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Direct deaminative functionalization with *N*-nitroamines

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Amines are among the most common functional groups in bioactive molecules[1]. Despite this prevalence, conventional means of converting aromatic amines rely heavily on diazonium intermediates[2], which pose significant safety risks due to the explosive nature of these salts[3,4]. Here, we report a direct deaminative strategy through the formation of *N*-nitroamines, allowing the direct conversion of inert aromatic C−N bonds into an array of other functional groups, C−X (C−Br, C−Cl, C−I, C−F, C−N, C−S, C−Se, C−O) and C−C bonds. This operationally simple, general protocol establishes a unified strategy for one-pot deaminative cross-couplings by integrating deaminative functionalization with transition-metal-catalyzed arylation, thereby streamlining synthesis and late-stage functionalization. The key advantages of this transformation over other deaminative functionalization methods lies in its versatility across nearly all classes of medicinally relevant heteroaromatic amines, as well as electronically and structurally diverse aniline derivatives, regardless of the position of the amino group. Mechanistic studies, supported by both experimental observations and theoretical analysis, suggest that the aryl cation equivalent reactivity of *N*-nitroamines is generally favoured in this deaminative process. This study highlights the significant potential of the direct deamination approach in synthetic chemistry, offering a safer alternative to the traditionally explosive and hazardous aryldiazonium chemistry.

Introduction

For decades, aryl halides and phenols have dominated as privileged arylating agents[5,6], serving as fundamental building blocks for transformations such as transition-metal-catalyzed cross-coupling reactions (Fig. 1A). In contrast, aromatic amines, structural cornerstones of natural products and medicinal compound libraries[7,8], remain severely underutilized as reactive species. Although stepwise functionalization strategies emerged as early as 1884 with the copper-mediated Sandmeyer reaction via diazonium intermediates, and subsequent developments expanded this reactivity largely through free-radical pathways[3,9]. In general, conventional diazotization protocols necessitate the utilization of explosive diazonium salts resulting in safety concerns. Accordingly, Ritter group devised an elegant safety-enhanced Sandmeyer variant employing transient aryldiazonium generation based on nitrate reduction chemistry (Fig. 1B)[10]. However, these aryldiazonium-based processes still suffer from stoichiometric copper consumption and restrictive substrate compatibility. Cornella group recently disclosed an innovative deaminative strategy wherein electron-deficient (hetero)aromatic systems, upon *in situ* generation of pyridinium intermediates, undergoing a S_NAr pathway[11,12]. In parallel, the Levin group demonstrated a nice radical-based deamination approach employing anomeric amide reagents to generate carbon-centered radical species[13,14]. Yet, these reactions often rely on reagents with poor atom economy and are typically restricted to either electron-deficient or electron-rich aromatic systems, thereby limiting their broader applicability. Building upon these advances, we set out to investigate whether an alternative activation mode could enable direct deaminative functionalization and thus provide access to previously unexplored reaction manifolds.

Our direct deaminative strategy makes use of the distinct reactivity of *N*-nitroamines through nitric acid-mediated nitrous oxide (N_2O) extrusion, enabling direct conversion of aromatic C−N bonds into an array of C−X (C−Br, C−Cl, C−I, C−F, C−N, C−S, C−Se, C−O) and C−C bonds. This approach establishes a route for one-pot deaminative cross-couplings that merges deaminative functionalization and transition-metal-catalyzed arylation, offering expeditious access to complex pharmacophores from ubiquitous aromatic amine precursors under mild conditions (Fig. 1C). Moreover, the process is readily scalable to kilogram-scale synthesis.

Reaction development

The direct substitution of amino groups within aromatic frameworks presents a formidable synthetic challenge due to the poor leaving-group capability of NH_2 moieties[2,15]. Building upon established deamination strategies for prefunctionalized aliphatic amines[16-18], we hypothesized that installing dual electron-withdrawing groups (e.g., acyl, sulfonyl) on the amino group could substantially weaken the C(sp^2)−N bond, thereby promoting subsequent nucleophilic substitution. In pursuit of suitable precursors for this transformation, we synthesized various substrates bearing different electron-withdrawing groups on the amino group (trifluorosulfonyl-, acetyl-, and benzoyl- etc.) (see Supplementary Information section 3 for full details). Unfortunately, these substrates proved ineffective under our initial investigations. Our exploration then shifted towards introducing two nitro groups via the nitration process, which unexpectedly led us to the identification of *N*-pyridylnitroamine **1** and *N*-(4-cyanophenyl)nitroamine **S122**, presumably formed through the dehydration of aromatic amines with nitric acid (see Supplementary Information section 7.1 for full experimental details). The structures of these compounds were elucidated through X-ray crystallographic analysis (see

Supplementary Information Fig. S41-S43). Despite their earliest discovery in 1893[19-21], the reactivity potential of heteroaromatic and aniline-derived nitroamines have remained largely unexplored.

A pivotal discovery emerged when *N*-pyridylnitroamine was treated with either magnesium chloride/nitric acid, aluminium trichloride, or thionyl dichloride, each efficiently yielding the deaminative chlorination product **2** (see Supplementary Information Fig. S1-S2). Mechanistic studies unveiled an unprecedented N_2O extrusion pathway accompanying this transformation, as confirmed by gas chromatography-mass spectrometry (GC-MS) analysis (see Fig. 2A and Supplementary Information Fig. S25-S28). This serendipitous result uncovered an operationally mild protocol for the deaminative chlorination of aminoheterocycles. The observed reactivity motivated us to streamline the process. We envisioned a practical protocol that involves the *in situ* generation of reactive *N*-nitroamine intermediates through nitric acid-mediated nitration of aromatic amines, followed by tandem deaminative chlorination, thereby obviating the need for nitroamine isolation. Indeed, upon exposure of 2-aminopyridine to nitric acid, we successfully detected the formation of *N*-pyridylnitroamine (see Supplementary Information Fig. S16-S17). After an extensive optimization, subjecting 2-aminopyridine to just 1.2 equivalent nitric acid under the optimized conditions successfully afforded the corresponding chlorination product **2** in good yield (see Fig. 2B and Supplementary Information Fig. S3-S10). These results suggest that the deamination process is initiated by the formation of *N*-pyridylnitroamine (**1**). It is worth noting that DMAP is critical for increasing the efficiency of this reaction, likely due to its dual role as a base and as an activator of $SOCl_2$, thereby facilitating the generation of nucleophilic chloride anions. Then we conducted kinetics study experiments, which suggest that the formation of the *N*-nitroamine intermediate might be the rate-determining step (see Supplementary Information Fig. S18-S22). Notably, direct exposure of preformed nitroamines to chlorination conditions resulted in complete conversion within 1.5 minutes. These findings support our hypothesis that the *N*-nitroamine might act as a transient intermediate that, once formed, rapidly collapses to the final product.

Building on these observations, a plausible mechanistic hypothesis for the deaminative process is depicted in Fig. 2C. The sequence initiates with the nitration of the aromatic amine to form an *N*-nitroamine **1**, which undergoes tautomerization to generate intermediate **4**. Upon treatment with the appropriate reagents, this species is converted to a labile intermediate **5**. Intermediate **5** then undergoes N_2O extrusion and is subsequently intercepted by a nucleophile, thereby delivering the deaminative functionalization product and driving the reaction to completion.

