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Molecular editing in natural product synthesis

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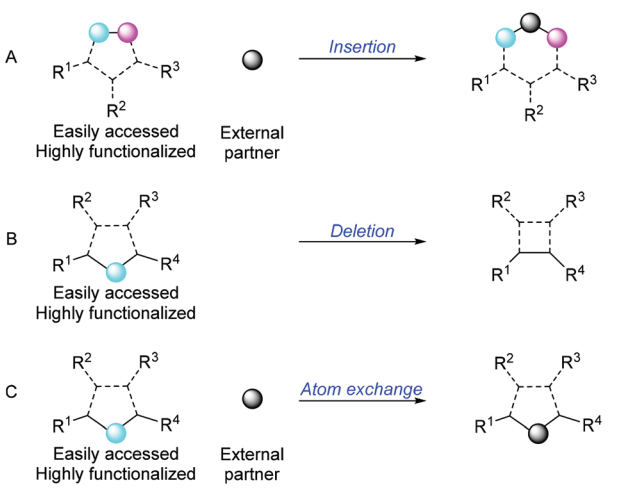
Many natural products have remarkable biological functions due to their fascinating molecular architectures. Despite many advances in synthetic method development, the efficient synthesis of highly functionalized and structurally intricate natural products to meet the demand for biological investigations remains a daunting challenge. Molecular editing encompassing insertion, deletion, or exchange of atoms of highly functionalized compounds has emerged as a hotspot in new method development and has been applied in complex natural product synthesis. In this highlight, the latest developments in molecular editing in natural product synthesis are discussed.

1. Introduction

Natural products and their structural analogues are a source of privileged scaffolds in drug design. Not surprisingly, natural products have been the cornerstone of drug discovery for decades, resulting in numerous FDA-approved drugs and research probes across a wide range of therapeutic areas such as cancer and virus infection.[1] In the past decades, advances in synthetic chemistry have improved the accessibility of structurally diverse and bioactive natural products for biological investigations. In particular, many state-of-the-art synthetic methods, such as transition-metal catalyzed cross-coupling reactions,[2] C–H bond functionalization reactions,[3] and selective ring formation,[4] have been applied widely in complex natural product synthesis. Nevertheless, the preparation of substrates carrying the necessary functionalities for a specific transformation usually requires multi-step synthesis, which inevitably compromises the overall synthetic efficiency. Molecular editing, which entails insertion, deletion, or exchange of atoms directly and selectively,[5] has emerged as a contemporary concept in structural modification to quickly prepare analogues of complex scaffolds (Scheme 1). More importantly, this concept has been implemented in new method development and complex natural product synthesis.[6] Although molecular editing by diverted total synthesis has been expertly reviewed by Carreria and Szpilman in 2010,[7] this highlight article aims to provide an overview of the latest research on molecular editing, with an emphasis on the chemical synthesis of natural products employing the molecular insertion and deletion reactions.

Conventionally, reactions involving inserting or deleting atoms of a given molecule are not uncommon. For instance, the Baeyer–Villiger oxidation enables the insertion of an oxygen atom into the C–C bond and converts cyclic ketones into lactones (Scheme 2A). The Ciamician–Dennstedt rearrangement enables the synthesis of 3-chloropyridines from pyrroles by inserting one carbon atom into the pyrrole scaffold (Scheme 2B). Recently, more elegant, unprecedented reactions have been developed that fit the concept of molecular editing.[6,8–11] Inspired by the mechanism of the Ciamician–Dennstedt rearrangement, Levin and co-workers reported a carbon atom insertion into indoles promoted by chlorodiazir-



Scheme 1 Schematic description of the concept of molecular editing.

