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REVIEW

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Skeletal Editing: Interconversion of Arenes and Heteroarenes

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Skeletal editing involves making specific point-changes to the core of a molecule through the selective insertion, deletion or exchange of atoms. It thus represents a potentially powerful strategy for the step-economic modification of complex substrates and is a perfect complement to methods such as C–H functionalization that target the molecular periphery. Given their ubiquity in biologically active compounds, the ability to perform skeletal editing on – and therefore interconvert between – aromatic heterocycles is especially valuable. This review summarizes both recent and key historical examples of skeletal editing as applied to interconversion of aromatic rings; we anticipate that it will serve to highlight not only the innovative and enabling nature of current skeletal editing methods, but also the tremendous opportunities that still exist in the field.

Keywords: atom deletion, atom exchange, atom insertion, drug design, drug discovery, insertion, molecular editing, skeletal editing.

1. Introduction

Achieving the *selective* functionalization of complex molecules is a longstanding challenge that has – in equal measure – inspired and frustrated the efforts of countless synthetic chemists. The requirement that such functionalizations be both general and concise is particularly pressing in the field of drug discovery, where the accessibility of new chemical entities directly affects the speed and efficiency with which drug candidates can be identified.[1] It is in this context that the concept of 'molecular editing' has recently become a topic of great interest.

Molecular editing, also referred to as 'site-directed mutagenesis',[1] has been defined as 'the insertion, deletion, or exchange of atoms in highly functionalized compounds at will and in a highly specific fashion'.[2] Given this broad remit, which necessarily encompasses the field of late-stage functionalization,[3–6] the mantle of 'molecular editing' is applicable to myriad reactivity manifolds and can concern transformations in almost any region of chemical space. Understandably however, the majority of existing molecular editing methodologies target readily accessible functionality on the exterior of the substrate,[7–9] such that the core molecular skeleton is left untouched.

The ability to modify the *core* of a molecule by interconverting between (hetero)aromatic substructures is potentially extremely valuable due to their ubiquity in biologically active compounds.[10–16] Although such transformations fall within the broader – and only recently defined – field of molecular editing, they include established concepts such as 'transannulation'[17] and have been referred to historically as 'heterocycle interconversions'.[18,19] In a 2022 review, *Sarpong*, *Levin*, and co-workers introduced another new term by defining '*skeletal* editing' as the subset of 'molecular editing' that concerns the precise modification of molecular skeletons, mainly ring systems.[20] Such transformations promise to facilitate the rapid diversification of complex molecular architectures while avoiding cost- and labor-intensive *de novo* synthesis. As such, they have the potential to accelerate both drug discovery and total synthesis.[21]

In this review, we provide an overview of skeletal editing as applied to the interconversion of (hetero)arenes. We seek to highlight not only contemporary examples of skeletal editing, but also key historical examples; transformations that generate an

aromatic system from non-aromatic precursors, or that result in destruction of an aromatic system, are not discussed in detail.

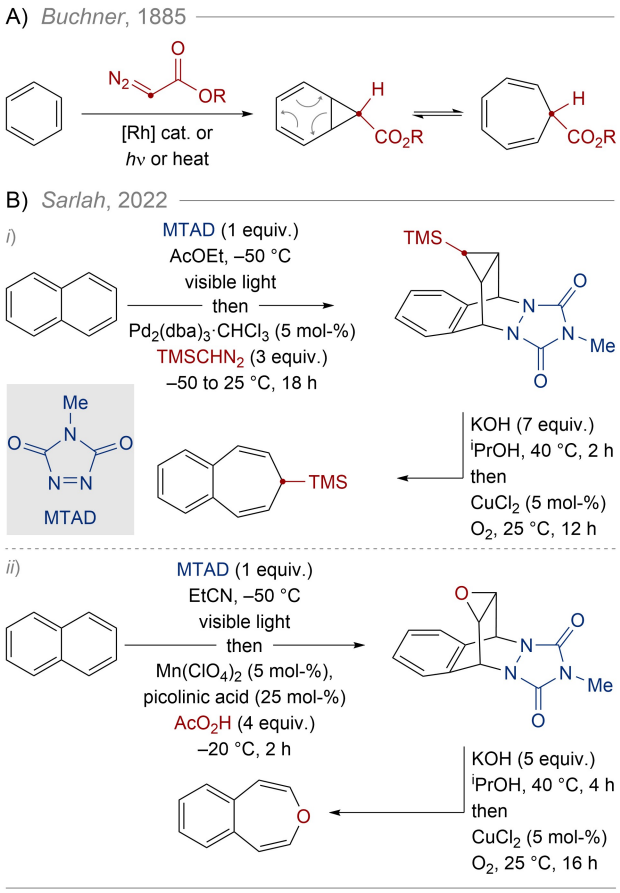
Transformations are categorized by whether they involve *1*) ring expansion, *2*) ring contraction, or *3*) an atom-exchange but with no net-change in the size of the (hetero)aromatic system. Ring expansions are necessarily accompanied by the insertion of new atoms and are thus further sub-divided by whether they involve *a*) insertion of a single C- or N-atom (while retaining all the original ring-atoms), or *b*) whether the expansion process involves exchange of one or more of the original ring-atoms for new atoms.

2. Ring Expansion

While ring expansion reactions are ubiquitous in carbonyl chemistry,[22–25] their application to aromatic systems is more limited due to the inherent stability of π-conjugated rings. Methodologies that insert new atoms into aromatic systems are therefore of great value for both *1*) their conceptual rarity, and *2*) their ability to significantly alter chemical reactivity and physicochemical properties.[11,14] The majority of ring expansion methodologies reported to date have concerned the insertion of C- or N-atoms, as outlined in the following sections.

2.1. *Ring Expansion with C-Atom Insertion*

One of the best-established ring expansions is the *Buchner* reaction (*Scheme 1,A*), first reported in 1885.[28,29] The transformation proceeds through cyclopropanation of the aromatic substrate with a diazoester, followed by 6π electrocyclic ring opening. In the initial incarnation of the methodology, cyclopropanation was achieved through thermal or photolytic activation of the diazoester and typically exhibited poor regioselectivity. However, in 1980 *Noels* and co-



Scheme 1. Ring expansion of benzenoids through formal C-atom insertions. A) General reaction scheme for the *Buchner* ring expansion. B) Ring expansion of polycyclic arenes through sequential [4 + 2] cycloaddition, cyclopropanation, and *retro*-[4 + 2].[26,27]

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workers reported a rhodium-catalyzed *Buchner* reaction which improved regioselectivity.[30,31] Subsequent advances have led to further improvements in both regioselectivity and reaction scope,[32–35] and in 2017, a regio- and enantioselective variant was demonstrated in flow.[36]

