Iron Catalyzed α-C-H Cyanation of Simple and Complex Tertiary Amines

Ozgur Yilmaz,[*‡†] Cagatay Dengiz,[§] Marion H. Emmert*[ℓ†]

[†]Department of Chemistry and Biochemistry, Worcester Polytechnic Institute, 100 Institute Road, Worcester, MA 01609, USA

[‡]Department of Chemistry, Faculty of Arts and Sciences, Mersin University, 33343 Mersin, Turkey

[§]Department of Chemistry, Middle East Technical University, 06800 Ankara, Turkey

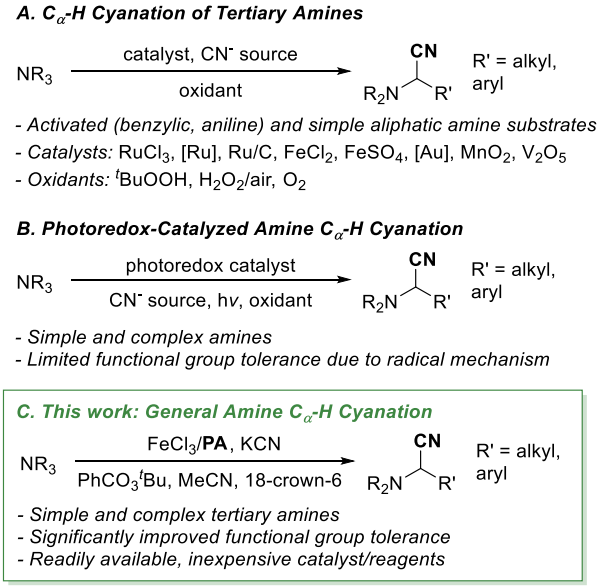
[ℓ]Process Research & Development, MRL, Merck & Co. Inc, 770 Sumneytown Pike, West Point, PA, 19486, U.S.A

ABSTRACT: This manuscript details the development of a general and mild protocol for the α-C-H cyanation of tertiary amines as well as its application in late stage functionalization. Suitable substrates include tertiary aliphatic, benzylic, and aniline-type substrates as well as complex substrates. Functional groups tolerated under the reaction conditions include various heterocycles, as well as ketones, amides, olefins, and alkynes. This broad substrate scope is remarkable, as comparable reaction protocols for α-C-H cyanation frequently occur via free radical mechanisms, and are thus fundamentally limited in their functional group tolerance. In contrast, the presented catalyst system tolerates functional groups that typically react with free radicals, suggesting an alternative reaction pathway. All components of the described system are readily available, allowing implementation of the presented methodology without the need for lengthy catalyst synthesis.

INTRODUCTION

Direct and mild C-H functionalizations of complex substrates with control of site selectivity is one of the key goals for catalyst development in the field. Methods that introduce new C-C bonds in molecules exhibiting basic amine functionalities are particularly rare and frequently not general enough for late stage functionalization of complex substrates. Among the existing methods for C-H functionalization, the α-C-H cyanation of basic amines is particularly valuable, as the introduced cyanide group can subsequently be converted into various different functionalities. Therefore, α-C-H cyanated amines are valuable synthetic intermediates, for example for the synthesis of α-amino acids.[1,2]

One general trend in the α-C-H cyanation of amines is that aniline-type structures appear to be more reactive,[3–16] possibly due to the lower bond dissociation energy of the functionalized α-C-H bond. In comparison, α-C-H cyanations of tertiary amines with unactivated (not benzylic or aniline-type) α-C-H bonds are not as well established. Diverse reactivity platforms have been reported to achieve this overall transformation. The existing protocols can be electrochemically driven,[17] photoredox-catalyzed,[18–20] Mn and Fe catalyzed,[21,22] ClO_2 driven,[23] **or** photochemical[24]; they also include a non-metal mediated process employing KSCN as cyanation reagent[25]. One common thread in all these methods is that they rely on free radical intermediates (Scheme 1A/B), which inherently limits their functional group tolerance. In an interesting extension of this principle, allyl amines can undergo α-C-H cyanation in the presence of ^{t}BuOOH/$FeCl_2$ (typical conditions that allow α-C-H cyanation), but then subsequently undergo functionalization at the olefin.[26]



Scheme 1. Previous α-C-H cyanation approaches and reported protocol. PA = 2-picolinic acid

Recent mechanistic work in the Fe catalyzed α-C-H oxidation of tertiary amines has uncovered a radical rebound

(instead of a free radical) mechanism by which tertiary aliphatic amines can undergo α-C-H functionalization.[27–29] We speculated that this reaction manifold could enable α-C-H cyanations with greater functional group tolerance than methods mediated by free radicals and thus be valuable for late-stage functionalization approaches in complex molecular settings (Scheme 1C). This manuscript details reaction optimizations and substrate scope studies employing this approach to establish a general catalyst system for the late-stage functionalization of tertiary amine substrates. The protocol tolerates the presence of double bonds, triple bonds, unprotected alcohols and ketones, five- and six-membered heterocycles, and various other functional groups. To the best of our knowledge, the reported protocol is the most general approach to the α-C-H cyanation of tertiary amines reported to date.

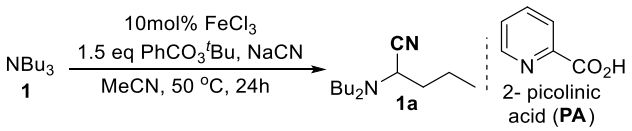
RESULTS AND DISCUSSION

The reaction optimization was initiated using conditions very similar to those reported for Fe catalyzed amine α-C-H oxygenation.[27,28] The one major difference we introduced for amine α-C-H cyanation was the departure from pyridine as a solvent to avoid incompatibilities caused by potential base sensitivities of complex substrates. Tri-*n*-butylamine (**1**) was chosen as a test substrate, as its α-C-H bonds do not exhibit additional activation (*i.e.*, benzylic or in aniline-type C-H bonds). We reasoned that establishing the desired reactivity with the unactivated substrate **1** should in turn also enable C-H functionalizations of anilines and benzylic amines, and thus provide a general reaction protocol.

Gratifyingly, minor changes to the reported conditions for α-C-H oxygenation[27,28] (use of MeCN as solvent; addition of NaCN as cyanide source instead of H_2O) afforded 49% of the desired α-C-H cyanation product **1a** after 24 h (Table 1, entry 1), using the reported $FeCl_3$/2-picolinic acid (**PA**) catalyst system. Extending the reaction time to 48 h resulted in a small increase in yield (57%, entry 2). Increasing the amount of FeCl3 in the reaction mixture (20 mol % instead of 10 mol %) afforded a similar yield after 24 h (55%, entry 3), suggesting that slow formation of product may be an issue limiting yields. This may be caused either by slow catalyst turnover or by sluggish cyanation of a putative iminium intermediate (for a mechanistic hypothesis, see Scheme 6 below). In order to accelerate the reactivity, we tested KCN instead of NaCN as a more soluble cyanide source and were able to see a small increase in yield to 63% (entry 4). Excitingly, the use of 18-crown-6 as additive further increased the yield to synthetically useful levels (86%, entry 5). Combination of a higher $FeCl_3$ loading (15 mol %) and 18-crown-6 (entry 6) provided almost quantitative yields of α-C-H cyanated product **1a** (94%).

