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Direct Deaminative Functionalization

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Abstract

Selective functional group interconversions in complex molecular settings underpin many of the challenges facing modern organic synthesis. Currently, a privileged subset of functional groups dominates this landscape, while others, despite their abundance, are sorely underdeveloped. Amines epitomize this dichotomy; they are abundant but otherwise intransigent toward direct interconversion. Here, we report an approach that enables the direct conversion of amines to bromides, chlorides, iodides, phosphates, thioethers, and alcohols, the heart of which is

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Supporting Information

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Experimental procedures, characterization data, and computational details (PDF)

Calculated properties of high throughput substrates (XLSX)

a deaminative carbon-centered radical formation process using an anomeric amide reagent. Experimental and computational mechanistic studies demonstrate that successful deaminative functionalization relies not only on outcompeting the H-atom transfer to the incipient radical but also on the generation of polarity-matched, productive chain-carrying radicals that continue to react efficiently. The overall implications of this technology for interconverting amine libraries were evaluated via high-throughput parallel synthesis and applied in the development of one-pot diversification protocols.

The functional group concept is central to organic chemistry, allowing classification of compounds on the basis of reactive substructures.[1-6] Some functional groups are clearly privileged in their ability to serve as points of diversification, with halides, carboxylic acids, organoboron compounds, and alcohols serving critical (and growing) roles in this capacity.[7-11] As such, it comes as no surprise that these groups comprise the bulk of fragment libraries used in drug discovery.[12-14] Accordingly, a great deal of effort has been undertaken to coax other nontraditional functional groups to behave more like their more diversifiable counterparts.[15-18] Despite their significant abundance in nature and in medicinal chemistry libraries,[19] amines have remained one of the most challenging groups for functional group interconversion, likely as a consequence of their low heterolytic nucleofugality, high homolytic C—N bond dissociation energy, and characteristic basicity.[20-24]

With few exceptions, transformations of amines into other functional groups rely on preactivation strategies, thus requiring a minimum of two distinct transformations to accomplish one desired interconversion (Figure 1A). The classical example of this is conversion of the amino group to a diazonium ion,[25,26] with more recent protocols employing Katrizky-type pyridinium salts[27-35] or electron-rich imines.[36,37] A rare instance of a direct deaminative functionalization was recently reported by Cornella,[38,39] in which *in situ* formation of a pyridinium ion allows deaminative functionalization via an S_NAr mechanism for electron-poor (hetero)aromatics. The rarity of one-step amine diversification processes is a stark reminder of the inadequacies in this area of synthetic chemistry.

Beyond the necessity for prefunctionalization, each of these prior examples is limited to either aliphatic or aromatic amines due to the instability of key intermediates and the underlying differences in reactivity between aromatic and aliphatic amines. For example, aliphatic diazonium ions are prone to elimination rather than substitution. Likewise, radical generation from Katrizky salts tends to be limited to sp^3-centered reactivity.[20]

To address this shortfall, we hypothesized that the anomeric amide-promoted deamination method previously reported by some members of our team,[40,41] which productively engages both aliphatic and aromatic amines (Figure 1B), could provide a unified solution to the question of deaminative functionalization. In particular, we suspected that the free radical intermediates involved in this process could be intercepted for productive bond formations beyond hydrogen atom transfer (HAT). Several challenges to this direct deaminative functionalization needed to be overcome for this hypothesis to be realized (Figure 1C). First, the nucleophilicity and basicity of amines as well as the electrophilicity and oxidizing properties of **1** introduce compatibility constraints that rule out common radical trapping

agents (e.g., Selectfluor and B_2Pin_2). Second, suitable reagents would need to outcompete the competitive HAT process—a nontrivial hurdle given the dramatic reducing capacity of the isodiazene intermediates involved in the original chain mechanism.[41] A third, more subtle requirement was ultimately uncovered through our mechanistic study (*vide infra*): the byproducts of the radical trapping process *must be productive chain carriers* in order to minimize the number of high-barrier initiation events required for reactivity. We report here the successful realization of this strategy, providing a method for deaminative bromination of both aromatic and aliphatic amines, along with more focused strategies allowing aromatic phosphonylation and thiolation as well as aliphatic hydroxylation.