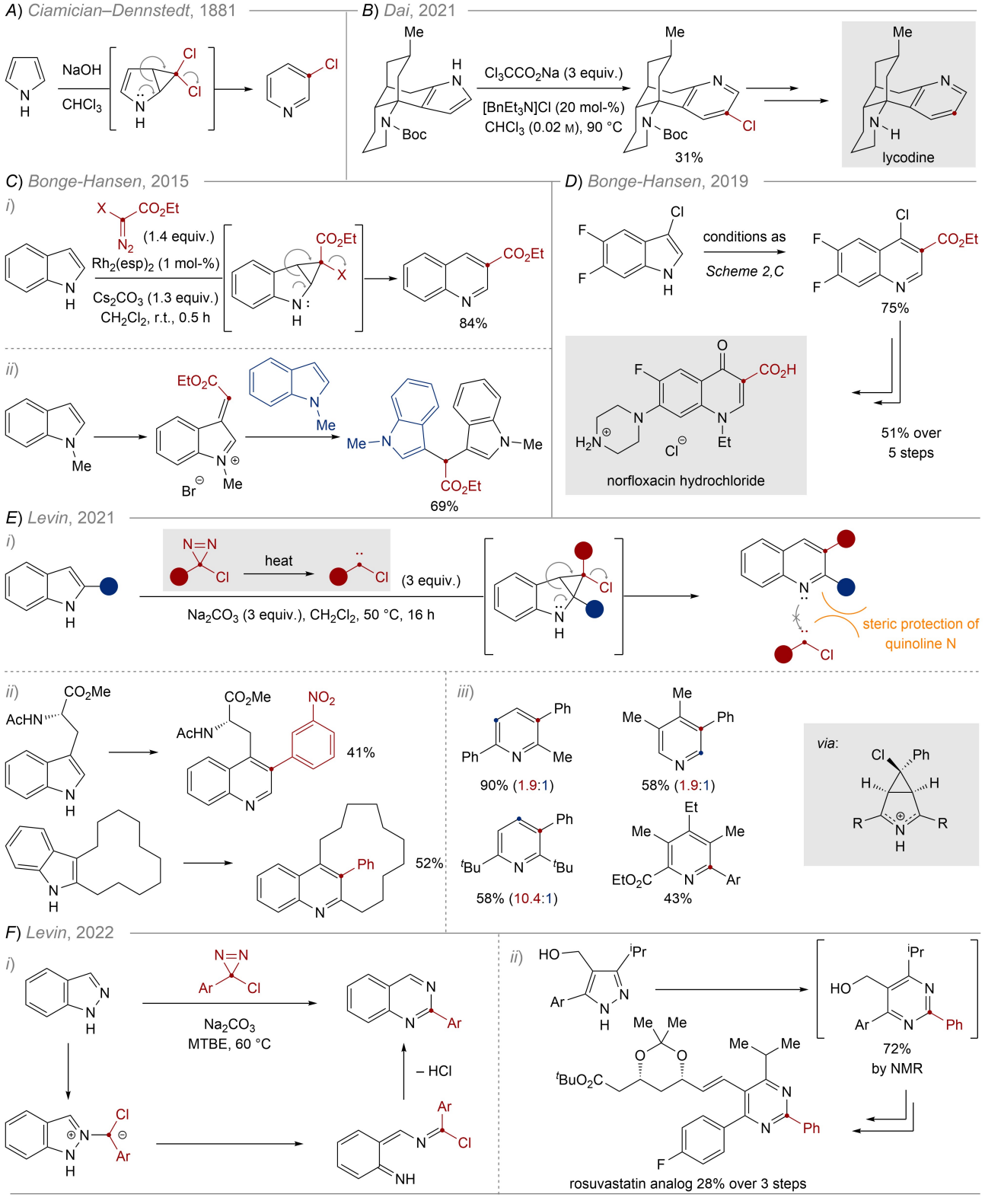
In 2022, *Sarlah* and co-workers reported the single C-atom insertion into polycyclic arenes through a dearomatization/cyclopropanation sequence (*Scheme 1,B-i*).[26] While the net transformation is similar to that of the *Buchner* reaction (*Scheme 1,A*), *Sarlah*'s strategy avoids the regioselectivity issues that plague the earlier methodology. First, the areneophile MTAD (4-methyl-1,2,4-triazoline-3,5-dione) undergoes [4 + 2] cycloaddition with a polycyclic arene under visible light irradiation. Cyclopropanation of the C(2)–C(3) position is now achievable on the isolated olefin by use of TMS-diazomethane and a palladium catalyst. *Retro*-[4 + 2] cycloaddition is then achieved through partial hydrolysis of the urazole, copper-catalyzed aerobic oxidation, and subsequent extrusion of dinitrogen. 6π Electrocyclization of the resulting cyclopropanated arene then affords the ring expanded benzocycloheptatriene. The reaction was applied to a range of substituted naphthalenes as well as quinolines and benzoquinolines. Earlier work by the group applied a similar concept to the synthesis of 3-benzoxepines through manganese-catalyzed epoxidation of the intermediate cycloadduct (*Scheme 1,B-ii*).[27]

The impact of ring expansion on a molecule's properties is particularly drastic when the substrate and/or the insertive reagent contain heteroatoms. For example, despite differing by only a single C-atom, indole and quinoline possess vastly different chemical and physicochemical properties: where the former is a weak acid that readily undergoes electrophilic aromatic substitution, the latter is weakly basic and is predisposed to nucleophilic aromatic substitution.[37]

Historically, the one-carbon expansion of both pyrroles and indoles has been achieved using the *Ciamician–Dennstedt* reaction (*Scheme 2,A*), first reported in 1881.[38] This occurs through generation of a dihalocarbene from the corresponding haloform in basic media, azole cyclopropanation, and subsequent fragmentation. Despite the appeal of the net chemical transformation, the competing *Reimer–Tiemann* formylation often leads to low yields of the desired azine (up to *ca* 40%) and the strongly basic conditions for generation of the carbene limit functional group compatibility.[39,45] A modified *Ciamician–Dennstedt* reaction employing sodium trichloroacetate as a thermally-activated dichlorocarbene source was reported by *Dai* and co-workers in 2021 as part of the total synthesis of lycopodium alkaloids, affording the desired 3-chloropyridine in a 31% yield (*Scheme 2,B*).[40]

In 2015, *Bonge-Hansen* and co-workers reported a rhodium-catalyzed variant of the *Ciamician–Dennstedt* reaction in which indoles are converted to quinoline-3-carboxylates using halodiazoacetates as the carbenoid precursor (*Scheme 2,C-i*).[41] Although readily accessible, the requisite halodiazoacetates are unstable at ambient temperatures.[46] The need for an electron withdrawing substituent on the diazo reagent to achieve even this modest level of stability necessarily restricts the ring expansion to installation of esters on the 3-position of the resulting quinoline. Despite this limitation, the reaction afforded high yields across a range of indole substrates. No reaction was observed when the indole nitrogen was protected with a Boc group, and methylation of the indole nitrogen resulted in the formation of a dimeric C(3)-alkylated product (*Scheme 2,C-ii*). The same ring expansion methodology was later applied to 3-chloroindoles to generate the 4-chloroquinoline-3-carboxylates, which could be hydrolyzed to afford the corresponding 4-quinolone (*Scheme 2,D*).[42] This strategy was utilized in the synthesis of norfloxacin from 5,6-difluoro-3-chloroindole.

In 2021, *Levin* and co-workers reported that arylchlorodiazirines can serve as carbene precursors for the ring expansion of indoles and pyrroles into the corresponding 3-arylazines (*Scheme 2,E-i*).[43] Chlorodiazirines are prepared conveniently by *Graham* oxidation of amidinium salts;[47] while still energetic materials,[48] they are more stable than the isomeric diazo compounds and can therefore be used to install aryl moieties. Although a range of functionality on the indole and diazirine was well tolerated, a substituent in the 2-position of the indole was required for high yields. In the absence of a 2-substituent, the quinoline product undergoes a deleterious addition into the free carbene,[49] both decomposing the desired product and consuming the carbene. Additionally, a superstoichiometric base was required to sequester the chloride anion co-product, which would otherwise also consume the carbene. Despite these limitations, the protocol is applicable to complex substrates and has been employed in tryptophan editing as well as in the synthesis of quinoline cyclophanes (*Scheme 2,E-ii*). In the case of pyrroles, the regioselectivity of cyclopropanation – and therefore of C-atom insertion – is determined by the steric profile of the 2- and 6-positions (*Scheme 2,E-iii*). Atom insertion preferentially occurs adjacent to the smaller substituent, although

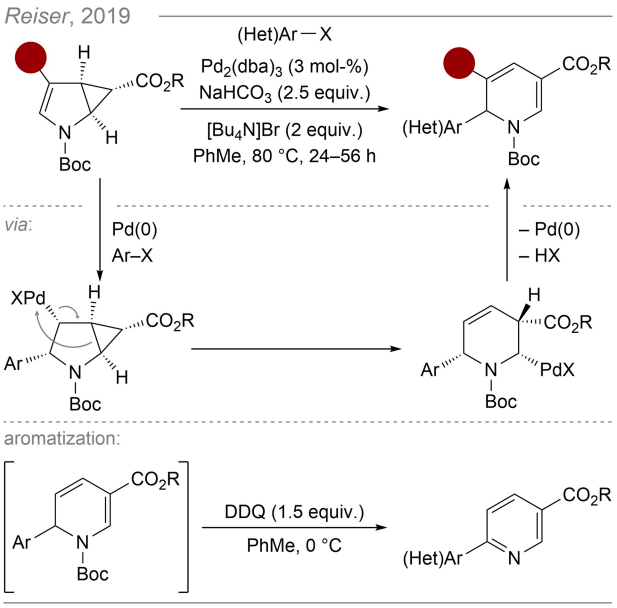


Scheme 2. Ring expansion of azoles and diazoles through *C*-atom insertion. *A*) General reaction scheme for the *Ciamician–Dennstedt* reaction.[38,39] *B*) Application of the *Ciamician–Dennstedt* reaction in the total synthesis of lycodine.[40] *C*), *D*) C-atom insertion into indoles mediated by halodiazoacetates.[41,42] *E*) Ring expansion of indoles and pyrroles mediated by chlorodiazirines.[43] *F*) C-Atom insertion into indazoles mediated by chlorodiazirines.[44] esp = α,α,α′,α′-tetramethyl-1,3-benzenedipropionic acid.

this steric control is overruled by the presence of H-bond donors, which guide insertion adjacent to themselves. Pyrroles with no steric bias afford minor products arising from atom insertion at the 4-position, which was interpreted computationally as proceeding through a stepwise pathway.

In addition to the ring expansion of indoles, *Levin* demonstrated that the ring expansion of pyrazoles and indazoles could also be achieved using chlorodiazirines (*Scheme 2,F*).[44] This reaction is proposed to proceed through formation of an ylide intermediate which then fragments with N–N cleavage through an electrocyclic ring-opening (*Scheme 2,F-i*). The resulting diazahexatriene undergoes ring closure with loss of HCl to afford the desired pyrimidine or quinazoline. The reaction tolerates several functional groups, including free alcohols, and has been applied to the modification of preexisting drug motifs and the synthesis of a rosuvastatin analog (*Scheme 2,F-ii*). It was noted that, if the starting diazole is too electron-poor, competitive dimerization can occur to give bis(pyrazolyl)methanes. This side-reaction was suppressed by using a 2-trimethylsilylethoxymethyl (SEM) protected substrate. Two major limitations were observed in the reaction scope: substrates with poor solubility in the MTBE solvent, and substrates bearing inductively electron-withdrawing substituents.

