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Photoredox-Induced Radical Relay toward Functionalized β-Amino Alcohol Derivatives

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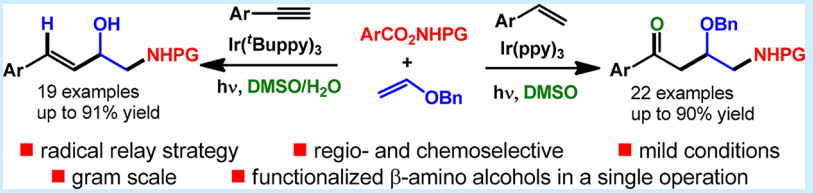
Supporting Information



ABSTRACT: A radical relay strategy is described to synthesize functionalized β-amino alcohols. This strategy is enabled by photoredox-catalyzed and nitrogen-centered radical-triggered cascade reactions of styrenes (or phenylacetylenes), enol derivatives, and *O*-acyl hydroxylamines in DMSO. The broad synthetic application of this method is demonstrated by the reaction of structurally diverse reaction components, including complex molecular scaffolds. Multiple functional groups of the resultant highly functionalized β-amino alcohol derivatives facilitate their further transformations.

β-Amino alcohols and their derivatives are highly valuable and found in a vast range of biologically important natural products, pharmaceuticals, and agrochemicals.[1] These compounds are also very useful synthons in chemical synthesis.[2] Although several stepwise functional group manipulations have been established,[1a] 1,2-oxyamination of olefins is arguably the most direct and efficient method for the synthesis of β-amino alcohol derivatives.[3] In this reaction, two carbon−heteroatom (N and O) bonds are constructed across the C=C bonds (Figure 1a).

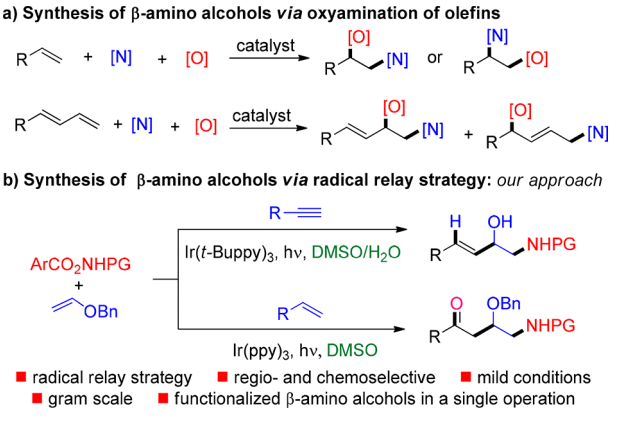


Figure 1. Strategies for the synthesis of β-amino alcohols.

However, some of these established methods suffer from poor regioselectivity.[4] Intermolecular oxyamination of 1,3-dienes, which delivers highly functionalized allyl amino alcohols, is even more challenging. 1,4-Oxyamination can compete with its 1,2-counterpart (Figure 1a).[5]

Radical cascade reactions remain a challenge due to the high reactivity of radical intermediates.[6] Photoredox-catalyzed and nitrogen-centered radical (N-radical)-involved cascade reactions are of current research interest and have evolved into powerful tools for the synthesis of nitrogen-containing molecules.[7] Inspired by these works and our continuing interest in N-radical chemistry,[8] we propose a novel radical relay strategy for the synthesis of functionalized amino alcohol derivatives based on C−C and C−N bond formations (Figure 1b). These cascade reactions are triggered by the intermolecular addition of amidyl N-radicals to electron-rich enol ether, followed by intermolecular C-radical trapping by another olefin (or alkyne). This method can provide functionalized β-amino alcohol derivatives in high regio- and chemoselectivity.

