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Photoredox-Catalyzed Decarboxylative Cross-Coupling of α-Amino Acids with Nitrones

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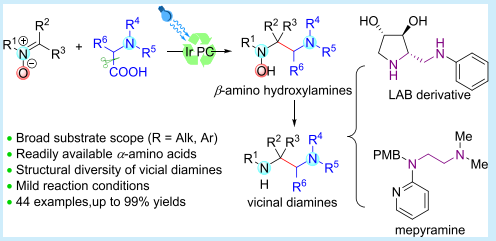
ABSTRACT: A decarboxylative cross-coupling reaction of α-amino acids with nitrones via visible-light-induced photoredox catalysis has been established for easy access to β-amino hydroxylamines and vicinal diamines with structural diversity, which is featured with simple operation, mild conditions, readily available α-amino acids, and a broad scope of nitrone substrates. The application of this protocol can furnish efficient synthetic strategies for some valuable vicinal diamine-containing molecules.



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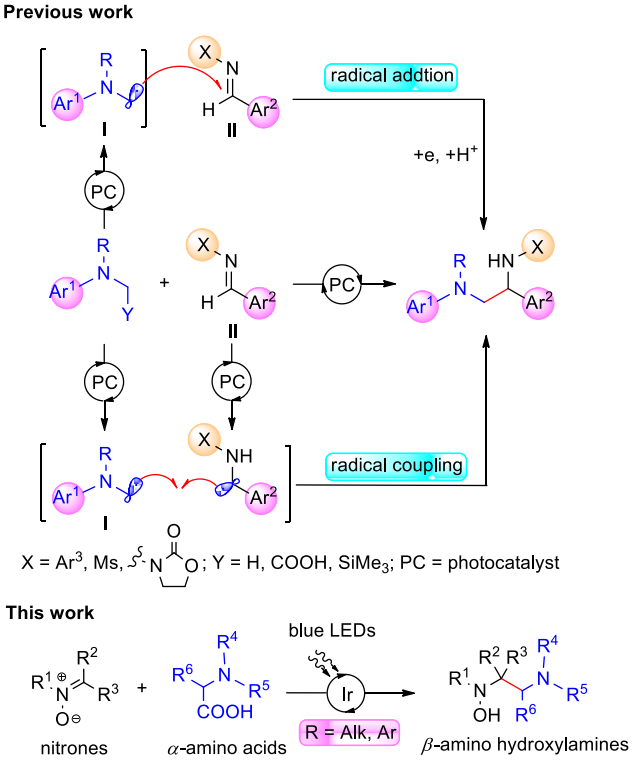
Vicinal diamine is an essential structural unit embodied in many important organic compounds. A wide variety of alkaloids, pharmaceuticals, ligands, and organocatalysts armed with a vicinal diamine moiety show eminent biological and catalytic activities.[1] Owing to these merits, incessant efforts have been devoted to the efficient synthesis of vicinal diamines and analogues, and many powerful methods have been established to date.[2,3] Notably, on the basis of the α-aminoalkyl radicals, the radical coupling of imines[4] is a flexible and straightforward approach that directly combines two C−N moieties to construct vicinal diamines. Recently, this elegant strategy has evolved in the realm of visible-light photoredox catalysis[5] with several variants in racemic[6] and enantioselective[7] manners under environmentally friendly conditions.[8] However, most of these methods rely on the reaction of *N*-aryl α-aminomethylene radicals **I** and aromatic aldimines **II** and thus suffer from a narrow substrate scope, rendering the vicinal diamine products structurally limited (Scheme 1).