While the reactions illustrated in *Scheme 2,A–2,E* exploit a halocyclopropanated azole to enable spontaneous ring expansion, *Reiser* and co-workers have shown that cyclopropanated azoles *without* a pendant nucleofuge can be opened through a palladium-catalyzed *Heck*-type arylation (*Scheme 3*).[50] Following regioselective carbopalladation, the reaction was proposed to proceed through ring opening and palladium migration to give a ring-expanded tetrahydropyridinyl palladium species. A postulated base-assisted elimination then affords the 2-aryl dihydropyridine product and regenerates the catalyst; *in situ* oxidation with DDQ affords the 2-aryl pyridine, providing a novel solution to the '2-pyridyl problem' that plagues *Suzuki–Miyaura* cross-coupling.[51] Although the 3-substituent is limited by the nature of the diazo-reagent required in the initial cyclopropanation, the reaction exhibits good compatibility with a number of substituted (hetero)aryl halides. Additionally, the reaction was applied to the synthesis of dihydropyrans from the monocyclopropanated furans with only minor adjustments to the reaction conditions.



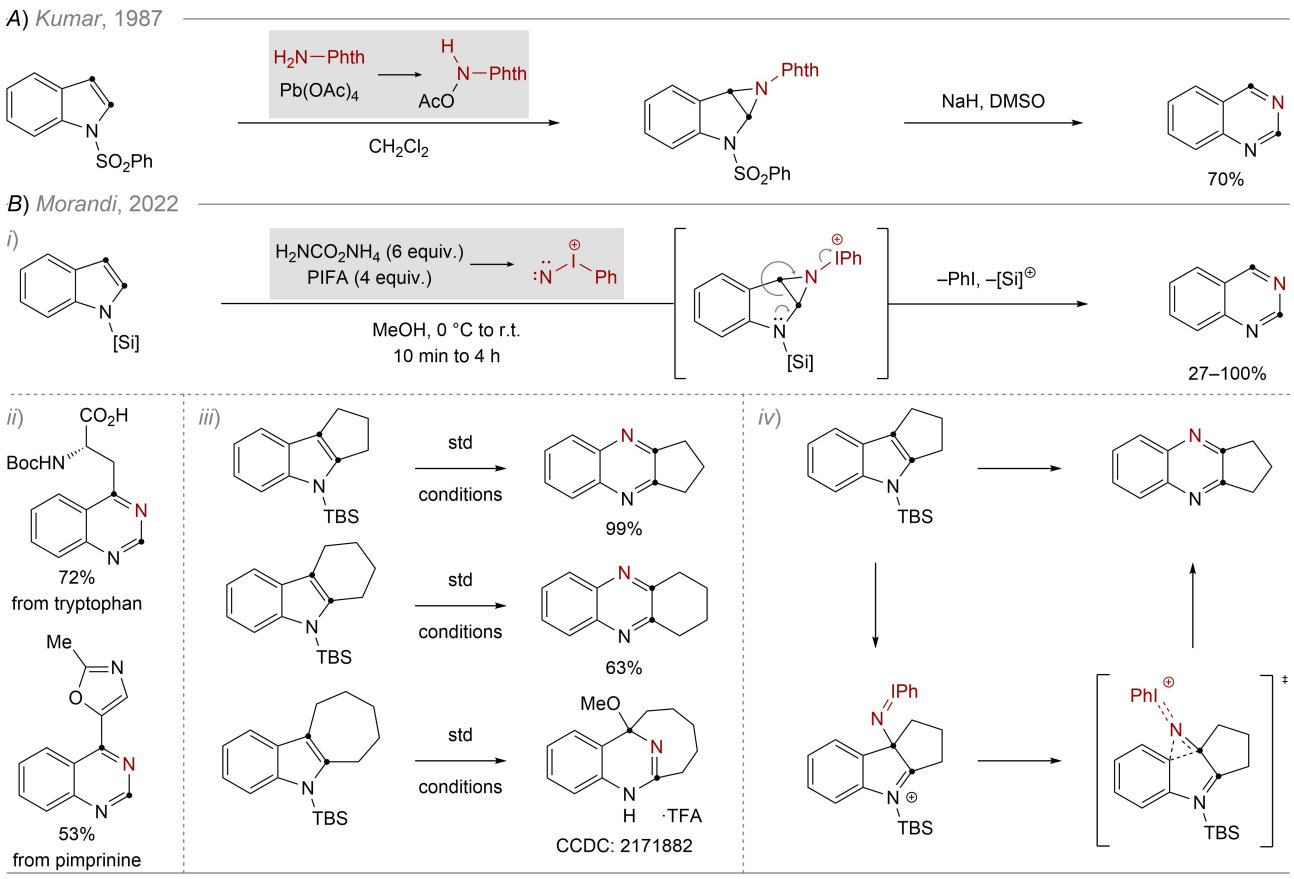
Scheme 3. Ring expansion of cyclopropanated pyrroles to dihydropyridines through *Heck*-type palladium-catalysis and *in situ* oxidation to pyridines.[50] X = halide.

2.2. Ring Expansion with N-Atom Insertion

The insertion of a N-atom into an aromatic skeleton is accompanied by particularly significant changes to the molecule's chemical and physicochemical properties, including (*Lewis*) basicity, H-bonding and polar surface area.[11,14] This edit is therefore of great interest in medicinal chemistry, where it has the potential to accelerate library diversification and the determination of structure–activity relationships. While formal nitrogen insertion methodologies have been known for decades, more broadly applicable protocols with greater functional group tolerance and wider reaction scope have been developed in recent years.

The *aza-Achmatowicz* reaction serves as a powerful method for the transformation of functionalized furans to piperidinones.[52] α-Furanylamines are readily converted to the ring expanded piperidinones upon oxidation with *m*-CPBA. Subsequent dehydration of the piperidinone ring allows access to substituted pyridines.

In 1987, *Kumar* reported the insertion of a N-atom into the aromatic skeleton of indoles to afford the corresponding quinazoline (*Scheme 4,A*).[53,54] Detailed studies by *Atkinson* suggest that oxidation of *N*-aminophthalimide by $Pb(OAc)_4$ forms an *N*-acetoxyaminophthalimide,[56] rather than a nitrene, and that this intermediate is responsible for aziridina-



Scheme 4. Ring expansions through N-atom insertion. *A*) Nitrogen insertion achieved by stepwise oxidative aziridination and deprotection.[53][54] *B*) N-Atom insertion mediated by an iodonitrene (*i*); applications in the editing of tryptophan and pimprinine (*ii*); the selectivity (*iii*) and proposed mechanism (*iv*) of insertion into various ring-fused indoles.[55] Phth = phthalimido; PIFA = bis(trifluoroacetoxy)iodobenzene; TBS = *tert*-butyldimethylsilyl.

tion of the protected indole substrate. Removal of the phenylsulfonyl protecting group with NaH in DMSO afforded the ring expanded quinazoline product with loss of phthalimide as a nucleofuge.

A conceptually similar, but much more general, N-atom insertion protocol has been developed recently by *Morandi* and co-workers for the conversion of indoles to quinazolines *(Scheme 4,B-i)*.[55] In contrast to *Kumar*'s methodology,[54] this reaction employs an *in situ* generated iodonitrene to achieve aziridination, which is proposed to occur in a stepwise fashion *via* a cationic intermediate. Subsequent fragmentation and expulsion of the iodobenzene nucleofuge affords the quinazoline product. A silyl protecting group was found to be crucial in preventing interaction of the nitrene with the indole N–H, stabilizing the cationic species generated by reaction with the nitrene, and finally acting as a sufficient electrofuge to release the free quinazoline product.

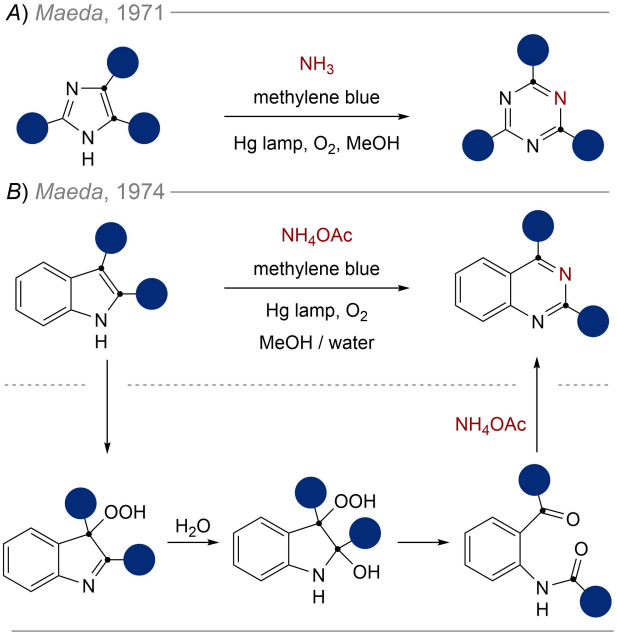
High tolerance is exhibited towards medicinally-important functional groups such as esters and sulfones, as well as functional groups typically considered sensitive to nitrenes, including carboxylic acids and alkenes (*Scheme 4,B-ii*). The chemistry was applied to the late-stage modification of protected, indole-containing pharmaceuticals such as *N*-feruloylserotonin, pindolol and brevianamide F (not shown).

