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Communication

Photoredox-Catalyzed Deaminative Alkylation via C−N Bond Activation of Primary Amines

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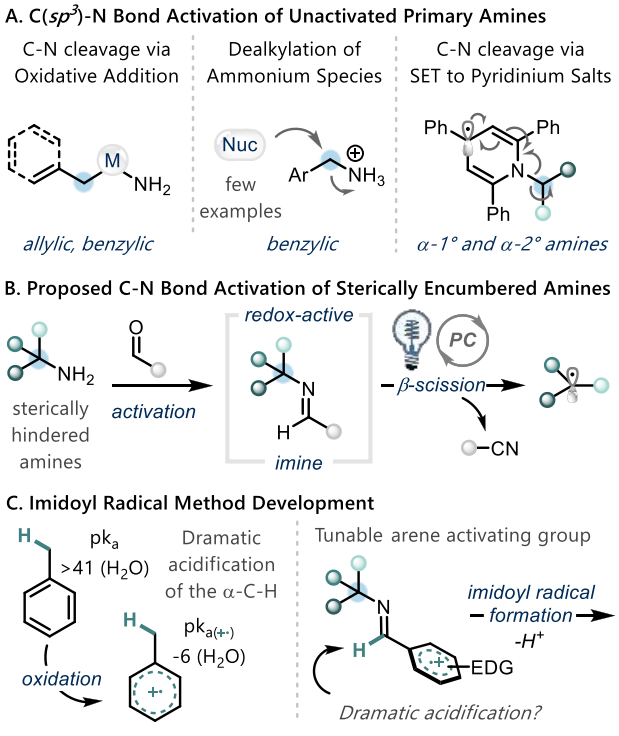
ABSTRACT: Primary amines are often cheap, naturally occurring, and chemically diverse starting materials. For these reasons, deaminative functionalization of amines has emerged as an important area of research. Recent advances in C−N activation transform simple α-1° and α-2° amines into alkylating reagents via Katritzky pyridinium salts. We report a complementary method that activates sterically encumbered α-3° primary amines through visible light photoredox catalysis. By condensing α-3° primary amines with electron-rich aryl aldehyde, we enable an oxidation and deprotonation event, which generates a key imidoyl radical intermediate. A subsequent β-scission event liberates alkyl radicals for coupling with electron-deficient olefins for the generation of unnatural γ-quaternary amino acids and other valuable synthetic targets.

Primary amines are present in a wide range of building blocks, and their use as synthetic handles in synthesis is vast. Traditionally, organic chemists have focused on N−H functionalization of amines, such as reductive aminations[1] or cross-couplings.[2] Additionally, amines can be employed as directing groups for C−H activation to achieve α,[3] β,[4] γ,[5] and δ[6] C−H functionalization. While amines offer immense synthetic leverage, harnessing the C−N bond as a functional handle for deaminative transformations remains underutilized. To achieve this, additional methods for C−N functionalization of unactivated primary amines are required. Until recently, most approaches were limited to allylic or benzylic amines (Scheme 1A).[7] The use of primary amines as alkyl precursors has garnered tremendous attention with the re-emergence of Katritzky salts.[8] In 2017, the Watson group demonstrated the transformative power of using C−N bonds for a deaminative Suzuki−Miyaura, in which the primary amine sources contained unactivated alkyl groups.[9] Since this seminal publication, many research groups have used pyridinium salts for a variety of transition-metal-catalyzed[10] and photoredox-catalyzed[11,12] deaminative functionalizations.[13] Notably, these salts are predominantly activated via a single-electron reduction (~−0.9 V vs SCE[14]).[15] The popularity of Katritzky salts as a functional handle is attributed to a catalyst-free, trivial activation step in which primary amines are condensed on pyrylium salts. However, this is limited to α-1° and α-2° amines, whereas more sterically encumbered α-3° amines do not condense.[16]

Our goal was two-fold: (1) create a method to activate C−N bonds of sterically congested primary amines and (2) liberate the alkyl radical via an oxidative event, to provide a complementary approach to Katritzky salt activation. We turned our attention to aromatic aldehydes as a potential activating group with the intention of forming an imidoyl radical, which could then undergo a β-scission event to liberate alkyl radical coupling partners.[17] Previously, imidoyl radicals have been formed through radical addition across isocya-