The applications of nitrones in radical reactions have drawn considerable attention in our lab.[9] Recently, several photocatalytic reactions utilizing nitrones as the radical acceptor have been reported,[10] including a synergistic photocatalytic and Lewis-acid-catalytic enantioselective reductive cross-coupling reaction of nitrones with aromatic aldehydes[10a] and a cross-coupling reaction of nitrones with aromatic tertiary amines via visible-light photoredox catalysis.[10d] On the other hand, α-amino acids are known as abundant, inexpensive, and naturally occurring synthetic materials and serve as precursors of α-aminoalkyl radicals in several photocatalysis reactions via an oxidative decarboxylation process.[11] We thus envisioned that by trapping α-aminoalkyl radicals generated from α-amino acids with nitrones, an efficient protocol for preparing vicinal diamines with structural diversity could be achieved (Scheme 1). Herein we present the decarboxylative cross-coupling reaction of α-amino acids with nitrones via visible-light-induced photoredox catalysis.

Scheme 1. Synthesis of Vicinal Diamines and Analogues by Visible-Light Photoredox Catalysis



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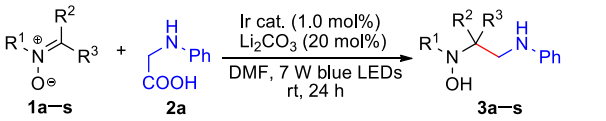
Our investigation into this photoredox-catalyzed protocol began by studying the model reaction of nitrone **1a** with *N*-phenylglycine **2a**. After various photocatalysts, bases, solvents, and light sources were screened (Table S1), the optimized reaction conditions were established as follows: By using 7 W blue LEDs as the light source, the cross-coupling was carried out in the presence of $Ir[dF(CF_3)ppy]_2(dtbbpy)(PF_6)$ (1.0 mol%) and Li_2CO_3 (20 mol%) in DMF at room temperature for 24 h to give the desired β-amino hydroxylamine **3a-1** in 83% yield. Control experiments showed that no product was formed in the absence of a photocatalyst, light source, or argon protection, which back up a photoredox catalytic oxidation mechanism. Furthermore, β-amino hydroxylamine **3a-1** was obtained in only 30% yield without a base additive. This indicates that the deprotonation of α-amino acid significantly facilitates the reaction (Table S2).

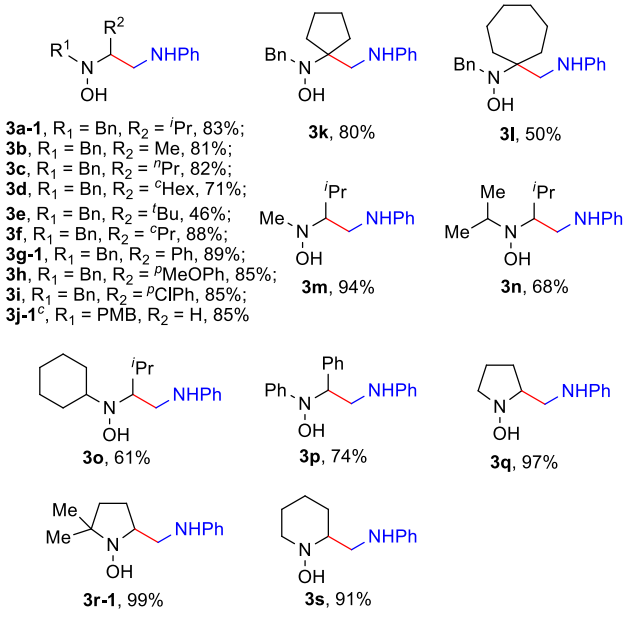
After identifying the optimized reaction conditions, we examined the scope of nitrones and found that the reaction tolerates a wide array of nitrone substrates. As for acyclic nitrones, various C-substituents (**1a–l**) and N-substituents (**1m–p**) on the nitrones were examined using *N*-phenylglycine **2a** as the reaction partner, and the desired β-amino hydroxylamines were obtained in moderate to good yields (Scheme 2). When electron-rich nitrone **1j** was used as an electrophilic radical acceptor, more Li_2CO_3 with water was needed to promote the deprotonation of α-amino acids and increase the concentration of α-aminoalkyl radicals, and thus a modified condition (**Protocol 1**) was adopted to give cross-coupling product **3j-1** in 85% yield. Compared with acyclic nitrones, cyclic nitrones exhibited higher reactivity under the general reaction conditions, and the desired products were formed in excellent yields (**3q–s**).

