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Photoredox-Catalyzed C_α−H Cyanation of Unactivated Secondary and Tertiary Aliphatic Amines: Late-Stage Functionalization and Mechanistic Studies

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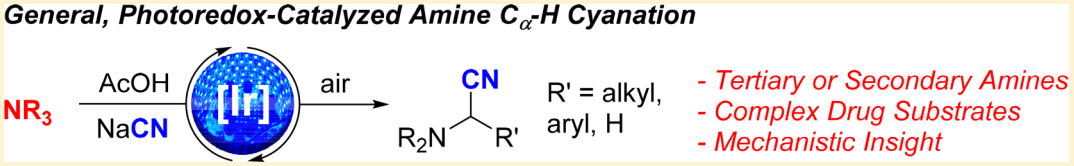
Supporting Information



ABSTRACT: This paper describes the development and mechanistic studies of a general, high-yielding amine C_α−H cyanation protocol via photoredox catalysis. Inexpensive NaCN is employed as the cyanide source and air is the external oxidant, resulting in mild and highly functional group tolerant conditions. Notably, efficient C_α−H cyanations of *secondary and tertiary* aliphatic amines and of complex, biologically active compounds (drugs) can be performed using the established methodology. Mechanistic studies suggest that the carboxylic acid additive has three effects: formation of a stabilizing hemiaminal intermediate, prevention of catalyst decomposition by protonating the substrate, and modulation of fluorescence quenching of the photoexcited catalyst species.

INTRODUCTION

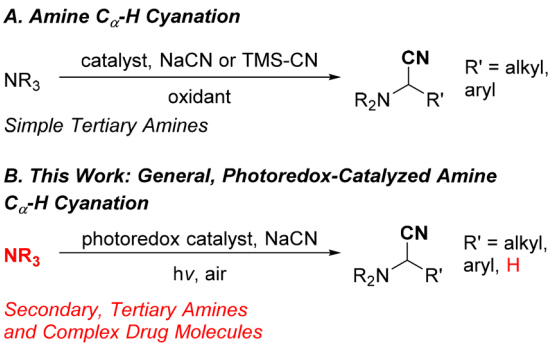
α-Aminonitriles are versatile intermediates for the synthesis of difunctionalized molecules such as amino acids, heterocycles, and pharmaceuticals.[1−4] Approaches toward their synthesis include the classical Strecker reaction,[5] the addition of cyanide nucleophiles to imines,[6−12] and reductive Strecker reactions via the cyanation of amides and lactams.[13] In contrast to such functional group interconversion strategies, C_α−H cyanations of amines promise to introduce cyano groups directly into complex molecules, thus enabling highly desirable late-stage diversifications of biologically active compounds.[14−19] Recent advances to this end (Scheme 1A) have focused on activated (aryl, benzyl, and cyclic) amine substrates with easily cleavable C_α−H bonds, often under strongly oxidizing conditions.[20−25] Few known reports substitute oxidants for O_2 or air to create milder protocols.[26,27]

In contrast to common functionalizations of amines with activated C_α−H bonds (e.g., benzylic, aryl amines),[28] fewer examples are known that employ tertiary alkyl amines as substrates for C_α−H functionalization.[29,30] Among these, only a handful of C_α−H cyanations affording high yields are known,[26,28,29,31] but it is often unclear how known methods would tolerate more complex molecules as substrates.

Finally, a general challenge in cyanation is the source of cyanide as a nucleophile, as more desirable cyanide sources such as NaCN are often insoluble in organic solvents. More soluble cyanide sources such as TMS-CN[22] are hazardous and thus less desirable to use on larger scales.

Herein, we report a general, high-yielding C_α−H cyanation protocol driven by photoredox catalysis. Inexpensive NaCN is employed as the cyanide source, and air is the external oxidant, resulting in mild and highly functional group tolerant conditions. Notably, the established protocol allows the efficient C_α−H cyanation of *unactivated and unprotected, secondary and tertiary* aliphatic, complex amine substrates (Scheme 1B).

Scheme 1. Previously Reported C_α−H Cyanations and Herein Described General Protocol



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RESULTS AND DISCUSSION

Reaction Optimization. Our initial investigations to establish a general, photoredox-catalyzed amine C_α–H cyanation focused on tributylamine as substrate. We reasoned that NBu_3 would be a suitable model compound due to the lack of proximal activating groups (i.e., arenes, double bonds, cyclic structures). Furthermore, we reasoned that the use of similarly simple tertiary amines as sacrificial reductants in photoredox catalysis[32] should readily provide access to reactive iminium ions, which could then react with a cyanide nucleophile present in solution.

As such, we first evaluated the reactivity of different photoredox catalysts (Figure 1) in combination with NaCN

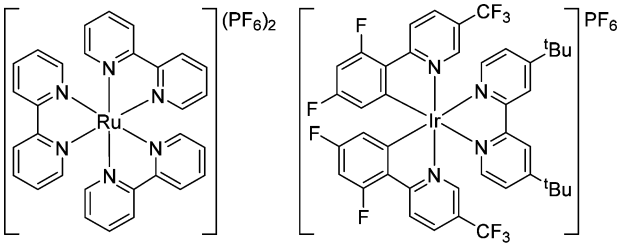


Figure 1. Structures of photoredox catalysts employed in the optimization studies.

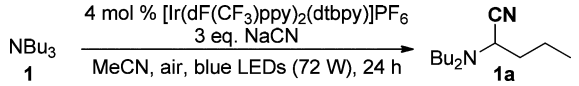
as nucleophile and blue LEDs as light source. Gratifyingly, these conditions afforded 45% of the desired product with 4 mol % of $[Ir(dF(CF_3)ppy)_2(dtbpy)]PF_6$ as photoredox catalyst (Table 1, entry 1); however, only 10% of α-aminonitrile **1a** was obtained with $Ru(bpy)_3(PF_6)_2$ (entry 2). Lower amounts of Ir catalyst (2 mol %; Table 1, entry 3) resulted in a significant decrease in yield to 26%. These data suggest a significant dependence of the reaction yield on the amount and identity of the used photoredox catalyst.

Changing the solvent to MeOH did not result in a dramatic decrease in yield (41%; Table 1, entry 4), suggesting that protic solvents are not detrimental to catalytic activity in this system. KCN provided very similar activity to NaCN (38%, entry 5).

In an effort to improve the yields of the reaction, we speculated that AcOH as additive may aid the reaction, in analogy to observations made in the C_α–H cyanation of activated amines by Rueping and co-workers.[27] The result of a reaction with 1.5 equiv of AcOH as additive (entry 6) was encouraging (67% yield); increasing the AcOH loading to 3.0 equiv afforded 93% of **1a** (entry 7). When the Ir photoredox catalyst loading was lowered under these conditions, the yield still suffered (both in the absence or presence of an excess of air; see entries 8/9), suggesting that catalyst decomposition may be an issue. Interestingly, high reactivity was observed in DMA as solvent (entry 10; 82%), while DMSO led to a decrease in yield (entry 11; 54%).

Intrigued by the reaction-enhancing effect of AcOH, several control experiments were performed to gain insights into the role of AcOH in the reaction. To test the hypothesis that AcOH may simply be enhancing the solubility of NaCN [pK_a(AcOH) = 4.76;[33] pK_a(HCN) = 9.40],[34] we performed a cyanation reaction with a more soluble source of cyanide: KCN in the presence of 18-crown-6 (1.5 equiv; entry 12). However, this reaction afforded only a moderate yield (46%),

Table 1. Selected Optimization and Background Studies



entry	changes to conditions[a]	yield[b] (%)
1	none	45
2	$Ru(bpy)_3(PF_6)_2$ (4 mol %)	10
3	$[Ir(dF(CF_3)ppy)_2(dtbpy)]PF_6$ (2 mol %)	26
4	MeOH instead of MeCN	41
5	KCN instead of NaCN	38
6	AcOH (1.5 equiv)	67
7	AcOH (3.0 equiv)	93
8	AcOH (3.0 equiv), 2 mol % [Ir]	47
9	AcOH (3.0 equiv), 2 mol % [Ir], air balloon	49
10	AcOH (3.0 equiv), DMA instead of MeCN	82
11	AcOH (3.0 equiv), DMSO instead of MeCN	54
12	KCN, 18-crown-6 (1.5 equiv)	46
13	$PhCO_2H$ (3 equiv)	95
14	AcOH (3.0 equiv), no light	<5
15	AcOH (3.0 equiv), no photocatalyst	<5
16	N_2 atmosphere[c]	12
17	AcOH (5.0 equiv), KCN (1.2 equiv), 1 mol % [Ir]	17

[a]Standard conditions: NBu_3 (50 mg, 0.27 mmol), MeCN (3 mL), blue LED reactor (72 W), NaCN (3 equiv), $[Ir(dF(CF_3)ppy)_2(dtbpy)]PF_6$ (4 mol %), 24 h. [b]Yields were determined by quantitative, crude ^{1}H NMR using 1,3-dinitrobenzene or ClH_2CCHCl_2 as internal standard. [c]All liquid reagents were purged for 20 min and introduced into a N_2-filled glovebox. The reaction mixture was prepared in a N_2-filled glovebox, and the reaction vial was sealed before removing it from the glovebox and placing it into the LED reactor.

implying that the beneficial effect of AcOH is not only due to increasing the solubility of NaCN. Alternatively, the structure or pK_a of the carboxylic acid additive may also have an influence on the C_α–H cyanation reactivity. Interestingly, the use of benzoic acid (entry 13; pK_a ($PhCO_2H$) = 4.19[35]) afforded an equally high yield of the α-aminonitrile **1a** (95%) as observed in the presence of AcOH.

Subsequently, a series of background reactions were performed to ensure the importance of each reaction parameter for reactivity. In the absence of light or photocatalyst, only traces (<5%, entries 14 and 15) of the desired compound were obtained, suggesting that the transformation is indeed driven by the energy of the blue LED light. Reactions prepared in a N_2-filled glovebox showed significantly decreased yield (entry 16; 12%), supporting the importance of O_2 as oxidant in the reaction.

Finally, the use of excess AcOH in combination with KCN (conditions reported for the oxidative cyanation of anilines)[27] was tested (entry 17). The low yield obtained (17%) suggests that the conditions optimized for NBu_3 (entry 7) may be more effective with regard to broad substrate scopes than the protocol devised in the previous report.