Interestingly, when the methodology was applied to indoles bearing medium-sized 2,3-fused rings, the isomeric quinoxaline product was observed in high yields (*Scheme 4,B-iii*). It was proposed that the high strain imposed by the fused ring prevented direct fragmentation of the aziridine to the quinazoline. Instead, computational calculations suggested a transition state in which the aziridinyl nitrogen inserts into the C(3)–C(4) σ-bond through a concerted C–N bond formation/fragmentation process (*Scheme 4,B-iv*). While quinoxalines are formed for five- and six-

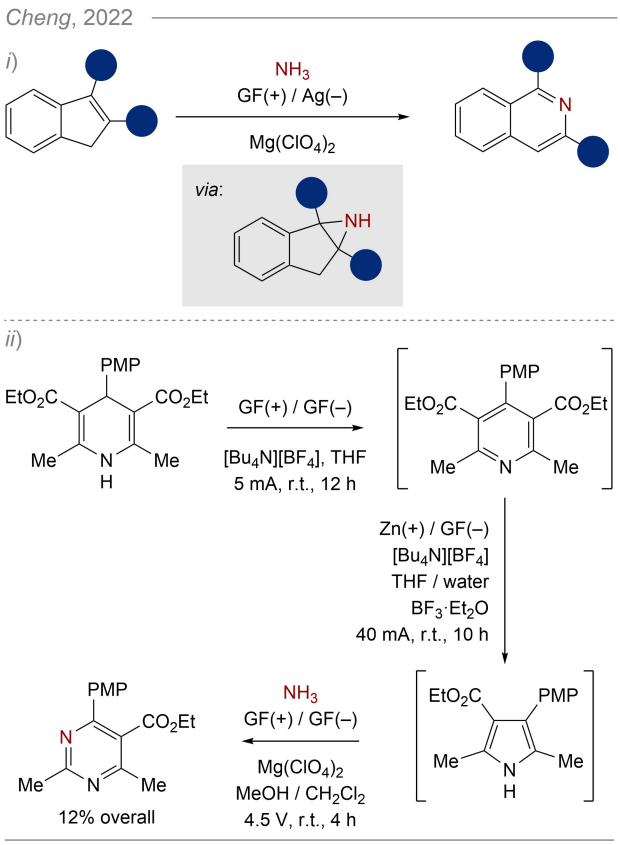
membered fused-rings, the standard regioselectivity is observed for seven-membered fused rings, albeit with formation of the dihydroquinazoline product resulting from addition of methanol.

Strategies for ring expansion through N-atom insertion are not limited to aziridination chemistry.[57] In 1971, *Maeda* and co-workers reported the synthesis of *s*-triazines from imidazoles in which N-atom insertion is achieved through an oxidative cleavage/condensation sequence (*Scheme 5,A*).[58] In this protocol, irradiation in the presence of methylene blue and oxygen resulted in oxidative cleavage of the imidazole C=C bond to give an amidoaldehyde intermediate. Condensation of both carbonyls with ammonia closed the ring to generate the triazine. This approach was later employed in the conversion of indoles to quinazolines (*Scheme 5,B*), which provided insight into the mechanism of the transformation.[59]

Electrochemistry has also emerged as a promising tool for skeletal editing due to its high atom economy and functional group tolerance.[60–64] In 2022, *Cheng* and co-workers reported the electrochemically-mediated insertion of ammonia into aromatic carbocycles to afford the corresponding isoquinoline (*Scheme 6,i*).[65] The reaction achieved over 99% theoretical atom economy, and is proposed to proceed through oxidative aziridination with ammonia followed by oxidative ring opening and rearomatization. While most substrates investigated were non-aromatic



Scheme 5. Ring expansion/N-atom insertion through oxidative cleavage of: *A*) imidazoles, and *B*) indoles.[58,59]



Scheme 6. N-Atom insertion through electrochemical oxidation demonstrated by the ring contraction/ring expansion of a *Hantzsch* ester.[65] GF = graphite felt; PMP = *para*-methoxyphenyl.

indenes, the method has been applied to aromatic systems (*Scheme 6,ii*). Thus, following conversion of a *Hantzsch* ester to a polysubstituted pyrrole through sequential electrochemical reduction and electrochemical atom deletion, N-atom insertion afforded the pyrimidine product. Although the overall yield was modest (12%), all steps were telescoped, and the only by-products were AcOEt and H_2.

2.3. Ring Expansion with Atom Exchange

A particularly well-explored approach to the expansion of ring systems is through [4+2] cycloaddition/*retro*-cycloaddition.[66] When such reactions employ five-membered heterocycles as the 4π-component, two new atoms are installed from the dienophile at the expense of one ring-atom of the substrate. The ring expansion process is thus accompanied by an atom exchange process.

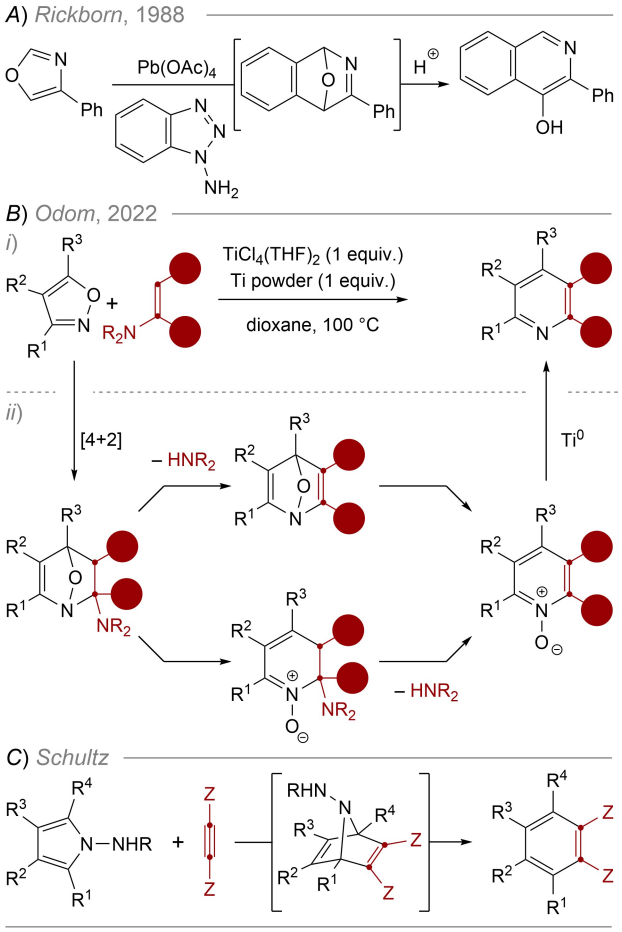
Oxazoles have been shown to be valuable substrates for these transformations.[66] For example, reaction of an oxazole with benzyne and subsequent acidolysis of the oxa-bridged bicyclic intermediate leads to the ring expanded isoquinoline (*Scheme 7,A*).[67,68]

Like oxazoles, isoxazoles can also undergo ring expansions through [4+2] cycloaddition. In 2022, *Odom* and co-workers reported the transformation of isoxazoles into pyridines through an inverse electron-demand *Diels–Alder* reaction (IEDDA; *Scheme 7,B*).[69] Here, expansion of the ring is accompanied by formal exchange of an O-atom for two C-atoms. This process proceeds through a regioselective *Lewis* acid-promoted [4+2] cycloaddition of the isoxazole with an enamine, resulting in a [2.2.1]-oxazabicyclic intermediate. Two alternative *Lewis* acid-promoted pathways were proposed for the formation of the pyridine *N*-oxide product: loss of the enamine-derived amine followed by ring opening, or the reverse. Addition of metallic titanium then reduces the pyridine *N*-oxide to the desired pyridine. An investigation of substrate scope demonstrated the applicability of this methodology to the synthesis of polysubstituted pyridines.

