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Programmable Deconstruction–Reconstruction Enables Divergent Skeletal Editing of Pyridines into Multisubstituted Benzenes

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Abstract

Skeletal editing has emerged as a powerful strategy for atom-precise molecular remodeling, yet pyridine-to-benzene editing remains largely limited to single-atom exchange, restricting structural diversification. Here, we report a programmable deconstruction–reconstruction strategy that converts pyridines into structurally diverse multisubstituted benzenes through single-atom and atom-pair skeletal editing. Controlled pyridine deconstruction followed by programmable reconstruction enables a formal (5 + 1) annulation to access nitrobenzenes, anilines, and nitroanilines, with product identity dictated by the nitroalkane coupling partner. In a complementary pathway, interception of a pyridine-derived diene intermediate enables atom-pair skeletal editing to furnish multi-substituted benzaldehydes and naphthaldehydes. Both transformations proceed under operationally simple conditions, exhibit broad substrate scope, and enable the direct installation of synthetically versatile nitro, amino, and aldehyde functionalities in substitution patterns difficult to access by conventional aromatic functionalization. The strategy is further demonstrated by the late-stage skeletal editing of pyridine-containing pharmaceuticals and bioactive amines, providing a general platform for the programmable synthesis of multisubstituted benzenes from abundant pyridines.

INTRODUCTION

The rapid generation of structurally diverse analogues is central to structure–activity relationship (SAR) studies in contemporary drug and agrochemical discovery.[1−4] Accordingly, synthetic strategies that enable the late-stage diversification of readily available feedstock molecules have become increasingly valuable. In this context, skeletal editing has emerged as a powerful platform for molecular remodeling by directly manipulating atomic connectivity.[4−11] Unlike conventional approaches that rely on multistep linear synthesis and peripheral functional-group modification, skeletal editing enables the insertion, deletion, or transmutation of atoms within the molecular backbone (Scheme 1a).[12−21] This capability provides rapid access to structurally distinct and previously inaccessible analogues from common precursors, obviating the need for *de novo* synthesis.[22−23] In this context, pyridines occupy a central position owing to their widespread occurrence in pharmaceuticals and bioactive natural products, as well as their ability to undergo controlled *N*-activation and ring opening to generate highly reactive intermediates.[24] Capitalizing on these intrinsic properties, several groups have established formal (5 + 1) deconstruction–reconstruction[25−31] as an effective strategy for converting pyridines into benzene derivatives, driven by the potential of *N*-to-*C* swap to enhance metabolic stability and bioavailability (Scheme 1a).[32] Despite their elegance, these methods reconstruct the arene through incorporation of a single carbon unit, intrinsically limiting access to benzenes bearing only one newly

introduced substituent (Scheme 1b). As a result, direct skeletal editing methods for the synthesis of multi-substituted benzenes from pyridines remain largely unexplored.

To overcome this intrinsic limitation, we envisioned reprogramming the reconstruction step of deconstructed pyridines (Zincke type intermediate, Scheme 1b). We hypothesized that these

intermediates could engage in either a formal (5 + 1) annulation followed by several distinguished rearomatization steps to deliver disubstituted benzenes or a fundamentally distinct (4 + 2) annulation pathway that incorporates a two-carbon fragment during ring reassembly, enabling direct access to multisubstituted benzenes or naphthalenes (Scheme 1b).

To reprogram the reconstruction event while preserving the deconstruction–reconstruction paradigm, we envision that condensation of deconstructed pyridine (Zincke-type) intermediates with nitroalkanes, followed by 6π-electrocyclization, generates a common cyclohexadiene intermediate **A** whose rearomatization is programmed by the nitroalkane substituent (Scheme 1c). For example, in case of nitromethane, conventional deamination is expected to deliver nitrobenzenes, whereas nitroethane and a nitromethane bearing a labile leaving group, such as α-bromonitromethane, can promote denitration and debromination, respectively, providing complementary access to alkyl-substituted anilines and nitroanilines (Scheme 1c, left).

Alternatively, the same Zincke-type intermediate can be exploited as a diene in a previously unexplored formal (4 + 2) annulation with alkynes or benzynes, providing direct access to multisubstituted benzaldehydes and fused aromatic aldehydes from a common pyridine precursor (Scheme 1c, right). Thus, realizing these concepts would provide a divergent and programmable platform for converting a single pyridine precursor into structurally diverse multisubstituted benzenes and naphthalenes, offering rapid access to substitution patterns that are difficult to obtain by conventional aromatic functionalization (Scheme 1c).