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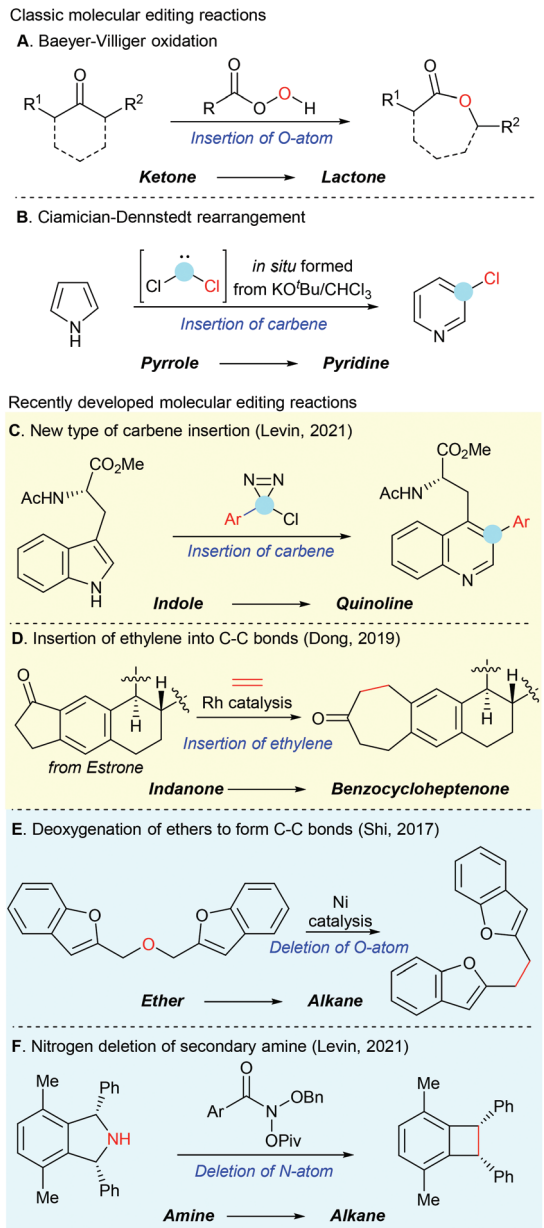


Scheme 2 Some chemical methods complying with the concept of molecular editing.

ines to produce quinolines (Scheme 2C).[9] The transformation of pyrrole into 3-arylpyridine was also possible using Levin's method. Besides molecular insertion into N-heterocycles, Dong and co-workers disclosed a two-carbon ring expansion strategy through a rhodium-catalyzed direct insertion of ethylene into the carbon–carbon bond in 1-indanones (Scheme 2D).[10a] This method allows the synthesis of benzocycloheptenones which are challenging to prepare otherwise. Meanwhile, molecular deletion of a heteroatom features as a new strategy to prepare chain-shortening and/or ring-contraction products. An oxygen-atom deletion of ethers promoted by nickel catalysis[11] and a nitrogen-atom deletion of secondary amines mediated by *N*-anomeric amide[6a] were invented by the Shi group in 2018 and the Levin group in 2021, respectively (Scheme 2E and F). Remarkably, the decent functional group compatibility demonstrated by these molecular deletion protocols reveals their potential for synthetic applications, *e.g.*, late-stage modification of functionalized bioactive scaffolds.