The reaction principle can be detailed by the combination of phenylacetylene **1**, benzyl vinyl ether **2a**, and *O*-acyl hydroxylamine **3**. As shown in Figure 2a, electrophilic N-radical **A** generated under photoredox catalysis adds to the electron-rich enol ether **2a** to give electron-rich C-radical **D** adjacent to the oxygen atom. Then, nucleophilic C-radical **D** is trapped by relatively electron poor alkyne **1**. The resultant vinyl radical **I** undergoes 1,5-hydrogen atom transfer (HAT) to give α-oxy benzyl radical **J**.[9] Subsequent oxidation and hydrolysis afford the final de-*O*-benzyl product **4**. A deuterium labeling experiment provides evidence of the 1,5-HAT process (Figure 2b). In addition, the isolation of aldehyde **9** provides further support for our reaction mechanism (for more details, see the Supporting Information). Alternatively, when styrene **5** is used instead of phenylacetylene **1**, C-radical **D** is trapped by styrene **5**. The

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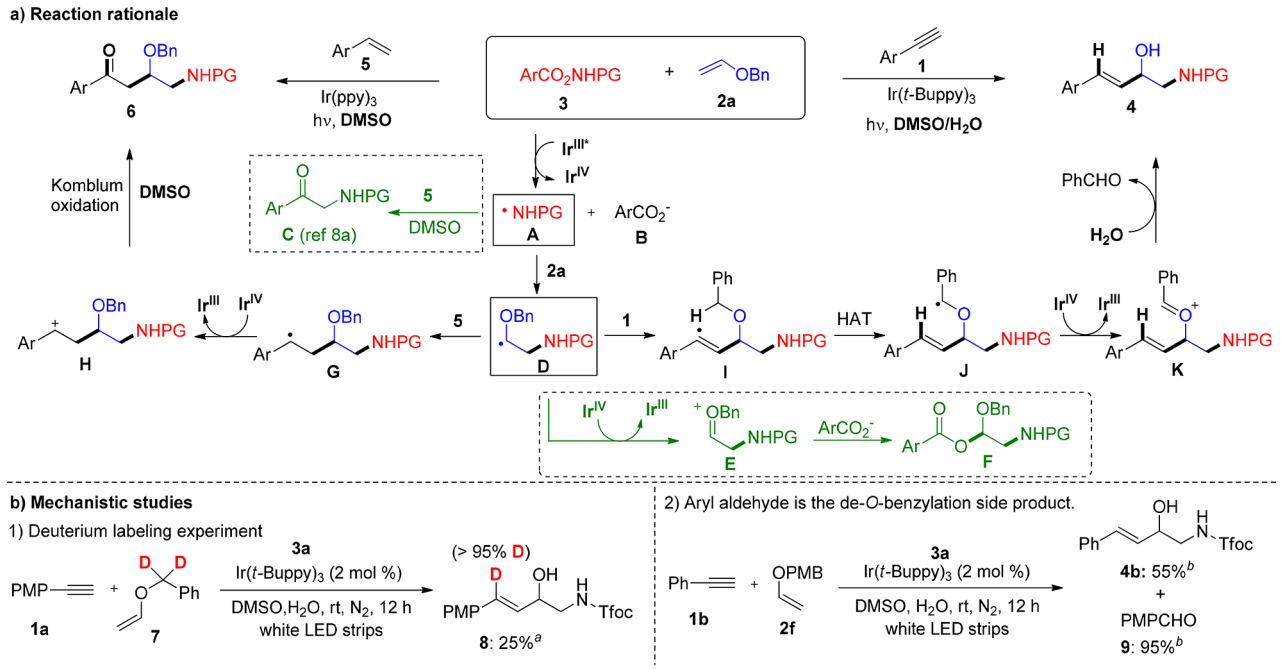

Figure 2. Rationale and challenges of our multicomponent radical cascade reaction. [a]Isolated yield. [b]Determined by ^{1}H NMR spectroscopy.

resultant C-radical **G** is prone to oxidation by the highly covalent photocatalyst to give the carbon cation **H**. The carbon cation **H** is trapped by DMSO to give the final ketone **6** following the Kornblum oxidation process.[10]

Although this radical relay strategy is designed, some challenges still remain: C-radical **D** can be easily oxidized to give oxocarbenium **E**, which can be trapped by the nucleophiles to give side products, such as **F**.[11,12] Therefore, the suppression of this potential side reaction is crucial to the success of our strategy. The chemoselectivity of this reaction is controlled by the polarity of the radical species. The amidyl N-radicals **A** are electrophilic, and they will always want to react with the more election-rich partners. So they react with enol derivatives first. The resultant C-radicals **D** are adjacent to the oxygen atom and nucleophilic. They therefore react with the relatively electron-poor species of styrenes or alkynes instead of polymerization.