Initial investigations uncovered CBr_4 as a trapping reagent that affords high yields of the corresponding bromodeamination products.[42,43] Given the utility of converting a nucleophilic handle into an electrophilic handle and the difficulty of accomplishing aliphatic bromodeamination by traditional means,[44,45] we sought to probe the generality of this method with respect to amine structure (Figure 2).

Both α-primary and α-secondary primary aliphatic amines as well as anilines (including several active pharmaceutical ingredients **2k**, **2l**, **2m**, and **2y**) were smoothly converted, even enabling multiple bromodeamination events on a single substrate (**3x**). Remarkably, despite the simplicity of the conditions, this deaminative bromination process exhibits a broader scope under milder conditions than our previously reported hydrodeamination protocol. For example, benzylic substrates (e.g., **2d** and **2e**) were generally not productively deaminated in the absence of CBr_4 but afford benzylic bromides under the conditions employed here. Ambient temperatures could be used for both amine classes, which stands in contrast to our prior work wherein deletion of aromatic amines typically required heating.

We then leveraged parallel synthesis and high-throughput purification platforms to further survey the reaction scope with a set of 75 commercially available amines. A diverse set of amines were chosen by selecting across multiple clusters in a self-organizing map,[46] while enriching for pharmaceutically relevant motifs, including saturated and unsaturated heterocycles, hydrogen bond donors, and hydrogen bond acceptors. A subset of the results are summarized in the bottom panel of Figure 2 with full details in the Supporting Information.[47] Together, our traditional and high-throughput scope evaluations offer insight into the merits and limitations of this method. In particular, we have categorized common failure modes that include poor nucleophilicity, competitive deamination, C–H bromination (a reaction that is not suppressed by the addition of halide scavengers and whose origin is unknown), spontaneous cyclization, and elimination. Further analysis of the high-throughput data can be found in the Supporting Information.

Inspired by the outcome of **HTS-40-ALT**, which undergoes spontaneous cyclization, we applied our deaminative bromination protocol to substrates bearing internal nucleophiles, with subsequent base-promoted cyclization affording the corresponding heterocycle for 4- (**4a**), 5- (**4b**, **4c**), and 6-membered (**4d**) ring formation (Figure 3A). Notably, this protocol could be applied to the calcium channel blocker Amlodipine, affording cyclized analogue **4f** in 62% overall yield over two steps, and to a lysine derivative, affording the far rarer pipecolic acid skeleton (**4e**).[48]

Intermolecular reactivity was next explored, specifically in the context of medicinally relevant motifs (Figure 3B-D). A commercially available aniline-based phenylalanine (Phe) derivative (**2af**) could be converted to a small library of unnatural Phes (**4g**–**4j**, Figure 3A). This process could be telescoped by the introduction of a simple liquid–liquid extraction to purge residual CBr_4 and related species.[49,50] Aliphatic amine building blocks could similarly be elaborated, including a recently identified, commercially available arene bioisosteric building block[51] (Figure 3C) and a precursor of the anticoagulant Xarelto (Rivaroxaban, **2ag**, Figure 3D).

We next surveyed additional trapping agents that would allow direct conversion of amines to other functional groups (Figure 4). Though none of the examined trapping reagents retained the generality of CBr_4, a number of valuable direct transformations were identified. CCl_4, for example, was found to chlorinate α-secondary aliphatic amines effectively but was unable to outcompete deamination for α-primary or aromatic amine substrates (Figure 4A). Isopropyl iodide was effective for both α-secondary and aromatic amines but afforded somewhat diminished yields for α-primary amines.[52,53]

Moving beyond halogenation, anilines were found to undergo productive phosphonylation with triethyl phosphite as well as thiolation with disulfides (Figure 4B), with the latter conditions requiring the addition of anhydrous inorganic base to suppress competitive hydrodeamination (and reduction of the anomeric amide) by the liberated thiol.[54-57] Aliphatic amines afforded lower yields with greater amounts of competitive hydrodeamination under these conditions.