Substrate Scope: Simple Substrates. We then turned our attention to demonstrating the synthetic utility of the catalytic system. Excitingly, both unactivated secondary (Scheme 2) and tertiary amines (Scheme 3) are readily functionalized by the developed methodology.

Due to the volatility of the products, the substrate scope for simple secondary amines was performed in MeCN-d_3, and yields were measured by quantitative ^{1}H NMR. Secondary amines with little steric hindrance around the amine

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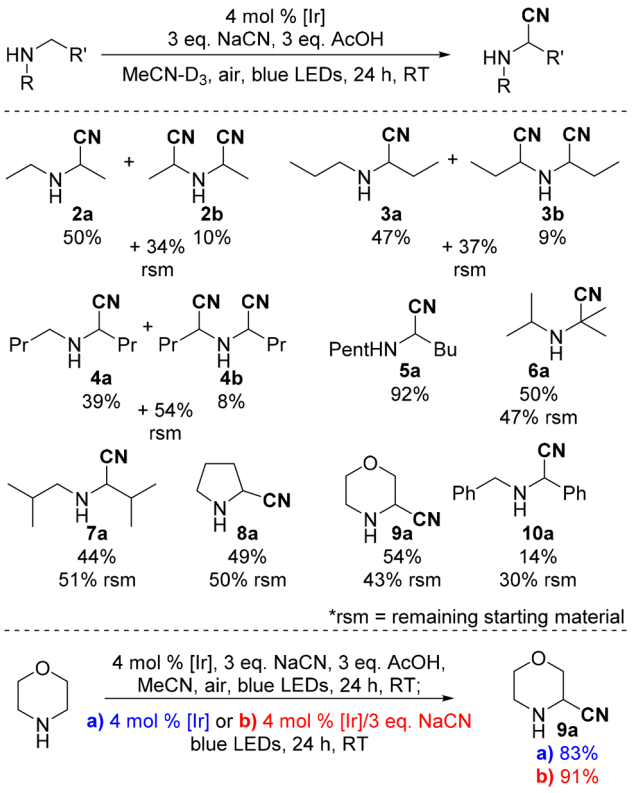
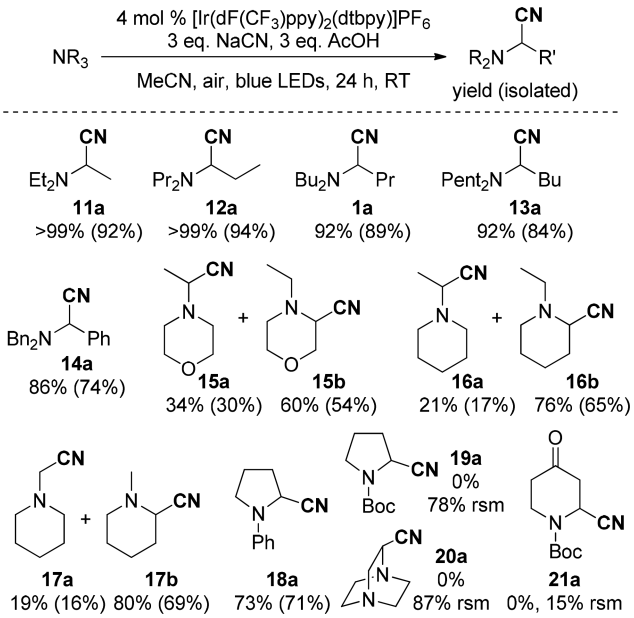
Scheme 2. Substrate Scope of Simple Secondary Amines[a]



[a]Yields were determined by quantitative ^{1}H NMR in the presence of an internal standard. [Ir] = $[Ir(dF(CF_3)ppy)_2(dtbpy)]PF_6$.

Scheme 3. Substrate Scope of Simple Tertiary Amines



functionality ($HNEt_2$, $HNPr_2$, HN^nBu_2) provided a mixture of mono- and dicyanated products (e.g., **2a**/**b**, **3a**/**b**, **4a**/**b**). In contrast, $HNPent_2$, HN^iPr_2, and HN^iBu_2 afforded the monocyanation products in 92%, 50%, and 44% yield, respectively (**5a**, **6a**, **7a**). Furthermore, C_α–H cyanation of cyclic, secondary amines was also successful: both pyrrolidine and morpholine reacted to afford moderate yields of the respective products **8a** (49%) and **9a** (54%). Finally, the C_α–H cyanation of $HNBn_2$ was also successful (albeit low yielding), providing 14% of **10a** (30% rsm).

In all cases with moderate yields, significant amounts of starting materials (34–54% rsm) were detected in the reaction mixtures, signifying excellent mass balances (>90%). This excludes substrate overoxidation or decomposition as the reason for low yields. To test if the observed low yields are due to catalyst and/or reagent decomposition, a second batch of Ir photoredox catalyst or both photocatalyst and NaCN (Scheme 2, bottom) were added to a reaction mixture with morpholine as substrate. Then the mixture was irradiated for another 24 h. Excitingly, significantly higher yields of **9a** (83% and 91%, respectively) were thus obtained, suggesting that catalyst decomposition is the reason for low yields with secondary amine substrates.

A wide range of tertiary aliphatic amines was successfully subjected to the optimized conditions (84 to 94% isolated yields for **1a**, **11a**, **12a**, and **13a**; Scheme 3). Additionally, activated (benzylic and aniline-type) amines provided good yields (**14a**; 74% isolated yield; **18a**; 71% isolated yield). Furthermore, the cyanation of tertiary, cyclic amines affords excellent yields, with a distinct preference for ring C_α–H cyanation (**15a**/**b**, **16a**/**b**,**17**/**b**) vs C_α–H cyanation at the acyclic substituent. Substrates without discernible C_α–H cyanation reactivity include DABCO and Boc-protected pyrrolidine (**19**). Such amines are often easily modified with LDA under highly basic conditions,[36] which makes the developed method complementary to existing approaches. Amine **21** bearing a ketone group forms the corresponding cyanohydrin by cyanide addition, thereby preventing formation of C_α–H cyanation to afford product **21a**. Overall, this substrate scope study of simple tertiary amines suggests that ketone functional groups, amines containing electron-withdrawing protecting groups, and conformationally strongly constrained amine substrates (e.g., DABCO) are incompatible with the established conditions.

Exploring Functional Group Tolerance via Intermolecular Reaction Screening. To gain further information on the functional group tolerance of the reaction, an intermolecular reaction screening protocol[37] was employed (Table 2). Interestingly, the reaction tolerates tertiary alcohols and cyano, ester, and pyridine functionalities well, with product yields not below 72% and >82% remaining additive in all cases (entries 2–5). Surprisingly, a drop in reactivity (62% **1a**) is observed in the case of anisole as additive, with only 77% of PhOMe remaining after the reaction. This indicates potential reactivity of aryl ethers or electron-rich aromatics under these conditions. Moreover, alkenes such as in 1-octene also slow reactivity (71% yield of **1a**), and only 69% of 1-octene remains after the reaction. Finally, ketones and aldehydes are not compatible with the protocol (entries 8 and 9) due to direct attack of the cyanide nucleophile at their carbonyl moiety.

Substrate Scope: Complex Substrates and Drugs. We then shifted our focus toward the late-stage functionalization of biologically active molecules. We chose two alkaloids (nicotine, gramine) and several known drugs (lidocaine, imipramine, gefitinib, (*R*)-(−)-phenylephrine, and Chantix; see Scheme 4) as model compounds to further explore the reactivity and functional group tolerance of the established protocol. Excitingly, many different functional groups (heterocycles, amides, ethers, unprotected alcohols, and phenols) were well tolerated. The C_α–H cyanation of nicotine resulted in the highest achieved yield in this series, affording 92% of ring

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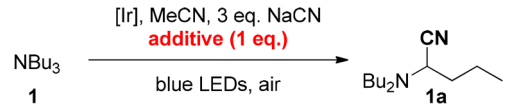
Table 2. Results of Intermolecular Reaction Screening[a]



Entry	Additive	Yield **1a**[b]	Remaining Additive	Remaining **1**
1	No additive	94% ✔	n/a	6%
2	^{t}BuOH	94% ✔	99% ✔	6%
3	PhCN	89% ✔	86% ✔	7%
4	$PhCO_2Et$	72% ✔	83% ✔	21%
5	2,6-Lutidine	93% ✔	87% ✔	6%
6	PhOMe	62% -	77% ✔	34%
7	1-Octene	71% ✔	69% -	27%
8	Cyclohexanone	68% -	44% -	27%
9	Octanal	73% ✔	0% ✘	26%

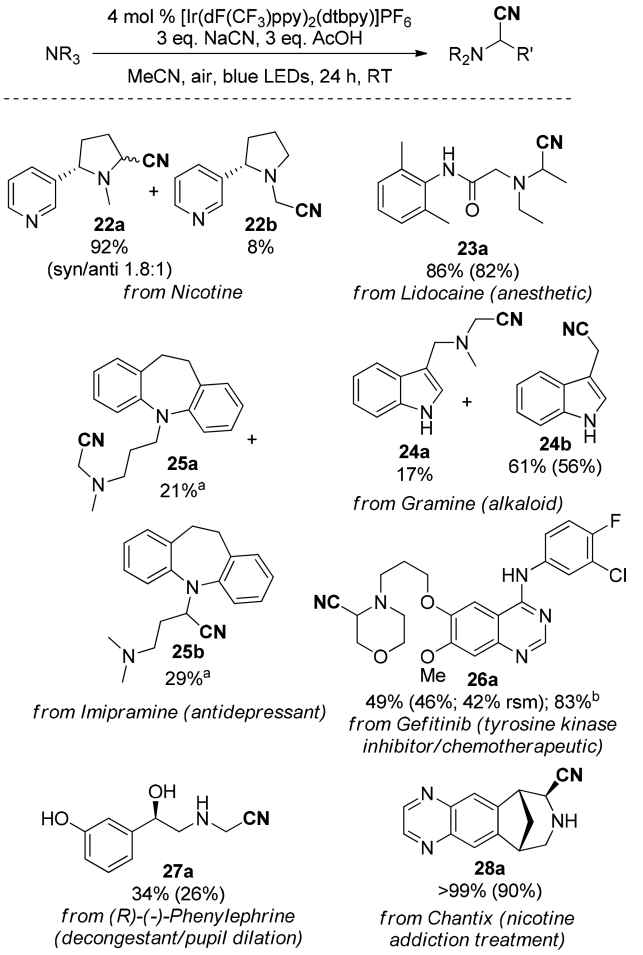
[a]Conditions: NBu_3 (50 mg, 0.27 mmol), additive (0.27 mmol), MeCN (3 mL), blue LED reactor (72W), NaCN (3 equiv), $[Ir(dF(CF_3)ppy)_2(dtbpy)]PF_6$ (4 mol %), 24 h. [b]Yields were determined by quantitative, crude ^{1}H NMR.

cyanation (**22a**) and 8% of methyl cyanation (**22b**). Likewise, C_α–H cyanation of lidocaine resulted in high yields (86% **23a** crude, 82% isolated).

