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Communication

Discovery of Oxygen α-Nucleophilic Addition to α,β-Unsaturated Amides Catalyzed by Redox-Neutral Organic Photoreductant

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ABSTRACT: The conjugate additions of oxygen-centered nucleophiles to conjugate acceptors are among the most powerful C−O bond formation reactions. The conjugate addition normally takes place at the β-position carbon to the electron-withdrawing group, resulting in the formation of a stabilized carbanion intermediate that can be quenched by proton or electrophiles to form the β-addition (i.e., hetero-Michael addition) products. On the contrary, the formation of α-hydroxyl or alkoxyl amides through conjugate addition needs an α,β-inverse addition. Nevertheless, a regio-inversed nucleophilic α-addition of oxygen-centered nucleophiles to α,β-unsaturated carbonyl compounds still remains less explored because of the electronic mismatch. In this research, we discovered the first α-specific nucleophilic addition of α,β-unsaturated amides with oxygen and fluoride nucleophiles. This region-inversed nucleophilic addition is enabled by the catalysis of a novel redox-neutral nondonor−acceptor organic photoreductant (**CBZ6**). As low as 0.5 mol % of visible light photoreductant was employed. The mechanistic insights were also explored. The oxidative potential of the excited state of **CBZ6** is obtained in −1.92 V (vs SCE), presenting a stronger reductive potential than representative metal-cored or organic photoredox catalysts. This feature enabled the umpolung of α,β-unsaturated amides to take place α-nucleophilic addition other than the normal β-addition.

The nucleophilic conjugate additions of oxygen-centered nucleophiles to conjugate acceptors are among the most powerful carbon−oxygen bond formation reactions.[1] Such reactions have been the key steps in the syntheses of numerous natural products and pharmaceutically relevant compounds.[2] A conjugate addition reaction involves the addition of a nucleophile to an electron-deficient double or triple bond (Figure 1a). The conjugate addition normally takes place at the β-position carbon to the electron-withdrawing group (EWG), resulting in the formation of a stabilized carbanion intermediate. At this point, the carbanion can be quenched by proton or electrophiles to form the β-addition (hetero-Michael addition) products. Nevertheless, a regioselectivity-reversed nucleophilic addition, namely, α-addition of oxygen-centered nucleophiles to α,β-unsaturated carbonyl compounds still remains less explored because of the electronic mismatch.[3] To our delight, the emergence of visible light-induced photochemical reaction provides an opportunity to introduce functional groups into organic substrates, which could not otherwise be possible owing to the low reactivity or the electronic mismatch, by changing the reaction pathway.[4,5] In our continuing efforts to develop novel and practical oxidation reactions,[6] we found that a novel and general α,β-umpolung strategy by employing a new redox-neutral nondonor−acceptor type organophotocatalyst enables a general regioselectivity-reversed α-specific addition of oxygen-centered nucleophiles (water, alcohol, etc.) or fluorides to α,β-unsaturated amides under mild conditions. This could realize the inversion of reactivity on the α-position of α,β-unsaturated amides from nucleophilic to electrophilic affording α-specific oxygen-substituted quaternary carbon centers. For the first time, a large variety of alcohols,[2] H_2O, D_2O, $H_2{}^{18}O$,[3] and HF,[4]

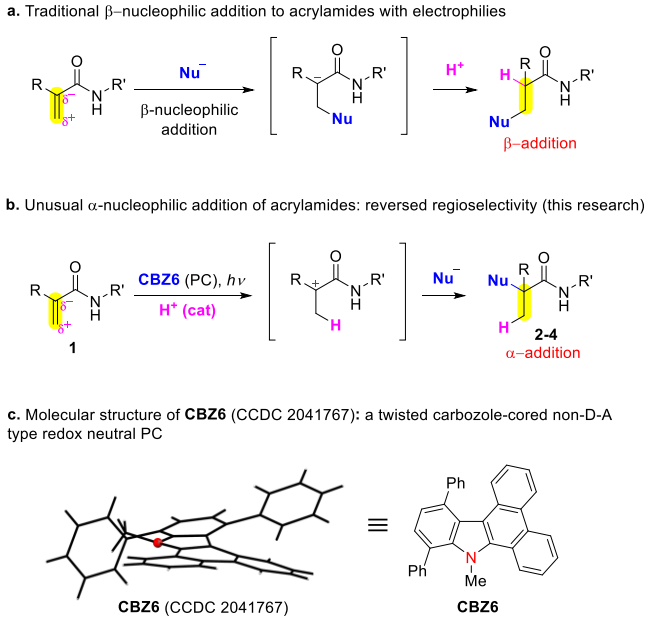

Figure 1. β-Nucleophilic addition reaction to acrylamides (well studied) (a), regioreversed α-nucleophilic oxygenation of acrylamides (this research) (b), and molecular structure of **CBZ6** (CCDC 2041767) (c).

