

Photoredox-Catalyzed Labeling of Hydroxyindoles with Chemoselectivity (PhotoCLIC) for Site-Specific Protein Bioconjugation

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Abstract: We have developed a novel visible light-catalyzed bioconjugation reaction, PhotoCLIC, that enables chemoselective attachment of diverse aromatic amine reagents onto a site-specifically installed 5-hydroxytryptophan residue (5HTP) on full-length proteins of varied complexity. The reaction uses catalytic amounts of methylene blue and blue/red light-emitting diodes (455/650nm) for rapid site-specific protein bioconjugation. Characterization of the PhotoCLIC product reveals a unique structure formed likely through a singlet oxygen-dependent modification of 5HTP. PhotoCLIC has a wide substrate scope and its compatibility with strain-promoted azide-alkyne click reaction, enables site-specific dual-labeling of a target protein.

Visible light-enabled photoredox catalysis has experienced a renaissance in the last decade, spawning countless innovative strategies to unlock novel reactivities.^[1] Photoredox catalysis has been leveraged to develop novel bioconjugation strategies targeting specific canonical amino acid residues, as well as the termini of peptides and proteins.^[2] However, there are several challenges limiting their practical utility in protein bioconjugation. These include incomplete conversion of full-length folded proteins, an intrinsic lack of control over site and stoichiometry of protein labeling, and off-target reactivity. Development of an efficient and chemoselective photoredox catalyzed reaction that can generate functional site-specific protein conjugates under mild conditions will be a valuable addition in the bioconjugation toolbox.^[3]

To develop such a strategy that is unconstrained by site restrictions, we sought to take advantage of the noncanonical amino acid (ncAA) mutagenesis technology.^[4] We hypothesized that targeting a chemically unique ncAA will provide a logical path for developing a chemoselective photoredox-catalyzed conjugation reaction. We recently engineered the EcTrpRS/tRNA pair to genetically encode 5HTP in both prokaryotes and eukaryotes.^[5] This aromatic ncAA is significantly more electron-rich than its canonical counterparts, which renders it with strong π -nucleophilicity, as well as highly susceptibility to oxidation. We have previously leveraged these unique chemical features to develop two different chemoselective strategies to label 5HTP: A rapid azo-coupling reaction (CRACR),^[6] and an oxidative cross-

coupling reaction.^[7] We thought that the same features may also enable the development of a chemoselective photoredox-catalyzed bioconjugation reaction targeting 5HTP (Figure S1).

To explore this possibility, we expressed the superfolder green fluorescent protein incorporating the 5HTP residue at the surface-exposed 151 site (sfGFP-151-5HTP; Figure S2),^[5] and used it to screen numerous reaction conditions. Whole-protein mass-spectrometry was used to monitor protein labeling. As a control for each reaction, we also tested the wild-type (WT) sfGFP protein in parallel, which contain a tyrosine residue at site 151, instead of 5HTP (Figure S3). Reaction conditions that led to the selective modification of sfGFP-151-5HTP, but not the nearly identical WT-sfGFP, were pursued further for optimization.

From these experiments (Figure S4), we found that sfGFP-151-5HTP (10 μ M; MW: 27636 Da) efficiently forms a stable conjugate with 4-aminophenylacetic acid (**1**, 4 mM), when irradiated with blue light (455 nm, 7 W), in the presence of catalytic amounts of methylene blue (Figure 1A, *optimized conditions* and Figure S5). The labeled product showed a mass of 27799 Da, consistent with the addition of **1** (+151 Da) accompanied by further oxidation (+12 Da). Under identical conditions, the WT-sfGFP did not form a similar adduct with **1**, indicating chemoselectivity (Figure 1B, Figure S6). The site-specificity of PhotoCLIC protein labeling was further substantiated by subjecting the conjugation product of sfGFP-151-5HTP and **1** to tryptic digestion followed by sensitive HPLC-coupled MS-MS analysis (Figure S7). The PhotoCLIC reaction strictly requires light and oxygen (Entry 2-3, Figure 1A). The optimized reaction conditions show little to none off-target protein oxidation (cf. Figure S8-S9). The conjugation reaction can be stopped and restarted by turning the light off and back on, respectively (Figure S10). Performing the reaction in separate but parallel reaction vessels enabled protein labelling on milligram scale (~1.1 mg sfGFP-151-5HTP) with >95% conversion.