We also explored the scope of α-amino acids. As shown in Scheme 3, decarboxylative cross-coupling of *N*-arylglycines with nitrone **1a** gave the desired β-amino hydroxylamines in moderate to good yields. As for para-substituted *N*-arylglycines, electron-donating methoxy gave a lower yield compared with electron-withdrawing halides and cyano substituents (**3a-5** vs **3a-2–4**). *Ortho*-, *meta*-, or *para*-Cl-substituted *N*-arylglycines gave almost identical and highest yields (**3a-3**, **3a-6**, and **3a-8**). *N*-Arylglycine **2i** with a polysubstituted aryl group gave a moderate yield of 65% (**3a-9**). For *C*-aryl nitrone **1g**, the reaction outcome was irrelevant to *N*-arylglycines, as products **3g-2–4** were obtained in nearly identical yields. Furthermore, the reaction of N-bis-substituted glycines proceeded smoothly under the general conditions to provide desired cross-coupling products in moderate yields (**3a-10–a-12**). It is worth mentioning that the decarboxylation of *N*-Boc glycine proceeded under harsher conditions (**Protocol 2**) to give the desired product **3a-13** in 61% yield. In addition, the reaction could also be applied to α-branched *N*-phenyl α-amino acids in moderate to good yields when the less sterically hindered nitrone **1j** was used as the

Scheme 2. Photoredox Decarboxylative Cross-Coupling of *N*-Phenylglycine with Nitrones[a,b]

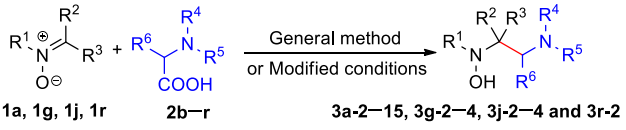


1a–s 2a 3a–s

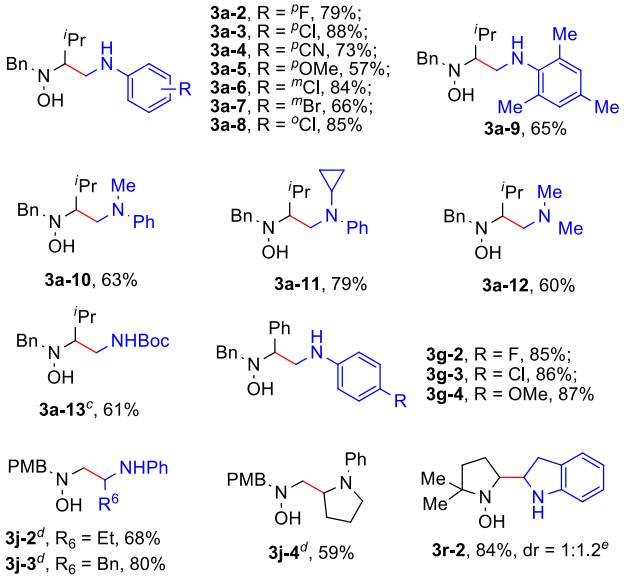


[a]General method: Nitrone (0.30 mmol), α-amino acid (0.90 mmol), $Ir[dF(CF_3)ppy]_2(dtbbpy)(PF_6)$ (1.0 mol%), Li_2CO_3 (20 mol%), DMF (1.5 mL), 7 W blue LEDs, room temperature, 24 h. [b]Isolated yield. [c]**Protocol 1**: Nitrone (0.30 mmol), α-amino acid (0.90 mmol), $Ir[dF(CF_3)ppy]_2(dtbbpy)(PF_6)$ (1.0 mol%) and Li_2CO_3 (100 mol%), DMF (1.2 mL) and H_2O (0.30 mL), 7 W blue LEDs, room temperature, 24 h.