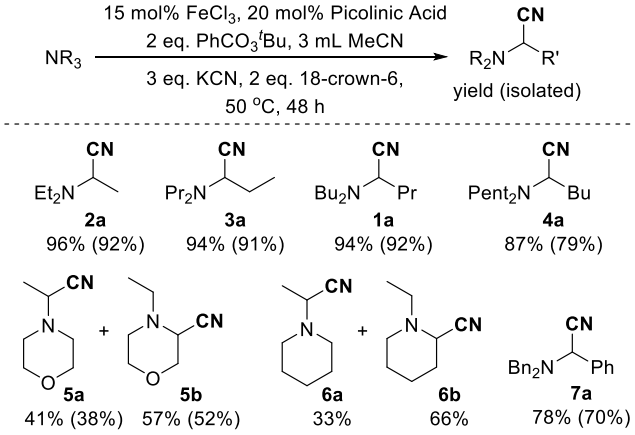
With the optimized conditions in hand (for further optimization details, see the SI), we first focused on establishing a substrate scope with simple tertiary amines (Scheme 2). We considered this a prudent first step to benchmark the protocol against other existing methods, as most known protocols[17,25] provide data for simple tertiary amines. Simple aliphatic amines (NEt_3, **2**; $N(n\text{-}Pr)_3$, **3**; $N(n\text{-}Pent)_3$, **4**) all afforded similarly high assay yields as obtained for the initial test substrate (96% **2a**, 94% **3a**, 87% **4a**). Isolated yields are shown in brackets in Scheme 2 and were generally only slightly lower than the assay yields.

Table 1. Selected Optimization Studies.



Entry	Changes to Conditions[a]	Yield[b]
1	20 mol% **PA**	49%
2	20 mol% **PA**, 48 h	57%
3	20 mol% FeCl3, 20 mol% **PA**	55%
4	20 mol% **PA**, 3 eq. KCN, 48 h	63%
5	20 mol% **PA**, 3 eq. KCN, 1.5 eq. 18-crown-6, 48 h	86%
6	15 mol% FeCl3, 20 mol% **PA**, 3 eq. KCN, 1.5 eq. 18-crown-6, 48 h	94%

[a]Standard Conditions: Anhydrous FeCl3 (0.0044 g, 0.027 mmol, 0.10 eq.), NaCN (0.02 g, 0.41 mmol, 1.5 eq.), PhCO3tBu (100 µL, 0.54 mmol, 2.0 eq.), NBu3 (64 µL, 0.27 mmol, 1.0 eq.), and anhydrous MeCN (3 mL). [b]Yields were determined by quantitative, crude ^{1}H NMR using 1,3-dinitrobenzene or ClH_2CCHCl_2 as internal standard or by GC using decane as internal standard.

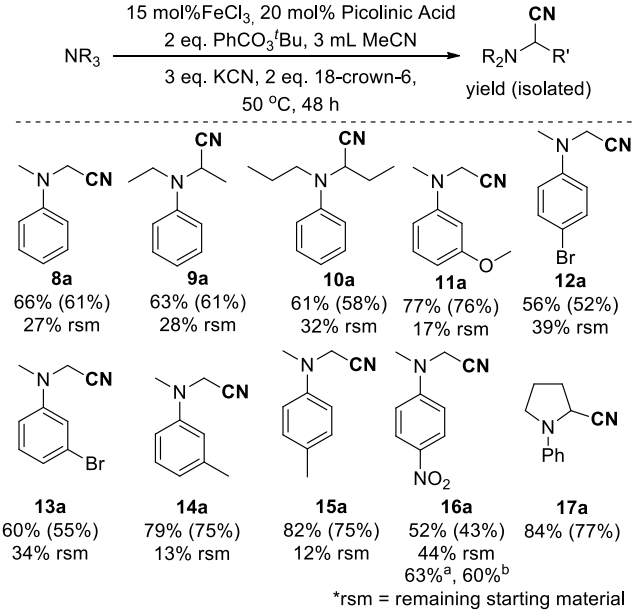


Scheme 2. Substrate Scope of Simple Tertiary Amines. Assay yields (determined by quantitative ^{1}H NMR of the crude reaction mixture or calibrated GC/FID in the presence of an internal standard) are shown outside of brackets; isolated yields are shown in brackets.

As morpholine and piperidines are important substructures of many biologically active molecules, our first exploration of simple substrates also included derivatives of these heterocycles. Both *N*-ethyl morpholine (**5**) and *N*-ethyl piperidine (**6**) afforded high yields (98% combined

and 99% combined, respectively) of regioisomeric mixtures with a close to statistical preference for ring cyanation to ethyl cyanation (~2:1 ring/ethyl ratio). Furthermore, a common benzylic test substrate in previous publications, tribenzylamine (**7**) also reacts readily to afford product **7a** in 78% assay yield (70% isolated). Overall, these excellent yields are in a similar range as observed in previous publications, suggesting that the new protocol shows reactivity for the synthesis of relatively simple building blocks that is on par with previous reports.[18,19,22,25,30]

Next, we turned our attention to aniline-type substrates (Scheme 3), which we considered to be good model substrates to gain further insights into electronic and steric effects. All aniline substrates employed were reactive under the optimized conditions, with yields ranging between 52% and 84% (Scheme 3). The protocol allows the functionalization of all employed aniline substrates, regardless of the substitution pattern on the arene (MeO vs. p/m-Me vs. p/m-Br vs. NO_2) or the aliphatic amine substituents (N-Me vs N-Et vs. N-Pr vs. pyrrolidine).

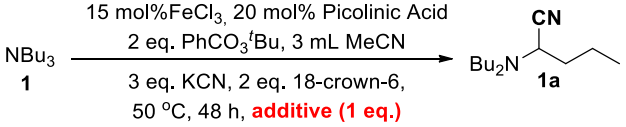


Scheme 3. Substrate Scope of Aniline Type Tertiary Amines. Assay yields (determined by quantitative 1H NMR of the crude reaction mixture or calibrated GC/FID in the presence of an internal standard) are shown outside of brackets; isolated yields are shown in brackets. [a]72 h. [b]3.0 eq. $PhCO_3{}^tBu$.

Interestingly, the yields obtained are considerably lower than the almost quantitative yields obtained for simple aliphatic substrates (see Scheme 2 above). However, remaining starting material is still present in all cases. The overall mass balances that are consistently >90% reflect very little side reactivity and clean reaction profiles. This suggests that either longer reaction times or faster turnover may improve the yields obtained under standard conditions. Indeed, when extending the reaction time from 48 h to 72 h with substrate **16**, an increase of 11% was observed (63% vs. 52% assay yield). An increase in oxidant loading (from 2 to 3 eq. $PhCO_3{}^tBu$) had a similar beneficial effect (60% vs. 52% assay yield **16a**) after 48 h. Overall, these data imply that higher yields are achievable with lower yielding substrates with relatively straightforward optimizations.

