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Synthesis of Sterically Hindered Primary Amines by Concurrent Tandem Photoredox Catalysis

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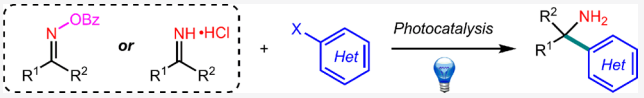
Supporting Information

ABSTRACT: Primary amines are an important structural motif in active pharmaceutical ingredients (APIs) and intermediates thereof, as well as members of ligand libraries for either biological or catalytic applications. Many chemical methodologies exist for amine synthesis, but the direct synthesis of primary amines with a fully substituted α carbon center is an underdeveloped area. We report a method which utilizes photoredox catalysis to couple readily available *O*-benzoyl oximes with cyanoarenes to synthesize primary amines with fully substituted α-carbons. We also demonstrate that this method enables the synthesis of amines with α-trifluoromethyl functionality. Based on experimental and computational results, we propose a mechanism where the photocatalyst engages in concurrent tandem catalysis by reacting with the oxime as a triplet sensitizer in the first catalytic cycle and a reductant toward the cyanoarene in the second catalytic cycle to achieve the synthesis of hindered primary amines via heterocoupling of radicals from readily available oximes.



INTRODUCTION

Primary amines are constituent members of ligand libraries as either final ligands or valuable synthetic intermediates.[1] When the retrosynthesis of a target molecule is designed, amines represent key points of disconnection, thereby having a significant impact on the choice of synthetic route. The ability to utilize amines in the synthesis of a diverse library of final ligands is directly affected by access to a wide array of primary amines. General motif **1** is readily found in a number of patented pharmaceutical agents, a small selection of which is illustrated in Figure 1.[2]

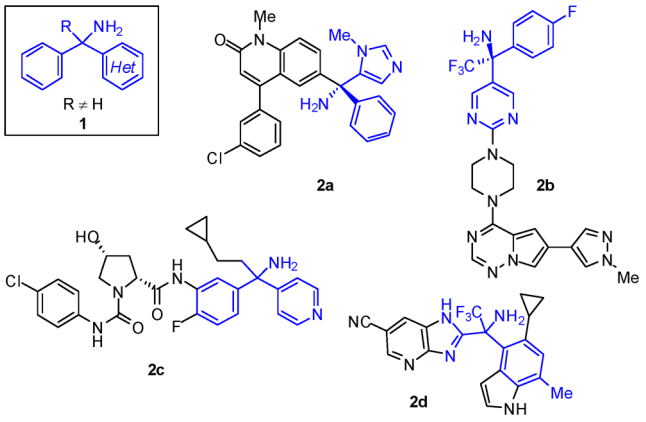


Figure 1. Pharmaceutical agents containing primary amines with fully substituted α-carbons.

The synthesis of amines is an area of research rich in methodologies which generate products via C−N bond formation, addition to C═N double bonds, and, more recently, α-C−H functionalization of amines.[3] When the synthesis of a primary amine is required, specifically one with a fully substituted α-carbon, the number of applicable methodologies decreases dramatically. These methodologies can be sorted into $2e^-$ approaches and 1 e^- approaches to amine synthesis.

The $2e^-$ approach, pioneered by Ellman and co-workers, can be effected via addition of nucleophiles to *tert*-butyl sulfinimides (Scheme 1A).[4] When this methodology is applied to the synthesis of primary amines with fully substituted α-carbons, the synthesis of ketone-derived sulfinimides often requires the use of strong Lewis acids and heat. The synthesis of amines from sulfinimides then requires an organometallic reagent, followed by deprotection with strong acid. We postulated that an alternative synthetic methodology based on a single-electron disconnection could bypass the need to utilize harsh organometallic reagents and enable the use of starting materials which are bench stable and easily synthesized.

The rapid adoption of photoredox catalysis has resulted in a multitude of methodologies which effect α-amino functionalization (Scheme 1B).[5] However, the vast majority of these methodologies require full substitution of the nitrogen with alkylations, arylation, or activating groups, a strategy that

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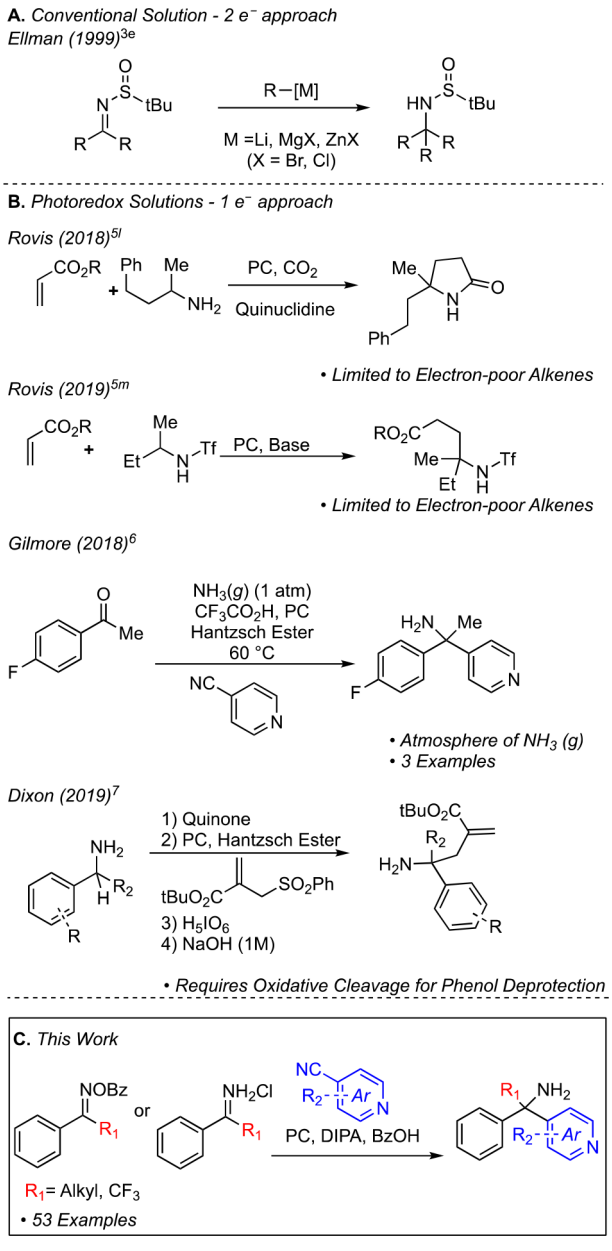
Scheme 1. Approaches to the Synthesis of Sterically Hindered Amines: (A) Prior Art of Conventional 2e⁻ Synthesis of Primary Amines; (B) Prior Art of Photoredox-Catalyzed Syntheses of Primary Amines Compared to This Work (C)



requires subsequent deprotection to yield a primary amine. Finally, many of these methodologies do not contain examples for synthesizing amine-bearing fully substituted carbons.

