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

Pritam Roychowdhury, Saim Waheed, Uddalak Sengupta, Roberto G. Herrera, and David C. Powers*

Department of Chemistry, Texas A&M University, College Station, TX 77843, USA

*powers@chem.tamu.edu

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.[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.[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.[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 β-hydride elimination among other challenges.[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.[14] Use of ammonia in transition metal-mediated processes is often stymied by coordination of Lewis basic ammonia to Lewis acidic transition metal ions.[15-19] To avoid these challenges, a variety of ammonia surrogates — phthalimides,[20] sulfonamides,[21] dioxazolones,[22] and benzotriazoles[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.

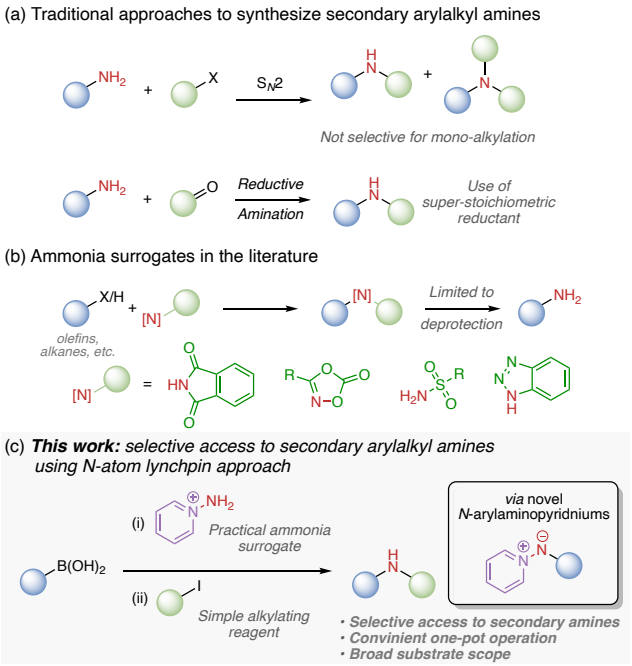


Figure 1. (a) Amine alkylation and reductive amination are classical synthetic methods for amine synthesis that utilize nucleophilic amine precursors. (b) Available ammonia surrogates do not provide a general platform to access partially substituted amines. (c) Here, we demonstrate self-limiting alkylation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

Cs_2CO_3. 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 synthons[24-30] 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 S_NAr 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.*, $TsNH_2$) 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 CuF_2-catalyzed Chan-Lam cross-coupling reaction that enables highly efficient access to *N*-aryl-*N*-aminopyridnium derivatives: Combination of 4-trifluoromethylphenyl boronic acid **2a**, *N*-aminopyridinium triflate (**1**), and catalytic CuF_2 in DMA at 70 ºC under an O_2 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).

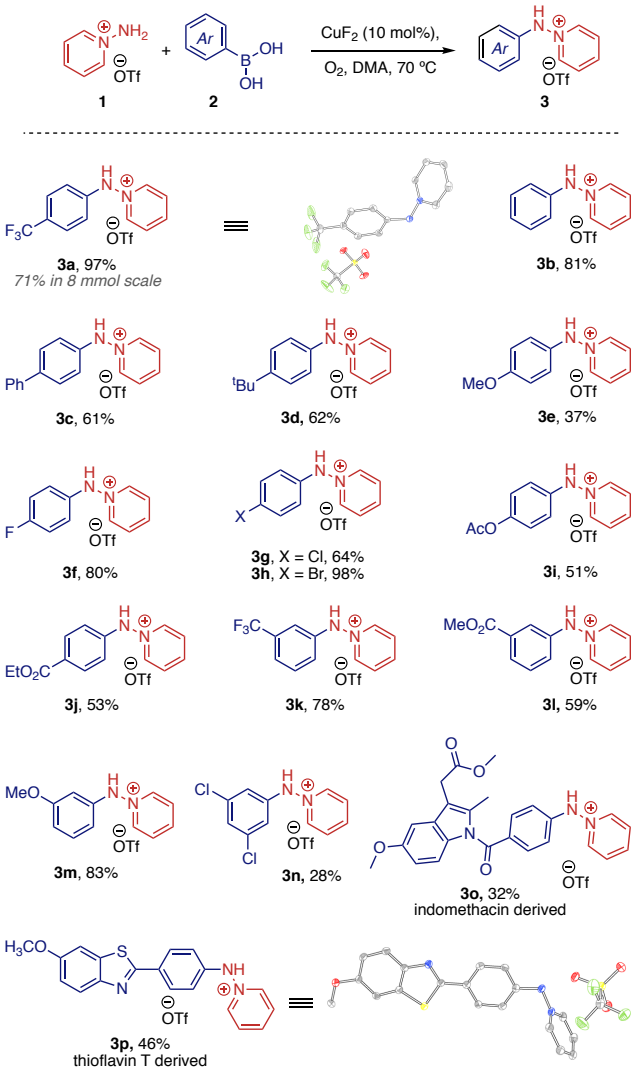


Figure 2. Scope of Cu-catalyzed coupling of **1** with aryl boronic acids (**2**) to afford *N*-arylaminopyridinium salts (**3**). Conditions: **1** (1.0 equiv), **2** (1.5 equiv), CuF_2 (10 mol%), DMA, O_2, 70 °C.