The feasibility of this strategy was first examined by the reaction of phenylacetylene **1**, benzyl vinyl ether **2a**, and hydroxylamine derivative **3** in a mixture of DMSO and water under photoredox catalysis conditions. The *N*-protecting group of hydroxylamine derivative **3** was found to play a key role in this reaction. Therefore, a series of hydroxylamine derivatives were synthesized and investigated (Figure 3). 2,2,2-Trifluoroethoxy carbonyl (Tfoc) was the optimal protecting group, providing an 84% yield based on ^{1}H NMR analysis (81% isolated yield) for the desired α-aminomethyl cinnamyl alcohol **4a** in exclusively the *E*-isomer. Other protecting groups, such as Cbz, Ac, Boc, and Ts, also worked but provided much lower yields. The ratio of the starting materials also had a significant impact on the outcome of this reaction. The optimal ratio of **1a**/**2a**/**3a** was established to be 1:3:3 (for more details, see the SI).

With the optimized conditions in hand, we sought to explore the generality and limitations of this radical relay reaction (Figure 4). The reaction was examined with respect to various aryl alkynes, which gave the desired products in up to 91% yields. Different functional groups, such as halides (**4e**, 84%; **4f**, 91%), cyano (**4d**, 63%), ester (**4g**, 70%), hydroxyl (**4h**, 46%), ketone (**4i**, 56%), and amide (**4l**, 70%), tolerated these conditions with

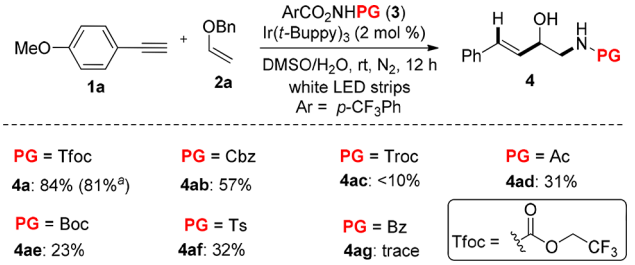

Figure 3. Protecting group screening of the N-centered radical precursors. Reaction conditions: a solution of **1a** (0.2 mmol, 1.0 equiv), **2a** (0.6 mmol, 3 equiv), **3** (0.6 mmol, 3 equiv), and Ir(^{t}Buppy)$_3$ (0.004 mmol, 2.0 mol %) in DMSO (1.8 mL) and H_2O (0.2 mL) was irradiated by white LED strips for 12 h. The yields are based on ^{1}H NMR analysis. [a]Isolated yield.

satisfactory yields. Phenylacetylenes with *meta*- and *ortho*-substitutions were efficiently transformed into the corresponding products **4j**−**4n** in 70−86% yields. *ortho*-MeO-phenylacetylene treated with Cbz-protected hydroxylamine **3b** afforded the desired product **4j′** in acceptable yield (69%). Naphthalene-, pyridine-, and thiophene-derived alkynes smoothly underwent this reaction to give the desired amino alcohols **4o**−**4r** in 49−71% yields. Notably, the products were isolated in single *E*-isomers in most cases except the reactions of phenylacetylenes with conjugated electron-withdrawing groups (**4d**, **4g**, **4i**, and **4o**), which led to lower *E*/*Z* ratios. This reaction was easily scaled up to a Gram-scale with a comparable isolated yield (64% yield for **4j′** on a 6 mmol scale). To our disappointment, aliphatic alkynes could not go through this reaction.