Herein, we report the development of this approach and introduce a programmable deconstruction–reconstruction strategy that transforms pyridines into structurally diverse multisubstituted benzenes through either single-atom or atom-pair skeletal editing. The platform enables the conversion of pyridines into nitrobenzenes, anilines, and nitroanilines *via* a formal (5 + 1) annulation involving a single-atom swap, with product identity programmed by the substitution pattern of the nitroalkane coupling partner. Furthermore, we delineate the integration of a pyridine-derived diene intermediate with skeletal editing to access benzaldehydes and naphthaldehydes through a formal atom-pair-swap process. Both transformations are operationally simple, exhibit broad substrate scope, and provide efficient access to structurally diverse benzene architectures. Notably, these complementary skeletal editing strategies enable the direct installation of synthetically versatile nitro, amino, and aldehyde functionalities that are challenging to introduce through conventional aromatic functionalization. The utility of the platform is further demonstrated by the late-stage skeletal editing of pyridine-containing drug precursors and fragments, as well as its excellent compatibility with structurally complex bioactive amines, highlighting its potential as a general strategy for programmable arene synthesis.

RESULTS AND DISCUSSION

We initiated our studies by examining the feasibility of the proposed deconstruction–reconstruction strategy (Scheme 2a). Pyridine **1a** was first converted into the corresponding pyridinium salt **2a** through

reaction with 1-chloro-2,4-dinitrobenzene. The resulting pyridinium salt was subsequently treated with a secondary amine to promote nucleophilic ring opening, followed by nitromethane (**3**) to trigger the successive ring closure event. Gratifyingly, employing pyrrolidine as the ring-opening nucleophile in toluene at 80°C afforded the desired nitro-substituted biaryl **4a** in 56% yield (Scheme 2a–I), thereby validating the viability of the deconstruction–reconstruction manifold.

Encouraged by this preliminary result, we systematically evaluated a series of secondary amines. Among those examined, morpholine proved to be optimal, furnishing **4a** in 94% isolated yield (Scheme 2a–I). With morpholine identified as the preferred nucleophile, the influence of solvent was next investigated. DCM, chloroform, 1,2-dichloroethane, THF, acetonitrile, and methanol all promoted the transformation, albeit with only moderate to good efficiencies, whereas toluene consistently provided the highest yield (Entry 1–3). Temperature also played a decisive role, as lowering the reaction temperature to 60°C or conducting the reaction at room temperature resulted in significantly diminished conversions (Entry 4).

To probe the structural requirements of the process, we next examined pyridinium salt **2'**, derived from unsubstituted pyridine (Scheme 2b). Under the optimized conditions, very trace amount of the corresponding nitrobenzene product was detected, highlighting the importance of substrate electronics and geometry for efficient skeletal editing (Scheme 2b).[28]

Having established the optimal reaction conditions and identified the key structural features required for productive reactivity, we explored whether the reconstruction event could be programmed by varying the nitroalkane

coupling partner. Replacing nitromethane with nitroethane (**5**) under similar conditions led to a striking change in reaction outcome. Instead of deamination, the reaction proceeded through selective denitration of intermediate **A'**, delivering the methyl-substituted aniline **6a** in 79% yield (Scheme 2c). Notably, employing bromonitromethane (**7**) unlocked another complementary pathway. Following the same deconstruction–reconstruction sequence, the resulting intermediate **A"** underwent selective debromination rather than denitration, furnishing the nitroaniline **8a** in an excellent 91% yield (Scheme 2c). These results demonstrate that the identity of the nitroalkane serves as a simple yet powerful programming element that dictates the final reconstruction event, ultimately leading to a two-fold functionalized arene core.

We next explored the substrate scope of this skeletal editing process (Scheme 3). The reaction exhibited broad generality across a diverse range of pyridines. Aryl-substituted pyridines bearing *ortho*-, *meta*-, and *para*-substitution patterns were all well tolerated, providing the corresponding nitroarenes **4b–4f** in good to excellent yields (79%–89%). Poly-substituted aryl groups likewise underwent efficient skeletal editing, delivering products **4g–4j** in uniformly high yields. Sterically demanding substrates were also compatible, as illustrated by the naphthyl- substituted pyridine, which afforded **4k** in 87% yield.

