restricts the applicability of this method to more complex medicinal substrates. In addressing these challenges, the same group improved their protocol one year later with the serendipitous discovery that lithium bis(trimethyl-



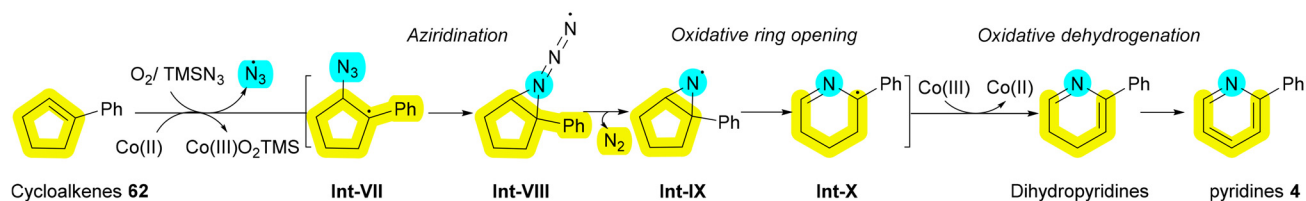
## A) Nitrenes as key intermediates for the nitrogen atom insertion of aryl azides



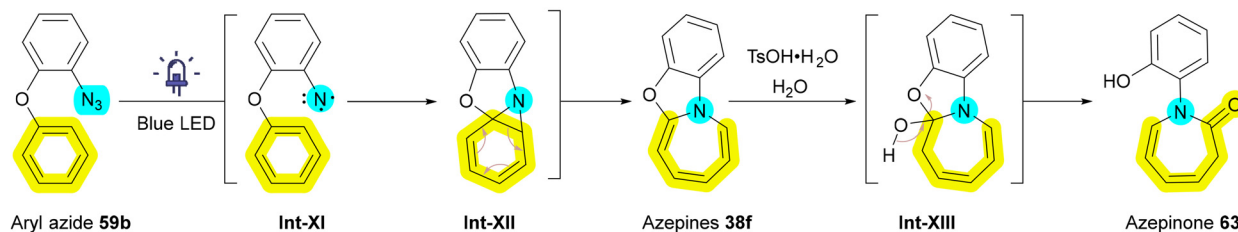
## B) Intramolecular Rh-catalysed nitrogen insertion (Xu &amp; Wei 2023)



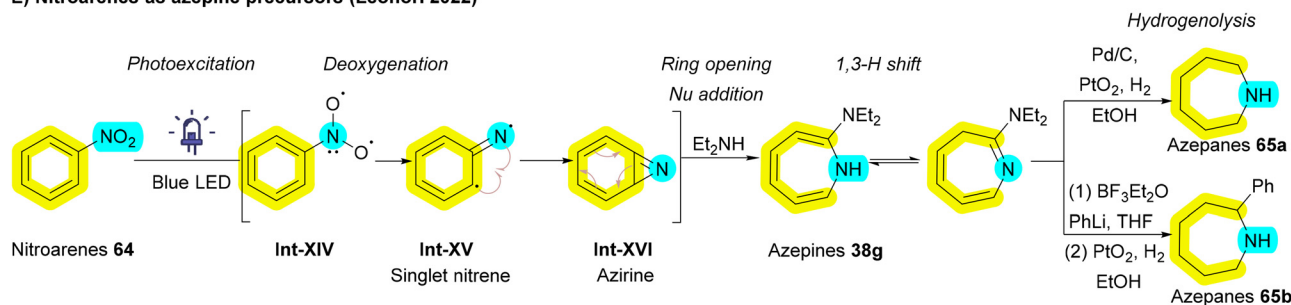
## C) Cobalt catalysed nitrogen insertion into cycloalkenes (Wei 2022)



## D) Metal free intramolecular nitrogen insertion (Tian, Ariafard, and Hashmi 2023)



## E) Nitroarenes as azepine precursors (Leonori 2022)



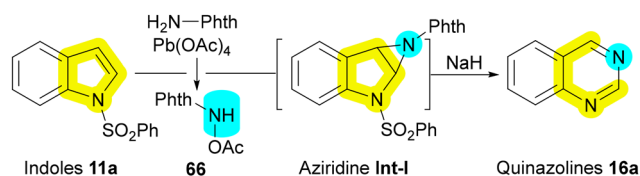
Scheme 7 Nitrogen atom insertion into the main skeleton of aryl azides and nitroarenes leading to ring expansion.

silyl)amide (LiHMDS) could serve a dual function as both a base and a nitrogen atom source. This allowed for the direct insertion of nitrogen atoms into 1*H*-indoles and 1*H*-pyrroles, even in complex bioactive molecules, overcoming previous

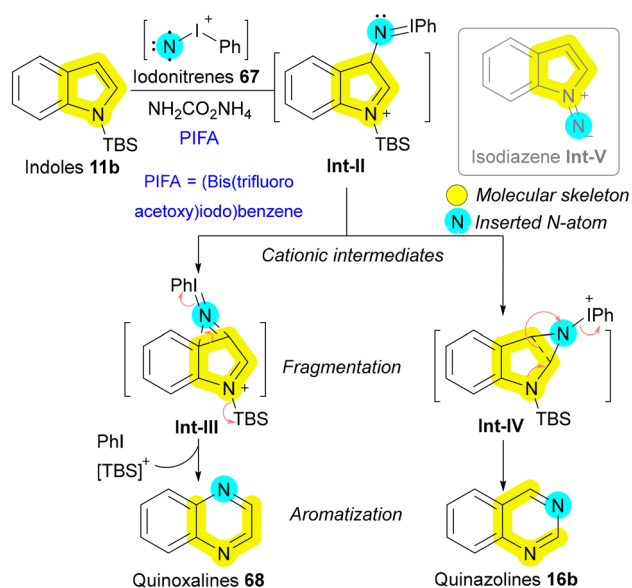
limitations and broadening the synthetic utility of this methodology.<sup>108</sup> In 2024, the same Morandi group applied their iodonitrene chemistry for transforming cyclopentenone derivatives into pyridones, through a strategy of silyl enol ether for-



## A) Nitrogen insertion into indoles (Kumar 1987)



## B) N-insertion into protected indoles via iodonitrene (Morandi 2023)

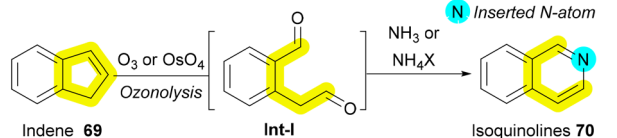


**Scheme 8** Nitrogen atom insertion into the main skeleton of indoles leading to ring expansion.

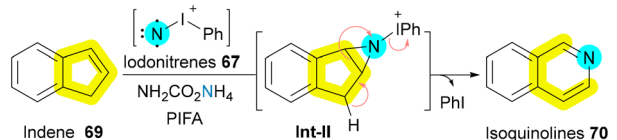
mation, followed by nitrogen insertion, and subsequent aromatization. Their strategy enabled as well to incorporate  $^{15}\text{N}$ -labels in various synthetic targets.<sup>109</sup>

Another significant class of compounds that have been explored for nitrogen insertion reactions is cyclic olefins, particularly indenes **69**, which can be transformed into isoquinolines **70**—a crucial scaffold in various pharmaceuticals.<sup>77</sup> Early studies by Fields, Frincke, and McLean demonstrated this transformation through oxidative cleavage (ozonolysis) of the indene backbone using ozone ( $\text{O}_3$ ) or osmium tetroxide ( $\text{OsO}_4$ ) in the presence of ammonia or ammonium salts as the nitrogen source (Scheme 9A).<sup>110–112</sup> However, the need for these harsh oxidative conditions limited the applicability of these methods. In 2023, The Morandi group advanced this area by applying their iodonitrene **67**-based approach for nitrogen insertion in indenes **69**, leading to isoquinolines **70** synthesis *via* an aziridination–fragmentation–aromatization pathway (Scheme 9B).<sup>113</sup> However, their protocol required strong oxidizing agents (hypervalent iodine), further constraining its substrate scope.<sup>113</sup> In 2024, Alcarazo and colleagues introduced a novel electrophilic nitrogen source, *N*-(sulfonio)sulfilimine **71** acting as sulfonitrene **72** precursors under rhodium catalysis. These reactive species **72** enabled the same reactivity for indenes **69** without the need for oxidizing agents, *via* aziridina-

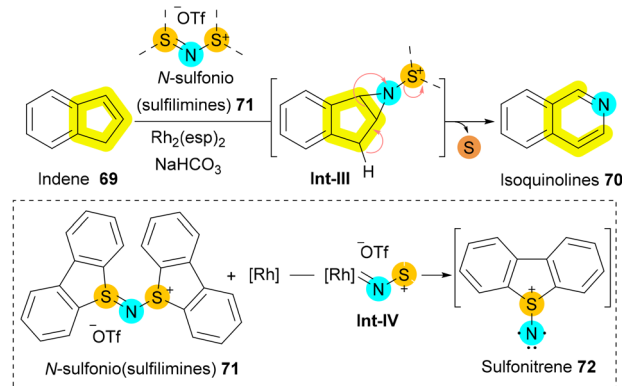
## A) Fields (1964), Frincke (1980), and McLean (1981)



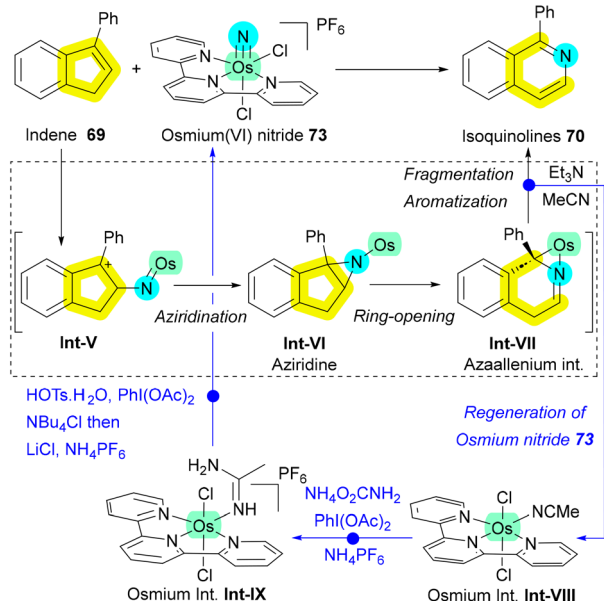
## B) Nitrogen insertion into indenes using iodonitrene (Morandi 2022)



## C) Nitrogen insertion into indenes using sulfonitrene (Alcarazo 2024)



## D) Nitrogen insertion into indenes using osmium nitride (Levin 2022)



**Scheme 9** Nitrogen atom insertion into the main skeleton of indenes leading to ring expansion.

tion followed by ring expansion (Scheme 9C). This protocol proved effective for indenes **69**, even in the absence of electron-donating groups or aryl rings, but encountered limitations when applied to unprotected indoles or pyrroles due to the inherent stability of iminium cations, which hindered aziridination.<sup>107</sup> Levin *et al.* also contributed to this field by



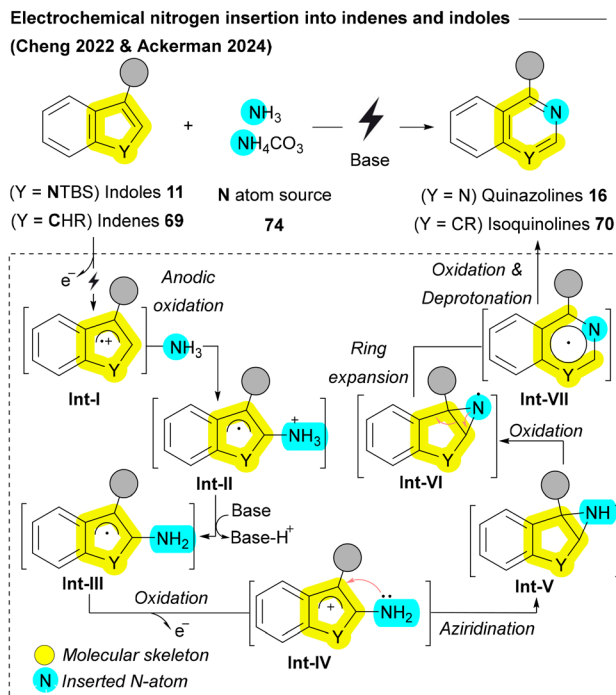
reporting the formation of isoquinolines **70** from indenes **69** through direct nitrogen atom insertion using osmium(VI) nitride **73**. The reaction proceeds *via* an aziridination and ring-opening sequence, leading to azaallenium **Int-VII** formation. The aromatization of this intermediate **Int-VII** occurs primarily

through base-assisted deprotonation, followed by stepwise regeneration of starting osmium(VI) nitride **73** (Scheme 9D).<sup>114</sup>

Recently, the Cheng group and Ackerman group achieved a groundbreaking milestone by successfully accomplishing direct ammonia **74** insertion into indenes **69** and indoles **11**, respectively, using an electrochemical approach (Scheme 10).<sup>115,116</sup> In their methods, a cation radical **Int-I** is generated through anodic oxidation, which then reacts with ammonia affording **Int-II**. A subsequent oxidation converts the neutral radical **Int-III** into a cation **Int-IV** which undergoes annulation to aziridine **Int-V**. A third electron transfer oxidation of nitrogen during the conversion of **Int-V** to **Int-VI** triggers deprotonation/rearrangement, yielding dihydroisoquinoline radical **Int-VII**. The fourth electron transfer and deprotonation results in the final products isoquinolines **70** or quinazolines **16** (Scheme 10).<sup>115,116</sup>

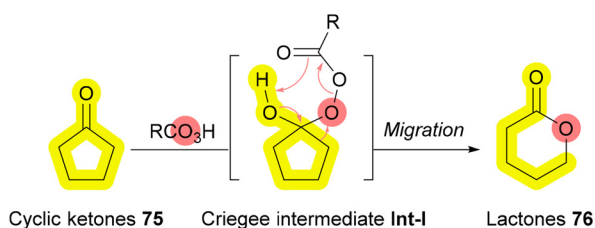
**2.1.3. Oxygen atom insertion.** Oxygen atom insertion into cyclic frameworks is a powerful tool for molecular diversification, though its exploration has been less extensive compared to carbon and nitrogen insertions.<sup>6</sup> One of the keystones in this area is the Baeyer–Villiger oxidation, discovered in 1899, which facilitates the conversion of cyclic ketones **75** into lactones **76** *via* oxygen insertion (Scheme 11A).<sup>18</sup> Despite its long-standing significance and proven utility in producing regio-, chemo-, and enantioselective lactones, the reaction's application has historically been constrained to specific substrates.<sup>117</sup>

In 2023, the Sarpong group investigated the structural remodeling of cyclic amines **77** through oxidative C–N and C–C bond cleavages, utilizing peroxydisulfate (persulfate) as the oxidant.<sup>118</sup> Their proposed mechanism involves the generation of an alkyl radical **Int-II** from the cyclic amine **77** *via* Ag(I)-