To further gain insight into the functional group tolerance of the protocol before investigating the protocol on more complex, drug-like substrates, an intermolecular reaction screening was performed (Table 2).[31] To this end, additives that may be labile towards oxidative and/or base-induced decomposition were added to the reaction mixture. After 48 h, both the yield of desired product **1a** as well as the amounts of remaining additive and substrate **1** were determined.

Table 2. Results of Intermolecular Reaction Screening.



Entry	Additive	Yield **1a**[a]	Remaining Additive	Remaining **1**
1	No additive	94% ✔	n/a	6%
2	^{t}BuOH	56% -	91% ✔	39%
3	Styrene	44% -	87% ✔	53%
4	Benzaldehyde[b]	89% ✔	14% ✘	8%
5	Cyclohexanone	93% ✔	93% ✔	5%
6	Cyclohexanol	84% ✔	83% ✔	14%
7	Benzyl alcohol[b,c]	94% ✔	0% ✘	0%
8	4-Chloro anisole	82% ✔	98% ✔	17%
9	Pyridine	94% ✔	97% ✔	5%
10	2-Methylimidazole	92% ✔	91% ✔	7%

[a]Yields were determined by GC. [b]1,2-Diphenyl-ethanone, 1,2-diphenyl-ethanedione and 2-(benzoyloxy)-1,2-diphenyl-ethanone were identified by GCMS analysis.[c]Obtained 95% Benzyl benzoate.

Interestingly, none of the tested additives completely inhibited the reaction. Strikingly, styrene is mostly stable (87% recovered; entry 3) under the reaction conditions, suggesting the absence of significant free radical reactivity. Even a secondary alcohol (cyclohexanol, 83% recovered) survives mostly intact. Only benzaldehyde and benzyl alcohol formed secondary products under the reaction conditions. Benzyl alcohol reacted to benzyl benzoate (95%),

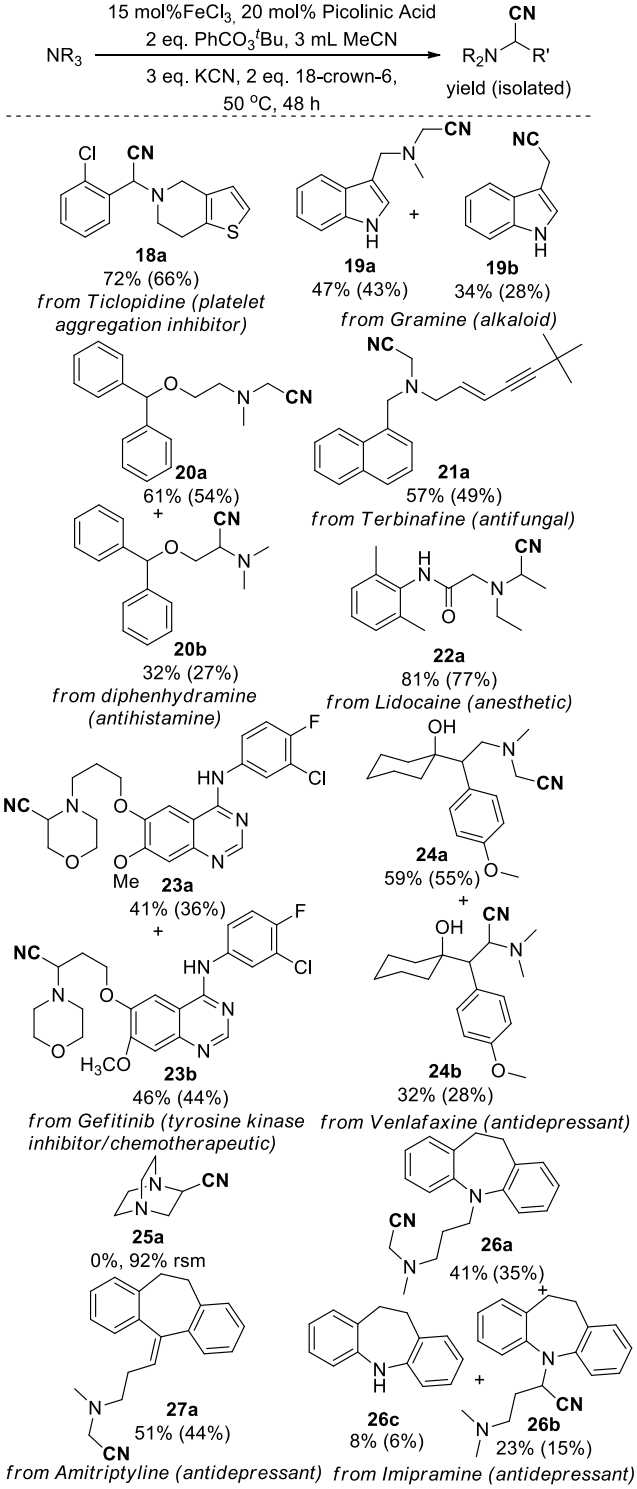
likely by nucleophilic attack of $PhCO_3{}^tBu$. In the reaction with benzaldehyde, various products [1,2-diphenyl-ethanone, 1,2-diphenylethanedione, and 2-(benzyloxy)-1,2-diphenyl-ethanone] were identified, which suggests more complex reaction mechanisms. Finally, the presence of common hetereocycles such as pyridine (entry 9) and 2-methyl imidazole (entry 10) is not detrimental to the cyanation reacticity, which proceeds as efficiently as in the absence of these additives (94% and 92% yield, respectively). Importantly, pyridine and 2-methyl imidazole also remain intact under the reaction conditions (97% and 91% recovered). This is notable, since these and similar heterocyclic substrates can form N-oxides in the presence of peroxide oxidants.[32,33] Overall, the intermolecular reaction screening predicts that the protocol should be applicable for the α-C-H cyanation of complex amine substrates.

Encouraged by these data, we then sought to demonstrate α-C-H cyanation as an avenue for late-stage functionalization. To this end, several biologically active substrates (drug APIs) containing tertiary amine moieties were employed as substrates (Scheme 4). Excitingly, every complex structure tested afforded the desired cyanated product(s) in at least 51% assay yield (44% isolated yield).

Successful substrates include triclopidine **18,** gramine **19**, and gefitinib **23** with heterocyclic substructures that remain untouched; terbinafine **21** and amitriptyline **17**, whose structures incorporate double and triple bonds; as well as venlafaxine **24** with an unprotected tertiary alcohol moiety. Additional functionalities that are tolerated are ethers (in diphenhydramine, **20**), amides (in lidocaine, **22**), and oxidizable/electron-rich arene groups (in lidocaine, **22**, gefitinib, **23**, and imipramine, **26**). In all cases, the obtained assay yields are above 50%, which is impressive for a protocol that was initially optimized with the entirely unfunctionalized substrate NBu_3 (**1**). This study demonstrates that breadth of functional groups tolerated is significantly improved when comparing the herein described protocol with photoredox-driven α-C-H cyanations,[18] the thus far mildest protocol to achieve an analogous tranformation.