Substrate scope exploration

With the established deaminative chlorination procedure in hand, we systematically explored its generality. This transformation demonstrates exceptional versatility across a diverse range of medicinally relevant aminoheterocyclic scaffolds. As depicted in Fig. 3, both *ortho*-, and *para*-aminopyridines bearing electronically varied substituents, such as trifluoromethyl, nitro, cyano, ester, halogen, ether, phenyl, and alkyl groups, underwent successful conversion to provide the corresponding chlorinated products in moderate to good yields (**6**-**20**, 55-96% yield). Notably, the protocol accommodates synthetically valuable functional handles such as alkenes (**6**), alkynes (**14**), and aryl boronates (**7**), which are particularly advantageous for downstream derivatization. A longstanding challenge in deaminative halogenation has been the functionalization of *meta*-aminopyridines, which typically suffer from poor reactivity under conventional conditions[10,11,14]. We were excited to find that our methodology successfully addresses this limitation, enabling efficient chlorination of *meta*-aminopyridines (**24**-**27**, 46-64% yield). The scope further extends to five-membered heteroaromatic amines, including thiazole, isothiazole, and 1,3,4-thiadiazole, delivering chlorinated products with useful levels of efficiency (**21**-**23**, **28**; 36-87% yield). Moreover, multinitrogen-containing heterocycles, such as pyrazole, imidazole, pyrimidine, pyrazine, and pyridazine, were all well-tolerated (**29**-**33**, 50-83% yield). The protocol is also compatible with fused polycyclic aromatics (**34**, 40% yield). Comparative studies with classical Sandmeyer conditions revealed the superior performance of our protocol, particularly in multi-nitrogen systems. While conventional copper-mediated aryldiazonium-based chemistry typically results in low yields (often undetectable), our approach reliably achieves satisfactory efficiency (Fig. 3, gray highlights). This enhanced reactivity is attributed to our unique mechanistic pathway, which circumvents traditional radical intermediates. This deaminative transformation exhibits good electronic tolerance and positional generality, enabling efficient chlorination of structurally diverse aniline derivatives. The protocol successfully accommodates substituents across the entire electronic spectrum, electron-donating, -neutral, and -withdrawing groups at all aromatic positions, furnishing chlorinated arenes in synthetically useful yields (**35**-**47**, 40-77% yield).

Given the importance of late-stage functionalization in drug discovery, we explored the applicability of our approach to more structurally complex bioactive molecules. The deaminative chlorination of procaine, a local anesthetic, proceeded smoothly in a yield of 45% (**42**), even with the presence of a tertiary amine fragment. Interestingly, the anti-inflammatory agents amlexanox and deuterated-amlexanox yielded the corresponding products in good yields (**48**, 68% yield**; 49**, 60% yield). Using starane, an agrochemical, as the substrate, the yield of **50** improved significantly to 95%. Moreover, the fused heterocyclic compound imiquimod, an immunomodulator, was also tolerated, yielding product **51** in 42% yield. Notably, the substrate trimethoprim, an antibacterial bearing two NH_2 groups, underwent smooth double deaminative chlorination (**52**, 30% yield). Chlorination of acid-sensitive, purin-based compounds like adefovir (*anti*-hepatitis B) and famciclovir (*anti*-viral) delivered **53** and **56** in moderate yields. Benzothiazole derivative from fasudil (*anti*-angina) and riluzole (*anti*-glutamate) were successfully converted with yields of 41% and 82%, respectively (**54**, **55**). This performance stands in stark contrast to Sandmeyer conditions, which largely failed for these

complex architectures. Our protocol thus represents a robust method for late-stage diversification of drug molecules. An additional 51 examples in Extended Data Fig. 1 further highlight the generality of this protocol.

The integration of diverse aromatic amines into chlorination reactions demonstrated the operational efficiency of our deaminative strategy, thus motivating us to systematically explore the reactivity with alternative nucleophiles. We initiated our investigation by exploring a range of deaminative transformations using *N*-nitroamines (see Supplementary Information Fig. S29). The *N*-nitroamine intermediates consistently afforded the desired products in good yields, indicating their pivotal role as reactive species in the deamination process. Building upon the established protocol for deaminative chlorination, wherein minimal quantities of nitric acid were introduced to activate amino moieties, this strategy exhibited remarkable versatility, enabling facile construction of an array of carbon-heteroatom bonds (C−Br, C−I, C−F, C−N, C−S, C−Se, C−O) and C−C bonds directly from aromatic amines (Fig. 4). When using simple halogenation reagents, such as $SOBr_2$, LiBr, and KI, deaminative halogenation proceeded smoothly. For example, aromatic amines with five- or six-membered heterocycles and benzene rings bearing electronically diverse array of functional groups, reacted efficiently to provide the halogenated products (**57**-**66**, **70**-**76**; 43-87% yield). Notably, a range of di- and tri-halogenated aromatic amines proved competent in this transformation (**57**-**60**, **64**, **70**). No halogen scrambling was observed, which represents a valuable feature with respect to further derivatization. Minor over-halogenation side products were also detected with electron-rich arenes in deaminative halogenation (Cl, Br, I), presumably due to NOx-induced oxidation of halide anions to the corresponding electrophilic equivalents. The incorporation of fluorinated groups into aromatic rings is of particularly significant due to its potential to alter their physical and biological properties[22]. We were delighted to find that 2-aminopyridines successfully underwent deaminative fluorination (**67**-**69**, 35%-45% yield). Subsequently, we further examined the compatibility of our new method towards other common nucleophiles. To our delight, the strategy demonstrated versatile engagement with *N*-, *S*-, and *Se*-centered nucleophiles, allowing access to a broad array of chemical diversity (**77**-**83**, 38-69% yield). However, the current nucleophile scope remains limited for species with low basicity. Significantly, the protocol proved productive in the C−O bond formation, demonstrating its potential for facilitating further cross-coupling reactions and late-stage modification of bioactive molecules[5,23-25]. Oxygen-centered reagents, including Ts_2O, Tf_2O, H_2O, EtOH and HFIP, exhibited excellent tolerance with the system, successfully accommodating a wide range of aromatic compounds, including pyridazine, quinoline, pyrazine, pyrimidine, purine, pyridine, and benzene derivatives (**84**-**96**, 38-88% yield). To comprehensively illustrate the compatibility of this method, several examples were tested under standard aryldiazonium-based conditions. As highlighted in Fig. 4, most cases provided significantly lower yields (often undetectable) compared to our protocol. The construction of carbon-carbon bonds is pivotal in organic synthesis and industrial production[26]. Encouraged by the preceding outcomes, we extended the scope to *C*-nucleophiles. Importantly, the direct utilization of C(sp^2)−H or C(sp^3)−H bonds as latent nucleophiles enabled streamlined access to both C(sp^2)−C(sp^2) and C(sp^2)−C(sp^3) bonds, potentially accelerating the synthesis of a myriad of organic compounds (**97**-**99**, **101**, **123**, **125**; 40-71% yield). An additional 29 examples for this deaminative functionalization are detailed in Extended Data Fig. 2. The bar graph in Extended Data Fig. 3 demonstrates an enhanced yield of our method for several representative substrates over conventional Sandmeyer or diazonium salt pathways.

One-pot strategy and application

We sought to improve operational simplicity further by developing a one-pot deaminative cross-coupling sequence. This makes use of *in situ* generated aryl (pseudo)halides in subsequent transition-metal-catalyzed coupling or nucleophilic substitution reactions without the need for intermediate isolation, enhancing its synthetic usefulness. Although there have been some instances of one-pot cross-coupling protocols[27,28], methods with broad applicability are still lacking.

The deaminative halogenation products require no purification and could be directly subjected to cross-coupling reactions by simply adding the appropriate coupling reagents under standard transition-metal catalysis (**102**-**108**, 38-52% yield) (Extended Data Fig. 4). Notably, a range of transformations, including Negishi coupling (**102**), reductive cross-coupling (**104**), Ullmann-Ma reaction (**105**), Buchwald-Hartwig amination (**106**), Hirao reaction (**107**), and sulfonylation (**108**), were all compatible with this one-pot deaminative cross-coupling sequence[29-34]. Furthermore, metallaphotoredox catalysis[35] was successfully integrated into the one-pot sequence, delivering azetidine product (**103**). An additional 16 examples using other coupling reagents are detailed in Extended Data Fig. 5. The broad compatibility of this one-pot protocol with diverse transition-metal-catalyzed couplings and its good tolerance toward multifunctional coupling partners, offers distinct retrosynthetic disconnections for the expedient synthesis of complex molecules from widely available native functionalities, thereby underscoring its significance for advancing medicinal chemistry. Encouraged by these results, we also initiated a preliminary exploration into direct deaminative cross-coupling and were pleased to achieve a direct deaminative Suzuki coupling (**109**, 47% yield) of aromatic amines.