Conversely, we found that saturation of the reaction solution with O_2 prior to addition of the amine substrate resulted in the formation of peroxide products, which could be reduced to the corresponding alcohols prior to isolation through treatment with triphenylphosphine (Figure 4C).[58] This net amine to alcohol conversion is of particular significance for medicinal chemistry as it allows one to retain a hydrogen bond donor (and acceptor) while drastically altering basicity. The process is applicable to a range of aliphatic substrates but was unfortunately poorly applicable to anilines. We attribute the divergence in these three methods to radical polarity effects, wherein nucleophilic aliphatic radicals more effectively engage triplet oxygen, while the electrophilic aromatic radicals are productively trapped by phosphites and disulfides.[59,60]

The peculiarities among these deaminative functionalization reactions with respect to amine structure, especially compared to the surprising broadness of the deaminative bromination, warranted a deeper mechanistic investigation. The proposed chain mechanism (omitting initiation and termination steps) is shown in Figure 5A; it is based on the analogous chain process previously determined to be operative in the parent deamination process[41] and is supported by computations at the DLPNO-CCSD(T)/def2-TZVPP-SMD(MeCN)//B3LYP-D3/def2-SVP-SMD(MeCN) level of theory.[61,62]

Experimental data also support this proposed mechanistic pathway (Figure 5B). Observation of **10** from a radical clock substrate as the sole product of deaminative bromination supports the intermediacy of an aryl radical. (Similar results were obtained for the hydroxylation

and thiolation; see the Supporting Information for details.) Additionally, in one attempted deaminative iodination with isopropyl iodide, a mixed aryl-isopropyl azo compound **11** was observed (and isolated as a mixture with the expected iodide). Together, these experiments are consistent with the generation of both carbon-centered (**R**) and diazenyl (**D**) radical intermediates.

In the absence of CBr_4, most benzylic amines underwent nonspecific decomposition, but in certain cases such as the mesityl substrate **2d**, the corresponding isotoluene product **12** can be detected by ^1H NMR as the major product (Figure 5B, bottom). Results from our computations suggest that this product could be formed via a concerted [2,3]-sigmatropic rearrangement of the intermediate isodiazene. Interestingly, the addition of carbon tetrabromide subverts this pathway and instead affords the benzylic bromide product **3d**. Addition of carbon tetrabromide to the isotoluene after its formation does not result in the formation of **3d**, suggesting that the CBr_4-mediated pathway intercepts the isodiazene intermediate prior to its rearrangement. This result, in turn, suggests that $^{\bullet}CBr_3$ is in fact a more effective chain carrier than the parent benzylic radical, undergoing more rapid HAT with the isodiazene.

Indeed, the computed rate constant for bromine atom transfer to ethyl radical is ~10^5 times slower than HAT (Figure 5C), suggesting that it is the far higher concentration of CBr_4 in comparison to the isodiazene that affords competitive radical trapping. Instead, the efficiency of this process seems to be driven by the capacity for $^{\bullet}CBr_3$ to carry the radical chain (via **B-TS-D**, $\Delta\Delta G^{\ddagger}$ = 2.7 kcal/mol compared to HAT by ethyl radical).[63] This model further accords with the observation that aromatic amines can be deaminated at lower temperatures in the presence of CBr_4 than in its absence—longer chains require fewer initiation events. Importantly, this facet of the CBr_4 radical chemistry serves to illustrate a general lesson: *a compound that successfully outcompetes reduction but does not generate a productive chain carrier is unlikely to be effective*.