Next, we investigated the radical relay reactions of styrenes **5** with enol ether **2** and acyl hydroxylamine **3a** (Figure 5). The optimal reaction conditions were determined after a series of exploration on substrate ratios, catalysts, solvents, and protecting groups (for the condition optimizations, see the SI). The reaction of styrene **5a**, enol ether **2a**, and acyl hydroxylamine **3a** was achieved in DMSO using Ir(ppy)$_3$ as the photocatalyst irradiated by white LEDs, and the desired β-alkoxy-γ-aminoketone **6a** was

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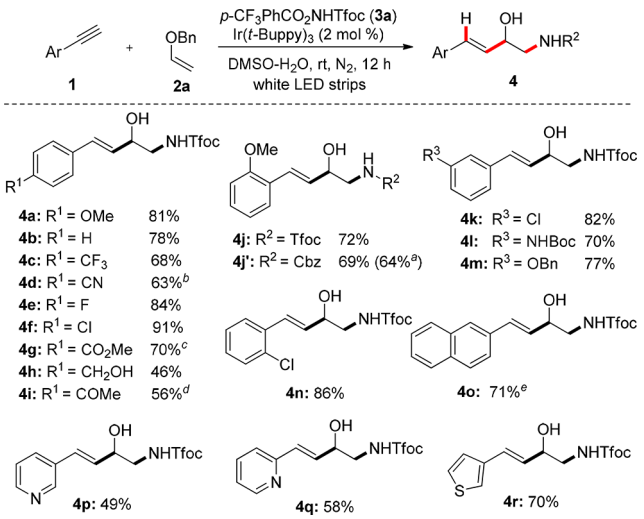


Figure 4. Scope of α-aminomethyl cinnamyl alcohols. Reaction conditions: a solution of **1** (0.2 mmol, 1.0 equiv), **2a** (0.6 mmol, 3 equiv), **3a** (0.6 mmol, 3 equiv), and Ir(*t*-Buppy)$_3$ (0.004 mmol, 2.0 mol %) in a mixture of DMSO (1.8 mL) and H_2O (0.2 mL) was irradiated by white LED strips for 12 h. Isolated yield. *E*/*Z* ratios were determined by ^{1}H NMR spectroscopy of the crude products. Unless otherwise noted, *E*/*Z* > 20:1. [a]The reaction was run on a 6 mmol scale. [b]*E*/*Z* = 7.0:1. [c]*E*/*Z* = 11:1. [d]*E*/*Z* = 3.6:1. [e]*E*/*Z* = 3.3:1.

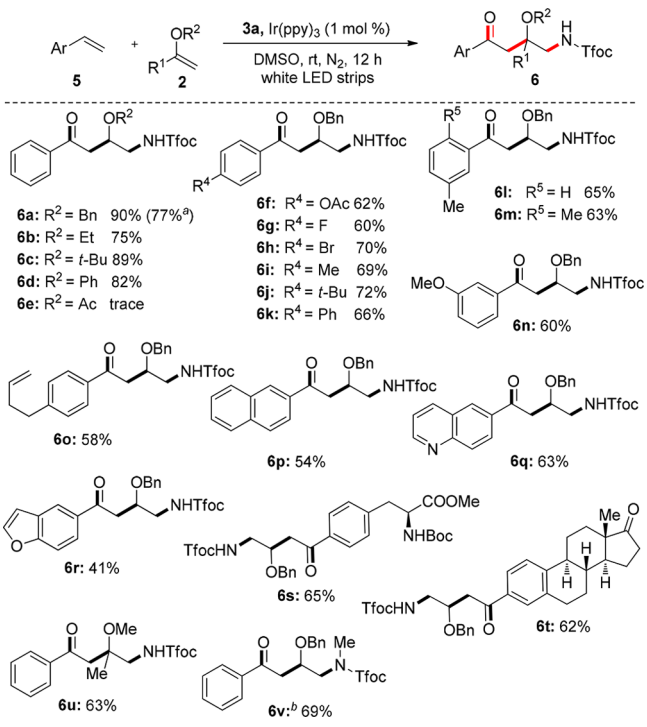
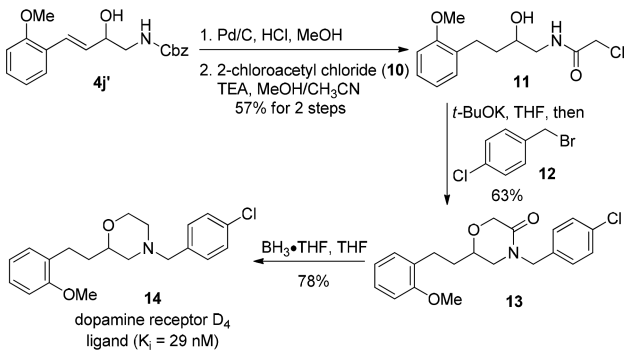