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could be utilized as effective oxygen or fluorine nucleophiles without prefunctionalization (Figure 1b). Here we report our results in detail.

Diphenyldibenzocarbazole **CBZ6**, the photocatalyst (PC) in this research, is a new redox neutral visible light organophotocatalyst bearing six six-membered rings, which is a highly twisted single carbazole-cored nondonor−acceptor type PC. **CBZ6** was readily available from the hydroisoxazole rearrangement and cyclization developed by our group.[7] It could be synthesized in large scale and recyclable after reaction, which illustrates a great advantage as a redox photocatalysis (Figure 2a).

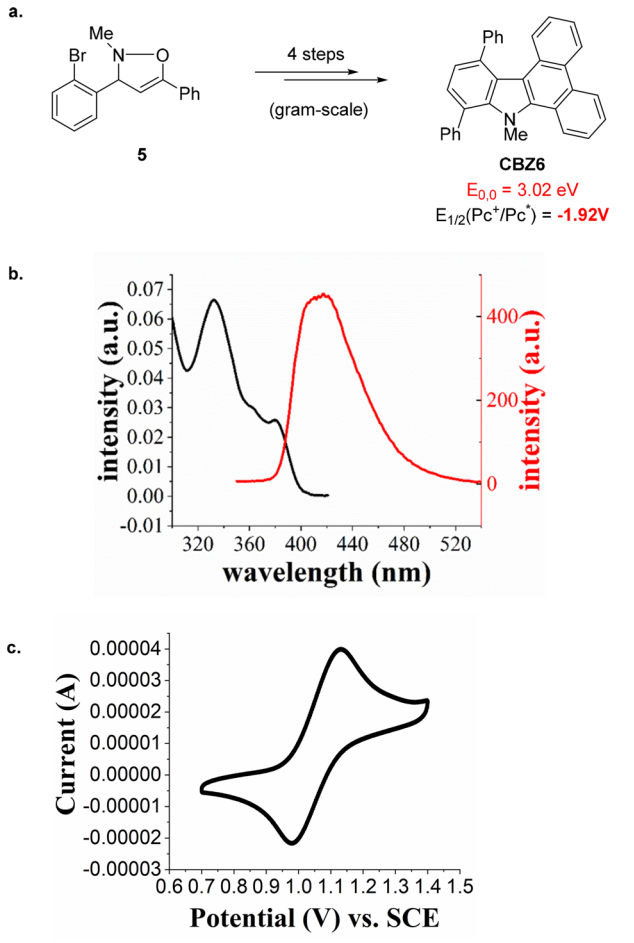

Figure 2. Synthesis of **CBZ6** (a), absorption spectrum (b), and cyclic voltammetry (c).

The excited state energy of **CBZ6** as well as its absorption spectrum and cyclic voltammetry is demonstrated in Figure 2. The energy of the first singlet excited state E_{00} of **CBZ6** is estimated from the position of the long wavelength tail of the absorption spectrum, along with cyclic voltammetry of **CBZ6** (Figure 2). The oxidative potential of the excited state of **CBZ6** is obtained in −1.92 V (vs SCE), presenting a stronger reductive potential than metal-core photoredox catalysts (e.g., $Ru(bpy)_3^{2+}$ −0.87/1.26; $Ir(ppy)_3^{3+}$ −1.73/0.78; etc.) and some organophotocatalyst (**4CzBN** −1.29/1.61; Eosin Y −1.58/2.31; **4DPAIPN** −1.28/1.34; etc.).[8−10] This feature enabled the umpolung of α,β-unsaturated amides to take place α-nucleophilic addition other than the normal β-addition (Figure 3a). The working model is demonstrated in Figure 3b.

