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Single-atom logic for heterocycle editing

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Abstract

Medicinal chemistry continues to be impacted by new synthetic methods. Particularly sought after, especially at the drug discovery stage, is the ability to enact the desired chemical transformations in a concise and chemospecific fashion. To this end, the field of organic synthesis has become captivated by the idea of ‘molecular editing’—to rapidly build onto, change or prune molecules one atom at a time using transformations that are mild and selective enough to be employed at the late stages of a synthetic sequence. In this Review, the definition and categorization of a particularly promising subclass of molecular editing reactions, termed ‘single-atom skeletal editing’, are proposed. Although skeletal editing applies to both cyclic and acyclic compounds, this Review focuses on heterocycles, both for their centrality in medicinal chemistry and for the definitional clarity afforded by a focus on ring systems. A classification system is presented by highlighting methods (both historically important examples and recent advances) that achieve such transformations, with the goal to spark interest and inspire further development in this growing field.

Modern approaches to drug discovery are increasingly impacted by the development of novel synthetic methods, with motivations that arise from the ability to enact the desired chemical transformations in a concise and chemospecific fashion[1–3]. Such innovations provide the ability to circumvent traditional hurdles in drug development, especially those associated with the synthesis of derivatives of a promising lead at late stages. To this end, the field of organic synthesis has become captivated by the idea of ‘molecular editing’, which has metaphorical roots in macroscopic, digital technologies; for example, can we make synthesis as easy as ChemDraw?

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author contributions

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Competing interests

The authors declare no competing interests.

Although a clear definition of molecular editing remains elusive, tied up in this pursuit is the idea of being able to rapidly build and/or subsequently tolerate complexity—privileging those transformations that are mild and selective enough to be employed at late stages of a synthetic sequence or in the context of the total synthesis of complex natural products. As often occurs in burgeoning fields, the nomenclature has become muddled, with a veritable zoo of terms that claim to describe the ways in which our collective works can be organized. For molecules we have skeletons, frameworks, scaffolds, structural motifs and cores. For reactions we have editing, surgery, modification, remodelling, distortion, deconstruction, scaffold hopping and diversification. Despite the chemical precision that many of the pioneering contributions offer, precision of language has been slow to develop alongside these efforts. Indeed, the term ‘molecular editing’ itself is inherently vague. Strictly speaking, any chemical transformation is a molecular edit of one flavour or another, which leaves room for the criticism that this blossoming of nomenclature is unnecessary, or worse, intentionally obfuscatory.

Although we cannot single-handedly resolve the definitional issues of the field, our laboratories are intimately involved in such efforts, and therefore we aim here to instead propose the definition and categorization of a subclass of molecular editing reactions that we suggest are particularly fertile territory for the discovery of new, powerful chemical transformations: single-atom skeletal editing. In this Review, we demonstrate our classification system specifically for cyclic systems by highlighting methods (both historically important examples and recent advances) that achieve such transformations, with the hope to spark interest and inspire further development in this growing field.

Definitions

Any discussion of molecular or skeletal editing immediately raises several important questions, the answers of which define the boundaries of the task at hand. We propose several definitions here.

What constitutes a molecular skeleton?

Depending on the context, molecular editing either subsumes or stands in contrast to C–H functionalization. Most chemists probably agree that C–H bonds are not part of the molecular skeleton, but instead occupy peripheral sites of the molecule. As soon as one moves beyond hydrogen atoms, however, the situation becomes murkier. For example, is a primary amine peripheral? What about a secondary methylamine?

Rings offer a natural dividing line, wherein a skeleton is defined by a molecule’s cyclic system(s). In this dichotomy, we propose that a change in the component atoms that comprise a ring system constitutes skeletal editing, whereas the analogous modification to an exocyclic atom is better construed as peripheral editing (Fig. 1a). We favour such a definition because there is no unambiguous way to distinguish the skeleton of an acyclic molecule from its periphery, although a strategy akin to IUPAC nomenclature, wherein the longest chain of heavy atoms is privileged, may be used when necessary for such systems. Although modification of the heavy-atom chains in acyclic systems no doubt represents a similarly important challenge, in this Review we have chosen to focus on heterocyclic

compounds not only for the definitional line they enable, but also for their prevalence in both naturally occurring and anthropogenic bioactive small molecules[4–6]. As such, methods capable of directly modifying late-stage ring systems have the propensity to substantially impact lead optimization and analogue synthesis in medicinal chemistry[2].

What is a single-atom skeletal edit?

For ring systems, the scale by which the ring is modified offers further classification categories. As the carbon and nitrogen atoms themselves bear exocyclic (peripheral) substituents, a focus on the constituent atoms of the ring system again serves as a natural demarcation. Regardless of the number or size of the exocyclic substituents, the essence of a single-atom edit is that the ring system being modified is changed by one atom (an n-membered ring is converted to the $n + 1$ or $n - 1$ analogue; Fig. 1b). As we discuss in greater detail in the Outlook section, single-atom editing can also include 'transmutations' wherein one of the constituent atoms is exchanged for another. This focus on the synthetic logic enabled by such single-atom changes is deliberate, for two major reasons:

1. 'Editing' evokes precision. Single-atom changes represent the most elementary of possible changes to a molecular skeleton, with more complex changes possible, in principle, as the combination of multiple single-atom edits.
2. The retrosynthetic simplicity of single-atom logic is enabling. Rearrangements of molecular skeletons often suffer from being difficult to see in a retrosynthetic sense, which limits their adoption. Indeed, the most used reactions in medicinal chemistry (cross-coupling, amide bond formation, nucleophilic aromatic substitution and reductive amination) have a common retrosynthetic simplicity that, in addition to their broad scope, has propelled their implementation.

We note that the focus in this Review does not represent a value statement, but instead a constraint on the ensuing discussion—many molecular editing strategies not covered in this Review are of immense potential interest. For example, advances in multi-atom editing, C–H functionalization, metathesis, homologation of acyclic chains, ring cleavage, transannular bond formation or annulation are simply beyond the scope of this Review[7–14].

A classification scheme

Within single-atom skeletal editing, two major dividing lines can be drawn, which result in four general reaction classes. The first is straightforward as it depends on whether the ring system in question is expanded ($n \rightarrow n + 1$) or contracted ($n \rightarrow n - 1$). Within this classification, there remains a question of whether the atom being edited begins (or is retained, respectively) as an exocyclic substituent of the ring system. We refer to such transformations as rearrangements, subdivided into contraction and expansion. Juxtaposed, deletions and insertions (collectively called mutations) denote skeletal edits in which the edited atom is not directly attached to the ring system in question[15]. Fig. 1b (right) provides an overview of this classification scheme for a simple (hetero)cyclic ring system.

Carbonyl chemistry has historically dominated the development of these kinds of transformations, with many named reactions that enable the manipulation of cyclic ketones

in a precise fashion. Modern approaches have sought to expand the mechanistic and conceptual template of these pioneering examples to aliphatic and aromatic heterocycles. Accordingly, we seek below to highlight classical, carbonyl-based approaches as context for the selected recent advances in single-atom skeletal editing of heterocycles, as well as specific transformations that exemplify this emerging area.

As a number of the transformations described herein require multiple steps to achieve the overall single-atom skeletal edit, there are several instances in which the classification of a particular transformation could vary based on the defined starting and ending points. We note these cases where they arise in our discussion. Indeed, the ability to toggle between rearrangements and mutations is itself a problem of peripheral editing, which highlights the synergy between the two pursuits. Ultimately, our selected transformations should serve as an inspiration for the future development of analogous, one-step methods that could serve as powerful, ideal chemical transformations to enable molecular editing with single-atom precision.

n − 1 single-atom editing

Contractions.

For carbocyclic systems, anionic, carbene and cationic intermediates have all been classically employed to realize ring contractions of cyclic ketones[16]. A widely exploited reaction for carbocyclic ring contraction is the Favorskii rearrangement. In this reaction, treatment of α-haloketones with a base results in a skeletal rearrangement, which occurs through a cyclopropanone intermediate **2** (although this can be bypassed in some systems, for example, a quasi-Favorskii rearrangement[17]). Ultimately, the carbonyl motif undergoes an endo-to-exocyclic transposition, which gives rise to acyl *n* − 1 cycloalkane products (Fig. 2a, top). The utility of this transformation has been demonstrated in several natural product syntheses. For example, starting from a (+)-pulegone derivative, a Favorskii ring contraction forms the corresponding methyl cyclopentane carboxylate **4**[18]. This versatile intermediate has been further elaborated in the total syntheses of several terpenoid natural products, such as (+)-epoxydictymene by Schreiber and co-workers[19] and (−)-iridomyrmecin by Wolf and co-workers[20].