Figure 5. Scope of β-alkoxy-γ-aminoketones. Reaction conditions: a solution of **5** (0.1 mmol, 1.0 equiv), **2** (0.25 mmol, 2.5 equiv), **3a** (0.15 mmol, 1.5 equiv), and Ir(ppy)$_3$ (0.001 mmol, 1.0 mol %) in DMSO (1.0 mL) was irradiated by white LED strips for 12 h. Isolated yield. [a]The reaction was run on a 4 mmol scale. [b]*p*-$CF_3PhCO_2NMeTfoc$ (**3h**) was used instead of **3a**.

isolated in 90% yield. The generality of this reaction was then explored (Figure 5). The reaction was first examined with respect to various vinyl enol ethers, which gave the desired products **6a**-**6e** and **6u** in up to 89% yields. The steric effect of the substituent on the *O*-atom of the vinyl enol ether did not significantly affect this reaction. Vinyl ether **6c** bearing a bulky *tert*-butyl group was converted to the corresponding product in 89% yield. Phenyl vinyl ether also gave **6d** in 82% yield. Disubstituted enol ether was also accommodated in the reaction to give the desired ketone **6u** with a quaternary carbon center in 63% yield. However, the electronic effect had a huge impact on this transformation. Vinyl acetate was not a suitable substrate in this reaction. Encouraged by the successful results of the enol ethers, we explored the scope of the reaction with respect to styrene derivatives. Styrene derivatives bearing both electron-donating and electron-withdrawing groups in the *para* position were well tolerated, giving the corresponding products **6f**−**6k** in good yields (60−72%). *meta*-Substituted styrenes also worked well to give the corresponding products **6l** and **6n** in 65% and 60% yields, respectively. Aliphatic alkenes survived this reaction (58% yield for **6o**). Other aromatic rings, such as naphthalene (**6p**, 54% yield), quinoline (**6q**, 63% yield), and benzofuran (**6r**, 41% yield), also tolerated this reaction. Alkenes derived from biologically important molecules smoothly underwent this transformation to afford the corresponding ketones **6s** and **6t** in 65% and 62% yields, respectively. *N*-Methyl hydroxylamine derivative **3h** furnished *N*-methyl product **6v** in 69% yield. This reaction was easily scaled up to the Gram-scale with a slightly lower isolated yield (77% yield for **6a** on a 4 mmol scale). Aliphatic alkenes failed to undergo this reaction.

The synthetic potential of this method was exemplified by the synthesis of dopamine D4 receptor ligand **14**.[13] As shown in Scheme 1, hydrogenation of α-aminomethyl cinnamyl alcohol **4j'**

Scheme 1. Synthesis of Dopamine Receptor D_4 Ligand



followed by acetylation of the resultant amino alcohol gave hydroxylamide **11** in 57% yield over 2 steps. Intramolecular *O*-alkylation and intermolecular *N*-benzylation delivered amide **13** in 63% yield. Finally, reduction of amide **13** with BH_3 produced the dopamine receptor D_4 ligand **14** in 78% yield.

In summary, we reported a novel radical relay strategy for the synthesis of functionalized β-amino alcohols. This strategy was enabled by photoredox-catalyzed and N-radical-triggered cascade reactions of phenylacetylenes (or styrenes), enol derivatives, and *O*-acyl hydroxylamines in DMSO. The broad synthetic application of this method was demonstrated by the reaction of structurally diverse reaction components, including complex molecular scaffolds. The resultant α-aminomethyl cinnamyl alcohols and β-alkoxy-γ-aminoketones are highly functionalized molecules, which facilitate their further transformations.

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■ ASSOCIATED CONTENT

Supporting Information

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Full experimental and characterization data for all compounds (PDF)

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Notes

The authors declare no competing financial interest.

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