The sole unreactive substrate in our hands was DABCO (**25**), for which not even traces of desired product **25a** were obtained. At the same time, 92% of remaining starting material were observed, suggesting that the formation of the proposed iminium intermediate (see Scheme 6 below for mechanistic discussion) is not easily feasible due to the ring strain of the bicyclic structure.

Finally, we also explored if secondary amines Et_2NH **28** and $^iPr_2NH$ **31** can undergo analogous α-C-H cyanation under the optimized conditions (Scheme 5). In contrast to a previously reported reaction protocol demonstrating clean α-C-H cyanation of secondary amines via a photoredox-catalysis,[18] the herein described Fe catalyzed protocol is not successful in promoting this transformation. Instead, benzamide **30** is obtained in 86% yield when Et_2NH **28** is employed as substrate. **30** is likely formed by amidation of the peroxyester oxidant. As established in the substrate scope using complex amines substrates (Scheme 4), amides do not undergo further α-C-H cyanation.

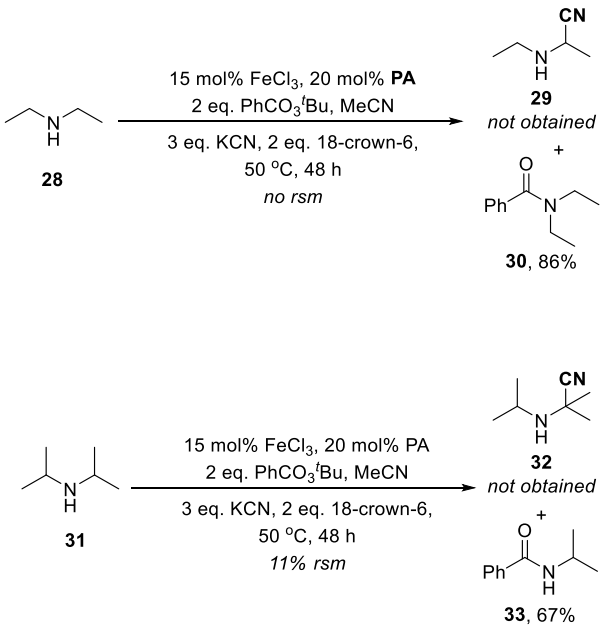


Scheme 4. Substrate Scope of Complex Amines and Drug Substrates. Assay yields are provided together with isolated yield in brackets.

When $^iPr_2NH$ **31** is employed as substrate, α-C-H cyanation is also not observed; instead, benzamide **33** is obtained in

67% yield, in which an ^{i}Pr group has been removed from the amino moiety. This is consistent with previous observations that ^{i}Pr-substituted amines undergo oxidative dealkylation reactions in the presence of $FeCl_3$/**PA**/$PhCO_3{}^{t}Bu$.[27] In the reaction shown in Scheme 5, oxidative dealkylation could proceed through a similar pathway as α-C-H cyanation (see proposed mechanism below, Scheme 6) - with the difference that the initially formed hemiaminal undergoes hydrolysis to $^{i}PrNH_2$, which in turn reacts with $PhCO_3{}^{t}Bu$ to form benzamide **33**.

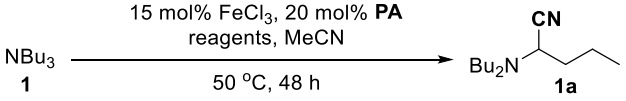
The fact that oxidative dealkylation occurs with $^{i}Pr_2NH$ **31** and not with Et_2NH **28** suggests that amidation as well as hemiaminal decomposition to RNH_2 is driven by steric factors that influence the ratio of rates of amidation and oxidative dealkylation: Et_2NH **28** is a significantly better nucleophile than $^{i}Pr_2NH$ **31** and therefore amidation is expected to be faster. In contrast, α-C-H oxidation is more rapid for $^{i}Pr_2NH$ **31**, but nucleophilic attack of cyanide at the sterically bulkyl hemiaminal or iminium intermediate is disfavored, while hydrolysis to acetone and $^{i}PrNH_2$ is favored due to release of steric strain.



Scheme 5. Attempted α-C-H cyanation reactions with secondary amine substrates.

To further elucidate the role of each reaction component under the optimized conditions, a series of omission experiments was carried out (Table 3), using NBu_3 (**1**) as test substrate. When omitting $FeCl_3$ from the reaction mixture, the obtained yield drops precipitously to 37% (entry 1). When omitting both $FeCl_3$ and **PA**, only 26% of the desired product are obtained. This suggests that a non-catalyzed background reaction exists under these conditions, which contributes at least 26% to the overall obtained yield. Interestingly, the magnitude of this background reaction (entry 3, 26%) is similar in magnitude to the drop in yield observed when the reaction is performed in the presence of BHT, an oxygen radical scavenger[34] (73%, entry 5; yield drop from general condition, entry 1: 21%). These data combined suggest that 26% yield are formed via a free radical process that does not require the presence of Fe catalyst or ligand. Formation of $^{t}BuOOH$[28] via hydrolysis of $PhCO_3{}^{t}Bu$ may be responsible for the non-catalyzed background reaction, as $^{t}BuOOH$ has previously been reported to enable α-C-H cyanations of simple amines.[25] This interpretation of the data is further supported by the fact that no detectable amount of product **1a** is formed in the absence of the peroxyester (Table 3, entry 5). Finally, the importance of 18-crown-6 for increased reactivity (likely by solubilizing the cyanide nucleophile in KCN) is supported by entry 6: a significantly reduced yield (51%) is obtained in the absence of 18-crown-6.

Table 3. Background Studies for proposed mechanism



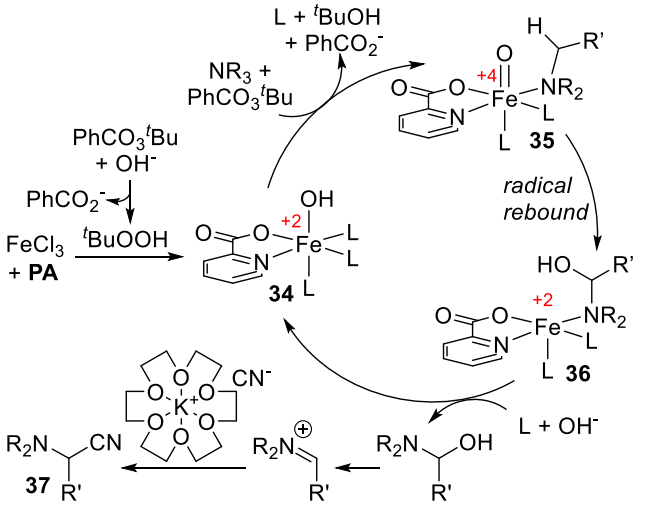
Entry	Conditions	Yield[a]
1	15 mol% FeCl3, 20 mol% **PA**, 3 eq. KCN, 1.5 eq. 18-crown-6, 48 h	94%
2	Without FeCl3	37%
3	Without FeCl3/**PA**	26%
4	With 50 mol% BHT[b]	73%
5	Without $PhCO_3{}^{t}Bu$	<5%
6	Without 18-crown-6	51%

[a]Yields were determined by quantitative, crude ^{1}H NMR using 1,3-dinitrobenzene or ClH_2CCHCl_2 as internal standard or by GC using decane as internal standard. [b]Butylated hydroxytoluene (2,6-Di-tert-butyl-4-methylphenol).