Two notable exceptions to the above statement have recently appeared. Dixon reported an interesting strategy toward α-amino functionalization of primary amines utilizing quinones as *in situ* oxidants to generate imine intermediates, with *in situ* alkylation by both two- and one-electron methods.[6] Concurrently with our work, Gilmore reported three examples of hindered amine syntheses via photoredox catalysis, utilizing ketones in the presence of excess ammonia gas (1 atm NH_3), strong acid, and excess Hantzsch ester at elevated temperature.[7] Our efforts focused on developing benchtop-stable starting materials, such as oximes and iminium salts, that could be utilized to generate α-amino radicals under mild conditions.

Herein (Scheme 1C), we report a photoredox-catalyzed method to synthesize primary amines starting from bench-stable, easily formed *O*-benzoyl oximes[8] or iminium chloride salts and a cyanoarene.[9] This methodology enables rapid access to fully substituted primary amines through easily synthesized bench-stable precursors without the requirement for subsequent deprotection.

RESULTS AND DISCUSSION

We utilized a high-throughput experimentation (HTE)[10] approach to identify conditions which would produce our desired product from oxime **3a** and cyanopyridine **4a** via photoredox catalysis (Table 1). This approach enabled rapid identification of a number of conditions that provide the desired product **5**, with the best results being in DMSO with diisopropylamine (DIPA) as the terminal reductant and Ir-based photocatalysts, particularly Ir[dF(Me)ppy]$_2$dtbbpyPF$_6$ (**PC1**), which furnishes product in 71% yield.

Interestingly, the tris-phenylpyridine derivative, Ir(ppy)$_3$ (**PC4**), affords only trace product, despite being the most reducing iridium-based photocatalyst in the screen.[11] The organic photocatalyst 4CZIPN (**PC8**), which has redox properties similar to those of **PC3**, also gives only trace product when DMSO is used as the solvent.[12] Reactions using acetonitrile or acetone as the solvent deliver only trace amounts of the desired product, while 1,2-dichloroethane proved unsuccessful, except for a moderate 19% yield when **PC2** was utilized as a photocatalyst. Analysis of the reaction profile revealed multiple pyridine-based byproducts, but no homocoupling of the reduced 4-cyanopyridine was observed (i.e., formation of 4,4′-dipyridyl).[13] Using 4-cyanopyridine in excess dramatically improves the reaction profile, eliminating most pyridine-based byproducts (Supporting Information, Table S2).

Using the oxime coupling partner as the limiting reagent and **4a** in excess (2.2 equiv), we chose to fine-tune our optimized reaction conditions. Photocatalyst loading could be decreased to as low as 2 mol% while maintaining high yields of product **5a**. Increasing the limiting substrate (oxime) concentration from 0.1 to 0.2 M did not affect the yield at a 0.3 mmol scale; under these conditions, however, the reaction became heterogeneous. We anticipated that a homogeneous reaction would be more advantageous for reaction scale-up, enabling improved light penetration into the reaction mixture, and therefore we elected to conduct our reactions at 0.1 M. We hypothesized that the overall transformation would generate benzoic acid during the course of the reaction via N−O bond scission of the oxime and DIPA oxidation. We elected to utilize 1 equiv of benzoic acid to prevent a potential induction phase for the reduction of 4-cyanopyridine, should this process require a proton source.[14] Empirically, we observed that, at high concentrations of DIPA, reactions initially form a biphasic mixture. We observed that the inclusion of benzoic acid improved the solubility of DIPA, generating a homogeneous solution after 30 s of mixing.

Our initial HTE experiments revealed that DIPA was the optimal stoichiometric reductant in DMSO when the oxime was used as the excess coupling partner. Diisopropylethylamine (DIPEA) is commonly used in photoredox chemistry as a stoichiometric reductant.[15] While DIPEA is easier to oxidize than DIPA, oxidation generates a secondary α-amino radical

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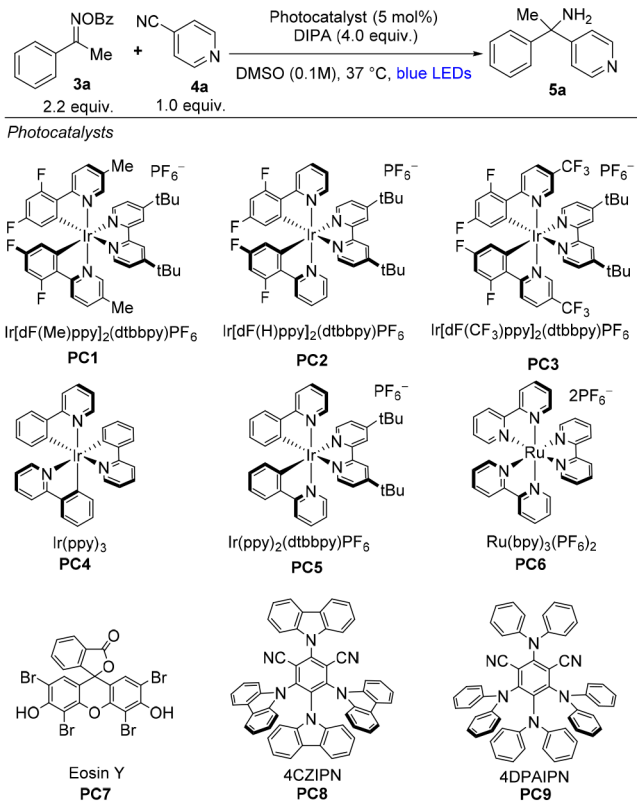
Table 1. Reaction Discovery via High-Throughput Experimentation[a]



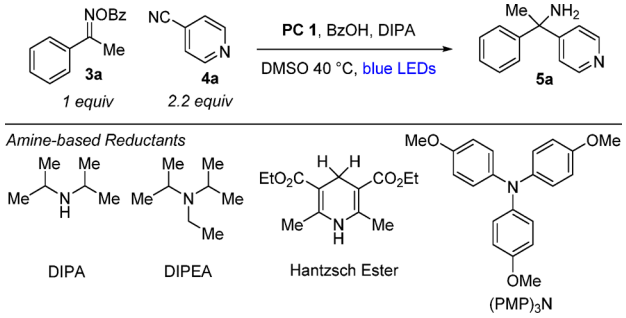
		Solvent				
		Acetone	DCE	MeCN	DMSO	DMSO
Photocatalyst	PC1	0%	0%	0%	71%	7%
	PC2	0%	19%	7%	68%	5%
	PC3	0%	0%	0%	50%	13%
	PC4	0%	0%	0%	3%	7%
	PC5	0%	2%	0%	43%	3%
	PC6	0%	0%	0%	0%	11%
	PC7	0%	0%	0%	0%	0%
	PC8	30%	0%	0%	2%	9%
	PC9	0%	0%	5%	4%	16%
		DIPA				DIPEA
		Reductant				