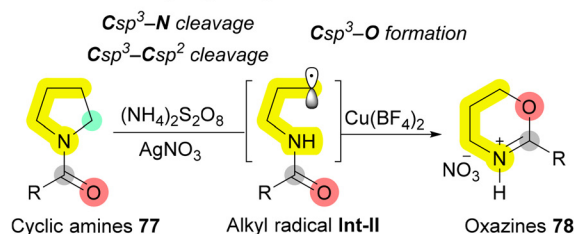


**Scheme 10** Electrochemical N-atom insertion into the skeleton of indoles and indenes leading to ring expansion.

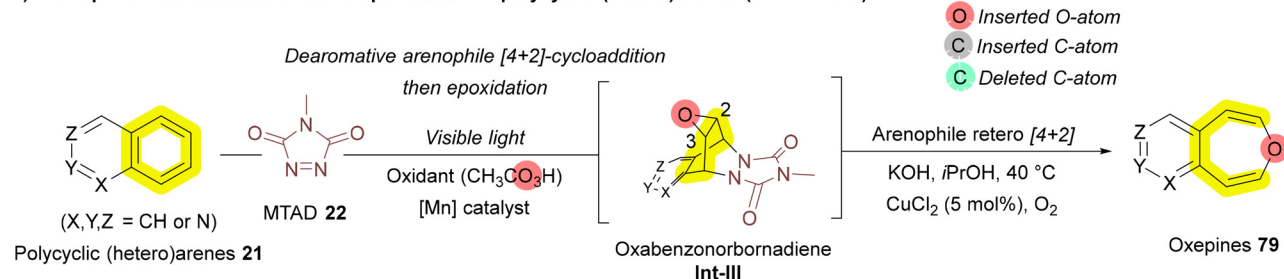
**A) Baeyer–Villiger oxidation (1899)**



**B) Autocyclization of cyclic amines using Cu(II) oxidation (Baik, Musaev, and Sarpong 2023)**



**C) Arenophile-mediated dearomative epoxidation of polycyclic (hetero)arenes (Sarlah 2020)**



**Scheme 11** Oxygen atom insertion strategies leading to ring expansion.



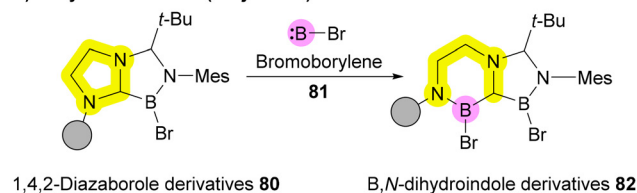
mediated activation by persulfate.<sup>119</sup> This alkyl radical **Int-II** subsequently interacts with Cu(II), forming a Cu-complex that undergoes intramolecular cyclization to yield oxazines **78** (Scheme 11B). In 2020, a novel arenophile-based dearomative approach developed by Sarlah and coworkers similar to their work on carbon insertion (Scheme 2B),<sup>57</sup> they employed 4-methyl-1,2,4-triazoline-3,5-dione (MTAD) **22** as the reactive arenophile to facilitate oxygen atom insertion. In their strategy, polycyclic (hetero)arenes **21** undergo visible light-induced [4 + 2]cycloaddition, leading to the formation of oxabenzonorbornadiene **Int-III**, which subsequently undergo a [4 + 2] cycloreversion to yield oxepines **79** (Scheme 11C). This method expands the scope of oxygen insertions, enabling the selective functionalization of polycyclic systems that were previously challenging to modify.<sup>120</sup> In 2023, the Liu group achieved the first transformation of pyrrolidine to 1,2-oxazinane *via* formal oxygen atom insertion, utilizing *meta*-chloroperbenzoic acid (*m*CPBA) as the insertive agent to produce complex, medicin-

ally significant bispiro[oxindole-oxazinane] hybrids with remarkable stereocontrol.<sup>121</sup>

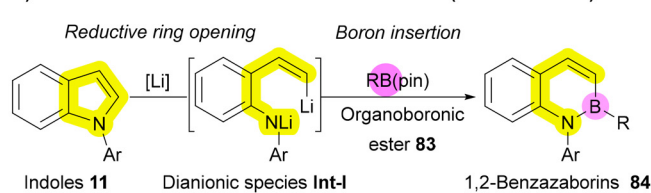
**2.1.4. Boron atom insertion.** The insertion of boron atoms into heterocycles can significantly modulate their properties and expand their applications. However, methods for achieving such transformation remain limited.<sup>122</sup> Historically, borylenes—analogs of carbenes and nitrenes—have been reported as reactive species that can be generated *in situ* and employed in various reactions.<sup>123</sup> In 1984, Pachaly and West demonstrated that a silyl-borylene, generated under photochemical conditions, inserted into the C–O bond of tetrahydrofuran (THF), producing the insertion product 2-triphenylsilyl-1,2-oxaborinane.<sup>124</sup>

In 2017, Kinjo and coworkers reported the insertion of highly reactive bromoborylene (BrB:) **81** into C–N bonds of substrate **80**, leading to N-heterocycle enlargement to afford compound **82** (Scheme 12A).<sup>125</sup> Recent approaches to boron insertion primarily involve reductive ring-opening using

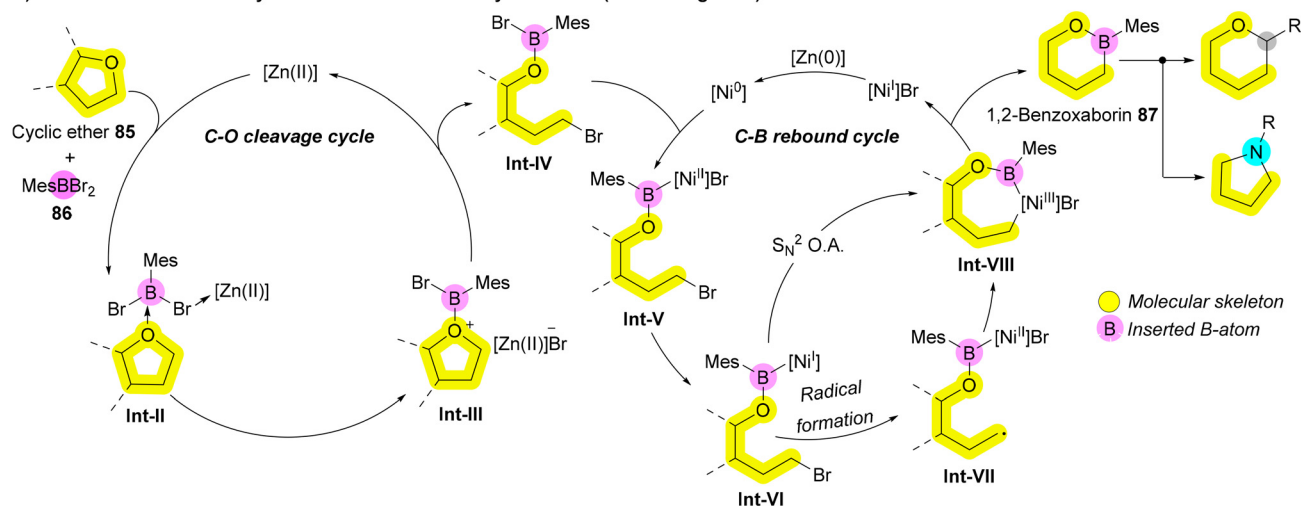
#### A) Borylene insertion (Kinjo 2017)



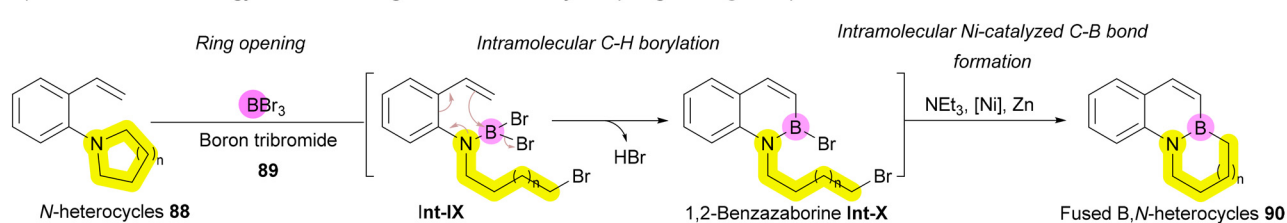
#### B) Lithium-mediated boron insertion into indoles (Yorimitsu 2019)



#### C) Tandem zinc/nickel catalyzed boron insertion into cyclic ethers (Lui & Dong 2021)



#### D) Boron insertion strategy for constructing fused BN-heterocycles (Yang & Song 2024)



**Scheme 12** Boron atom insertion strategies leading to ring expansion.



metals, followed by trapping of the resulting species with organoboronic esters. Yorimitsu's group has employed transition metals such as Ni and Mn to introduce boron into benzofurans.<sup>126,127</sup> In 2019, they extended this approach to indoles **11**, using lithium metal to achieve reductive ring-opening, followed by trapping of the resulting dianionic species **Int-I** with organoboronic esters **83**, producing 1,2-benzazaborins **84** (Scheme 12B).<sup>128</sup> Due to the higher aromatic stabilization energy of pyrrole rings compared to furan, a stronger reductive agent, such as lithium metal, was necessary to facilitate the ring opening.<sup>128</sup> In 2024, Jin, Wang, and Wu developed a facile BH<sub>3</sub>-mediated strategy for boron insertion into indoles and benzimidazoles *via* the hydroborative cleavage of C–N bonds.<sup>129</sup> In 2021, Dong, Liu, and coworkers reported boron insertion into cyclic ethers **85** using tandem zinc/nickel catalysis. Similar to other recent strategies, this process follows a cleavage-then-rebound mechanism, where the ether ring **85** undergoes Zn-enabled reductive ring opening, followed by either radical **Int-VII** formation or S<sub>N</sub><sup>2</sup> oxidative addition facilitated by the Ni catalyst. This produces the desired benzoxaborin **87**, which can be further transformed to achieve boron-to-carbon transmutations or oxygen/boron-to-nitrogen replacement including one-atom deletion (Scheme 12C).<sup>130</sup> Despite these advances, the limited substrates and the need for strong reductants still restricts the broader application of these reactions. In 2024, Yang, Song, and coworkers introduced a more practical boron insertion method for constructing fused BN-heterocycles **90** without strong reducing agents like lithium. This development significantly broadens the scope of these reactions, enhancing their potential in fields such as medicinal chemistry and functional materials. The process begins with boron tribromide (BBr<sub>3</sub>) **89** inducing the ring opening of N-heterocycles **88** to form intermediate **Int-IX**, followed by intramolecular C–H borylation that generates the 1,2-benzazaborine **Int-X**. Finally, the B–N heterocycle **90** is accomplished through intramolecular B–Br/C–Br reductive coupling *via* Ni catalyst (Scheme 12D).<sup>122</sup>

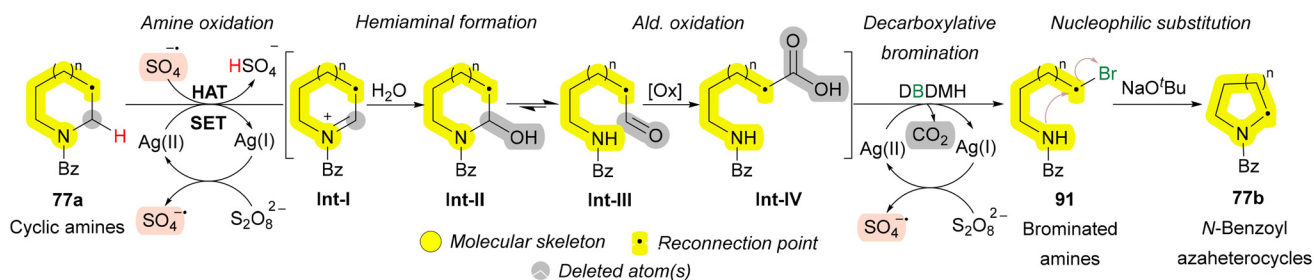
## 2.2. Ring contraction strategies through atom deletion

Ring contraction *via* atom deletion or rearrangement of the core skeleton is an efficient strategy in skeletal editing, enabling the selective removal of one or more atoms from the cyclic frameworks to create smaller rings with modified structural and functional features.<sup>4</sup> This approach has been well-established for carbocyclic systems, where anionic, carbene, and cationic intermediates have been classically utilized to achieve ring contractions of cyclic ketones.<sup>131</sup> Some widely exploited reactions in this context are the Favorskii rearrangement, and the benzilic acid rearrangement. Recent advancements have extended these strategies to non-carbonyl ring systems, including azacyclic compounds, often leveraging photo-induced protocols to achieve the desired transformations.<sup>87,132–134</sup> In this review article, we will focus on recent advances subclassifying them based on the type of atom removed; for example, the deletion of carbon or heteroatoms such as boron or nitrogen.

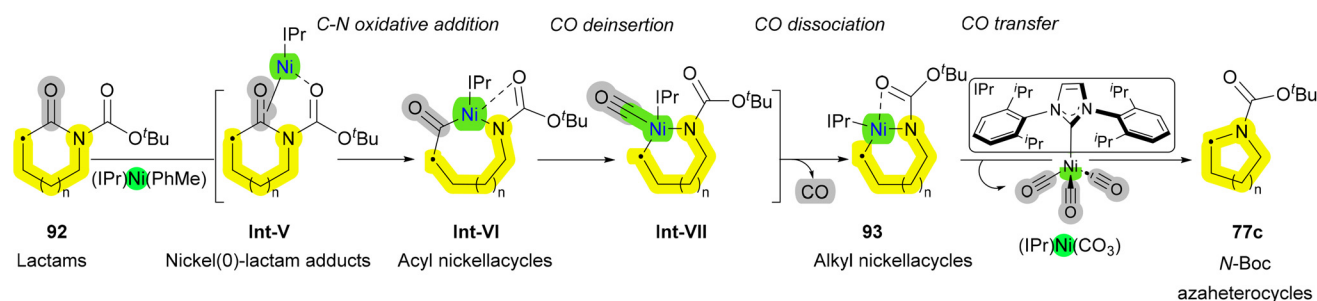
**2.2.1. Carbon atom deletion.** Carbon atom deletion is a key strategy that involves the removal of one or more carbon atoms from a cyclic structure, leading to ring contraction. This process often employs photolysis or other reactions to cleave carbon–carbon or carbon–heteroatom bonds, transforming larger rings into smaller, more reactive systems.<sup>6</sup> Although most success in this field of chemistry has been achieved with carbonyl systems through Favorskii rearrangement and photodecarbonylation, recent approaches aim to extend these techniques to include non-carbonyl ring systems.<sup>4</sup> The Sarpong group's work in 2018 exemplifies the application of carbon atom deletion as a deconstructive strategy for ring contraction, specifically targeting cyclic amines **77a** like piperidines and pyrrolidines. Their method involves a two-step, one-pot process where *N*-protected saturated cyclic amines **77a** reacts with sulfate radical anions through hydrogen atom transfer (HAT), generating an  $\alpha$ -amino radical. This radical subsequently oxidizes *via* silver to form an iminium ion **Int-I**, which then undergoes hydrolysis to yield a hemiaminal **Int-II** that equilibrates to an aldehyde **Int-III**. The aldehyde **Int-III** is oxidized to a carboxylic acid **Int-IV**, leading to the formation of an acyclic bromamide **91** *via* silver-catalyzed decarboxylative bromination. Finally, intramolecular cyclization results in a cyclic amine **77b** that is one carbon atom smaller than the original structure **77a** (Scheme 13A).<sup>119</sup> In 2024, Arisawa and Murai developed a protocol for ring contraction of piperidines *via* the oxidative rearrangement with hypervalent iodine PhI(OAc)<sub>2</sub>. The reaction proceeded through iminium ion intermediates that are trapped by nucleophiles (*e.g.*, NaBH<sub>4</sub>, H<sub>2</sub>O) yielding the corresponding pyrrolidine derivatives.<sup>135</sup> In 2023, Morandi *et al.* developed a metalation strategy that enables the conversion of *N*-Boc-protected lactam rings **92**—a prevalent structural motif in bioactive molecules—into well-defined organonickel reagents **93**. This approach relies on the selective activation of unstrained amide C–N bonds, facilitated by an easily accessible Ni(0) reagent [(IPr)Ni(PhMe)]. The Ni(0)-lactam adduct **Int-V** undergoes oxidative addition to form an acyl nickellacycle intermediate **Int-VI**. The reaction proceeds with efficient CO deinsertion, yielding intermediate **Int-VII**, followed by dissociation to form **93** under mild conditions. This process effectively replaces the carbonyl group of **92** with a nickel atom in a formal carbonyl-to-nickel exchange. The resulting stable organonickel reagent **93** can be isolated and subsequently transformed into a variety of desired N-heterocycles **77c**, making it a valuable tool for synthetic applications (Scheme 13B).<sup>136</sup> Cyclopropane derivatives **94** can be obtained from their corresponding cyclobutenes **62** using *N*-(sulfonio)sulfilimine **71** reagent, which generates sulfonitrene **72** in the presence of a Rh catalyst. Unlike ring expansion reactions involving the same reagent (Scheme 9C), cyclobutenes **62** do not undergo aziridination. Instead, a tertiary carbocation intermediate **Int-VIII** is formed through the attack of sulfonitrene **72**, followed by a [1,2]-alkyl shift to produce a sulfoimine intermediate **Int-IX**. Then, cyanocyclopropanes **94** are obtained through deprotonation and elimination of the dibenzothioiophene moiety (Scheme 13C).<sup>107</sup>