To further demonstrate the potential application of this method, we sought to explore the capability to efficiently construct drug-like molecular complexity in a highly expedient yet modular fashion via chemoselectively sequential deaminative functionalization (Fig. 5A). To this end, compound **110**, which contains two NH_2 groups of similar reactivity, was chosen as the starting material. Encouragingly, deaminative chlorination occurred at the isoquinolinyl aromatic ring, delivering mono-chlorinated product **111** in 60% yield with high regioselectivity by simply controlling the reaction temperature. Interestingly, increasing the amount of chlorinating reagents smoothly facilitated a double deaminative chlorination to product **112** in 51% yield. Subjection of the resulting chloride **111** to a stepwise Chan-Lam coupling followed by a Suzuki-Miyaura coupling afforded the diarylation product **117**. Alternatively, treatment of **111** under Suzuki-Miyaura coupling conditions followed by our newly developed deaminative cross-

coupling sequence provided the drug like compound **115** with good efficiency. Remarkably, the reaction of the substrate 5-bromopyridin-2-amine (**118**) was successfully scaled up to 1 kilogram, yielding the product **119** in a high yield of 90% with simple recrystallization (Fig. 5B). This operational robustness offers distinct industrial advantages, particularly for discovery chemistry and process development across other industries[36].

Moreover, our one-pot methodology enables streamlined synthesis of multifunctional (hetero)arenes but typically necessitates overcoming multiple challenges, including the electronic and steric properties of electrophiles and nucleophiles, choice of catalysts, ligands, additives, and solvents. Subsequently, we investigated the selective and sequential functionalization of three sites on a pyridine ring. Excitedly, the iterative conversion of C−Br, C−Cl and C−NH_2 bonds in a commercially available starting material was achieved successively to deliver etocoxib **121**[37] in a three-steps, one-pot operation with a synthetically useful yield of 28% (Fig. 5C).

Mechanistic studies

On the basis of our proposed mechanism (Fig. 2C), we conducted a series of experiments to gain some mechanistic insights into the key product-forming step of this deaminative transformation (See supplementary Information section 3 for full experimental details). Whether the transformation proceeds through an aryl cation intermediate[38,39] or a direct nucleophilic aromatic substitution (S_NAr) pathway remains a subject of ongoing discussion. Previous literature has extensively documented the Mascarelli-type reaction as a classical example of intramolecular C–H insertion mediated via aryl cation intermediates[40]. Notably, substrates **100** and **122** underwent smooth deamination, yielding the corresponding C−H insertion products in 43% and 40% isolated yields, respectively. Additionally, treatment of substrate **124** under nitric acid conditions afforded intramolecular electrophilic substitution product **125** in 60% yield. These initial results support the possible formation of aryl cation intermediates during the reaction (Extended Data Fig. 6A). Subsequently, we conducted further experiments to investigate the nature of the reactive species. *Ortho*-*n*-butyl aniline **126** underwent intramolecular C–H insertion in ethyl acetate under nitric acid conditions, affording the deaminative cyclization product **127**, whereas selective deaminative arylation product **128** was obtained when benzene was used as solvent (Extended Data Fig. 6B). Alternatively, when *meta*-*n*-butyl aniline was used as the precursor under identical conditions, arylation product was obtained in 36% yield, likely occurring through an electrophilic aromatic substitution process (see Supplementary Information Fig. S32). These findings further corroborate the intermediacy of aryl cations in these transformations[39]. Moreover, under Ritter-type conditions, the formation of deaminoamidation product **130** provides additional support for the aryl cation intermediate acting as the key electrophilic species (Extended Data Fig. 6C). A Hammett analysis was also conducted with a series of *para*-substituted aniline derivatives under standard deaminative chlorination conditions. Plotting $\log(k_X/k_H)$ against the substituent parameter σ resulted in a linear correlation with the negative slope (ρ = −0.229), consistent with the proposed aryl cation intermediate in the transition state (Extended Data Fig. 6D). Although these results collectively support the involvement of aryl cation intermediates in the deaminative reaction, we recognize that the electronic properties of the substrates may significantly influence the stability of these intermediates, potentially leading to divergent mechanistic pathways.

To gain deeper mechanistic insight, we performed the density functional theory (DFT) calculations (see Supplementary Information Section 3.8 for full computational analysis, Fig. S39; S40). The DFT results suggest that the reaction proceeds through the energetically favored **pathway a**, which aligns with experimental observations. As depicted in Extended Data Fig. 6E, loss of chloride anions from intermediate **131** affords intermediate **5**, which then undergoes N_2O extrusion to form aryl cation **133** (ΔG = 11.1 kcal/mol). This highly reactive electrophilic species is subsequently captured by nucleophiles to furnish the deaminative functionalization product. Unlike the stable aryldiazonium intermediate, intermediate **5** could not be isolated due to the rapid N_2O elimination. The superior leaving group ability of N_2O facilitates this process with a barrier of only 7.3 kcal/mol relative to **5** via transition state **132** (overall $\Delta G^{\ddagger}$ = 17.0 kcal/mol). However, we cannot rule out the possibility that a competing S_NAr process (**pathway b**) operates in parallel. It is likely that the reaction mechanism may depend on the nature of the substrate and nucleophile. To investigate this, DFT calculations were performed using seven different nucleophiles (Cl, Br, I, OTf, $OCH(CF_3)_2$, SCN, NTf_2) across a variety of electronically diverse (hetero)arylamines for both the aryl cation and S_NAr pathways (see Supplementary Information Fig. S40). When employing strongly electron-deficient aromatic amines in deaminative halogenation (Cl, Br, I), the S_NAr pathway via intermediate **134** was favored over the aryl cation route[41]. Conversely, in other deaminative functionalizations, the aryl cation mechanism was generally preferred regardless of the electronic nature of the arylamine substrates, including electron-donating (**S114**), neutral (**S117**; **S118**), and electron-withdrawing (**S115**; **S116**) substituents.

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Data availability

All data supporting the findings of this study are available within the Article and its Supplementary Information. The supplementary crystallographic data for this paper are available free of charge from the Cambridge Crystallographic Data Centre (CCDC) under accession numbers CCDC 2328567 (compound **1**), CCDC 2474737 (compound **S120**), CCDC 2474761 (compound **S122**). Copies of the data can be obtained free of charge via https://www.ccdc.cam.ac.uk/structures/.

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Author contributions

X.Z. and F.Z. conceived the project. X.Z. designed and supervised the project. G.T., K.X., X.C. and H.Z. conducted the experimental work and analyzed the data. H.X. and X.X. performed the computational studies. G.T., K.X., X.C. and X.Z. wrote the manuscript with input from all authors.

Competing interests

H.Z., F.Z., X.Z., X.C., G.T., and K.X. are inventors on Chinese patent applications (Application No. CN 2023118572004 and 2024101567075). The remaining authors declare no competing interests.

Additional information

Supplementary information The online version contains supplementary material available at

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Figure Legends

Fig. 1 | **Direct deaminative functionalization of aromatic amines.** (A) Relative commercial availability of common aryl donors used in cross-coupling reactions (data retrieved from the Reaxys database). (B) Recent advances in deaminative functionalization of aromatic amines. (C) Aromatic amines as direct precursors to aryl donors with *in situ* rapid diversification (this work). Het., heterocycle.

Fig. 2 | Reaction development and proposed mechanism. (A) Serendipitous finding. (B) Standard condition. (C) Mechanistic hypothesis. See Supplementary Information Section 3 for full experimental details. LG, leaving group.

Fig. 3 | **Scope of direct deaminative chlorination.** Isolated yields. [a]^{1}H NMR yield. See Supplementary Information Section 4-6 for full experimental details. DMAP, 4-dimethylaminopyridine; Bpin, bispinacolboronate; Bn, benzyl; TMS, tetramethylsilane; Ph, phenyl; Bz, benzoyl; Piv, pivaloyl; Ac, acetyl; Sandm., Sandmeyer conditions; n.d., not detected.