Lower Yield — Higher Yield

[a]Assay yields determined by ultraperformance liquid chromatography (UPLC) analysis of crude reactions (10 μmol scale) relative to an internal standard.

which we observed to compete for coupling with 4-cyanopyridine. Interestingly, DIPA was never observed to cross-couple with 4-cyanopyridine. To test the role of the reductant in the reaction under the conditions utilizing pyridine as the excess coupling partner, we compared DIPA, DIPEA, Hantzsch ester, and tris-*p*-methoxyphenylamine ($(PMP)_3N$) in the reductive coupling reaction (Table 2). We observed that, in larger scale reactions (0.3 mmol), DIPA gives product **5a** in 86% yield. As expected, removing DIPA as a reductant produces no product in the reaction. The use of the more oxidizable tertiary amine DIPEA results in a much lower yield

Table 2. Optimized Reaction and Control Experiments



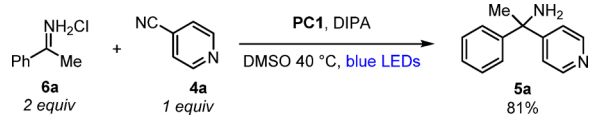
entry	deviation from standard reaction conditions	yield (%)[b]
1	none	86
2	no DIPA	0
3	no photocatalyst	0
4	DIPEA instead of DIPA	27
5	Hantzsch Ester instead of DIPA	26
6	$(PMP)_3N$ amine instead of DIPA	0

[a]**3a** (0.3 mmol), **4a** (2.2 equiv), benzoic acid (1.0 equiv), **PC1** (2.0 mol%), amine base (3.6 equiv), DMSO (0.1 M), blue LEDs (455 nm, 5W per reaction), 40 °C. [b]Assay yield determined by a UPLC calibrated to an authentic sample of purified product.

(27%). Additionally, adducts of DIPEA and 4-cyanopyridine were observed via UPLC-MS analysis. Reactions with Hanstzch ester give yields similar to those obtained using DIPEA as the terminal reductant. The use of $(PMP)_3N$ instead of DIPA does not afford any product **5a**. From this result we inferred the importance of DIPA as both an electron source and either a proton or hydrogen atom source for the reaction. While the solvent can function as a hydrogen atom donor in many radical reactions, we note that the estimated bond dissociation energy of the α-amino C−H bonds in DIPA should be significantly lower than those of the C−H bonds present in DMSO. DFT calculations predict that hydrogen atom abstraction from DMSO by the α-amino radical of DIPA is unfavorable, based on the Gibbs free energy for the reaction being +17.4 kcal/mol.[16]

Encouraged by the success of the reaction and postulating that it proceeds via a benzylic α-amino radical, we wondered if this radical intermediate could also be attained via the reduction of iminium salts. The reduction potential of benzylic ketimines in the presence of strong acid was reported to be ca. −0.7 V vs SCE.[7] Based on these results, the photocatalytic manifold could reduce benzylic iminium salt **6a**, the analog of the oxime **3a**, for coupling with cyanopyridine toward generating product **5a** (Scheme 2).

Scheme 2. Reductive Coupling via Iminium Chloride Salt



As a model reaction, we subjected iminium salt **6a** to a photocatalytic reaction with our optimal photocatalyst, **PC1**, and DIPA as stoichiometric reductant. With the concern that the α-amino radical may dimerize more readily under these conditions, we utilized the iminium salt as the excess reagent (2.2 equiv). Gratifyingly, our first reaction under these

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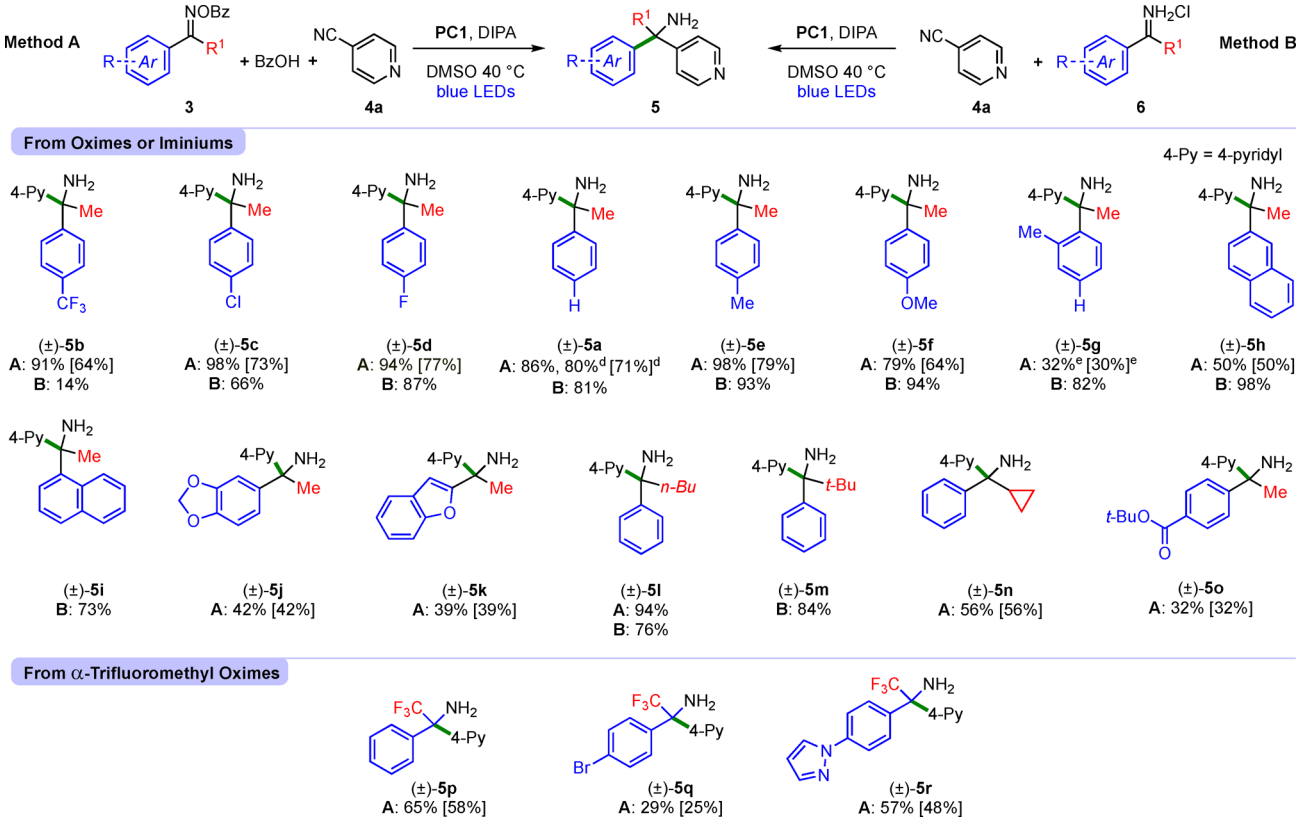
Table 3. Oxime and Iminium Chloride Scope for Primary Amine Synthesis[a,b]