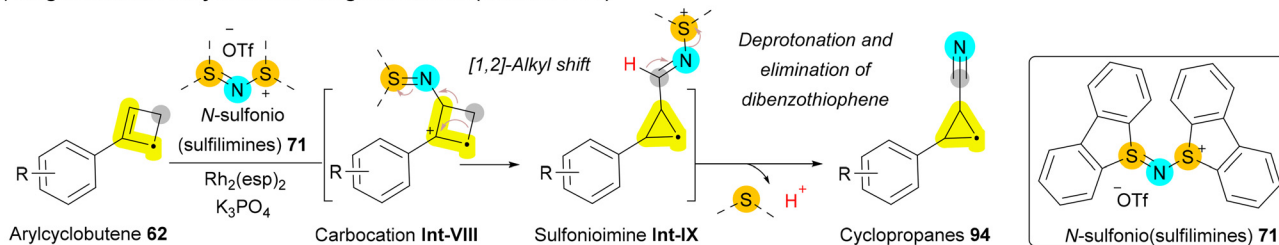
## A) Single carbon atom ring contraction of cyclic amines (Sarpong 2018)



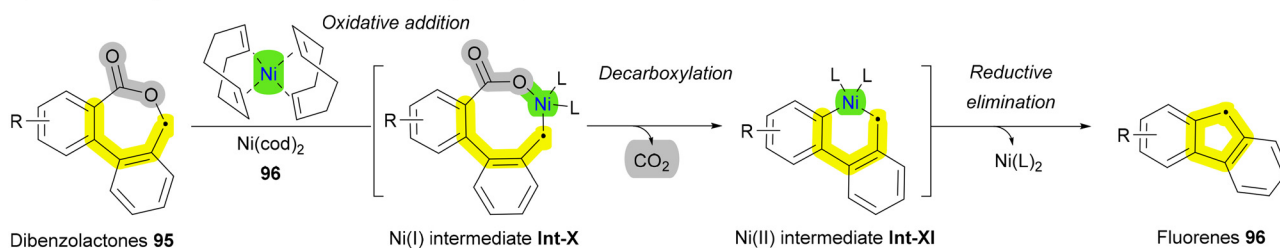
## B) Single carbon atom ring contraction of lactams (Morandi 2023)



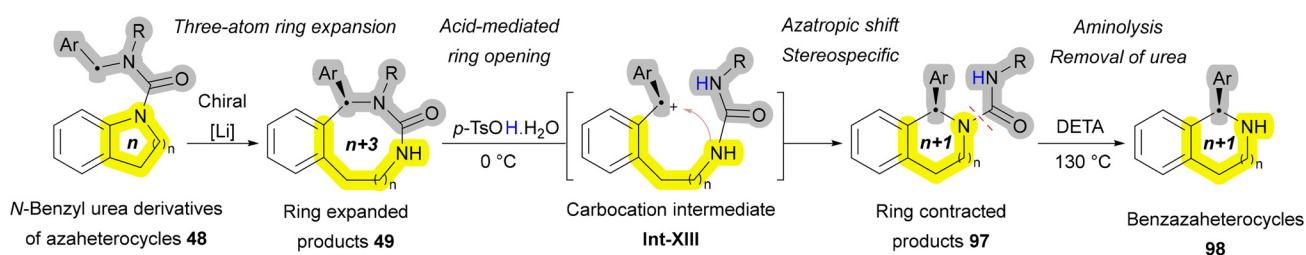
## C) Ring contraction of cyclobutene using sulfonitrene (Alcarazo 2024)



## D) Two-atom ring contraction of dibenzolactones (Li 2023)



## E) Stereospecific two-atom ring contraction via an azatropic shift (one urea nitrogen displaces the other) (Clayden 2024)



Scheme 13 Single and multiple carbon atom deletion of non-classical ring systems.

Besides single-atom deletion approaches, multiple atom deletion has also been reported, though with fewer examples. These strategies involve the removal of two or more atoms

from the molecular framework, often resulting in more significant skeletal rearrangements. Dibenzolactone **95** is one of the substrates that has been shown to undergo two-atom ring con-



traction, yielding the corresponding fluorenes **96** through Ni- or Pd-catalyzed decarboxylative intramolecular coupling. In 2023, the Li group developed a practical approach for the skeletal editing of dibenzolactones **95**, which does not require inductively electron-withdrawing *ortho* substituents on the aryl carboxylate moiety or metal additives. The reaction proceeds *via* a sequence of oxidative addition, CO<sub>2</sub> deinsertion (decarboxylation), and reductive elimination (Scheme 13D).<sup>137</sup> As discussed earlier in Scheme 5B, the Clayden group reported an example of multiple carbon atom insertion *via* the asymmetric deprotonation of *N*-benzyl urea derivatives of nitrogen heterocycles **48**. This process leads to the enantioselective insertion of the benzylic substituent into an aromatic C–N bond *via* a chiral lithium complex, yielding **49** (Scheme 5B). Subsequent treatment of the ring-expanded (*n* + 3) ureas **49** with acid triggers a two-atom ring contraction—an “azatropic shift”, in which one urea nitrogen displaces the other—resulting in almost complete retention of stereochemistry. Removal of the urea substituent from **97** was achieved through aminolysis with diethylenetetramine, yielding enantiopure 1-aryl-tetrahydrobenzazaheterocycles **98** (Scheme 13E).<sup>75</sup>

The potential of ring contraction strategies has been explored to include heteroaromatic systems as well. Early studies catalogued by Buchardt, Kaneko, Streith, and Albini demonstrated that photolysis of azaarenes, such as quinoline *N*-oxides **99**, could result in carbon deletion *via* the formation of benzoxazepine intermediates **Int-III** and **Int-IV**.<sup>138,139</sup> However, the use of unselective mercury lamp excitation led to the generation of undesired two-photon byproducts alongside the desired ring contraction products (Scheme 14A). To address this challenge, Levin *et al.* introduced a selective 390 nm LED light source, significantly enhancing excitation selectivity and improving reaction outcomes. The mechanism involves the formation of a 3,1-benzoxazepine intermediate **Int-III** *via* an oxaziridine intermediate **Int-I**, followed by acid-mediated rearrangement and *in situ* hydrolysis through two concurrent pathways (**Int-V** and **Int-VI**) leading to the formation of *N*-phenylamides **100**. These *N*-phenylamides **100** then undergo ring closure to form *N*-acylindoles **11a**, which can subsequently undergo deacylation to yield indoles **11b** (Scheme 14B).<sup>132</sup> In 2021, Tang and Pan *et al.* reported an oxygen- and visible light-mediated synthesis of pyrroles **1** from pyridinium salts **39** using rhodamine B (RhB) as the photocatalyst. Upon excitation by visible light, RhB facilitates the formation of a pyridinium radical **Int-VII**, which interacts with molecular oxygen to generate an alkoxy dioxy radical **Int-VIII**. Following a proton-coupled electron transfer (PCET) between these intermediates, RhB is regenerated, leading to the formation of an unstable 1,2-dioxetane intermediate **Int-X**. This intermediate **Int-X** then undergoes fragmentation and subsequent base-catalyzed aldol condensation, ultimately yielding 3-formylpyrrole **1** (Scheme 14C).<sup>133</sup>

Pyrimidines **15** are the most prevalent diazines in FDA-approved drugs, while pyrazoles **13** are the most common diazoles.<sup>140,141</sup> In 1968, Van der Plas and Jongejan pioneered the conversion of pyrimidines **15** to pyrazoles **13** using excess

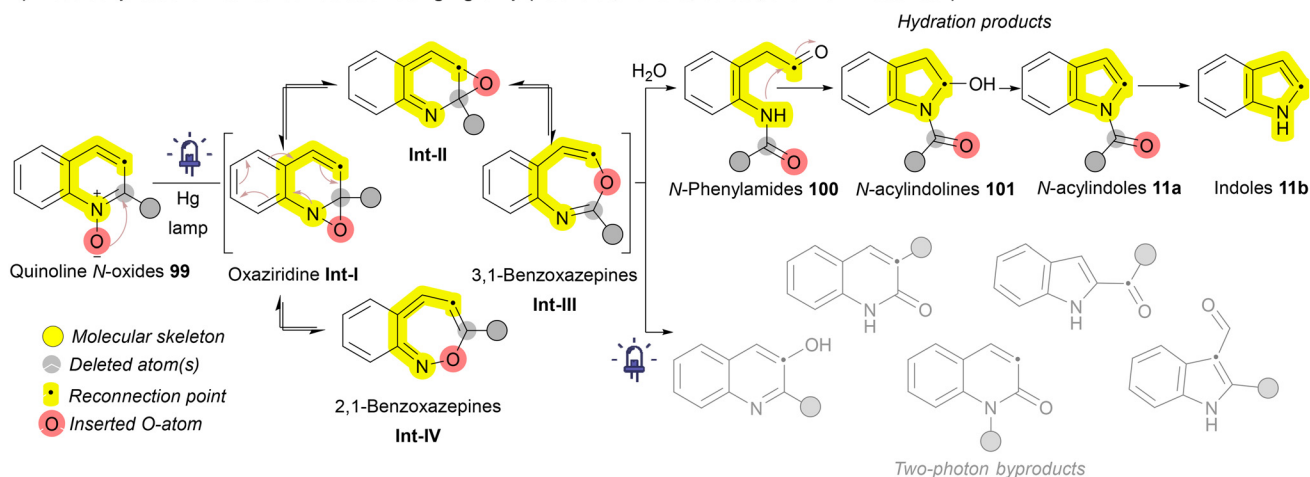
hydrazine (NH<sub>2</sub>NH<sub>2</sub>) at extreme temperatures (200 °C). Further investigation revealed that *N*-methylation with iodomethane enabled successful transformation at a reduced temperature of 100 °C (Scheme 15A).<sup>142</sup> Although these methods enabled the conversion of pyrimidines **15** into pyrazoles **13**, they typically proceed with low yields and under harsh conditions. In 2022, Sarpong group reported milder conditions, tolerate a wide range of functional groups, and allows for the simultaneous regioselective introduction of *N*-substituents on the resulting pyrazole **13**. The key to the success of this one-carbon deletion method is the *N*-triflylation of pyrimidines **15**, which significantly decreases the LUMO energy of **102b**, facilitating hydrazine attack at 23 °C. After nucleophilic attack by hydrazine, intermediate **Int-I** is formed, followed by **Int-II** *via* a 3,3-sigmatropic rearrangement, resulting in the ring-opening. Subsequently, the terminal hydrazone nitrogen engages with the ring-opened species **Int-III** (following tautomerization) at C4, yielding a charge-separated species. Finally, a subsequent proton transfer generates **Int-IV**, and elimination of *N*-triflylformamidine through a 1,5-sigmatropic H-shift results in the formation of the pyrazole product **13** (Scheme 15B).<sup>143</sup>

Another skeletal editing approach for generating pyrazoles **13** was developed in 2024 by Ghiazza and Moreau. While investigating a photochemical method for the ring expansion of pyridinium ylides **57** into 1,2-diazepines **58** (Scheme 6D), they serendipitously discovered a concurrent ring contraction when excess TMS-Cl was applied alongside light, yielding pyrazoles **13**. The authors proposed a mechanism in which the Lewis acid TMS-Cl, combined with the residual water present in the medium, facilitates the opening of the 1,2-diazepine ring **58** affording **Int-V**. Subsequently, a 1,4-addition of the nucleophilic amino group, followed by a retro-Mannich reaction, leads to the formation of the pyrazole ring **13**, with the restoration of aromaticity serving as the driving force of the sequence (Scheme 15C).<sup>87</sup> Ring contraction in macrocycles, such as cyclic peptides **103**, has also been achieved by Yudin *et al.* through the Cornforth rearrangement. The mechanism involves the formation of a nitrilium intermediate **Int-VIII** through the opening of the oxazole ring, followed by nucleophilic attack from the adjacent carbonyl group on the nitrilium ion, resulting in the reformation of the oxazole moiety. The final ring-contracted peptide macrocycle **104** exhibited a conformational change, creating more space for studies related to conformation (Scheme 15D).<sup>144</sup>

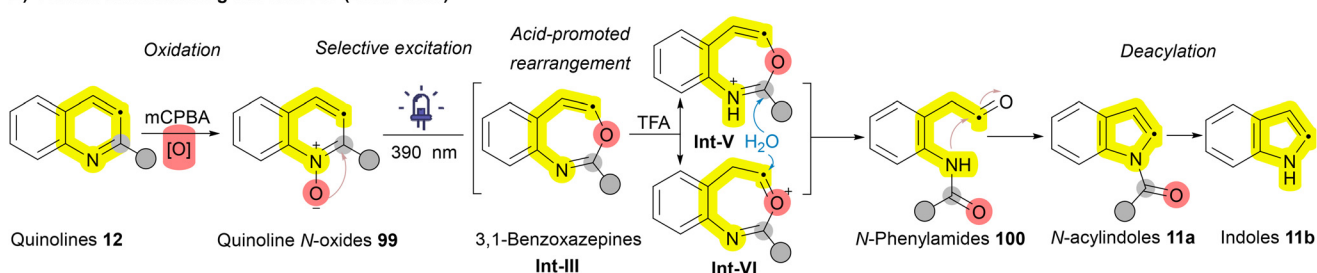
**2.2.2. Nitrogen atom deletion.** Nitrogen-containing compounds play a crucial role in various domains especially medicinal chemistry, and the deletion of nitrogen atom(s) to craft carbocycles is a valuable technique in retrosynthetic analysis.<sup>5</sup> The primary pathway for single nitrogen-atom deletion includes the intermediary formation of isodiazenes (1,1-diazene) **Int-I**, which, after N<sub>2</sub> extrusion, generate diradical species **Int-II** that can undergo intramolecular C–C bond formation. In 1965, Rave *et al.* used Angeli's salt **106** to generate a 1,1-diazene intermediate **Int-Ia**, which underwent N<sub>2</sub> extrusion, forming a radical species **Int-IIa** and ultimately yielding a dibenzyl product **107** (Scheme 16A).<sup>145</sup> Similarly, in 1978,