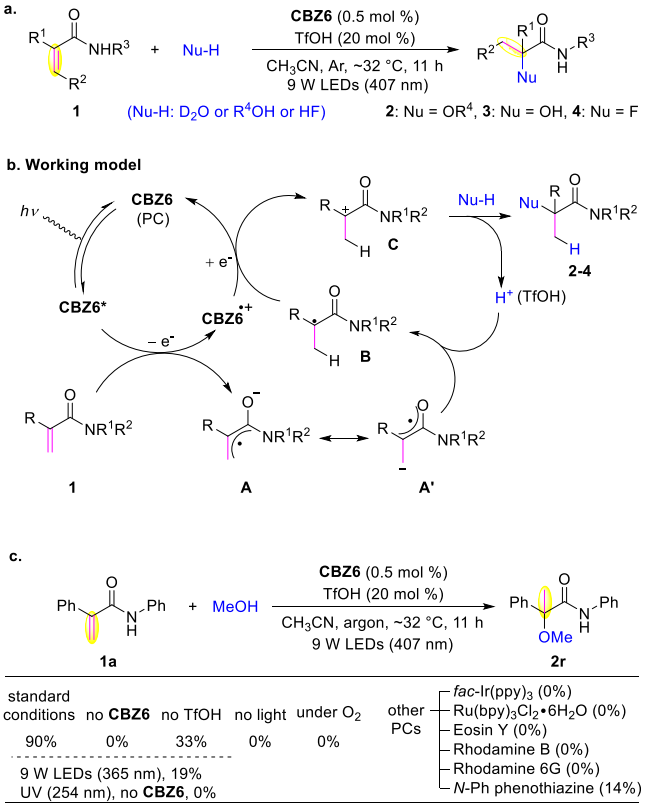

Figure 3. Oxygen and fluorine α-nucleophilic addition to α,β-unsaturated amides catalyzed by **CBZ6** (a), working model (b), and control reactions (c).

Acrylamide **1** catches an electron from exited **CBZ6*** to form radical anion **A** or **A′** along with radical cation of **CBZ6**, followed by protonation to afford radical **B**. The ETOxidation of **B** with the radical cation of **CBZ6** to cation **C**, which can easily be quenched by a nucleophile such as H_2O or alcohol, etc. Consequentially, **CBZ6** returns to the ground state.

In the further study of the nucleophilic α-addition reaction of **1a** with water or MeOH as a nucleophile (Figure 3), **CBZ6** and several common PCs such as *fac*-$Ir(ppy)_3$, $Ru(bpy)_3Cl_2$, Eosin Y, Rhodamine B, and Rhodamine 6G have been investigated, whereas only **CBZ6** (90% yield) was found reactive. Other organic reductants such as *N*-phenylphenothiazine or phenoxazine[9] were found much less reactive and only 14% yield of **2r** was obtained. This redox catalysis involves reduction **1** to **A** and oxidation radical **B** to cation **C**. The strong photoreductants might be able to accomplish the reduction step but probably failed in oxidation step. The failure of metal-core PCs might be due to the instability under acidic conditions. **CBZ6** can be recovered without losing the reactivity whereas $Ir(ppy)_3$ cannot. Standard reaction conditions were then established by using 0.5 mol % of **CBZ6** in the presence of 0.2 equiv of triflic acid in CH_3CN under the irradiation of 9 W LEDs (λ_{max} = 407 nm) (Figure 3c). Control experiments confirm the necessity of all the components for the reaction as no conversion of **1a** was observed in the absence of either **CBZ6** or light irradiation (Figure 3c). The yield of **2r** drops dramatically to 33% in the absence of triflic acid, indicating triflic acid is not necessary but can increase the yields.