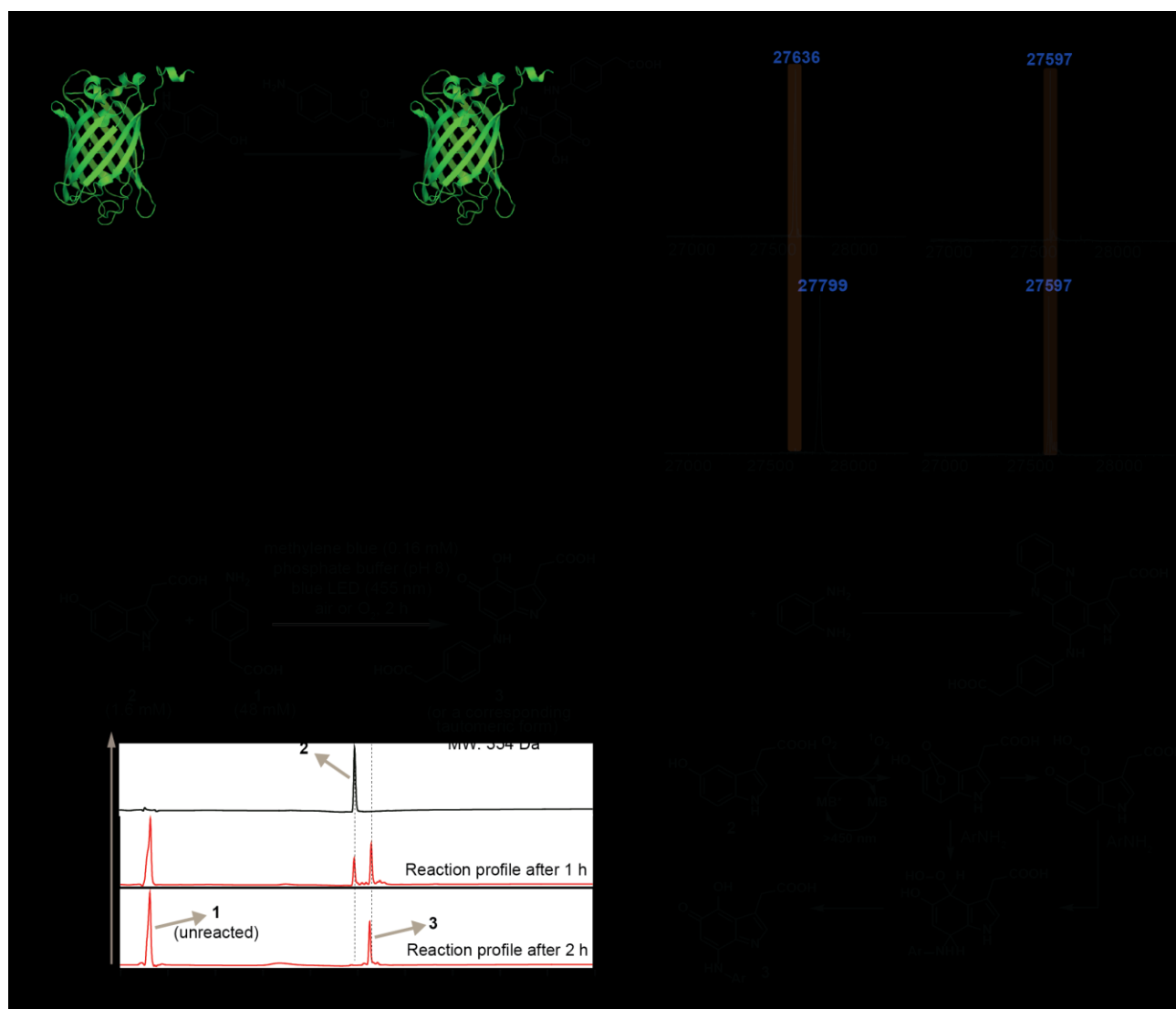


Figure 1. (A) Optimized PhotoCLIC conditions and necessary elements of the optimization (Entries 1-9). ^aconversion to product (%) assessed by whole-protein MS analysis. ^bReaction time was 45 min. ^cProduct MS shows off-target oxidation, ^dProduct MS shows pronounced off-target oxidation. (B) ESI-MS of sfGFP-151-5HTP labeled with **1** under the optimized PhotoCLIC conditions; no labeling was observed for the wild-type sfGFP control under identical conditions. (C) LC-MS analysis of the PhotoCLIC reaction modeled at the small-molecule level; chemical derivatization studies of **3** shown in (D). **3** may exist in different tautomeric forms; A_{254} represents absorbance at 254 nm. (E) Plausible mechanism for the formation of **3**; MB: methylene blue