This chain-carrying effectiveness can be attributed to radical polarity effects. The isodiazene is hydridic, such that electrophilic radicals ($^{\bullet}CBr_3$, $^{\bullet}OOR$, and $^{\bullet}SR$) undergo more rapid HAT[64] (see the Supporting Information for a detailed computational analysis). Phosphites, on the other hand, afford chain carriers of near-equal efficiency to the parent hydrodeamination process ($^{\bullet}Et$), consistent with the necessity to heat these reactions.

In summary, a suite of direct functional group interconversions for amines have been developed that complements the abundant nature of this functionality. By identifying productive chain carriers, various anomeric amide-mediated deaminative functionalization reactions were realized, with the tribromomethyl radical being uniquely effective for enabling bromodeamination of both aliphatic and aromatic amine substrates. The innate value of this process was benchmarked in a high-throughput library assay and used for the diversification of API building blocks. Deaminative phosphonylation, thiolation, and hydroxylation were shown to be possible applying the same mechanistic manifold (albeit to more specific amine classes). Mechanistic studies rationalized the disparity between deaminative bromination and other functionalization modes, supporting the superior chain-carrying nature of the polarity-matched carbon tribromide radical. As demonstrated, the

deaminative functionalization processes here provide practitioners with a new tool for amine diversification and will ultimately accelerate drug discovery efforts.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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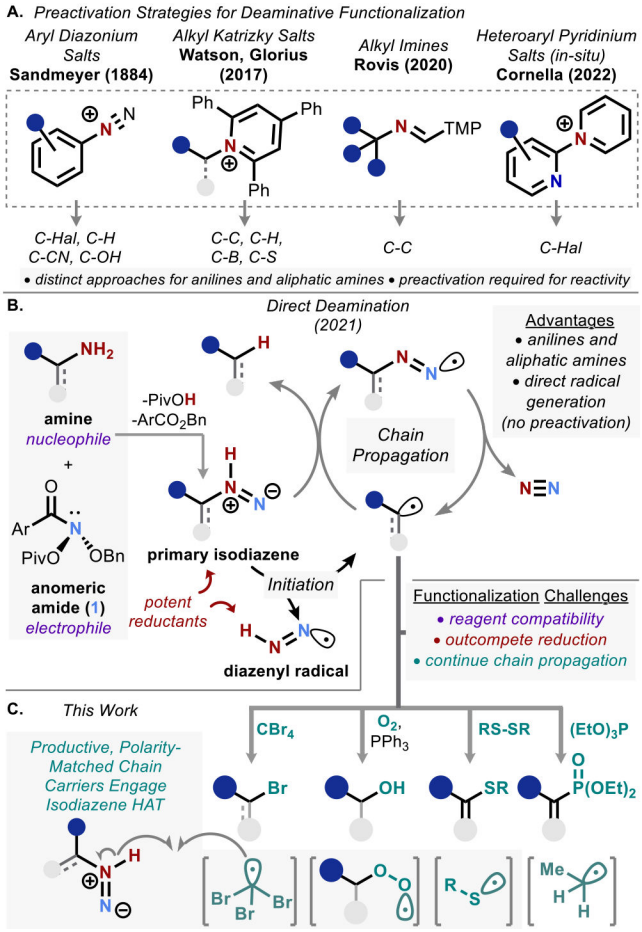

Figure 1.

Introduction. (A) State-of-the-art deaminative functionalization methods requiring preactivation. TMP = trimethoxyphenyl. (B) Previously reported direct deamination. (C) Challenges for radical trapping and successful direct deaminative functionalization relying on productive chain carrier generation.

