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Photoredox-Catalyzed Direct Reductive Amination of Aldehydes without an External Hydrogen/Hydride Source

Rauful Alam and Gary A. Molander*

Roy and Diana Vagelos Laboratories, Department of Chemistry, University of Pennsylvania, 231 South 34th Street, Philadelphia, Pennsylvania 19104-6323

Abstract

The direct reductive amination of aromatic aldehydes has been realized using a photocatalyst under visible light irradiation. The single electron oxidation of an *in situ* formed aminal species generates the putative α -amino radical that eventually delivers the reductive amination product. This method is operationally simple, highly selective, and functional group tolerant, which allows the direct synthesis of benzylic amines by a unique mechanistic pathway.

Graphical Abstract

Amines and their derivatives are ubiquitous in pharmaceuticals, agrochemicals and biologically relevant natural products.¹ Reductive amination represents one of the most convenient and versatile methods for their synthesis.² In fact, a recent survey has revealed that reductive amination is the sixth most frequently used reaction in the pharmaceutical industry.³ Although various methods are known, direct reductive amination (DRA) is considered the most practical method for the synthesis of amines, and therefore, is the most widely used. DRA has been used mainly for synthesizing secondary amines; however, the synthesis of tertiary amines has been described as challenging, and few methods are reported in the literature.⁴ In addition to an amine and a carbonyl compound, the traditional reductive amination requires hydrogen (H_2) or a hydride source such as borohydride or a hydrosilane

*Corresponding Author: gmolandr@sas.upenn.edu.

ORCID

Gary A. Molander: 0000-0002-9114-5584

Rauful Alam: 0000-0003-0021-3607

Notes

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Supporting Information

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Experimental procedures and characterization data for all compounds (PDF)

reagent. Application of these reagents is often associated with toxicity issues, poor selectivity, air and moisture sensitivity, use of an external activator, and/or purification issues.^{4a, 5} Recently, several methods have been reported regarding metal-catalyzed reductive amination of aldehydes under external H₂/hydride-free conditions.^{4b, 6} Despite the conceptual simplicity, these methods usually require the application of high pressure CO gas and high temperatures (120–140 °C).

Recently, visible light-mediated photoredox catalysis has emerged as an enabling platform to access new synthetic transformations through single-electron transfer (SET) events.⁷ In particular, the generation of carbon-centered α -amino radicals and their use in coupling reactions with various electrophilic partners has become a powerful strategy in organic synthesis.⁸ Such radical species have been generated from α -amino acids,⁹ α -amino trifluoroborates¹⁰ and silylamines,^{8b} among others. Amine scaffolds have also been used to generate α -amino radicals through successive oxidation and α -deprotonation steps.^{7e} Considering these recent advancements in this area, we questioned whether it might be feasible to use aldehydes and amines to generate α -amino radicals *in situ*, capable of undergoing reduction to give amines by a unique mechanistic pathway. Scouring the literature, we found DRA under photoredox catalysis is an underexplored area.¹¹ Considering the prevalent role of reductive amination reactions, we conjectured that a photoredox-based DRA approach would offer utility in terms of mild reaction conditions, chemoselectivity, and functional group compatibility.

Herein, we report a novel method for direct reductive amination from aromatic aldehyde feedstocks and readily available secondary amines to synthesize tertiary benzylic amines under photoredox catalysis using iridium-based- or organic photocatalysts (Scheme 1).

At the outset of our studies, methyl 4-formylbenzoate **2a** and piperidine **3a** were chosen as model substrates for the desired reductive amination (Table 1). A variety of photocatalysts were screened that possessed sufficiently high excited-state redox potentials to provide the desired amine compound **4aa**. Although 4CzIPN ($E^*_{1/2}$ = 1.35 V vs SCE)¹³ proved to be a viable photocatalyst, the Ir catalyst **1** ($E^*_{1/2}$ = 1.32 V vs SCE)¹² provided superior yields (entries 1–2, Table 1). The yield was decreased when the catalyst **1** was replaced by Ru(bpy)₃(PF₆)₂, which has a high reduction potential, but relatively low oxidation potential ($E^*_{1/2}$ = 0.77 V vs SCE). Although MesAcr (mesitylacridinium) has a high oxidation potential in the excited state ($E^*_{1/2}$ = 2.06 V vs SCE),¹⁴ no product was observed (entry 5), likely because of its low reduction potential. Other organophotocatalysts such as Eosin Y were also ineffective (entry 4) under these reaction conditions, most likely because of their low oxidation potentials ($E^*_{1/2}$ = 0.79 V vs SCE).¹⁵ Importantly, the reaction was also unsuccessful in the absence of either photocatalyst **1** or light (entries 7–8).