The benzilic acid rearrangement is another powerful method to achieve ring contractions (Fig. 2b). Treatment of cyclic α-diketones with a base triggers a rearrangement sequence initiated by the addition of the nucleophile across the C=O bond. Collapse of the resulting tetrahedral intermediate **5** and subsequent alkyl migration furnishes the corresponding ring-contracted cyclic α-hydroxy acid. This transformation has been applied toward the total syntheses of numerous natural products. In their 1996 synthesis of (+)-K252a, Stoltz and Wood used a stereoselective benzilic acid rearrangement to convert a precursor pyranoindolocarbazole **7** into the desired furanoindolocarbazole core (Fig. 2b, bottom left)[21]. More recently, Xie and co-workers demonstrated the synthetic applicability of this transformation in the total synthesis of (−)-isatisine A (Fig. 2b, bottom right)[22]. Here a biomimetic benzilic acid rearrangement converts indole glucoside **8** into the densely functionalized indole furanoside **9** upon contraction.

Recent advances have enabled similar ring-contraction rearrangements in non-carbonyl-containing ring systems. Saturated azacyclic systems, for example, can be induced via bicyclic quaternary ammonium intermediates to undergo a formal ring contraction following nucleophilic attack on an endocyclic electrophile[23,24]. Building on previous accounts by Suárez and co-workers[25,26], Sarpong and co-workers recently reported a photomediated ring contraction of acyl azacyclic scaffolds, wherein the nitrogen atom undergoes an endocyclic to exocyclic migration (Fig. 3a)[27]. Under a radical-polar-crossover manifold, irradiation of α-acylated **10** results in excitation and intersystem crossing to give **11** in the triplet state. A Norrish type II 1,5-hydrogen atom abstraction then affords the corresponding 1,4-diradical **12**, which undergoes a C–N bond fragmentation to generate tethered imine-enol **13**. The desired cyclopentane product is then formed following an intramolecular Mannich reaction. The versatility of this transformation was demonstrated by its application towards the late-stage remodelling of several biologically active small-molecule derivatives (Fig. 3a, **14**–**16**). This rearrangement was also rendered enantioselective with the use of chiral phosphoric acid derivatives—a combination of hydrogen-bonding and ion-pairing interactions leads to an organized transition state, and the chiral phosphoric acid backbone favours the attack on one enantio-face, which gives rise to (+)-**18** in up to a 90% e.e.

Photochemical transformations have also been successfully employed for the skeletal editing of aromatic heterocycles[28,29]. In particular, pyridine N-oxides undergo unique rearrangements on photoirradiation; Streith et al. reported a ring contraction rearrangement that affords 2-formyl pyrrole products (Fig. 3b, top left)[30]. Building on this precedent, Weber and Rohn demonstrated pyridinophane ring contractions to afford ketopyrrolophane and macrocyclic azirene products, albeit in low yields[31]. After reaction optimization, Harran and co-workers recently demonstrated the utility of this skeletal modification in their synthesis of the prodigi-nine alkaloid, (+)-marineosin A[32]. Mechanistically, excitation of the N-oxide generates the corresponding oxaziridine[33]. An ensuing electrocyclic ring expansion generates 1,2-oxazepine **24**. Under the photoirradiation conditions, excitation of **24** leads to N–O bond lengthening and subsequent nitrene formation, which then undergoes a 1,5-electrocyclization and tautomerization to provide ketopyrrolophane **23**. A competitive 1,3-electrocyclization process forms the corresponding azirene, which was converted into lactam **21** on silica gel chromatography. Under the reaction conditions, the in situ generated azirine was also reported to be unstable, and was converted into bicyclic pyrrole **22** after rearrangement through a nitrile ylide intermediate, which could then cyclize to give the observed product[34,35]. The unique photoreactivity of such heteroaromatic N-oxides was also applied in photo-Dimroth-like rearrangements of pyridazines (not shown), which further highlights the versatility of these photoinduced ring-opening processes to achieve dramatic skeletal editing through formally contractive rearrangements[36].

Deletions.

The formal deletion of a single, selected atom from a cyclic skeleton to afford ring-contracted products can conceptually (and chemically) be related to ring-contraction rearrangements by removal of the extruded exocyclic substituent. For carbonyls, in an extension of the Favorskii rearrangement discussed above, decarboxylation of the rearranged substrates affords ring-contracted products in which the carbonyl carbon of the starting

material is excised from the skeleton (Fig. 4a). This sequence to achieve ring contraction by formal atom deletion (specifically, contraction followed by removal of the resulting peripheral substituent), was elegantly applied in the first synthesis of cubane by Eaton and Cole in 1964. In that case, treatment of α-bromoketone **27** with potassium hydroxide effected the Favorskii rearrangement to afford cuban-ecarboxylic acid **28**. Conversion into the related *t*-butyl perester **29** facilitated a subsequent thermal decarboxylation, and ultimately generated cubane on overall deletion of the highlighted carbon (Fig. 4a)from the skeleton[37,38].

Alternatively, carbonyl carbon deletion can also be achieved directly (Fig. 4b). Photodecarbonylation of carbocycles that bear photoreactive carbonyl groups flanked by fully substituted sp^3-hybridized carbons constitutes a carbonyl deletion that can stereoselectively forge contiguous all-carbon quaternary centres[39]. Irradiation of cyclic ketones affords diradical intermediates **30** that can undergo a Norrish type I fragmentation, loss of CO and subsequent radical recombination (**31**) to produce ring-contracted products wherein the original carbonyl carbon is excised from the cyclic skeleton. An early report of this kind of decarbonylative ring contraction was discussed by Nicolaou et al. on the observation of an unexpected ring-contracted side product during their total syntheses of several hamigeran natural products[40]. Subsequently, this chemistry was developed as a solid-state photodecarbonylation method by Garcia-Garibay and co-workers, and then applied in the total syntheses of (±)-herbertenolide[41], (+)- and (−)-α-cuparenone[42], and various piperidinoindoline bis(cyclotryptamine) alkaloids, which included psychotriadine[43,44]. In a similar vein, Xie and co-workers reported an oxidative deformylation ring contraction (not shown) that affords related ring-contracted products on the treatment of α-formyl cyclic ketones with hydrogen peroxide[39].

Efforts to develop skeletal editing tools have extended the ability to delete an atom from cyclic systems beyond carbocyclic frameworks that contain a carbonyl functional handle. In 2018, Sarpong and co-workers developed a method that formally achieves the deletion of a single carbon from saturated nitrogen heterocycles, such as piperidines (Fig. 5a)[45]. In the proposed mechanism, persulfate oxidizes a ligand-bound Ag(I) to Ag(II) and subsequently disproportionates into a sulfate dianion and sulfate radical anion. Saturated *N*-Bz protected cyclic amines then undergo hydrogen-atom transfer with the sulfate radical anion to afford an α-amino radical that is further oxidized to the iminium ion by Ag(II). This iminium ion intermediate is then trapped by H_2O to afford a hemiaminal species, which, on equilibration to the aldehyde and oxidation to the carboxylic acid, undergoes silver-catalysed decarboxylative bromination to afford an acyclic bromoamide that possesses one less carbon atom. In a subsequent step, this ω-bromoamide can undergo base-promoted intramolecular cyclization to furnish ring-contracted amine products (a lower-yield one-pot process is also possible). This formal carbon deletion strategy was demonstrated on a series of simple cyclic amines, which ranged from substituted piperidines (to yield **34**) to azepanes (to yield **35**)[45].

Single-atom nitrogen deletion from saturated azacycles is also highly desirable, particularly because such deletion transformations would turn ubiquitous C–N bonds into surrogates for the formation of C–C bonds[46]. Levin and co-workers recently disclosed a method that deletes nitrogen from secondary aliphatic amines under mild conditions in a single step

to yield ring-contracted, intramolecular carbon–carbon coupling products (Fig. 5b, top)[47]. In this system, nucleophilic substitution of electrophilic *N*-pivaloyloxy-*N*-alkoxyamides (anomeric amides) by secondary amine substrates followed by reductive elimination of $ArCO_2Bn$ affords isodiazene intermediates that extrude dinitrogen to produce highly reactive diradical species **37** that couple intramolecularly to form a new C–C bond between the carbons originally bound to nitrogen. Not only does this transformation exhibit a high functional group tolerance, nitrogen deletion was also successfully applied towards the synthesis of the marine metabolite polysiphenol, and utilized in the late-stage skeletal editing of several bioactive compounds, which included **38** (giving rise to an H_3 receptor modulator precursor) and the advanced glycation endpoint inhibitor tenilsetam (to afford **39**)[47].