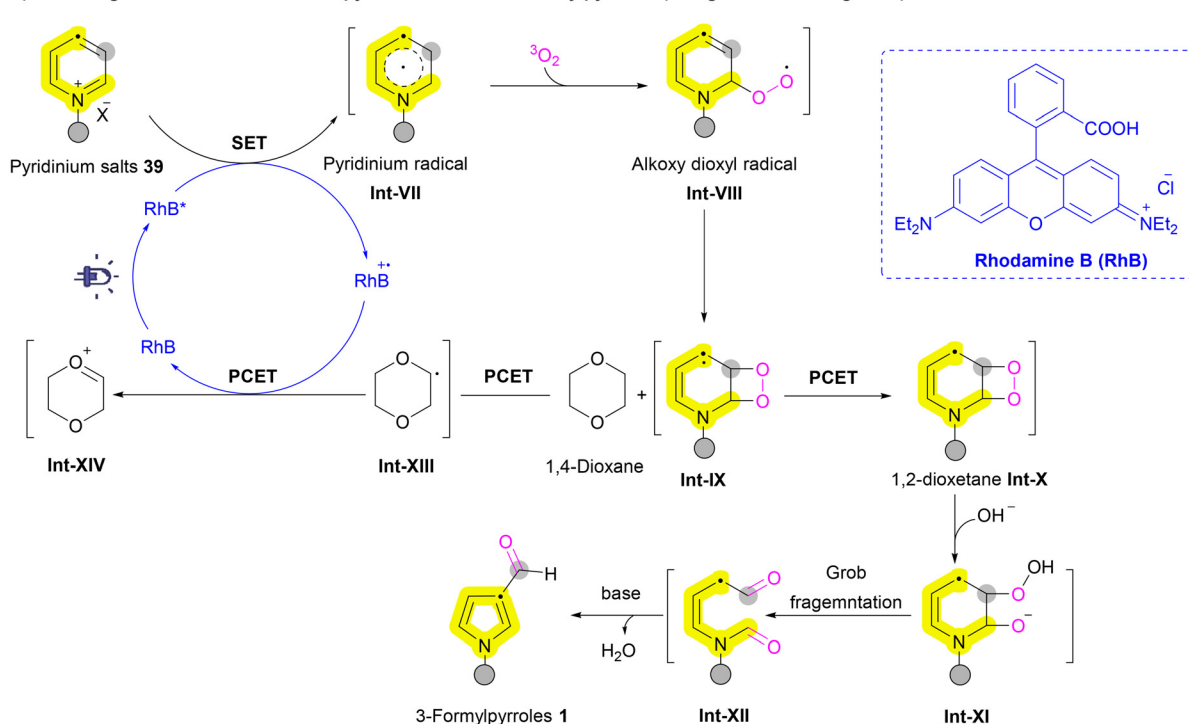
## A) Classical photochemical carbon deletion using Hg lamp (Buchardt, Kaneko, Streith, and Albini 1966-1987)



## B) Carbon deletion using 390 nm LED (Levin 2022)



## C) Visible light-enabled conversion of pyridinium salts to 3-formylpyrroles (Wang, Pan, and Tang 2021)

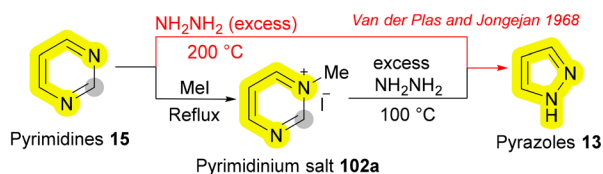
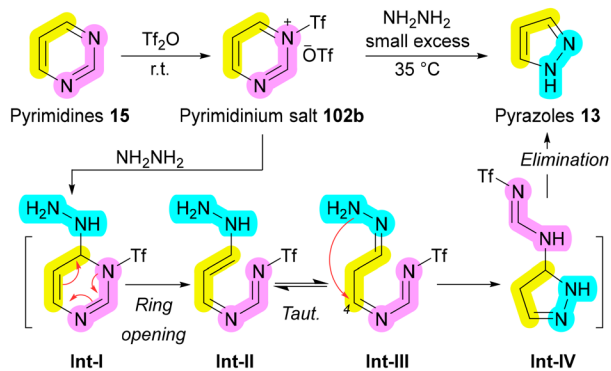
Scheme 14 Single carbon atom deletion of azaarenes (quinoline *N*-oxides and pyridinium salts).

Dervan employed a sequence of *N*-nitrosation, reduction of *N*-nitroso compounds, and oxidation of 1,1-hydrazines to achieve nitrogen deletion.<sup>146</sup> Despite their utility, these

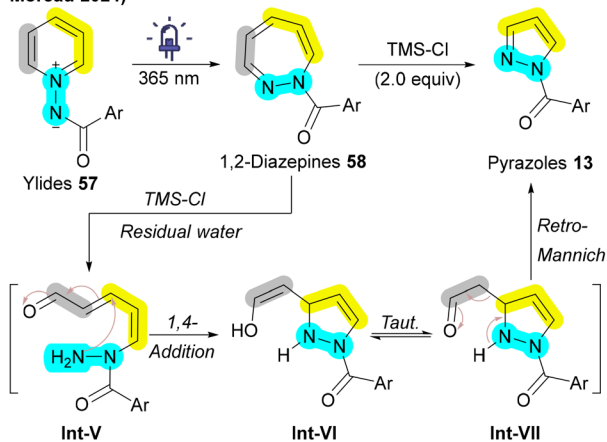
methods are constrained by limited scope, hazardous reagents, and unwanted side products. Levin group addressed these challenges in a great development published in 2021 by



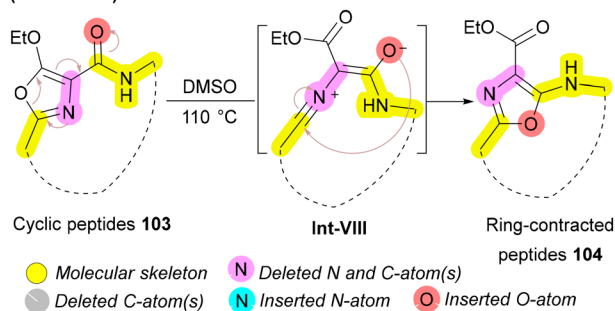
## A) Carbon atom deletion of pyrimidines to pyrazoles

B) *N*-Triflylation of pyrimidines to get pyrazoles at mild conditions (Sarpong 2022)

## C) Pyrazole formation by photochemical carbon deletion (Ghiazza &amp; Moreau 2024)



## D) Ring contraction of peptide macrocycles (Cornforth rearrangement) (Yudin 2022)



**Scheme 15** Carbon atom deletion of azaarenes (pyrimidines, pyridinium ylides, and macrocycles).

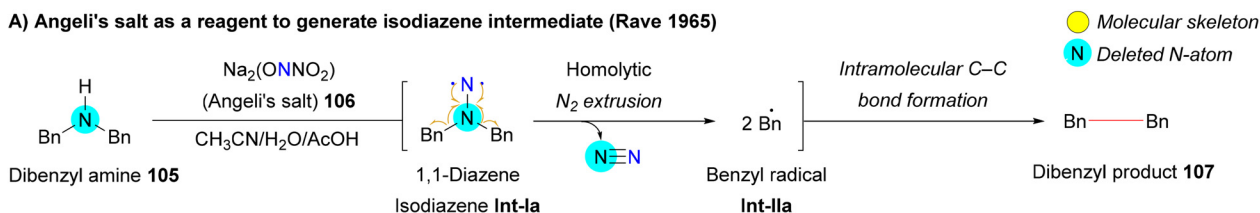
using anomeric amides,<sup>5</sup> such as *N*-pivaloyloxy-*N*-alkoxyamides **108**, to generate isodiazene intermediates **Int-Ib** from secondary cyclic amines **77d**. This method activates the amine **77d**,

and enables the sequence of isodiazene **Int-Ib** formation, N<sub>2</sub> extrusion, and intramolecular C–C coupling to yield the (*n* – 1) carbon framework **109ac** (Scheme 16B).<sup>147</sup> Recently, the same group reported another pathway with an unexpected spirocyclic dearomatized intermediate **Int-IV**, which converges to the expected indanes **109aa** and **109ab** by a facile 1,3-sigmatropic rearrangement.<sup>148</sup> Sarpong's group further demonstrated the practicality of this approach by synthesizing BCP (Bicyclo [1.1.1]pentanes) from aza-BCP (azabicyclo[2.1.1] hexanes).<sup>149</sup> However, anomeric amides **108** may pose mutagenic risks, and side products may arise due to their oxidative capacity and potential rearrangement of the isodiazene intermediates **Int-I**. Building on their previous work with sulfamoyl azides,<sup>150</sup> Lu and colleagues developed a method for nitrogen-atom deletion from azaheterocycles **77e**. Initially, they got the sulfamoyl azide intermediate **Int-V** via nucleophilic substitution of cyclic amines **77e** with N<sub>3</sub>SO<sub>2</sub>N<sub>3</sub> **110**, subsequently forming an isodiazene intermediate **Int-Ic** through Curtius-type rearrangement. Following N<sub>2</sub> expulsion, a diradical species **Int-Iic** was generated, which then coupled to yield the nitrogen-deleted product **109b** (Scheme 16C).<sup>151</sup> In 2021, Antonchick group employed iodonitrenes **67** to enable the formation isodiazene intermediate **Int-I** from pyrrolidine, ultimately producing cyclobutanes via a similar radical coupling pathway.<sup>152</sup> In 2021, the Sarpong group introduced a novel landmark photochemical approach for nitrogen deletion from saturated cyclic amines **77f**, following a ring-opening sequence coupled with a rebound mechanism. Initially, the reaction was proposed to proceed via a concerted 1,5-hydrogen atom transfer (1,5-HAT) mechanism to form intermediate **Int-VIII**. This intermediate **Int-VIII** would then undergo fragmentation (ring opening) to yield **Int-IX**, followed by Mannich cyclization to produce the ring-contracted product **109c**.<sup>134</sup> However, subsequent studies in 2024 with electron-rich substrates revealed that **Int-VIII** is actually generated through electron transfer and proton transfer (ET/PT), rather than the initially proposed concerted (1,5-HAT) mechanism (Scheme 16D).<sup>153</sup> Biaryl-linked dihydroazepines **111** can undergo a deaminative ring contraction cascade reaction, excising nitrogen and forming an aromatic core, as reported by Roberts and colleagues.<sup>154</sup> This strategy involves the *in situ* methylation of **111** to generate a cyclic ammonium ylide **Int-X**, which undergoes a base-induced [1,2]-Stevens rearrangement followed by dehydroamination (Hofmann elimination), yielding a benzo[*h*]quinoline core **112** the core structure in various biologically active compounds, including toddaquinoline (Scheme 16E).<sup>155</sup> Recently, Shima, Kang, and Hou unlocked a new challenge by reporting the first nitrogen deletion reaction of pyridine, yielding cyclopentadienyl species using a dititanium tetrahydride complex with rigid acridane-based PNP-pincer ligands.<sup>156</sup>

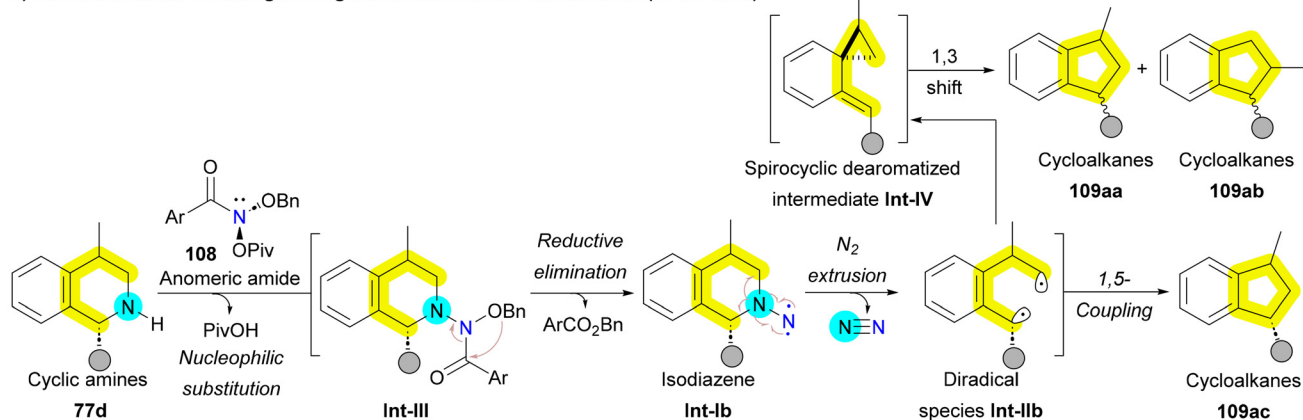
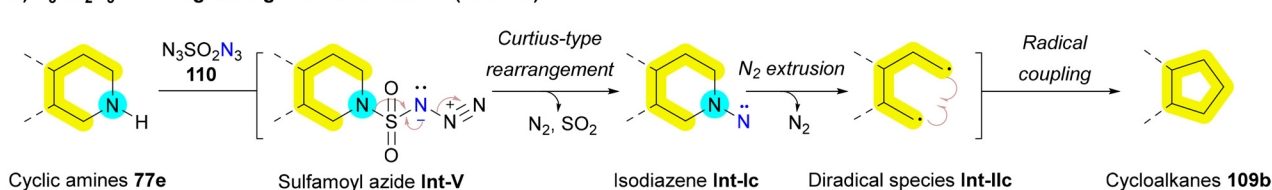
**2.2.3. Boron atom deletion.** A boron atom has also been reported to undergo deletion or rearrangement within molecular cores, enabling the formation of highly strained cyclobutyl boronic esters. In 2020, Aggarwal *et al.* introduced a novel light-driven approach to synthesize cyclobutyl boronic esters **115** via the ring contraction of readily accessible cyclic alkenyl



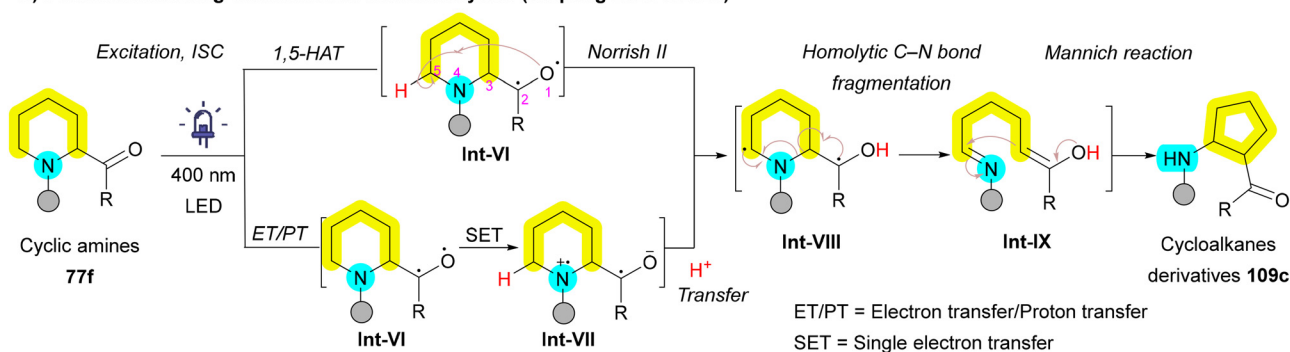
## A) Angeli's salt as a reagent to generate isodiazeno intermediate (Rave 1965)