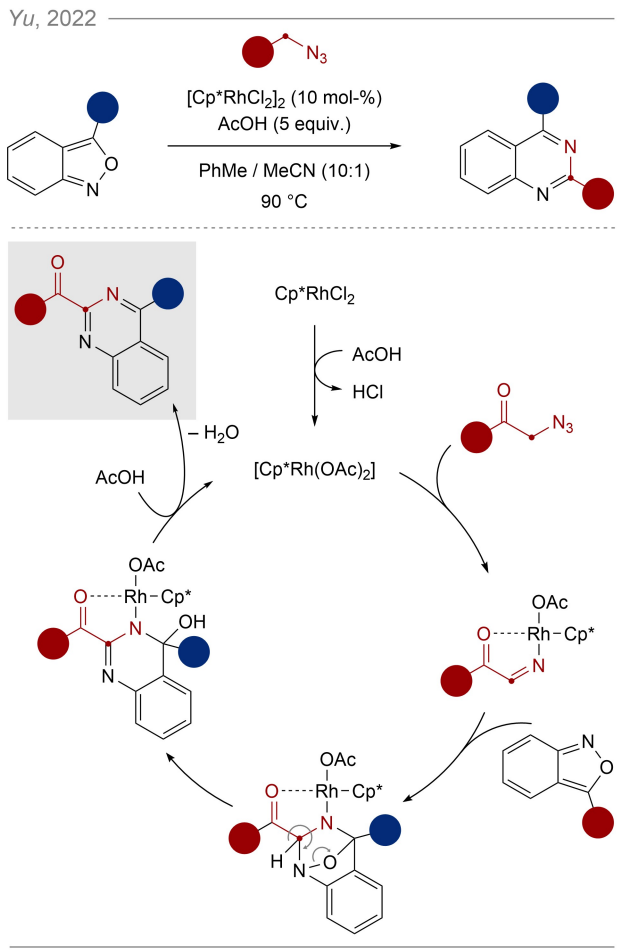
Diels–Alder reactions can also be applied to the conversion of pyrroles to benzene derivatives, in which ring expansion is accompanied by exchange of nitrogen for carbon (*Scheme 7,C*).[70] Specifically, [4+2] cycloaddition of 1-aminopyrroles with electron-deficient alkynes and subsequent extrusion of an aminonitrene affords the ring expanded benzenoid. This strategy can be applied to both simple and 2,3-fused pyrroles, but is very sensitive to the electronic properties of the substrate. It has been employed in the total synthesis of juncusol.[71]

The rhodium-catalyzed synthesis of quinazolines from benzisoxazoles was reported by *Yu* and co-workers in 2022 (*Scheme 8*).[72] Here, insertion of both a C- and an N-atom from a 2-azidoketone was accompanied by loss of an O-atom from the benzisoxazole substrate. The proposed mechanism involves the formation of a rhodium-bound ketoimine by loss of dinitrogen, prior to aza-[4+2] cycloaddition with the benzisoxazole. Subsequent ring opening breaks the N–O bond, then sequential protodemetallation and dehydration afford the ring-expanded product.

A photoredox catalyzed annulation of thiophenes to afford benzene derivatives was reported by *Chiang*, *Lei*, and co-workers in 2019 (*Scheme 9*).[73] This marks a significant practical advance on the thiophene transannulations reported previously under thermal[74] and UV-photolysis[75] conditions. While following a similar overall mechanism to the (is)oxazole and pyrrole *Diels–Alder* transannulations (*Scheme 7*), *Chiang* and *Lei*'s methodology is proposed to involve [4+2] cycloaddition of radical cation species (*Scheme 9,iii*). First, the excited acridinium photocatalyst undergoes single electron transfer (SET) with thiophene to generate a thiophenyl radical cation. A [4+2] cycloaddition affords an annulated radical cation, which is then reduced by SET from the photocatalyst. Extrusion of molecular sulfur from the cycloadduct affords the ring expanded arene. In addition to thiophenes, selenophenes were also shown to undergo the transformation with extrusion of atomic selenium.



Scheme 7. Ring expansion of 5-membered heterocycles through [4+2] cycloaddition. Expansion with exchange of an O-atom for two C-atoms utilizing: *A*) benzyne/isoxazole cycloaddition;[67,68] and *B*) cycloaddition/reduction of oxazoles and enamines.[69] *C*) Expansion of *N*-aminopyrroles with accompanying exchange of a N-atom for two C-atoms (Z = electron withdrawing group).[71]



Scheme 8. Ring expansion of benzisoxazoles through Rh-catalyzed cycloaddition with 2-azidoketones.[72]

3. Ring Contraction

As the direct opposite of ring expansion, ring contraction is accompanied by deletion of an atom from a given ring system. The deleted atom can either be removed from the molecule entirely or may remain tethered to the ring system (*Scheme 10*). As for ring expansions, ring contraction and deletion reactions are well known for carbonyl-containing compounds,[76] but are less well developed in aromatic systems.

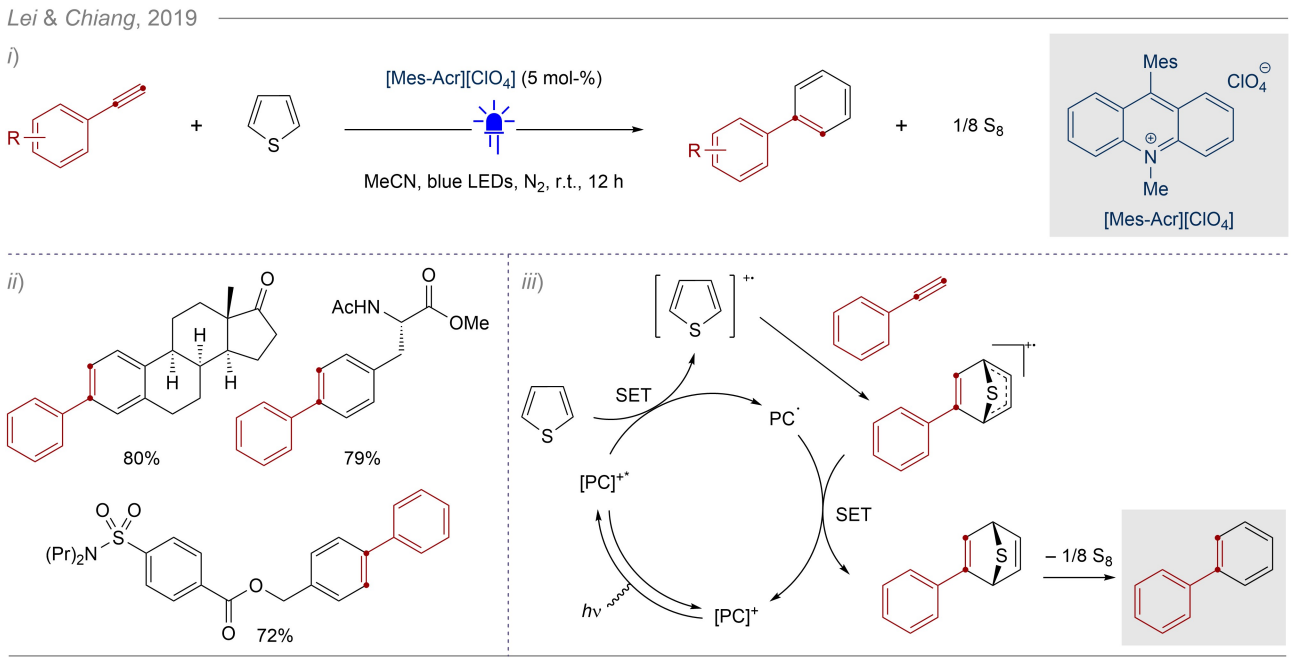
A prominent class of ring contraction is the conversion of quinoline *N*-oxides and *N*-amides to indoles through C-atom deletion. These reactions all proceed through an initial light-mediated ring expansion to a benzoxazepine or benzodiazepine (*Scheme 11,A*), with the former having been demonstrated in near-quantitative yields on multi-gram scales using flow photochemistry.[82] As discussed below, several different strategies have been developed to trigger the subsequent ring contraction.

In 1980, *Kaneko* and co-workers reported the ring contraction of benzoxazepines to 3-formyl indoles promoted by UV light (254 nm; *Scheme 11,B-i*).[77] 3-Methoxycarbonyl indoles could be accessed by photochemically or thermally promoted ring contraction of the analogous methyl oxazepine-5-carboxylates (*Scheme 11,B-ii*). The mechanistic pathways of these transformations – which proceed through sequential ring opening, cyclization and decarboxylation/deformylation – were discussed in detail.[77]

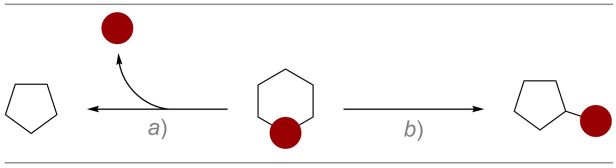
Kaneko and co-workers also demonstrated that the same benzoxazepine-5-carboxylate intermediates can be converted to oxindoles (*Scheme 11,B-iii*).[78] In this reaction, ring opening to a 2-benzamidoacrylate intermediate is triggered by the triethylamine-promoted attack of an alcohol. Deprotonation of the resulting amide with NaH, followed by condensation with the adjacent ester, affords the oxindole.

