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Divergent Late-Stage (Hetero)Aryl C–H Amination by the Pyridinium Radical Cation

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Abstract: (Hetero)arylamines constitute some of the most prevalent functional molecules, especially as pharmaceuticals. But currently, structurally complex aromatics cannot be converted to arylamines, so instead, each product isomer must be assembled through a multistep synthesis from simpler building blocks. Here we describe a late-stage aryl C–H amination reaction for the synthesis of complex primary arylamines that other reactions cannot access directly. We show and rationalize through a mechanistic analysis how to obtain the wide substrate scope and the constitutional diversity of the reaction, which gives access to molecules that would not have been readily available otherwise.

Late-stage aryl C–N bond formation is desirable in small molecule discovery because a quarter of the top 200 pharmaceuticals by US retail sales in 2015 contain (hetero)arylamines.[1] However, broadly applicable C–H amination of complex aromatic compounds has yet to be achieved. Two challenges exist: Limitations with respect to functional-group-tolerance and limitations with respect to the electronic substrate scope. Electrophilic aromatic nitration with the nitronium (NO_2^+) electrophile is able to functionalize both electron-rich and -poor arenes, but the high reactivity of NO_2^+ limits the functional-group-tolerance.[2] Modern amination reactions exhibit improved functional-group-tolerance, but the electrophilic aminating reagents[3] are not sufficiently reactive to react with electron-deficient arenes such as methyl benzoate. One–electron oxidation of the arene to an arene radical cation with subsequent nucleophilic attack by a nitrogen nucleophile has been established via both electrochemical- and photo-oxidation.[4] However, in both cases, the arene must be sufficiently electron-rich for the oxidation to occur, which limits the substrate scope also to electron-rich arenes.[5]

The limitations of the known amination reactions with respect to their reactivity profiles can be understood in light of well-appreciated polarity matching in the transition state (Figure 1). Specifically, electrophilic reagents will preferentially react with nucleophilic π-systems, and *vice versa*. The more the polarity preference is pronounced, the more challenging it becomes to reach a large electronic substrate scope. In other words, for each approach, whether oxidized nitrogen-based reagent or arene oxidation, the aminating species is intrinsically limited to react with substrates that can elicit suitable polar interactions.

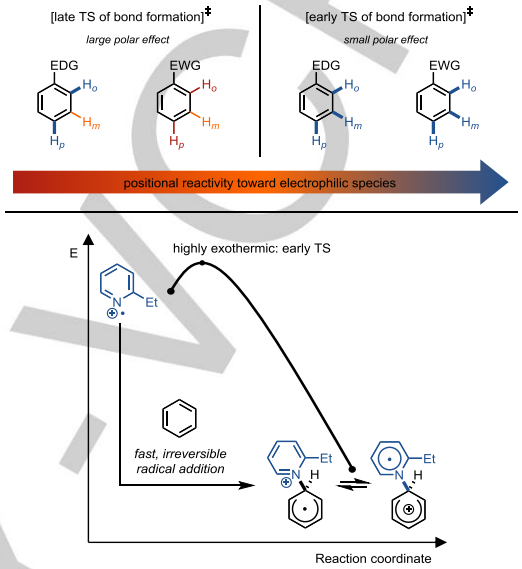

Figure 1. Polarity-matching-dependent aromatic reactivity toward electrophilic bond-forming species, and conceptual energy diagram of cationic pyridinium σ-radical's addition. TS, transition state; EDG, electron-donating group; EWG, electron-withdrawing group.

In addition to the consequence on substrate scope, polarity matching results in the predictable positional selectivity of most aryl C–H bond functionalization reactions. For example, with electron-rich substrates the NO_2^+ electrophile has a bias for the *ortho*- and *para*- positions, whereas electron-withdrawing substituents will primarily direct the electrophile to the *meta*-position[6] (Figure 2a). Modern amination reactions also provide product mixtures reminiscent of polarity matching. Reactions based on one-electron arene oxidation exhibit *para*-selectivity, due to the electron distribution in the arene radical cation.[4a] If other isomers are desired, different syntheses must be designed.