2. Molecular editing in natural product synthesis

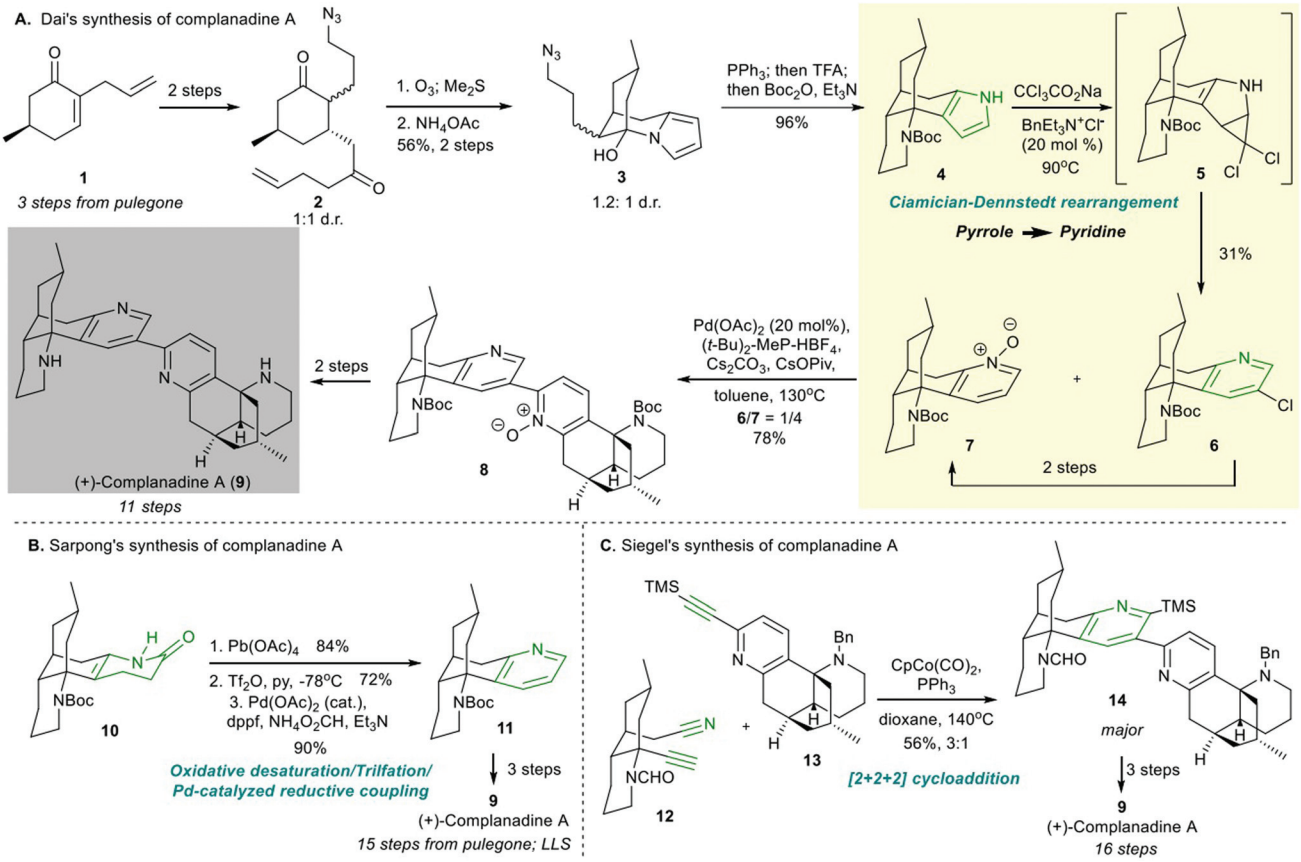
2.1 Molecular editing *via* insertion

In 2021, Dai and co-workers reported the synthesis of complanadine A (**9**) featuring a modified Ciamician–Dennstedt rearrangement as a key step to synthesize the desired 3-chloropyridines from pyrroles *via* one-carbon insertion (Scheme 3A).[6c] With *N*-Boc protected tetracyclic pyrrole **4** in hand, a modified Ciamician–Dennstedt rearrangement was carried out using CCl_3CO_2Na to give 3-chloropyridine **6** presumably *via* intermediate **5** resulting from selective [2 + 1] cycloaddition. The synthesis of the polycyclic pyridine scaffold in the previously reported syntheses of complanadine A (**9**) required either a three-step synthesis from enamide **10** including oxidation/triflation/catalytic reductive coupling (Scheme 3B)[12] or a cobalt-mediated [2 + 2 + 2] cycloaddition of elegantly designed alkyne-nitrile **12** and pyridyl-alkyne **13** (Scheme 3C).[13]