Similar to a previous report,[26] the reaction of gramine resulted in low yields of C_α–H cyanated product **24a** (17%). An interesting deamination reaction is responsible for this low yield (**24b** is the major product). In the case of imipramine, two expected C_α–H cyanation products were obtained in relatively low yields under our standard conditions (23% **25a**, 4% **25b**). Further studies with isolated C_α–H cyanation product **25b** (see SI) showed that hydrolysis of **25b** occurs at room temperature, which can be minimized by adding $NaHCO_3$ to the reaction mixture; this affords cyanation product **25b** in higher yield (29%).

In contrast to the mixture of products obtained with the relatively simple substrate imipramine, the C_α–H cyanation of the complex drug gefitinib cleanly formed **26a** (49% crude, 46% isolated) as the only product. Excitingly, this yield can be significantly improved to 83% when a second batch of Ir catalyst (4 mol %) and NaCN (3 equiv) is added after 24 h, followed by another 24 h of irradiation. This suggests that low conversions and yields can generally be addressed by recharging catalyst and nucleophile. (*R*)-(−)-Phenylephrine, a drug with an unprotected phenol functionality, an unprotected secondary alcohol group, and a secondary amine moiety also underwent C_α–H cyanation under the standard reaction conditions, providing 34% (26% isolated) of product **27a**. Excitingly, Chantix, a drug with a bicyclic secondary amine substructure, provided the resulting C_α–H cyanation product **28a** quantitatively (90% isolated) as a single *cis*-diastereomer.

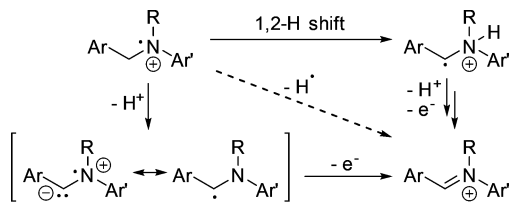
Scheme 4. Substrate Scope of Complex Amines and Drug Substrates*



*Conditions as described in Schemes 2 and 3. [a]Reaction in the presence of 2 equiv of $NaHCO_3$. [b]Yield after addition of a second batch of Ir catalyst (4 mol %) and NaCN (3 equiv) after 24 h and additional reaction time of 24 h.

Mechanistic Studies. As mentioned above, studies by Rueping and co-workers[27] had previously shown that AcOH improves photoredox-catalyzed C_α–H cyanations of activated amines (anilines). However, no detailed studies of the enhancing effect of AcOH were performed, resulting in the absence of a mechanistic explanation for the phenomenon (Scheme 5).[27] To enable further development by rationally guided reaction design, we thus focused on elucidating the role of AcOH in the reported methodology.

Scheme 5. Previously Proposed Mechanistic Possibilities of Iminium Ion Formation in C–H Cyanation of Tertiary Anilines[a]



[a]Adapted from ref 27.

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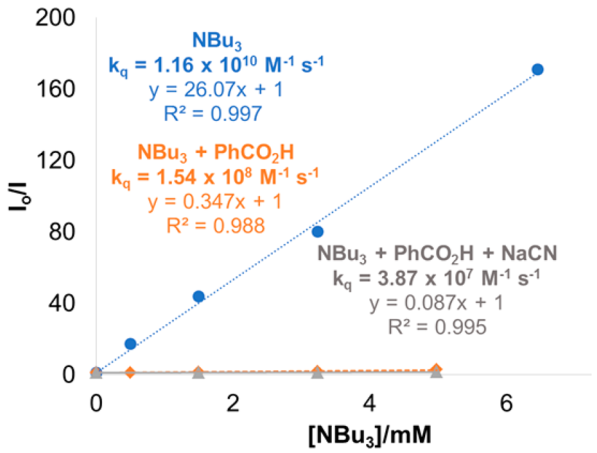
To this end, fluorescence-quenching experiments were performed. The ability of NBu_3 to quench the fluorescence of the photoexcited state *[Ir(dF(CF$_3$)ppy)$_2$(dtbpy)]PF$_6$ in the absence of additional reagents was first established (blue trace, Scheme 6). The quenching constant k_q obtained by

Scheme 6. Stern–Volmer Analysis of [Ir] Fluorescence Quenching by NBu_3[a]

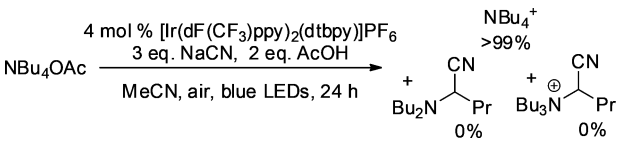


[a] k_q = quenching constant.

Stern–Volmer analysis of the data (see SI) was determined to be 1.16×10^{10} M^{-1} s^{-1}, which is in a similar range as the previously measured k_q for NEt_3 (1.20×10^9 M^{-1} s^{-1}).[38,35] Interestingly, in the presence of acid ($PhCO_2H$; orange trace, Scheme 6) and NaCN (gray trace, Scheme 6), the obtained k_q values for fluorescence quenching by NBu_3 are much lower (1.54×10^8 M^{-1} s^{-1} and 3.87×10^7 M^{-1} s^{-1}, respectively). This suggests that photoredox-catalyzed oxidation of NBu_3 is slower in the presence of acid, which may be rationalized by equilibrium protonation of NBu_3 under catalytic conditions.

Mechanistically, two different scenarios may cause the low rates of *Ir fluorescence quenching in the presence of acid/NaCN: (a) Inherently slow oxidation of the protonated ammonium salt [$HNBu_3$][O_2CR] or (b) slow oxidation that is due to the small amount of free amine in solution. To distinguish these two possibilities, we reasoned that the first scenario may be modeled by the use of a "permanent" ammonium salt, mimicking the charge and electronic properties of the protonated amine. Therefore, we attempted to perform C_α–H cyanation of NBu_4OAc (Scheme 7).

Scheme 7. Reaction To Probe Direct Oxidation of Ammonium Salt



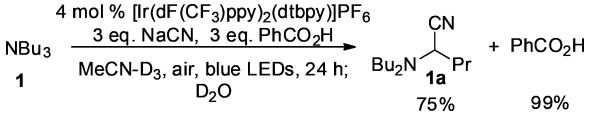
Interestingly, no trace of cyanation product was observed; instead, quantitative ^{1}H NMR analysis of the crude reaction mixture showed >99% of NBu_4^+ after 24 h. We conclude from this experiment that catalytic amine C_α–H cyanation proceeds via oxidation of the equilibrium concentration of non-protonated amine.

If amine oxidation is rate determining in C_α–H cyanation, slower fluorescence quenching in the presence of acids as shown by Stern–Volmer analysis would typically be expected to also result in lower yields in the presence of acid. However, higher yields of C_α–H cyanation products were observed in the presence of AcOH and $PhCO_2H$ than in their absence. As such, we hypothesized that these carboxylic acid additives have additional, beneficial effects.

For further mechanistic studies, we therefore considered three mechanistic hypotheses for the involvement of the carboxylic acid additive: (a) The formation of carboxyl radicals; (b) the stabilization of a reaction intermediate by AcOH (or $PhCO_2H$), i.e. carboxylic acids functioning as co-catalysts; and (c) a role for carboxylic acid in preventing catalyst decomposition.

Formation of carboxyl radicals via photoredox catalysis using [Ir(dF(CF$_3$)ppy)$_2$(dtbbpy)]PF$_6$ ($E_{1/2}^{red}$ (Ir^{III}*/Ir^{II}) = +1.21 V versus SCE in MeCN)[38,39] have previously been described,[40,41] particularly as precursors for stabilized, tertiary, and secondary alkyl radicals. To investigate the possibility of carboxyl radical formation in the protocol under investigation, we tested if the acid additive is being consumed under the conditions of C_α–H cyanation, indicating decomposition pathways of carboxyl radicals. Thus, we analyzed the mass balance of a reaction in the presence of $PhCO_2H$ (Scheme 8), as byproducts formed

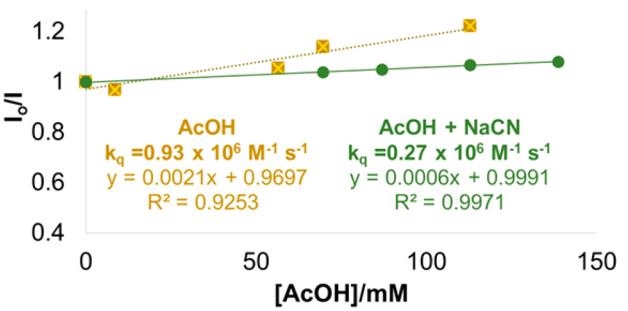
Scheme 8. Mass Balance of Amine C_α–H Cyanation



by decarboxylation of $PhCO_2H$ (e.g., PhH or PhPh) are more easily detectable than volatile byproducts formed from AcOH (e.g., CH_4 and CH_3CH_3). Interestingly, quantitative ^{1}H NMR analysis showed that 99% of $PhCO_2H$ remained after the reaction, and no other aromatic products were detected in the reaction mixture. These data imply that the additive $PhCO_2H$ does not decompose via decarboxylation of $PhCO_2^\bullet$ radicals. Therefore, carboxyl radicals formed from AcOH and $PhCO_2H$ under the reaction conditions are either stable against decarboxylation or are not involved in the catalytic pathway.

To compare the rate of carboxyl radical formation by photoredox-catalyzed oxidation of carboxylic acid additives to the rate of photoredox-catalyzed amine oxidation, a series of *Ir fluorescence quenching studies were performed with AcOH as quencher (Scheme 9; for details, see the SI).