Consistently with the discussed data, we propose a mechanistic hypothesis that enables substrate oxidation without the intermediacy of free radical species (Scheme 6). This hypothesis was formulated in analogy to detailed mechanistic studies[28] of amine α-C-H oxidation with $FeCl_3$/**PA**/$PhCO_3{}^{t}Bu$.

We propose that **PA** coordination to Fe in a chelating fashion and reduction of Fe(+3) to Fe(+2) (by $^{t}BuOOH$) initiates the catalytic cycle via formation of complex **34**. Coordination of one amine molecule and oxidation by $PhCO_3{}^{t}Bu$ to the Fe(+4) oxo intermediate **35** is then followed by a radical rebound step, resulting in α-C-H hydroxylation of the coordinated amine to yield Fe(+2) intermediate **36**. Dissociation of the hemiaminal is then followed by the formation of an iminium intermediate, which in turn reacts with the cyanide nucleophile that is solubilized by 18-crown-6 to obtain product **37**. Coordination of

hydroxide and another ligand L to Fe completes the catalytic cycle and reforms **34**.



Scheme 6. Mechanistic hypothesis for Fe catalyzed α-C-H cyanation. L = NR_3, MeCN, H_2O, Cl^-, CN^-, $PhCO_2^-$.

The proposed mechanism lacks the intermediacy of free radicals necessary for productive turnover. This hypothesis is consistent with the ability to tolerance double and triple bonds in the amine substrates without further reactivity at those sites; the significant remaining catalytic activity of the system in the presence of BHT; higher yields obtained with 18-crown-6; and the dealkylation products observed with $^{i}Pr_2NH$ **31** and imipramine **26** as substrates.

In summary, we have established a general and mild protocol for the α-C-H cyanation of tertiary amines. Suitable substrates include tertiary aliphatic, benzylic, and aniline-type substrates as well as complex substrates. Functional groups tolerated under the reaction conditions include various 6- and 5-membered and bicyclic heterocycles, ketones, amides, olefins, and alkynes. This broad substrate scope is remarkable, as comparable reaction conditions for the α-C-H cyanation of tertiary amines frequently employ peroxide-based oxidants (e.g., ^{t}BuOOH). Such oxidants typically lead to free radicals as reaction intermediates,[35–37] which can attack olefinic,[38] alkyne,[39,40] and heterocyclic[41] substructures of complex amine substrates and are thus fundamentally limited in their scope. The presented work circumvents this issue by designing an Fe-based catalyst system that potentially relies on substrate binding and a radical-rebound mechanism. This hypothesis supports that functional groups labile in the presence of radicals are readily tolerated. Importantly, all reaction components of the catalytic system are readily available, allowing implementation of the presented methodology without lengthy catalyst synthesis. Due to all these benefits, we consider the presented protocol to be the most general methodology for the α-C-H cyanation of tertiary amines to date.

EXPERIMENTAL SECTION

General Procedure.

$FeCl_3$ (anhydrous; 6.6 mg, 0.041 mmol, 0.15 eq.), picolinic acid (6.6 mg, 0.054 mmol, 0.20 eq.) and KCN (0.053 g, 0.81 mmol, 3.0 eq.) were weighed into a 4 mL glass vial equipped with a stir bar and a vial cap. $PhCO_3{}^{t}Bu$ (100 µL, 0.54 mmol, 2 eq.), NBu_3 (64 µL, 0.27 mmol, 1.0 eq.), 18-crown-6 (0.104 g, 0.41 mmol, 1.5 eq.) and MeCN (anhydrous, 3 mL) were added and the reaction mixture was stirred for 48 h at 50 °C under an air atmosphere.

To determine crude assay yields by GC, decane or dodecane was added to the reaction mixture. The mixture was sampled by diluting an aliquot with MeCN or EtOAc, followed by filtration, and analysis of the filtrate by GC-FID.

To determine crude assay yields by quantitative ^{1}H NMR, the reaction mixture was evaporated. Then, MeCN-d_3 and 1,1,2-trichloroethane as internal standard (3.47 uL, 37.4 umol; 0.14 equiv.) were added. The resulting suspension was mixed well, filtered, and analyzed by quantitative ^{1}H NMR.

Characterization and Spectral Data.

2-(Dibutylamino)pentanenitrile (1a). Purification Solvent: EtOAc, yield 52.2 mg (93%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 3.58 (t, J = 7.8 Hz, 1H), 2.57 (ddd, J = 13.0, 8.3, 7.3 Hz, 2H), 2.34 (ddd, J = 13.0, 8.0, 4.9 Hz, 2H), 1.74 – 1.64 (m, 2H), 1.52 – 1.44 (m, 2H), 1.44 – 1.23 (m, 8H), 0.95 (t, J = 7.4 Hz, 3H), 0.91 (t, J = 7.2 Hz, 6H) ppm. The spectral data were in agreement with literature data.[18]

2-(Diethylamino)propanenitrile (2a). Purification Solvent: EtOAc, yield 29.1 mg (92%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 3.82 (q, *J* = 7.2 Hz, 1H), 2.76 (dq, *J* = 13.1, 7.3 Hz, 2H), 2.45 (dq, *J* = 13.0, 7.0 Hz, 2H), 1.49 (d, *J* = 5.7 Hz, 3H), 1.12 (t, *J* = 7.2 Hz, 6H) ppm. The spectral data were in agreement with literature data.[18]

2-(Dipropylamino)butanenitrile (3a). Purification Solvent: EtOAc, yield 39.4 mg (91%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 3.51 (t, *J* = 7.8 Hz, 1H), 2.54 (ddd, *J* = 13.0, 8.4, 7.7 Hz, 2H), 2.41 (ddd, *J* = 13.0, 8.2, 4.7 Hz, 2H), 1.87 – 1.71 (m, 2H), 1.58 – 1.42 (m, 4H), 1.08 (t, *J* = 7.4 Hz, 3H), 0.92 (t, *J* = 7.4 Hz, 6H) ppm.The spectral data were in agreement with literature data.[18]

2-(Dipentylamino)hexanenitrile (4a). Purification Solvent: EtOAc, yield 43.8 mg (79%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 3.49 (t, *J* = 7.8 Hz, 1H), 2.56 – 2.42 (m, 2H), 2.28 (ddd, *J* = 13.1, 8.4, 4.8 Hz, 2H), 1.69 – 1.61 (m, 2H), 1.40 – 1.19 (m, 16H), 0.89 – 0.83 (m, 9H) ppm. The spectral data were in agreement with literature data.[18]

2-Morpholinopropanenitrile (5a). Purification Solvent: EtOAc, yield 14.5 mg (38%). **5a** was isolated from a reaction mixture that also contained **5b**. ^{1}H NMR (500 MHz, $CDCl_3$): δ 3.77 – 3.61 (m, 4H), 3.55 (q, *J* = 7.3 Hz, 1H),

2.66 – 2.56 (m, 2H), 2.46 – 2.37 (m, 2H), 1.40 (d, *J* = 7.3 Hz, 3H) ppm. The spectral data were in agreement with literature data.[18]