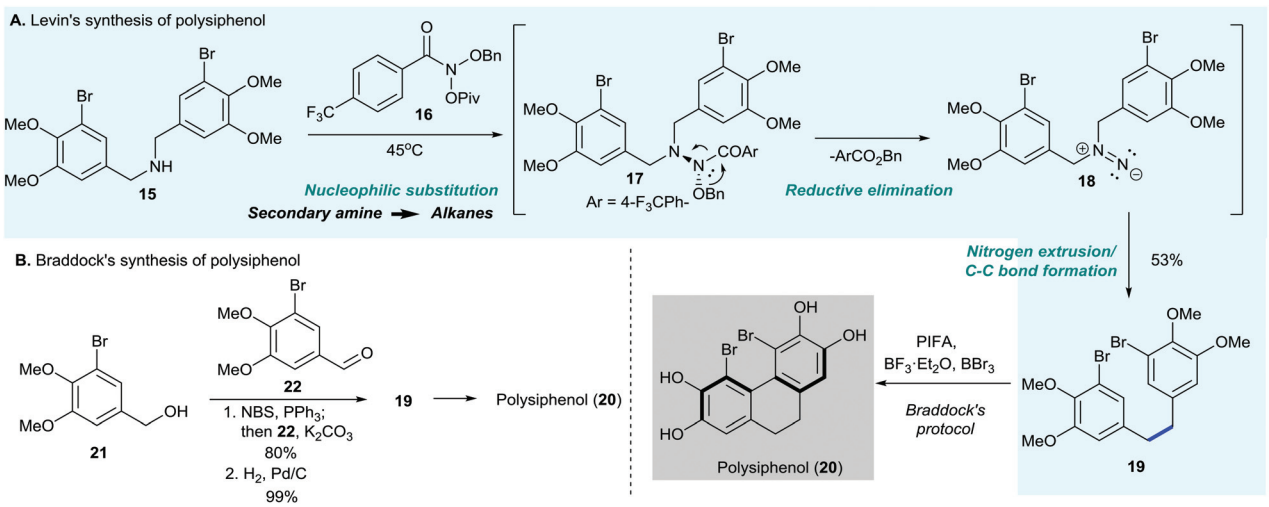
Dai's synthesis of complanadine A (**9**) began with a three-step synthesis of **2** from enone **1**, which was prepared from (*R*)-(+)-pulegone (Scheme 3A).[14] Ozonolytic cleavage of olefin **2** followed by a Paal–Knorr reaction afforded pyrrole **3** in 56% yield in two steps. The resultant pyrrole **3** was then subjected to sequential Staudinger reduction, hemiacetal hydrolysis, and intramolecular Mannich reaction to give a tetracyclic secondary amine, followed by Boc group protection to afford **4** in 96% yield. Next, treatment of the freshly prepared pyrrole **4** with CCl_3CO_2Na in the presence of a catalytic amount of $BnEt_3NCl$ upon heating at 90 °C resulted in a Ciamician–Dennstedt rearrangement, affording 3-chloropyridine **6** in 31% yield. The authors reported that the use of CCl_3CO_2Na upon heating facilitated the release of dichlorocarbene as an active species for the Ciamician–Dennstedt rearrangement, whereas the use of conventional conditions (*i.e.*, $CHCl_3$ and a base) gave the undesired Reimer–Tiemann formylation product.[15] The palladium-catalyzed cross-coupling reaction[16,17] between 3-chloropyridine **6** and pyridine *N*-oxide **7**, which was derived from **6** in two steps, afforded precursor **8** in 78% yield. Finally, the conversion of precursor **8** to complanadine A (**9**) was achieved in two steps. Among the reported synthetic protocols of complanadine A (**9**), Dai's method has the shortest steps, which largely benefits from the efficient molecular editing strategy.