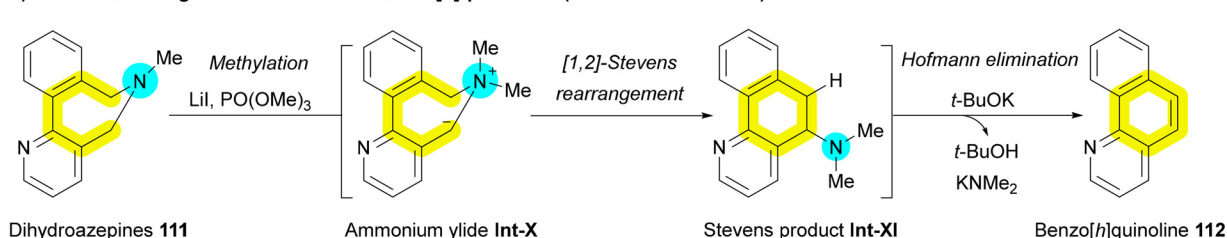
## B) Anomeric amide as a reagent to generate isodiazeno intermediate (Levin 2021)

C)  $\text{N}_3\text{SO}_2\text{N}_3$  as a reagent to generate isodiazeno (Lu 2021)

## D) Photochemical ring contraction of azaheterocycles (Sarpong 2021 &amp; 2024)



## E) Deaminative ring contraction to form benzo[h]quinolines (Roberts 2022 &amp; 2023)

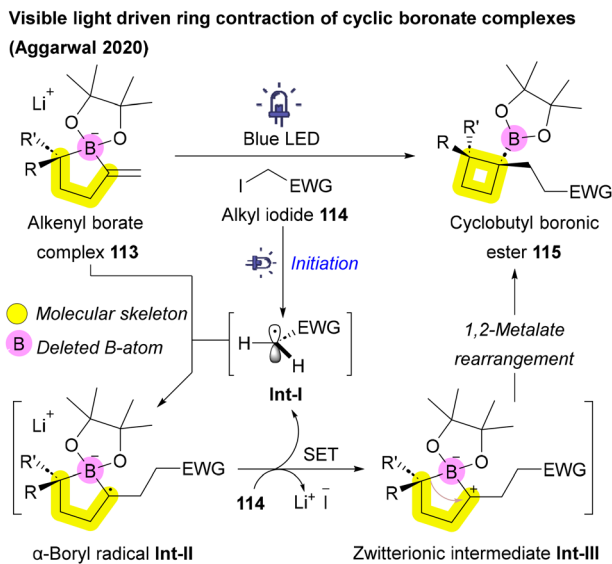


Scheme 16 Ring contraction strategies through single nitrogen-atom deletion.

boronate complexes **113**. This process proceeds through the formation of an  $\alpha$ -boryl radical **Int-II**, generated by the addition of an electrophilic radical **Int-I** to the electron-rich

alkenyl boronate complex **113**, followed by one-electron oxidation and a 1,2-metalate rearrangement to yield cyclobutyl boronic ester **115**. The authors demonstrated that various





**Scheme 17** Ring contraction through boron-atom deletion.

radical precursors and vinyl boronates could be utilized, allowing access to chiral cyclobutanes with high stereocontrol (Scheme 17).<sup>157</sup>

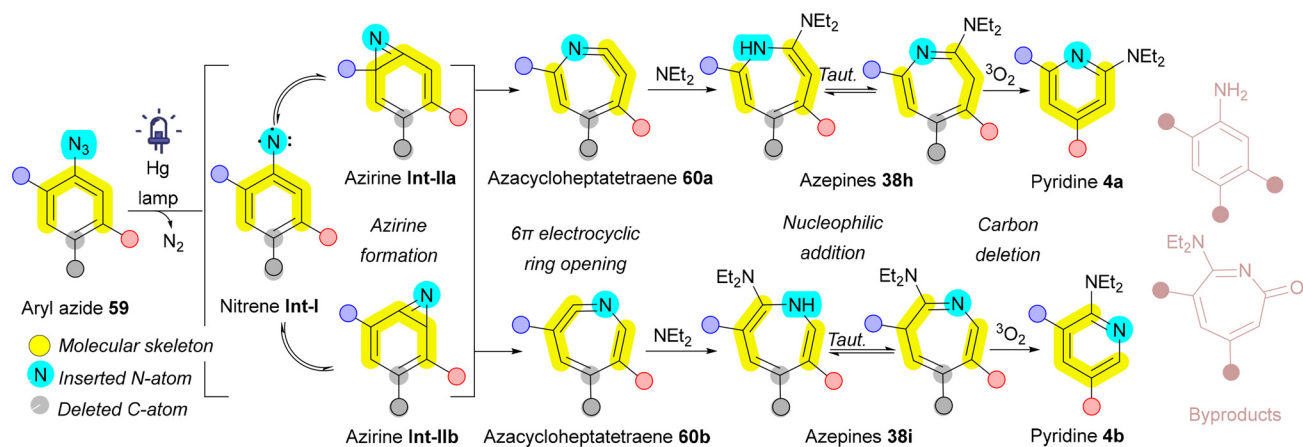
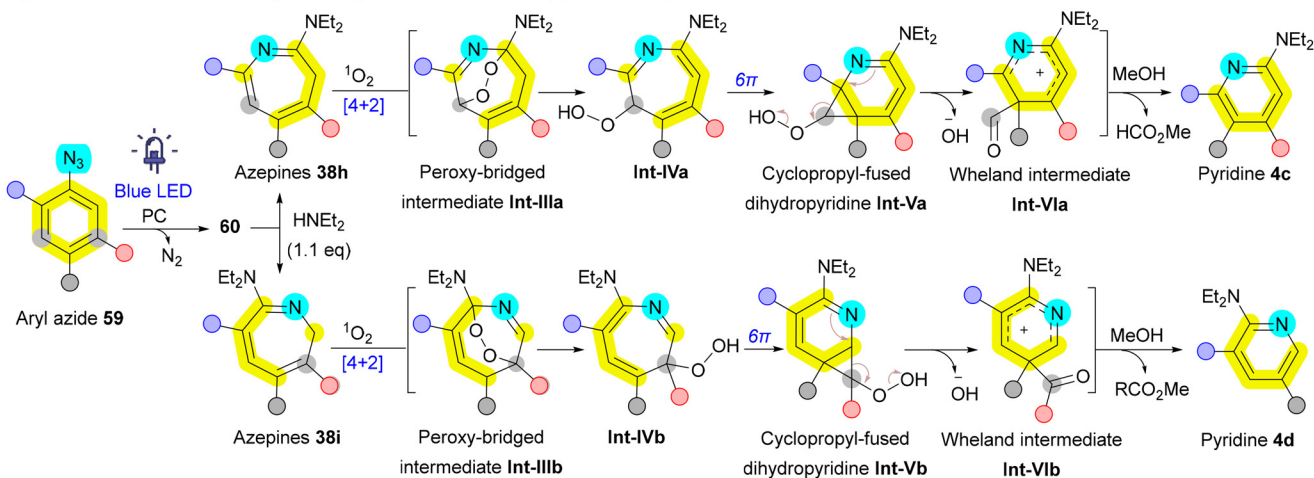
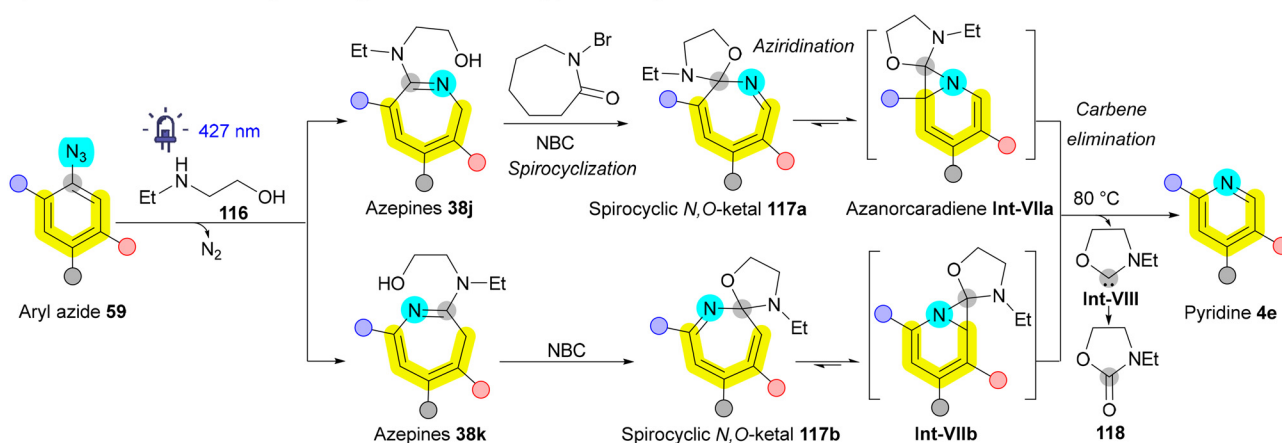
### 2.3. Transmutation strategies through atom exchange

Transmutation in skeletal editing aims to maintain the structural integrity of a ring system while swapping one or more atoms for others, which is especially valuable in medicinal chemistry.<sup>4</sup> Achieving these transformations enables a more direct examination of how subtle changes—such as substituting nitrogen for carbon—affect a molecule's biological activity without altering its core shape.<sup>158</sup> This process can be further subdivided based on the nature of the atoms being exchanged.

**2.3.1. Carbon-to-nitrogen (C-to-N) transmutation.** This strategy involves replacing a carbon atom with nitrogen within a molecular skeleton while maintaining its ring size.<sup>159</sup> In pharmaceuticals, this has the potential to be applied for “nitrogen scan” where carbon atoms in lead compounds are systematically swapped for nitrogen to create aza-analogues.<sup>160</sup> This strategy leverages the essential nitrogen effect—nitrogen's capacity to modulate electronic properties, hydrogen bonding, and stability, thus enhancing drug profiles. The typical method for C-to-N transmutation involves sequential ring expansion and contraction, enabling these structural modifications while conserving the ring's integrity.<sup>161</sup> In 1972, Sundberg *et al.* reported a mixture of nitrogen insertion and transmutation products during the photolysis of aryl azides **59** using a medium-pressure mercury lamp with diethylamine as the solvent. In this reaction, similar to the ring expansion pathway (Scheme 7), aryl azides **59** undergo photolysis, producing nitrene intermediates **Int-I** that rapidly cyclize to form unstable azirines **Int-IIa** and **Int-IIb**. These azirines **Int-II** subsequently undergo  $6\pi$  ring opening and nucleophilic addition with diethylamine, generating *1H*-azepines **38h** and **38i**. In the presence of triplet oxygen, their tautomers afford a mixture of

pyridines **4a** and **4b** alongside various byproducts (Scheme 18A).<sup>162</sup> While these results are impressive, the Sundberg protocol has several limitations. The reaction requires diethylamine in solvent-level quantities and a high-intensity mercury lamp, both of which reduce functional group compatibility and give various byproducts with low yields of desired transmutation products **4a** and **4b**. To improve these conditions, Burns *et al.* introduced a lower-energy blue light source, alongside a photosensitizer such as acenaphthylene and oxygen, enabling the synthesis of pyridines **4c** and **4d** from aryl azides **59** with near-stoichiometric amounts of diethylamine (Scheme 18B). Similar to previous pathway, aryl azides **59** undergo photolysis generating azepines **38h** and **38i**. In the presence of singlet oxygen, a  $[4 + 2]$  cycloaddition creates a peroxy-bridged intermediates **Int-IIIa** and **Int-IIIb**, which then undergoes ring opening and  $6\pi$  electrocyclicization to yield cyclopropyl-fused dihydropyridine **Int-Va** and **Int-Vb**. Further cyclopropane ring opening and loss of hydroxide yield the Wheland intermediates (arenium ions) **Int-VIA** and **Int-VIb**, which, following methanol-mediated deformylation, produces the final 2-aminopyridine products **4c** and **4d** (Scheme 18B).<sup>163</sup> The Sundberg and Burns protocols differ in the specific carbon deletion that accompanies nitrogen insertion. In the Sundberg protocol, a “*para*” carbon deletion occurs (Scheme 18A), while the Burns method demonstrates a “*meta*” carbon deletion (Scheme 18B), affecting the substitution pattern of the final products relative to the starting materials. *para*-Carbon deletion leads to a single positional shift (either *ortho-to-meta* **4b**, or *meta-to-para* **4a**), whereas *meta*-carbon deletion requires two shifts (*ortho-to-meta* and *para-to-meta* **4d**, or *para-to-meta* and *meta-to-para* **4c**).<sup>162,163</sup> Both approaches, however, encounter challenges due to differing selectivity in nitrogen insertion and carbon deletion, which can result in complex mixtures, especially with non-symmetric aryl azides **59**. This also complicates distal functional group retention, promotes rearrangement of the arene skeleton, and retains the incoming amine nucleophile ( $\text{Et}_2\text{N}$ ). In a 2023 study, the Levin group proposed an innovative solution to these limitations by achieving selective *ipso*-carbon deletion of azepines **38j** and **38k**, enabling the formation of a single pyridine isomer **4e** without skeletal rearrangement or loss of functional groups.<sup>160</sup> This highly efficient approach offers a more predictable “nitrogen scan” as the azide's initial installation site directly determines the final nitrogen placement. The overall transformation involves integrating the nitrene nitrogen at the former carbon site. The team's design was based on the hypothesis that oxidizing azepine **38j** and **38k** could produce an azaheptatriene species **117**, which would then undergo cheletropic extrusion of the *ipso*-carbon via an azanorcaradiene intermediates **Int-VIIa** and **Int-VIIb** (Scheme 18C). To facilitate this process, they employed aminoalcohol **116** featuring a second pendant donor, instead of the amine nucleophile, promoting spirocyclization to relieve angle strain and enable carbene elimination. Using *N*-bromocaprolactam (NBC) as an oxidant, they obtained the spirocyclic *N,O*-ketals **117a** and **117b**. Heating these ketals at 80 °C induced carbene elim-



A) C-to-N Transmutation of aryl azides (*para*-carbon deletion) (Sundberg 1972)B) C-to-N Transmutation of aryl azides (*meta*-carbon deletion) (Burns 2022)C) C-to-N Transmutation of aryl azides (*ipso*-carbon deletion) (Levin 2023)

Scheme 18 Carbon-to-nitrogen (C-to-N) single-atom transmutation of pyridines via nitrene internalization.

ination, forming pyridine **4e** and separating *N*-ethyl oxazolidinone **118** from the azanorcaradiene intermediates **Int-VIIa** and **Int-VIIb** (Scheme 18C).<sup>160</sup>