Fig. 4| **Scope of deaminative functionalization with other nucleophiles.** Isolated yields. [a]^{1}H NMR yield. See Supplementary Information Section 4-6 for full experimental details. General halogenation conditions: amine (0.5 mmol), $SOBr_2$ (1.25 mmol) as a bromine source, HNO_3 (2.0 equiv.), DMAP (2.5 equiv.), DCE (5.0 mL), 70 ℃, 1 h; amine (0.5 mmol), KI (2.0 mmol) as an iodine source, HNO_3 (6.0 equiv.), DCE (5.0 mL), 70 ℃, 1 h; amine (0.2 mmol), AgF_2 (0.6 mmol) as a fluorine source, HNO_3 (3.0 equiv.), DCE (2.0 mL), 70 ℃, 2.5 h. Nuc, nucleophiles; Piv, pivaloyl; Ph, phenyl; Ac, acetyl; Tf, trifluoromethanesulfonyl; Ts, tosyl; Sandm., Sandmeyer conditions; Diaz.s., diazonium salts; n.d., not detected.

Fig. 5| **Synthetic applications.** (A) Chemoselective deamination toward divergent synthesis of complex molecules. (B) Kilogram-scale synthesis. [a]The product was purified by simple recrystallization. (C) Efficient synthesis of drug molecules. [b]Previous route see reference 37. All yields are isolated. See Supplementary Information Section 8 for full experimental details. r. r., regioselective ratio.

Extended Data Figure legends

Extended Date Fig. 1 | Additional 51 substrates as extended scope (deaminative chlorination). Isolated yields. [a]^{1}H NMR yield. See Supplementary Information Section 4-6 for full experimental details. DMAP, 4-dimethylaminopyridine; Ph, phenyl; Bn, benzyl; Sandm., Sandmeyer conditions.

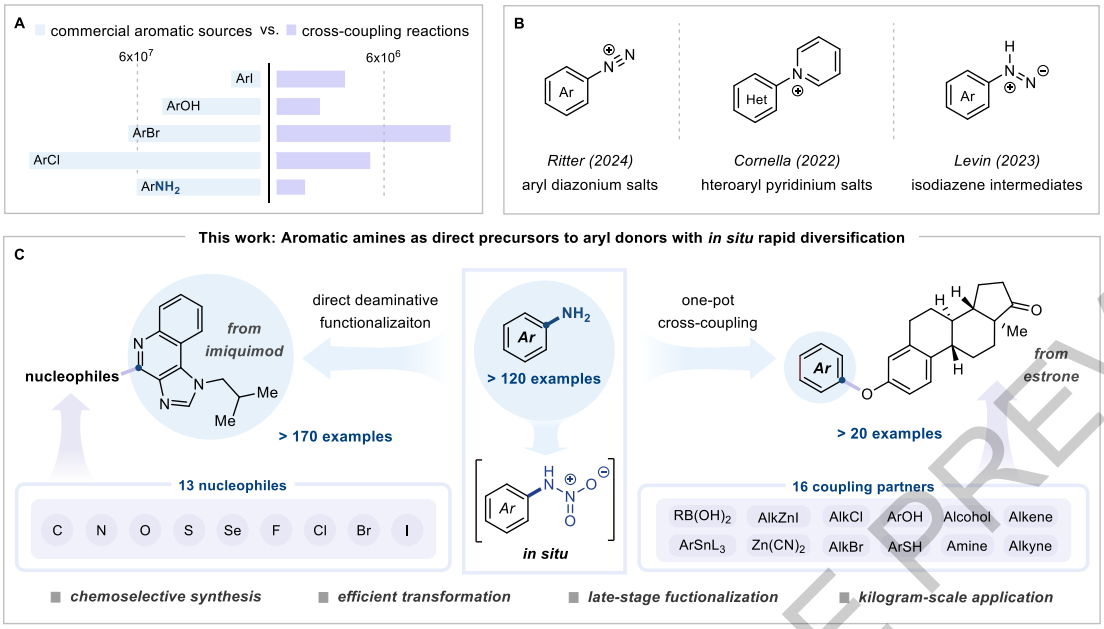
Extended Data Fig. 2 | Additional 29 substrates as extended scope (deaminative functionalization). Isolated yields. [a]^{1}H NMR yield. See Supplementary Information Section 4-6 for full experimental details. General halogenation conditions: amine (0.5 mmol), $SOBr_2$ (1.25 mmol) as a bromine source, HNO_3 (2.0 equiv.), DMAP (2.5 equiv.), DCE (5.0 mL), 70 ℃, 1 h; amine (0.5 mmol), KI (2.0 mmol) as an iodine source, HNO_3 (6.0 equiv.), DCE (5.0 mL), 70 ℃, 1 h. Nuc, nucleophiles; Ph, phenyl; Tf, trifluoromethanesulfonyl; Sandm., Sandmeyer conditions; n.d., not detected.

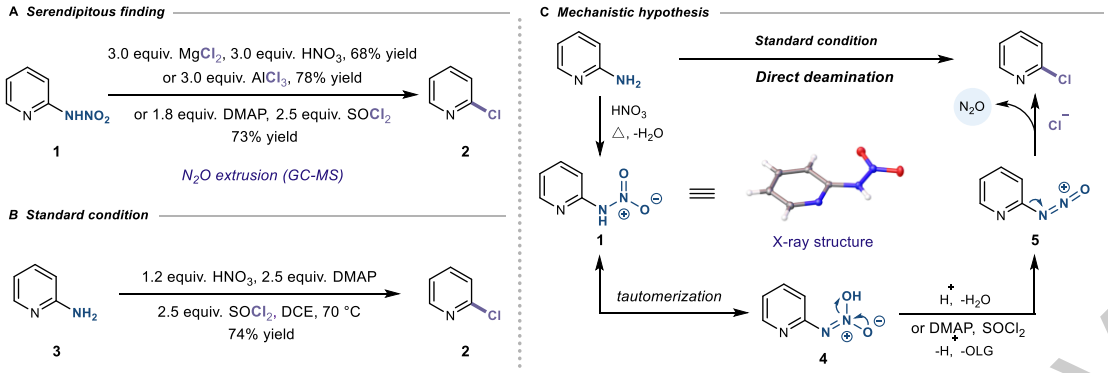
Extended Data Fig. 3 | Improved yields of representative substrates compared to Sandmeyer or diazo methods. [a]^{1}H NMR yield.See section 4-6 for full experimental details. Nuc, nucleophiles; Sandm., Sandmeyer conditions; Diaz.s., diazonium salts; n.d., not detected.