Lu and co-workers have also reported a method for N-atom deletion from azacycles, wherein treatment of secondary amines with $N_3SO_2N_3$ produces sulfamoyl azide intermediates (Fig. 5b, bottom)[48]. After purification, these isolated sulfamoyl azide species **40** undergo Curtius-type rearrangements on treatment with *t*-BuOLi at 120 °C to generate 1,2-diazene intermediates that subsequently extrude dinitrogen to afford the ring-contracted products over two steps. More recently, Antonchick and co-workers reported an approach to access the same intermediates through in situ generated iodonitrenes at 80 °C[49]. Notably, the complementary oxygen deletion under reductive conditions was reported by Cao and Shi in 2017, but this transformation, to date, has only been demonstrated on acyclic dibenzyl ethers[50].

Methods that accomplish ring contractions are powerful for manipulating heterocycles. Although we have highlighted selected examples that involve nitrogen, general transformations that involve other heteroatoms and carbocyclic systems hold substantial promise moving forward.

n + 1 single-atom editing

Expansions.

Exocyclic substituents have been widely employed in carbonyl chemistry to achieve ring expansions. Common reaction pathways involve semi-pinacol-like expansions, wherein cyclic tertiary carbinols with exocyclic leaving groups undergo the incorporation of the exocyclic methylene and formation of a carbonyl group[51]. Related to carbonyl-specific transformations, the Dowd–Beckwith rearrangement (Fig. 6a, top) homologates cyclic ketones through the generation of the exocyclic β-radical **42** from the corresponding halomethyl compound **41**, which typically requires an additional ester substituent for high yields[52,53]. As noted in the introduction, the classification of this transformation depends on the defined starting point. Starting from α-halomethylated compound **41**, the ring-expanded γ-keto ester product constitutes a ring expansion, whereas defining the beginning of this transformation as the β-keto ester prior to halomethylation renders the overall transformation an insertion (see below). Both six- and seven-membered β-keto esters can readily undergo ring expansions to the seven- and eight-membered γ-keto esters, albeit with somewhat limited functional group tolerance. The Dowd–Beckwith rearrangement was notably applied as a key retrosynthetic disconnection in the total synthesis of salvileucalin C, wherein the

[5,6]-bicycle framework **45** was prepared by expanding the five-membered β-keto ester precursor **44** (Fig. 6a, bottom)[54].

Dong and co-workers developed an analogous ring expansion that does not require a halogen atom for initiation (Fig. 6b)[55]. Insertion of a rhodium catalyst into benzocyclobutenones **46** and subsequent β-hydride elimination generates the key metal hydride–olefin complex **47**, which undergoes migratory reinsertion of the hydride to afford the expanded metallocycle **48** and ultimately a ring-expanded product[55]. This transformation facilitates an exo-to-endocyclic carbon atom incorporation, allows for ring expansion to occur with a net 1,2-hydrogen migration and also demonstrates an excellent regioselectivity for the formation of α-substituted indanones.

The template exemplified by the carbonyl-based transformations was expanded to other classes of heterocycles. The Wengryniuk group reported the ring expansion of benzylic tertiary alcohols through the action of bis(pyridine)-ligated I(III) dications[56]. Subsequent treatment of the resulting hexafluoroisopropanol ketals **50** with triethylsilane under Lewis acid conditions affords the ring-expanded cyclic ethers over two steps (Fig. 7a). Similar rearrangements for primary benzylic amines were reported by Murai and co-workers—providing access to cyclic amines (Fig. 7a, bottom)—and for aminal derivatives on treatment with *N*-halosuccinimides to afford cyclic amidines through nitrogen-insertion rearrangements (not shown)[57].

Aromatic systems can also undergo ring expansion through migrations that involve reactive unsaturated species, such as carbenes and nitrenes. Beeler and co-workers recently reported a photochemical Stevens-like rearrangement of in situ generated pyridinium ylides to afford azepine derivatives in flow (Fig. 7b)[58]. This transformation is part of a larger class of related aromatic nitrene and carbene chemistry, some of which proceeds thermally, and includes the formation of related azepines from arylnitrenes[59–63].

Insertions.

Perhaps the widest assortment of classical carbonyl rearrangements falls into this last category, atom insertions, with notable entries such as the Bayer–Villiger, Tiffaneau–Demjanov, and Schmidt reactions. The Beckmann rearrangement (Fig. 8a), reported in 1886, is particularly notable given its modern applications[64]. Indeed, the classical synthesis of caprolactam from cyclohexanone is still employed on a multiton scale (it accounts for around 90% of the global demand for Nylon)[65]. At the opposite end of the complexity scale, another notable example is the synthesis of azithromycin, the first 15-membered macrolide antibiotic. In 1980, azithromycin was synthesized from erythromycin A by PLIVA Laboratories using a Beckmann rearrangement followed by reduction and concomitant reductive methylation, which led to an increase in the overall potency and half-life of the resulting compound (azithromycin) compared with that of the parent macrolide[66].

Again, here the classification of this transformation is dependent on the defined starting and ending points. If the oxime **51** is isolated and defined as the beginning of the transformation, the rearrangement process can be construed as an expansion rather than as an insertion process of the cyclic alkanone.

Cyclopropanation with halocarbenes offers an alternative approach for bimolecular insertion. In this vein, Conia and co-workers reported in 1976 the ring expansion of cyclohexanone-derived silyl enol ethers **53** using dibromocarbene generated in situ from bromoform and potassium *tert*-butoxide[67]. Ring opening of the intermediate dibromocyclopropane **54** under acidic or thermal conditions led to the formation of α-bromo-α,β-unsaturated ketones (Fig. 8b, top). Dibromocarbene was also reported to react with enol ethers[68,69], enamines[70] and enol acetates[71] to produce ring-expanded products in varying yields. Recently, Gaich and co-workers employed a similar approach en route to an asymmetric synthesis of (+)-pepluanol A[72]. Synthesis of the key seven-membered enone **56** was realized from the carene-derived silyl enol ether **55**.

In contrast to these carbonyl-based transformations, single-atom ring expansions in other settings remain relatively rare. In 1881, Ciamician and Dennstedt reported the ring expansion of pyrroles to give 3-halo-pyridines using haloform as a carbynyl cation equivalent[73]. Despite its potential, the reaction is limited by poor yields and a low functional group tolerance, due in part to the competitive Reimer–Tiemann formylation[74]. Recently, a variant of this transformation was reported by Levin and co-workers in which aromatic chlorodiazirines were used as alternative, isolable and stable carbynyl cation equivalents, which gave direct access to 3-arylpyridine and quinoline motifs from the corresponding pyrroles and indoles, respectively, in moderate-to-good yields and with a wide functional group tolerance (Fig. 9a, top)[75]. The requisite chlorodiazirines can be accessed in a single step by Graham oxidation of commercially available amidinium salts[76].

The potential of this transformation was further demonstrated by ring expansion of a protected tryptophan (to yield **58**), and a 2,3-fused indole cyclophane (to afford **59**), as well as late-stage skeletal editing of *N*-des-alkyl Lipitor (to provide **60**). Dai and co-workers employed the classical Ciamician–Dennstedt ring expansion as a key step in their synthesis of complanadine A, transforming a pyrrole **61** into pyridine **62**[77]. Notably, this tactical decision took an electron-deficient (electrophilic) pyridine back to an electron-rich (nucleophilic) pyrrole in their retrosynthesis and enabled transformations that would have been impossible (for example, Mannich-type cyclization) in the forward direction with the electron-deficient heterocycle (Fig. 9a, bottom).

Cleavage of alkyl ether bonds typically requires harsh and strongly acidic conditions (for example, BBr_3, HBr or HI). Recently, Dong and co-workers described an elegant approach for boron insertion into C(sp^3)−O bonds in the presence of a nickel catalyst and zinc reductant through a ‘cleavage-then-rebound’ pathway[78]. Notably, the versatility of the resulting boronic esters **63** was leveraged for subsequent one-carbon homologation (with a net two steps, Fig. 9b).

Outlook

For single-atom logic to reach its full potential, each of the four classes of transformations detailed above must be developed to a level of maturity that enables context-independent deployment. That is, the toolbox will only be complete once chemists have control of editing at the single-atom level in both aromatic and aliphatic ring systems at any given position and

with complete selectivity. Although carbonyl chemistry has served, and continues to serve, as a useful guide in the development of such reactions, non-traditional reactivity manifolds will clearly need to be embraced if this collective outcome is to be realized (Fig. 10).