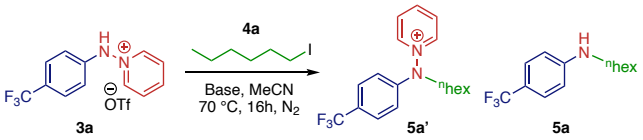
Electron-deficient and -neutral substrates were coupled with the highest yields (**3a-3c**). Electron-rich substrates, such as **2d** and **2e** engage is less efficient coupling; compounds **3d** and **3e** were obtained in 62% and 37% yield, respectively. This trend is in contrast to many Chan-Lam reactions,[9, 35-36] but mirrors observations from a recent electrochemical Chan-Lam coupling.[37] 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*-aminopyridnium 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 ºC 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_2CO_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_3CN, 70 °C, 16 h; yields are measured using 1,3,5-trimethoxybenzene as the internal standard.



entry	base	yield of 5a' (%)	yield of 5a (%)
1	CsOAc	98	0
2	$NaHCO_3$	78	0
3	Na^tBuO	0	23
4	K_2CO_3	18	45
5	**Cs_2CO_3**	**0**	**79**

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 demonstrate 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*-arylaminopyridnium derivatives **3**. Both electron-neutral (**5n-5o**) and electron-donating (**5p-5q**) aminopyridnium derivatives were converted to their respective secondary aryl-alkyl amines efficiently. Moreover, thioflavin-T

derived *N*-aminopyridnium derivative **3p** was converted to methylated amine **5r**, which is used in investigational studies of Alzheimer's disease, in 74% yield.

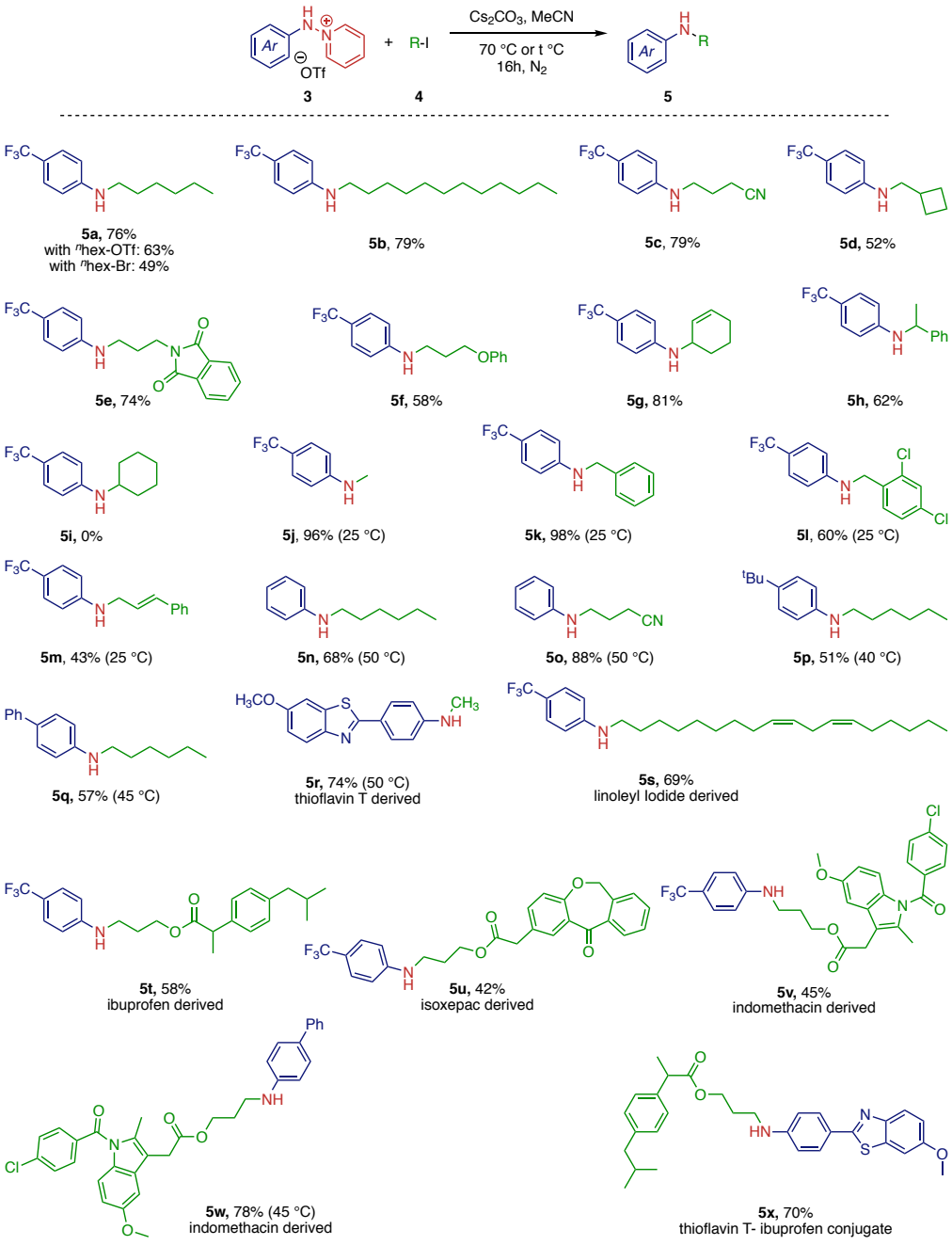
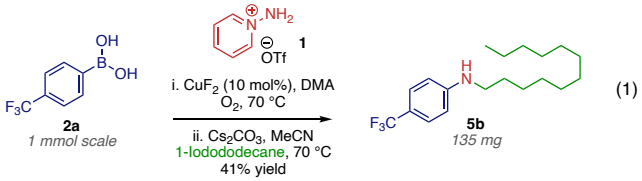