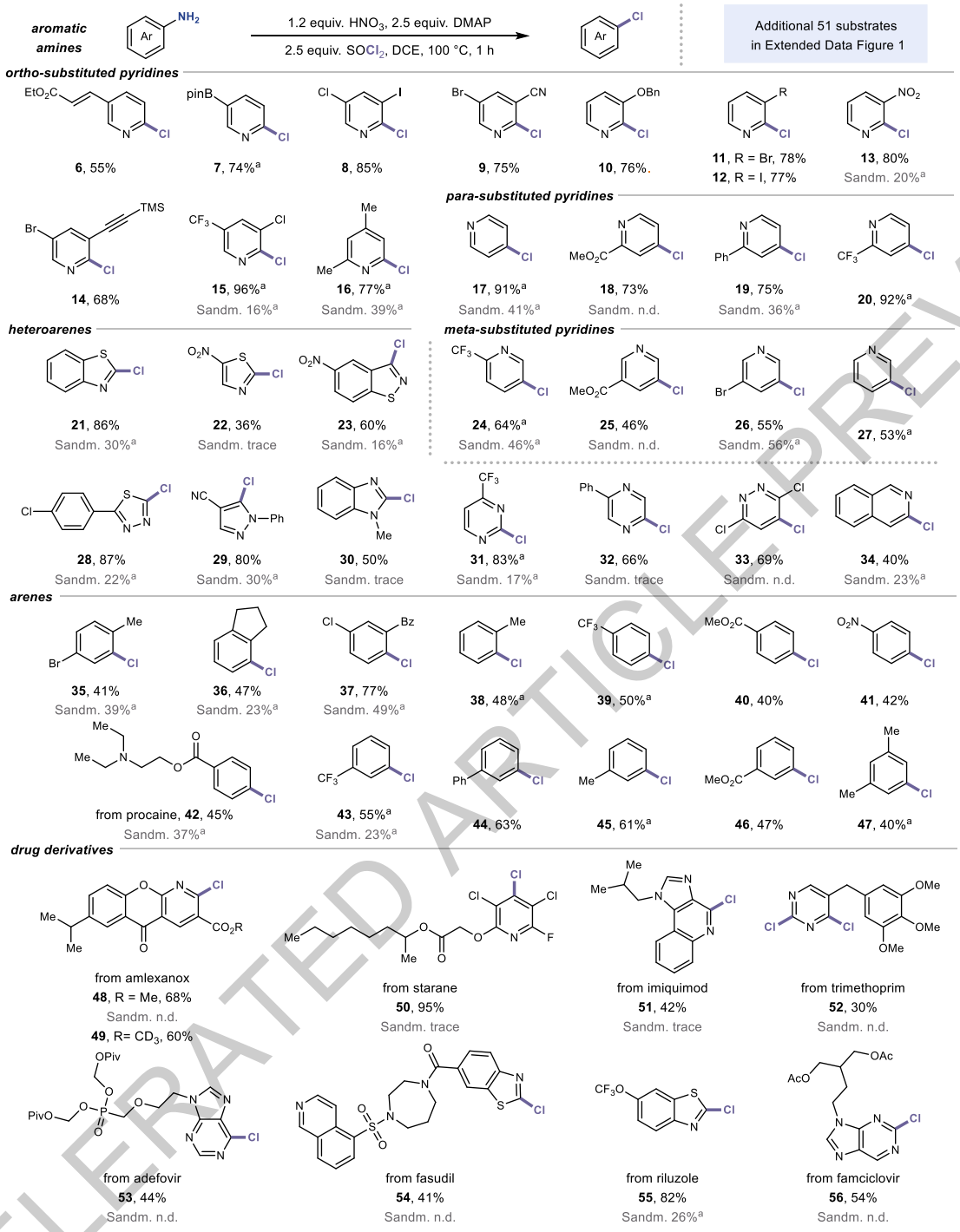
Extended Data Fig. 4 | One-pot deaminative cross-coupling reactions. All yields are isolated. See Supplementary Information Section 4 and 8 for full experimental details. Boc, *tert*-butyloxy carbonyl; Ph, phenyl.

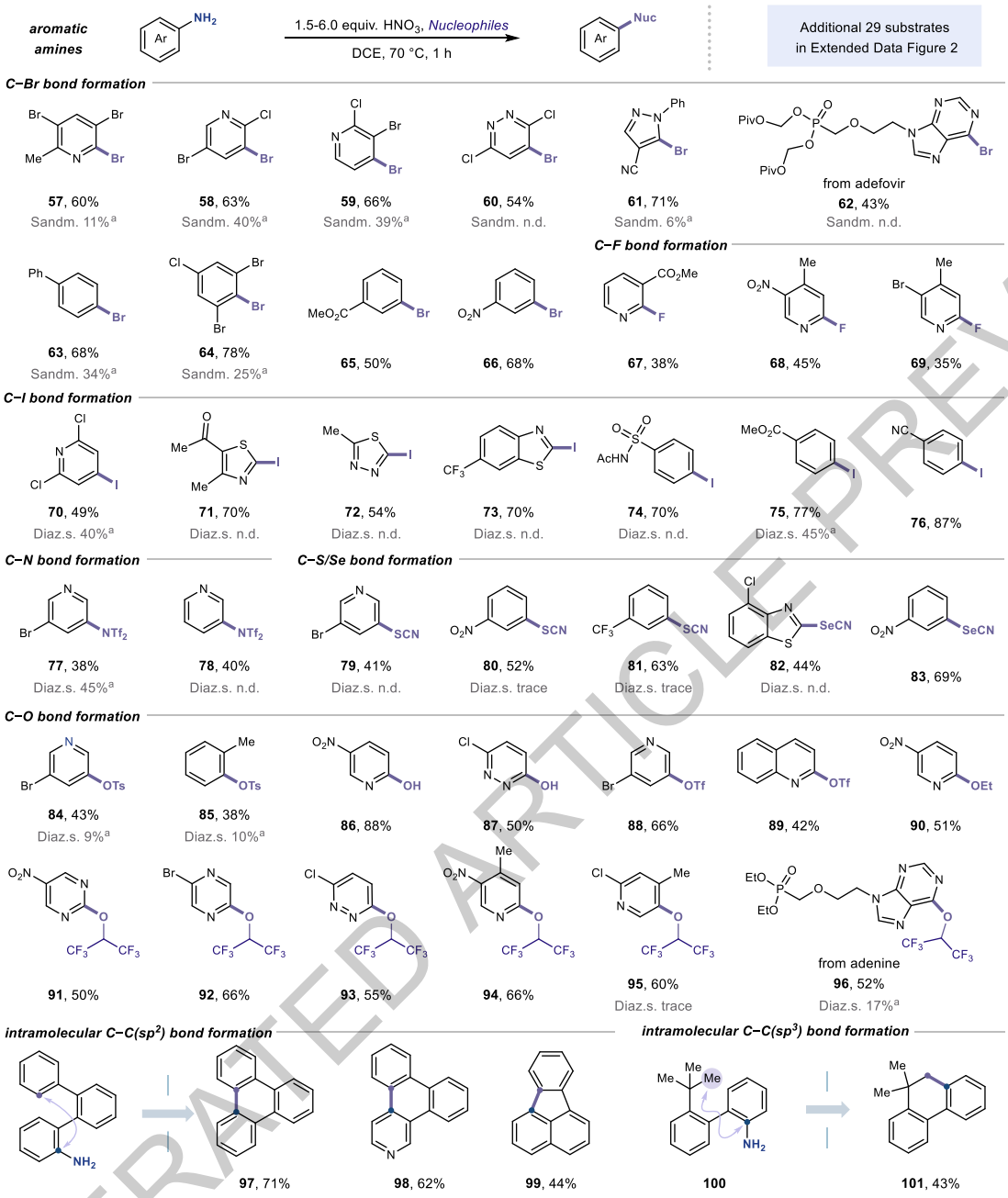
Extended Data Fig. 5 | Additional 16 examples for one-pot cross-coupling. All yields are isolated. See Supplementary Information Section 4 and 8 for full experimental details. Ph, phenyl; Ac, acetyl; ^{t}Bu, *tert*-butyl; Boc, *tert*-butyloxy carbonyl.