An early transition state of bond formation would involve small polar interactions between the reactants, and therefore, would minimize substrate/positional bias with respect to electronic structure. One approach towards such a transition state is to select an aminating species that can undergo a highly exothermic addition to an arene (Figure 1). Minisci demonstrated that the exothermicity of ammonium radical addition can engender relatively low selectivity,[7] but reactivity towards electron-poor substrates was not synthetically useful (5% yield for benzonitrile) and the reaction requires an acidic solvent. We rationalized that the cationic pyridinium σ-radical should be more reactive than conventional nitrogen radicals because its unpaired electron is located in an sp^2-hybridized orbital.[8] As a simple surrogate, we have calculated the bond dissociation energy (BDE) of the N–H bond in the pyridinium ion to be 88 kJ·mol^{-1} higher relative to the dimethylammonium ion (see SI).

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Charge delocalization in the ensuing cyclohexadienyl radical upon C–N bond formation would contribute to a larger enthalpy gain, when compared to additions of aliphatic aminium radicals, for which delocalization may not be significant. A catalytic system that generates the pyridinium radical cation would be able to access a large substrate scope with constitutional diversity in a synthetically useful transformation.

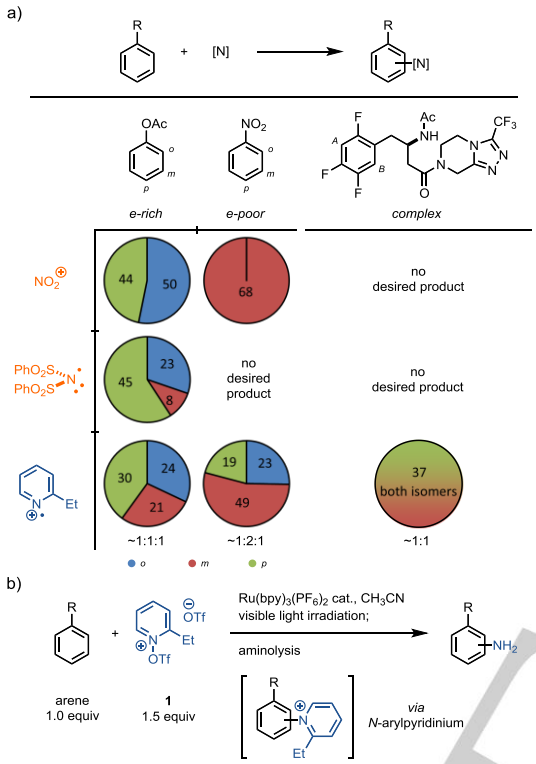

Figure 2. Strategy for general, diversifying aryl C–H amination. a) Selectivity profiles and % yields of aromatic substitution with aminating species. b) Aryl C–H amination using reagent **1**. R, generic substituent; [N], generic aminating species; Ac, acetyl; *o*, *ortho*; *m*, *meta*; *p*, *para*; Ph, phenyl; Et, ethyl; equiv, equivalents; Tf, trifluoromethanesulfonyl; bpy, 2,2'-bipyridine; cat., catalyst.

The pyridinium radical cation **1** shown in Figure 2a, generated through reduction of an activated pyridine *N*-oxide by a visible-light-excited metal catalyst, adds to both phenyl acetate and nitrobenzene to provide products in a 1:1:1 and 1:2:1 mixture, respectively, in contrast to other known amination reactions. Conventional nitration provides products in ratios to be expected for electrophilic substitution reactions, whereas nitrogen-based radical addition has as of yet not been observed for electron-poor arenes at all. As shown in Figure 2a, amination with the pyridinium radical cation can also provide late-stage access to complex arylamines that other methods cannot. Various nitration reaction attempts either failed to achieve conversion or led to substrate decomposition into an intractable mixture, while other modern amination methods are generally not reactive enough to react with arenes as electron-poor as the example shown.