[a]Method A: 0.3 mmol of oxime **3** at 0.1 M in DMSO containing 4-cyanopyridine (2.2 equiv), *i*-Pr_2NH (3.6 equiv), benzoic acid (1.0 equiv), **PC1** (2 mol%) illuminated by blue LEDs (455 nm, 5W per reaction) at 40 °C for 2.5 h. [b]Method B: 4-cyanopyridine (0.3 mmol) at 0.1 M in DMSO containing iminium salt **6** (2.2 equiv), *i*-Pr_2NH (3.6 equiv), **PC1** (2 mol%) illuminated by blue LEDs (455 nm, 5W per reaction) at 40 °C for 2.5 h. [c]Yields from Method A and Method B are denoted by values next to the letters A and B and unless noted otherwise are assay yields determined by a UPLC calibrated to an authentic sample of purified product. Value in brackets are isolated yields. [d]Reaction was run on a 3.6 mmol scale. [e]Reaction duration of 3.5 h. [f]Reaction duration of 16 h.

conditions furnished the desired product in 81% yield. The reaction profile showed clean formation of product without the formation of significant amounts of side products.[17] Therefore, we elected to move forward with these conditions to elaborate a complementary scope using either oximes (Method A) or iminium chloride salts (Method B) for coupling with cyanoarenes (Table 3).

With optimized catalytic conditions in hand, we chose to explore the scope of the oxime coupling partner in the reaction (Method A, Table 3). We began by testing our reaction at a 0.3 mmol scale, utilizing our model oxime **3a** (1 equiv) and excess 4-cyanopyridine **4a** (2.2 equiv). The reaction was irradiated for 2.5 h in a temperature-controlled (40 °C) TAK 120 photoreactor with 455 nm light (5 W per vial), enabling up to 10 reactions to be run in parallel at a time.[18] These optimized conditions provided primary amine **5a** in 86% yield. Next, we tested the scope of oximes compatible in the reductive coupling.

First, benzylic oximes which contain para-substituents of varying electronic properties were tested using the optimized reaction conditions. Gratifyingly, electronically varied products **5a**–**5f** are obtained in excellent yield, regardless of whether the substituent on the arene is electron-withdrawing or electron-donating. Compound **5g**, containing an *ortho*-methyl substituent, is formed in 32% yield, requiring extended reaction times of 16 h for complete consumption of the oxime (*vide infra*). Products that incorporate larger arenes (**5h**–**5k**) or longer alkyl groups (**5l**) were successfully synthesized. Compound **5n**, containing a cyclopropyl substituent, was synthesized in 56% yield without producing the related ring-opened product.[19] Synthesis of compound **5o** provides a desirable ester functionality in 32% yield. The analogous 2-pyridyl-derived oxime reacts to form only trace amounts of primary amine product.[20] Other heterocyclic oximes tested did not yield product.[21]

When expanding our scope, we recognized that primary amines containing an α-trifluoromethyl group represent a unique architecture which is not easily accessed with traditional synthetic methodologies. Based on our initial mechanistic hypothesis, we thought this functional group should be well tolerated in the reaction. Therefore, we tested the reactivity of *O*-benzoyl oximes derived from readily available trifluoromethyl ketones. Compound **5p**, a primary amine with an α-trifluoromethyl group, was synthesized in 65% yield. We note that aryl bromides are also tolerated in the reaction, with compound **5q** forming in 29% yield. Compound **5r** containing a pyrazole is assembled in 57% yield, indicating the oxime reaction tolerates heterocycles more efficiently when they are included through a biaryl linkage to the benzylic oxime (i.e., separating the α-amino radical from the heterocycle via a phenylene linker is beneficial for high yield of the coupling product). Trifluoromethyl derivatives of acetophe-

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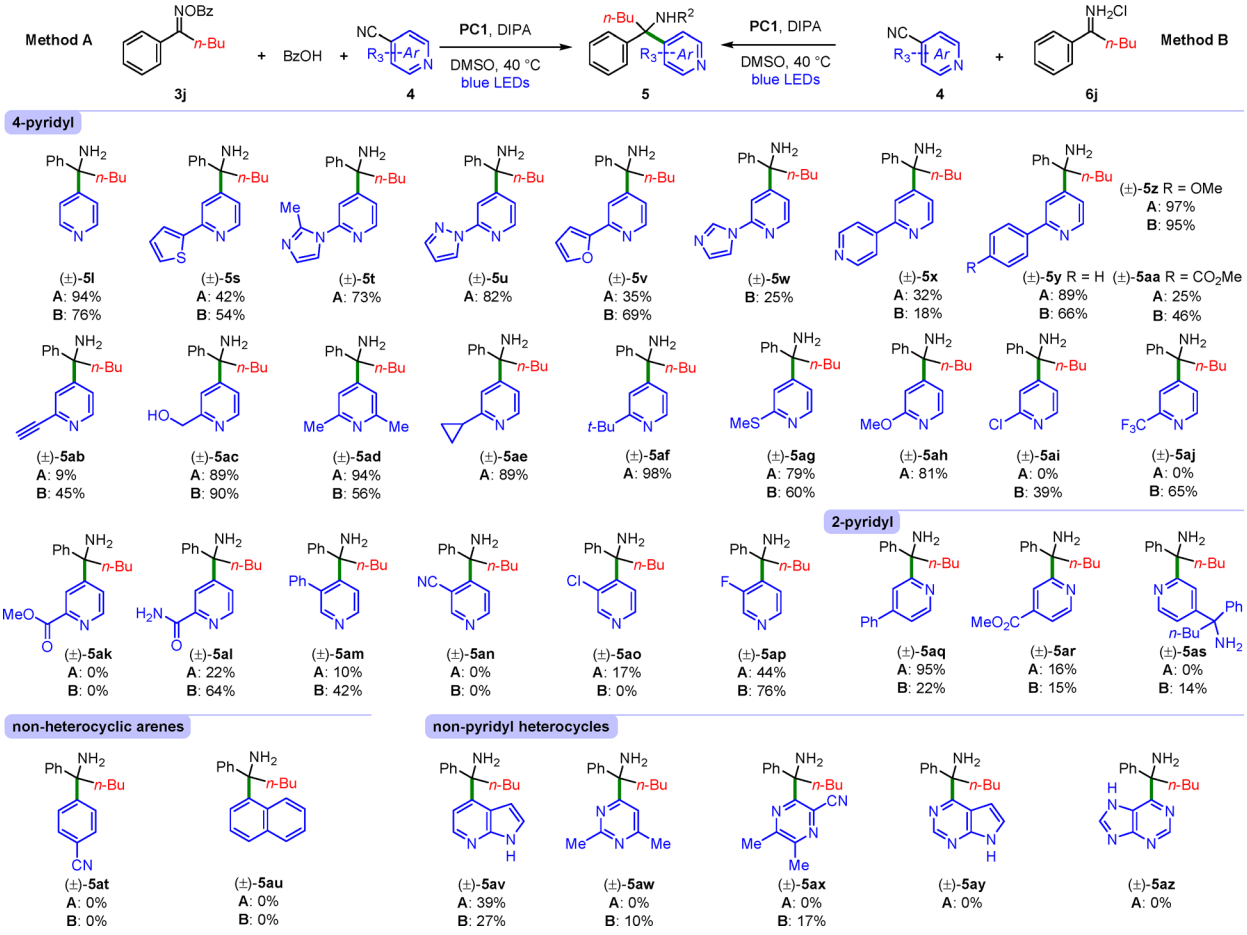
Table 4. Cyanoarene Scope for Primary Amine Synthesis[a,b,c]