Levin *et al.* extended this expansion/contraction approach to convert quinolines **12a** into quinazolines **16**. Quinolines **12a**

were initially transformed into quinoline *N*-oxides **99**, which under LED light (390 nm) undergo rearrangement to 3,1-benzoxazepine intermediates **Int-I**. Subsequent treatment with ammonium carbamate as a nitrogen source, combined with oxidative conditions (O<sub>3</sub> and pyridine), yields an intermediate



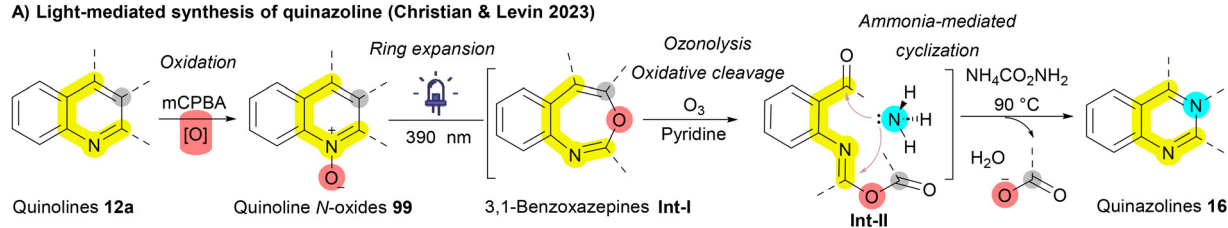
with two carbonyl termini **Int-II**. The carboxylate group then acts as a leaving group, allowing the nitrogen source (ammonia) to react with the imidic anhydride, ultimately forming quinazoline **16** (Scheme 19A).<sup>164</sup> Xu and Wei applied an iron-mediated ring expansion/contraction strategy for C-to-N atom exchange in arenols **119a**. Arenols undergo the addition of nucleophile, ring opening, and ring closing (ANRORC) mechanism. Bromination using *N*-bromosuccinimide (NBS) produces a brominated ketone intermediate **Int-III**, which converts to an azido ketone *via*  $N(n\text{-Bu})_4\text{N}_3$  giving intermediate **Int-IV**. A 1,2-aryl migration initiates ring expansion affording metal-nitrene intermediate **Int-V** then, forming an *N,O*-hemiketal **Int-VI** upon OH nucleophilic addition. Ring opening produces an amino-ketone intermediate **Int-VII**, which cyclizes and dehydrates to yield quinolines **12b** (Scheme 19B).<sup>165</sup> In a parallel strategy, the Wei group employed Cu-catalyzed ring expansion to generate benzo[*b*]azepines **38l** from arenols **119b**. This approach was further adapted to achieve a subsequent ring contraction, facilitating a one-carbon-to-nitrogen exchange. Benzazepine **38l**, in the presence of *m*CPBA, forms an oxaziridine intermediate **Int-X** that undergoes cleavage of N–O bond affording radical intermediate **Int-XI**. Rearrangement of this radical intermediate **Int-XI** then produces the desired N-heterocycle **120b** (Scheme 19C).<sup>100</sup> Wang and Luan developed a silver-catalyzed aminative dearomatization strategy for transmutation of naphthols affording the corresponding isoquinolines.<sup>101</sup> Another notable approach introduced by Hrobárik *et al.* involves the silver-mediated synthesis of benzo[1,2,3]thiadiazoles **124** from benzothiazol-2(3*H*)-ones **122** and 2-halobenzothiazoles **121**. This reaction involves the formation of NO<sup>+</sup> facilitated by Ag<sup>+</sup>, which, through *N*-nitrosation, converts 2-hydroxybenzothiazole **123** into *N*-nitrosated benzothiazol-2(3*H*)-one **Int-XIII**. Further interaction with Ag<sup>+</sup> and NO<sub>2</sub><sup>−</sup> initiates ring opening, followed by ring closure through a nucleophilic sulfur attack on the diazo intermediate **Int-XVII**, resulting in the formation of the isothiadiazole ring in benzo[1,2,3]thiadiazole **124** (Scheme 19D).<sup>166</sup>

**2.3.2. Nitrogen-to-carbon (N-to-C) transmutation.** While Burns and Levin's groups explored converting carbon to nitrogen *via* nitrene chemistry,<sup>160,163</sup> the reverse—transforming pyridines to benzenes—offers a challenging yet valuable synthetic strategy. The distinct reactivities of benzene and the electron-deficient pyridine ring allow for selective pyridine functionalization to access difficult-to-make benzenes *via* an N–C switch. Given pyridines' central role in drug discovery, understanding their pharmacological properties remains crucial. Pyridine to benzene rearrangements have historically been achieved through Zincke pyridinium chemistry.<sup>167,168</sup> In the 1970s, Kost and Sagitullin demonstrated the rearrangement of 2-methylpyridinium salts **39a** to anilines **125a** under basic conditions, proceeding *via* a Zincke-imine intermediate **Int-IIa** (Scheme 20A).<sup>169,170</sup> More recently, Kano, Morofuji developed a modern variant of this approach under milder conditions, utilizing streptocyanine intermediates **Int-IV**. In 2021, they introduced a stepwise ring-opening and ring-closing sequence to

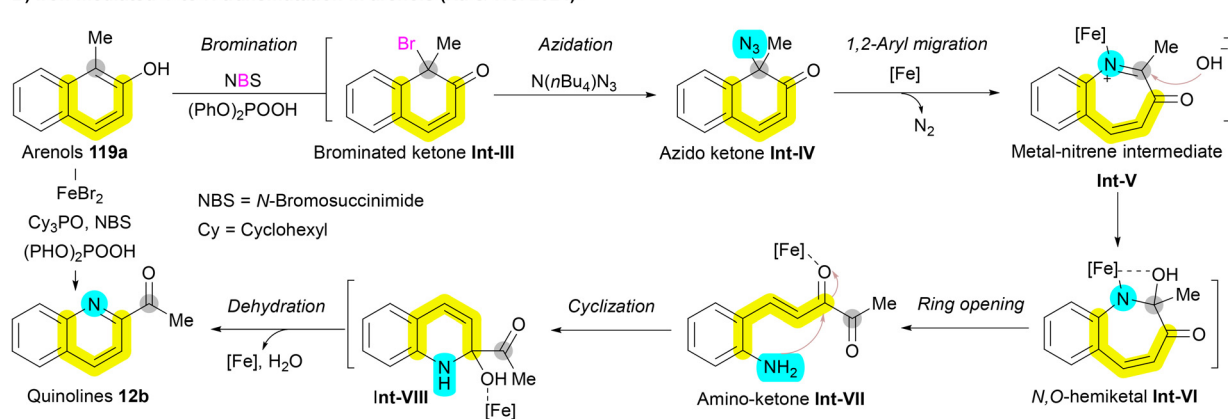
convert *para*-substituted pyridine **4a** to *meta*-dialkylamino-substituted benzene **125b**, achieving both skeletal and peripheral edits. Starting from *N*-phenylpyridinium salt **39b** (*via* *N*-arylation of *para*-substituted pyridine **4a**), treatment with excess secondary amine **126a** such as piperidine (3.0 equivalent) forms a key streptocyanine intermediate **Int-IVa** *via* ring opening. A dimethylsulfonium methylide **127** then attacks the iminium group, forming a sulfonium **Int-V** that, upon deprotonation and elimination of dimethyl sulfide, yields a triene **Int-VI**. A 6π electrocyclization then produces cyclohexadiene **Int-VII**, and elimination of an amine yields the *meta*-substituted aniline **125b** (Scheme 20B).<sup>171</sup> In 2023, the same group promoted this approach to overcome the necessity to use excess piperidine **126b** and isolation of the streptocyanine intermediate **Int-IVb** *via* introducing streptocyanine as a novel amine catalysis activation mode. Starting from 3-alkenyl-substituted pyridines **4b**, which undergo *N*-arylation in the presence of aryl tosylate, forming *N*-arylpyridinium salts **39c**. This pyridinium **39c**, with catalytic piperidine **126b**, produces a streptocyanine intermediate **Int-IVb** that closes to form a benzene ring **128**, releasing the amine catalyst **126b**. The alkene moiety in the starting material is thereby incorporated into the benzene ring, efficiently converting various alkene-substituted pyridiniums **39c** to formyl-substituted benzene derivatives **128** (Scheme 20C).<sup>172</sup> Building on Schmerling and Toekelt's work,<sup>173</sup> the Greaney group developed a general pyridine-to-benzene conversion strategy that avoids reliance on rearranging a pre-existing carbon substituent (refer to Scheme 20A and C). This transformation follows ANRORC process with diethylmalonate **129** as the nucleophile, providing significant advantages. In their approach, pyridine **4c**, in the presence of triflic anhydride (Tf<sub>2</sub>O) and a carbon nucleophile **129**, undergoes nucleophilic addition followed by ring opening, forming a carbo-Zincke intermediate **Int-IXa**. Subsequent recyclization leads to a carbocyclic intermediate **Int-X**, and elimination yields the desired benzene ring **130** (Scheme 20D).<sup>174</sup> However, this method is limited to *para*-substituted pyridines and yields products as benzoates **130**. To address the limited scope of these transformations, the Gutierrez and Glorius group developed an innovative strategy involving a ring opening induced by Tf<sub>2</sub>O and dibenzylamine **126c**, producing a Zincke-imine intermediate **Int-IIb**. Hydrolysis in the presence of base generates the corresponding Zincke-aldehyde **Int-IIIb**, which undergoes selective olefination *via* a phosphine reagent **131** to form a Zincke-alkene intermediate **Int-IXb**. Subsequent 6π electrocyclization yields the target benzene **132** (Scheme 20E).<sup>175</sup> This method demonstrates remarkable functional group tolerance, effectively converting both *para*- and *meta*-substituted pyridines **4d** and allowing for the direct replacement of nitrogen with various functionalized carbons to edit the molecular scaffold of these heterocycles. However, it does not succeed with *ortho*-substituted pyridines, as the corresponding Zincke ketones **Int-III** do not participate in olefination. Similarly, pyrimidines are incompatible with the reaction due to the preferential hydrolysis of the non-terminal imine in the corresponding aza-Zincke imine intermediates **Int-II** under basic conditions.



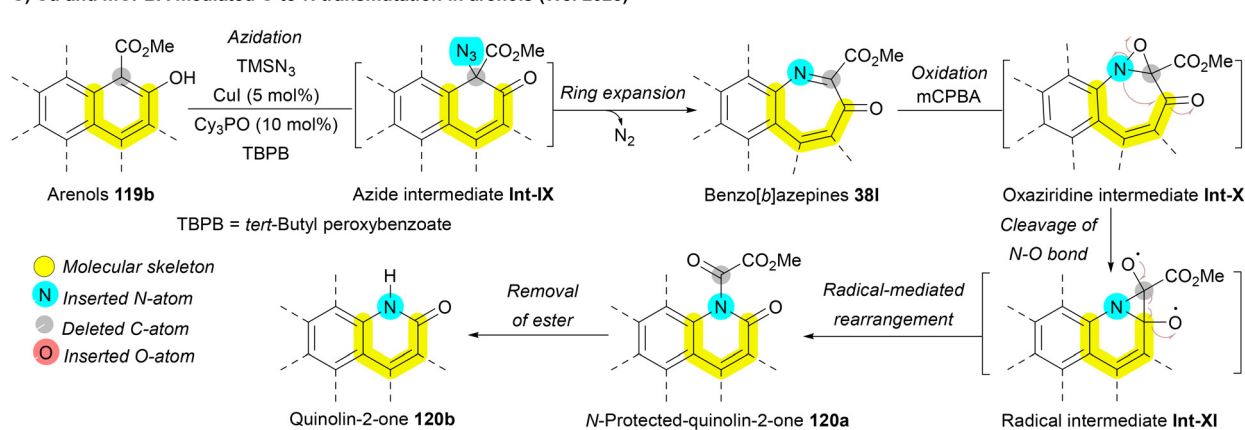
## A) Light-mediated synthesis of quinazoline (Christian &amp; Levin 2023)



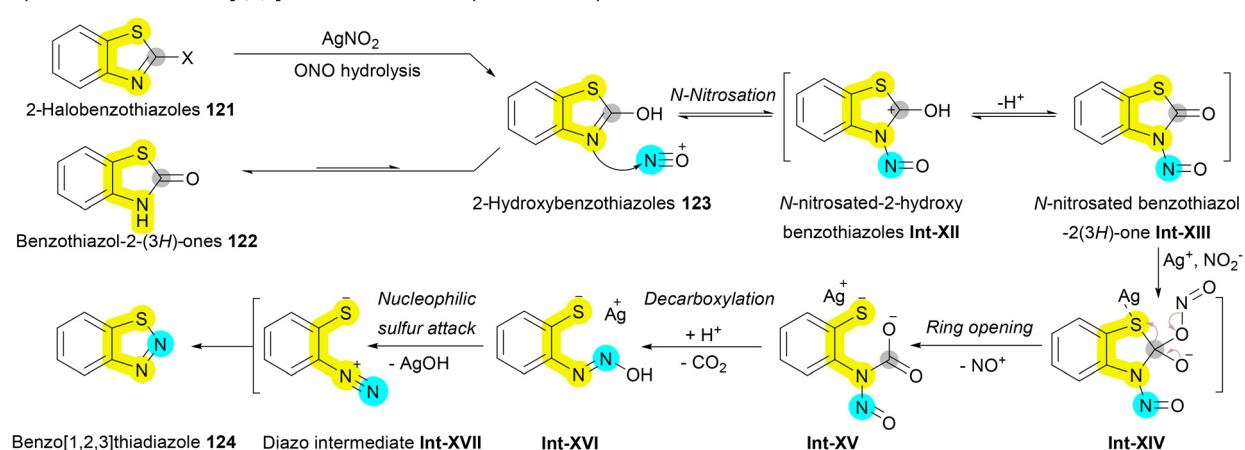
## B) Iron-mediated C-to-N transmutation in arens (Xu &amp; Wei 2024)



## C) Cu and mCPBA mediated C-to-N transmutation in arens (Wei 2023)



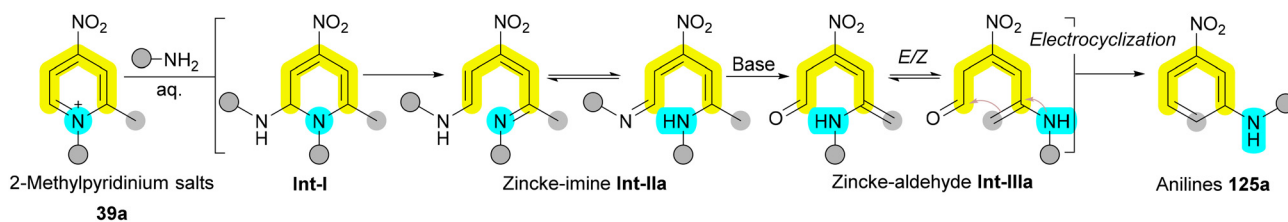
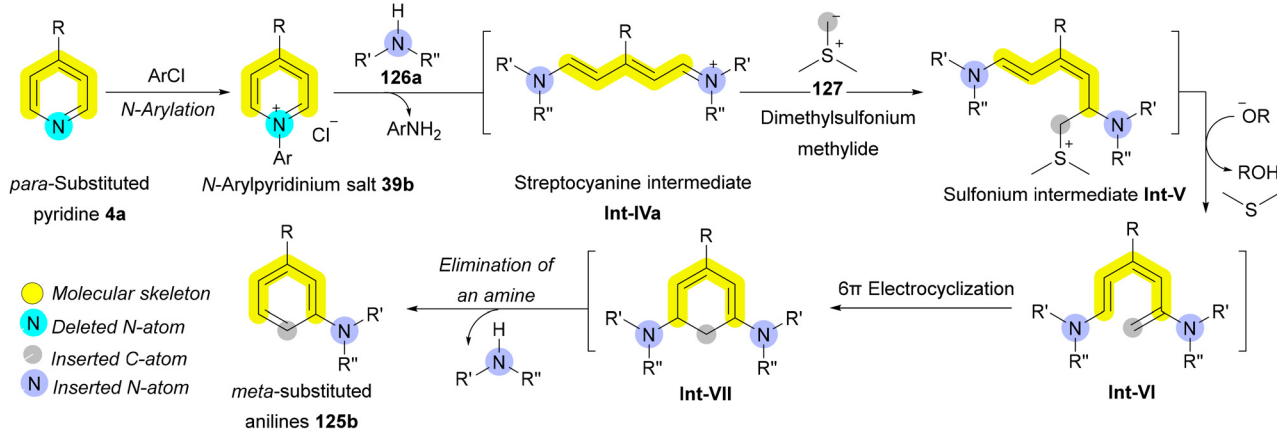
## D) Silver-mediated benzo[1,2,3]thiadiazole formation (Hrobárik 2024)