2.2 Molecular editing *via* deletion

In 2021, Levin and co-workers disclosed their protocol for nitrogen deletion of a secondary amine using an *N*-anomeric amide (Scheme 4A).[6a] Treatment of a secondary amine with anomeric amide **16** led to *N*-amination/reductive elimination/dinitrogen extrusion to give the nitrogen deletion product **19**



Scheme 3 (A) Total synthesis of complanadine A (**9**) featuring a Ciamician–Dennstedt rearrangement as the key reaction (Dai, 2021).[6c] (B) Sarpong's synthesis of complanadine A (**9**) preparing pyridine using sequential oxidative desaturation/triflation/Pd-catalyzed reductive coupling (Sarpong, 2010).[12] (C) Siegel's synthesis of complanadine A (**9**) making use of a [2 + 2 + 2] cycloaddition to forge the pyridine motif (Siegel, 2010).[13]

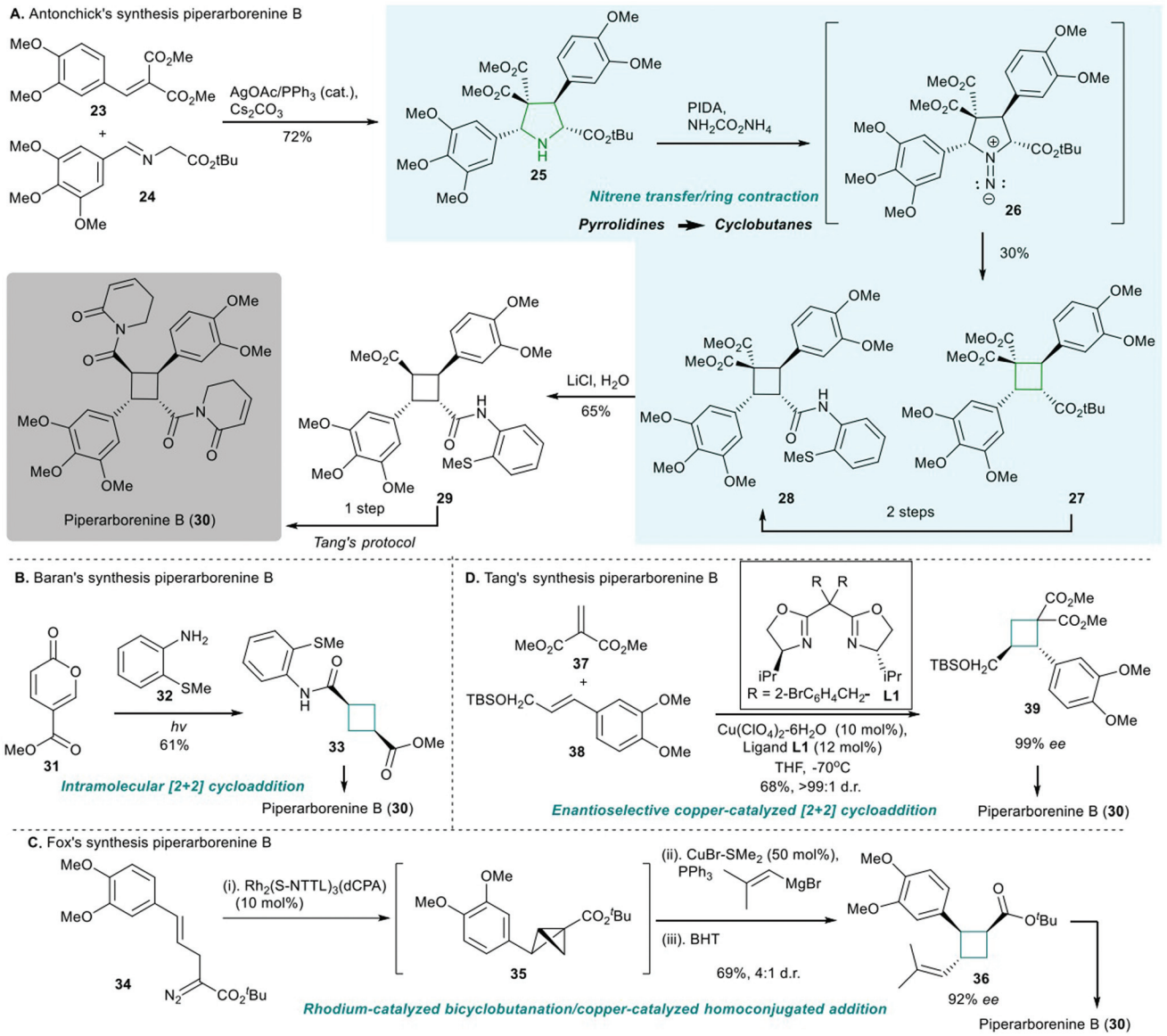


Scheme 4 (A) Synthesis of the marine metabolite polysiphenol (**20**) featuring *N*-anomeric amide promoted nitrogen deletion of secondary amines (Levin, 2021).[6a] (B) Another synthesis of polysiphenol (**20**) making use of sequential Witting olefination and catalytic hydrogenation as synthetic key steps (Braddock, 2011).[18]

in 53% yield. Cyclization of **19** effected by bis(trifluoroacetoxy) iodobenzene (PIFA) followed by demethylation produced polysiphenol (**20**). Alternatively, polysiphenol (**20**) could be achieved *via* one-pot bromination/phosphine ylide formation of **21** followed by a Wittig olefination with aldehyde **22** to give an alkene (not depicted) (Scheme 4B).[18] Hydrogenation of the

resultant alkene produced **19** in 99% yield, which was then converted to polysiphenol (**20**) *via* oxidative cyclization. In summary, Levin's anomeric amide approach selectively cleaves off the nitrogen atom of functionalized secondary amines, providing an opportunity for the late-stage modification of complex structural scaffolds.