4-Ethylmorpholine-3-carbonitrile (5b). Purification Solvent: EtOAc, yield 19.7 mg (52%). **5b** was isolated from a reaction mixture that also contained **5a**. ^{1}H 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), 3.66 (dd, *J* = 11.4, 2.7 Hz, 1H), 3.63 (d, *J* = 2.0 Hz, 1H), 3.53 (ddd, *J* = 11.36, 10.70, 3.33 Hz, 1H), 2.57 – 2.43 (m, 4H), 1.04 (t, *J* = 7.2 Hz, 3H) ppm. The spectral data were in agreement with literature data.[18]

2-(Piperidin-1-yl)propanenitrile (6a). Crude yield: 33%. ^{1}H NMR (500 MHz, $CDCl_3$): δ 3.64 (q, *J* = 7.3 Hz, 1H), 2.70 – 2.64 (m, 2H), 2.41 (dd, *J* = 9.4, 5.5 Hz, 2H), 1.74 (m, 4H), 1.48 (d, *J* = 7.3 Hz, 3H). The spectral data were in agreement with literature data.[17,18]

1-Ethylpiperidine-2-carbonitrile (6b). Crude yield: 66%. ^{1}H 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.[17,18]

2-(Dibenzylamino)-2-phenylacetonitrile (7a). Purification Solvent: 1:9 EtOAc/Hexane, yield 59.3 mg (70%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.52 – 7.47 (m, 2H), 7.35 – 7.23 (m, 11H), 7.24 – 7.19 (m, 2H), 4.82 (s, 1H), 3.81 (d, *J* = 13.4 Hz, 2H), 3.33 (d, *J* = 13.4 Hz, 2H) ppm. The spectral data were in agreement with literature data.[18]

2-(Methyl(phenyl)amino)acetonitrile (8a). Purification Solvent: 1:3 EtOAc/Hexane, yield 24.1 mg (61%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32 (t, *J* = 8.0 Hz, 2H), 6.92 (t, *J* = 7.3 Hz, 1H), 6.87 (d, *J* = 8.0 Hz, 2H), 4.18 (s, 2H), 3.01 (s, 3H) ppm. The spectral data were in agreement with literature data.[11]

2-(Ethyl(phenyl)amino)propanenitrile (9a). Purification Solvent: 1:9 EtOAc/Hexane, yield 28.7 mg (61%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33 – 7.28 (m, 2H), 7.02 – 6.96 (m, 3H), 4.47 (q, *J* = 7.2 Hz, 1H), 3.43 – 3.27 (m, 2H), 1.56 (d, *J* = 7.2 Hz, 3H), 1.18 (t, *J* = 7.1 Hz, 3H). The spectral data were in agreement with literature data.[11]

2-(Phenyl(propyl)amino)butanenitrile (10a). Purification Solvent: 1:9 EtOAc/Hexane, yield 32.3 mg (58%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50 (t, *J* = 7.7 Hz, 1H), 7.33 (dd, *J* = 8.8, 7.3 Hz, 2H), 7.02 (d, *J* = 8.8 Hz, 2H), 4.23 (t, *J* = 7.9 Hz, 1H), 3.34 – 3.14 (m, 2H), 1.95 (p, *J* = 7.5 Hz, 2H), 1.75 – 1.49 (m, 4H), 1.13 (t, *J* = 7.4 Hz, 3H), 0.96 (t, *J* = 7.4 Hz, 3H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ 147.68, 129.30, 129.22, 121.63, 119.11, 56.10, 51.11, 25.72, 21.23, 11.43, 10.67 ppm. HRMS (ESI), m/z: calculated for $C_{13}H_{18}N_2$ $[M+H]^+$: 203.1548, found: 203.1541. FT-IR (KBr) ν= 3016, 2948, 2232, 1594, 1397, 1246, 959, 849 cm^{-1}.

2-((3-Methoxyphenyl)(methyl)amino)acetonitrile (11a). Purification Solvent: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26 (t, *J* = 8.2 Hz, 1H), 6.51 (dt, *J* = 8.2, 2.4 Hz, 2H), 6.43 (t, *J* = 2.4 Hz, 1H), 4.20 (s, *J* = 8.6 Hz, 2H), 3.84 (s, 3H), 3.04 (s, *J* = 7.9 Hz, 3H) ppm. The spectral data were in agreement with literature data.[3,4]

2-((4-Bromophenyl)(methyl)amino)acetonitrile (12a). Purification Solvent: 1:3 EtOAc/Hexane, yield 31.6 mg (52%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 – 7.37 (m, 2H), 6.76 – 6.71 (m, 2H), 4.15 (s, 2H), 3.00 (s, 3H) ppm. The spectral data were in agreement with literature data.[10]

2-((3-Bromophenyl)(methyl)amino)acetonitrile (13a). Purification Solvent: 1:3 EtOAc/Hexane, yield 34.5 mg (55%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.20 (t, *J* = 8.1 Hz, 1H), 7.07 (ddd, *J* = 7.9, 1.7, 0.8 Hz, 1H), 7.03 – 7.01 (m, 1H), 6.80 (ddd, *J* = 8.3, 2.5, 0.7 Hz, 1H), 4.20 (s, 2H), 3.05 (s, 3H) ppm. The spectral data were in agreement with literature data.[4]

2-(Methyl(m-tolyl)amino)acetonitrile (14a). Purification Solvent: 1:3 EtOAc/Hexane, yield 33.5 mg (75%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26 – 7.20 (m, 1H), 6.79 (d, *J* = 7.5 Hz, 1H), 6.74 – 6.69 (m, 2H), 4.20 (s, 2H), 3.03 (s, 3H), 2.38 (s, 3H) ppm. The spectral data were in agreement with literature data.[10]

2-(Methyl(p-tolyl)amino)acetonitrile (15a). Purification Solvent: 1:3 EtOAc/Hexane, yield 33.5 mg (75%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.15 (dd, *J* = 8.7, 0.6 Hz, 2H), 6.84 (d, *J* = 8.7 Hz, 2H), 4.17 (s, 2H), 3.00 (s, 3H), 2.32 (s, 3H) ppm. The spectral data were in agreement with literature data.[10,20]

2-(Methyl(4-nitrophenyl)amino)acetonitrile (16a). Purification Solvent: 1:1 EtOAc/Hexane, yield 22.8 mg (43%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.25 (d, *J* = 9.4 Hz, 2H), 6.85 (d, *J* = 9.4 Hz, 2H), 4.34 (s, 2H), 3.23 (s, 3H) ppm. The spectral data were in agreement with literature data.[10]

1-Phenylpyrrolidine-2-carbonitrile (17a). Purification Solvent: 1:3 EtOAc/Hexane, yield 36.1 mg (73%). ^{1}H 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.[18]

2-(2-Chlorophenyl)-2-(6,7-dihydrothieno[3,2-c]pyridin-5(4H)-yl)acetonitrile (18a). Purification Solvent: 1:9 EtOAc/Hexane, yield 51.5 mg (66%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51 – 7.47 (m, 1H), 7.42 – 7.38 (m, 1H), 7.28 – 7.24 (m, 2H), 7.16 (d, *J* = 5.2 Hz, 1H), 6.86 (d, *J* = 5.2 Hz, 1H), 4.74 (s, 1H), 4.05 (d, *J* = 13.9 Hz, 1H), 3.96 (d, *J* = 13.9 Hz, 1H), 3.10 – 2.94 (m, 3H), 2.86 – 2.77 (m, 1H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ 136.62, 134.87, 134.46, 130.67, 129.96, 129.03, 128.32, 126.86, 124.54, 124.19, 116.29, 56.54, 51.98, 46.78, 25.32 ppm. HRMS (ESI), m/z: calculated for $C_{15}H_{13}ClN_2S$ $[M+H]^+$: 289.0561, found: 289.0564. FT-IR (KBr) ν= 3106, 2918, 2822, 2219, 1571, 1442, 1167, 1037, 865, 699 cm^{-1}.

