RESEARCH ARTICLE

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In situ Generation of Quinoliziniums for Dual Visible Light-induced Gold(III)-catalyzed Alkynylation and Peptide Modification

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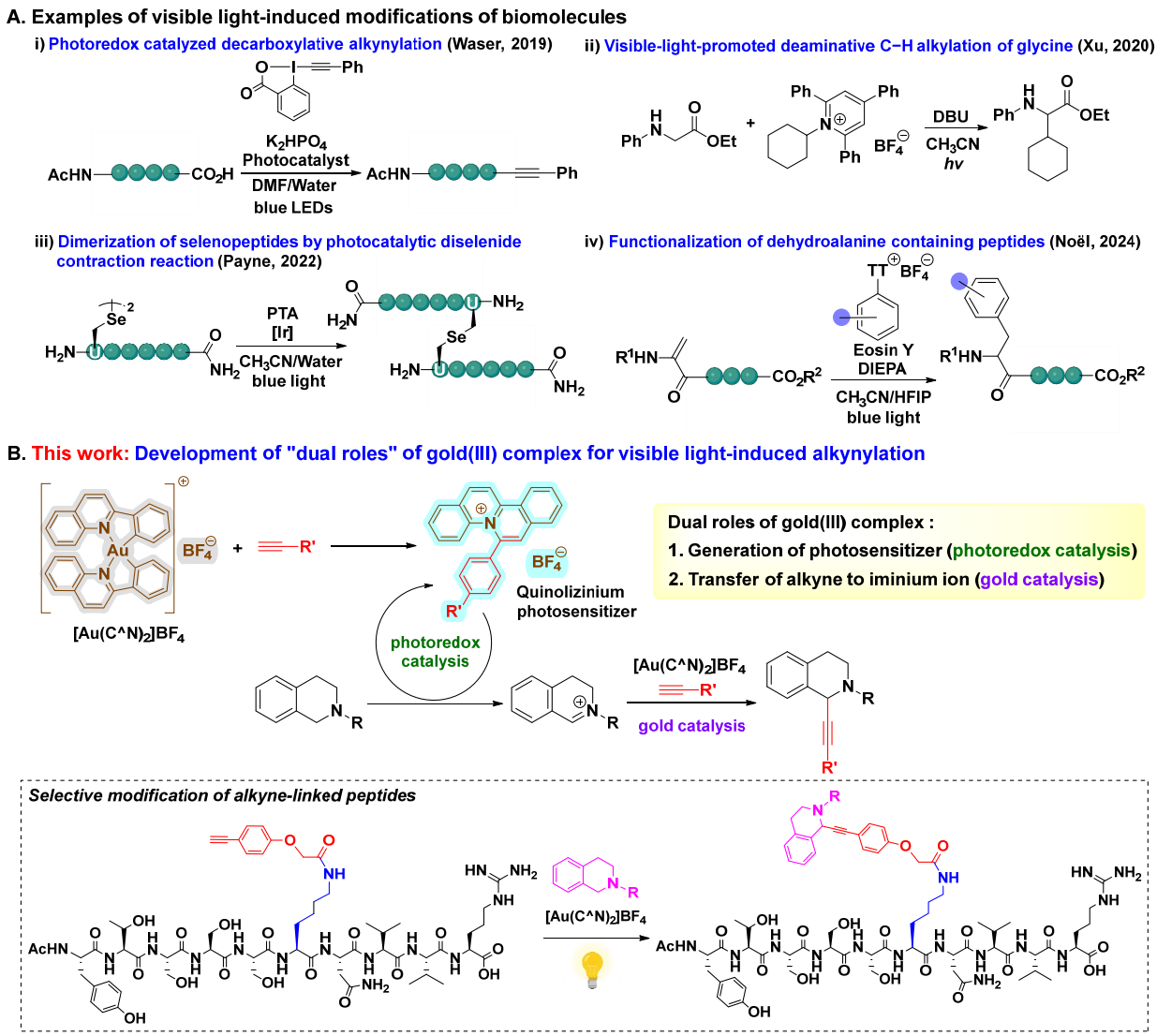
Abstract. A new approach of dual visible light-induced gold(III)-catalyzed alkynylation and its application in selective modification of alkyne-linked peptides has been developed. The bis-cyclometalated gold(III) complex exhibited dual roles of (1) *in situ* generation of quinolizinium-based photosensitizer (λ_{em} = 500 – 594 nm) and (2) alkynylation of iminium ions. Under optimized conditions, alkynylated products were afforded in good yields up to 73%. The application of this strategy in selective modification of alkyne-linked peptides gave modified peptides in up to 67% conversion. Our dual visible light/gold(III) catalysis exemplifies the potential of merging photocatalysis and transition metal catalysis to develop novel bioconjugation.