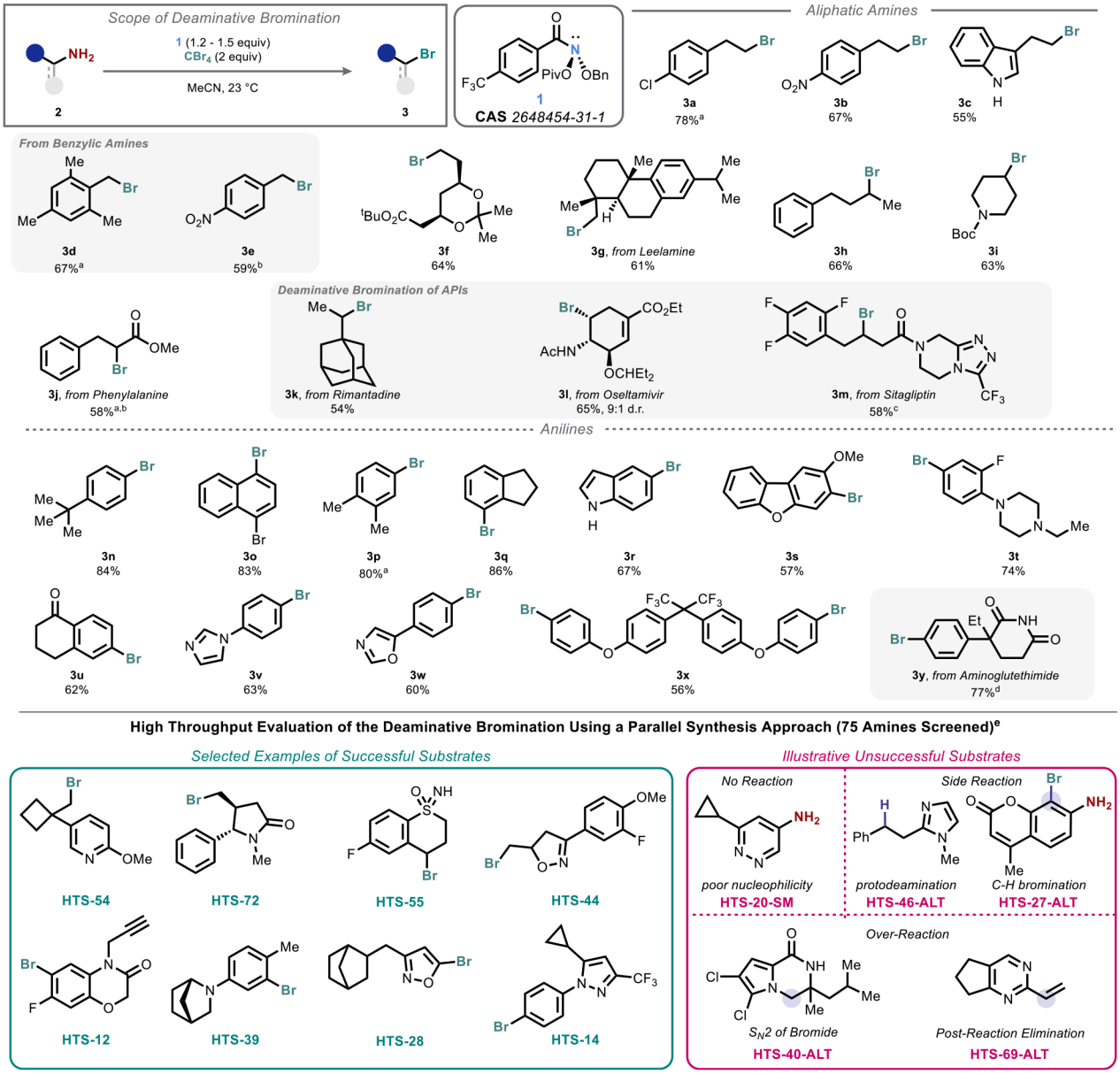

Figure 2.