Scheme 9. Stern–Volmer Analysis of [Ir] Fluorescence Quenching by AcOH



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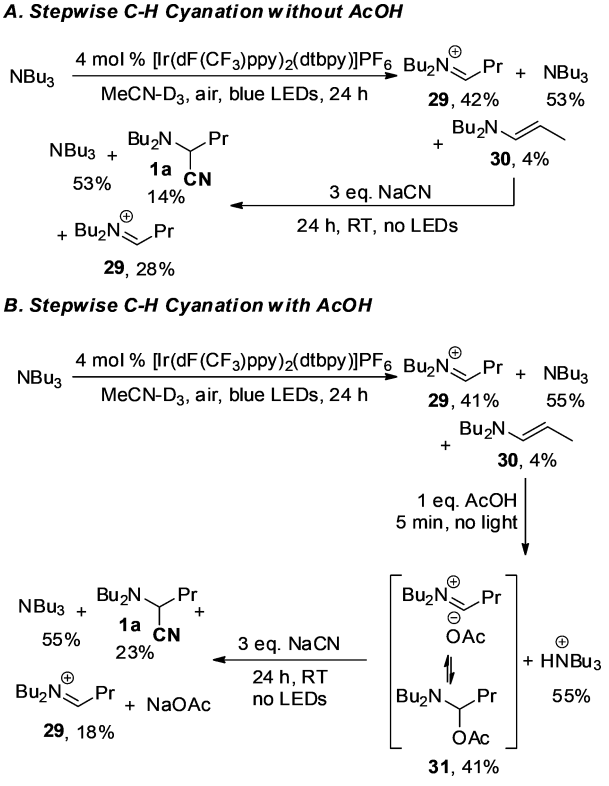
Interestingly, very small rates of *[Ir(dF(CF$_3$)ppy)$_2$(dtbbpy)]-PF$_6$ fluorescence quenching were observed with only AcOH as quencher (k_q = 0.93 × 10^6 M^{-1} s^{-1}) or with a mixture of AcOH and NaCN (k_q = 0.27 × 10^6 M^{-1} s^{-1}). Both values are much lower than the quenching rate constants associated with NBu$_3$ (1.16 × 10^{10} M^{-1} s^{-1} in the absence of acid; 1.54 × 10^8 M^{-1} s^{-1} in the presence of acid; Scheme 6 above), implying that amine oxidation outperforms carboxyl radical formation by several orders of magnitude. Put together, these studies show that carboxyl radical formation is significantly slower than amine oxidation under catalytic conditions. Therefore, the concentration of carboxyl radicals in the reaction is too low to play an important role in the observed catalytic reactivity.

One alternative mechanistic possibility for the role of carboxylic acids (as mentioned above) is that these additives act as co-catalysts by stabilizing transient intermediates. To pinpoint relevant intermediates, we attempted to separate the steps of the reaction pathway leading to C$_\alpha$–H cyanation; these reactions were performed in MeCN-d_3 to allow direct analysis by ^{1}H NMR.

First, the reaction mixture was irradiated for 24 h in the absence of any acid additive or NaCN (Scheme 10A/B).

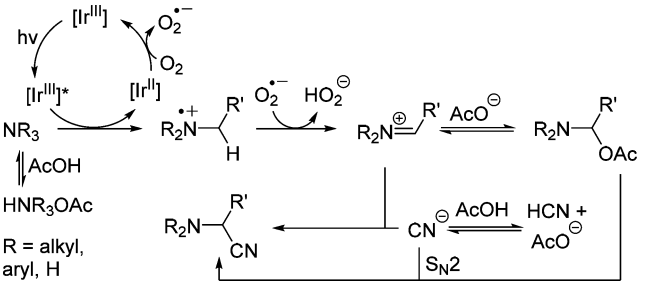
Scheme 10. Stepwise C$_\alpha$–H Cyanation Experiments



Under these conditions, ~45% of NBu$_3$ was converted to form two new compounds **29** and **30**. The lower yielding compound **30** (4%) was identified as the enamine Bu$_2$NCH=CHEt by independent synthesis (see the SI). Based on this knowledge and the similarity of the ^{1}H NMR shifts of **29** to the spectrum of NBu$_3$, we propose that compound **29** (41–42% yield) is the iminium compound [Bu$_2$N=CHPr]$^+$. This mixture of enamine, NBu$_3$, and **29** was then treated with 3 equiv of NaCN and allowed to react for 24 h (Scheme 10A) or treated with 1 equiv of AcOH before NaCN addition (Scheme 10B). In the first experiment, NaCN addition resulted in the formation of 14% of C$_\alpha$–H cyanation product **1a**. Noteworthy, the yield of **1a** was significantly higher (23%) in the second experiment, suggesting that the addition of AcOH is beneficial for cyanation of the iminium intermediate. Interestingly, a new compound **31** (41%) was detected in the reaction mixture right after AcOH addition. The 41% yield of **31** is comparable to the yield of **29** in the first step; however, the C$_\alpha$–H signal undergoes a downfield shift of ~0.3 ppm in comparison to **29**. This suggests that compound **31** is either the hemiaminal Bu$_2$NCH(OAc)Pr, a tight ion pair of [Bu$_2$N = CHPr]OAc, or an equilibrium mixture of both compounds, as shown in Scheme 10B.

We conclude from these experiments that the steps shown in Scheme 10B are analogous to the reaction pathway of C$_\alpha$–H cyanation in the presence of AcOH. Furthermore, the obtained data imply a mechanistic role for AcOH: The stabilization of the iminium intermediate by the formation of a hemiaminal or iminium ion pair **31**. The resulting mechanistic pathway for the photoredox-mediated amine C$_\alpha$–H cyanation in the presence of AcOH is shown in Scheme 11. This pathway begins with the

Scheme 11. Proposed Reaction Mechanism for Amine C$_\alpha$–H Cyanation



free amine oxidation by the long-lived photoexcited state *Ir^{III} (2.25 μs),[38b] producing an aminyl radical cation and an Ir^{II} species. The Ir^{II} species is reoxidized to its Ir^{III} ground state by O_2, forming $O_2^{\bullet-}$ ($E_{1/2}^{red}$ (Ir^{III}/Ir^{II}) = −1.37 V versus SCE in MeCN; $E_{1/2}^{red}$ ($O_2/O_2^{\bullet-}$) = −0.87 V versus SCE in MeCN).[35,39] Hydrogen atom transfer from the aminyl radical cation to $O_2^{\bullet-}$ produces an iminium intermediate, which is in equilibrium with the corresponding hemiaminal intermediate. Analogous hemiaminals and their substitution reactivity in the presence of cyanide have previously been described in the literature.[42,43] Reaction of the iminium compound with cyanide produces the α-functionalized amine. As an alternative mechanistic pathway, a direct S$_N$2-type substitution could occur at the hemiaminal, if required by the substrate geometry.

We then set out to gain further insight into the role of O_2 in the reaction mixture. Our mechanistic hypothesis (Scheme 11 above) suggests that O_2 is responsible for reoxidation of the Ir^{II} species formed by amine oxidation. However, production of singlet O_2, which may directly react with the substrate, has been considered as a mechanistic possibility in previous work;[44] thus, the effect of O_2 on *Ir fluorescence quenching needs to be investigated. To this end, we performed Stern–Volmer quenching studies under an air atmosphere. The quenching constants k_q in air and under N_2 were then compared (Table 3). Expectedly, *Ir fluorescence quenching by NBu$_3$ in the absence of any other reagents is significantly less effective in air, as characterized by a k_q value that is smaller by one order of magnitude (1.10 × 10^9 M^{-1} s^{-1} in air vs 1.16 ×

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Table 3. Comparison of Quenching Constants k_q Obtained via *Ir Fluorescence Quenching Studies under N_2 and Air Atmospheres

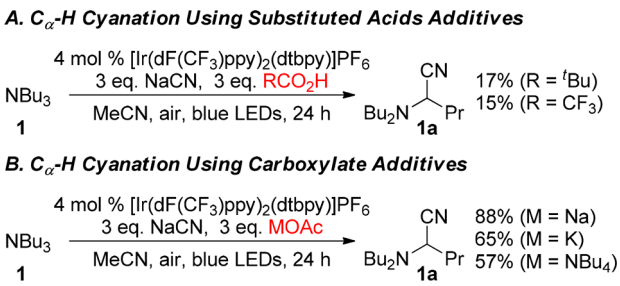
conditions	k_q under N_2	k_q under air
no acid, no NaCN[a]	1.16×10^{10} M^{-1} s^{-1}	1.10×10^{9} M^{-1} s^{-1}
with $PhCO_2H$, no NaCN[b]	1.54×10^{8} M^{-1} s^{-1}	0.85×10^{8} M^{-1} s^{-1}
with $PhCO_2H$, with NaCN[c]	3.87×10^{7} M^{-1} s^{-1}	1.33×10^{8} M^{-1} s^{-1}

[a]Conditions: 4.0 mg (3.47 μmol) of $[Ir(dF(CF_3)ppy)_2(dtbpy)]PF_6$, MeCN (2.00 mL), standard solution of NBu_3 in MeCN added. [b]Conditions as in fnt [a] with $PhCO_2H$ (20 mg, 0.16 mmol); standard solution of NBu_3 in MeCN added. [c]Conditions as in fnt [a] with $PhCO_2H$ (20 mg, 0.16 mmol) and NaCN (8 mg, 0.16 mmol); standard solution of NBu_3 in MeCN added.