To elucidate the structure of the PhotoCLIC product, we modelled this reaction using 5-hydroxyindoleacetic acid (5HIAA; **2**) and **1**. (Figure 1C). Liquid chromatography-coupled MS (LC-MS) of the reaction mixture revealed a product mass of 354 Da, corroborating the observations with sfGFP-151-5HTP PhotoCLIC reaction. We used a combination of NMR spectroscopy, MS and chemical derivatization (Figure 1D) to deduce the structure of this adduct **3** (Figure S11). Mechanistically, the formation of the product **3** can be explained through a possible endoperoxide intermediate (Figure 1E and Figure S12); similar endoperoxide species have been implicated in several reactions involving electron rich aromatic groups and oxygen under photochemical conditions.^{[21], [8]} Analogous photocatalytic reactions involving singlet oxygen have also been used for proximity-dependent interactome profiling.^{[21], [9]} Although methylene blue is known to cause nonspecific protein oxidation through light-dependent

production of reactive oxygen species,^[10] our optimized reaction conditions minimized such off-target oxidation.

A number of different primary aniline derivatives (**4-9**, Figure 2) were found to conjugate efficiently to sfGFP-151-5HTP under the optimized PhotoCLIC condition to generate clean monolabeled products (Figure 2, Figure S13). As expected, these aniline derivatives failed to label WT-sfGFP under identical conditions (Figure S14). We also expressed four additional proteins harboring a 5HTP residue at a surface-exposed site: myoglobin, nanoluciferase, anti-HER2-nanobody,^[11] and a full-length humanized antibody Trastuzumab with 5HTP at 198 residue of heavy chain (HC). Treatment with the biotin-aniline **9** under PhotoCLIC conditions resulted in efficient single-labeling of each protein (Figure 3), but not the corresponding wild-type proteins (Figure S15). Anti-biotin Western blot analysis was used to further confirm specific labeling of the HC of Trastuzumab-HC-198-5HTP (Figure S16).