[a]Method A: 0.3 mmol of oxime 3 at 0.1 M in DMSO containing 4-cyanopyridine (2.2 equiv), *i*-Pr_2NH (3.6 equiv), benzoic acid (1.0 equiv), PC1 (2 mol%) illuminated by blue LEDs (455 nm, 5 W per reaction) at 40 °C for 2.5 h. [b]Method B: 4-cyanopyridine (0.22 mmol) at 0.1 M in DMSO containing iminium salt (2.2 equiv), *i*-Pr_2NH (3.6 equiv), PC1 (2 mol%) illuminated by blue LEDs (455 nm, 5 W per reaction) at 40 °C for 2.5 h. [c]Yields from Method A and Method B are denoted by values next to the letters A and B and unless noted otherwise are assay yields determined by a UPLC calibrated to an authentic sample of purified product.

none are widely commercially available and can easily provide bench-stable α-trifluoromethyl oxime derivatives suitable for generation of products **5p**–**5r**. We believe this methodology represents a uniquely rapid method of synthesizing α-trifluoromethyl primary amines, substructures of high interest to medicinal chemists as a result of their improved resistance toward oxidative metabolic degradation and improved membrane permeability arising from the increase in lipophilicity imparted by the incorporation of fluorine atoms.[22]

To complement oxime reactivity (Method A), we explored the coupling reaction of iminium chlorides (Method B). When using electronically varied iminium salts (**6a**–**6f**), the yield is clearly affected, in contrast to reactions with the analogous oximes (**3a**–**3f**). Iminium salts containing electron-donating substituents afford higher yields in the coupling reaction. Specifically, reaction efficiency correlates directly with the electron-rich nature of the aromatic ring, with electron-donating *p*-methoxy compound **6f** yielding primary amine product **5f** in 94% yield. The strongly electron-deficient trifluoromethyl group significantly diminishes product formation, resulting in a yield of 14% for compound **5b**. In contrast, the corresponding oxime chemistry is less sensitive toward the impact of electronic substituents, converting *p*-trifluoromethyl oxime (**3b**) into **5b** in 91% yield (*vide supra*).

Ortho-methyl substitution improves the coupling reaction when using iminium salts, delivering primary amine **5g** in excellent yield. In contrast, oximes with an *ortho*-methyl substituent do not efficiently convert into the desired product **5g**, requiring 16 h to consume the starting oxime. In both cases, *ortho*-methyl substitution causes the arene ring to rotate out of the plane of either the iminium or oxime, resulting in a decrease in the extent of conjugation between the π-system of the phenyl ring and the imine C═N group. In the case of the iminium substrate, the energy of the LUMO is raised, analogous to the placement of an electron-donating group at the *para*-position. Additionally, the resulting benzylic α-amino radical is postulated to be more reactive due to decreased resonance delocalization. In the case of the oxime substrate, additional effects are present, related to the energy of its triplet excited state, that may lead to decreased reactivity (*vide infra*). Further, Method B produces amines with sterically demanding groups (e.g., *t*-Bu) adjacent to the new C–C bond (**5m**) in good yield.

Photochemical reactions are sometimes limited in their scalability due to light penetration. To test this, we increased

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the scale of our reaction of **3a** and **4a** by 12-fold. To accommodate the larger reaction vessel volume, we utilized a PennOC m1 photoreactor which can accommodate a 40 mL glass vial.[23] Gratifyingly, on this scale, 3.6 mmol of **3a** gives product **5a** in 80% yield. At temperatures slightly above room temperature, ca. 35−40 °C, we observed the reaction to be homogeneous at a concentration of 0.1 M in oxime **3a**, allowing for greater light penetration.

Next, the cyanoarene coupling partner scope was tested with both oxime **3j** and iminium salt **6j**. Heterocycles are tolerated in the cyanoarene substrate scope in the form of 2-biaryl-4-cyanopyridines (**5s**−**5x**) (Table 4). More electron-rich heterocycles couple more efficiently with oxime (**3j**) coupling partners. As a comparison, product **5y** is formed in 89% yield when the pyridine contains a 2-phenyl substituent, **5z** is produced in 97% yield with 4-methoxyphenyl, and **5aa** is generated in only 25% yield when the pyridine contains a 2-carbomethoxyphenyl. For the analogous iminium salt (**6j**), product formation follows a trend similar to that of the respective oxime reaction (**5s**−**5aa**).

Functional groups in the 2-position of the cyanopyridine coupling partner have a strong influence on reactivity with both oxime (**3j**) and iminium (**6j**) coupling partners. For reactions with **3j**, products containing electron-donating substituents (**5ac**−**5ah**) increased the efficiency of the coupling reaction. Coupling of **3j** with the respective cyanoarene produced no product for compounds (**5ai**−**5ak**). Coupling of iminium salt **6j** with electron-rich cyanoarenes produced results similar to those obtained for the reaction with oxime **3j**. Notably, iminium **6j** couples effectively with cyanoarenes containing electron-withdrawing groups at the 2-position (**5ai**, **5aj**). This complementary reactivity between oximes and iminiums allows this catalytic manifold to access a greater substrate scope than the oxime reaction alone. Substituents at the 3-position are also tolerated, as witnessed with **5am** and **5ap**.

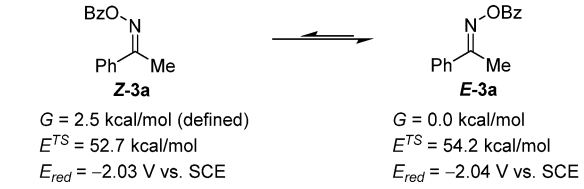
Coupling of oximes and iminium salts with 2-cyanopyridine derivatives occurs with similar reactivity to their 4-cyanopyridine analogs (**5aq**, **5ar**). The reaction does not occur with non-heterocyclic cyanoarenes (**5at**, **5au**). The reaction was also tested with other heterocyclic cyanoarenes, where both **3j** and **6j** couple to form azaindole **5av**. More electron-poor heterocycles can be synthesized using iminium salt **6j** to afford products **5aw** and **5ax**.