We prepared 2-ethylpyridine *N*–OTf (**1**) by triflation of commercially available 2-ethylpyridine *N*-oxide.[9] Other evaluated pyridine derivatives afforded aminated products but in lower yields. Irradiation of a solution containing arene, the photoredox catalyst $Ru(bpy)_3(PF_6)_2$, and reagent **1** in acetonitrile affords *N*–arylpyridinium salts (Figure 2b). Irradiation with a 70 W blue light-emitting diode (LED) with 2 mol% catalyst loading led to complete benzene conversion within 30 seconds (see SI), while more complex substrates were converted over 15–90 minutes; the reaction can also be performed with a 23 W compact fluorescent lamp (CFL), in which case the reaction time increases to up to 24 h. Reagent **1** can be prepared in situ, or synthesized independently and stored for at least 6 months under inert atmosphere; it can be used for a short period of time in air, which facilitates a practical reaction setup. Both the ruthenium catalyst and irradiation are crucial for the reaction to occur, although upon initiation, the reaction does proceed in the dark, albeit less efficiently (see SI), presumably through a chain transfer process.[10] Subsequent in situ aminolysis of the *N*–arylpyridinium salts with butylamine, propylamine, or piperidine, reminiscent of the Zincke salt reactivity,[11] liberates arylamines.

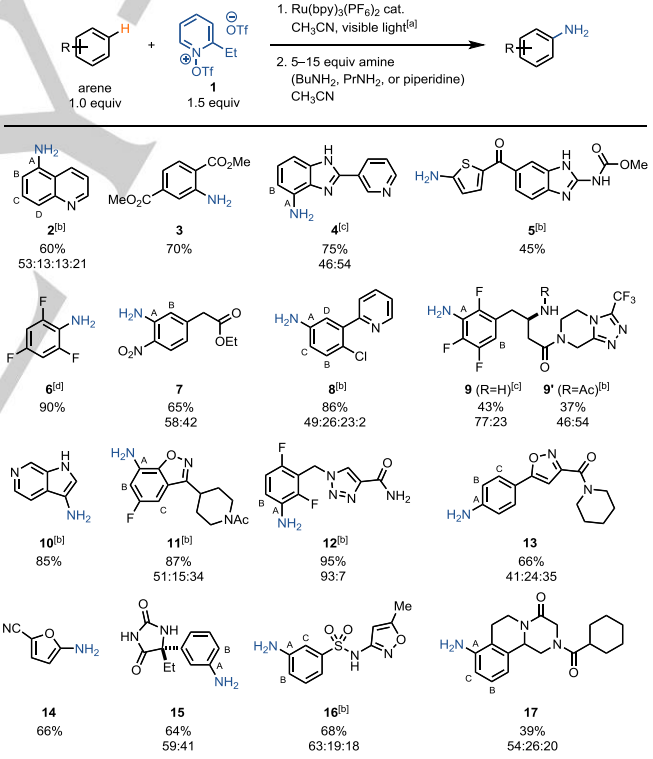

Figure 3. Late-stage direct arene C–H amination. [a] Reaction conditions with blue LED: 2 mol% $Ru(bpy)_3(PF_6)_2$, 40 W or 70 W blue LED, 30 °C, 15–90 min; Reaction conditions with CFL: 5 mol% $Ru(bpy)_3(PF_6)_2$, 23 W CFL, 23–25 °C, 24 h; see SI for details. [b] 1.0 equiv TfOH. [c] 2.0 equiv TfOH. [d] Derivatized due to volatility of the product. Bu, butyl; Pr, propyl; Me, methyl.

The substrate scope of the cationic pyridinium radical substitution (Figure 3) encompasses arenes with a broad range of electronic structure and functional complexity. A majority of the substrates presented are marketed drug molecules and

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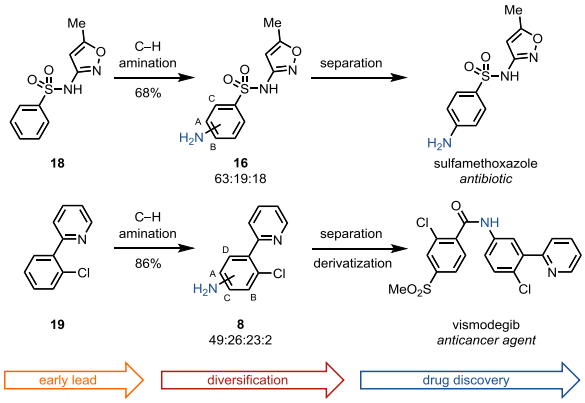
common pharmacophores, whose aminated analogues are often challenging to access by other transformations, especially at a late stage of a synthesis. Each constitutional product isomer was isolated by chromatographic separation, based on standard and/or C18-reversed phase silica gel, and characterized as analytically pure compound. The ability to deliver diversified products from biologically privileged structures in pure form renders the late-stage amination relevant and promising toward streamlined exploration of chemical space for pharmaceutical innovations.