In 2021, Antonchick and co-workers reported a stereoselective synthesis of multi-substituted cyclobutanes from the corresponding pyrrolidines using iodonitrene, which was applied to the synthesis of piperarborenine B (**30**) (Scheme 5A).[6b] Reactions between the highly-functionalized and stereocongested pyrrolidines and the iodonitrene[19,20] which was generated *in situ* from (diacetoxyiodo)benzene (PIDA) and ammonium carbamate, afford cyclobutanes in a stereoretentive manner, thus making this approach appealing to the preparation of complex cyclobutanes. Before Antonchick's seminal work, several elegant syntheses of piperarborenine B (**30**) were reported by Baran's group,[21] Fox's group[22] and Tang's group,[23] respectively. Baran's first total synthesis of piperarborenine B (**30**) adopted an intramolecular [2 + 2] cycloaddition to prepare the cyclobutane core **33** (Scheme 5B). Later, the enantioselective synthesis of piperarborenine B (**30**) was enabled by using Fox's rhodium-catalyzed bicyclobutanation/copper catalyzed homoconjugated addition[22] or Tang's enantioselective copper-catalyzed [2 + 2] cycloaddition[23] as a crucial step to prepare the enantio-



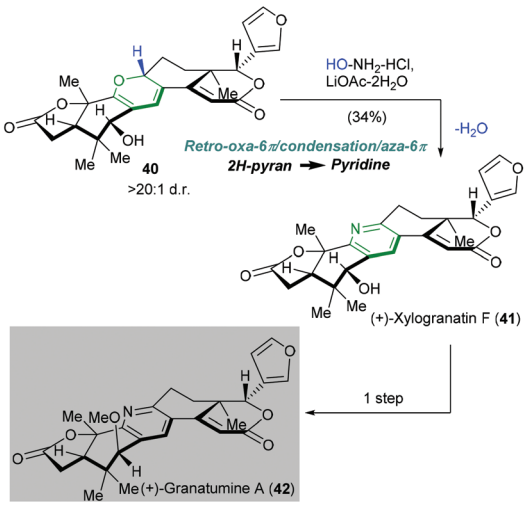
Scheme 5 (A) Contractive synthesis of cyclobutane from pyrrolidines featuring as a key reaction in the synthesis of piperarborenine B (**30**). (B) Baran's synthesis of piperarborenine B (**30**) using an intramolecular photo[2 + 2] cycloaddition to prepare disubstituted cyclobutane **33** (Baran, 2011).[21] (C) Fox's synthesis of piperarborenine B (**30**) making use of the rhodium-catalyzed bicyclobutanation/copper-catalyzed homoconjugated addition as a key strategy to forge the enantioenriched cyclobutane **36**. (D) Tang's synthesis of piperarborenine B (**30**) relying on an enantioselective copper-catalyzed [2 + 2] cycloaddition to prepare **39**.