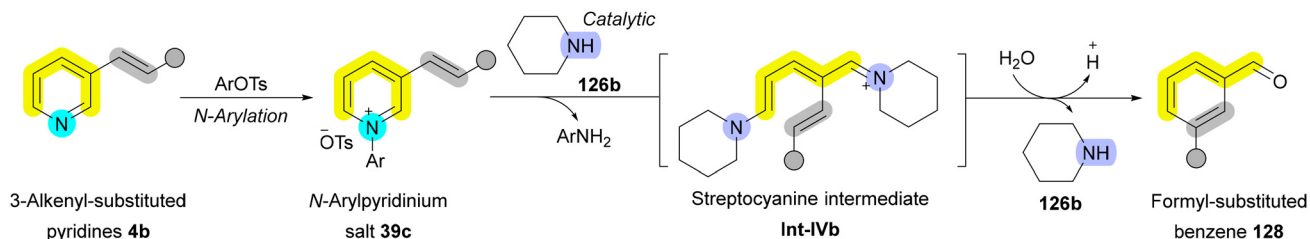
Scheme 19 Carbon-to-nitrogen single-atom transmutation of arens and heteroarens via expansion/contraction sequence.



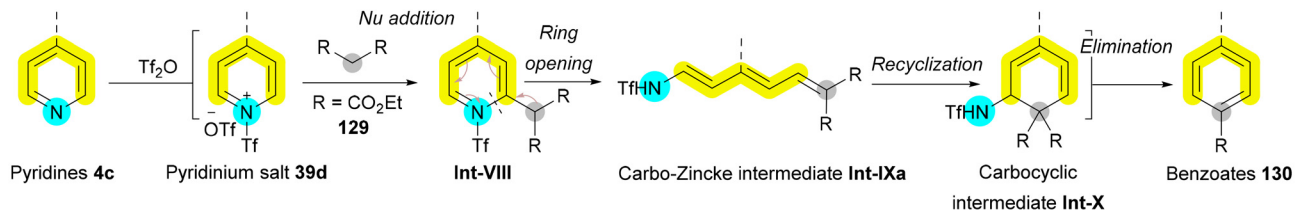
## A) Kost Sagitullin rearrangement, 1978

B) Stepwise conversion of *para*-substituted pyridine to *meta*-dialkylamino-substituted benzene (Kano & Morofuji 2021)

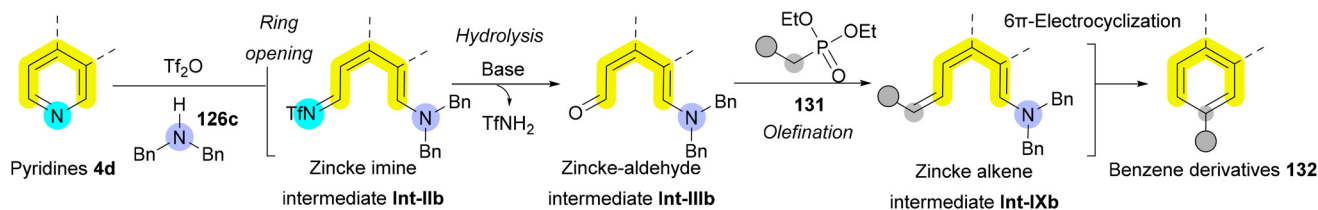
## C) Streptocyanine catalysis for the conversion of pyridine rings to benzene rings (Kano &amp; Morofuji 2023)



## D) Addition of soft carbon nucleophiles enabling pyridines-to-benzene transformation (Greaney 2024)



## E) selective olefination of Zincke-aldehyde enabling pyridines-to-benzene transformation (Glorius 2024)



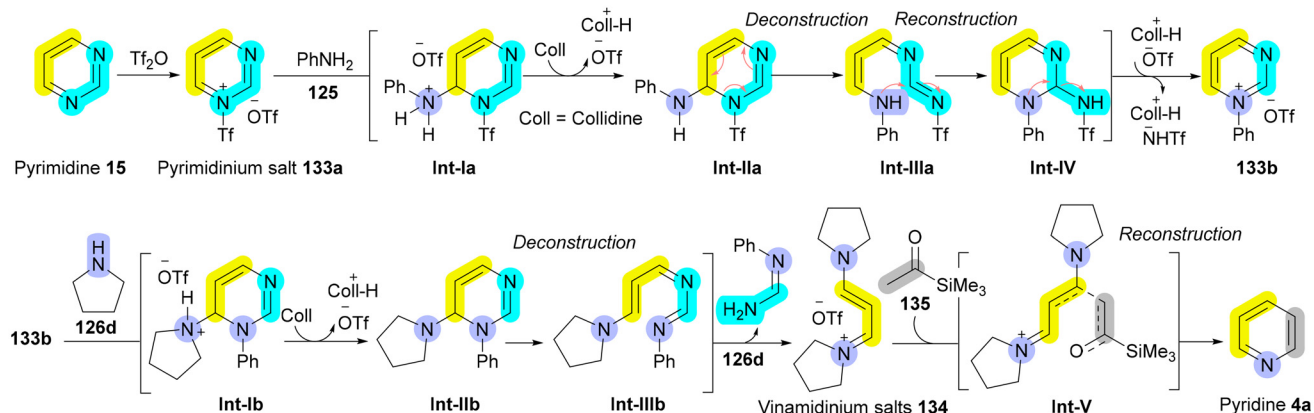
Scheme 20 Pyridine to benzene rearrangements (N-to-C transmutation) achieved through Zincke pyridinium chemistry.



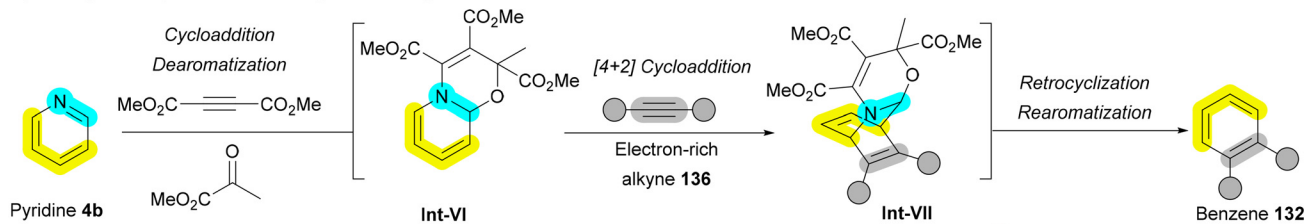
In 2024, a great development by Paton and McNally who achieved a deconstruction–reconstruction process to convert pyrimidines **15** into pyridines **4a** (Scheme 21A).<sup>176</sup> After gener-

ating the pyrimidinium salt **133b**, pyrrolidine **126d** acts as a nucleophile to cleave the pyrimidine, yielding vinamidinium salts **134**. Employing Marcoux's protocol with the lithium

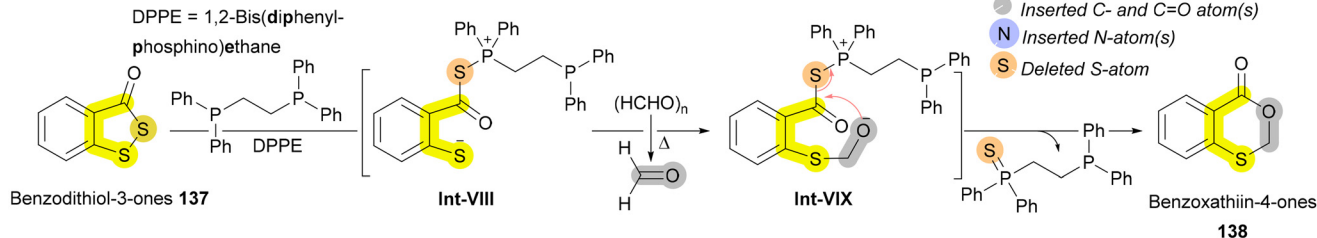
### A) Deconstruction–reconstruction process to convert pyrimidines into pyridines (Paton & McNally 2024)



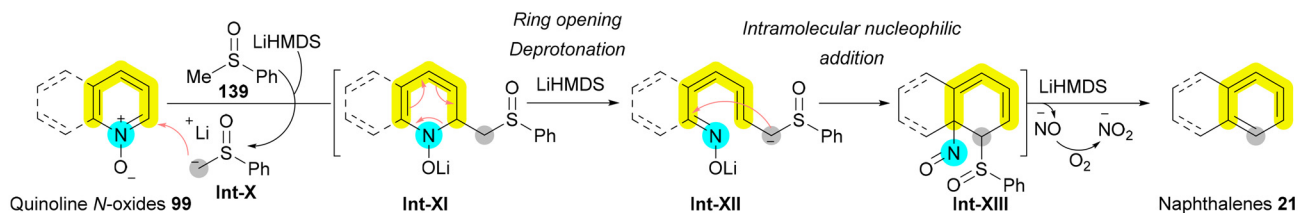
### B) Atom-pair swap from CN to CC (Studer 2024)



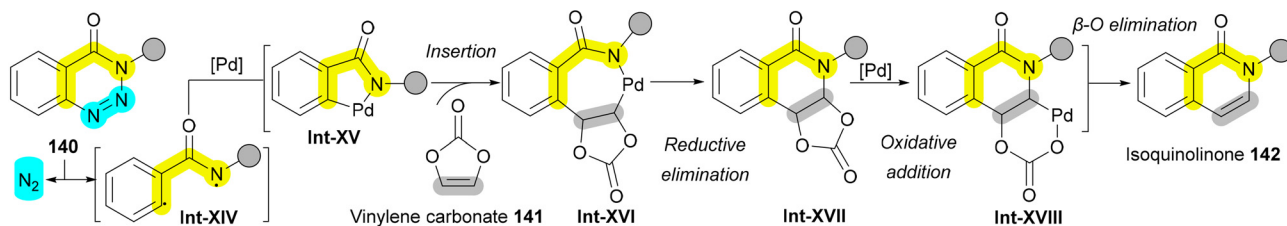
### C) Atom swap from S to CO ring expansion with atom exchange (Zhou 2024)



### D) Skeletal editing of pyridine and quinoline N-oxides through nitrogen to carbon single atom swap (Song 2024)



### E) Palladium-catalyzed transmutation of N=N atom pair to C=C (Nan 2024)



Scheme 21 Various strategies for nitrogen -to-carbon (N-to-C) transmutation of heteroarenes.



enolate of commercially available acetyltrimethylsilane **135**, followed by a combination of ammonium acetate ( $\text{NH}_4\text{OAc}$ ) and acetic acid ( $\text{AcOH}$ ), the vinamidinium salts **134** undergo reaction with ketone-derived enolates and ammonium salts, forming substituted pyridines **4a** through intermediate **Int-V**. Under the reaction conditions, the C–Si bond is cleaved after pyridine formation (Scheme 21A).<sup>176</sup> Recently, Studer and coworkers described a two-atom switch approach using cycloaddition chemistry. The mechanism involves an initial dearomative cyclization of the pyridine ring **4b**, forming an electron-rich diene **Int-VI** within an oxazino-pyridine structure. In the presence of electron-rich dienophiles, such as alkynes **136**, the oxazino-pyridine **Int-VI** undergoes a [4 + 2] cycloaddition, yielding a bridged intermediate **Int-VII**. This intermediate **Int-VII** then retrocyclizes and rearomatizes, affording the target benzene ring **132** (Scheme 21B).<sup>177</sup> Boswell *et al.* introduced a similar two-atom switch approach inspired by water-displacement for the transformation of pyridines to benzenes. A sequence of 1,2-addition, [4 + 2] cycloaddition, and retero-[4 + 2] with alkyne moiety enabled the late stage diversification of various substituted pyridines.<sup>178</sup> When such cycloaddition chemistry employ five-membered heterocycles as the  $4\pi$ -component, two new atoms are installed from the dienophile at the expense of one ring-atom of the substrate achieving ring expansion with atom exchange.<sup>6</sup> Specific examples include isoxazoles into pyridines through inverse electron-demand Diels–Alder reaction (IEDDA),<sup>179</sup> pyrroles to benzene through Diels–Alder reaction (DA),<sup>180</sup> and benzisoxazoles to quinazolines.<sup>181</sup> In 2024, Zhou and coworkers introduced the first example of swapping from an S atom to C–O pair atoms, enabling the direct transformation of benzodithiol-3-ones **137** into benzo[*d*][1,3]oxathiin-4-ones **138** (Scheme 21C). The reaction proceeds in the presence of 1,2-bis(diphenylphosphino)ethane (DPPE) to enable phosphine mediated S–S bond cleavage affording **Int-VIII** that can undergo nucleophilic addition with formaldehyde giving **Int-IX** followed by cyclization to the corresponding benzo[*d*][1,3]oxathiin-4-ones **138**.<sup>182</sup>