It is also evident in many of the above examples that the challenge of skeletal editing to date has often required resorting to multistep sequences. Although some of these pioneering efforts could not have been accomplished without such a concession, the development of single-step (or single-operation) transformations is imperative for the broad adoption of single-atom editing. The deletion of carbon atoms from *N*-benzoyl piperidines discussed above, for example, suffered substantial yield losses when telescoped to a single operation due to competitive reactivity with by-products of the first step[45]. There is no doubt that continued development will overcome this challenge.

Finally, in addition to $n + 1$ or $n - 1$ skeletal editing, the ability to maintain the ring size while replacing one atom in a ring system with another represents, in many ways, the ultimate goal of skeletal editing. Such transmutations, once more broadly developed, would enable the direct interrogation of shape-conserving structure–activity relationships of the kind central to modern medicinal chemistry (Fig. 10b). Indeed, the so-called ‘necessary nitrogen effect’ has prompted lead optimization campaigns to conduct ‘nitrogen scans’, wherein carbon atoms of a lead scaffold are replaced by nitrogen (for example, **67** to **68**); this endeavour requires tedious resynthesis (often re-engineering the synthetic route altogether) to access the aza-analogues of the lead molecule[79]. The reverse nitrogen-to-carbon transmutation has also been employed successfully in drug discovery, as exemplified by the discovery of the indole-containing polyadenosine diphosphate ribose polymerase inhibitor rucaparib from benzimidazole precursor **69**[80].

Although such transmutations have yet to be achieved in a broadly applicable way, the literature holds promising examples of this chemistry using stoichiometric organometallic complexes (such as **70**), as well as some multistep approaches (for example, **74** to **76**) that achieve such transformations in a formal sense (Fig. 10c)[81,82]. In a similar vein, the boron insertion developed by the Dong group, discussed above, also enables a three-step net oxygen-to-nitrogen replacement (Fig. 10d, **77** to **79**). Although these initial reports are extremely exciting and provide a foundation for future investigation, substantial work remains to be done: we highlight in Fig. 10 a small selection of ‘dream reactions’, which embody the spirit of our call-to-action here. These transformations (which include transmutations and heteroatom scans) can all, in principle, be accomplished through a combination of the transformation classes discussed above or, more tantalizingly, in a single transformation. At that point, single-atom logic will have truly reached maturity.

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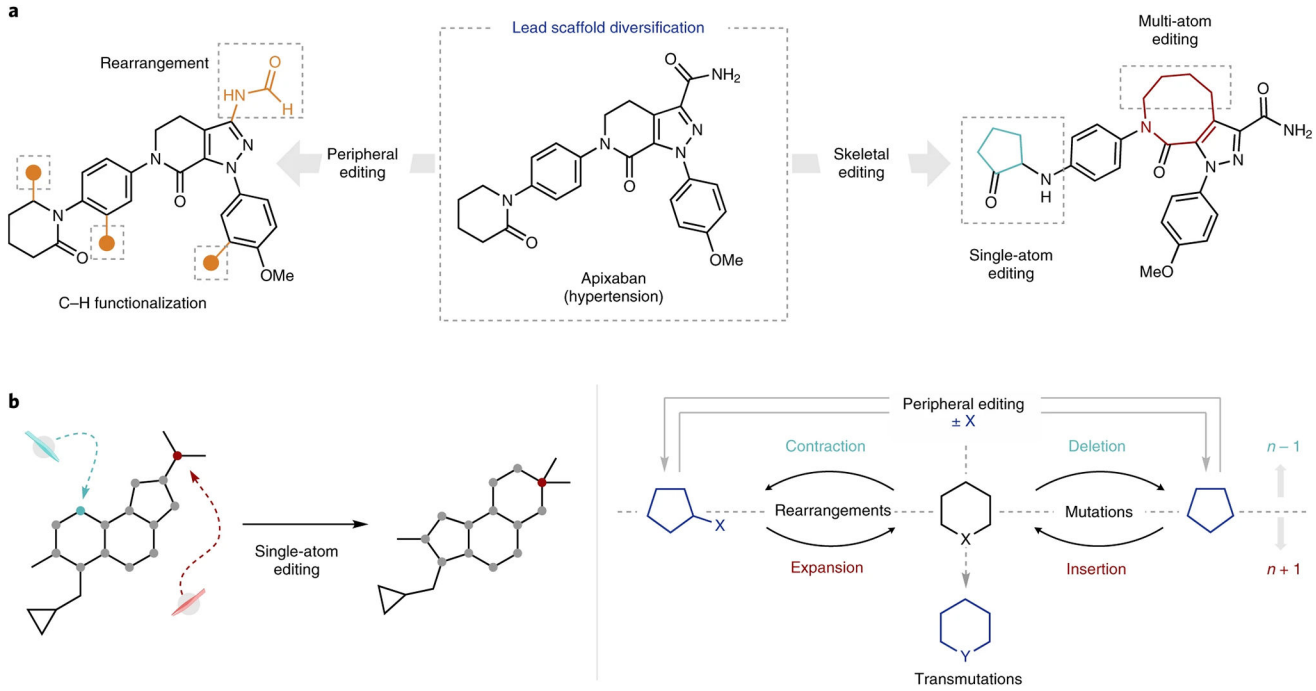

Fig. 1 |. Definition and classification of single-atom molecular editing.

a, The anatomy of molecular editing. Examples of peripheral editing (left) and skeletal editing (right) conceptually applied towards the diversification of apixaban. **b**, Classification of single-atom editing. A depiction of single-atom editing applied to a representative molecule (left) and the related classification scheme (right).

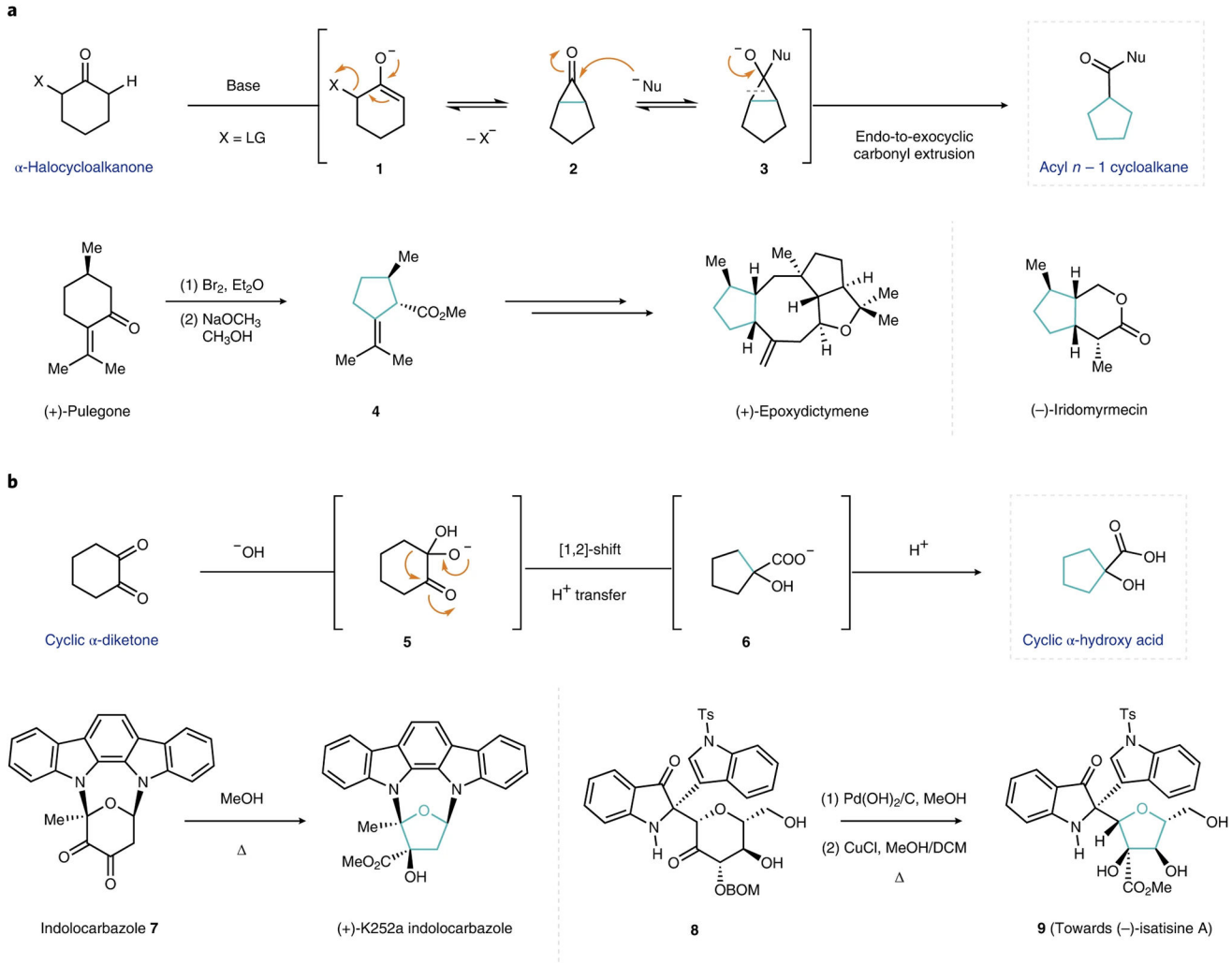

Fig. 2 |. Ring contractions that leverage classical carbonyl chemistry.

a, General reaction mechanism for the Favorskii rearrangement reaction (top) with synthetic applications demonstrated in the syntheses of (+)-epoxydictymene[19] and (−)-iridomyrmecin[20] (bottom). **b**, General reaction mechanism for the benzilic acid rearrangement reaction (top) and applications towards (+)-K252a[21] and (−)-isatisine A[22] (bottom). Contracted rings are highlighted in blue for clarity. LG, leaving group; Nu, nucleophile; DCM, dichloromethane; BOM, benzyloxymethyl acetal group; Ts, *para*-toluenesulfonyl group.