10^{10} M^{-1} s^{-1} under N_2). This suggests that the majority of excited-state *Ir reacts with O_2 under these conditions, possibly via a process that produces singlet O_2. Interestingly, this is not observed in the presence of $PhCO_2H$ and NaCN: Those conditions show k_q values in similar ranges (0.85×10^8 M^{-1} s^{-1} in air vs 1.54×10^8 M^{-1} s^{-1} under N_2 for $PhCO_2H$ added; 1.33×10^8 M^{-1} s^{-1} in air vs 3.87×10^7 M^{-1} s^{-1} under N_2 for $PhCO_2H$/NaCN added). These data imply that *Ir fluorescence quenching by O_2 does not play a major role under the reaction conditions of C_α–H cyanation. These findings further suggest that formation of singlet O_2 is not a major pathway for product formation in the established protocol; analogous conclusions have been drawn in prior investigations due to vastly different concentrations of substrate and O_2 in solution, which affect the relevant *Ir quenching rates during catalysis.[44b]

To further support the role of carboxylate in the proposed mechanism, we performed a series of reactions with different carboxylic acids and acetate salts (Scheme 12). We reasoned

Scheme 12. Reactions To Probe the Role of Different Carboxylic Acid Additives



that acids with low nucleophilicity (e.g., with very low pK_a or bulky substitutents) would lead to significantly decreased yields. Indeed, very low yields (17% and 15%) of product **1a** were obtained with $^tBuCO_2H$ and F_3CCO_2H as acid additives (Scheme 12A), supporting the importance of carboxylic acid as a nucleophilic co-catalyst.

If the role of acid is to provide access to a hemiaminal intermediate, addition of acetate salts should also prove beneficial for reactivity. Thus, we substituted AcOH for NaOAc, KOAc, and NBu_4OAc as additives (Scheme 12B). Excitingly, all these reactions provided C_α–H cyanation product **1a** in higher yields than in the absence of any additive. The highest yield was obtained with the least soluble acetate salt NaOAc (88%), while the most soluble salt NBu_4OAc (57%) afforded the lowest yield. This suggests that the solubility of acetate salts plays a role in the reaction. As NaOAc precipitation is typically observed in the catalytic reaction mixture, precipitation may be an important contributor to the reaction driving force.

These data also imply that acetate salts are inferior to AcOH as an additive. Based on the Stern–Volmer analysis of *Ir fluorescence quenching by NBu_3 (Table 3), it is clear that the rate of amine oxidation is higher in the absence of acid. However, one critical factor, the stability of the photoredox catalyst, is yet to be considered; as our data on the C_α–H cyanation of morpholine and gefitinib shows, catalyst decomposition is an important limitation in this chemistry. Ir catalyst decomposition can occur by ligand exchange. Such reactivity would be expected to be highly pronounced in the presence of nucleophilic additives (e.g., a mixture of NaOAc, NaCN, and amines, especially less sterically hindered secondary amines). In contrast, exchange of ligands at the Ir center would be less pronounced in a buffer system (e.g., AcOH/NaCN/amine), in which the potential nucleophiles cyanide and amine are partially protonated; this likely results in slowing down catalyst decomposition. In conclusion, the detailed mechanistic studies discussed in the previous paragraphs provide three distinct explanations for the beneficial role of carboxylic acid additives: formation of a stabilizing hemiaminal intermediate, modulating fluorescence quenching of the photoexcited catalyst species, and preventing catalyst decomposition by protonating amine and cyanide catalyst poisons.

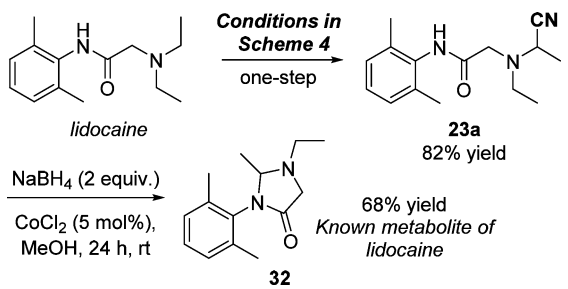
Synthetic Utility of α-Aminonitriles Obtained from Drugs. To demonstrate the application of α-aminonitriles as versatile intermediates for the synthesis of new compounds and pharmaceutical molecules, cyanated lidocaine **23a** was selected for further derivatization.

(*Z*)-*N*-(3-Ethyl-2-methyloxazolidin-5-ylidene)-2,6-dimethylaniline (**32**) is a major metabolite of lidocaine in monkeys.[45,46] Studies into the identification of enzyme(s) responsible for this metabolism in monkeys is of interest.[46] While **32** can be accessed from lidocaine through enzymatic synthesis,[45] its nonenzymatic chemical synthesis remains elusive. Delightfully, after exploration of various reaction conditions, a unique reductive condition ($NaBH_4$, catalytic amount of $CoCl_2$ in MeOH at room temperature) was discovered for the chemical synthesis of compound **32** as the only product from **23a** (Scheme 13).

SUMMARY AND CONCLUSIONS

In summary, this paper describes the development and mechanistic elucidation of a general C_α–H cyanation methodology, which introduces a cyanide group in secondary and

Scheme 13. Chemical Synthesis of Lidocaine Metabolite 32 via C_α–H Cyanation



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tertiary amines via aerobic photoredox catalysis under mild conditions. The broad functional group tolerance allows functionalizations of complex molecules such as known drugs and alkaloids. Detailed mechanistic studies elucidate the role of carboxylate additives and suggest iminium ions and hemiaminals as key intermediates. We further conclude that hemiaminal intermediates act as a "stable" reservoir of iminium intermediates that are less prone to other side reactions such as hydrolysis or dealkylation, thus promoting C_α–H cyanation. Overall, the presented studies provide a convenient methodology for the direct C_α–H diversification of basic amines with applications in late-stage functionalization, as well as insights into the mechanism of this process.

EXPERIMENTAL SECTION

General Information. All chemicals were obtained from commercial suppliers (e.g., Alfa Aesar, TCI America, Sigma-Aldrich) and used as obtained unless otherwise specified in the procedure. Deuterated solvents used as reaction media or for NMR measurements were obtained from Cambrige Isotopes or Sigma-Aldrich.

All NMR experiments were carried out on a Bruker BioSpin 500 MHz Avance III Digital NMR spectrometer. All quantitative ^{1}H NMR measurements were performed using an adjusted method (15 s relaxation time, NS = 32) with 1,3-dinitrobenzene or 1,1,2-trichloroethane as internal standard. All NMR spectra were recorded at room temperature unless otherwise noted. Alternatively, NMR spectra were recorded on a Bruker 400 Avance III with a 5 mm BBFO probe (400 MHz for ^{1}H; 101 MHz for ^{13}C). The proton signal for nondeuterated solvent (δ = 2.50 ppm for DMSO) was used as an internal reference for ^{1}H NMR spectra. For ^{13}C NMR spectra, chemical shifts are reported relative to δ = 39.51 ppm resonance of DMSO-d_6.

High-resolution mass spectrometry was performed at the University of Massachusetts Medical School mass spectroscopy facility. Alternatively, HRMS spectra were recorded by Intertek. Analyses were conducted on an Agilent 6220 TOF mass spectrometer (Agilent Technologies, Wilmington, DE) in positive or negative electrospray mode. The system was calibrated to greater than 1 ppm accuracy across the mass range prior to analyses according to manufacturer's specifications. The mass accuracy was calculated for all observed isotopes against the theoretical mass ions derived from the chemical formula using MassHunter software (Agilent Technologies, Wilmington, DE).

Reactions were observed by *in situ* FTIR, using a Mettler Toledo ReactIR 10 instrument with MCT Detector using HappGenzel apodization. As probe, a SiComp (Silicon) probe connected via AgX (Silver Halide; 6 mm × 1.5 m fiber) was employed. Measurement was performed between 3000 and 650 cm^{-1} at a resolution of 4 cm^{-1} (scan option: AutoSelect; gain: 1×). Data collection and analysis were performed using Mettler Toledo iCIR v4.3.35 SP1 software and Microsoft Excel 2010.

Representative Procedure for Stern–Volmer Studies: [Ir(dF(CF$_3$)ppy)$_2$(dtbbpy)]PF$_6$ Fluorescence Quenching by NBu$_3$ under N$_2$. A 4.0 mg (3.47 × 10^{-3} mmol) portion of [Ir(dF(CF$_3$)ppy)$_2$(dtbbpy)]PF$_6$ was dissolved in dry, degassed MeCN (2.00 mL) in a glovebox filled with N$_2$ atmosphere. The solution was transferred to a fluorimeter cuvette (Starna Cells 3-Q-10-GL14-S, window material Spectrosil Quartz or equivalent, usable range: 170–2700 nm), equipped with a septum. A standard solution of NBu$_3$ was degassed and transferred to a microliter syringe under N$_2$. The syringe was capped with a septum. Both the filled fluorimeter cuvette and the syringe containing the standard solution of the quencher were removed from the glovebox. The filled fluorimeter cuvette was placed in the fluorimeter (Hitachi F-4500 FL spectrophotometer), and Ir fluorescence was recorded (excitation wavelength: 380 nM; measurement between 440 and 560 nM; scan speed 60 nm/s; delay: 0 s; excitation and emission slit 5.0 nm; response: 0.5 s). Then aliquots of the standard solution of NBu$_3$ were added to obtain the respective NBu$_3$ concentrations detailed in the legend of each corresponding figure (see the SI). After each NBu$_3$ addition, a fluorescence spectrum was recorded. Stern–Volmer analysis of the obtained signals was performed by averaging the observed absorption intensity I for the wavelengths between 498 and 502 nm (λ_{max} = 500 nm) and correcting for the respective change in volume of the solution.

General Procedure for Amine C_α–H Cyanation. A tertiary or secondary amine (0.27 mmol, 1.0 equiv) was dissolved in 3 mL of MeCN, and then NaCN (0.81 mmol, 0.040 g, 3.0 equiv), [Ir(dF(CF$_3$)ppy)$_2$(dtbbpy)]PF$_6$ (0.011 mmol, 0.012 g, 4.0 mol %), and AcOH (0.81 mmol, 0. 49 g, 46 μL, 3.0 equiv) were added to the stirred solution under an air atmosphere. The vial was then sealed tightly with a Teflon-lined vial cap, and the mixture was stirred at room temperature under irradiation with blue LEDs for 24 h. Reactions were monitored by TLC. After the reaction time was completed, the solvent was removed under reduced pressure. To determine crude yields, 1,3-dinitrobenzene (0.5 mL of a standard solution of 300 mg of 1,3-dinitrobenzene in 10 mL of CDCl$_3$ or MeCN-d_3) or 1,1,2-trichloroethane (0.5 mL of a standard solution of 300 mg of 1,3-dinitrobenzene in 10 mL of CDCl$_3$ or MeCN-d_3) was added the mixture as internal standard and the crude yield was determined by quantitative ^{1}H NMR (15 s relaxation time to improve accuracy of measurement). Alternatively, the crude residue was directly purified on silica gel using EtOAc or EtOAc–hexanes mixtures as eluent to provide the corresponding α-cyanated amines.

