Synthesis of Secondary Amines via Self-Limiting Alkylation of N-Aminopyridinium Salts

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Abstract Partial amine alkylation to prepare secondary amines is challenging due to the enhanced N-nucleophilicity that accompanies alkylation. Here we introduce N-aminopyridinium salts as ammonia surrogates for the synthesis of secondary amines via self-limiting alkylation chemistry. A one-pot protocol based on N-aminopyridinium arylation followed by N-alkylation and in situ depyridylation provides access to aryl alkyl amines. The method is compatible with complex molecular settings and overcomes classical challenges in selective amine alkylation by accomplishing alkylation via transient pyridinium ylide intermediates. These findings both establish N-aminopyridinium salts as ammonia synthons and provide a new disconnection for the construction of structurally complex secondary amines.
Basic nitrogen sites are ubiquitous in biologically active organic small molecules due to the importance of electrostatic and H-bonding interactions in enzymatic molecular recognition.\cite{1-3} Many common synthetic methods towards amines leverage the intrinsic $N$-centered nucleophilicity of trivalent nitrogen: $N$-alkylation protocols, reductive amination reactions, and metal-catalyzed C–N cross-coupling methods all employ nucleophilic amines in combination with appropriate electrophilic partners.\cite{4-10} While these methods enable access to families of nitrogen-containing compounds, each faces significant limitations. Substitution reactions are often plagued by poor selectivity: $N$-centered nucleophilicity increases upon alkylation which renders partial alkylation, for example to access secondary amines, difficult. In addition, substitution chemistry is often accompanied by competing elimination processes. Reductive amination protocols are challenging to implement with either sterically encumbered amines or ketones.\cite{11-12} In addition, these methods rely on super stoichiometric quantities of hydride reagents and thus imply the generation of significant waste streams (Figure 1a). Finally, despite the incredible progress in metal-catalyzed C–N bond cross-coupling, application to C(sp$^3$)–N bonds is limited due to facile $\beta$-hydride elimination among other challenges.\cite{13}

Application of ammonia, the simplest amine, as a nitrogen source in synthesis is particularly challenging. Synthesis of primary or secondary amines via partial alkylation is difficult due alkylation-induced enhancement of amine nucleophilicity.\cite{14} Use of ammonia in transition metal-mediated processes is often stymied by coordination of Lewis basic ammonia to Lewis acidic transition metal ions.\cite{15-19} To avoid these challenges, a variety of ammonia surrogates — phthalimides,\cite{20} sulfonamides,\cite{21} dioxazolones,\cite{22} and benzotriazoles\cite{23} — have been advanced. While new amination reactions have been enabled by these reagents, the downstream chemistry is typically limited to deprotection to afford primary amines. Elaboration of the nitrogen valences of
these species confronts all of the aforementioned difficulties (Figure 1b). As a result, application of ammonia or its surrogates to selective amine synthesis remains a significant challenge.

![Figure 1](https://doi.org/10.26434/chemrxiv-2023-jm56l)

**Figure 1.** (a) Amine alkylation and reductive amination are classical synthetic methods for amine synthesis that utilize nucleophilic amine precursors. (b) Available ammonia surrogates do not provide a general platform to access partially substituted amines. (c) Here, we demonstrate self-limiting alkylation of \( N \)-aminopyridinium salts enables selective synthesis of secondary amines.

Here, we demonstrate \( N \)-aminopyridinium reagents are useful ammonia synthons in the selective construction of secondary amines. Chan-Lam coupling of aryl boronic acids with \( N \)-aminopyridinium triflate provides ready access to a diverse set of \( N \)-aryl-\( N \)-pyridinium amines. Deprotonation of these salts affords highly nucleophilic pyridinium ylides that engage is facile substitution chemistry with alkyl halides. The resulting pyridinium salts are much less nucleophilic than the ylide precursor, which enforces selective monoalkylation. Further, *in situ* reductive cleavage of the N–N bond (*i.e.* removal of pyridinium moiety) affords secondary amines. Mechanistic experiments suggest that the depyridylation is triggered by electron transfer from
Cs₂CO₃. The N-arylation, N-alkylation sequence can be applied in the context of complex, pharmaceutically relevant molecules and can be conveniently performed as a one-pot procedure. These results extend the burgeoning chemistry of N-aminopyridinium salts as bifunctional amine synthons²⁴-³⁰ and introduce self-limiting alkylation as a conceptual approach for selective synthesis of secondary amines (Figure 1c).