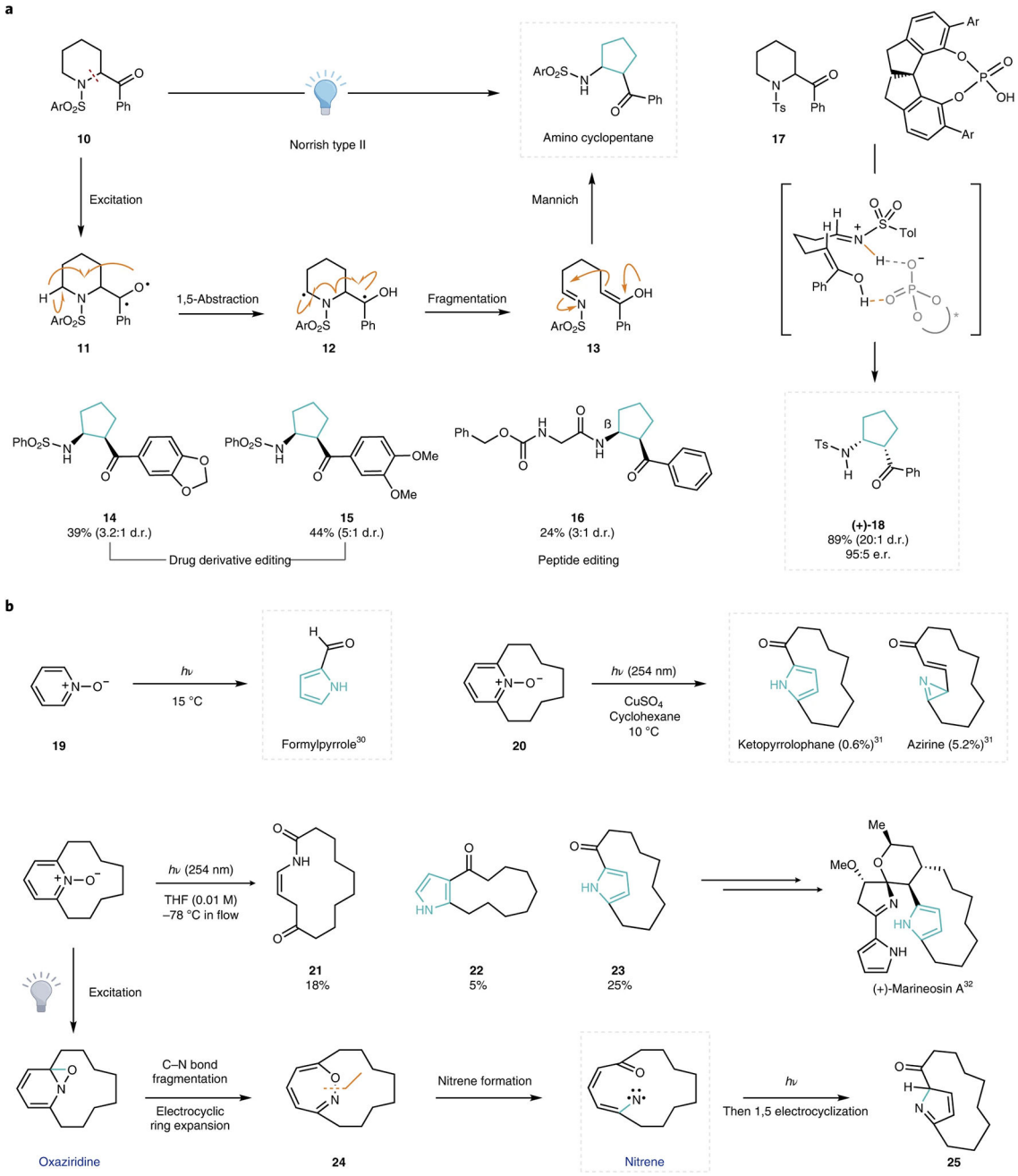

Fig. 3 |. Select developments in single-atom ring contractions of heterocycles.

a, Photomediated ring contractions of acyl piperidine scaffolds[27]. **b**, Photochemical ring contractions of pyridine N-oxides[30–33]. Contracted rings are highlighted in blue for clarity. d.r., diastereomeric ratio; e.r., enantiomeric ratio.

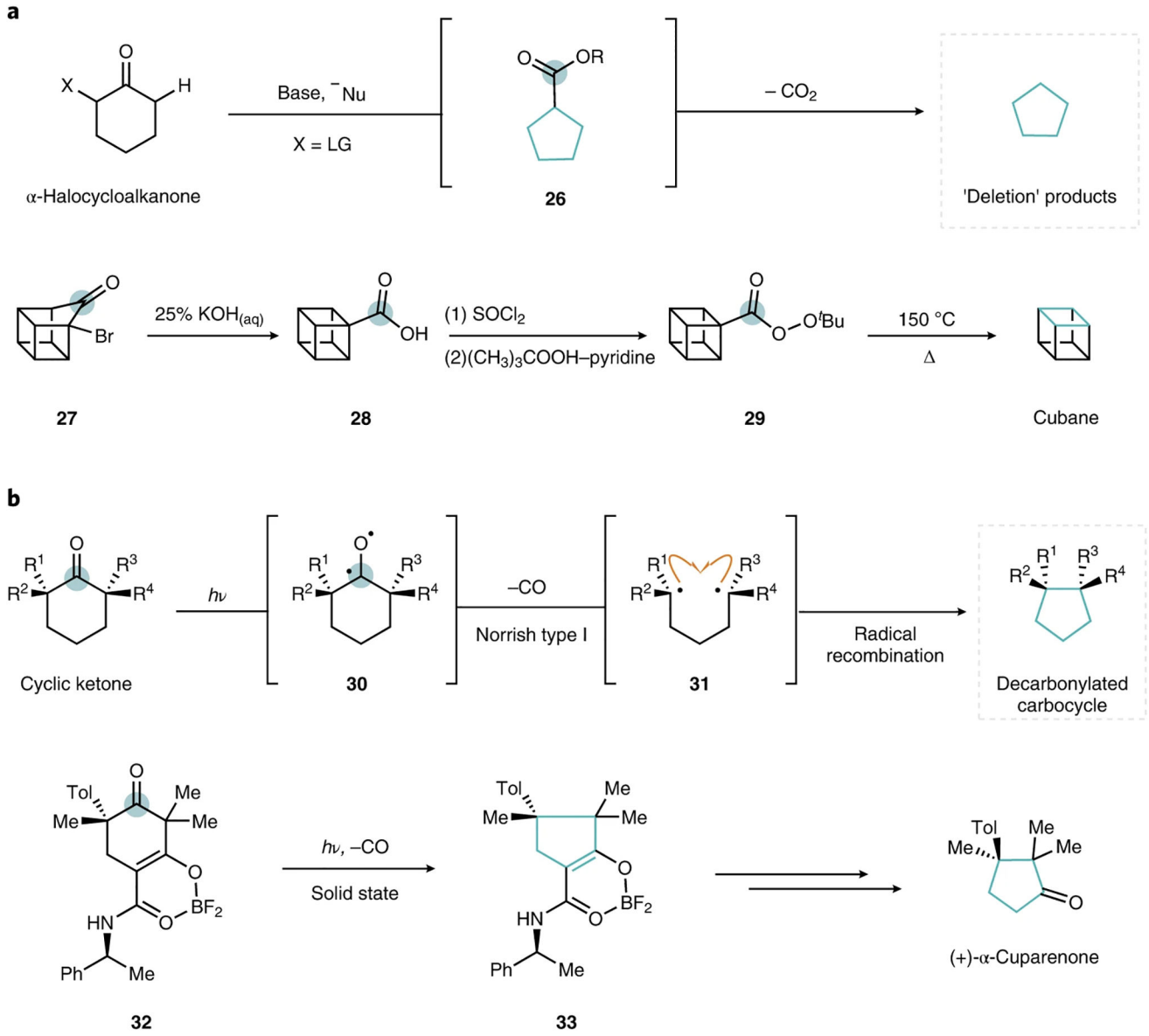

Fig. 4 |. Single-atom deletions that leverage carbonyl chemistry.

a, General reaction mechanism for the Favorskii rearrangement reaction and decarboxylation (top) with the application demonstrated in the synthesis of cubane[37,38] (bottom). **b**, General reaction mechanism for photodecarbonylation (top) and the application towards (+)-α-cuparenone[42] (bottom). Deleted carbon atoms are circled, and contracted rings are highlighted in blue for clarity. Tol, tolyl group.