Keywords: Gold catalysis; Visible light photoredox catalysis; Gold(III) complexes; Alkynylation; Quinolizinium; Bioconjugation

Introduction

Chemical modification of biomolecules has become an essential synthetic tool for the construction of novel bioconjugates for biological studies and drug discovery.[1] The advancement of bioconjugation technologies allows the installation of functional moieties (e.g. drugs, fluorophores, affinity tags) in peptides and proteins, which has substantially contributed to the development of targeted cancer therapy,[2] tissue engineering,[3] vaccine,[4] and molecular imaging.[5] These novel applications benefited by bioconjugation are however limited by their intrinsic stringent requirements of high reaction efficiency, excellent selectivity and mild aqueous reaction conditions.[6] Therefore, it is of ongoing interest on the development of efficient approaches for selective modification of biomolecules.

Transition metal-mediated reactions have emerged as useful methods for bioconjugation owing to their unique reactivity, high selectivity and good functional group compatibility.[7] The rational choice of metal ions and ligands allowed the extension of these reactions to selective modification of biomolecules.[8-10] A wide range of efficient transition metal-mediated bioconjugation strategies have been reported in the past decades, such as rhodium-catalyzed tryptophan[11-12] and cysteine[13] modifications, iridium-promoted lysine[10a] and phenylaniline[14] modifications, as well as gold[15-21] and palladium-mediated[22-25] modifications of cysteine and lysine. In particular, the use of gold(III) complexes in bioconjugation has received much attention in recent years.[26] In 2014, we first reported the use of cyclometalated gold(III) C^N complexes for cysteine modification through C–S bond formation by reductive elimination.[15a] With excellent reactivity and good compatibility in aqueous reaction medium, various approaches of chemoselective arylation at cysteine and lysine using organometallic gold(III) complexes have been also



Scheme 1. Our strategy of dual visible light-induced gold(III)-catalyzed alkynylation and peptide modification.

reported.[15b,16-21] Given these advancements, the use of gold(III) complexes as effective catalysts for selective modification of biomolecules is worth further exploring.

Visible light photoredox catalysis has become a powerful strategy for novel transformations in organic synthesis.[27] The study of transition metal complexes in photocatalysis have been extensively explored in literatures.[28] In particular, the application of gold complexes in photocatalysis takes advantage of the valence change of the gold center by electron transfer and radical addition, which eliminates the need for exogenous oxidants.[29] With the use of mononuclear gold(I), dinuclear gold(I) and gold(III) complexes, versatile strategies for novel visible light-induced organic transformations have been developed.[30-35]

Compared to traditional catalytic strategies, photoredox catalysis allows activation of organic substrates under mild reaction conditions at ambient temperature with the use of visible light as a sustainable source of energy, which offers high biocompatibility with less damage to biomolecules compared to UV light.[36] Therefore, different photocatalytic strategies have been applied to selective modification of peptides and proteins (Scheme 1A).[37-49] Moreover, the use of a combination of photoredox and transition metal catalysis have also been reported, which offers alternative selectivity for direct modifications of unreactive and aliphatic amino acids.[50-52] With the recent advances of the dual photoredox catalysis with transition metal catalysis, the development of new dual catalysis for selective modification of biomolecules is of great importance.