Scope of the deaminative bromination and high-throughput screening data. Conditions: **1** (aliphatic amines −1.2 equiv, aromatic amines −1.5 equiv), CBr_4 (2 equiv), CH_3CN (0.1 M), 23 °C, 3 h (aliphatic) or 10 h (aromatic). Isolated yields unless otherwise indicated. [a]NMR yield. [b]Deamination also observed. [c]Isolated as TFA salt. [d]24 h. [e]See the Supporting Information for details.

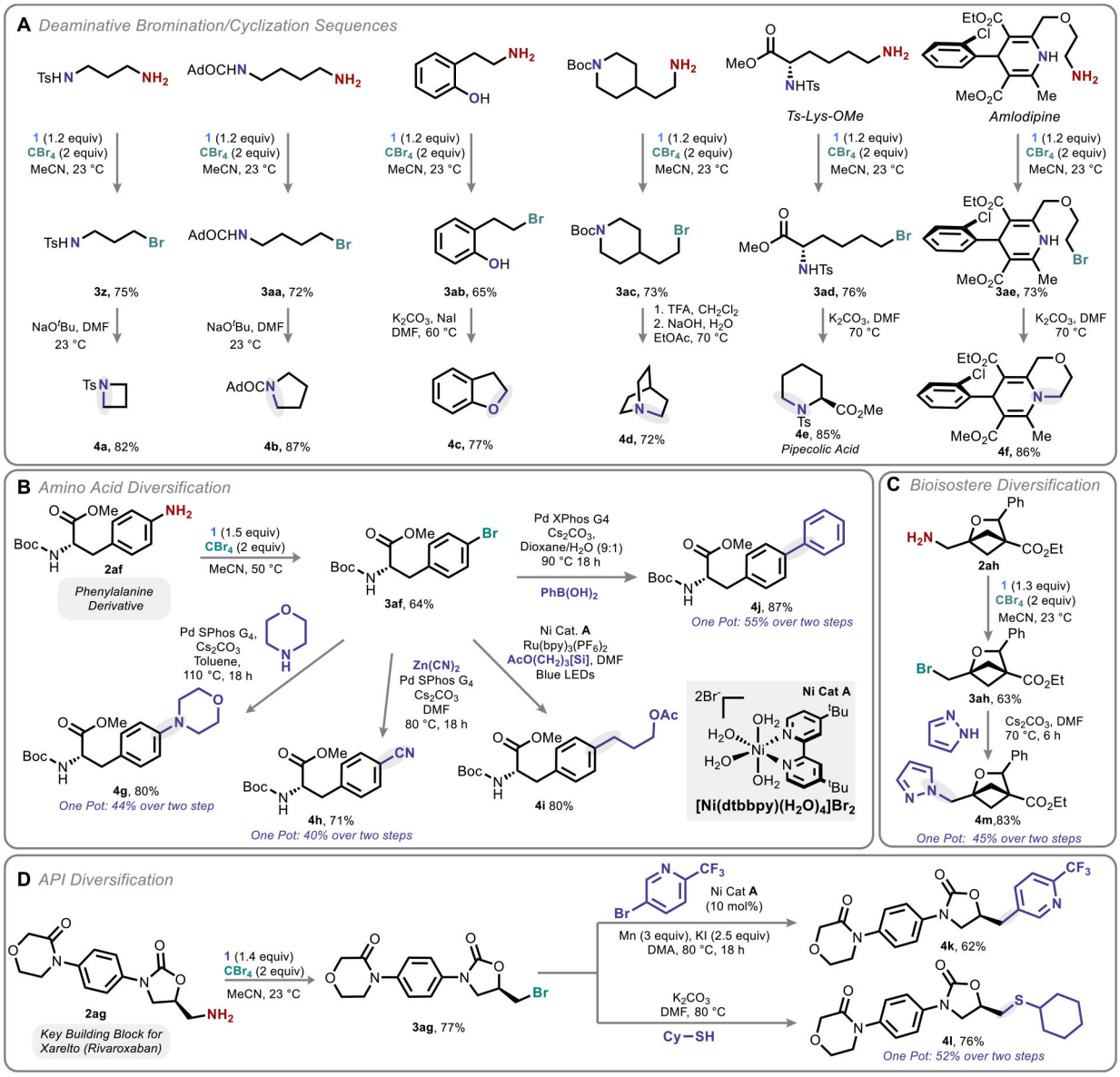

Figure 3.