Figure 3. Scope of monoalkylation of **3**. Conditions: **3** (1.0 equiv), **4** (2.0 equiv), Cs_2CO_3 (3.0 equiv), CH_3CN, t °C, 16 h; yields are isolated.

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*-aminopyridinum 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 Cs_2CO_3 and 1-iododododecane were added (Equation 1). Heating at 70 °C for 16 h afforded amine **5b** in 41% yield.



(1)

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 Cs_2CO_3; 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 ^{1}H 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_2CO_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_2CO_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_2CO_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_2CO_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_2CO_3 without 15-cr-5) did not evolve CO_2 (see Section C.7 of Supporting Information). These data suggest that Cs_2CO_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]

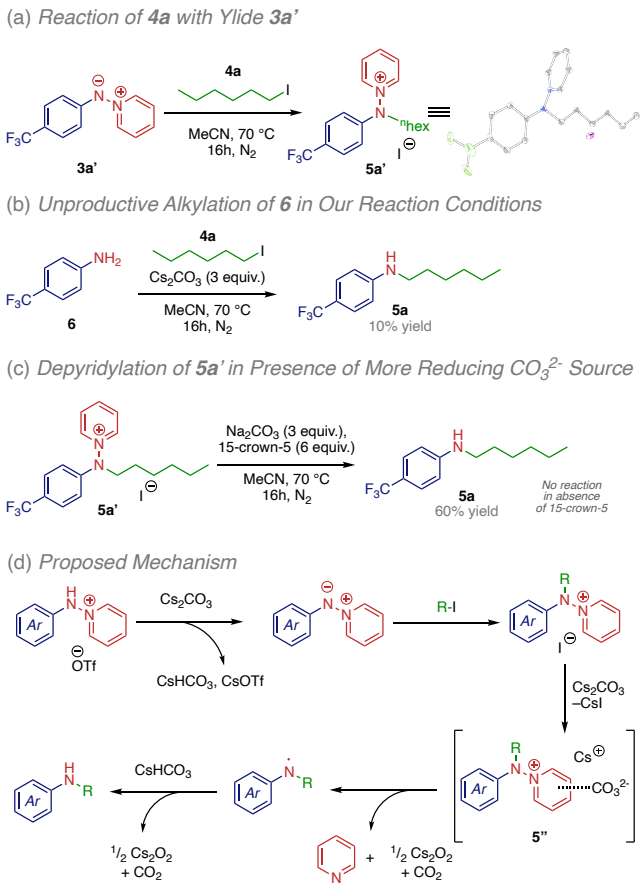


Figure 4. Preliminary mechanistic studies. (a) Reaction of ylide **3a'** with **4a** yields intermediate **5a'**. (b) Aniline **6** does not undergo alkylation. (c) Depyridylation of **5a'** proceeds with Na_2CO_3 and 15-crown-5. (d) Proposed mechanism for the alkylation/depyridylation sequence.

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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