Initially, we hypothesized that *O*-benzoyl oximes could be reductively deprotected *in situ* to generate low concentrations of the corresponding N−H imine in solution. Previously, Zard and co-workers described single-electron reductive methods for iminyl radical generation from *O*-benzoyl oximes.[24] They proposed, using SmI_2, single-electron reduction of the benzoyl moiety, which then undergoes beta-scission to release an iminyl radical and benzoate. While our HTE screen revealed reaction conditions which promoted the desired reductive coupling, our data did not support direct reduction of the *O*-benzoyl oxime. Specifically, the data reveals that the magnitude of the reduction potential of a catalyst does not correlate with oxime consumption (cf. Table 1). Interestingly, iridium-based photocatalysts catalyzed decomposition of the oxime across a wide range of catalyst reduction potentials. Ruthenium-based and organic photoredox catalysts which possess reduction potentials similar to those of the successful iridium-based photocatalysts do not catalyze oxime consumption.

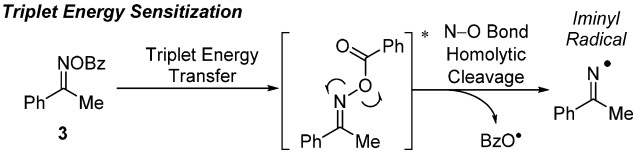
Interestingly, **PC4**, the most reducing iridium-based photocatalyst (Ir^{II}, E_{red} = 2.20 V vs SCE), is not the most efficient catalyst for oxime consumption.[11] **PC1** has a maximum reduction potential in the reduced state (Ir^{II}) of −1.43 V vs SCE.[25] We utilized DFT calculations to determine the single-electron reduction potential of *O*-benzoyl oximes and found that the model compound **3a** has a reduction potential of −2.03 V vs SCE (Table 5). This reduction potential indicates that reduction of the oxime by **PC1** would be a significantly endergonic process (13.8 kcal mol^{-1}), thus making direct reduction unlikely.

Table 5. Triplet Energy Sensitization of *O*-Benzoyl Oximes by Photoredox Catalysts

DFT Calculated Values[a]



Triplet Energy Sensitization



entry	photocatalyst	$E(T_1-S_0)$ [kcal·mol^{-1}][b]	E_{red} (V) vs SCE	E^*_{ox} (V) vs SCE	oxime remaining (%)[c]
1	**PC1**	55.8	−1.42	0.97	0
2	**PC3**	61.8	−1.37	1.21	51
3	**PC4**	58.1	−2.20	0.31	0
4	**PC6**	46	−1.33	0.77	98
5	**PC7**	43.6	−1.06	0.83	98

[a]Triplet−singlet energy gap ($E[T_1-S_0]$) refers to triplet (T_1) to singlet (S_0) energy gap calculated using M06-2X/6-31+G(d,p) SMD=DMSO. [b]Catalyst triplet-state energy values are experimental values.[25,30,34a] [c]**3a** (0.3 mmol), **4a** (2.2 equiv), benzoic acid (1.0 equiv), **PC1** (2.0 mol%), DMSO (0.1 M), blue LEDs (455 nm, 5 W per reaction), 40 °C. No stoichiometric reductant included.

Based on these results, we considered that N−O bond cleavage could occur via an alternative, nonreductive pathway.[24,26−28] To test this, we revisited our control reaction where the terminal reductant DIPA was excluded (Table 5). The reaction was irradiated in a temperature-controlled (40 °C) TAK 120 photoreactor with 455 nm light at a power of 5 W per vial at a reaction scale of 0.3 mmol. Under these conditions, **PC1** caused decomposition of 100% of the starting oxime **3a** and the formation of a new byproduct which was identified as azine dimer **7** (Scheme 3). We envisioned that **7** could form via the dimerization of two iminyl radicals generated from N−O bond scission. However, it appears unlikely that the catalyst would reduce the oxime with high efficiency under these conditions, because no stoichiometric reductant is available to reduce the photocatalyst to turn over the catalyst and complete the catalytic cycle. Furthermore, we observe no consumption of the 4-cyanopyridine coupling partner in reactions where DIPA is excluded. The reduction potential of the heterocycle is dramatically more electro-

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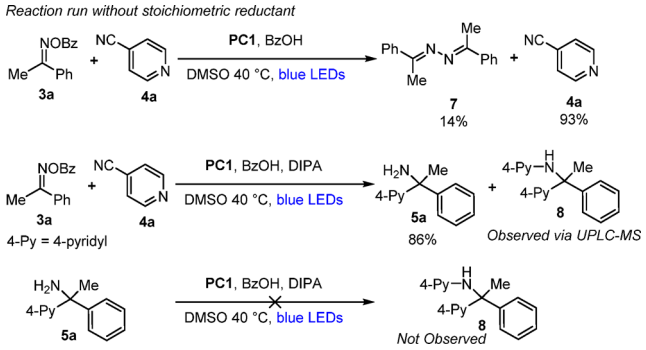
Scheme 3. Evidence of Iminyl Radical Formation

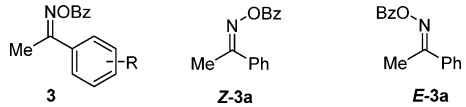


positive than the reduction potential of the oxime. Therefore, it is unlikely that the *O*-benzoyl oxime would be preferentially reduced in comparison to the 4-cyanopyridine. The presence of an iminyl radical intermediate is further supported by the observation of off-pathway byproducts in the syntheses of general compound **5** that are unique to Method A (e.g., Table 3).[29]

Photoredox catalysts can also act as triplet sensitizers as an alternative to engaging in redox chemistry.[31] It has been observed previously that oximes which are promoted into the triplet state can undergo N−O bond homolysis to generate an N-centered radical.[14,32,33] Triplet energy sensitization has been invoked in multiple reactions which utilize photoredox catalysts to induce excited-state reactivity in an electron-neutral process.