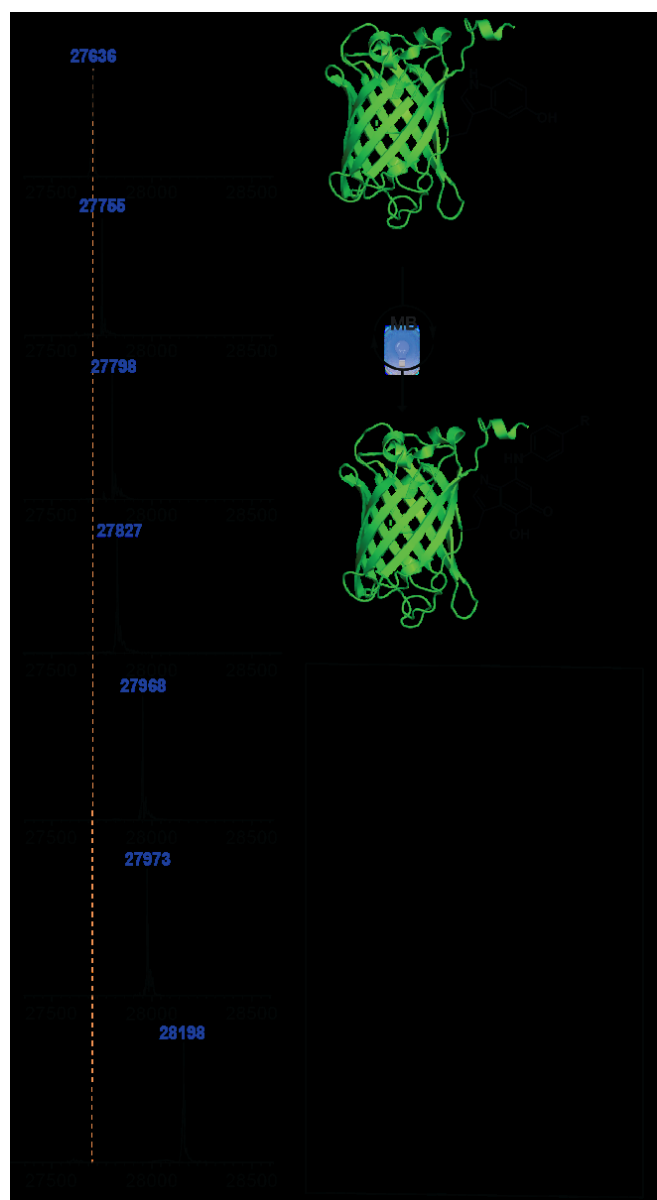


Figure 2. PhotoCLIC labeling of sfGFP-151-5HTP with different aniline derivatives (**4-9**); under the identical conditions WT-sfGFP showed no labelling with **4-9** (Figure S12); MB: methylene blue

Next we explored the use of PhotoCLIC for the preparation of fluorescently labeled affinity reagents, such as antibodies and nanobodies, which are useful for diverse applications.^[4b] The anti-HER2-nanobody-69-5HTP (Figure 4A-B) as well as sfGFP-151-5HTP (Figure S17) were found to cleanly conjugate with aromatic amine containing fluorescein reagents, as shown by MS analysis and SDS-PAGE followed by fluorescence imaging (Figure S17-S18). Corresponding reaction with the wild-type nanobody showed no labeling (Figure 4A-B and Figure S18). This fluorescently labeled nanobody stained the HER2-overexpressing SK-BR-3 cell line, as evidenced by fluorescence-activated cell-sorting (FACS) (Figure 4C), confirming that the conjugate remained functional.