We initially envisioned a two-step protocol for secondary amine synthesis based on sequential N-arylation and N-alkylation of N-aminopyridinium salts and set out to identify conditions for each of these transformations. Previous reports of N-arylation of N-aminopyridinium via either SₐₙAr or Pd-catalyzed coupling were limited to electron-deficient, heteroaryl halide coupling partners.³¹,³² We previously suggested that N-aminopyridinium salts function as plug-in replacements for toluenesulfonamide (i.e., TsNH₂) in various amination reactions.²⁵-²⁶ We envisioned that Chan-Lam coupling, which had been demonstrated for sulfonamides,³³-³⁴ could represent a general strategy to arylation of N-aminopyridinium salts. Based on the sulfonamide-to-aminopyridinium analogy, we rapidly identified CuF₂-catalyzed Chan-Lam cross-coupling reaction that enables highly efficient access to N-aryl-N-aminopyridinium derivatives: Combination of 4-trifluoromethylphenyl boronic acid 2a, N-aminopyridinium triflate (1), and catalytic CuF₂ in DMA at 70 °C under an O₂ atmosphere afforded 1-((4-(trifluoromethyl)phenyl)amino)pyridinium triflate (3a) in 97% yield (Figure 2). No products of double arylation of 1 were detected. Optimal yields were obtained by adding the catalyst in two portions (i.e., 2 × 5 mol%). Varying the catalyst, solvent, and temperature did not improve reaction efficiency; optimization details are described in Table S4. The developed procedure was readily translated to gram-scale synthesis: Compound 3a was prepared in 71% yield on an 8 mmol scale (2.2 g product).
Figure 2. Scope of Cu-catalyzed coupling of 1 with aryl boronic acids (2) to afford N-arylaminopyridinium salts (3). Conditions: 1 (1.0 equiv), 2 (1.5 equiv), CuF$_2$ (10 mol%), DMA, O$_2$, 70 $^\circ$C.

Electron-deficient and -neutral substrates were coupled with the highest yields (3a-3c). Electron-rich substrates, such as 2d and 2e engage is less efficient coupling; compounds 3d and 3e were obtained in 62% and 37% yield, respectively. This trend is in contrast to many Chan-Lam reactions, but mirrors observations from a recent electrochemical Chan-Lam coupling. Substrates featuring halogen substitution (i.e., 2f to 2h) as well as protected alcohols (2i) and acids (2j) are all converted to the corresponding N-aminopyridinium salts 3f-3j in good yield. The developed reaction tolerates various substitution patterns (i.e., synthesis of 3k–3n). Further,
pharmaceutically derived $N$-aminopyridinium salts can be simply prepared, which highlights the applicability of the developed method: Indomethacin-derived boronic acid (2o) and thioflavin T-derived boronic acid (2p) were converted to their respective to aminopyridinium derivatives 3o and 3p in 32% and 46% yield, respectively.

With robust conditions for the preparation of $N$-aryl-$N$-pyridinium amines, we turned our attention to developing alkylation chemistry that would provide access to secondary aryl alkyl amines and used salt 3a for development and optimization studies. While we initially envisioned a two-step $N$-alkylation, reductive depyridylation sequence would be necessary, we rapidly realized a one-step protocol that delivered secondary amines selectively.