Implications of deaminative bromination for downstream diversification. See the Supporting Information for detailed reaction conditions. [Si] = diisopropylammonium bis(catechol)silicate.

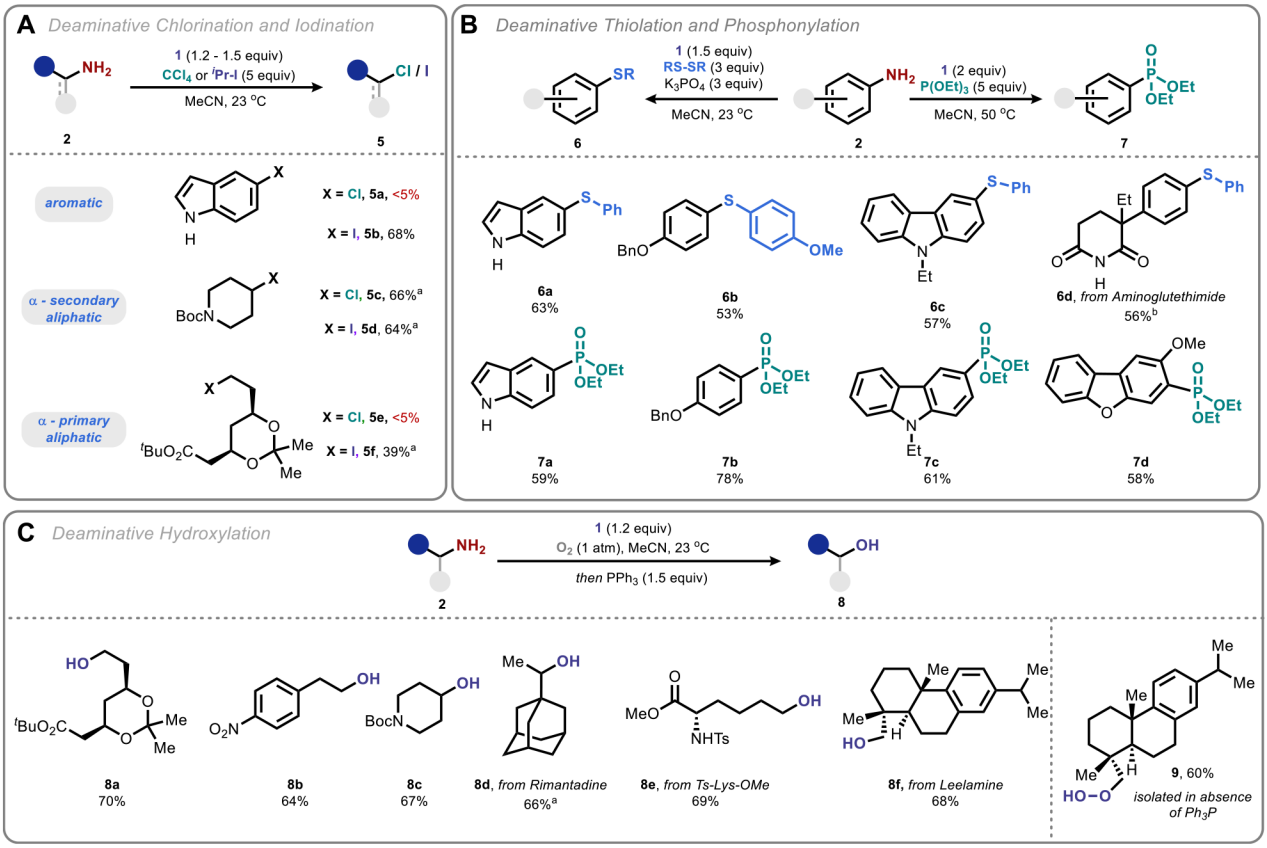

Figure 4.