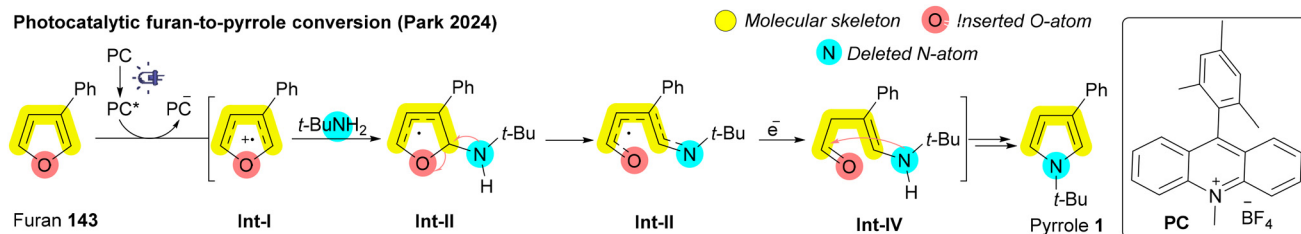
In 1977, Hamada and Takeuchi discovered that benzo[*h*]quinoline *N*-oxide could be transformed into anthracene using DMSO as a carbon source; however, this strategy proved ineffective for broader substrates.<sup>183</sup> Recently, the Song and Sorensen groups enhanced this approach by employing *n*-butyllithium or LiHMDS, significantly increasing conversion efficiency and broadening the substrate scope.<sup>184,185</sup> In this method, phenyl methyl sulfoxide (PhSOME) **139** with LiHMDS

generates a methylsulfinyl carbanion **Int-X**, which acts as a nucleophile for addition, forming an intermediate **Int-XI** that subsequently undergoes ring opening. Following deprotonation and intramolecular nucleophilic addition, ring closure occurs with nitrite release as  $\text{NO}^-$ , yielding the desired naphthalene **21** (Scheme 21D).<sup>184</sup> In 2024, Nan and coworkers reported a rare example of palladium-catalyzed atom-pair exchange in benzotriazinones **140**, converting  $\text{N}=\text{N}$  to  $\text{C}=\text{C}$  and yielding isoquinolinones **142**. Benzotriazinone **140** first undergoes *in situ* denitrogenation, generating radical species **Int-XIV**, which then forms a five-membered cyclopalladium intermediate, **Int-XV**. Migratory insertion of vinylene carbonate **141** produces a seven-membered cyclopalladium intermediate, **Int-XVI**, followed by reductive elimination to afford tricyclic intermediate **Int-XVII**. This intermediate **Int-XVII** then undergoes a sequence of oxidative addition and  $\beta$ -O elimination, giving isoquinolinone derivatives **142** (Scheme 21E).<sup>186</sup>

**2.3.3. Oxygen-to-nitrogen (O-to-N) transmutation.** In 2024, the Park group introduced a landmark photocatalytic strategy for oxygen-to-nitrogen transmutation, achieving the direct conversion of furans **143** to pyrrole analogues **1** (Scheme 22).<sup>187</sup> Upon photoexcitation, the catalyst PC facilitates the oxidation of furan to form a furanic cation **Int-I**, whose reversed polarity enables nucleophilic amine addition to yield adduct **Int-II**. This intermediate **Int-II** undergoes ring opening *via* C–O bond cleavage, producing **Int-III**. Electron transfer from the reduced catalyst  $\text{PC}^-$  then generates a singlet, ring-opened intermediate **Int-IV**, which subsequently undergoes Paal–Knorr-type condensation, giving the pyrrole ring **1**.<sup>187</sup> Ng and coworkers demonstrated another example of late-stage oxygen-to-nitrogen transmutation, achieving precise lactone-to-lactam editing to alter the pharmacological profile of bilobalide.<sup>188</sup>

**2.3.4. Isotopic exchange.** Isotopic exchange has numerous applications across materials science, biology, and chemistry.<sup>189–191</sup> However, most of the current techniques rely on *de novo* synthesis, which is often labour-intensive and resource-inefficient. Skeletal editing offers a direct pathway to obtain isotopically labelled scaffolds through isotopic transmutation. As illustrated in (Scheme 13B), Morandi and colleagues in 2023 developed a metallation approach that converts *N*-Boc-protected lactam rings **92** into organonickel intermediates **93**. By introducing  $^{13}\text{CO}(\text{g})$ , the Ni metal in **93** is replaced with  $^{13}\text{C}$ , resulting in isotopically labelled lactams **92'** (Scheme 23A).<sup>136</sup>

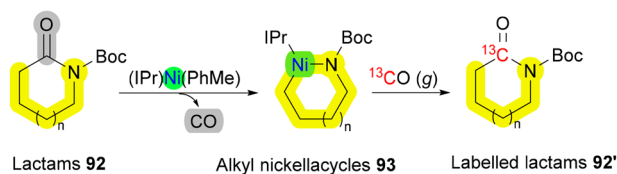
#### Photocatalytic furan-to-pyrrole conversion (Park 2024)



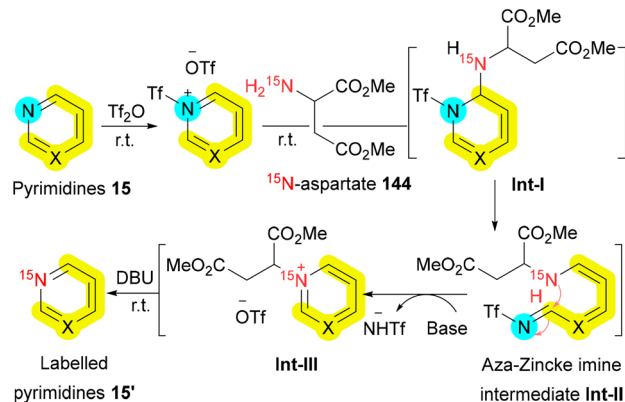
Scheme 22 Oxygen-to-Nitrogen (O-to-N) transmutation.



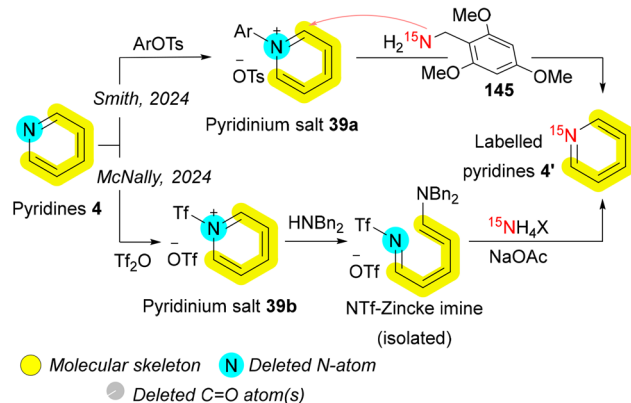
## A) Carbon isotope exchange (Morandi 2023)



## B) Nitrogen isotope exchange (Sigman, Yeung, and Sarpong 2024)



## C) Nitrogen isotope exchange of pyridine (Smith 2024 &amp; McNally 2024)



**Scheme 23**  $^{12}\text{C}$ -to- $^{13}\text{C}$  and  $^{14}\text{N}$ -to- $^{15}\text{N}$  isotopic exchange via skeletal editing.

Due to nitrogen- $^{15}\text{N}$ 's extensive applications in pharmaceuticals—spanning applications from biomolecular NMR,<sup>192,193</sup> structural analysis,<sup>194</sup> and mechanism elucidation<sup>117,195,196</sup> to bioimaging spin hyperpolarization (e.g., SABRE-SHEATH)<sup>197</sup>—an efficient  $^{14}\text{N}$  to  $^{15}\text{N}$  exchange is highly valuable. In 2024, three groups independently reported similar approaches for  $^{14}\text{N}$  to  $^{15}\text{N}$  exchange in various azaheterocycles<sup>198–200</sup> by adapting the Zincke reaction.<sup>168</sup> Sigman, Yeung and Sarpong established a protocol that enabling direct  $^{14}\text{N}$   $\rightarrow$   $^{15}\text{N}$  single atom transmutation across diverse nitrogen heteroaromatics, particularly pyrimidines **15**, using an easily prepared  $^{15}\text{N}$ -enriched aspartate derived diester **144**. Central to this transformation is a low-temperature *N*-triflylation step that activates the heterocyclic nitrogen, allowing a room-temperature Zincke-type ring-opening and ring-closing sequence mediated by  $^{15}\text{N}$ -aspartate nucleophile **144**. This sequence yields an *N*-succinyl intermedi-

ate **Int-III** with the nitrogen isotopically swapped. *In situ* elimination of the succinyl group as fumarate or maleate reveals the labeled heterocycle **15'** (Scheme 23B).<sup>198</sup> Similarly, Smith and McNally applied a  $^{15}\text{N}$  labeling strategy to pyridines **4**. Upon activation via *N*-triflylation or *N*-arylation, pyridinium salts **39** undergo ANRORC, ultimately producing labeled pyridines **4'** (Scheme 23C).<sup>199,200</sup>

## 2.4. Stereochemical editing

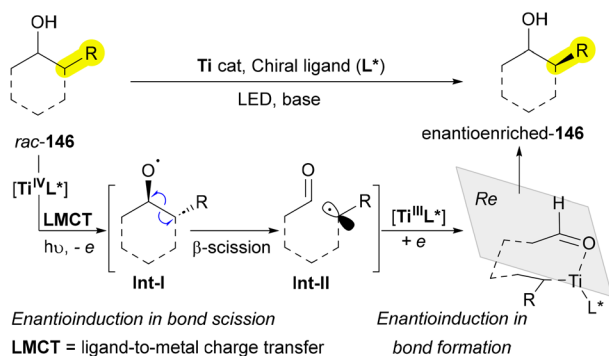
Stereochemical editing is a cutting-edge approach in organic synthesis that enables the direct modification of stereocenters, allowing for the adjustment of relative stereochemistry at a late stage. This technique decouples stereochemistry-defining steps from the main structural assembly, enhancing flexibility and efficiency in generating diverse isomers from a single compound. By utilizing photocatalysis, stereochemical editing can effectively overcome traditional thermodynamic limitations, making it a powerful tool in synthetic chemistry.<sup>201,202</sup>

**2.4.1. Photochemical deracemization.** In 2018, Bach and colleagues achieved a significant advance in stereochemical editing with their energy transfer-enabled deracemization of piperidin-2-one-containing allenes, utilizing a chiral thioxanthone as a photosensitizer to attain high optical enrichment.<sup>203</sup> More recently, Luo and co-workers developed a photochemical *E/Z* isomerization strategy for the deracemization of  $\alpha$ -branched aldehydes, efficiently converting racemic mixtures into their enantiomers.<sup>204</sup> Additionally, research by Hu, Chen, and Meggers has made notable progress in the deracemization of secondary alcohols and pyridyl ketones through various photocatalytic methods.<sup>205,206</sup> In 2023, Zuo group have introduced a light-driven deracemization method for alcohols using a single chiral titanium catalyst that effectively breaks and remakes carbon–carbon bonds, achieving high enantiomeric excess across a wide range of substrates by integrating two enantioselective processes into one reaction (Scheme 24A).<sup>207</sup>

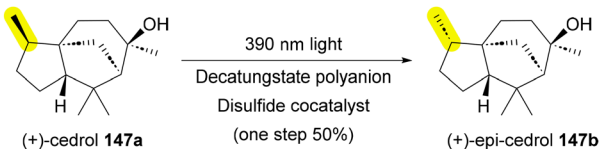
**2.4.2. Photochemical epimerization.** Photochemical epimerization is an efficient method for the selective interconversion of stereoisomers at a late stage in synthesis. Wendlandt and MacMillan have independently developed innovative strategies for the photochemical epimerization of sugars and cyclic diols, utilizing radical reactions that target homolytically weak C–H bonds.<sup>208–211</sup> This process involves a combination of hydrogen atom abstraction and donation, enabling the breaking and reforming of stereogenic centres, thereby facilitating the transformation of stereoisomers. In 2022, Wendlandt group developed a novel stereochemical editing method enabling the inversion of unactivated tertiary C–H bonds in a single step through a mild, light-catalyzed process via a decaying-state polyanion and disulfide cocatalyst. This reaction operates through a radical mechanism, where a hydrogen atom is abstracted from a nonacidic C–H bond and then reintroduced to invert the stereocenter, demonstrating its applicability to various complex molecules, including the fragrance compound (+)-cedrol **146**. The method's tolerance for multiple functional groups allows chemists to apply it in late-stage synthetic sequences (Scheme 24B).<sup>212</sup>



## A) Deracemization of alcohols via asymmetric LMCT catalysis (Zuo 2023)



## B) Epimerization of unactivated tertiary stereocenters (Wendlandt 2022)



Scheme 24 Stereochemical editing.

## 3. Conclusions and perspectives

The field of skeletal editing has grown rapidly, with impressive advances that allow atom-level modifications in molecular frameworks—offering transformative applications in pharmaceuticals and beyond. Through strategies like insertion, deletion, and transmutation, chemists have successfully reshaped molecular scaffolds with increasing precision and sustainability.<sup>4–6</sup> Although significant progress has been made, achieving a level of maturity that enables context-independent deployment remains a challenge. Several limitations hinder further progress and need to be overcome before the field can reach its full potential, and can be summarized as follows:

**1. Generality:** the limited availability of methods that enable diverse transformations by simply altering the insertive agent or reactive species highlights a significant gap in the field of skeletal editing.<sup>101</sup> To advance this area of research, it is essential to develop more robust strategies that can reliably achieve various modifications with high selectivity. As discussed in this review, many existing methods share similar underlying mechanisms, suggesting that there is potential for expanding their applicability to meet these objectives.<sup>21,56,88</sup>

**2. Selectivity:** high chemo-, regio-, and stereoselectivity remains a significant challenge in skeletal editing, hindering the field's progress. Many current methods exhibit non-selective conditions, resulting in lower yields and unwanted byproducts. Furthermore, the literature on asymmetric skeletal editing is limited, with very few reported examples.<sup>75</sup> Notably, Wendlandt and Zuo have made significant contributions to the area of stereochemical editing, highlighting its potential to advance the field.<sup>207,208,212</sup> This lack of selectivity complicates product purification and restricts the practical application of these approaches in the synthesis of complex molecules that require high selectivity.<sup>213,214</sup>

**3. Diversity:** current methods predominantly focus on carbon and nitrogen, which can be fully understood in the context of drug development. However, there is a need to develop efficient techniques that incorporate a broader range of heteroatoms.<sup>130</sup> Expanding diversity will not only enhance the functionality and complexity of synthesized scaffolds but also advance applications in materials science and optoelectronics enabling atom doping and allows for direct comparative studies without *de novo* synthesis.<sup>14</sup>

**4. Efficiency and complexity:** most existing methods for skeletal editing rely on stepwise sequences, which could be enhanced by developing streamlined, single-step processes. Furthermore, many studies focus on simple monocyclic structures lacking other functionalities. The true potential of skeletal editing will be realized when it is applied to the synthesis of complex materials, challenging molecular skeletons, or natural products, as seen in some reports from the Sarpong group,<sup>58</sup> and Ng group.<sup>188</sup>

**5. Sustainability:** although skeletal editing aligns with sustainability objectives by conserving resources, effort, and time, chemists often compromise these advantages when attempting complex transformations. As a result, many reported methods exhibit low atom economy, limited scalability, and reliance on expensive or hard-to-source metal reagents. Recently, many research groups have recognized these issues and are focusing on more sustainable approaches, employing more practical methods, and greener alternatives such as electrochemistry.<sup>115,116</sup>

Addressing these limitations and exploring underdeveloped areas is vital for unlocking the full potential of skeletal editing. Future efforts should prioritize ambitious reactions, such as the migration of heteroatoms and enhanced transmutation methods, which would enable straightforward diversification of drug candidates after lead identification. Collaboration between medicinal and synthetic chemists is essential for translating these methods into novel drug designs and structure-oriented approaches, including drug-oriented rational molecular editing (DORME) and structure-guided rational molecular editing (SGRME).<sup>9</sup> By tackling these challenges and exploring new avenues, skeletal editing can reach full maturity as a powerful tool for remodelling molecular frameworks with atom-level precision.

## Author contributions

R. S. and M. S. H. S. wrote and drafted the manuscript; M. S. H. S. reviewed and edited the manuscript; M. A. and S. T. provided guidance and supervision throughout the work. All authors have approved the manuscript.

## Data availability

No primary research results, software or code have been included and no new data were generated or analysed as part of this review.



## Conflicts of interest

There are no conflicts to declare.

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