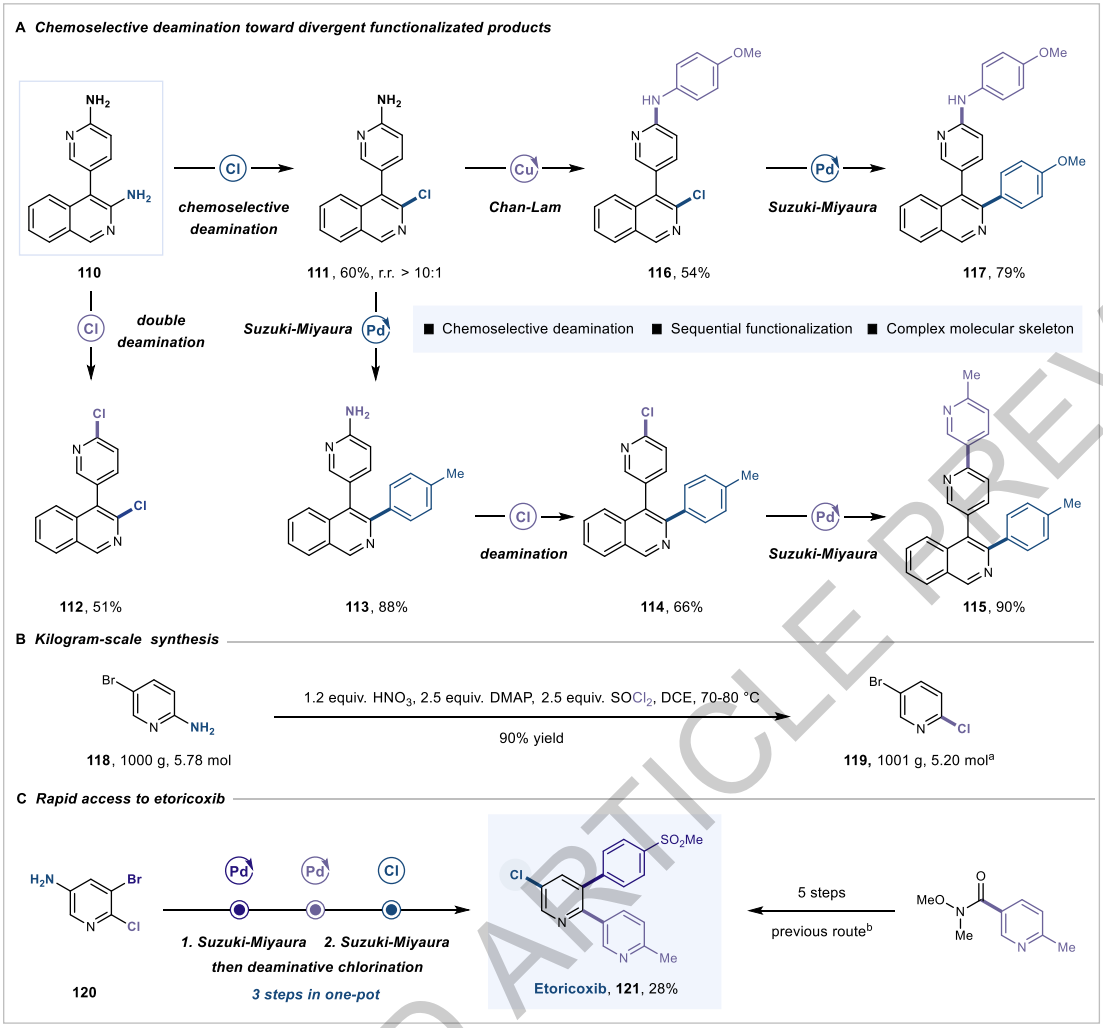
Extended Data Fig. 6 | Mechanistic studies. (A) C−H insertion and electrophilic substitution. (B) Control experiments. (C) Ritter-type reaction. (D) Hammett analysis. (E) Proposed mechanism. See Supplementary Information Section 3 for full experimental details.