2-(((1H-Indol-3-yl)methyl)(methyl)amino)acetonitrile (19a). 19a was obtained in a mixture with **19b**. Purification Solvent: 1:3 EtOAc/Hexane, yield 23.2 mg (43%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.05 (s, 1H), 7.66 (d, *J* = 7.9 Hz, 1H), 7.32 (dt, *J* = 8.1, 0.8 Hz, 1H), 7.15 (d, *J* = 1.0 Hz, 1H), 7.13 (d, *J* = 1.4 Hz, 1H), 7.09 – 7.05 (m, 1H), 3.74 (s, 2H), 3.39

(s, 2H), 2.43 (s, 3H). The spectral data were in agreement with literature data.[18,19]

2-(1H-Indol-3-yl)acetonitrile (19b). Purification solvent: 1:3 EtOAc/Hexane, yield 14.8 mg (28%). ^{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.[18]

2-((2-(Benzhydryloxy)ethyl)(methyl)amino) acetonitrile (20a). 20a was obtained in a mixture with **20b**. Purification Solvent: 1:4 EtOAc/Hexane, yield 40.8 mg (54%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 – 7.24 (m, 10H), 5.35 (s, 1H), 3.63 (s, 2H), 3.58 (t, *J* = 5.1 Hz, 2H), 2.76 (t, *J* = 5.1 Hz, 2H), 2.41 (s, 3H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ 141.98, 128.45, 127.56, 126.93, 114.98, 84.15, 67.43, 55.29, 45.65, 42.96 ppm. HRMS (ESI), m/z: calculated for $C_{18}H_{20}N_2O$ $[M+Na]^+$: 303.1467, found: 303.1461. FT-IR (KBr) ν= 3061, 2917, 2230, 1632, 1492, 1452, 1102, 1074, 742, 652 cm^{-1}.

3-(Benzhydryloxy)-2-(dimethylamino)propanenitrile (20b). Purification Solvent: 1:4 EtOAc/Hexane, yield 20.4 mg (27%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 – 7.29 (m, 10H), 5.44 (s, 1H), 3.83 (t, *J* = 6.6 Hz, 1H), 3.68 (dd, *J* = 6.6, 2.1 Hz, 2H), 2.32 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 141.21, 128.58, 128.53, 128.51, 127.96, 127.82, 127.78, 127.12, 127.06, 127.01, 115.42, 84.51, 68.06, 59.03, 42.56 ppm. HRMS (ESI), m/z: calculated for $C_{18}H_{20}N_2O$ $[M+Na]^+$: 303.1467, found: 303.1469. FT-IR (KBr) ν= 3161, 2918, 2848, 2231, 1659, 1493, 1090, 1029, 742, 656 cm^{-1}.

(*E*)-2-((6,6-Dimethylhept-2-en-4-yn-1-yl)(naphthalen-1-ylmethyl)amino)acetonitrile (21a). Purification Solvent: 1:9 EtOAc/Hexane, yield 41.9 mg (49%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.19 (d, *J* = 7.9 Hz, 1H), 7.89 – 7.80 (m, 2H), 7.55 – 7.40 (m, 4H), 6.09 – 6.00 (m, 1H), 5.81 (d, *J* = 15.8 Hz, 1H), 4.10 (s, 2H), 3.39 (s, 2H), 3.35 (d, *J* = 6.2 Hz, 2H), 1.24 (s, 9H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ 136.79, 134.01, 132.31, 132.21, 128.93, 128.57, 128.00, 126.16, 125.95, 125.25, 124.44, 114.90, 114.59, 99.71, 77.22, 56.78, 56.34, 40.67, 30.92, 28.04 ppm. HRMS (ESI), m/z: calculated for $C_{22}H_{24}N_2$ $[M+Na]^+$: 339.1832, found: 339.1832. FT-IR (KBr) ν= 3046, 2920, 2211, 1597, 1509, 1361, 1265, 959, 775 cm^{-1}.

2-((1-Cyanoethyl)(ethyl)amino)-N-(2,6-dimethyl-phenyl)acetamide (22a). Purification Solvent: 1:1 EtOAc/Hexane, yield 53.9 mg (77%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.26 (s, 1H), 7.11 – 6.90 (m, 3H), 3.84 (q, *J* = 7.2 Hz, 1H), 3.42 (t, *J* = 16.6 Hz, 1H), 3.21 (d, *J* = 17.6 Hz, 1H), 2.82 (dq, *J* = 12.8, 7.3 Hz, 1H), 2.76 – 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. The spectral data were in agreement with literature data.[18]

4-(3-((4-((3-Chloro-4-fluorophenyl)amino)-7-methoxyquinazolin-6-yl)oxy)propyl)morpholine-3-carbonitrile (23a). 23a was obtained in a mixture with **23b**. Purification Solvent: 1:7 MeOH/$CHCl_3$, yield 45.6 mg (36%). ^{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), 7.21 (d, *J* = 7.3 Hz, 1H), 4.29 (t, *J* = 6.1 Hz, 2H), 4.05 – 4.02 (m, 4H), 4.00 (d, *J* = 11.7 Hz, 1H), 3.91 – 3.87 (m, 1H), 3.74 (dd, *J* = 11.6, 2.6 Hz, 1H), 3.62 (td, *J* = 11.4, 2.7 Hz, 1H), 2.83 – 2.75 (m, 3H), 2.61 (td, *J* = 11.7, 3.2 Hz, 1H), 2.14 (p, *J* = 6.5 Hz, 2H). The spectral data were in agreement with literature data.[18]

4-((4-((3-Chloro-4-fluorophenyl)amino)-7-methoxyquinazolin-6-yl)oxy)-2-morpholinobutanenitrile (23b). Purification Solvent: 1:7 MeOH/$CHCl_3$, yield 55.7 mg (44%). ^{1}H NMR (500 MHz, MeOD) δ 8.34 (s, 1H), 7.90 (dd, *J* = 6.7, 2.6 Hz, 1H), 7.61 (s, 1H), 7.57 (ddd, *J* = 8.9, 4.2, 2.7 Hz, 1H), 7.16 (t, *J* = 9.0 Hz, 1H), 7.07 (s, 1H), 4.15 (t, *J* = 6.2 Hz, 2H), 3.89 (s, 3H), 3.64 – 3.58 (m, 4H), 2.54 (t, *J* = 7.3 Hz, 2H), 2.43 (s, 4H), 2.01 (dt, *J* = 14.8, 6.3 Hz, 2H)ppm. ^{13}C NMR (126 MHz, MeOD) δ 157.03, 155.58, 152.42, 149.26, 146.33, 124.44, 122.52, 116.08, 115.90, 109.07, 105.83, 101.97, 67.18, 66.29, 55.33, 55.18, 53.43, 25.73 ppm. HRMS (ESI), m/z: calculated for $C_{23}H_{23}ClFN_5O_3$ $[M+H]^+$: 472.1546, found: 472.1537. FT-IR (KBr) ν= 3382, 3069, 2925, 2167, 1631, 1569, 1419, 1196, 1112, 852 cm^{-1}.