Scheme 3. Photoredox Decarboxylative Cross-Coupling of *N*-Substituted Glycines with Nitrones[a,b]



1a, 1g, 1j, 1r 2b–r 3a-2–15, 3g-2–4, 3j-2–4 and 3r-2



[a]General method: Nitrone (0.30 mmol), α-amino acid (0.90 mmol), $Ir[dF(CF_3)ppy]_2(dtbbpy)(PF_6)$ (1.0 mol%), Li_2CO_3 (20 mol%), DMF (1.5 mL), 7 W blue LEDs, room temperature, 24 h. [b]Isolated yield. [c]**Protocol 2**: Nitrone (0.40 mmol), α-amino acid (0.40 mmol), $Ir[dF(CF_3)ppy]_2(dtbbpy)(PF_6)$ (1.0 mol%), CsF (100 mol%), DMF (2.0 mL), 32 W blue LEDs, room temperature, 36 h. [d]**Protocol 1**. [e]dr values were determined by ^1H NMR analysis of crude products.

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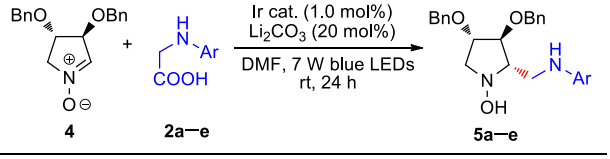
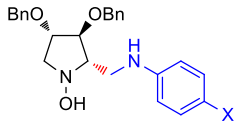
reaction partner under the modified conditions (**Protocol 1**, **3j-2**–**4**). Notably, halide, nitrile, and indolinyl groups were well tolerated in this reaction. The decarboxylative cross-coupling of indoline-2-carboxylic acid **2r** with nitrone **1r** provided the desired product in good yield with a low diastereoselectivity (**3r-2**).

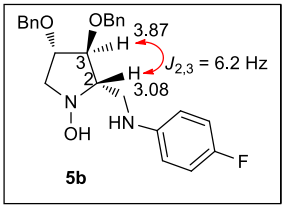
We next investigated the stereoselective decarboxylative cross-coupling of *N*-arylglycines with chiral nitrone **4** derived from D-tartaric acid.[9b] As shown in Scheme 4, the electron-

Scheme 4. Photoredox Decarboxylative Cross-Coupling of *N*-Aryl Glycines with Nitrone 4[a,b,c]





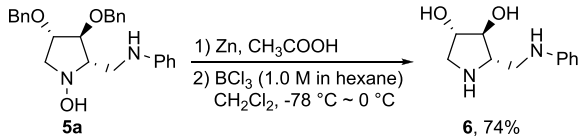
5a, X = H, 61%, dr: 5:1;
5b, X = F, 75%, dr: 11:1;
5c, X = Cl, 74%, dr: 6:1;
5d, X = CN, 78%, dr: 15:1;
5e, X = OMe, 57%, dr: 8:1



[a]General method. [b]Isolated yield. [c]dr values were determined by ^{1}H NMR analysis of crude products.

deficient *N*-arylglycines gave the highest yields. Moderate to good diastereoselectivities were obtained, and *N*-arylglycines with *para*-fluoro and nitrile groups gave the higher diastereoselectivity (**5b** and **5d**). The relative stereochemistry of **5b** was established on the basis of nuclear Overhauser effect spectroscopy (NOESY) experiment to be 2,3-*anti*. In addition, through the cleavage of N–O[12] and O–Bn[13] bonds, *β*-amino hydroxylamine **5a** was easy converted to vicinal diamine **6**, which is a LAB derivative with glycosidase inhibitory properties (Scheme 5).[14]