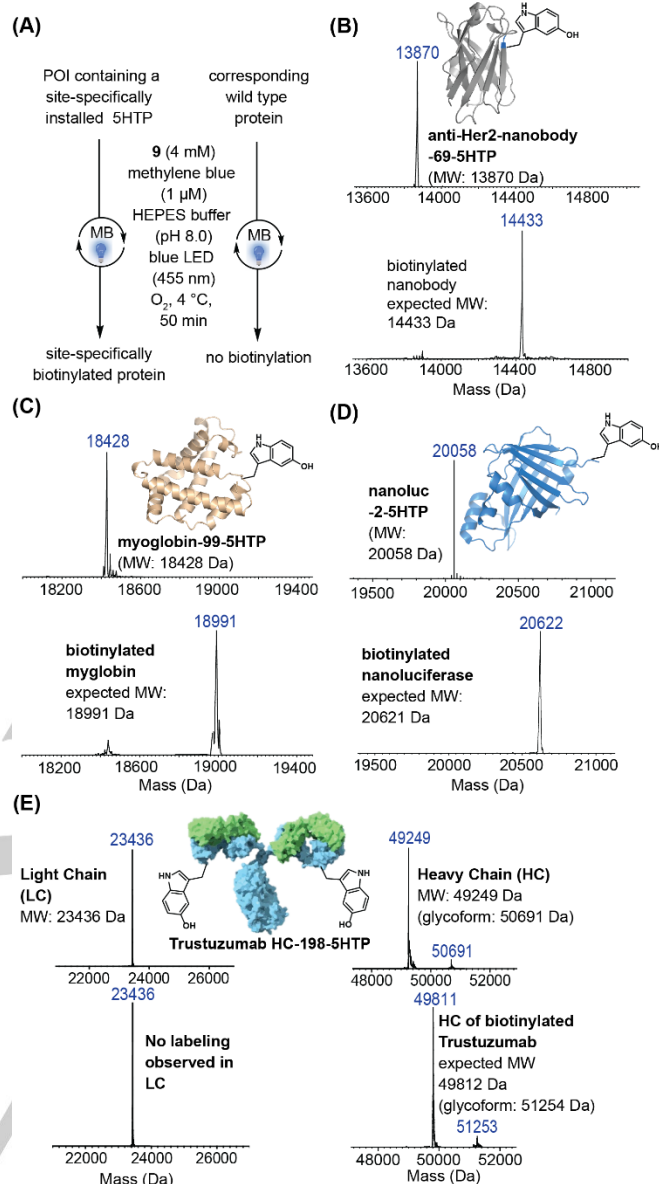


Figure 3. (A) PhotoCLIC enables hydroxyindole-selective biotinylation (using **9**) of different proteins of interest (POI): (B) anti-HER2-nanobody-69-5HTP, (C) myoglobin-99-5HTP, (D) nanoluciferase-2-5HTP and (E) full length Trustuzumab having HC-198-5HTP. Corresponding wild type proteins (lacking 5HTP) showed no labelling under otherwise identical conditions (Figure S13). For unlabeled and labeled Trustuzumab, LC-MS was done after reductive separation of HC and LC followed by PNGase F digestion to remove the glycan PTM on N297 of HC.

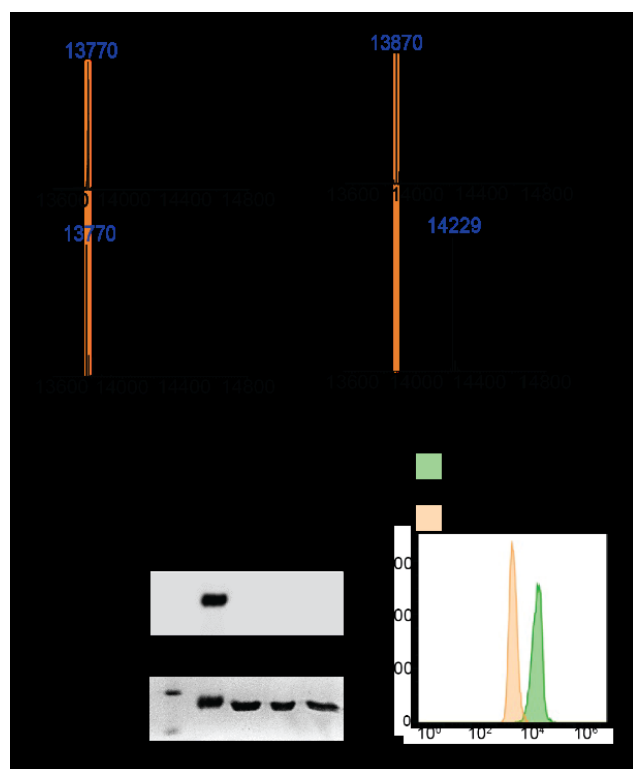


Figure 4. (A) Fluorophore labeling of anti-Her2 nanobody using PhotoCLIC. MS analysis demonstrates selective labeling of anti-Her2-nanobody-69-5HTP with 5-aminofluorescein, while the corresponding wild-type protein remains unreacted upon identical treatment. (B) SDS-PAGE followed by fluorescence imaging shows PhotoCLIC-mediated fluorophore labeling of anti-Her2-nanobody-69-5HTP, but not the corresponding wild-type protein under identical conditions. (C) FACS analysis demonstrating successful staining of SK-BR-3 cells by fluorophore-labeled anti-Her2-nanobody.

Precise labeling of a protein with multiple distinct cargo at predefined sites is an emerging technology with countless potential applications.^[12] This technology relies on access to conjugation chemistries that are mutually compatible. We surmised that PhotoCLIC could be compatible with the strain-promoted azide-alkyne cycloaddition reaction (SPAAC),^[13] one of the most popular bioorthogonal conjugation reactions for site-specifically labeling proteins. To test this notion, we generated a sfGFP reporter protein, where site 3 and 151 harbors two distinct ncAAs, 5HTP and AzK, respectively (sfGFP-3-5HTP-151-AzK).^[12b] Treatment of sfGFP-3-5HTP-151-AzK first with BCN alcohol, then PhotoCLIC reaction with **1** led to efficient formation of cleanly dual-labeled protein (Figure 5, Figure S19).