N-Aryl-substituted tetrahydroisoquinoline (THIQ) is a privileged structure in medicinal chemistry due to its wide range of bioactivities and pharmacological properties,[53-54] in which the synthetic strategies for α-functionalization of THIQ have been widely explored through cross-dehydrogenative coupling reactions

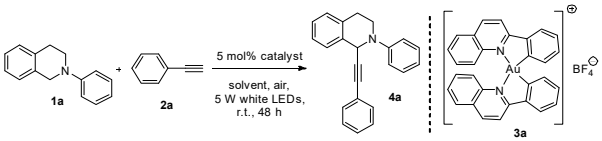
(CDC) and visible light photoredox catalysis.[27d,55-62] The CDC reaction of THIQ with alkynes through a dual photoredox/transition metal catalysis using $[Ru(bpy)_2(dtbbpy)](PF_6)_2$ and $(MeCN)_4CuPF_6$ has been previously reported by Rueping *et al.* , which allowed efficient formation of alkynylated products under mild conditions.[56] Although these transformations have been extensively studied in organic synthesis, investigation on their applicability in peptide modification has been rarely explored. Given the intrinsic advantages provided by the combination of photoredox catalysis and transition metal catalysis, we are interested in developing a single catalyst capable of performing dual catalysis. Along with our ongoing interest in gold-catalyzed organic transformations and the development of bioconjugation reactions,[15] herein we report a new approach of dual visible light-induced gold(III)-catalyzed alkynylation of tetrahydroisoquinolines and its application in selective modification of alkyne-linked peptides (Scheme 1B).

In this work, visible light-mediated CDC reaction of tetrahydroisoquinolines **1** with terminal alkynes **2** is achieved by using bis-cyclometalated gold(III) complex $[Au(C^N)_2]BF_4$ **3a** (HC^N = 2-phenylquinoline) as an effective catalyst under mild reaction conditions. The bis-cyclometalated gold(III) complex **3a** plays two roles in the CDC reaction, resulting in dual visible light/gold(III) catalysis. A quinolizinium-based photosensitizer is generated *in situ* by the reaction between **3a** and terminal alkynes to oxidize tetrahydroisoquinolines **1**, while **3a** itself functions as the effective catalyst to activate the terminal alkynes for alkynylation. This newly developed visible light-induced gold(III)-catalyzed alkynylation could achieve selective modification of alkyne-linked peptides.

Results and Discussion

To begin our study, a model reaction was conducted by treatment of N-phenyl-1,2,3,4-tetrahydroisoquinoline **1a** (0.1 mmol) and phenylacetylene **2a** (5 equiv.) with $[Au(C^N)_2]BF_4$ **3a** (5 mol%) as catalyst under irradiation of 5 W white LEDs for 24 h under air at room temperature. Alkynylated product **4a** was obtained in 22% isolated yield (Table 1, entry 1). Increasing the reaction time to 48 h and 72 h gave higher yields of 60% and 62%, respectively (entries 2-3). Using **3a** as the metal catalyst, the reaction could also be performed in CH_3CN, CH_3OH and H_2O (entries 4-6). Control experiment under N_2 or in dark gave no product, suggesting that visible light and oxygen played key roles in the reaction (entries 7-8). Further screening of different catalysts, including $[Au(bpy)Cl_2]$ (Hbpy = 2-benzylpyridine), $KAuCl_4$, AuCl, $Cu(OTf)_2$, $Zn(OTf)_2$, $Ru(bpy)_3Cl_2$ and $Ru(bpy)_3Cl_2$/CuI, gave lower yields (up to 41% yield) or no product formation (entries 9-15). Overall, the reaction conditions of treating 1 equivalent of **1a** and 5 equivalents of **2a** in CH_2Cl_2 under 5 W white LEDs for 48 h under air at room temperature were used for the subsequent studies.