Despite the appeal of these early reports, their practical utility is limited by modest substrate scope and yields. However, in 2022 the ring contraction of quinoline *N*-oxides was generalized and optimized for a broad range of substrates by *Levin* and co-workers (*Scheme 11,C-i*).[79] By employing narrow-band 390 nm light, 2-substituted quinoline *N*-oxides could be transformed selectively into the corresponding 3,1-benzoxazepines without competition from deleterious two-photon processes. *In situ* acidolysis promoted both the ring opening and the subsequent ring contraction to form 1-acylindoles (*Scheme 11,C-ii*). The reaction was applied to a number of highly functionalized molecules, such as the leukotriene receptor antagonist montelukast (*Scheme 11,C-iii*) and was shown to tolerate different heterocyclic substrates including 1,8-naphthyridines and quinoxalines.

Like the *N*-oxides, quinoline *N*-amides undergo photochemically promoted ring expansion to the analogous benzodiazepines (*Scheme 11,D*).[80] *Tsuchiya* and co-workers reported that good yields were obtained for quinoline *N*-amides bearing electron-donating substituents at the 6- or 8-position, whereas electron-poor substrates suffered from deleterious N–N bond cleavage. The mechanism of ring expansion is proposed to involve initial formation of a 3-membered diazirane by attack of the exocyclic nitrogen onto C(2) of the quinoline, followed by N–N cleavage, aziridine formation and finally C–C cleavage to give the benzodiazepine.[83] Subsequent treatment of the benzodiazepine with aqueous HCl afforded the ring opened amido-enamine (*Scheme 11,D*); further



Scheme 9. Light-mediated transannulation of thiophenes to benzenes with mechanistic insight and representative functionalized examples.[73] Mes = 2,4,6-trimethylphenyl.



Scheme 10. Ring contractions *a*) involving complete excision of the deleted atom and *b*) extrusion of the deleted atom to a tethered side chain.

treatment with HCl and heating at 80 °C resulted in the formation of the 1-acyl indole.

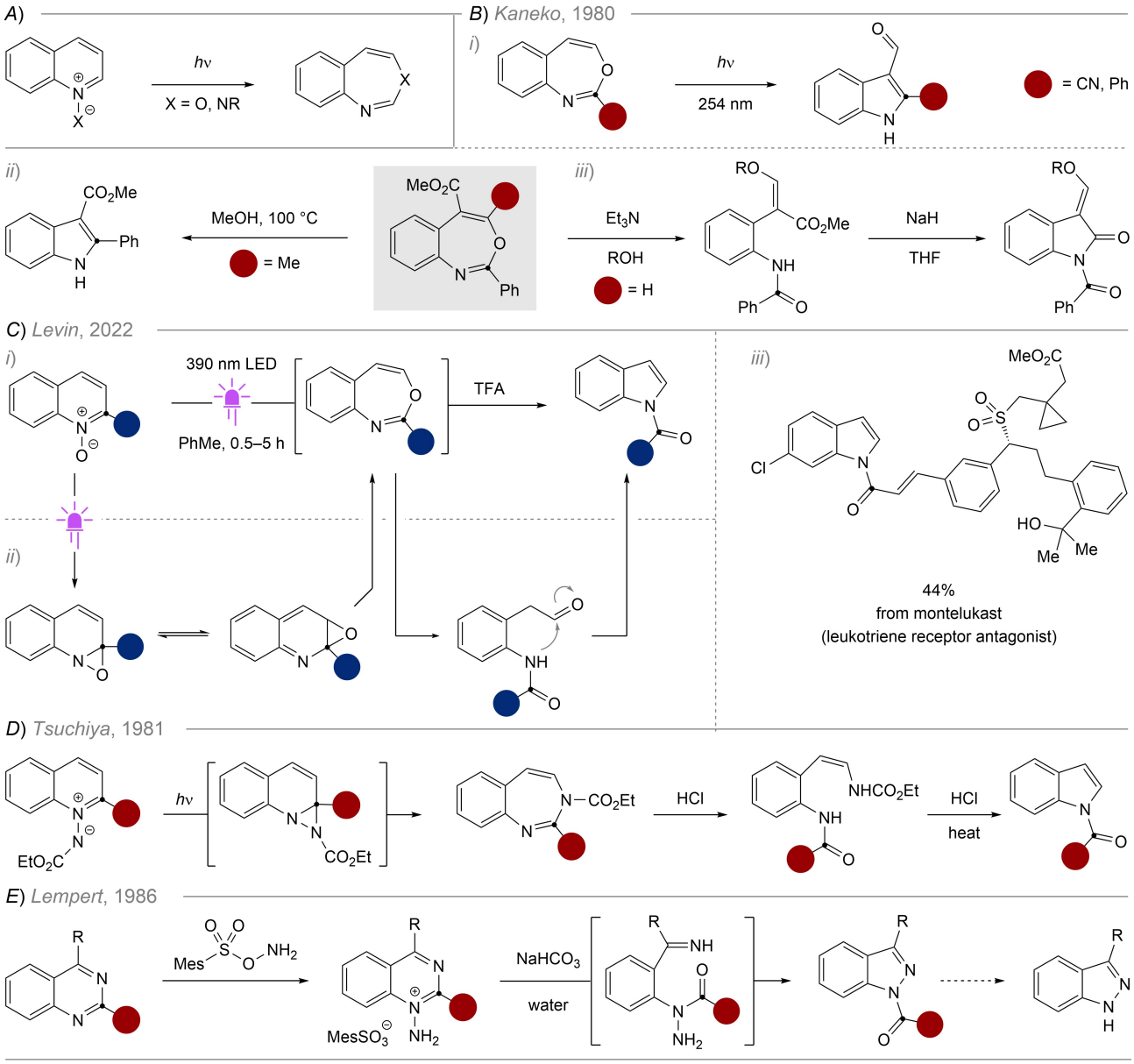
A similar ring-contraction strategy has been demonstrated for the conversion of quinazolines to indazoles (*Scheme 11,E*).[81] Oxidation to the 1-amino quinazolinium salt followed by hydrolysis led to a ring opened hydrazido imine. Cyclization with loss of ammonia formed the 1-acylindazole, prior to formation of the free indazole by *in situ* deprotection.

Ring contraction through C-atom deletion has also been reported by *Sarpong* and co-workers (*Scheme 12*).[84] This method transforms six-membered pyrimidines to five-membered pyrazoles by a ring opening/condensation strategy. Initial reaction with triflic anhydride activates the substrate towards nucleophilic attack from hydrazine. The subsequent intermediate then undergoes a [3,3]-sigmatropic rearrangement, resulting in a ring-opened species analogous to a *Zincke* intermediate. Tautomerization followed by ring closure gives the desired five-membered ring and rearomatization by expulsion of the amidine nucleofuge affords the pyrazole product. The reaction was found to tolerate a broad range of functional groups on both the pyrimidine core and peripheral groups and has been employed in the late-stage modification of drug molecules such as rivaroxaban and in the synthesis of an intermediate of functionalized celecoxib.

4. Atom Exchange

The final class of skeletal edit leaves the ring size unchanged but makes selective exchanges of atoms within the ring. It is therefore distinct from atom exchanges that accompany ring expansion or ring contraction processes (*cf. Sections 2* and *3*).

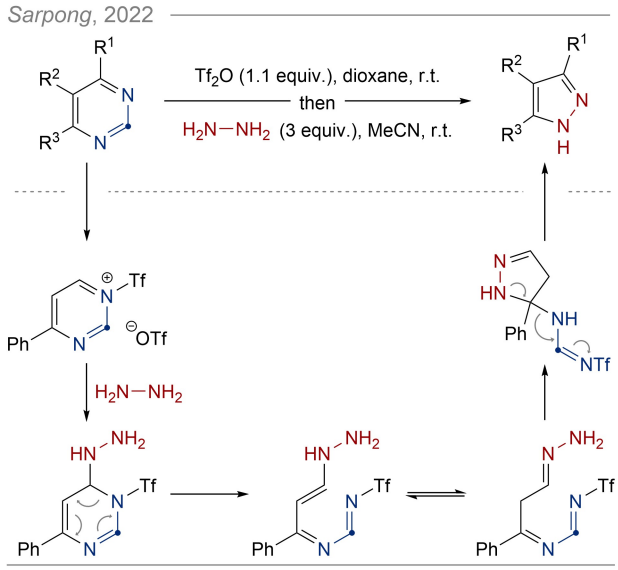
One of the most common atom exchange transformations made in aromatic systems is the formation of *Katritzky* salts by condensation of an amine with a pyrylium salt (*Scheme 13,A*).[90–93] *N*-Alkyl pyridinium salts prepared in this way have been widely used as precursors to alkyl radicals,[94] whereas *N*-aryl pyridi-



Scheme 11. Ring contraction strategies. *A*) Initial ring expansion of quinoline *N*-oxides/amides enables subsequent ring contraction. *B*) Light-mediated ring contraction of benzoxazepines to 3-formylindoles.[77,78] *C*) Ring contraction of quinolone *N*-oxides through benzoxazepines.[79] *D*) Ring expansion of quinolone *N*-amides to benzodiazepines and ring contraction to 1-acylindoles.[80] *E*) Ring contraction of quinazoline *N*-amides to indazoles.[81]

nium salts have been engaged in S_NAr processes that ultimately displace the aniline-derived nitrogen.[95,96]

Another well-established instance of atom exchange is the *Dimroth* rearrangement (*Scheme 13,B*).[85] In this case, rather than one atom being exchanged for a different element, one N-atom is typically exchanged for another N-atom already present in the molecule. There are two classes of *Dimroth* rearrangement: type 1 involves the ring opening of aminotriazoles to imidoyl-diazo compounds, in which rotation of the diazomethyl group and subsequent recyclization affords the atom-exchanged product (*Scheme 13,B-i*). Type 2 involves the exchange of exocyclic and endocyclic N-atoms in six-membered heterocycles (*Scheme 13,B-ii*). Type 1 rearrangements are typically promoted by heating, whereas type 2 rearrangements often require a nucleophilic base such as hydroxide or alkoxides to occur.