With the standard reaction conditions in hand, the scope of substrates was explored (Figure 4). First, various amides were

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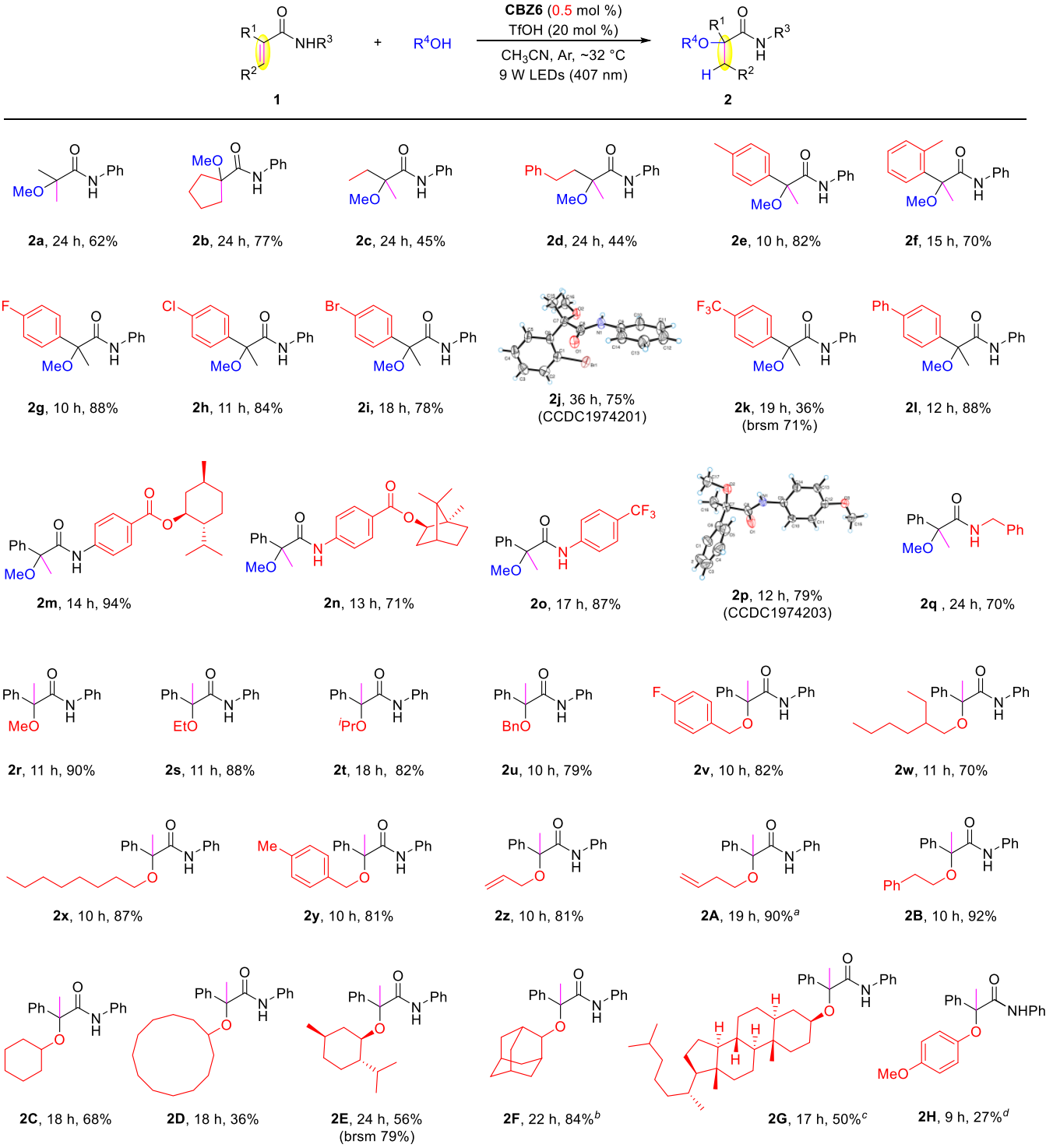

Figure 4. Scope of alcohol for the α-oxygenation of α,β-unsaturated amide. [a]Reaction conditions: **CBZ6** (0.5 mol %), **1** (0.5 mmol), alcohol (5 mmol), TfOH (20 mol %) in 2 mL of CH_3CN, 9 W (3 W × 3) LEDs (407 nm), Ar atmosphere, about 32 °C, isolated yields. Variations to conditions for **2a−2d**: **1** (0.2 mmol), **CBZ6** (5 mol %), TfOH (50 mol %) in 4 mL of MeOH, 18W (3W × 6) LEDs (407 nm). [b]0.5 equiv of TfOH. [b]DCM (4 mL) as solvent. [c]2 equiv of dihydrocholesterol, 0.5 equiv of TfOH and DCM (5 mL) as solvent. [d]**1** (0.2 mmol), **CBZ6** (1 mol %), without TfOH, 18W (3W × 6) LEDs (407 nm).