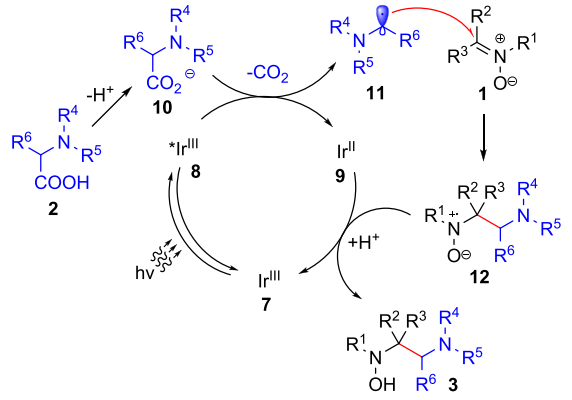
Scheme 5. Synthesis of LAB Derivative 6



By combining the results from the aforementioned studies and the control experiments shown in Supporting Information, a reaction mechanism was proposed, as shown in Scheme 6. The deprotonation of *α*-amino acid **2** generates *α*-amino acid anion **10**, which is oxidized by the visible-light-exited Ir(III) complex to form *α*-aminoalkyl radical **11** with the release of carbon dioxide. The *α*-aminoalkyl radical **11** is captured by nitrone **1** to form radical **12**, which is reduced by Ir(II) complex **9** and is protonated by *α*-amino acid **2** to furnish *β*-amino hydroxylamine **3**. In this free-radical chain mechanism, the base is just an initiator of the reaction. This rationalizes the fact that a substoichiometric amount of base is sufficient for completion of the reaction.

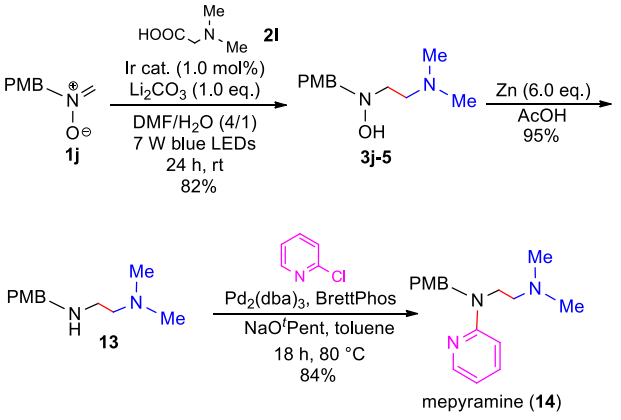
With the aim of demonstrating the utility of this photoredox catalytic protocol, we undertook the synthesis of mepyramine,

Scheme 6. Plausible Mechanism for Photoredox Decarboxylative Cross-Coupling of *α*-Amino Acids with Nitrones



an antihistamine drug (Scheme 7).[15] Under the modified reaction conditions (**Protocol 1**), the decarboxylative cross-

Scheme 7. Synthesis of Mepyramine



coupling of *N*,*N*-dimethylglycine **2l** with nitrone **1j** gave *β*-amino hydroxylamine **3j-5** in 82% yield. After the zinc-mediated reduction[12] of **3j-5**, vicinal diamine **13** was obtained in 95% yield. Finally, the Pd-catalyzed *N*-arylation[16] of **13** with 2-Cl-pyridine gave mepyramine (**14**) in 84% yield.

In summary, we have developed a visible-light photoredox Ir-catalyzed decarboxylative cross-coupling of *α*-amino acids with nitrones for easy access to *β*-amino hydroxylamines and vicinal diamines with structural diversity. This method affords the advantages of simple operation, mild conditions, readily available *α*-amino acids, and a broad scope of nitrone substrates. By using this method, a step-economy synthesis of a glycosidase inhibitory LAB derivative and a concise synthetic strategy for the antihistamine drug mepyramine have been established. The extension of the photoredox-catalyzed enantioselective decarboxylative cross-coupling of *α*-amino acids with nitrones is in progress in our laboratory and will be reported in due course.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c04101.

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Experimental procedures, characterization, and spectral data (PDF)

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Author Contributions

[§]H.-H.L. and J.-Q.L. contributed equally.

Notes

The authors declare no competing financial interest.

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