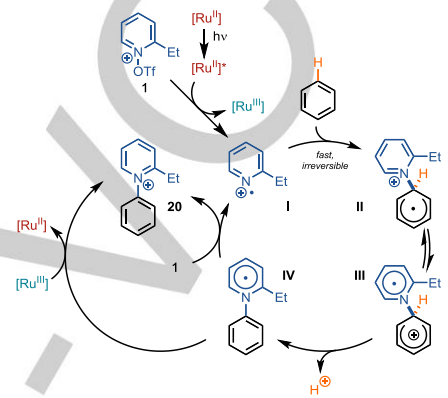


Scheme 1. Synthetic utility of late-stage amination for streamlined drug discovery.

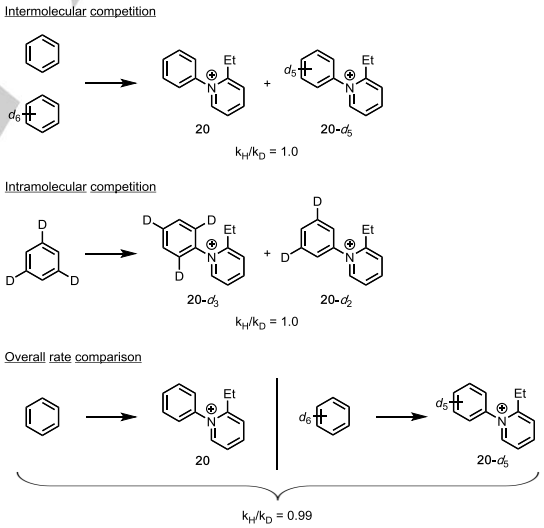
We demonstrate the utility of the aryl C–H amination by simulating the discovery of two marketed drugs (Scheme 1). Amination of **18** and **19** afforded multiple aminated products through carboarene functionalization. After purification and/or derivatization,[12] the antibiotic sulfamethoxazole and the anticancer agent vismodegib are quickly accessible, respectively. In a hypothetical drug discovery scenario, our method provides access to aminated analogues of which the isomer with the best biological activity could then be identified.

We propose the mechanism for aryl pyridination shown in Scheme 2. Reduction of the reagent **1** by the photo-excited ruthenium catalyst generates the pyridinium σ-radical cation (**I**),[13][14][15] which adds to an arene; the early transition state of addition is proposed to be the origin of both the broad substrate scope and the constitutional diversity. The early transition state should result in a small, if any, secondary KIE. When measured, both the inter- and the intra-molecular competition resulted in KIE of 1.0 (Scheme 3). The KIE value of unity in nitrogen radical aromatic substitution is unusual, and reflects a transition state of addition with a small degree of re-hybridization of the carbon atom on which the substitution occurs. The small electronic bias of the radical addition is quantified as a Hammett ρ value of –0.81 (Figure 4a), which was compared to those of substitution by ammonium and dimethylaminium radicals, generated via redox catalysis[16] (see SI). These aminium radicals have ρ values of –2.7 and –5.2, respectively, significantly larger in magnitude, in agreement with a smaller electronic substrate scope.

The selectivity of the presented amination reaction between different C–H bonds is best illustrated in a Brown-Stock diagram (Figure 4b) to other electrophilic and radical aromatic substitution reactions.[17] Brown-Stock analysis describes a linear free-energy relationship with respect to substrate- and positional selectivity. In this analysis, arene functionalization by the pyridinium radical cation emerges as the transformation with the smallest electronic bias, at least among the practically useful reactions for which Brown-Stock data are available (see SI).



Scheme 2. Plausible reaction mechanism. Triflate (⁻OTf) anions were omitted for clarity. The two depicted pathways for the single-electron oxidation of **IV** are, presumably, both operative at the same time.



Scheme 3. Kinetic isotope effect measurements; see SI. D, deuterium.