Characterization and Spectral Data. *2-(Dibutylamino)-pentanenitrile (**1a**).* Eluent: EtOAc. Yield: 52.8 mg (93%). ^{1}H NMR (500 MHz, CDCl$_3$): δ 3.51 (t, J = 7.8 Hz, 1H), 2.50 (ddd, J = 13.0, 8.4, 7.3 Hz, 2H), 2.27 (ddd, J = 13.0, 8.1, 4.9 Hz, 2H), 1.64–1.62 (m, 2H), 1.45–1.18 (m, 10H), 0.88 (t, J = 7.4 Hz, 3H), 0.85 (t, J = 7.3 Hz, 6H) ppm. The spectral data were in agreement with literature data.[26]

*2-(Ethylamino)propanenitrile (**2a**) and 2,2′-Azanediyldipropanenitrile (**2b**).* The ^{1}H NMR spectra of compounds **2a** and **2b** were extracted from ^{1}H NMR and COSY spectra of the crude mixture. The ^{13}C NMR spectra of compounds **2a** and **2b** were extracted from ^{13}C NMR, HSQC, and HMBC spectra of the crude mixture.

2a. Crude yield: 50%. ^{1}H NMR (500 MHz, CD$_3$CN): δ 3.66 (q, J = 7.0 Hz, 1H), 2.71 (dq, J = 13.1, 7.3 Hz, 1H), 2.36 (dq, J = 13.1, 7.0 Hz, 1H), 1.39 (d, J = 7.0 Hz, 3H), 1.08 (t, J = 7.1 Hz, 3H) ppm. ^{13}C NMR (126 MHz, CD$_3$CN): δ 110.4, 44.7, 43.2, 18.6, 13.8 ppm. HRMS (ESI) m/z: [M + H]$^+$ calcd for $C_5H_{10}N_2$ 99.0917 , found 99.0911.

2b. Crude yield: 10%. ^{1}H NMR (500 MHz, CD$_3$CN): δ 3.89 (q, J = 7.2 Hz, 2H), 1.38 (d, J = 7.2 Hz, 6H) ppm. ^{13}C NMR (126 MHz, CD$_3$CN): δ 121.0, 44.5, 17.1 ppm. HRMS (ESI) m/z: [M + H]$^+$ calcd for $C_6H_9N_3$ 124.0869, found 124.0864. The ^{13}C NMR data of **2b** were in agreement with literature data.[47]

*2-(Propylamino)butanenitrile (**3a**) and 2,2′-Azanediyldibutanenitrile(**3b**).* The ^{1}H NMR spectra of compounds **3a** and **3b** were determined using ^{1}H NMR and COSY spectra of the crude mixture. The ^{13}C NMR spectra of compound **3b** were determined using ^{13}C NMR, HSQC, and HMBC spectra of the crude mixture.

3a. Crude yield: 47%. ^{1}H NMR (500 MHz, CD$_3$CN): δ 3.41 (dd, J = 7.6, 6.3 Hz, 1H), 2.78 (ddd, J = 11.1, 8.0, 6.5 Hz, 1H), 2.53 (ddd, J = 11.1, 8.1, 6.1 Hz, 1H), 1.80–1.65 (m, 2H), 1.55–1.37 (m, 2H), 1.04 (dd, J = 7.5, 7.5 Hz, 3H), 0.89 (dd, J = 7.4, 7.4 Hz, 3H) ppm. HRMS (ESI) m/z: [M + H]$^+$ calcd for $C_7H_{15}N_2$ 127.1230, found 127.1227. The spectral data of **3a** were in agreement with literature data.[31a]

3b. Crude yield: 9%. ^{1}H NMR (500 MHz, CD$_3$CN): δ 3.62 (t, J = 7.9 Hz, 2H), 2.32 (ddd, J = 12.8, 7.9, 4.7 Hz, 4H), 0.91 (t, J = 7.4 Hz, 1H). ^{13}C NMR (126 MHz, CD$_3$CN): δ 120.4, 55.7, 24.6, 10.6 ppm. HRMS (ESI) m/z: [M + H]$^+$ calcd for $C_8H_{13}N_3$ 152.1182, found 152.1176.

*2-(Butylamino)pentanenitrile (**4a**) and 2,2′-Azanediyldipentanenitrile (**4b**).* The ^{1}H NMR spectra of compounds **4a** and **4b** were determined using ^{1}H NMR and COSY spectra of the crude mixture.

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Also, the ^{13}C NMR spectra of compounds **4a** and **4b** were determined using ^{13}C NMR, HSQC, and HMBC spectra of the crude mixture.

4a. Crude yield: 39%. ^1H NMR (500 MHz, CD_3CN): δ 3.56 (t, J = 7.2 Hz, 1H), 2.75 (ddd, J = 12.8, 7.5, 5.0 Hz, 1H), 2.27 (ddd, J = 12.8, 7.5, 5.0 Hz, 1H), 1.71−1.62 (m, 2H), 1.51−1.22 (m, 6H), 0.93 (t, J = 7.3 Hz, 6H). ^{13}C NMR (126 MHz, CD_3CN): δ 110.5, 50.8, 49.9, 46.6, 34.8, 19.9, 19.7, 12.9, 12.8 ppm. HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_9H_{18}N_2$ 155.1543, found 155.1536.

4b. Crude yield: 8%. ^1H NMR (500 MHz, CD_3CN): δ 3.68 (t, J = 7.8 Hz, 2H), 1.71−1.62 (m, 4H), 1.51−1.22 (m, 4H), 0.93 (t, J = 7.3 Hz, 6H). ^13C NMR (126 MHz, CD_3CN): δ 120.6, 53.7, 33.2, 18.6, 12.5 ppm. HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{10}H_{17}N_3$ 180.1495, found 180.1488.

*2-(Pentylamino)hexanenitrile (**5a**).* The ^1H NMR spectrum of compound **5a** was determined using ^1H NMR and COSY spectra of the crude reaction mixture in MeCN-d_3. Also, the ^{13}C NMR spectrum of compound **5a** was determined using ^{13}C NMR, HSQC, and HMBC spectra of the crude mixture. Crude yield: 92%. ^1H NMR (500 MHz, $CDCl_3$): δ 3.53 (t, J = 7.2 Hz, 1H), 3.10 (s, 1H), 2.88 (ddd, J = 11.1, 8.2, 6.4 Hz, 1H), 2.62 (ddd, J = 11.1, 8.3, 6.0 Hz, 1H), 1.81−1.72 (m, 2H), 1.58−1.44 (m, 4H), 1.43−1.32 (m, 6H), 0.97−0.90 (m, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 120.38, 50.65, 47.68, 33.16, 29.25, 29.20, 27.66, 22.37, 22.06, 13.86, 13.68. HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{11}H_{22}N_2$ 183.1856, found 183.1849.

*2-(Isopropylamino)-2-methylpropanenitrile (**6a**).* The ^1H NMR spectrum of compound **6a** was determined using ^1H NMR and COSY spectra. Crude yield: 50%. ^1H NMR (500 MHz, CD_3CN): δ 3.00 (hept, J = 6.2 Hz, 1H), 1.39 (s, J = 1.8 Hz, 6H), 1.08 (d, J = 6.4 Hz, 6H) ppm. The spectral data were in agreement with literature data.[48]

*(Isobutylamino)-3-methylbutanenitrile (**7a**).* The ^1H NMR spectrum of compound **7a** was determined using ^1H NMR and COSY spectra. Also, the ^{13}C NMR spectrum of compound **7a** was determined using ^{13}C NMR, HSQC and HMBC spectra. Crude yield: 43%. ^1H NMR (500 MHz, CD_3CN): δ 3.37 (d, J = 6.6 Hz, 1H), 2.60 (dd, J = 11.3, 7.0 Hz, 1H), 2.40 (dd, J = 11.0, 4.4 Hz, 1H), 1.99−1.91 (m, 1H), 1.75−1.64 (m, 1H), 0.94 (d, J = 5.4 Hz, 3H), 0.94 (d, J = 5.4 Hz, 6H), 0.93 (d, J = 5.4 Hz, 3H) ppm. ^{13}C NMR (126 MHz, CD_3CN): δ 119.7, 57.0, 55.2, 30.9, 25.6, 19.7, 19.6 ppm. HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_9H_{18}N_2$ 155.1543, found 155.1536.

*Pyrrolidine-2-carbonitrile (**8a**).* The ^1H NMR spectrum of compound **8a** was determined using ^1H NMR and COSY spectra. Crude yield: 42%. ^1H NMR (500 MHz, CD_3CN): δ 4.06 (dd, J = 8.0, 4.5 Hz, 1H), 3.01−2.89 (m, 2H), 2.15−2.06 (m, 1H), 1.90−1.85 (m, 2H), 1.80−1.72 (m, 1H). The spectral data were in agreement with literature data.[31a]

*Morpholine-3-carbonitrile (**9a**).* The ^1H NMR spectrum of compound **9a** was determined using ^1H NMR and COSY spectra. ^1H NMR (500 MHz, CD_3CN): δ 3.92 (td, J = 2.8, 0.5 Hz, 1H), 3.82 (dd, J = 11.5, 2.6 Hz, 1H), 3.77 (dt, J = 11.2, 2.9 Hz, 1H), 3.70 (dt, J = 11.5, 3.3 Hz, 1H), 3.56 (ddd, J = 11.2, 10.2, 2.8 Hz, 1H), 3.07 (dddd, J = 12.5, 10.2, 3.2, 0.6 Hz, 2.75 (dt, J = 12.5, 2.7 Hz, 1H). The spectral data were in agreement with literature data.[49]

*2-(Benzylamino)-2-phenylacetonitrile (**10a**).* The ^1H NMR spectrum of compound **9a** was determined using ^1H NMR and COSY spectra. Crude yield: 15%. ^1H NMR (500 MHz, CD_3OD): δ 7.55 (dd, J = 7.3, 1.8 Hz, 2H), 7.45−7.40 (m, 4H), 7.40 (m, 3H), 7.33−7.29 (m, 1H), 4.76 (s, 1H), 4.07 (d, J = 13.0 Hz, 1H), 3.97 (d, J = 13.0 Hz, 1H), 1.89 (bs, 1H). The spectral data were in agreement with literature data.[50]