Scheme 12. C-Atom deletion of pyrimidines to pyrazoles by ring-opening/hydrazine condensation.[84]

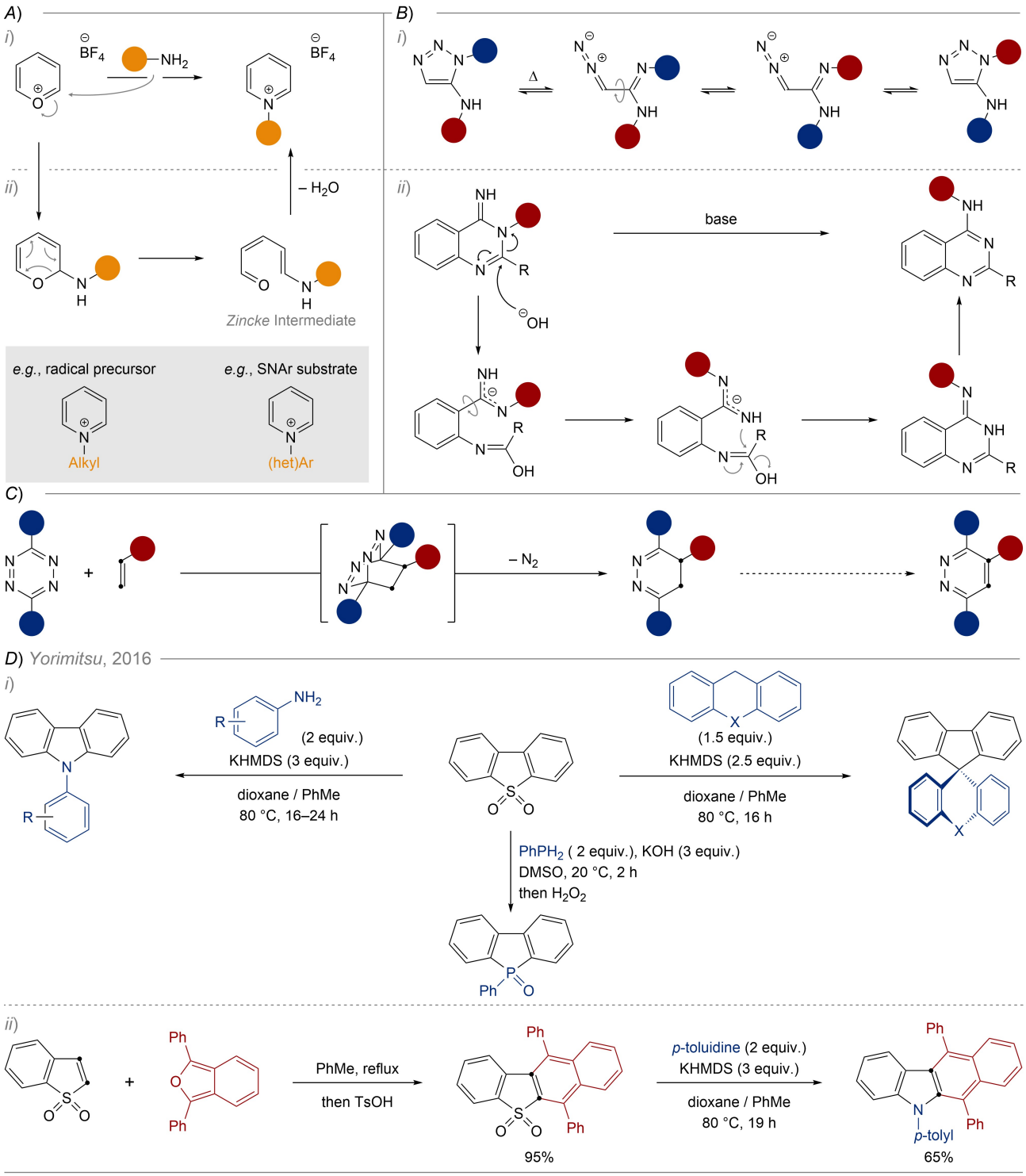
As discussed in the context of ring expansion chemistry, sequences of [4+2] cycloadditions/*retro*-cycloadditions allow for atom exchanges within aromatic ring systems. A common transformation of this type is based on the IEDDA reaction of tetrazines or triazines.[86] For example, reaction of a 1,2,4,5-tetrazine with an alkene or alkyne simultaneously exchanges two N-atoms for C-atoms (*Scheme 13,C*). If an alkyne is used as the dienophile, the immediate product is aromatic, and no additional oxidation step is required to reach the pyridazine. The IEDDA reactions of tetrazines have become powerful tools for bio-orthogonal functionalization of biomolecules,[97] and have been reviewed extensively elsewhere.[66,86,98] Similar in concept, 2-pyrones are able to undergo IEDDA reactions to exchange a C- and O-atom for two C-atoms with release of CO_2.[99,100]

Atom exchanges of dibenzothiophenes have been reasonably well developed,[101] as described in recent reviews.[102,103] For example, *Yorimitsu* and co-workers have reported a series of methods that rely on oxidation of a dibenzothiophene to the corresponding *S,S*-dioxide to enable sequential S_NAr displacement of the S-atom (*Scheme 13,D-i*).[87–89] By combining it with an initial *Diels–Alder* reaction between a 1,1-dioxobenzothiophene and an isobenzofuran, this strategy has been applied to the synthesis of π-extended carbazoles (*Scheme 13,D-ii*).[87]

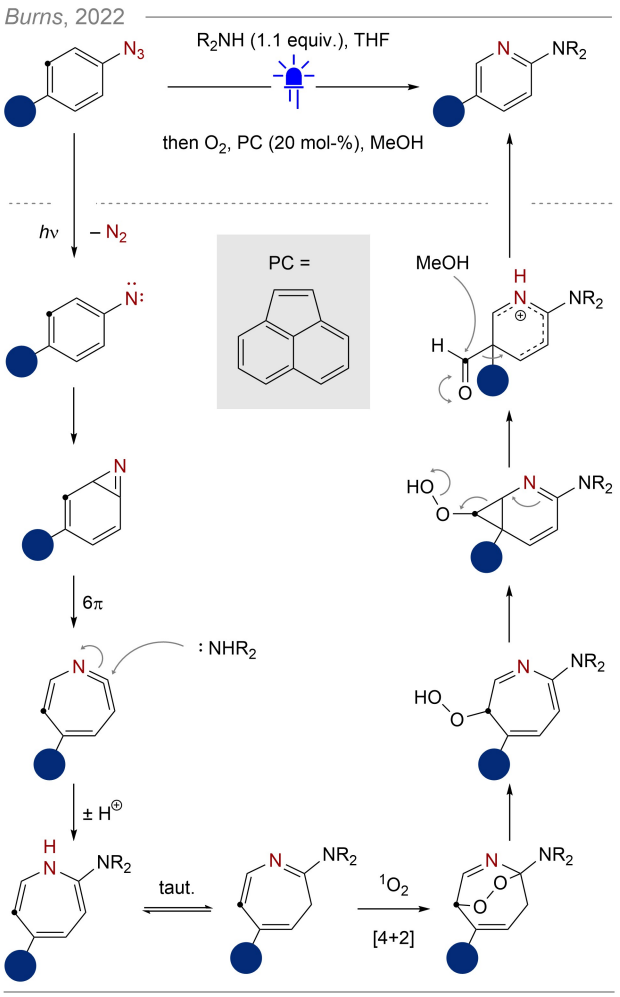
Recent work by *Burns* and co-workers reported the light-mediated conversion of aryl azides to aminopyridines, which represents formal exchange of a benzenoid C-atom for a N-atom (*Scheme 14*).[104] The reaction is based on the known ability of an arylnitrene – accessed here by photolysis of an arylazide – to insert into the adjacent arene π-bond, initially forming a strained 2*H*-azirine.[105,106] A thermal 6π electrocyclic ring opening affords a cyclic ketenimine that reacts with the amine additive, before tautomerism generates a stable 2-aminoazepine. The required ring contraction[107–110] is triggered by reaction with photochemically-generated singlet oxygen, which undergoes a [4+2] cycloaddition to give a peroxy-bridged intermediate. Subsequent ring opening gives the exocyclic peroxide and a 6π electrocyclization affords a *Wheland*-type intermediate that is quenched by solvolytic deformylation. Mechanistic investigations provided evidence for the *Wheland* intermediate as well as the selectivity for deletion of carbons *meta* to the initial azido group. The reverse N-to-C atom exchange with concomitant C–H amination was reported by *Morofuji*, *Kano* and co-workers in 2021 (*Scheme 15*).[111] Like in the O-to-N exchange of *Katritzky* salts, a key ring opened intermediate is required. This is achieved by quaternization of the pyridine substrate through S_NAr, followed by addition of a secondary amine to afford the ring opened intermediate. The key carbon insertion step is achieved by reaction with trimethylsulfinium ylide, providing an enamine which undergoes 6π electrocyclization. Elimination of an amine then affords the aniline product.