Although the reaction worked smoothly in the absence of B₂O₃, (entry 8), this additive was beneficial for affording high yields. Most likely, the boron trioxide acts as a weak Lewis acid, as well as a desiccant.¹⁶ B(OMe)₃ was as efficient as B₂O₃ for the reaction, but boron trioxide was chosen, given its cost efficiency and ease of handling. Other dehydrating agents¹⁷ such as SiO₂ and molecular sieves (MS) gave lower yields (entries 11–12).

Although different aprotic solvents were examined for the amination reaction, acetonitrile (MeCN) was found to be superior to any other explored solvents (entries 13–16).

During the reaction optimization (entries 6–7, Table 1), we observed the clean formation of an aminor species in the reaction mixture. Intrigued by this result and its mechanistic implications, we set out to synthesize the corresponding aminor **5** (Figure 1). It has been reported that aminorals can be used for reductive alkylation and allylation in the presence of Zn and strong Lewis acids, although the mechanism is not fully understood.¹⁸

We anticipated that aminor **5** could be an intermediate in the amination reaction. To gain further insight, we measured the redox potential of **5** ($E_{ox} = +0.95$ V vs SCE), which indicated the viability of oxidation with the excited state of Ir photocatalyst **1** ($E^*_{1/2} = 1.32$ V vs SCE). Next, we subjected aminor **5** to the photocatalyst and light to examine the reactivity of this species. As outlined in Scheme 2, compound **5** afforded the amine **4aa** in the presence of photocatalyst **1**, although the yield was low (eq 1). Surprisingly, in the presence of piperidine (1 equiv), a three-fold increase of the yield was observed (eq 2). Different bases other than piperidine have also been tested. For example, the reaction also worked smoothly in the presence of diisopropylethylamine (DIPEA), with no cross-amination product (eq 3).¹⁹ Furthermore, as anticipated, aminor **5** was fully recovered, and no product was observed, in the absence of either photocatalyst or light.

These results suggest that the aminor is most likely an active intermediate for the amination *via* generation of an α -aminobenzyl radical upon oxidation by the photoexcited catalyst (See Supporting Information (SI) for more experimental support).

As outlined in Figure 2, we propose that an *in situ* formed aminor intermediate, **5a**, undergoes single-electron oxidation by photoexcited catalyst **1** to form cationic radical species **5b**, which subsequently forms the α -amino radical **5c**.²⁰ Fragmentation of **5b** is likely to be facilitated by the presence of a base (Scheme 2, eqs 2–3), with concomitant formation of **6a**. Notably, when pyrrolidine was used for the amination reaction, the formation of 1-pyrroline was observed (See SI). Next, amino benzyl radical **5c** can undergo a single electron reduction by the reduced photocatalyst **1b** to form benzylic anion **5d**,²¹ and the subsequent protonation would deliver the final amine **4**.²²

Unfortunately, this reductive amination protocol was not uniformly generalizable. When we employed electron-rich aldehydes such as *p*-anisaldehyde, the amination did not work under the standard conditions described in Table 1. This discrepancy was unexpected and showed that the substituent on the aromatic ring plays a crucial role beyond the condensation step. It is well known that the single electron reduction of benzylic radicals (e.g., **5c**) is heavily dependent on the substituent of the arene ring.²³ For example, benzyl radicals bearing electron-withdrawing substituents on the aromatic ring have lower reduction potentials (e.g., -0.77 vs SCE for *p*-CN) than those bearing electron-donating substituents on the arene ring (e.g., -1.75 vs SCE for *p*-OMe). Therefore, we hypothesized that because of this, a *p*-methoxybenzyl radical would not be reduced by photocatalyst **1b** ($E^{pc/-pc} = -1.37$ V vs SCE).²⁴ To resolve this issue, we envisioned an alternative pathway (blue arrow, Figure 2).