2-((2-(1-Hydroxycyclohexyl)-2-(4-methoxyphenyl)ethyl)(methyl)amino)acetonitrile (24a). 24a was obtained in a mixture with 24b. Purification Solvent: 1:1 EtOAc/Hexane, yield 50.9 mg (55%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.01 (d, *J* = 8.7 Hz, 2H), 6.77 (d, *J* = 8.7 Hz, 2H), 3.72 (s, 3H), 3.48 (s, 2H), 3.08 (dt, *J* = 15.5, 7.7 Hz, 1H), 2.74 (ddd, *J* = 14.4, 13.4, 6.4 Hz, 2H), 2.34 (d, *J* = 4.0 Hz, 3H), 1.56 – 1.39 (m, 7H), 1.28 (td, *J* = 13.0, 4.4 Hz, 1H), 1.18 (s, *J* = 5.4 Hz, 1H), 1.06 (td, *J* = 13.3, 3.8 Hz, 1H), 0.93 (dd, *J* = 12.4, 3.6 Hz, 1H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ 158.56, 131.57, 130.13, 114.37, 113.61, 73.76, 56.67, 55.21, 52.19, 45.29, 42.34, 36.88, 33.33, 25.75, 21.63, 21.52 ppm. HRMS (ESI), m/z: calculated for $C_{18}H_{26}N_2O_2$ $[M+Na]^+$: 325.1887, found: 325.1887. FT-IR (KBr) ν= 3363, 2930, 2850, 2234, 1610, 1527, 1462, 1179, 1033, 834, 732 cm^{-1}.

2-(dimethylamino)-3-(1-hydroxycyclohexyl)-3-(4-methoxyphenyl)propanenitrile (24b). Purification Solvent: 1:1 EtOAc/Hexane, yield 25.9 mg (28%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.98 (d, *J* = 8.7 Hz, 2H), 6.75 (d, *J* = 8.7 Hz, 2H), 3.72 (s, 3H), 3.22 (t, *J* = 12.4 Hz, 1H), 2.88 (dd, *J* = 12.2, 3.5 Hz, 1H), 2.25 (s, *J* = 4.0 Hz, 6H), 1.68 – 1.53 (m, 3H), 1.52 – 1.40 (m, 3H), 1.32 – 1.18 (m, 2H), 0.92 – 0.77 (m, 2H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ 158.30, 132.80, 130.16, 113.34, 74.27, 70.63, 61.22, 55.21, 51.69, 45.46, 38.07, 31.21, 26.01, 21.63, 21.36 ppm. HRMS (ESI), m/z: calculated for $C_{18}H_{26}N_2O_2$ $[M+Na]^+$: 325.1887, found: 325.1889. FT-IR (KBr) ν= 3368, 2937, 2231, 1581, 1534, 1445, 1125, 1035, 812, 776 cm^{-1}.

2-((3-(10,11-Dihydro-5H-dibenzo[b,f]azepin-5-yl)propyl)(methyl)amino)acetonitrile (26a). 26a was obtained in a mixture with **26b** and **26c**; each of these compounds was purified by flash chromatography. Purification Solvent: 1:3 EtOAc/Hexane, yield 58.2 mg (35%). ^{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. The spectral data were in agreement with literature data.[18]

2-(10,11-Dihydro-5H-dibenzo[b,f]azepin-5-yl)-4-(dimethylamino)butanenitrile (26b). 26b was obtained in a mixture with **26a** and **26c**; each of these compounds was

purified by flash chromatography. **26b** 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-5H-dibenzo[b,f]azepine (**26c**). Purification Solvent: 1:3 EtOAc/Hexane, yield 25.0 mg (15%). ^{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. The spectral data were in agreement with literature data.[18]

10,11-Dihydro-5H-dibenzo[b,f]azepine (26c). **26c** was obtained in a mixture with **26a** and **26b**; each of these compounds was purified by flash chromatography. Purification Solvent: 1:3 EtOAc/Hexane, yield 8.5 mg (8%). ^{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.[18]

2-((3-(10,11-Dihydro-5H-dibenzo[a,d][7]annulen-5 ylidene)propyl)(methyl)amino) acetonitrile (27a). Purification Solvent: 1:1 EtOAc/Hexane, yield 47.3 mg (44%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.32 – 7.30 (m, 1H), 7.26 – 7.16 (m, 6H), 7.10 – 7.06 (m, 1H), 5.87 (t, *J* = 7.3 Hz, 1H), 3.44 (s, 3H), 3.40 – 3.29 (m, 1H), 3.01 (s, 1H), 2.78 (s, 1H), 2.62 – 2.52 (m, 2H), 2.36 – 2.27 (m, 5H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ 144.32, 141.04, 139.86, 139.36, 137.09, 130.05, 128.55, 128.28, 128.15, 128.11, 127.61, 127.17, 126.06, 125.87, 114.61, 55.51, 44.91, 41.95, 33.76, 31.99, 27.52 ppm. HRMS (ESI), m/z: calculated for $C_{18}H_{26}N_2O_2$ $[M+H]^+$: 303.1856, found: 303.1850. FT-IR (KBr) ν= 3060, 2918, 2852, 2229, 1733, 1600, 1485, 1452, 1262, 1027, 711 cm^{-1}.

***N,N*-diethylbenzamide (30).** Purification Solvent: 1:3 EtOAc/Hexane, yield 37.6 mg (86%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 – 7.35 (m, 5H), 3.54 (bs, 2H), 3.25 (bs, 2H), 1.30 – 1.05 (m, 6H). The spectral data were in agreement with literature data.[42]

***N*-isopropylbenzamide (31).** Purification Solvent: 1:3 EtOAc/Hexane, yield 24.9 mg (67%) .^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75 (d, *J* = 7.0 Hz, 2H), 7.51 – 7.42 (m, 3H), 5.90 (s, 1H), 4.39 – 4.19 (m, 1H), 1.27 (d, *J* = 6.5 Hz, 6H) ppm. The spectral data were in agreement with literature data.[43]

ASSOCIATED CONTENT

Supporting Information. Reaction optimization details, synthetic procedures, characterization for new and known compounds.

AUTHOR INFORMATION

Corresponding Authors

*mhemmert@wpi.edu;
*yilmazozgur@mersin.edu.tr;

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