examined using methanol as an oxygen nucleophile and the corresponding α-methoxyl amides **2a−2l** were obtained in moderate to high yields. α-Aryls are better substituents for stabilizing α-carbon cations; therefore, better yields are achieved from α-aryl substrates. The *N*-substituents of amides were also investigated. Either simple or complex substitutes or even benzyl group are suitable and as high as 94% yields were obtained (**2m−2q**). A wide spectrum of alcohol nucleophiles have been subjected to the standard reaction conditions and all alcohols were found suitable (**2r−2z** and **2A−2G**). Phenol and acetic acid are less reactive nucleophiles under acidic conditions and the corresponding products were obtained in

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low yields. For example, the reaction of 4-methoxylphenol in the absence of TfOH afforded the corresponding product **2H** in 27% yield.

Water was next surveyed as a nucleophile instead of alcohols. Using deuterated water (D_2O) as a nucleophile, the corresponding α-hydroxyl amides (**3a**–**3j**) were obtained in generally high deuterium incorporation (Figure 5). Besides

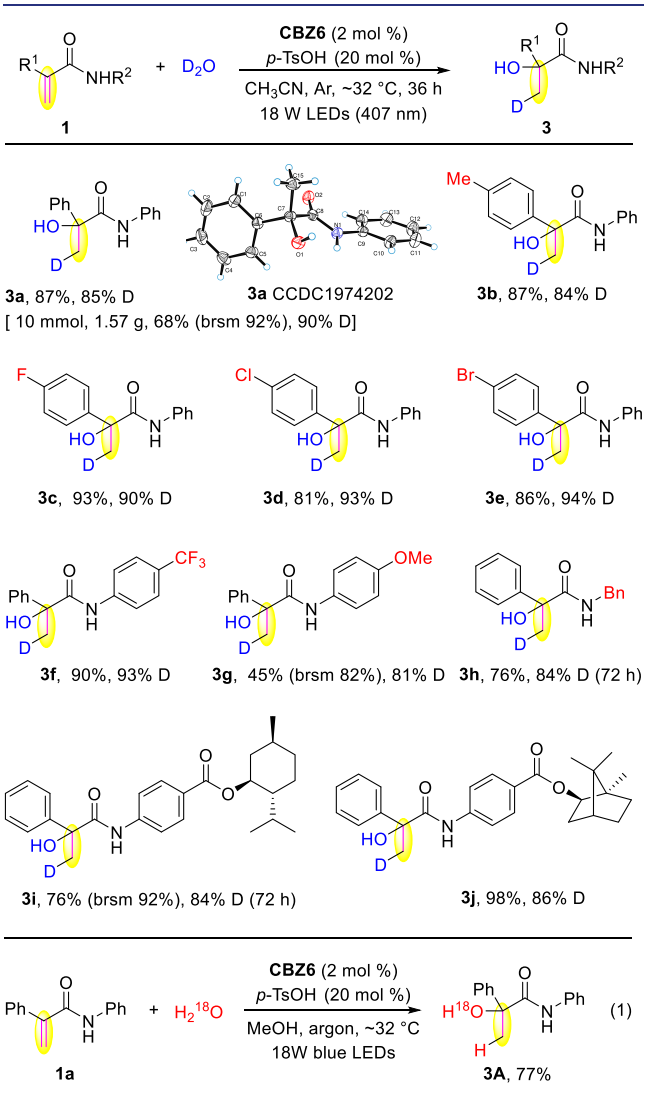

Figure 5. Scope for β-deuterative α-oxygenation of α,β-unsaturated amide. Reaction conditions: **1** (0.5 mmol), D_2O (5 mmol), **CBZ6** (2 mol %), p-TsOH·H_2O (20 mol %) in 2 mL of CH_3CN, 18W (3W × 6) LEDs (407 nm), argon, about 32 °C, isolated yields.

D_2O, $H_2{}^{18}O$ was also tested and the corresponding α-^{18}OH amide **3A** was obtained in 77% yield (eq 1). The α-hydroxyl amides bearing either simple or complex substituents are available. This reaction provides an efficient and practical method for synthesis deuterated hydroxyl amides as well as α-^{18}OH amides.