Scheme 1. C−N Bond Activation: Amines as Alkyl Precursors



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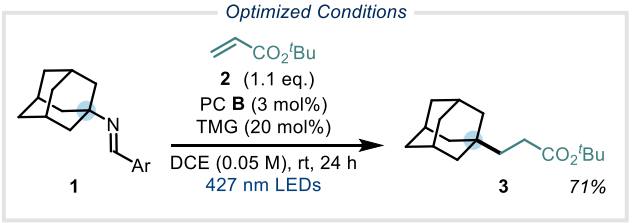
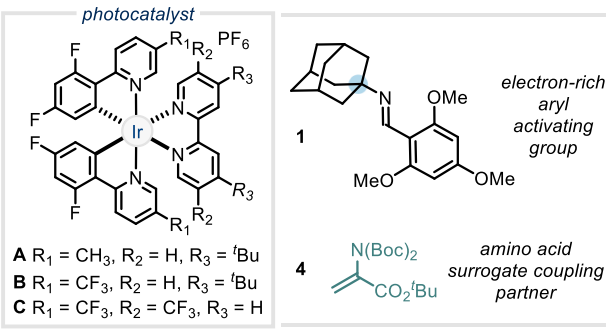
nides[18] often for heteroarene synthesis.[19] We speculated that imidoyl radicals could potentially be generated by a single-electron oxidation and deprotonation of electron-rich imines, given that proton-coupled electron-transfer is a known strategy to activate strong C−H bonds.[20] Imines are commonly activated through a single electron reduction event;[21] however, we postulated if we tune the arene toward an oxidation event, the imidoyl C−H would be primed for deprotonation. For example, when considering an analogous system, upon oxidation of toluene ($E_{p/2}$ = 2.36 V vs SCE)[22] the resulting radical cation is an extremely strong π-acid (pK_a of −6; Scheme 1C).[23] We aimed to translate this reactivity to imines via oxidation of the arene activating group followed by deprotonation of an acidified imidoyl C−H to form imidoyl radicals.

We first explored the oxidation potential of imines by condensing adamantylamine on a variety of aldehyde activating groups. We found 2,4,6-trimethoxybenzaldehyde to be a viable activating group. Initial conditions gave desired product in a 19% yield (Table 1, entry 1). Switching to a more oxidizing photocatalyst, [Ir(dF-CF$_3$-ppy)$_2$(dtbbpy)PF$_6$] (PC **B**; Ir(III)*/Ir(II) = 1.21 V vs SCE) leads to an increase in yield to 46% (entry 2). Trifluorotoluene and 1,2-dichloroethane as solvents give similar yields, yet DCE is preferred due to improved photocatalyst solubility. Stoichiometric amount of TMG as base is tolerated (entry 3); indeed, the reaction works even in its absence (entry 7; we assume the imine nitrogen is sufficiently basic to perform the deprotonation), but a substoichiometric amount is optimal (20 mol %). Furthermore, diluting the reaction results in higher yield of product (entries 5 and 6 vs optimal conditions). To our delight, switching to coupling partner **4** provides high yields and enables access to unnatural γ-quaternary amino acids.

Table 1. Optimization and Control Studies[a]



entry	deviation	yield (%)[b]
1	2 equiv **2**, 2 equiv K_3PO_4, $PhCF_3$ (0.1 M), PC **A**	19
2	2 equiv **2**, 2 equiv K_3PO_4, $PhCF_3$ (0.1 M)	46
3	1 equiv TMG	72
4	2 equiv acrylate	54
5	0.10 M DCE	68
6	0.20 M DCE	60
7	no TMG	40
8	no 427 nm LEDs	0
9	no photocatalyst, 427 nm LEDs	0
10	no photocatalyst, 75 °C	0
11	coupling partner **4**	91[c]
12	coupling partner **4**, PC **C**	55



[a]Optimized conditions: **1a** (0.1 mmol), **2** (0.11 mmol), [Ir(dF-CF$_3$-ppy)$_2$(dtbbpy)]PF$_6$ (3 mol %), 1,1,3,3-tetramethylguanidine (TMG, 20 mol %) in 1,2-dichloroethane (DCE, 0.05 M). [b]GCMS yield using mesitylene as internal standard. [c]Isolated yield.