The distonic radical cations **II** and/or **III**, resulting from the radical addition, would undergo deprotonation to afford the arylpyridine radical **IV**, from which single-electron oxidation by the oxidized ruthenium complex or by **1** would afford the arylpyridinium salt **20**. The absence of a significant overall rate difference (KIE of 0.99) between the pyridination reactions of benzene and perdeuterated benzene (Scheme 3) is in agreement with a fast C–H bond cleavage event.

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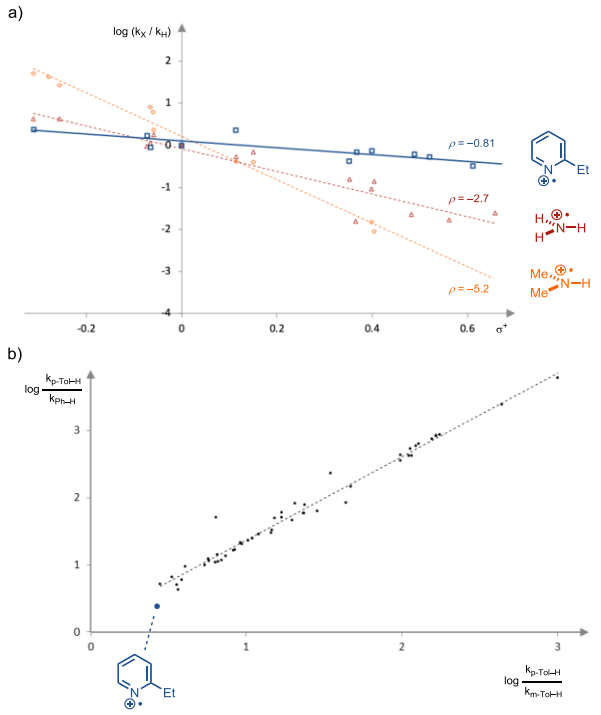

Figure 4. Linear free-energy relationship analysis; see SI for details. a) Comparison of Hammett plots for radical substitution of mono-substituted arenes (PhX, X = Me, ^{i}Pr, ^{t}Bu, H, F, Cl, Br, CO_2Et, CO_2Me, CF_3, CN). b) Fitting of the pyridinium radical cation into the Brown-Stock diagram, which plots the substrate selectivity ($k_{p\text{-Tol–H}}$ vs. $k_{Ph–H}$) against the positional selectivity ($k_{p\text{-Tol–H}}$ vs. $k_{m\text{-Tol–H}}$). The black points represent data for aliphatic aminium radical substitution and electrophilic substitution; see ref [16]. X, generic substituent; Tol, tolyl; ^{i}Pr, isopropyl; ^{t}Bu, *tert*-butyl.

The presented C–N bond forming reaction illustrates a synthetic strategy of how to access structural complexity that goes beyond the scope accessible through conventional amination reactions. The reaction is expected to expedite discovery of biologically active small molecules via late-stage functionalization. Other reagents that would elicit early transition states of bond formation between reactive species and π-systems may access molecular diversity for other carbon–heteroatom bond forming reactions beyond what we have shown here. It has not escaped our attention that, in principle, the analysis provided here should also enable the design of highly regioselective aromatic C–H functionalization reactions.

Acknowledgements

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Keywords: aromatic substitution • amination • radical reactions • photocatalysis • synthetic methods

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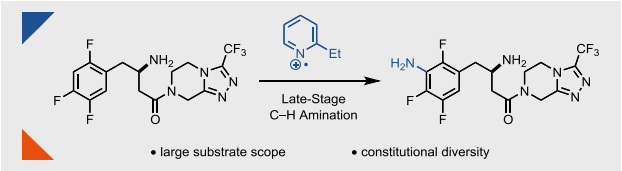

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Page No. – Page No.

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Generation of highly reactive pyridinium radical cation enables C–H amination of both electron-rich and -poor (hetero)arenes. The method is compatible with a broad range of structurally complex molecules, and provides access to aminated analogues that are difficult to synthesize otherwise. High exothermicity of the pyridinium radical addition to an arene is proposed to engender the extremely low electronic bias, both substrate- and position-wise.

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