After establishing oxygen nucleophiles, fluoride was also tested. The halogenation of either electron-rich alkenes with NXS (X = Cl, Br, I) or electron-deficient alkenes with HX (X = Cl, Br, I) has well been established. The analogical fluorination normally involves more hazardous and expensive electrophilic reagents such as diethylaminosulfur trifluoride (DAST), selectfluor, $PhIF_2$, XeF_2, etc. By **CBZ6**-catalyzed nucleophilic functionalization of unsaturated amides, various α-fluoro amides (**4a**–**4h**) can be obtained (Figure 6). This reaction provides a feasible method for α-fluorination of amides.

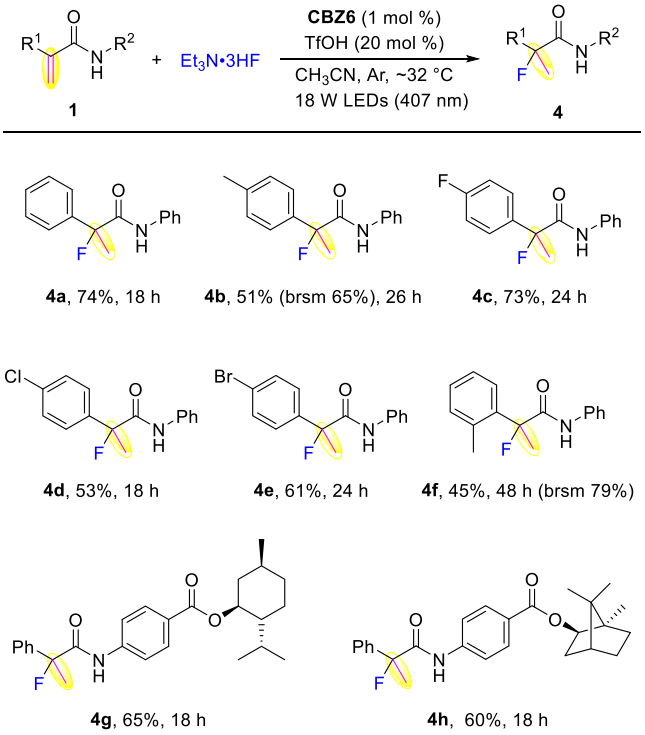

Figure 6. Conditions: **1** (0.5 mmol), 3HF·Et_3N (3 mmol), **CBZ6** (1 mol %), TfOH (20 mol %) in 2 mL of CH_3CN, 3W × 6 LEDs (407 nm), argon, ~32 °C, isolated yields.

Fluorescence quenching experiments of **CBZ6** show the quenching effect with **1a** (Figure 7a). The Stern–Volmer plot indicates that the excited state of the sensitizer was quenched by **1a** and the quenching effect increased with the increase of the concentration of **1a** (Figure 7b).

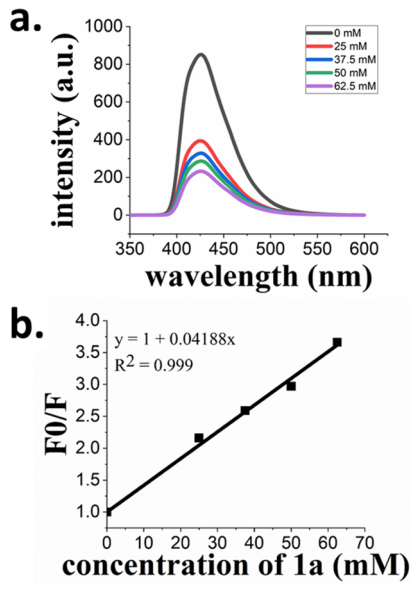

Figure 7. Fluorescence quenching effect (a) and Stern–Volmer plot (b).