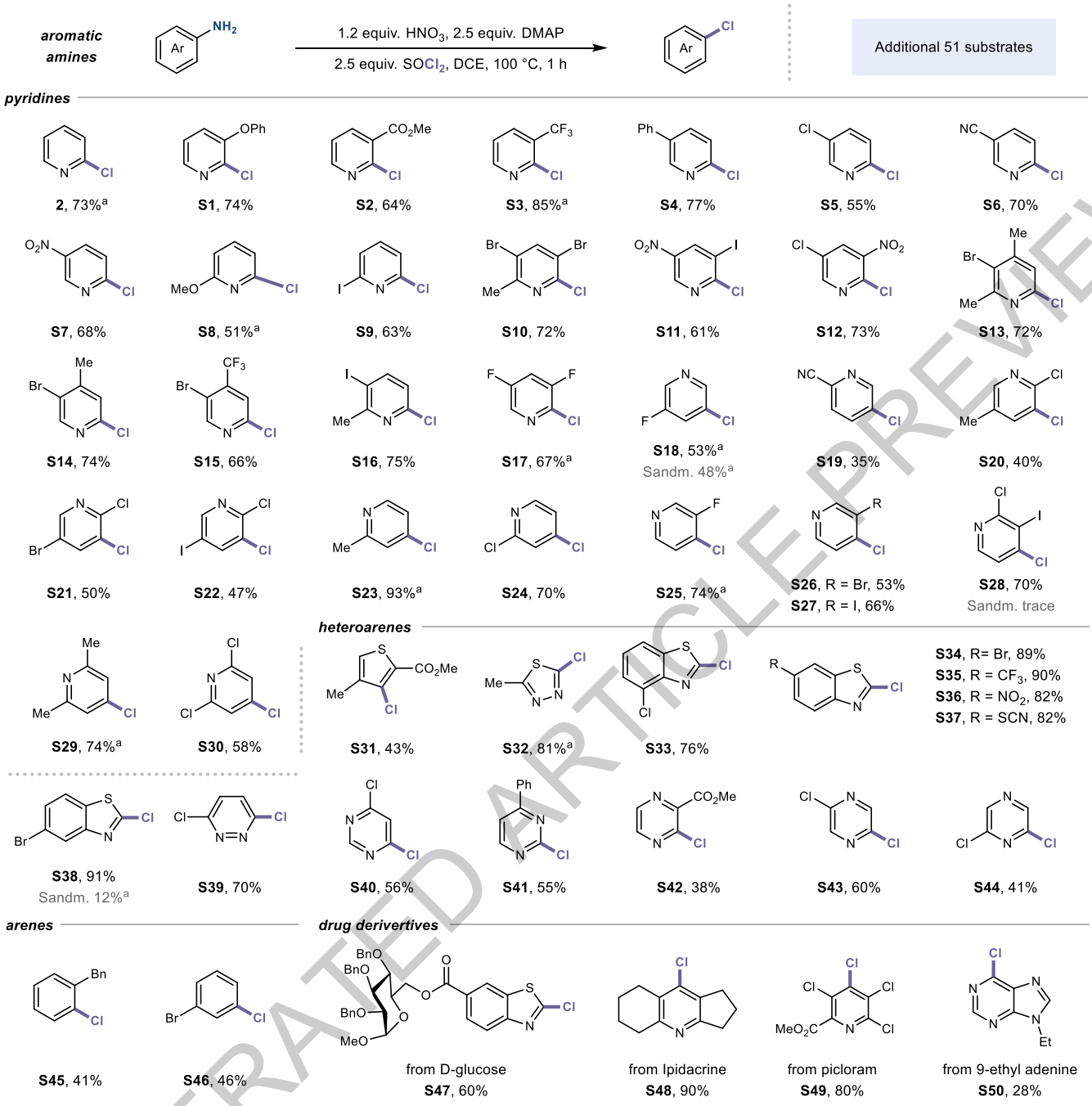












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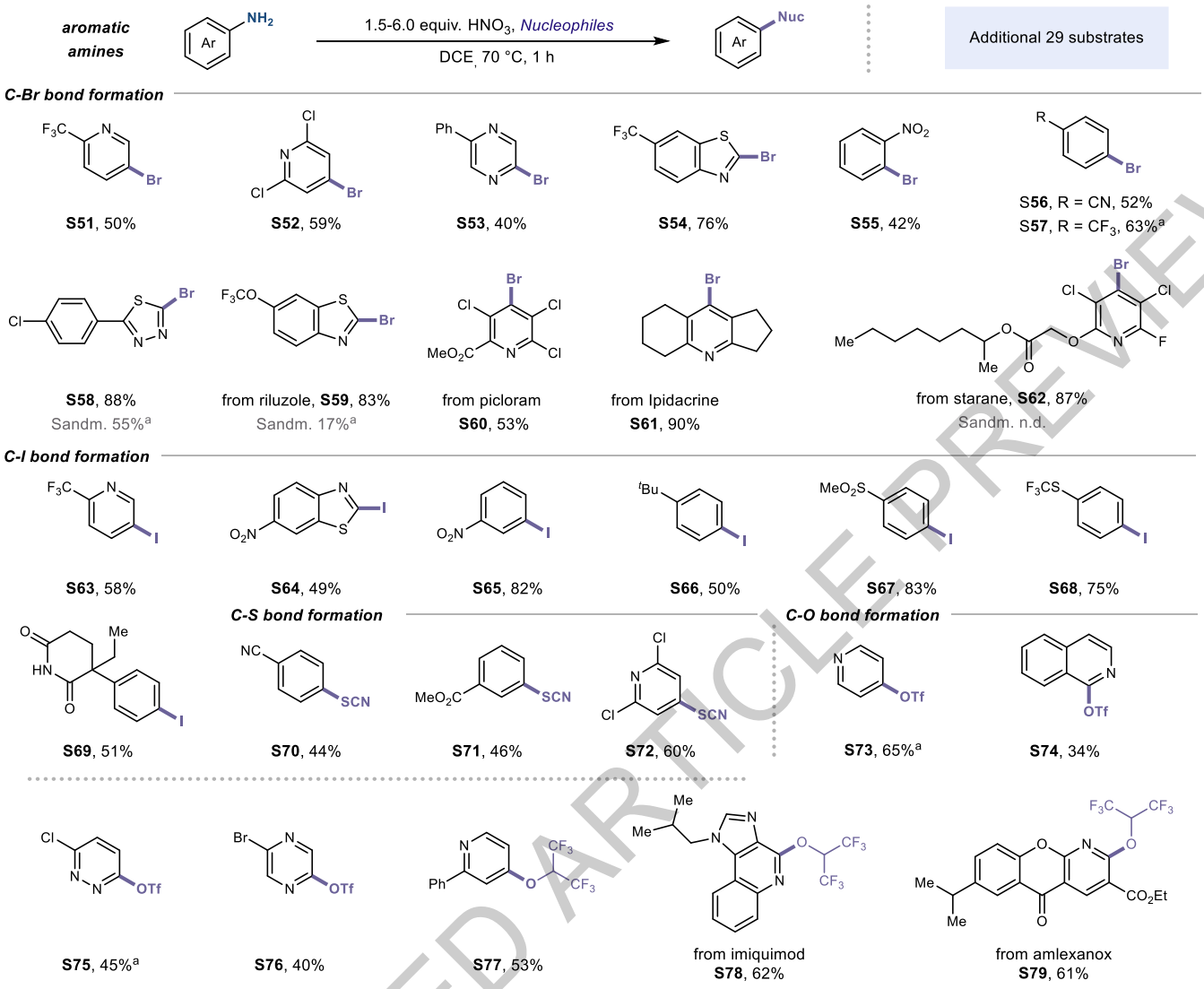

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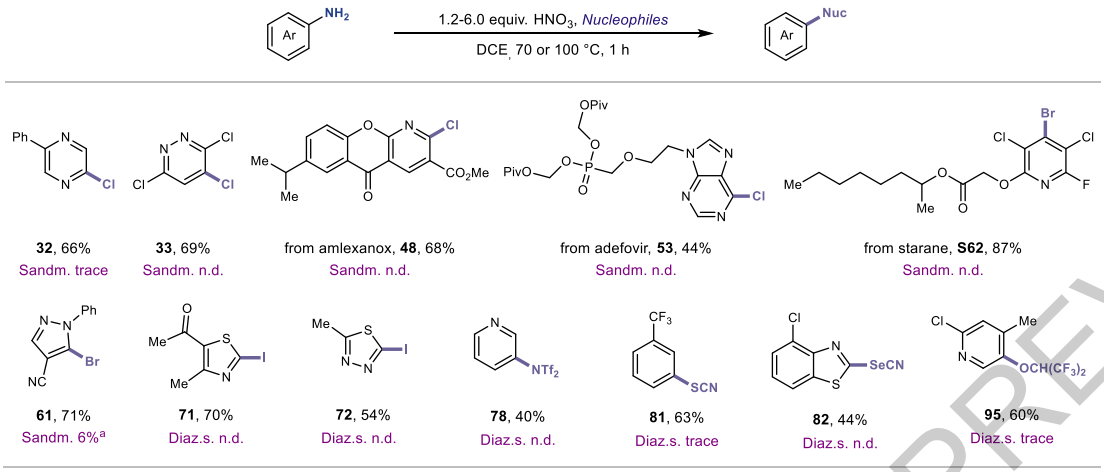

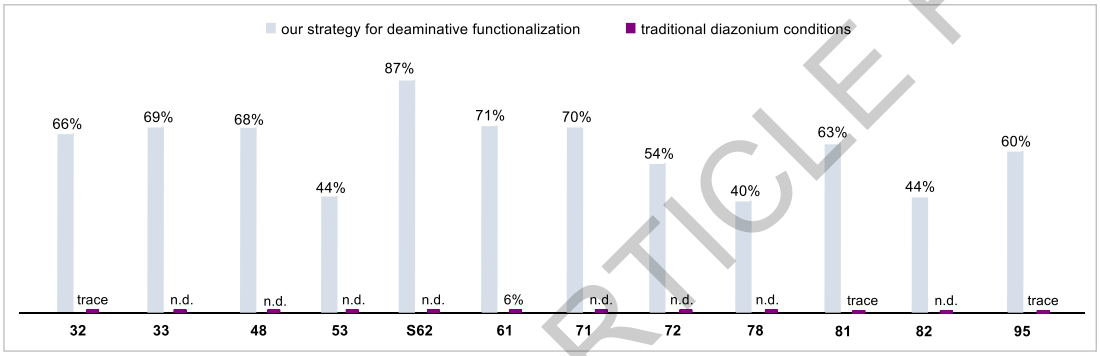

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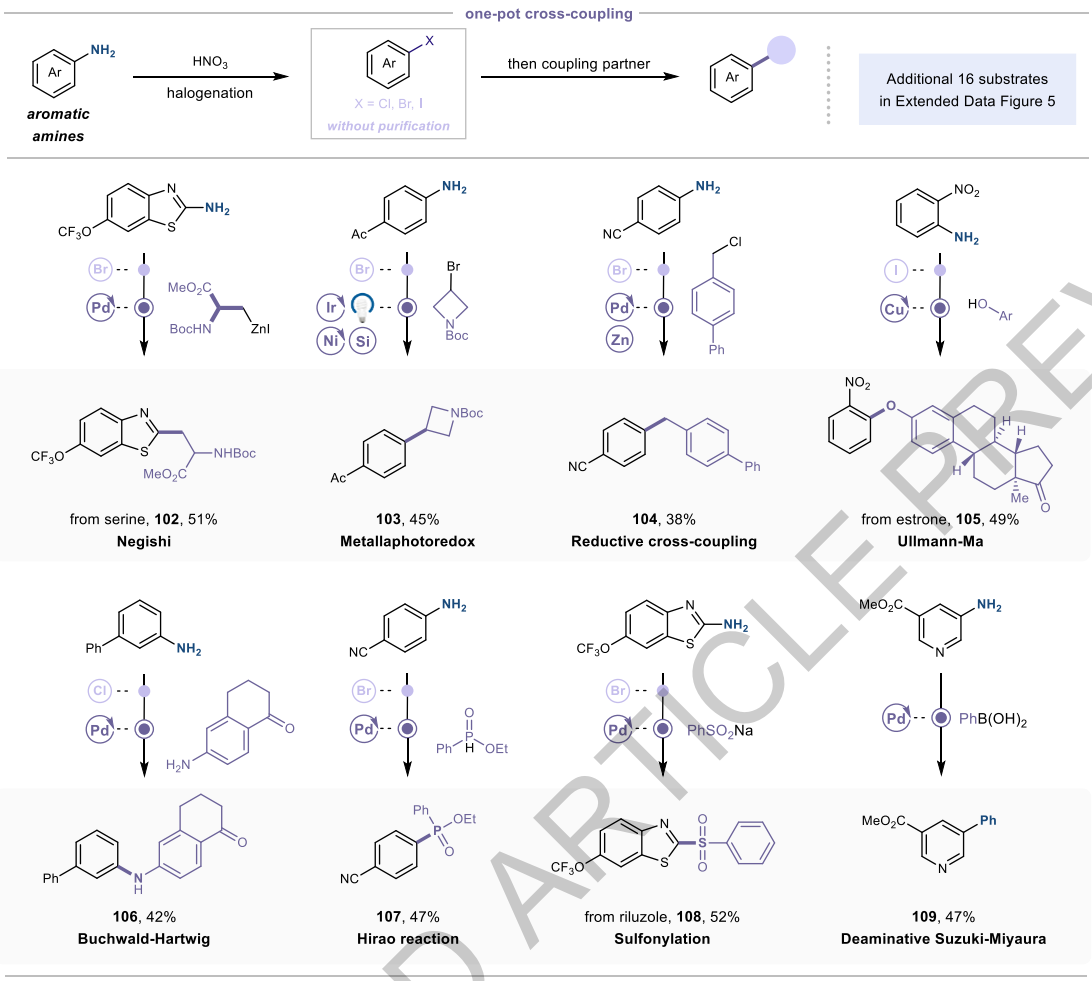

