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Introduction

Single-atom skeletal editing has been receiving increasing interest because it enables the modification of underlying molecular skeletons and provides unique opportunities to synthesize complex molecules through completely different strategies.^{1–9} In particular, nitrogen atom insertion into a ring skeleton presents a distinct strategy for accessing heterocyclic structures, which are highly valuable scaffolds in drug discovery, materials science, and synthetic chemistry (Fig. 1A).¹⁰ The earliest examples of this class of reactions include well-known processes such as Ciamician–Dennstedt rearrangement (1881),¹¹ Beckmann rearrangement (1886),¹² and Schmidt rearrangement (1924).¹³ Recent noteworthy advances include nitrogen insertion into heterocycles^{14–16} and cycloalkenes (Fig. 1B).^{17–21} However, nitrogen atom insertion into the aromatic carbocyclic skeleton is still difficult because of the inherent inertness of the carbon–carbon bonds of aromatic rings.^{22–25}

N-Heterocycles present the unique class of cyclic structural frameworks present in various natural and non-natural products. Big data analytics reveal that heterocycle formation has been one of the most frequently used reactions in medicinal chemistry over the past several decades.^{26,27} Benzazepines are

Nitrogen atom insertion into arenols to access benzazepines†

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Advances in site-selective molecular editing have enabled structural modification on complex molecules. However, thus far, their applications have been restricted to C–H functionalization chemistry. The modification of the underlying molecular skeleton remains limited. Here, we describe a skeletal editing approach that provides access to benzazepine structures through direct nitrogen atom insertion into arenols. Using widely available arenols as benzazepine precursors, this alternative approach allowed the streamlined assembly of benzazepines with broad functional group tolerance. Experimental mechanistic studies support a reaction pathway involving dearomatizative azidation and then aryl migration. This study further highlights the potential for carbon–nitrogen transmutation sequences through combinations with oxidative carbon atom deletion, providing an alternative for the development of N-heteroarenes and demonstrating significant potential in materials chemistry.

among the most important N-heterocycle skeletons and have received considerable attention owing to their pharmacological properties and promising applications in organic synthesis (Fig. 1C).²⁸ For instance, OPC-41061, a human vasopressin V2-receptor antagonist,²⁹ clomipramine, an antidepressant agent,³⁰ and benazepril, an ACE inhibitor,³¹ all contain the benzazepine skeleton. Therefore, substantial efforts have been

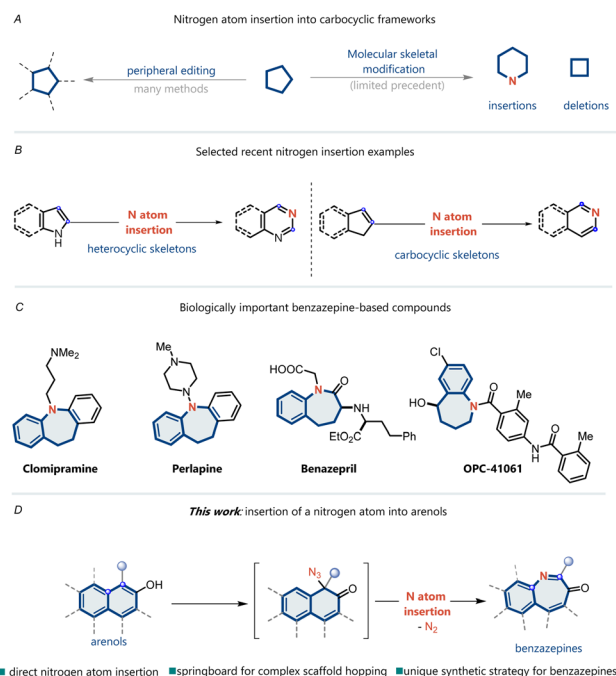


Fig. 1 Insertion of a nitrogen atom into arenols.

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devoted to the development of efficient methodologies for preparing benzazepine skeletons. Single-atom insertions represent one of the most intriguing methods for the synthesis of heterocycles and have established new opportunities for accessing valuable benzazepines.

Herein, we report a reaction wherein a nitrogen atom is directly inserted into an arenol to yield the corresponding benzazepine ring through an azide intermediate (Fig. 1D). To achieve nitrogen atom insertion into arenes, we propose utilizing of arenols as substrates, which can disrupt the stability of the aromatic ring through dearomatization. Moreover, arenols can function as directing groups in site-selective nitrogen insertion. Unlike classical nitrene addition into benzene rings,^{32–35} this strategy facilitates C–C bond cleavage and, more importantly, achieves site-selective nitrogen atom insertion.