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Control experiments were carried out to gain insight into the reaction mechanism. The reaction without of **CBZ6** did not afford the addition product (Figure 8a). The reaction in the

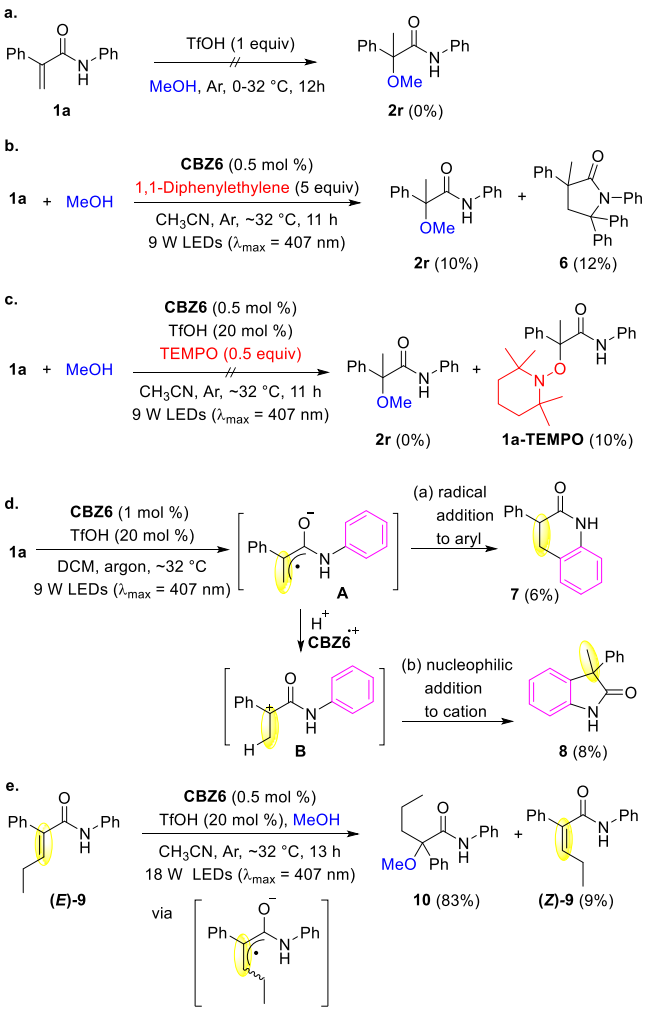

Figure 8. Control experiments.

presence of radical trapping reagents inhibited the reaction (Figure 8b,c). A radical cyclization product **6** from amide **1a** and 1,1-diphenylethene was also observed. The TEMPO trapping adduct was obtained in 10% yield (Figure 8c). In the absence of alcohols, the cyclization product **7** through radical anion **A** was obtained in 6% yield (Figure 8d). In the meantime, an aryl nucleophilic addition product **8** via cation **B** was also obtained (Figure 8d). The isomerization of (*E*)-**9** together with the control reactions demonstrated in Figure 8d and Figure 8b,c are all the evidence for involving radical anion intermediates. Therefore, the working model demonstrated in Figure 3b is rational. The synergistic catalytic role of **CBZ6** as a photoredox catalyst and TfOH as a proton catalyst enabled the α,β-inversed nucleophilic oxygenation and fluorination of α,β-unsaturated amides. **CBZ6** is highly twisted heteroarene. The influence of the geometry to the exited state properties is not clear yet and still under study.

In conclusion, we discovered the first α-specific nucleophilic addition of α,β-unsaturated amides with oxygen and fluoride nucleophiles. This region-inversed nucleophilic addition is enabled by the catalysis of a novel redox-neutral non-donor–acceptor organic photoreductant (**CBZ6**). By employing as low as 0.5 mol % photoreductant, the corresponding α-hydroxyl amides and α-alkoxyl amides were obtained in up to 94% yields under the standard reaction conditions and more than 50 examples have been presented. Besides α-oxygenation products, α-fluoro amides could also be achieved. The mechanistic insights based on experimental evidence were also explored. The oxidative potential of the excited state of **CBZ6** is obtained in −1.92 V (vs SCE), presenting a stronger reductive potential than representative metal-cored and other organic photoredox catalysts. This feature enabled the umpolung of α,β-unsaturated amides to take place α-nucleophilic addition other than the normal β-addition.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/jacs.0c10707.

Experimental procedures, tables of conditions, chemical structures and characterization data, UV–vis absorption spectrum, fluorescence spectra, and luminescence quenching experiments, CV, molecular structures, crystal data, and NMR spectra (PDF)

Crystal data for **2j** (CIF)

Crystal data for **2p** (CIF)

Crystal data for **3a** (CIF)

Crystal data for **CBZ6** (CIF)

Crystal data for **CBZ6** (PDF)

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Notes

The authors declare no competing financial interest.

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