enriched and functionalized cyclobutane nucleus (Scheme 5C and D). Commonly, these synthetic methods prepared cyclobutanes with three substituted carbons at most, implying that further functionalization step(s) are necessary to install the necessary aryl group(s) to complete piperarborenine B's synthesis. In contrast, Antonchick's approach directly accesses the fully functionalized cyclobutane core of piperarborenine B, thus providing the shortest route to the target natural product (*i.e.*, six steps). Antonchick's synthesis of piperarborenine B (**30**) began with a AgOAc/PPh_3-catalyzed [3 + 2] cycloaddition[24] of olefin **23** with imine **24** to afford pyrrolidine **25** (Scheme 5A). Exposure of pyrrolidine **25** to (diacetoxyiodo) benzene and ammonium carbamate facilitated the electrophilic amination of pyrrolidine's nitrogen *via* nitrene transfer, which led to nitrogen extrusion/ring contraction to give cyclobutane **27** in 30% yield. Hydrolysis of the *tert*-butyl ester on **27** using TFA gave the corresponding carboxylic acid which was then converted to the corresponding acyl chloride followed by amidation with aniline **32** to give **28** in 67% yield. The freshly prepared cyclobutane **28** was subjected to the subsequent Krapcho dealkoxycarbonylation to give precursor **29**, which was converted to piperarborenine B (**30**) using Tang's protocol.[23]

3. Conclusion and outlook

In summary, in this article, we highlight the recent advances in the application of molecular editing in natural product synthesis. Unlike the conventional ring contraction and ring expansion reaction, synthesis by applying molecular editing enables the chemoselective alternation of the molecular skeleton. More importantly, insertion, deletion, or exchange of atoms in the molecular editing strategy can be efficiently achieved in one step. In the case studies we discussed above, the Ciamician–Dennstedt rearrangement of pyrroles (insertion of one carbon atom) and nitrogen deletion of secondary amines (deletion of one nitrogen atom) are present as the major types of reactions that have been successfully applied in natural product synthesis. Some novel reactions, such as Shi's deoxygenation of ether and Dong's ethylene insertion, are expected to play important roles in natural product synthesis.[10b–e] In particular, Antonchick's synthesis of piperarborenine B (**30**) represents a good example which shows that molecular editing could significantly improve the synthetic efficiency towards a highly functionalized cyclobutane core. We envision that the development of molecular editing reactions would offer a more economical way towards bond disconnection for retrosynthetic analysis and demonstrate their advantages in an increasing number of complex natural product synthesis practices.

One major issue that still needs to be addressed is the exchange of atoms in highly functionalized compounds, given the challenge that the exchange of any single atom in a cyclic structure requires the cleavage of two chemical bonds followed by the formation of two new chemical bonds stitching the newly incorporated atom. A thought-provoking work reported



Scheme 6 Direct conversion of 2*H*-pyran to pyridine *via* a *retro*-oxa-6π electrocyclization/condensation/aza-6π electrocyclization in the synthesis of (+)-granatumine A (**42**).

by Newhouse's group featured the direct conversion of 2*H*-pyran to pyridine *via* a retro-oxa-6π electrocyclization/condensation/aza-6π electrocyclization followed by spontaneous loss of a water molecule in their total synthesis of (+)-granatumine A (**42**) (Scheme 6).[25] The net change from 2*H*-pyran **40** to pyridine **41** involved the replacement of an oxygen atom with a nitrogen atom, and one proton was removed. Fascinated by the impressive methods including Newhouse's conversion of 2*H*-pyran to pyridine, the variants of the Ciamician–Dennstedt rearrangement, and nitrogen deletion of secondary amines, we expect that molecular editing of various types of heterocycles will continue to be a hot research area in pursuit of new method development.

Conflicts of interest

There are no conflicts to declare.

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