Treatment of a MeCN solution of 3a with hexyliodide 4a and CsOAc at 70 °C resulted in $N$-alkylation to pyridinium amine 5a’ in 98% yield (Table 1). During studies to optimize the base used in this alkylation reaction, we observed that while carboxylate and bicarbonate bases afforded alkylated product 5a’ (Table 1, Entries 1 and 2), tert-butoxide or carbonate bases afforded secondary amine 5a, the product of $in situ$ depyridylation of 5a’, directly (Entries 3–5). Ultimately, Cs$_2$CO$_3$ was identified as the optimized base and promoted a one-pot alkylation/depyridylation sequence to furnish secondary amine 5a in 79% yield (see below for discussion of the depyridylation mechanism).
Table 1. Optimization of the alkylation-depyridylation protocol. Conditions: 3a (1.0 equiv), 1-iodohexane (4a, 2.0 equiv), base (3.0 equiv), CH$_3$CN, 70 °C, 16 h; yields are measured using 1,3,5-trimethoxybenzene as the internal standard.

<table>
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The developed alkylation/depyridylation protocol provided access to a broad array of secondary aryl alkyl amines (Figure 3). Diverse functional groups, including long alkyl chains (5a and 5b), cyanides (5c), amides (5e), and protected alcohols (5f) are well-tolerated. The reaction could be accomplished from the corresponding alkyl bromide or triflate, as demonstrated for the synthesis of 5a, in 63% and 49% yield, respectively. While secondary allylic and benzylic iodides engage is efficient alkylation, as demonstrated by the examples 5g (81%) and 5h (62%), unactivated secondary alkyl iodides do not engage in alkylation (i.e., 5i). For highly electrophilic starting materials, e.g., 4j–4m, a lower reaction temperature was used to prevent overalkylation: methyl iodide engaged in selective monoalkylation to afford 5j in 96% yield; primary benzyl iodides 4k and 4l were converted to secondary amines 5k and 5l in 98% and 60% yield, respectively; and primary allyl iodide 4m afforded secondary amine 5m in 43% yield. The reaction also showed good substrate tolerance for various N-arylaminoypyridinium derivatives 3. Both electron-neutral (5n-5o) and electron-donating (5p-5q) aminopyridinium derivatives were converted to their respective secondary aryl-alkyl amines efficiently. Moreover, thioflavin-T
derived N-aminopyridinium derivative 3p was converted to methylated amine 5r, which is used in investigational studies of Alzheimer's disease, in 74% yield.

Figure 3. Scope of monoalkylation of 3. Conditions: 3 (1.0 equiv), 4 (2.0 equiv), Cs₂CO₃ (3.0 equiv), CH₃CN, t °C, 16 h; yields are isolated.
The developed alkylation/depyridylation chemistry could be implemented in the context of natural products and drug molecules. Linoleyl iodide was transformed into 5s in 69% yield. Ibuprofen-derived alkyl iodide was converted to amine 5t in 58% yield. Isoxepac-derived and indomethacin-derived alkyl iodides were successfully coupled to give the corresponding products 5u and 5v in 42% and 45% yields, respectively. Biphenyl derived aminopyridinium 3c can also be coupled with indomethacin-derived alkyl iodide 4v to give the corresponding product 5w in 78% yield. The thioflavin T-derived N-aminopyridinium salt 3p can be coupled with ibuprofen-derived alkyl iodide 4t to yield the drug conjugate 5x in 70% yield. These examples highlight the compatibility of C–N bond construction with pharmaceutically relevant basic heterocycles, amides, carbamates, and basic amines.

With conditions developed for both N-arylation and and N-alkylation/depyridylation to furnish secondary amines, we sought to combine these reaction steps into a one-pot protocol. This objective was straightforwardly reduced to practice: Following Cu-catalyzed coupling of 1 and 2a, the reaction mixture was cooled to 23 °C and diluted with MeCN before Cs₂CO₃ and 1-iodododecane were added (Equation 1). Heating at 70 °C for 16 h afforded amine 5b in 41% yield.

After developing a robust one-pot protocol towards secondary amines from N-aminopyridinium salts, we pursued a series of experiments to clarify the mechanistic basis for 1) the observed partial alkylation and 2) the origin of in situ depyridylation.