We rationalized that for those radicals **5c** exhibiting a high reduction potential, hydrogen atom transfer (HAT) would provide a means to bypass the single electron reduction and give a direct mechanistic pathway to **4**.²⁵ To validate this idea, we briefly screened different thiols. We found that 2,6-dimethylbenzenethiol (**7**) was highly efficient for the reductive amination of electron-rich *p*-anisaldehyde. Of note, aliphatic thiols such as *t*-BuSH were completely ineffective in providing the reductive amination product, likely as a result of mismatched polar effects.²⁶ Consequently, it appears that amino benzyl radical species **5c** can undergo two different pathways (SET or HAT) to give the amine, depending on the reduction potentials of the benzyl radicals and the reaction conditions.²⁷

We next turned our attention to the scope of this amination reaction, as shown in Scheme 3. The reaction proceeded well for both electron-rich and electron-deficient aromatic aldehydes (**4aa-4qa**). Aldehyde **2a** reacted cleanly with piperidine, affording a good yield of the desired product. Importantly, the reaction was also scalable. Performing the amination on a larger scale (6.1 mmol, 12-fold increase) proved viable without compromising the yield (**4aa**). Other electron-withdrawing functional groups such as a nitrile (**4fa**), sulfone (**4ga**), and a benzyl ester (**4ba-ca**) were also compatible under the standard reaction conditions. In particular, boronate esters were untouched under the reaction conditions (**4ca**), thereby permitting the possibility of further functionalization using Chan-Lam amination²⁸ or cross-coupling.²⁹ Electron-rich aromatic aldehydes could be used when catalytic amount of 2,6-dimethylbenzenethiol (**7**) was used to afford the desired amines. Various electron-donating groups such as methoxy (**4ha**), and phenoxy (**4ia**) were well suited. The latter could be prepared on gram scale (5.05 mmol) using organic photocatalyst 4CzIPN (\$6/gram). This provided a 63% yield of **4ia**, and the catalyst was recyclable. Allyloxy (**4jl**), propargyloxy (**4kl**), thiomethyl (**4ma**), and amino groups (**4oa**) were also well tolerated and afforded the corresponding products in moderate to good yields. Of note, we did not observe any hydroaminated product when the allyl- or propargyl ether functionalized aldehydes were used (**4jl-4kl**).²⁵ Interestingly, an *O*-glycoside aldehyde could be employed to synthesize **4na**, although in modest yields. Sterically demanding 2-chlorobenzaldehyde could be used to synthesize the amine **4qa** in acceptable yield. Finally, trifluoromethylated heterocyclic amine **4ra** was accessed in modest yield after a prolonged reaction time (48 h). In an attempt to expand the aldehyde scope further, we also used aliphatic aldehydes such as isobutyraldehyde and pivalaldehyde. Unfortunately, none of these gave the desired amines (**4sa-ta**). Spectroscopic analysis showed that a lack of amination was the likely cause.

Next, we turned our attention to explore the amine scope for the reductive amination (**4ab-4fm**). Morpholines are highly represented among small molecules that are biologically and therapeutically relevant, including many natural products.³⁰ Consequently, we used morpholine (**4ab**) and thiomorpholine (**4hc**) for the amination, finding that both were well tolerated. Likewise, substituted piperidines were also well accommodated to afford tertiary amines (**4ad-4ae** and **4ge**) in good yields. Compound **4ef** bearing two carbonyl groups showcases the excellent chemoselectivity of this method. Phenyl- and nitrile-substituted piperidines (**4gh**, **4fg**) could also be used. A spiro-piperidine reacted cleanly to afford **4aj**. Furthermore, the Boc-protected piperazine could be used to synthesize **4ak**, providing a direct method to access an important class of molecules³¹ from aldehyde feedstocks.