With optimized conditions in hand, we examined the reaction scope of primary amines (Scheme 2) with adamantyl-amine-derived substrates affording products in 92% (**5**) and 75% (**6**) yields. Acyclic α-3° amines afford the desired product in high yields (**7**−**9**). Small drug molecule phenantramine (**10**) and fluorinated derivative (**11**) demonstrate high reactivity. A variety of functional groups are well-tolerated forming products bearing Boc-protected amines (**12**, **18**), ethers (**17**), esters (**13**, **14**), and protected alcohols (**9**). A slightly more strained [2.2.2]-bicycle proceeds in a 57% yield (**14**). Products bearing various ring sizes are formed well (**12**, **13**, **15**, **16**) with more strained oxetane- and azetidine-derived amines providing coupling product in 58% (**17**) and 63% (**18**) yield.[24]

We then turned our attention to expanding this methodology to a range of electron-deficient olefin coupling partners. Using the Karady−Beckwith chiral Dha substrate,[25] the reaction proceeds in high diastereoselectivity and 70% yield (**19**). Simple acrylates participate in moderate yields (**3**, **20**, **21**) and introduction of substitution at the α-carbon leads to an improved yield (**22**−**26**). We hypothesize that substitution decreases undesired oligomerization of the resulting radical upon addition into the acrylate, as well as diminishes any group transfer byproducts.[26] Exocyclic acrylates and enones are coupled in 52% (**27**) and 70% with **28** isolated as a single isomer. Vinyl sulfones and methacrylonitrile also form the desired products (**29**−**30**).

We next turned our attention to mechanistic interrogation to determine the mode of C−N activation and alkyl radical formation (Scheme 3). In situ LED NMR monitoring suggests the reaction is first order in the imine and acrylate coupling partner (Scheme 3B). Based on these findings, we propose that upon condensation of the primary amine onto the aldehyde activating group, the redox-active imine successfully quenches the excited state of the PC **B**, as evident by Stern−Volmer quenching studies (Scheme 3C). A proton transfer event forms the key imidoyl radical intermediate. A subsequent β-scission liberates the alkyl radical which couples to electron-deficient olefins. A final reduction and protonation leads to desired product formation and regenerates the ground state of PC **B**.

The remaining crucial mechanistic detail to elucidate was determining the route from imine to imidoyl radical. Spin density plotting of the imine radical-cation reveals an appreciable amount of spin density on both the imine nitrogen and arene carbon (C_1; Scheme 3D). This led us to envision two potential routes to imidoyl radical formation: (1) a nitrogen radical-cation acting as a hydrogen atom transfer (HAT) reagent or (2) oxidation of the arene and subsequent deprotonation of an acidified imidoyl hydrogen. To test the feasibility of a potential HAT pathway, we conducted a competition experiment between **34** and **35** (Scheme 3E). The oxidation of imine **35** ($E_{p/2}$ = +1.86 V vs SCE) is well outside the range of the iridium excited state, yet when comparing imidoyl C−H bond strength, it is similar to that of **34**.

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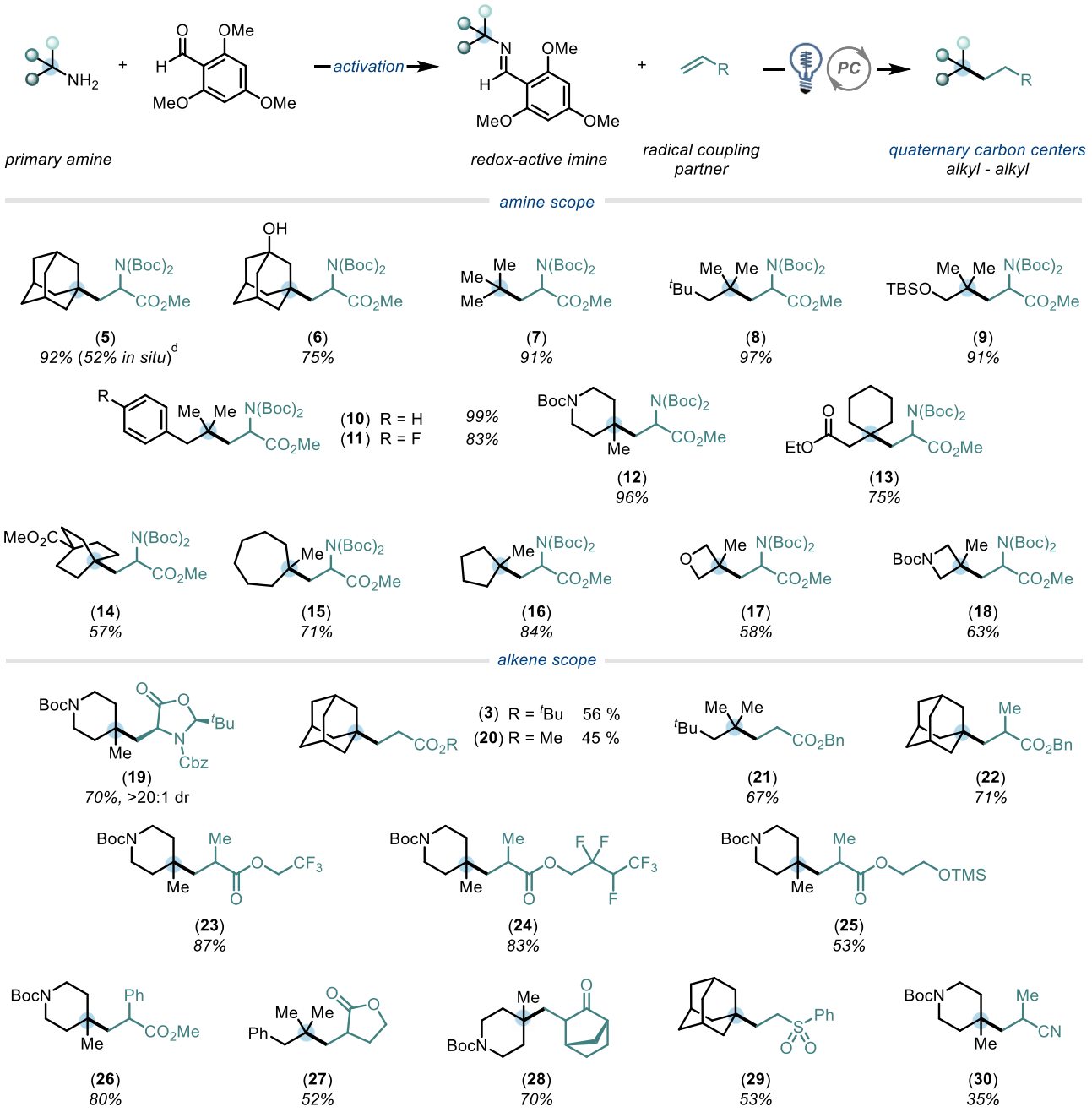
Scheme 2. Scope[a,b,c]