Results and discussion

This study was initiated with the use of phenanthren-9-ol (**1a**) as the model substrate (Table 1). The reaction parameters, including different catalysts, ligands, solvents, and temperatures, were carefully optimized (see Tables S1–S4 in the ESI†). The desired product **2** was obtained in 80% yield using a combination of CuI/Cy₃PO and *tert*-butyl peroxybenzoate (TBPB) as the oxidant in toluene (entry 1). Thereafter, a series of

control experiments were performed to gain deeper insights into this reaction. The Cu catalyst plays a critical role in this transformation, and the desired product cannot be obtained without it (entry 2). Other Cu salts, including CuCl, CuBr, and Cu(OAc)₂, could also undergo this reaction, but with lower efficiencies (entries 3–5). Furthermore, when other established metal nitrenoid formation catalysts,^{36,37} including iron and cobalt, were utilized, the desired product was not obtained (entries 6 and 7). This result suggests that CuI is suitable for both dearomatization azidation and aryl migration. Among the various ligands examined, the yield drastically increased when Cy₃PO was used as the ligand (entries 8–12). The reaction can proceed in the absence of the ligand (entry 13), suggesting that CuI alone can catalyze the nitrogen insertion reaction, albeit with lower efficiency. Further screening of other azide sources indicated that only TMSN₃ facilitated this transformation (entries 14 and 15).

Having established the optimized reaction conditions, we investigated the substrate scope based on the naphthalene scaffold (Fig. 2). Various multi-arenols, including naphthol (**2–33**), phenanthrol (**34–44**), tetraphenol (**45**), and benzo[*c*]phenanthrenol (**46**), can effectively undergo the desired nitrogen atom insertion. Notably, the substituents at the 2-positions of the arenol proved to be significant. When the substituent was a phenyl group (**3**, **4**, and **44**) or an electron-withdrawing group such as CO₂Me, the corresponding arenols underwent nitrogen atom insertion smoothly in moderate-to-good yields. The presence of an alkyl at the 2-position was found to inhibit this reaction. Substrates containing heterocycles, such as furan and thiophene (**7** and **8**), performed well. Various functional groups known to participate in this reaction, such as esters (**2**), methyl ethers (**9** and **18**), thioether (**12**), trimethylsilyl (**13**), aryl halides (**14**, **15** and **19**), cyanide (**16**), and trifluoromethyl (**17**), were found to be compatible under the optimized conditions. In addition to methyl esters, other esters were evaluated. Phenyl (**20**), allyl (**21**), and cycloalkyl (**22**) ester derivatives were competent substrates, affording the desired azepine products in moderate-to-good yields. Bulkier esters, such as isopropyl (**23**) and *tert*-butyl (**24**), also worked smoothly. Moreover, 2-naphthol bearing an oxime group (**25**) at the 1-position was well tolerated. Given the broad substrate scope, we aimed to demonstrate this reaction in a more complex setting. Naphthols with ester-linked natural products and drug derivatives readily participated in this nitrogen atom insertion reaction. Various complex molecules with diverse structural features, such as steroids (**27** and **28**), N-heteroarenes (oxazole **30** and indole **32**), and carbohydrate (**31**), were readily converted into their corresponding products.

In addition to the naphthol scaffold, various phenanthrol derivatives can react under standard conditions to afford the “nitrogen insertion” products (**34–44**). Different aliphatic chains (**34–36**), aromatic rings (**37** and **44**), halides (**38** and **39**), cyanide (**40**), and trifluoromethyl (**41** and **42**), are well tolerated. Moreover, fused heteroarens such as naphtho[1,2-*b*]thiophene (**47**) and pyrrolo[1,2-*a*]quinoline (**48**) can be incorporated, providing pharmaceutically intriguing fused-ring

Table 1 Screening of reaction conditions^a

Entry	Variation from 'standard conditions'	Yield ^b %
1	None	80
2	w/o CuI	0
3	CuCl instead of CuI	72
4	CuBr instead of CuI	65
5	Cu(OAc) ₂ instead of CuI	60
6	Fe(TPP)Cl instead of CuI	0
7	T(<i>p</i> -OMe)PPCo instead of CuI	<10
8	ⁿ Bu ₃ PO instead of Cy ₃ PO	68
9	Ph ₃ PO instead of Cy ₃ PO	40
10	bpy instead of Cy ₃ PO	17
11	L1 instead of Cy ₃ PO	53
12	L2 instead of Cy ₃ PO	56
13	w/o Cy ₃ PO	30
14	NaN ₃ instead of TMSN ₃	<10
15	N(ⁿ Bu) ₄ N ₃ instead of TMSN ₃	Trace

^a Unless otherwise specified, all reactions were carried out using **1a** (0.1 mmol) and TMSN₃ (0.3 mmol), with CuI (5 mol%), Cy₃PO (10 mol%) and TBPB (2.0 equiv.) in toluene at 120 °C for 12 h. ^b Isolated yields after chromatography.

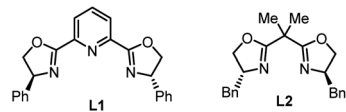




Fig. 2 Substrate scope.

skeletons. Notably, the structures of **20**, **46** and **48** were identified by X-ray crystallography.

This nitrogen atom insertion protocol provides a basis for the development of more complex skeletal editing

transformations. A longstanding challenge in skeletal editing has been the selective exchange of individual atoms, including swapping a carbon for a nitrogen atom in a ring.^{38–44} Based on this nitrogen atom insertion transformation, we design a ring





Fig. 3 Application potential of the atom-swapping process.