*2-(Diethylamino)propanenitrile (**11a**).* Eluent: EtOAc. Yield: 31.3 mg (99%). ^1H NMR (500 MHz, $CDCl_3$): δ 3.83 (q, J = 7.2 Hz, 1H), 2.77 (dq, J = 13.1, 7.3 Hz, 2H), 2.46 (dq, J = 13.0, 7.0 Hz, 1H), 1.48 (d, J = 7.2 Hz, 3H), 1.12 (t, J = 7.2 Hz, 6H) ppm. The spectral data were in agreement with literature data.[51]

*2-(Dipropylamino)butanenitrile (**12a**).* Eluent: EtOAc. Yield: 42.7 mg (99%). ^1H NMR (500 MHz, $CDCl_3$): δ 3.50 (t, J = 7.8 Hz, 1H), 2.54 (ddd, J = 13.0, 8.4, 7.7 Hz, 1H), 2.39 (ddd, J = 13.0, 8.2, 4.7 Hz, 1H), 1.86−1.72 (m, 2H), 1.57−1.41 (m, 4H), 1.07 (t, J = 7.4 Hz, 3H), 0.92 (t, J = 7.4 Hz, 6H) ppm. The spectral data were in agreement with literature data.[26]

*2-(Dipentylamino)hexanenitrile (**13a**).* Yield: 57.2 mg (84%). ^1H NMR (500 MHz, $CDCl_3$): δ 3.60 (t, J = 7.8 Hz, 1H), 2.62−2.55 (m, 2H), 2.37 (ddd, J = 13.1, 8.4, 4.8 Hz, 2H), 1.80−1.67 (m, 2H), 1.52−1.25 (m, 16H), 0.98−0.89 (m, 9H) ppm. The spectral data were in agreement with literature data.[52]

*2-(Dibenzylamino)-2-phenylacetonitrile (**14a**).* Eluent: 1:9 EtOAc/hexane. Yield: 62.7 mg (74%). ^1H NMR (500 MHz, $CDCl_3$): δ 7.53−7.49 (m, 2H), 7.35−7.24 (m, 11H), 7.22−7.19 (m, 2H), 4.84 (s, 1H), 3.81 (d, J = 13.4 Hz, 2H), 3.34 (d, J = 13.4 Hz, 2H) ppm. The spectral data were in agreement with literature data.[53]

*2-Morpholinopropanenitrile (**15a**).* Eluent: EtOAc. Yield: 11.4 mg (30%). Compound **15a** was isolated from a reaction mixture that also contained **15b**. ^1H NMR (500 MHz, $CDCl_3$): δ 3.73−3.63 (m, 4H), 3.55 (q, J = 7.3 Hz, 1H), 2.66−2.60 (m, 2H), 2.45−2.39 (m, 2H), 1.40 (d, J = 7.3 Hz, 3H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$): δ 117.3, 66.6, 52.6, 16.8 ppm. HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_7H_{12}N_2O$ 141.1022, found 141.1016. FT-IR (KBr) ν = 2957, 2921, 2851, 2164, 1454, 1115 cm^{-1}.

*4-Ethylmorpholine-3-carbonitrile (**15b**).* Eluent: EtOAc. Yield: 20.4 mg (54%). Compound **15b** was isolated from a reaction mixture that also contained **15a**. ^1H NMR (500 MHz, $CDCl_3$): δ 3.95 (dd, J = 11.4, 0.9 Hz, 1H), 3.82 (dt, J = 11.4, 2.1 Hz, 1H), 3.67 (dd, J = 11.4, 2.7 Hz, 1H), 3.63 (d, J = 2.0 Hz, 1H), 3.55 (ddd, J = 11.36, 10.70, 3.33 Hz, 1H), 2.58−2.42 (m, 4H), 1.04 (t, J = 7.2 Hz, 3H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$): δ 115.4, 67.9, 67.0, 52.2, 50.1, 48.6, 11.7 ppm. HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_7H_{12}N_2O$ 141.1022, found 141.1017. FT-IR (KBr) ν = 2959, 2922, 2855, 2165, 1455, 1116 cm^{-1}.

*2-(Piperidin-1-yl)propanenitrile (**16a**).* Yield 6.3 mg (17%). Compound **16a** was isolated from a reaction mixture that also contained **16b**. ^1H NMR (500 MHz, $CDCl_3$): δ 3.65 (q, J = 7.3 Hz, 1H), 1.47 (d, J = 7.3 Hz, 3H) ppm. The spectral data were in agreement with literature data.[54]

*1-Ethylpiperidine-2-carbonitrile (**16b**).* Eluent: EtOAc. Yield: 24.3 mg (65%). Compound **16b** was isolated from a reaction mixture that also contained **16a**. ^1H NMR (500 MHz, $CDCl_3$): δ 3.84 (t, J = 3.6 Hz, 1H), 2.76−2.70 (m, 1H), 2.52−2.36 (m, 2H), 2.23 (td, J = 11.7, 3.0 Hz, 1H), 1.89−1.82 (m, 1H), 1.79−1.70 (m, 1H), 1.67−1.57 (m, 2H), 1.57−1.44 (m, 2H), 1.03 (t, J = 7.2 Hz, 3H) ppm. The spectral data were in agreement with literature data.[54]

*2-(Piperidin-1-yl)acetonitrile (**17a**).* Eluent: 1:3 EtOAc/hexane. Yield: 5.4 mg (16%). Compound **17a** was isolated from a reaction mixture that also contained **17b**. ^1H NMR (500 MHz, $CDCl_3$): δ 3.43 (s, 2H), 2.46 (t, J = 5.4 Hz, 4H), 1.57 (p, J = 5.6 Hz, 4H), 1.38 (p, J = 5.9 Hz, 2H) ppm. The spectral data were in agreement with literature data.[54]

*1-Methylpiperidine-2-carbonitrile (**17b**).* Eluent: 1:3 EtOAc/hexane. Yield: 23.1 mg (69%). Compound **17b** was isolated from a reaction mixture that also contained **17a**. ^1H NMR (500 MHz, $CDCl_3$): δ 3.67 (t, J = 3.6 Hz, 1H), 2.58 (dt, J = 11.2, 2.9 Hz, 1H), 2.30 (s, 4H), 1.88−1.73 (m, 2H), 1.63−1.57 (m, 2H), 1.54−1.43 (m, 3H) ppm. The spectral data were in agreement with literature data.[54]

*1-Phenylpyrrolidine-2-carbonitrile (**18a**).* Eluent: 1:3 EtOAc/hexane. Yield: 34.1 mg (73%). ^1H NMR (500 MHz, $CDCl_3$): δ 7.23 (dd, J = 8.73, 7.37 Hz, 2H), 6.76 (tt, J = 7.40, 0.97 Hz, 1H), 6.63 (dd, J = 8.72, 0.93 Hz, 2H), 4.38 (dd, J = 7.30, 1.70 Hz, 1H), 3.40 (td, J = 8.51, 8.31, 2.81 Hz, 1H), 3.31 (dt, J = 10.78, 7.89 Hz, 1H), 2.39−2.32 (m, 1H), 2.28−2.11 (m, 3H) ppm. The spectral data were in agreement with literature data.[55]

*Regioisomers **22a** and **22b** and 5′-Cyanonicotine (**22c**).* The mixture of cyanation products was identified by 1H NMR in a crude mixture, as a similar product mixture had been previously described. The spectral data were in agreement with literature data.[26]

22a. Crude yield: 33%. ^1H NMR (500 MHz, $CDCl_3$): δ 8.54 (dd, J = 8.6, 2.0 Hz, 1H), 8.52 (d, J = 1.8 Hz, 1H), 7.73 (dt, J = 7.8, 2.0, Hz, 1H), 7.32−7.25 (m, 1H), 3.37 (t, J = 7.9 Hz, 1H), 3.36 (d, J = 7.7 Hz, 1H), 2.52−2.08 (m, 3H), 2.31 (s, 3H), 1.93−1.69 (m, 1H) ppm.

22b. Crude yield: 59%. ^1H NMR (500 MHz, $CDCl_3$): δ 8.54 (dd, J = 8.6, 2.0 Hz, 1H), 8.52 (d, J = 1.8 Hz, 1H), 7.64 (dt, J = 7.8, 2.0, Hz,

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1H), 7.32−7.25 (m, 1H), 4.14 (d, J = 7.8 Hz, 1H), 3.57 (d, J = 8.0 Hz, 1H), 2.52−2.08 (m, 3H), 2.29 (s, 3H), 1.93−1.69 (m, 1H) ppm.

22c. Crude yield: 8%. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.60−8.44 (m, 2H), 7.76−7.58 (m, 1H), 7.32−7.25 (m, 1H), 3.62−3.60 (m, 1H), 3.59 (d, J = 17.3 Hz, 1H), 3.31 (d, J = 17.3 Hz, 1H), 3.21 (td, J = 8.4, 3.0 Hz), 2.75 (q, J = 8.8 Hz), 2.05−2.08 (m, 2H), 2.08−1.91 (m, 2H) ppm.

*2-((1-Cyanoethyl)(ethyl)amino)-N-(2,6-dimethylphenyl)-acetamide (**23a**).* Purification solvent: 1:1 EtOAc/hexane. Yield: 57.4 mg (82%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.26 (bs, 1H), 7.04 (m, 3H), 3.84 (q, J = 7.2 Hz, 1H), 3.43 (d, J = 17.6 Hz, 1H), 3.21 (d, J = 17.6 Hz, 1H), 2.82 (dq, J = 12.8, 7.3 Hz, 1H), 2.77−2.68 (m, 1H), 2.15 (s, 6H), 1.51 (d, J = 7.2 Hz, 3H), 1.19 (t, J = 7.2 Hz, 3H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$): δ 168.3, 135.0, 133.4, 128.4, 127.5, 117.9, 54.7, 49.9, 48.8, 18.6, 18.0, 13.4 ppm. HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{15}H_{21}N_3O$ 260.1657, found 260.1647. FT-IR (KBr) ν = 3232, 2978, 2943, 2921, 2164, 1663, 1595, 1507, 1458, 1428, 1204, 1118, 1096, 782 cm^{-1}.