[a]Reaction was performed with imine (0.1 mmol), alkene (0.11 mmol), [Ir(dF-CF_3-ppy)$_2$(dtbbpy)]PF_6 (3 mol %), 1,1,3,3-tetramethylguanidine (TMG, 20 mol %) in 1,2-dichloroethane (DCE, 0.05 M). [b]Yields are reported from the premade imine. [c]Imines were synthesized under Dean–Stark conditions in high to near quantitative yields and used without further purification (see SI for more details). [d]Reaction was performed with adamantylamine (0.1 mmol), 2,4,6-trimethoxybenzaldehyde (0.105 mmol) **2a** (0.11 mmol), [Ir(dF-CF_3-ppy)$_2$(dtbbpy)]PF_6 (3 mol %), TMG (20 mol %), 4 Å mol sieves in trifluorotoluene (0.05 M) at 100 °C.

Therefore, we rationalized if we observe the formation of **5**, it would likely be through a HAT event from a **34** nitrogen radical-cation. By only detecting **13** and accounting for the remaining **35**, we conclude that for C–N bond activation to occur, an oxidation event of the substrate is crucial.

Having determined a nitrogen radical-cation promoted HAT event as unlikely, we propose a mechanism in which the spin density of the imine radical cation residing on C_1 is vital. A crystal structure of **1** (Scheme 3F) reveals that the C–N double bond is not in full conjugation with the π-system of the arene ring, resulting in the imine C–H residing out-of-plane with the ring system. Oxidation of the arene ring thus leads to acidification of the imidoyl C–H in parallel to that observed for toluene, as explained previously. By computationally determining the imidoyl C–H bond dissociation energy of our imine and experimentally determining the oxidation potential ($E_{p/2}$ = 1.43 V vs SCE), we estimate the pK_a of the imine radical cation to be ~15 (see SI for details).[27] This greatly acidified imidoyl C–H is now easily deprotonated. A spin-centered-shift leads to imidoyl radical formation, and a