The protocol further accommodated a variety of polycyclic aromatic motifs, including phenanthrene (**4l**) and fluorene (**4m**), furnishing desired products in high yields. Importantly, heteroaromatic substituents

also proved compatible, providing **4n** and **4o** without compromising reaction efficiency. The synthetic utility of the method was further demonstrated through the late-stage skeletal editing of biologically relevant scaffolds, enabling the direct conversion of precursors derived from the VU60019966 and JKT-853 fragments into the corresponding nitroarene analogues **4p** and **4q** in 78% and 83% yields, respectively. Beyond C4-arylpyridines, C3-substituted pyridines also proved to be competent substrates, affording valuable nitroarenes **4r–4y** in good yields. Notably, this strategy complements classical nitration by enabling access to *meta*- and *para*-nitroarenes, substitution patterns that are often inaccessible through electrophilic nitration. Furthermore, it selectively installs the nitro group on the pyridine-derived phenyl ring in the presence of more electron-rich arenes, thereby circumventing the intrinsic chemoselectivity limitations of conventional nitration methods (Scheme 3).

We then sought to exploit the substrate-divergent nature of this platform by switching the reaction manifold from deamination to denitration, thereby enabling the synthesis of substituted aniline derivatives (Scheme 4). The transformation proved broadly applicable to a wide range of secondary amines. Cyclic aliphatic amines of varying ring sizes, including piperidine (**6b**), thiomorpholine (**6c**), azepane (**6d**), oxazepane (**6e**), and azocane (**6f**), underwent the transformation efficiently to furnish the corresponding aniline derivatives in uniformly high yields. Fused cyclic amines, such as tetrahydroquinoline (**6g**), indoline (**6h**), and tetrahydroisoquinoline (**6i**), were likewise competent coupling partners, delivering the desired products in good to excellent yields. The protocol also accommodated structurally distinct acyclic secondary amines (**6j**–**6l**), affording the corresponding products in consistently high yields.

The utility of this strategy was further demonstrated through the late-stage functionalization of pharmaceutically relevant amines (Scheme 4). Precursors derived from the antiplatelet agent clopidogrel, the antidepressant vortioxetine, and the antihistamine desloratadine were readily converted into the corresponding aniline derivatives **6m**–**6o** in high yields. Besides variation of the amine component, the scope of the transformation was further extended to a broad range of substituted pyridines. The C4-substituted pyridines bearing electronically diverse aryl groups (**6p**–**6s**), polycyclic aromatic frameworks (**6t–6x**), and heteroaromatic substituent (**6y**) all participated efficiently, providing the desired products in uniformly high yields. Also, employing a C3-substituted pyridine, the aminated product **6z** was prepared in 72% yield.

Notably, this amination reaction modality is also amenable to late-stage skeletal editing of biorelevant motifs, as exemplified by the direct functionalization priralfinamide and JKT-853 fragments, into their corresponding aniline derivatives (**6za**–**6zb**) in high yields. Furthermore, a precursor of the antidiabetic drug canagliflozin was successfully transformed into **6zc** in 85% yield (Scheme 4).

To further expand the synthetic versatility of the deconstruction–reconstruction platform, we investigated bromonitromethane as the coupling partner. Interestingly, in contrast to the denitration pathway observed with nitroethane derivatives, bromonitromethane underwent selective debromination to furnish multisubstituted nitroaniline derivatives under the standard reaction conditions (Scheme 5).

Pyridines bearing polycyclic aromatic substituents smoothly participated in the reaction, affording the corresponding nitroanilines (**8b**–**8d**) in high yields. Likewise, pyridines derived from biologically relevant molecules and pharmacophore fragments (**8e**–**8h**) were readily converted into the desired products with uniformly high efficiency. The protocol was readily applicable to diverse bioactive amines, providing the corresponding nitroaniline derivatives (**8i**–**8k**) in high yields and highlighting its utility for the late-stage diversification of medicinally relevant scaffolds.

We next turned our attention to explore the deconstruction–reconstruction manifold for the synthesis of diversely substituted benzaldehydes by validating the proposed temporal (4 + 2) annulation of deconstructed Zincke type intermediates (Scheme 6). We posited that the Zincke-type intermediate would engage in a sequential formal (4 + 2) annulation/elimination cascade with dimethyl acetylenedicarboxylate (DMAD, **9**) to reconstruct a highly substituted benzene framework.

Consistent with this hypothesis, the in situ generated streptocyanine from **2a** was reacted with **9** to afford benzaldehyde **10a** in 60% yield. After extensive optimization (see the Supporting Information), the desired tetra-substituted benzaldehyde **10a** was obtained in 78% yield by treating the morpholine-derived Zincke aldehyde with DMAD **(9)** in the presence of K_2CO_3 in toluene at 60°C.