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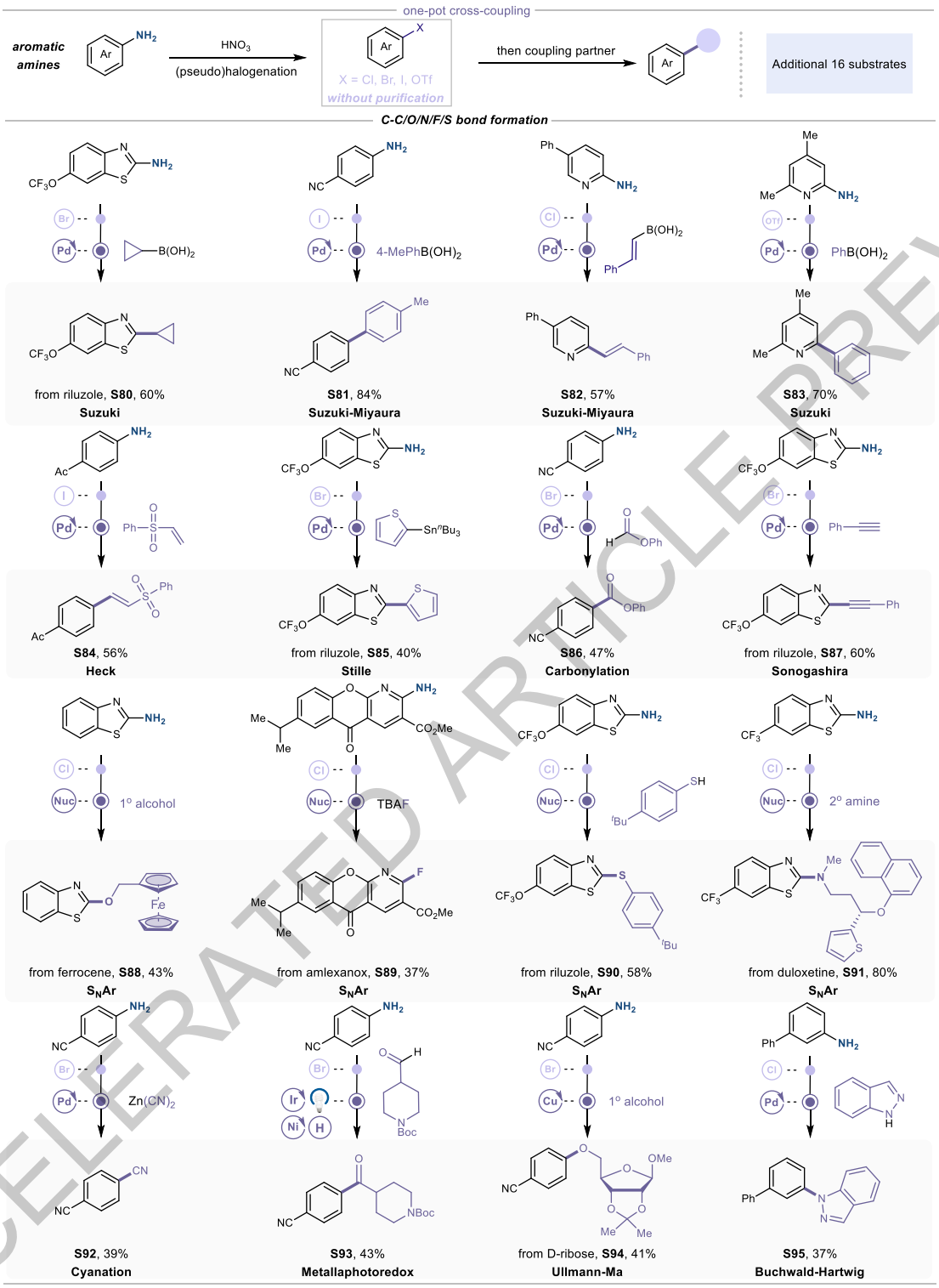

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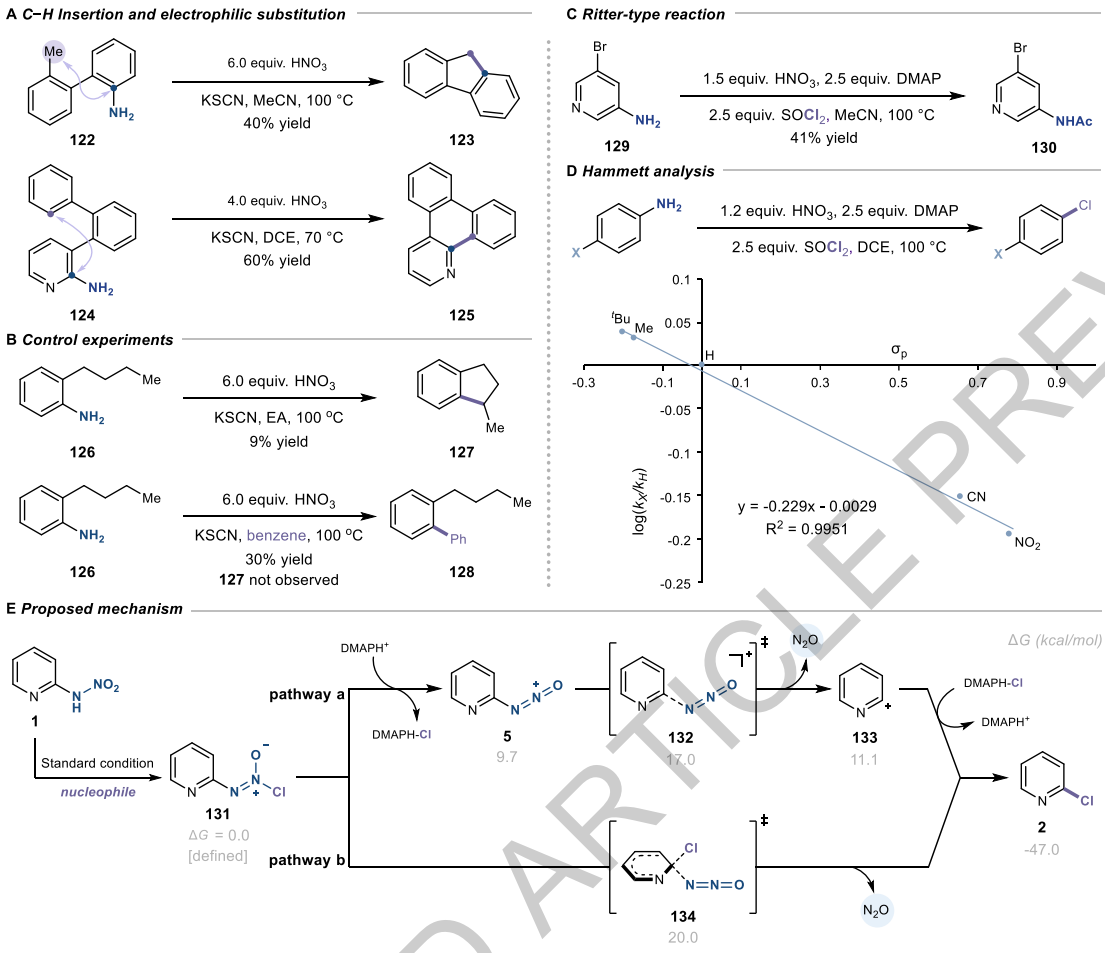

Extended Data Fig. 6