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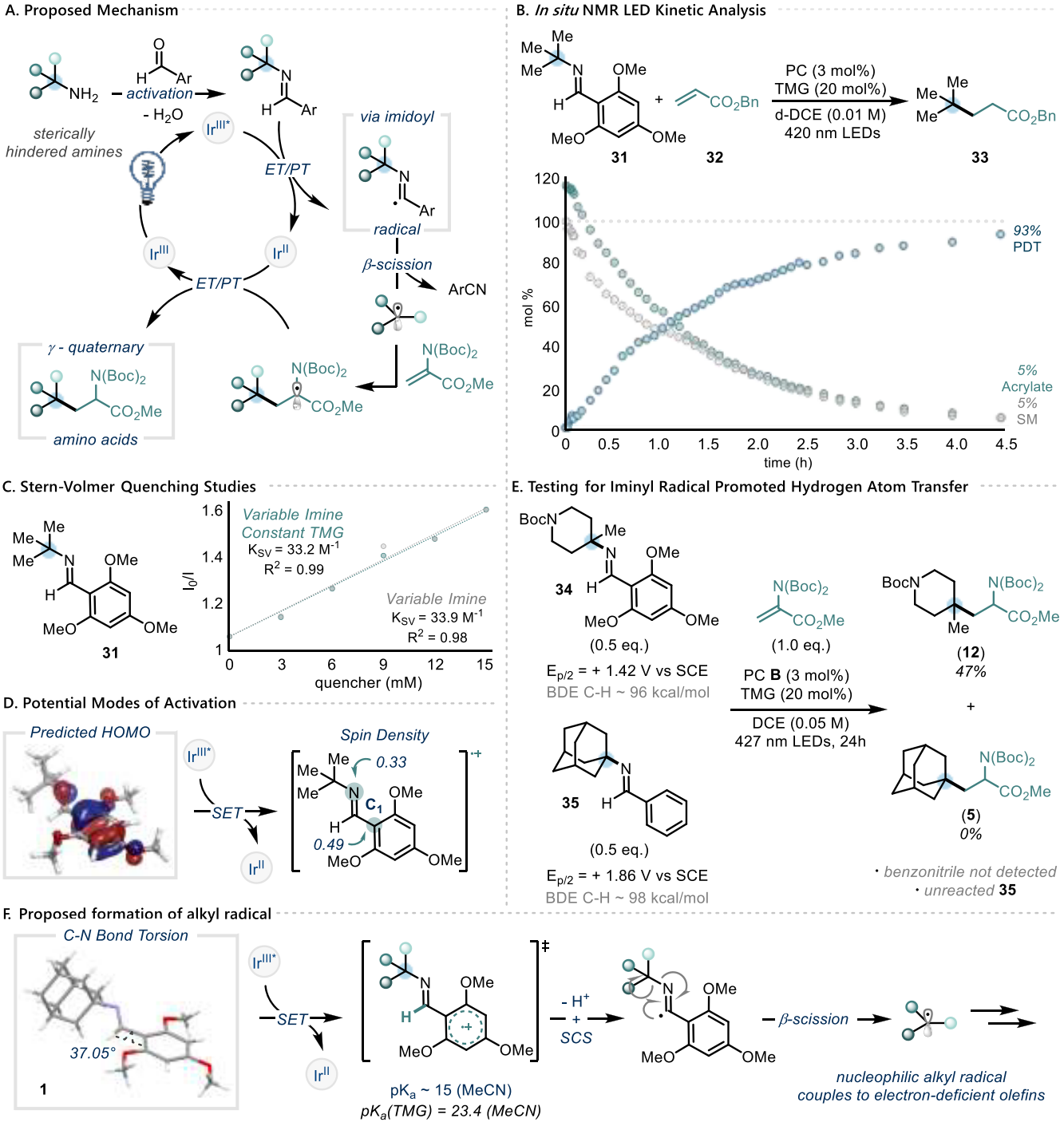
Scheme 3. Mechanistic Analysis



[a]Atomic spin densities obtained from Mulliken analysis. [b]Imine C−H BDEs determined for *N*-*tert*-butyl-1-(2,4,6-trimethoxyphenyl)methanimine and *N*-*tert*-butyl-1-phenylmethanimine. [c]pK_a of radical cation **31** calculated using the computed imine C−H BDE and experimentally obtained oxidation potential. See SI for more details.

subsequent β-scission event releases an alkyl radical for further coupling with electron-deficient olefins. Given that the oxidation is slightly endergonic, and complicated by the fact our substrate can act as a base itself, we are unable to differentiate between a stepwise or concerted PCET event.[28]

We have developed a protocol to activate C−N bonds of sterically encumbered amines through formation of redox-active imines. Upon an oxidation, a dramatic acidification of the imidoyl C−H is observed. Deprotonation of this C−H and a spin-centered shift forms the key imidoyl radical intermediate. A subsequent β-scission provides nucleophilic alkyl radicals which are coupled with electron-deficient alkenes to access unnatural γ-quaternary amino acid derivatives and various synthetic targets. Given the large impact of Katritzky salts for C−N activation of α-1° and α-2° amines, we believe the complementarity of this reductive method for C−N

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activation of sterically congested α-3° amines will be of significant interest.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/jacs.0c08595.

Experimental procedures, spectral characterization, and additional data (PDF)
Crystal data (CIF)

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Notes

The authors declare no competing financial interest.

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