Beyond bromination: aromatic phosphonylation, aromatic thiolation, chlorination, iodination, and aliphatic hydroxylation. See the Supporting Information for detailed reaction conditions. [a]NMR yield. [b]50 °C.

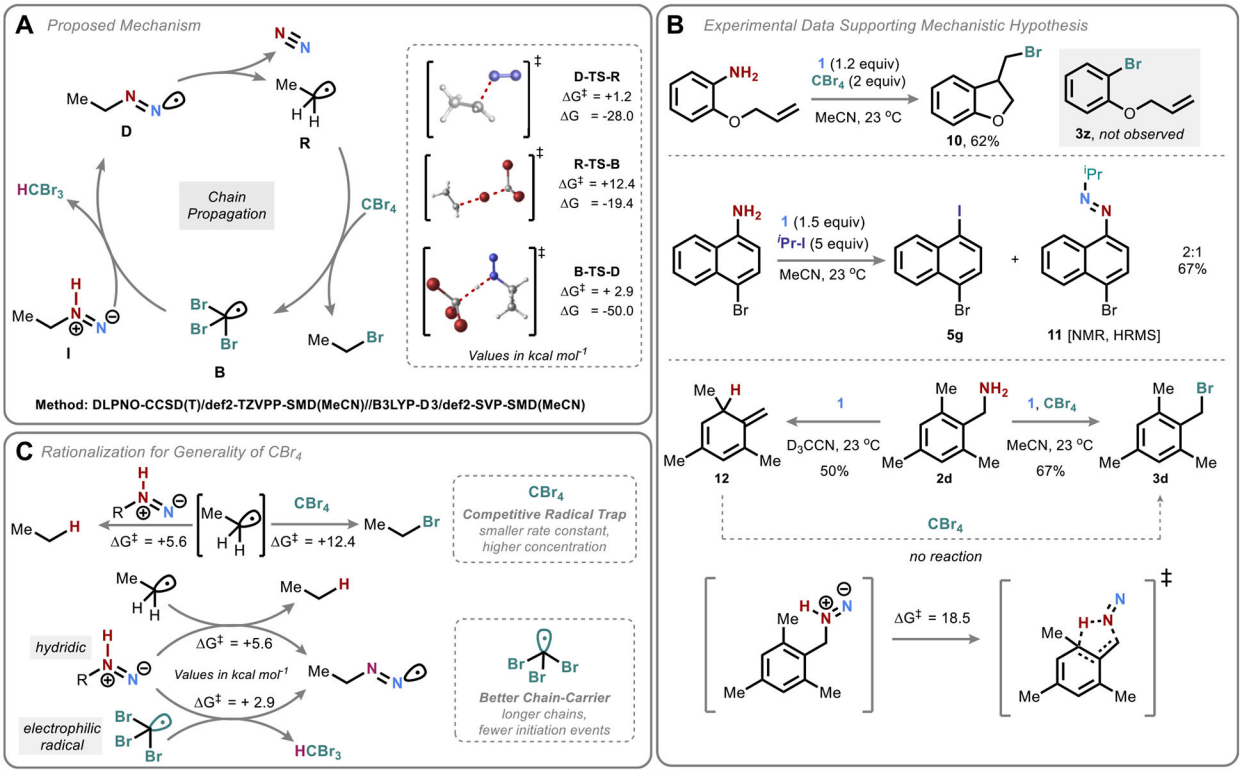

Figure 5.

Mechanistic and computational study. (A) Proposed mechanism with computed energetics. (B) Experimental mechanistic evidence. (C) Rationalization of the generality of CBr_4.