With the optimized conditions established, the scope of this skeletal editing process was investigated (Scheme 6). Consistent with the preceding transformations, the reaction displayed broad substrate generality. Pyridines bearing a variety of *ortho*- and *para*-substituted aryl groups underwent efficient skeletal editing to furnish functionally enriched benzaldehydes **10b–10j** in 59%–78% yields. Arenes comprising multiple substituents at different positions were likewise well tolerated, providing products **10k–10o** in good yields. Sterically demanding polycyclic aromatic substituents, including naphthyl and anthracenyl groups, participated efficiently to furnish **10p** and **10q** in 72% and 78% yields, respectively. Importantly, heteroaromatic substituents were also compatible with the reaction, affording **10r** and **10s** in good yields. The product **10r** was crystallized and its structure was unambiguously established by single-crystal *X*-ray diffraction analysis. The methodology was equally applicable to C3-substituted pyridines, furnishing products **10t–10w** in good yields. However, neither the pyridinium salt derived from unsubstituted pyridine nor methyl propiolate as the alkyne coupling partner afforded the desired product, emphasizing the necessity of pyridine substitution and a doubly activated alkyne for this deconstruction–reconstruction process (Scheme 6).

We further investigated the use of benzyne precursors in place of activated alkynes to diversify the reconstruction process (Scheme 6). Gratifyingly, the Kobayashi benzyne precursor (*o*-trimethylsilyl aryl triflate) underwent efficient (4 + 2) annulation with the deconstructed Zincke intermediate to furnish valuable naphthaldehydes **11a**–**11d** in good to high yields (Scheme 6). The scope of this transformation further encompassed pyridines bearing biologically relevant motifs and complex molecular fragments, affording naphthaldehydes **11e–11h** in synthetically useful yields (Scheme 6).

Notably, the skeletal editing protocols are readily scalable, with the efficiencies observed on small scale being largely retained under gram-scale conditions, furnishing **4a**, **6a**, and **8a** in 85%, 71%, and 80% yields,

respectively (Scheme 7a). The practicality of this molecular editing strategy was further demonstrated through a one-pot sequential protocol that streamlined the skeletal editing sequence, offering **4a** in 83% overall yield with improved pot- and step-economy (Scheme 7b). Furthermore, the strategy is amenable to iterative skeletal editing, enabling the simultaneous remodeling of two pyridine nuclei to afford **13** and **15** in 74% and 71% yields, respectively (Scheme 7c). Remarkably, the protocol also exhibits excellent chemoselectivity. When a C2–C3-linked bipyridine substrate (**16**) was examined, selective editing of only one pyridine ring occurred to furnish **17** in 72% yield, presumably due to steric differentiation between the two pyridine units (Scheme 7d). The versatility of the strategy is further demonstrated by its extension to chemoselective two-fold skeletal editing, furnishing the compound **19** in 69% yield (Scheme 7e). Importantly, these examples demonstrate how skeletal editing complements classical nitration by enabling direct access to regioisomers that are challenging through conventional electrophilic nitration.

Scheme. 7 | Synthetic applications of the programmable deconstruction-reconstruction strategy. Isolated yields were provided.

CONCLUSION

In summary, we have developed a programmable deconstruction–reconstruction strategy that substantially expands the scope of pyridine skeletal editing by integrating single-atom and atom-pair remodeling within a unified platform. Through controlled molecular deconstruction and selective reconstruction, the strategy enables both formal (5 + 1) and the previously elusive formal (4 + 2) annulation manifolds, providing streamlined access to structurally diverse multisubstituted benzenes bearing synthetically versatile nitro, amino, and aldehyde functionalities. A defining feature of this platform is the programmable use of nitroalkanes as reconstruction partners, which dictate the reconstruction pathway and enable divergent access to distinct aromatic architectures. Moreover, exploiting the diene character of Zincke intermediates extends the strategy to Diels–Alder reactions with alkynes and benzynes, providing complementary routes to multisubstituted benzaldehydes and naphthaldehydes. The broad substrate scope, excellent functional-group compatibility, operational simplicity, and applicability to late-stage skeletal editing highlight the versatility of the method. More broadly, this work establishes Zincke intermediates as versatile diene synthons and nitroalkanes as programmable reconstruction partners, providing a general blueprint for deconstruction–reconstruction-based skeletal editing and opening new opportunities for the programmable interconversion of heteroarenes into structurally complex carbocyclic frameworks.

Declarations

AUTHOR CONTRIBUTIONS

M.B., K.P. and T.C. have conceptualized the idea. K.P., T.C., M.M., and P.R. carried out the experiments and analyzed experimental data. All the authors discussed the results and co-wrote the manuscript.

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Schemes

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