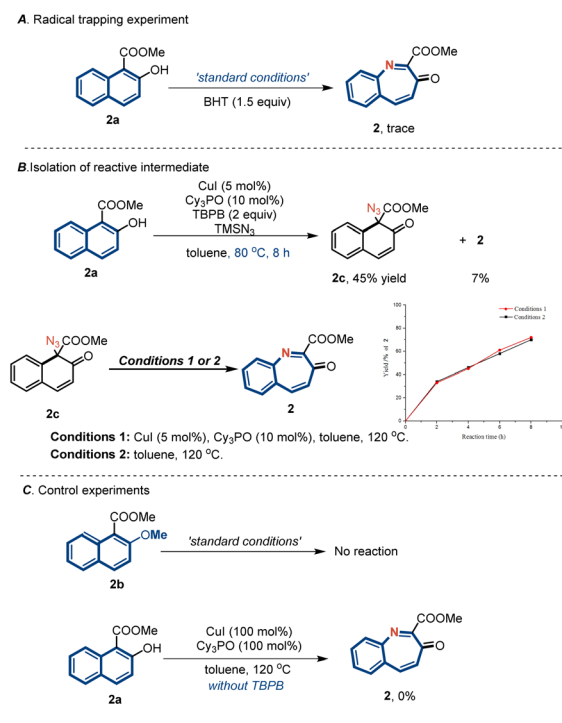


Fig. 4 Mechanistic studies.



Fig. 5 Proposed reaction mechanism.

expansion–contraction sequence to realize carbon-to-nitrogen transmutation. Various arenol derivatives can react to produce carbon-to-nitrogen transmutation products (Fig. 3A). A plausible mechanism was proposed (Fig. 3B). Initially, the mCPBA-mediated oxidation of the corresponding naphthol **2** affords oxaziridine intermediate **I**. Subsequently, a cleavage of the nitrogen–oxygen band occurs, generating radical intermediate **II**. Next, a radical-mediated rearrangement of intermediate **II** affords intermediate **III**, which in turn removes the ester to yield **61**.

A series of experiments were performed to gain insights into the reaction mechanism (Fig. 4). First, reactions in the presence of a radical inhibitor (BHT) under standard conditions did not furnish any nitrogen atom products, which was consistent with a radical mechanism (Fig. 4A). By changing the reaction temperature to 80 °C, we were able to separate the reactive quaternary azide intermediate **2c**. In addition, thermal activation allowed for the smooth initiation of subsequent aryl migration to furnish product **2** in excellent yield (Fig. 4B). Control experiments indicated that the copper catalyst did not affect the rate of the migration step. Further, the phenolic OH group of **2a** was protected by a methyl group and subjected to standard conditions (Fig. 4C). This reaction failed to furnish either the azidated intermediate or the nitrogen insertion product, indicating that the phenolic OH groups of arenols played an important role in this reaction. Furthermore, the reaction performed using stoichiometric amounts of CuI and Cy₃PO in the absence of TBHP did not yield the desired product. This finding indicates that TBHP plays a key role in initiating the catalytic cycle.

A plausible mechanism based on literature reports and our observations was proposed (Fig. 5).^{45–48} Initially, a single-electron transfer between Cu(I) and TBPB initiates the reaction by generating a *tert*-butoxyl radical and Cu(II) species. A radical relay process then occurs between **2a** and the *tert*-butoxyl radical to afford radical intermediate **A**.^{49,50} Subsequently, ligand exchange delivers Cu(II)N₃, which then reacts with the internal radical to deliver the azidation intermediate **B** and regenerate the Cu(I) catalyst. Finally, intermediate **B** undergoes aryl migration to eventually yield product **2** through the extrusion of N₂.^{51,52}



Conclusions

In conclusion, we reported a unique strategy for the straightforward insertion of nitrogen atoms into arenols. Nitrogen atom insertion exhibits reasonable site-selectivity, whereas copper catalysis disrupts the aromaticity of arenols. A carbon-to-nitrogen atom-swapping process was achieved *via* a combination of oxidative carbon-atom deletions. This protocol exhibited a wide substrate scope, encompassing a variety of multi-arenols, including naphthol, phenanthrol, benzo[*c*]phenanthrenol, and tetraphenol, along with various functional groups. It can produce the corresponding benzazepines in a highly site-selective manner. This report establishes a framework for creating new skeletal editing processes for aromatic molecules *via* an azido intermediate.

Data availability

Detailed synthetic procedures and complete characterization data for all new compounds can be found in the ESI.†

Author contributions

H. W. conceived and designed the project and composed the manuscript. Y. H., J. W. and T. Z. conducted the experiments and analyzed the data. J. W. and Z. Z. discussed the experimental results and commented on the manuscript. H. W. conducted general guidance, project directing, and manuscript revisions.

Conflicts of interest

There are no conflicts to declare.

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