We next tested this hypothesis by repeating the experiment with multiple photocatalysts, where the oxime starting material, 4-cyanopyridine, and benzoic acid were mixed in DMSO in the absence of DIPA. We chose to screen five catalysts which differ in both triplet energies and reduction potentials.[25,34] We then compared the amount of *O*-benzoyl oxime consumption in each reaction (0.3 mmol scale) and found again that only iridium-based photocatalysts catalyze the decomposition of oxime **3a** (Table 5). The reduction potential of $Ru(bpy)_3PF_6$, **PC6**, in the reduced state (Ru^{I}) is −1.33 V vs SCE, similar to the reduced state iridium-based (Ir^{II}) **PC1** and **PC3**. However, **PC6** does not catalyze oxime decomposition, while both **PC1** and **PC3** do under these reaction conditions. If an active redox cycle is occurring at the catalyst, some 4-cyanopyridine (−1.60 V vs SCE) or 4-cyanopyridinium (−0.69 V vs SCE) should have been reduced in an off-pathway reaction.[35] In all cases, minimal consumption of 4-cyanopyridine starting material is observed. For each of the five photocatalysts screened on scale, a triplet (T_1)-to-singlet (S_0) energy gap [$E(T_1-S_0)$], commonly referred to as triplet energies, has been reported in the literature. We next utilized DFT to calculate the triplet-to-singlet energy gap[36] for our model *O*-benzoyl oxime substrate (**3a**). Oximes *Z*-**3a** and *E*-**3a** have a predicted triplet−singlet energy gap of 52.7 and 54.2 kcal/mol, respectively (Table 6). Iridium-based photocatalysts **PC1**, **PC3**, and **PC4** all possess a triplet-singlet energy gap >55 kcal/mol, and all these photocatalysts can consume oxime **3** in the absence of a reductant. In contrast, both **PC6** and **PC7** have triplet-to-singlet energy gaps below 50 kcal/mol (46.0 and 43.6 kcal/mol, respectively) and are unable to consume oxime **3a** in the absence of a reductant. Based on the dichotomy related to triplet-to-singlet energies and oxime consumption in these

Table 6. DFT Calculated Triplet Energy Values and Reduction Potentials



R	oxime geometry	G_Z relative to G_E [kcal·mol^{-1}]	$E(T_1-S_0)$ [kcal·mol^{-1}]	E°_{red} vs SCE [V]
4-CF_3	*Z*	+1.6	51.9	−1.74
	E		53.5	−1.75
4-Cl	*Z*	+1.8	52.2	−2.01
	E		54.0	−2.10
4-F	*Z*	+6.6	52.0	−1.81
	E		54.6	−1.99
4-H	*Z*	+2.3	52.7	−2.03
	E		54.2	−2.04
4-Me	*Z*	+1.7	57.8	−2.03
	E		54.5	−2.00
2-Me	*Z*	−0.2	75.8	−2.03
	E		57.9	−2.02
4-MeO	*Z*	+1.6	57.2	−2.04
	E		54.6	−2.01

[a] $E(T_1-S_0)$ refers to triplet (T_1) to singlet (S_0) energy gap calculated using M06-2X/6-31+G(d,p) SMD=DMSO.

experiments, we infer that triplet sensitization is responsible for the decomposition of the N−O bond in *O*-benzoyl oximes.

A Stern−Volmer analysis of the emission of **PC1*** (0.01 M in DMSO) using various concentrations of oxime **3a** (0−15 mM) reveals **3a** can quench the excited state of **PC1** (see Supporting Information for details), consistent with the proposed mechanism. While the Stern−Volmer relationship supports quenching of the excited state of **PC1**, it cannot be used alone to determine if this proceeds via an energy-transfer or electron-transfer mechanism. To discern between the two potential mechanisms, we photolyzed (450 nm) solutions of oxime **3a** in the presence of various photocatalysts (2 mol%) in the absence of a terminal reductant (DIPA). If oxime consumption is observed in quantities significantly greater than the amount of photocatalyst present, this would rule out an electron-transfer process and support an energy-transfer mechanism. Indeed, photocatalysts **PC1**−**PC3** successfully consumed oxime (see Table 5) well beyond the amount of catalyst present in solution. This data supports an energy-transfer process to convert oxime via N−O bond scission. Due to the lack of spectral overlap between the UV−vis emission spectrum of photocatalyst **PC1** and the UV−vis absorption spectrum of oxime **3a** (see Supporting Information for details), we rule out a Förster energy-transfer process in favor of a Dexter energy-transfer process.

In most photoredox reactions, the concentration of radicals is often estimated to be approximately the concentration of photocatalyst. While reductive couplings are commonly achieved with stoichiometric metal reductants, intermediates which require single-electron reduction are in much lower concentrations relative to the species responsible for the single-

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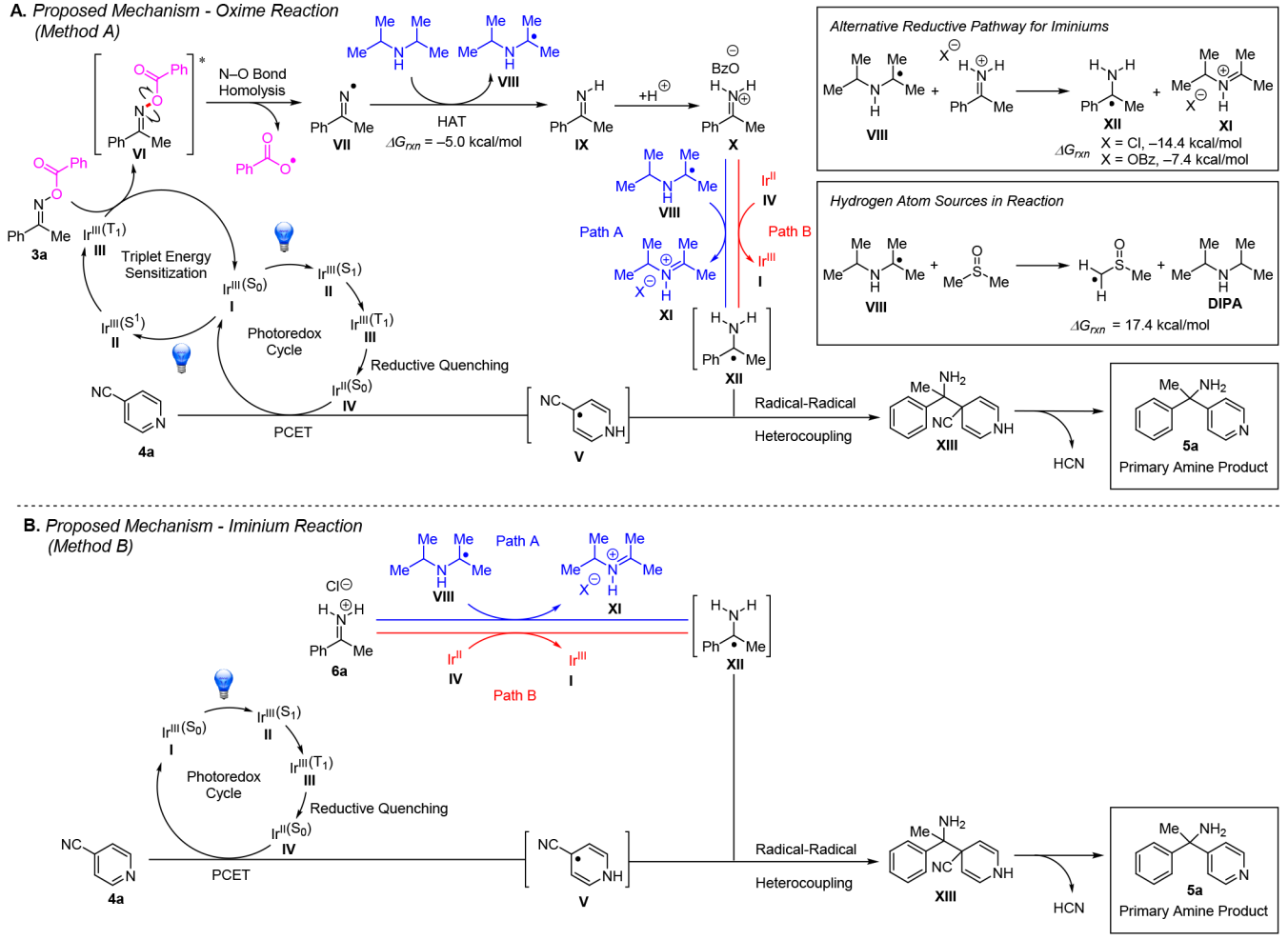
Scheme 4. Mechanistic Insight into the Synthesis of Sterically Hindered Primary Amines: (A) Proposed Mechanism for the Coupling of *O*-benzoyl Oximes and 4-Cyanopyridine (Method A); (B) Proposed Mechanism for the Coupling of Iminium Chloride Salts and 4-Cyanopyridine