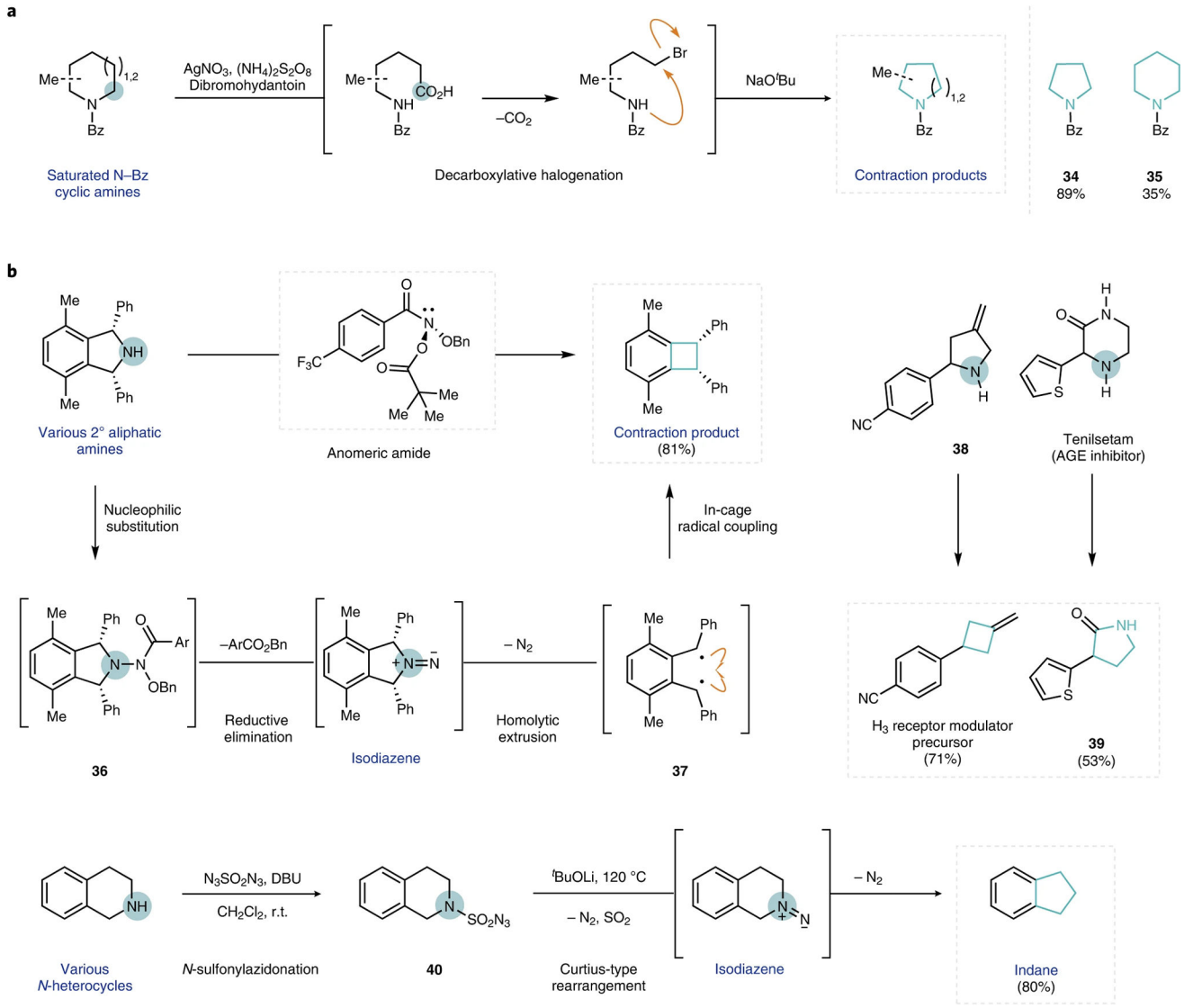

Fig. 5 |. Select developments in single-atom deletions from nitrogenous heterocycles.

a, Representative examples of a carbon deletion reaction in nitrogen heterocycles[45]. **b**, Representative examples of nitrogen deletion reactions applied to azacyclic frameworks[47,48]. Deleted atoms are circled, and contracted rings are highlighted in blue for clarity. AGE, advanced glycation end product; DBU, diazabicycloundecene. r.t., room temperature.

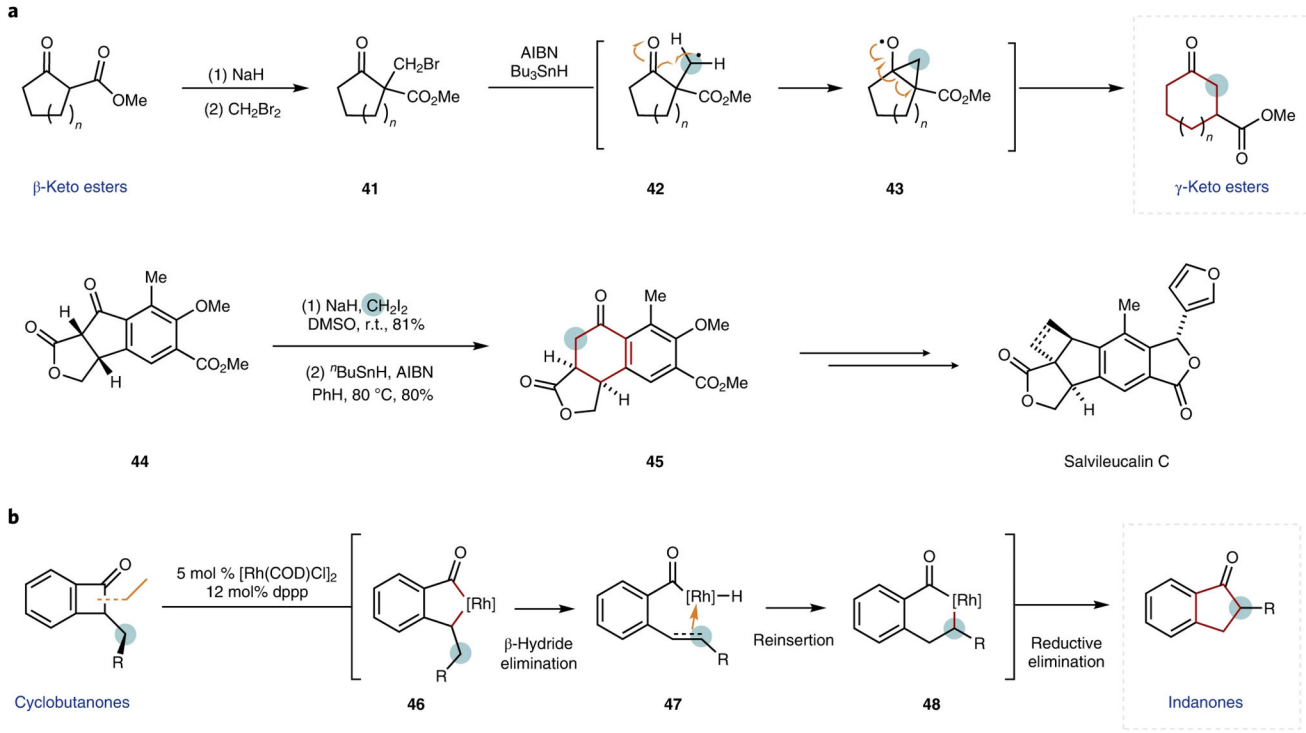

Fig. 6 |. Ring expansions that leverage carbonyl chemistry.

a, General reaction mechanism for the Dowd–Beckwith rearrangement reaction[52] (top) with application demonstrated in the synthesis of salvileucalin C[54] (bottom). **b**, Representative example of a rhodium-catalysed cyclobutanone rearrangement[55]. Expanded rings are highlighted in red for clarity. AIBN, azobisisobutyronitrile; COD, 1,5-cyclooctadiene; dppp, 1,3-bis(diphenylphosphino) propane.