To investigate the origin of partial alkylation, we treated pyridinium amine 3a with Cs₂CO₃; conversion to the corresponding pyridinium ylide (3a⁺) was evidenced by disappearance of the N–H resonance and shifts of the pyridinium C–H resonances in the ¹H NMR spectrum. Treatment of
Ylide 3a’ with alkyl iodide 4a led to rapid evolution of 5a’ (Figure 4a, see Section C.1 of Supporting Information). In contrast, neither p-trifluoromethyl aniline 6 nor amine 5a undergo deprotonation in the presence of Cs$_2$CO$_3$ and subsequent exposure to 4a did not result in appreciable alkylation products (Figure 4b, see Section C.3 of Supporting Information). These data indicate that the presence of an electron-withdrawing pyridinium substituent in 3a lowers the N–H pKa and enables access to ylide 3a’. Ylide 3a’ is more nucleophilic than amine 6 and thus undergoes alkylation under conditions that 6 is unreactive. In contrast to typical amine alkylation reactivity trends (vide infra), because depyridylation proceeds in situ, the products (i.e., 5a) are less nucleophilic than the starting material (i.e., ylide 3a’).

To investigate the unexpected in situ depyridylation reaction, we treated an independently synthesized sample of compound 5a’ to each of the reagents present during the alkylation reaction (see Section C.4 of Supporting Information). Treatment of 5a’ with excess Cs$_2$CO$_3$ results in efficient depyridylation to afford 5a in 79% yield along with pyridine (26%) and pyridine-derived products (see Section C.5 of Supporting Information). Further, alkylation of 3a in the presence of 1 equiv. of Cs$_2$CO$_3$ instead of the 3 equiv. used in the optimized conditions, resulted in alkylated pyridinium amine 5a’ (78%), not secondary amine 5a (see Section C.6 of Supporting Information). Based on these observations, we hypothesized that carbonate is the reductant responsible for the depyridylation chemistry. Consistent with the hypothesis, while Na$_2$CO$_3$ does not promote efficient depyridylation of 5a’, addition of 15-cr-5 to sequester Na$^+$ and generate a more reducing carbonate source, promotes efficient depyridylation (60% yield of 5a, Figure 4c). Analysis of the reaction headspace revealed the formation of CO$_2$ during successful deprotection reactions whereas unproductive conditions (i.e., Na$_2$CO$_3$ without 15-cr-5) did not evolve CO$_2$ (see Section C.7 of Supporting Information). These data suggest that Cs$_2$CO$_3$ is both responsible for ylide
formation from 3a and promotes depyridylation of alkylated pyridinium amine 5a' and are consistent with depyridylation via single-electron transfer from an electron donor-acceptor complex (i.e., 5''), which have previously been proposed.38-41

(a) Reaction of 4a with Ylide 3a'

(b) Unproductive Alkylation of 6 in Our Reaction Conditions

(c) Depyridylation of 5a' in Presence of More Reducing CO$_3^{2-}$ Source

(d) Proposed Mechanism

Figure 4. Preliminary mechanistic studies. (a) Reaction of ylide 3a' with 4a yields intermediate 5a'. (b) Aniline 6 does not undergo alkylation. (c) Depyridylation of 5a' proceeds with Na$_2$CO$_3$ and 15-crown-5. (d) Proposed mechanism for the alkylation/depyridylation sequence.

In summary, we describe a one-pot synthesis of secondary amines via self-limiting alkylation of N-aminopyridinium salts. The strategy displays broad substrate tolerance and can be applied to complex molecules. The demonstrated self-limiting N-alkylation chemistry overcomes the classical challenge of amine overalkylation by harnessing nucleophilic pyridinium ylides and in situ depyridylation chemistry. Mechanistic investigations reveal an unexpected role for carbonate, which both provides access to the ylide intermediates and serves a noncanonical role as reductant.
to effect depyridylation. The resulting method represent a new approach to secondary amines and validate \(N\)-aminopyridinium compounds as ammonia surrogates in synthetic chemistry.

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