*2-(((1H-Indol-3-yl)methyl)(methyl)amino)acetonitrile (**24a**).* Compound **24a** was obtained in a mixture with **24b**; **24b** was purified by flash chromatography. Crude yield: 17%. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.17 (s, 1H), 7.74 (d, J = 8.0 Hz, 1H), 7.38 (dt, J = 8.0, 1.1 Hz, 1H), 7.23 (ddd, J = 8.0, 7.0, 0.9 Hz, 1H), 7.18 (d, J = 2.5 Hz, 1H), 7.15 (ddd, J = 8.0, 7.0, 1.1 Hz, 1H), 3.81 (s, 2H), 3.46 (s, 2H), 2.50 (s, 3H) ppm. The spectral data were in agreement with literature data.[26]

*2-(1H-Indol-3-yl)acetonitrile (**24b**).* Purification solvent: 1:3 EtOAc/hexane. Yield: 29.5 mg (56%). ^{1}H NMR (500 MHz, CD_3OD): δ 7.48 (dt, J = 8.0, 0.9 Hz, 1H), 7.28 (dt, J = 8.2, 0.9 Hz, 1H), 7.14 (s, 1H), 7.06 (ddd, J = 8.2, 7.1, 1.1 Hz, 1H), 6.98 (ddd, J = 8.0, 7.1, 1.0 Hz, 1H), 3.84 (d, J = 0.9 Hz, 2H) ppm. The spectral data were in agreement with literature data.[56]

*2-((3-(10,11-Dihydro-5H-dibenzo[b,f]azepin-5-yl)propyl)-(methyl)amino)acetonitrile (**25a**).* Compound **25a** was obtained in a mixture with **25b** and **25c**; each of these compounds was purified by flash chromatography. Purification solvent: 1:3 EtOAc/hexane. Yield: 18.3 mg (22%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.08−6.98 (m, 6H), 6.85 (td, J = 7.40, 1.30 Hz, 2H), 3.71 (t, J = 6.80 Hz, 2H), 3.37 (s, 2H), 3.09 (s, 4H), 2.42 (dd, J = 9.44, 4.63 Hz, 2H), 2.21 (s, 3H), 1.65 (p, J = 7.00 Hz, 2H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$): δ 148.2, 134.3, 129.9, 126.4, 122.6, 119.9, 114.6, 53.6, 48.2, 45.3, 42.0, 32.2, 25.9 ppm. HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{20}H_{23}N_3$ 306.1965, found 306.1951. FT-IR (KBr) ν = 3057, 3002, 2924, 2949, 2164, 1585, 1573, 1499, 1452, 1330, 1180, 851 cm^{-1}.

*2-(10,11-Dihydro-5H-dibenzo[b,f]azepin-5-yl)-4-(dimethylamino)butanenitrile (**25b**).* Compound **25b** was obtained in a mixture with **25a** and **25c**; each of these compounds was purified by flash chromatography. Compound **25b** is stable in $CDCl_3$ solution at 8 °C and below but decomposes in solution at room temperature and higher temperature to 10,11-dihydro-5*H*-dibenzo[*b*,*f*]azepine (**25c**). Purification solvent: 1:3 EtOAc/hexane. Yield: 18.5 mg (23%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.19−7.08 (m, 6H), 6.97 (td, J = 7.4, 1.3 Hz, 2H), 3.96−3.86 (m, 2H), 3.67 (t, J = 7.8 Hz, 1H), 3.19 (s, 4H), 2.29 (s, 6H), 2.07−1.98 (m, 2H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$): δ 147.87, 134.30, 130.05, 126.59, 123.03, 119.69, 116.56, 56.39, 46.50, 41.82, 32.10, 30.02. HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{20}H_{23}N_3$ 306.1965, found 306.1955.FT-IR (KBr) ν = 3055, 3004, 2923, 2949, 2165, 1583, 1500, 1450, 1330, 1181, 851 cm^{-1}.

*10,11-Dihydro-5H-dibenzo[b,f]azepine (**25c**).* Compound **25c** was obtained in a mixture with **25a** and **25b**; each of these compounds was purified by flash chromatography. Purification solvent: 1:3 EtOAc/hexane. Yield: 26.5 mg (50%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.00 (td, J = 6.82, 1.57 Hz, 2H), 6.97 (dd, J = 7.45, 1.24 Hz, 2H), 6.70 (td, J = 7.39, 1.14 Hz, 2H), 6.66 (dd, J = 7.94, 1.01 Hz, 2H), 5.91 (bs, 1H), 3.01 (s, 4H) ppm. The spectral data were in agreement with literature data.[57]

*4-(3-((4-((3-Chloro-4-fluorophenyl)amino)-7-methoxyquinazolin-6-yl)oxy)propyl)morpholine-3-carbonitrile (**26a**).* Purification solvent: 1:7 MeOH/$CHCl_3$. Yield: 62 mg (49%). ^{1}H NMR (500 MHz, CD_3OD): δ 8.47 (s, 1H), 8.02 (dd, J = 6.7, 2.6 Hz, 1H), 7.75 (s, 1H), 7.70 (ddd, J = 8.9, 4.1, 2.7 Hz, 1H), 7.29 (t, J = 9.0 Hz, 1H), 7.20 (s, 1H), 4.29 (t, J = 6.1 Hz, 2H), 4.06−4.02 (m, 4H), 4.00 (d, J = 11.7 Hz, 1H), 3.91−3.86 (m, 1H), 3.74 (dd, J = 11.6, 2.6 Hz, 1H), 3.62 (td, J = 11.4, 2.7 Hz, 1H), 2.82−2.75 (m, 3H), 2.61 (td, J = 11.7, 3.2 Hz, 1H), 2.13 (p, J = 6.5 Hz, 2H) ppm. ^{13}C NMR (126 MHz, CD_3OD): δ 157.1, 155.6, 152.5, 149.2, 146.4, 124.5, 122.6, 122.5, 116.1, 115.9, 115.4, 109.1, 105.9, 102.0, 67.7, 66.8, 66.7, 55.2, 52.5, 48.5, 25.8 ppm. HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{23}H_{23}ClFN_5O_3$ 472.1546, found 472.1530. FT-IR (KBr) ν = 3380, 3075, 2926, 2856, 2164, 1625, 1578, 1499, 1426, 1213, 1144, 1117, 856 cm^{-1}.

*(R)-2-((2-Hydroxy-2-(3-hydroxyphenyl)ethyl)amino)acetonitrile (**27a**).* Purification solvent: EtOAc. Yield: 13 mg (26%). ^{1}H NMR (500 MHz, CD_3OD): δ 7.17 (t, J = 8.0 Hz, 1H), 6.87−6.84 (m, 2H), 6.71 (ddd, J = 8.1, 2.4, 1.0 Hz, 1H), 4.73 (dd, J = 8.9, 3.8 Hz, 1H), 3.76 (s, 2H), 2.70 (dd, J = 13.1, 8.9 Hz, 1H), 2.60 (dd, J = 13.1, 3.9 Hz, 1H) ppm. ^{13}C NMR (126 MHz, CD_3OD) δ 157.20, 144.51, 128.99, 116.86, 114.88, 114.06, 112.52, 70.94, 63.23, 44.63 ppm. HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{10}H_{12}N_2O_2$ 193.0972, found 193.0967. FT-IR (KBr) ν = 3270, 3080, 2920, 2165, 1592, 1456, 1280, 1156, 1073, 842 cm^{-1}.

*(6R,7S,10S)-7,8,9,10-Tetrahydro-6H-6,10-methano-azepino[4,5-g]quinoxaline-7-carbonitrile (**28a**).* The reaction was carried out on a 200 mg scale (0.95 mmol), following the general procedure above. Purification: Silica gel column chromatography, 5:95 MeOH/$CHCl_3$. Yield: 201 mg (90% isolated yield, single *cis*-diastereomer). ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.33 (s, 2H), 8.41 (s, 1H), 8.40 (s, 1H), 4.64 (d, 4.0 Hz, 1H), 4.09 (d, 4.0 Hz, 1H), 3.91 (s, 1H), 3.83 (d, 12 Hz, 1H), 3.43 (d, 12 Hz, 1H), 2.97 (s, 2H) ppm. ^{13}C NMR (100 MHz, DMSO-d6): δ188.6, 186.1, 183.7, 183.5, 182.8, 161.5, 161.1, 159.6, 156.5, 88.3, 86.2, 82.4, 80.3, 78.7 ppm. HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{14}H_{13}N_4$ 237.1100; Found 237.1080. FT-IR (KBr) ν = 529, 536, 553, 563, 576, 603, 610, 636, 699, 725, 748, 773, 808, 856, 880, 902, 936, 965, 1007, 1028, 1054, 1069, 1103, 1134, 1164, 1186, 1205, 1253, 1288, 1327, 1359, 1455, 1470, 1477, 1559, 1669, 1987, 2110, 2217, 2822, 2963, 3348, 3648, 3903.

*Synthesis of 3-(2,6-Dimethylphenyl)-1-ethyl-2-methylimidazolidin-4-one (**32**) from Cyanated Lidocaine **23a**.* The procedure was adapted from a literature procedure.[58] Nitrile **23a** (1 mmol) was added to a reaction flask; then MeOH (3 mL), $NaBH_4$ (2 mmol), and cobalt chloride (5 mol %) were added. The reaction was stirred for 24 h. The solvent was removed under reduced pressure, and the crude reaction was purified over a short pad of silica (elution with EtOAc). The expected reduction product was not obtained; instead, the decyanation product **32** was obtained, as characterized by ^{1}H NMR and comparison with the relevant literature; the spectral data were in agreement with literature data.[45] Purification solvent: EtOAc. Yield: 28 mg (62%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.15−7.04 (m, 3H), 4.39 (qt, J = 5.7, 1.5 Hz, 1H), 3.71 (dd, J = 14.7, 1.2 Hz, 1H), 3.12 (dd, J = 14.6, 1.8 Hz 1H), 2.86 (dq, J = 11.7, 7.4 Hz, 1H), 2.40 (dq, J = 11.7, 7.0 Hz, 1H), 2.20 (s, 3H), 2.15 (s, 3H), 1.12 (t, J = 7.2 Hz, 3H), 1.07 (d, J = 5.7 Hz, 3H) ppm.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.8b01700.

Reaction optimization details, synthetic procedures, and characterization for new and known compounds (PDF)

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Notes

The authors declare no competing financial interest.

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