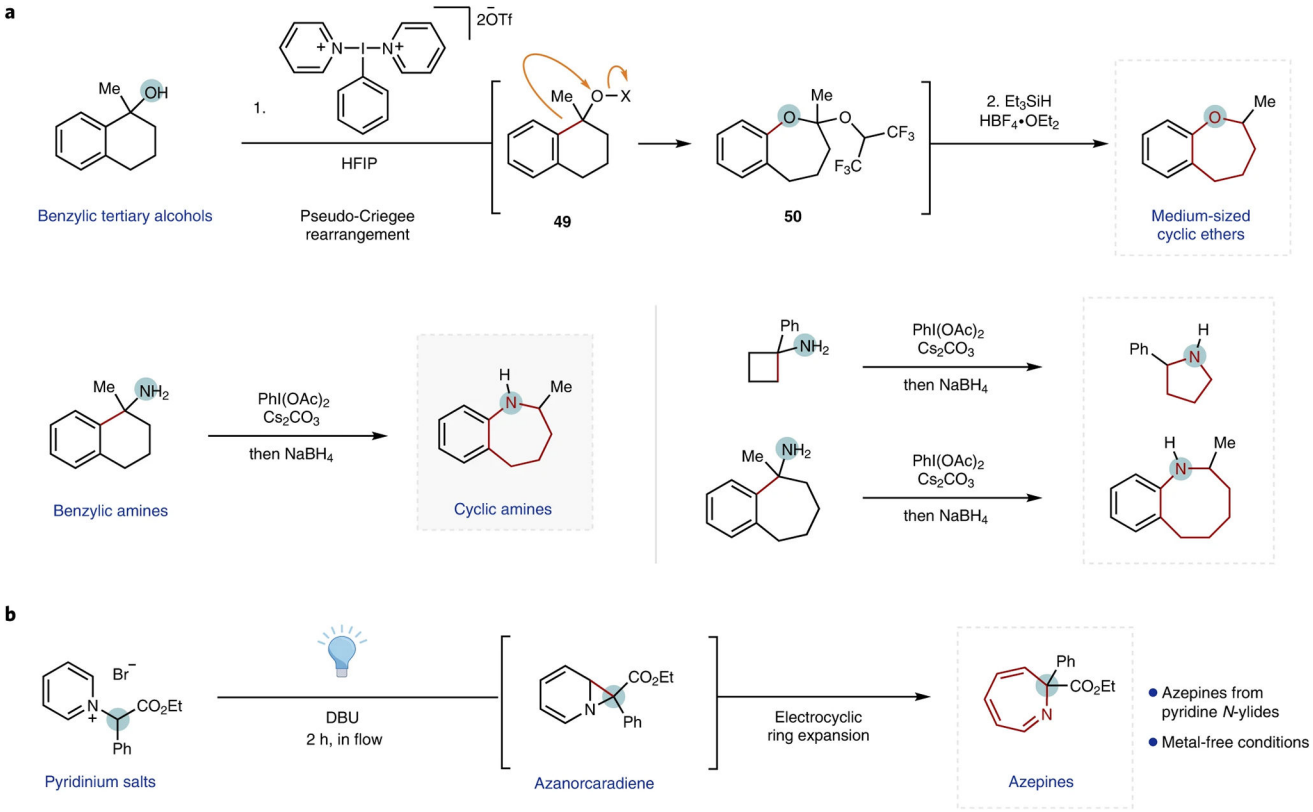

Fig. 7 |. Select advances in single-atom ring expansions.

a, Representative examples of oxidative ring expansions in benzylic alcohols[56] (top) and amines[57] (bottom). **b**, Photochemical ring expansion of pyridinium salts[58]. Expanded rings are highlighted in red for clarity. HFIP, hexafluoroisopropanol; Tf, trifluoromethanesulfonyl.

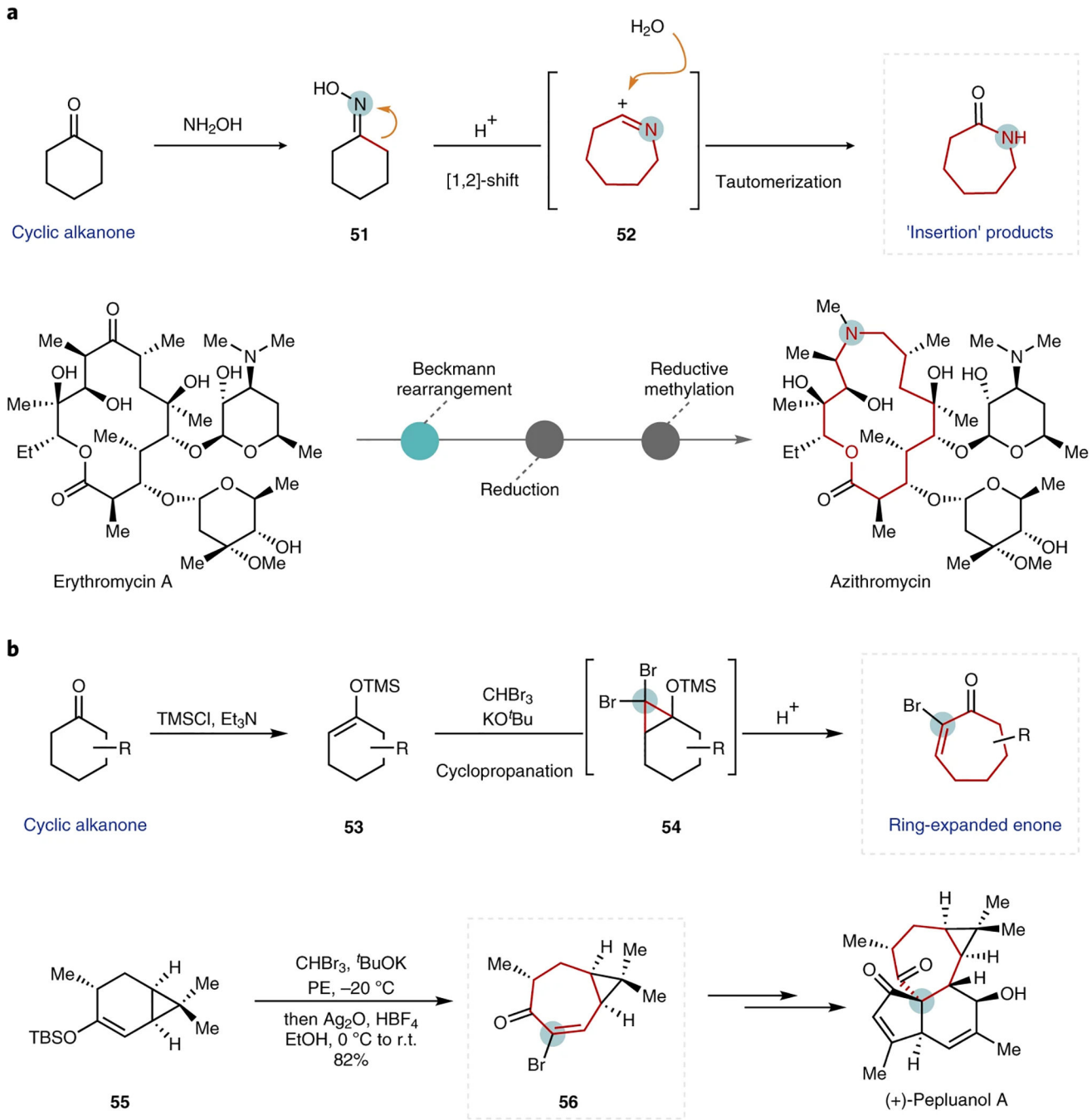

Fig. 8 |. Single-atom insertions that leverage carbonyl chemistry.

a, General reaction mechanism for a Beckmann rearrangement reaction (top) with the application demonstrated in the synthesis of azithromycin[66] (bottom). **b**, Representative example of a cyclopropanation reaction used to achieve ring expansion (top) and a synthetic application shown in the synthesis of (+)-pepluanol A[72] (bottom). Inserted atoms are circled, and expanded rings are highlighted in red for clarity. TMS, trimethylsilyl; TBS, *tert*-butyldimethylsilyl.