In conclusion, we have developed a novel visible light-promoted method to site-specifically label proteins at 5HTP residues. It represents a rare example an oxidative bioconjugation reaction enabling site-specific labeling of proteins of diverse complexity using long-wavelength light.^[14] 5HTP can be readily introduced into a chosen site of any recombinant protein using the nonsense suppression technology, both in prokaryotic and eukaryotic host cells. Using similar technology, it has been possible to express therapeutically relevant proteins in

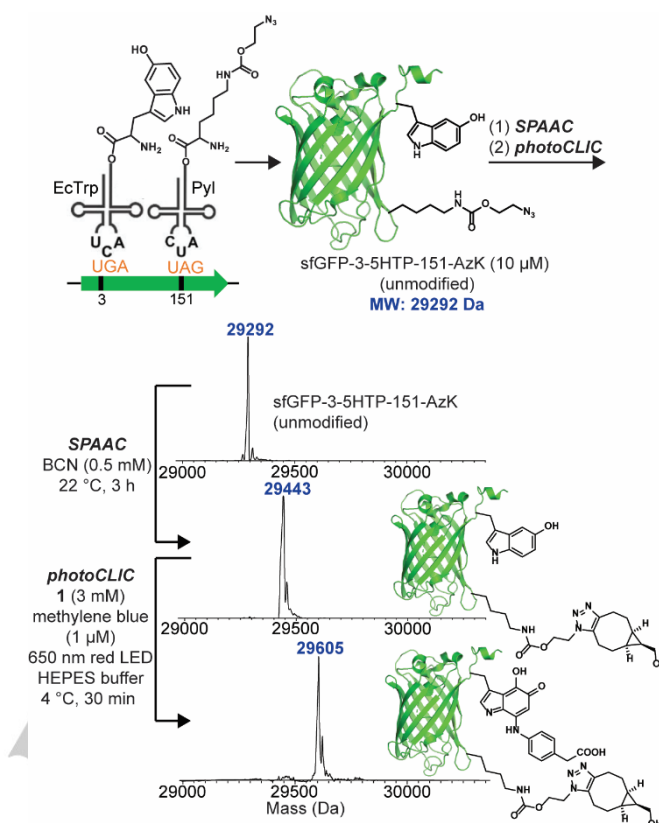


Figure 5. An sfGFP with site-3 mutated to 5HTP and site 151 mutated to AzK (sfGFP-3-5HTP-151-AzK) was recombinantly expressed in *E. coli* using our dual nonsense suppression technology. Sequential double modification of the resulting protein, first using SPAAC followed by PhotoCLIC, demonstrated by whole-protein MS analysis.

commercial scale (grams/L).^[15] Both 5HTP and primary anilines are drastically less expensive relative to other common click chemistry reagents. Furthermore, 5HTP can be biosynthetically generated in the cell, completely obviating the need of exogenous supply.^[16] Although a few other photo-induced bioconjugation reactions have been reported for similarly labeling a genetically encoded ncAA with chemoselectivity, these typically require irradiation in the UV region (<400 nm).^[17] In contrast, PhotoCLIC is the first example of a visible light promoted (up to 650 nm) chemoselective modification of a site-specifically incorporated ncAA. Taken together, PhotoCLIC offers a novel chemoselective conjugation strategy which would find numerous applications from biotechnology to material science.

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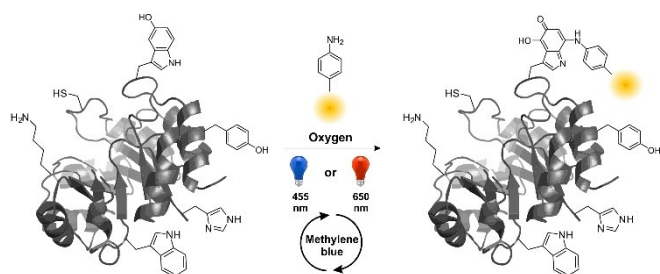
Notes

A patent application has been submitted on the PhotoCLIC strategy for bioconjugation. A.C. is a cofounder and advisor at BrickBio, Inc.

Keywords: photoredox catalysis • bioconjugation • protein labeling • chemoselectivity

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Entry for the Table of Contents



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A novel visible light-catalyzed bioconjugation reaction, PhotoCLIC, has been developed for chemoselective attachment of aromatic amines onto a 5-hydroxytryptophan (5HTP) residue site-specifically preinstalled in a full-length protein using genetic code expansion technology. PhotoCLIC has a wide substrate scope and is compatible with the strain-promoted azide-alkyne cycloaddition to enable site-specific dual-labeling of target proteins

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