Pyrrolidine also worked smoothly with **2a** to give **4al** in good yield. Moreover, an enantioenriched amine (**4fm**) was prepared without any stereochemical ablation, indicating the stereochemical fidelity of the method. Unprotected β -amino alcohols such as 4-piperidinol reacted with *p*-anisaldehyde to afford **4hi**, demonstrating the high functional group compatibility and mildness of this method. Unfortunately, acyclic amines were unsuitable for the process (**4hn**). Spectroscopic analysis of the reaction between diethylamine (HNEt₂) and *p*-anisaldehyde revealed the lack of aminal intermediate formation, which seems likely to be the cause of the unsuccessful reaction.

In summary, a novel method for the direct synthesis of benzylic, tertiary amines from aromatic aldehydes is reported. To the best of our knowledge, this reaction is the first example of the direct reductive amination of aromatic aldehydes to generate tertiary amines under photoredox catalysis. Furthermore, the excellent functional group compatibility and mild reaction conditions favor its implementation in late-stage functionalization of complex structural motifs. Notably, a new protocol for accessing α -amino radicals *via* aminal formation/oxidation/fragmentation has been reported, with demonstrated potential for the discovery of new transformations.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Figure 1.
Synthesis of aminal compound **5**

Figure 2.
Plausible mechanism for the reductive amination

Scheme 1.

Photoredox-catalyzed reductive amination of aldehydes

Scheme 2. Reactivity of intermediate **5 under various conditions.^a**

^a**5** (1.0 equiv, 0.1 mmol), piperidine **3a** (1.0 equiv), DIPEA (1.0 equiv), Ir catalyst **1** (2 mol %), MeCN-*d*₃ (0.20 M), rt, 24 h. ^bYield was determined by ¹H NMR using 1,3,5-trimethoxybenzene as an internal standard.

Scheme 3. Evaluation of Aldehydes and Amine Under Photoredox-Catalyzed Reductive Amination^a

^aGeneral reaction conditions: aldehyde **2** (1.0 equiv, 0.5 mmol), amine **3** (3.0 equiv, 1.5 mmol), B₂O₃ (1.0 equiv, 0.5 mmol), Ir-catalyst **1** (2 mol %), MeCN (0.20 M), rt, 24 h.

^bYield for the reaction using 2 equiv of amine. ^cYield for the 6.1 mmol scale reaction. ^dYield for the reaction (36 h) using 5 mol % 4CzIPN instead of **1**. ^e10 mol % 2,6-dimethylbenzenethiol (**7**) was used. ^fYield for a 5.0 mmol scale reaction. ^gReaction time 48 h

Table 1

Optimization of the Reaction Conditions^a

entry	deviation from standard condition	yield (%) ^b
1	no change	78
2	5 mol % 4CzIPN instead of Ir cat.	53
3	2 mol % Ru(bpy) ₃ instead of Ir cat.	29
4	2 mol % Eosin Y instead of Ir cat.	0
5	2 mol % MesAcr instead of Ir cat.	0
6	in absence of photo catalyst	0
7	in absence of light	0
8	in absence of B ₂ O ₃	50
9	1 equiv B(OH) ₃ instead of B ₂ O ₃	67
10	1 equiv of B(OMe) ₃ instead of B ₂ O ₃	73
11 ^c	SiO ₂ instead of B ₂ O ₃	48
12 ^c	4 Å MS instead of B ₂ O ₃	24
13	DME instead of MeCN	22
14	1,4-dioxane instead of MeCN	<5
15	THF instead of MeCN	<5
16	DMF- <i>d</i> ₇ instead of MeCN	56

^a General reaction conditions: **2a** (1.0 equiv, 0.1 mmol), piperidine **3a** (3.0 equiv, 0.3 mmol), Ir catalyst **1** (2 mol %), MeCN-*d*₃ (0.20 M), rt, 24 h.^b Yield was determined by ¹H NMR using 1,3,5-trimethoxybenzene as an internal standard.^c 50 mg of SiO₂ and molecular sieves (4 Å) were used.