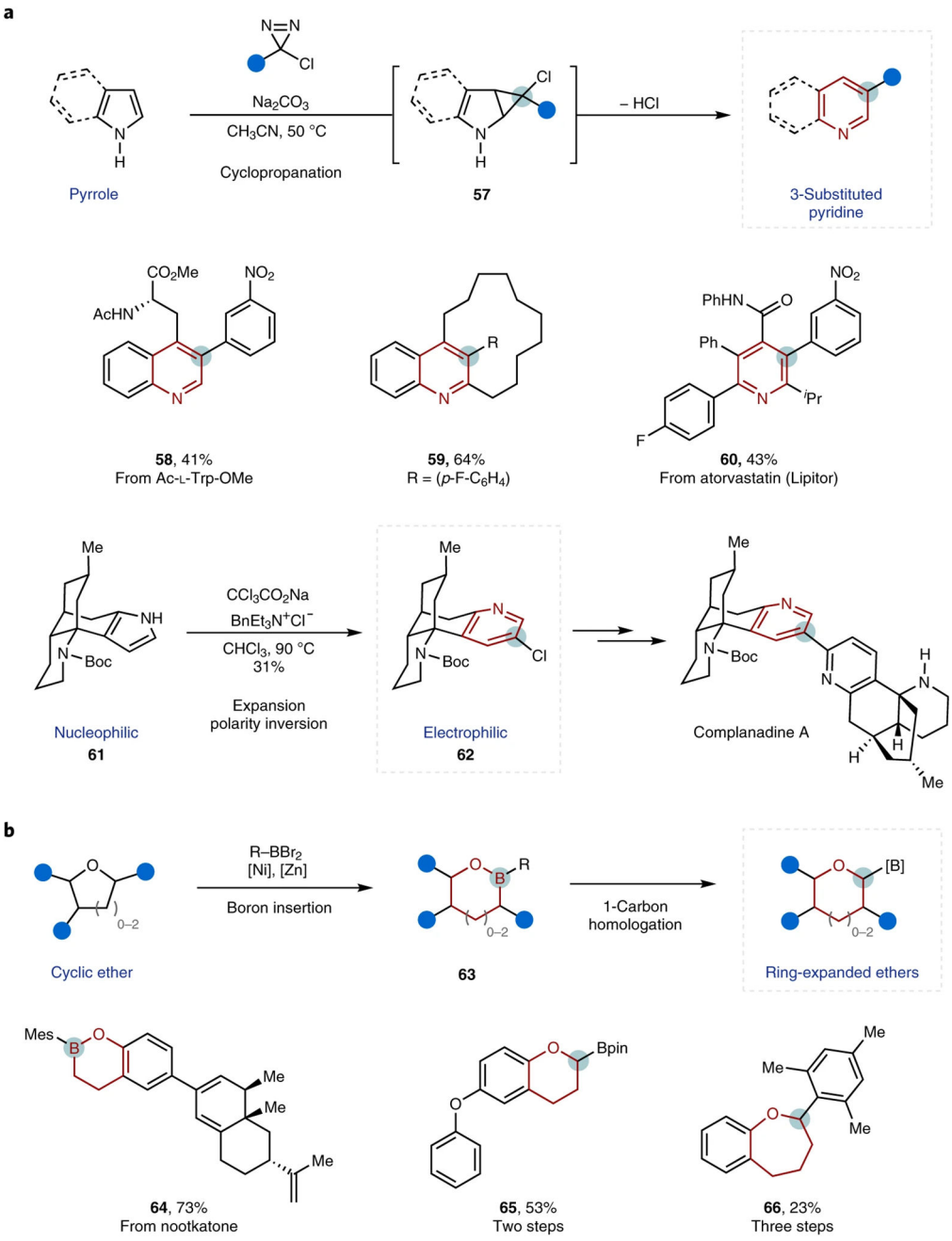

Fig. 9 |.

Recent advances in single-atom insertions into heterocycles. a, Representative azole-carbon insertion reaction[75] (top), and applications of a related insertion reaction in the synthesis of complanadine A[77] (bottom). **b**, Ether–boron insertion reactions[78]. The inserted atoms are circled, and the expanded rings are highlighted in red for clarity. Boc, *tert*-butoxycarbonyl group; Pin, pinacol; Mes, mesityl group.

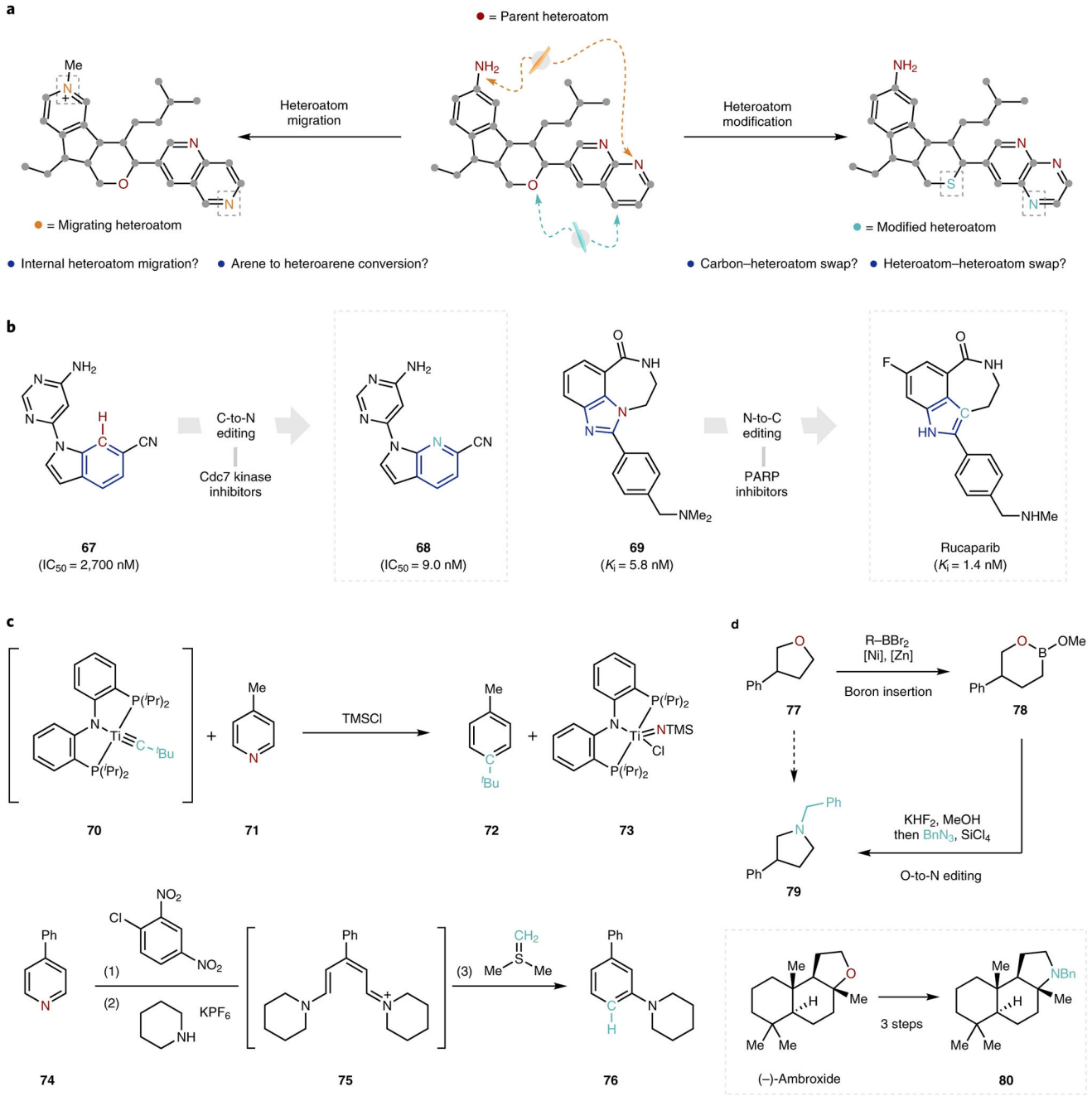

Fig. 10 |. Dream reactions in single-atom skeletal editing and promising precedents.

a, Wishlist of single-atom editing reactions applied to a complex molecule. **b**, Examples of the idealized single-atom editing logic in drug discovery shown through carbon-to-nitrogen (left) and nitrogen-to-carbon (right) atom swaps. **c**, Selected examples of carbon–nitrogen transmutations from Mindola and co-workers[81] (top) and Kano and co-workers[82] (bottom). **d**, Representative example of oxygen–nitrogen transmutation[78]. 'Edited' atoms are highlighted for clarity. Cdc7, Cell division cycle 7; PARP, polyadenosine diphosphate ribose polymerase; IC_{50}, half maximal inhibitory concentration; K_i, inhibitory constant.