electron reduction. The relatively low concentration of reduced photocatalyst present in the reaction makes the successive reduction of radical intermediates to anions increasingly unlikely, thus strengthening the alternate pathway involving triplet sensitization.

We hypothesize that this reductive coupling proceeds through a catalytic mechanism (Scheme 4) where the iridium engages in concurrent tandem catalysis,[37] acting simultaneously as both a photoredox catalyst and a triplet sensitizer.[38] First, photocatalyst **I** absorbs a photon to generate its corresponding excited singlet state (**II**), and subsequent intersystem crossing provides excited-state triplet **III**. This excited state **III** can be quenched reductively to generate a ground state Ir^{II} (**IV**). **IV** can then reduce 4-cyanopyridine via a proton-coupled electron-transfer (PCET) mechanism[14] to generate persistent radical **V** and a ground state **I**.[35] Excitation of **I** can again generate excited state **III** via photon absorption and intersystem crossing, where relaxation occurs via Dexter energy transfer[39] between **III** and *O*-benzoyl oxime **3a**. Triplet-state oxime **VI** can undergo N−O bond homolysis, resulting in iminyl radical **VII**. DFT calculations reveal that a hydrogen atom transfer event between iminyl radical **VII** and DIPA is exothermic (Scheme 4, inset), making this a likely pathway for the formation of imine **IX**. Alternatively, iminyl radical **VII** could be reduced by **IV**; however, due to the large disparity in concentration in **IV** when compared to DIPA, this pathway is unlikely. The resultant imine **IX** possesses a high reduction potential (ca. −2.4 V vs SCE). However, protonation occurs to generate iminium salt **X**, which is much more easily reduced (ca. −0.8 V vs SCE).[35]

Iminium **X** can be reduced via two likely reaction intermediates, illustrated in Scheme 4. In path A, iminium **X** can be reduced via the α-amino radical of DIPA, **VIII**.[40] Radical **VIII** is generated either by the reductive quenching of excited state photocatalyst **III**, followed by deprotonation, or via hydrogen atom abstraction by iminyl radical **VII** on DIPA. DFT calculations reveal that electron transfer between α-amino radical of DIPA (**VIII**) and iminium **X** is substantially exothermic, with a ΔG_{rxn} of −7.4 kcal/mol (Scheme 4, inset), generating α-amino radical **XII** and hindered iminium **XI**. In path B (Scheme 4) iminium **X** is reduced by the reduced-state photocatalyst **IV**, regenerating catalyst **I** and forming radical **XII**.

Penultimate intermediate **XIII** can be formed via a heterocoupling between persistent radical **V** and radical **XII**. Intermediate **XIII** can formally lose both a proton and a cyanide to give the reaction product **5a**.

We hypothesize that the analogous photocatalyzed reaction from iminium salts (e.g., **6**) occurs via a similar mechanistic pathway to that of the oximes, including the reduction of **4a** via

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PCET from the photoexcited catalyst (*vide supra*). The iminium reaction differs from the oxime reaction by removing the requirement to generate the iminium *in situ*. Excited-state photocatalyst **III** can oxidize DIPA, generating an ammonium radical cation. The α-C−H bonds of an ammonium radical cation become markedly more acidic than those in the parent amine.[3a] A second unit of DIPA or **4a** could deprotonate the ammonium radical cation, resulting in radical **VIII**. The iminium **6a** can be reduced by both pathways considered for the oxime reaction, where either reduced photocatalyst **IV** or radical **VIII** can donate an electron to **6a**, leading to α-amino radical **XII**. Subsequent heteroradical coupling of **XII** and **V** and formal loss of both a proton and cyanide would afford product **5a**.

CONCLUSION

In summary, we have developed photoredox-catalyzed methodology for the direct synthesis of primary amines without the use of harsh organometallic reagents. We have demonstrated that two separate bench-stable starting materials, benzylic *O*-benzoyl ketoximes and benzylic iminium chloride salts, can be coupled efficiently with 4-cyano-heteroarenes and tolerate a great diversity of functional groups. Further, we have identified a reaction where the photoredox catalyst is able to efficiently catalyze a net reductive coupling by acting as both a reductant and a triplet sensitizer, resulting in a reaction which is facilitated by concurrent tandem catalysis. This method enables scientists to synthesize libraries of hindered primary amines via parallel photoredox, including potential high-throughput experimentation for medicinal chemists.[41,42]

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/jacs.9b10871.

Synthetic procedures, spectral data, compound characterization, and Cartesian coordinates of computational structures (PDF)

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Notes

The authors declare no competing financial interest.

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(13) Products of Minisci-type heteroarene alkylation were observed via UPLC-MS analysis of crude reaction mixtures. See Supporting Information, Figure S1, for more information.

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(19) We utilized DFT calculations to estimate the stability of the cyclopropylmethyl radical intermediate. We observed that the ring-closed intermediate is favored by ca. 11 kcal/mol (Supporting Information, Figure S93) over its analogous ring-opened structure, in agreement with our experimental results.

(20) Product was identified via LC/MS analysis. The yield was calculated to be <10%.

(21) Benzylic oximes were prepared containing furan, pyridine, and pyrazine as their aromatic components. Furan- and pyrazine-derived oximes produced no detectable product. The starting oximes were completely consumed in the reaction.

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