N-to-C atom exchange has also been reported by *Mindiola* and co-workers (*Scheme 16*).[112] The protocol employs as stoichiometric titanium complex (generated *in situ)* to insert into the aromatic skeleton, forming a seven-membered aza-titanacycle. Addition of TMSCl as an electrophile initiates release of a titanium-imide complex and insertion of the *tert*-butyl carbynyl group to form the aromatic carbocycle. The transient titanium alkylidene required for the insertion can then be regenerated over five steps.

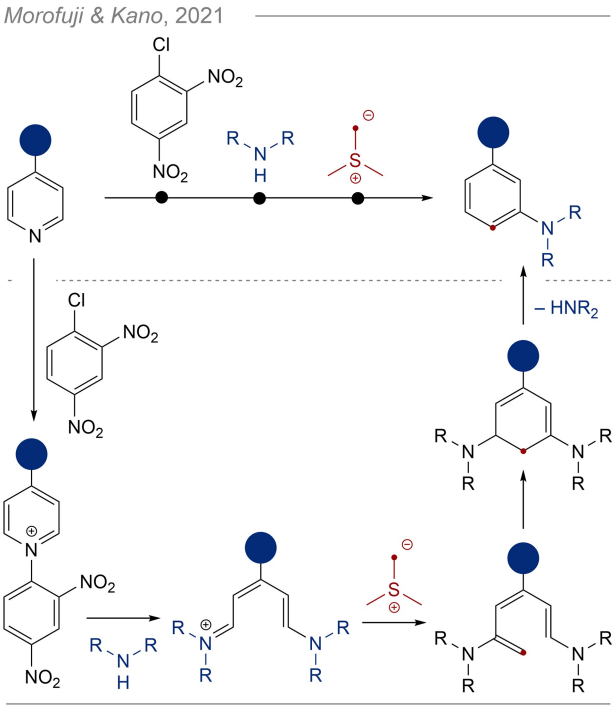
Another well explored class of atom exchange is the denitrogenative annulation of 1,2,3-triazoles and 1,2,3,4-tetrazoles (*Scheme 17*).[115] These compounds exist in an equilibrium of a closed- and open-form. It is from this open form that radical denitrogenation can occur in the presence of a metal catalyst such as cobalt-porphyrins. The resulting carbon- (for triazoles) or nitrogen-centered radical (for tetrazoles) can attack alkynes or nitriles that then cyclizes to give the atom-exchanged product. In addition to sp-centers, a copper-catalyzed variant employs primary amines or



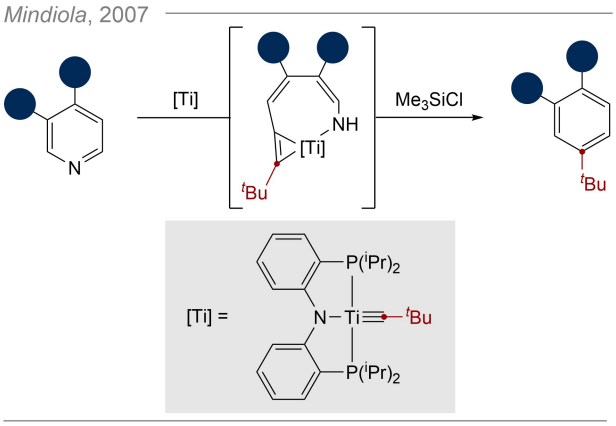
Scheme 13. Strategies for atom exchange. *A*) Synthesis of *Katritzky* salts and the proposed mechanism. *B*) Representative examples of the *Dimroth* rearrangement.[85] *C*) Inverse electron demand *Diels–Alder* (IEDDA) reaction of tetrazines.[86] *D*) S-Atom exchange of dibenzothiophene to carbazoles,[87] spirocyclic diarylfluorenes[88] and phospholes.[89]



Scheme 14. C-to-N-Atom exchange of phenylazides to aminopyridines.[104]



Scheme 15. Conversion of pyridines to anilines through N-to-C atom exchange.[111]

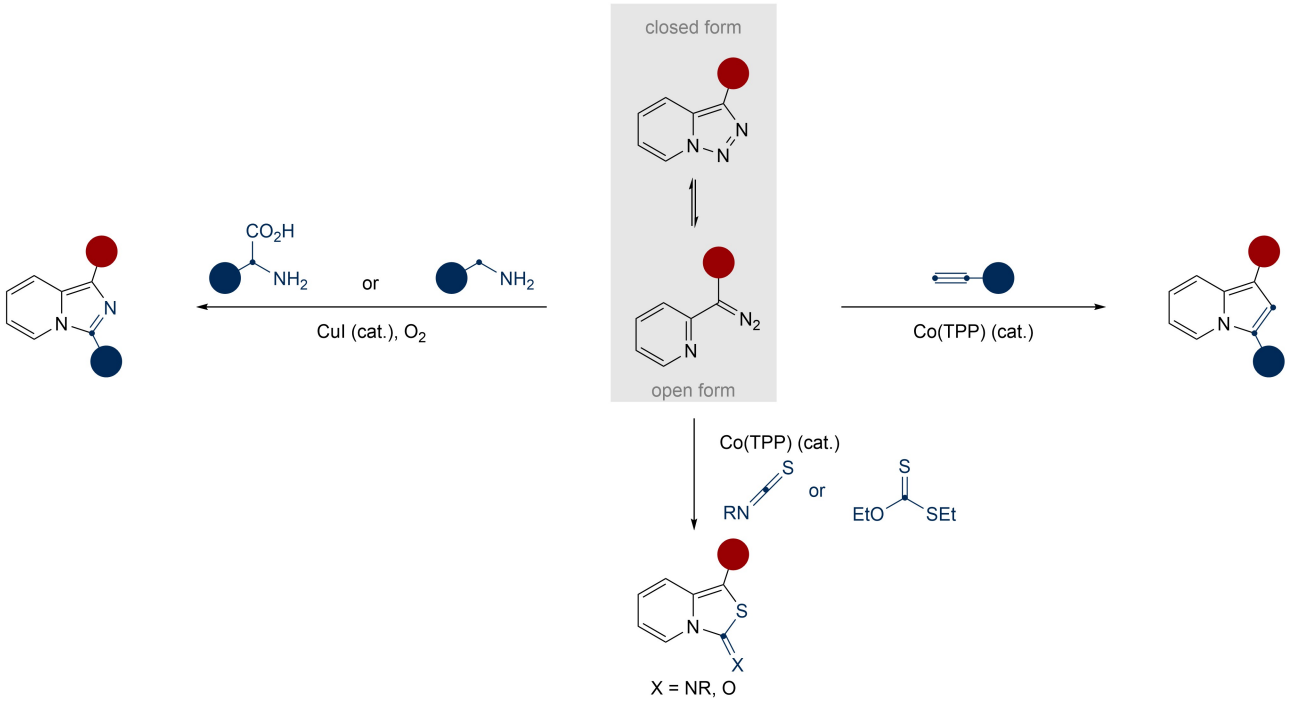


Scheme 16. Ti-mediated N-to-C atom exchange for the conversion of pyridines to benzenoids.[112]

amino acids to achieve atom exchange.[113] Isocyanates and isothiocyanates have also been employed as annulating agents.[114,117] In addition to radical methods, ionic pathways for this transformation have also been reported.[117]

5. Conclusions and Outlook

Despite only having entered the chemical lexicon in recent years, the term 'skeletal editing' can be applied retrospectively to numerous decades-old methodologies and encompasses the well-established concept of heterocycle interconversion.[18,19] As highlighted in this Review, there is a significant and ever-growing suite of strategies available for the skeletal editing of *aromatic* systems, whether by selective ring expansion, ring contraction or atom exchange. By building on historical foundations, recent works have made particular contributions to reaction scope and functional group tolerance and have increasingly demonstrated applicability to complex substrates. However, the litmus-test will be whether the emerging methods find independent application in target-oriented synthesis – for example total synthesis or drug discovery – such that



Scheme 17. Atom exchange through metal-catalyzed denitrogenative annulation of triazoles. TPP = tetraphenylporphyrin.[113–115]

the field can fulfil its potential as a powerful tool for rapid, site-specific molecular diversification.

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Data Availability Statement

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

Author Contribution Statement

B. J. and *L. B.* wrote and revised the manuscript.

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