Table 1. Optimization of reaction conditions.[a]



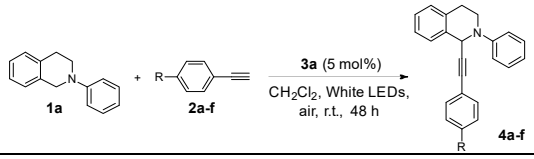
Entry	Catalyst	Light	Air /N_2	Sol-vent	Yield [%][b]
1[c]	**3a**	White	Air	CH_2Cl_2	22
2	**3a**	White	Air	CH_2Cl_2	60
3[d]	**3a**	White	Air	CH_2Cl_2	62
4	**3a**	White	Air	CH_3OH	54
5	**3a**	White	Air	H_2O	45
6	**3a**	White	Air	CH_3CN	44
7	**3a**	White	N_2	CH_2Cl_2	0
8	**3a**	-	Air	CH_2Cl_2	0
9	$[Au(bpy)Cl_2]$	White	Air	CH_2Cl_2	30
10	$KAuCl_4$	White	Air	CH_2Cl_2	30
11	AuCl	White	Air	CH_2Cl_2	41
12	$Cu(OTf)_2$	White	Air	CH_2Cl_2	23
13	$Zn(OTf)_2$	White	Air	CH_2Cl_2	0
14	$Ru(bpy)_3Cl_2$	White	Air	CH_2Cl_2	0
15	$Ru(bpy)_3Cl_2$/ CuI	White	Air	CH_2Cl_2	26

[a] Reaction conditions: treatment of **1a** (0.1 mmol), **2a** (5 equiv.) with catalyst (5 mol%) in 2 mL of CH_2Cl_2 under irradiation and air at room temperature for 48 h.
[b] Isolated yield.
[c] The reaction was performed for 24 h.
[d] The reaction was performed for 72 h.

We further explored the substrate scope of this reaction by treatment of substrate **1a** with various terminal alkynes **2b-f** (Table 2). The reaction was compatible with alkynes bearing different substituents, giving the formation of **4b-e** in moderate to good yields between 31 and 73%, in which more favorable formation of alkynylated product **4b** was found with electron donating 4-ethynylanisole **2b** (entries 2-5). Alkyne **2f** bearing an amine as substituent gave no production formation (entry 6).

As the light source was important for this transformation and the bis-cyclometalated gold(III) complex $[Au(C^N)_2]BF_4$ **3a** was non-emissive, we hypothesized that a photosensitizer was generated *in situ* in the reaction. To provide insight on this transformation, we used 2-(4-methoxyphenyl)-1,2,3,4-tetrahydroisoquinoline **1b** and 4-ethynylanisole **2b** for the visible light-mediated

Table 2. Optimization of reaction conditions.[a]



En-try	1	Terminal Alkynes 2		Product 4	Yield [%][b]
		2	R		
1	1a	2a	H	4a	60
2	1a	2b	OMe	4b	73
3	1a	2c	F	4c	36
4	1a	2d	CF_3	4d	31
5	1a	2e	CN	4e	40
6	1a	2f	NH_2	4f	0

[a] Reaction conditions: treatment of **1a** (0.1 mmol), **2a-f** (0.5 mmol, 5 equiv.) with **3a** (5 mol%) in 2 mL of CH_2Cl_2 under irradiation of white LEDs and air at room temperature for 48 h.
[b] Isolated yield.

alkynylation. The crude reaction mixture was analyzed by HRMS after 2 h. MS spectra showed the presence of iminium ion **1b'** (*m/z* 238.12) as the key reaction intermediate and the resulting alkynylated product **4g** (*m/z* 370.18) in the reaction. Moreover, we observed the possible formation of quinolizinium **5b** (*m/z* 336.14).

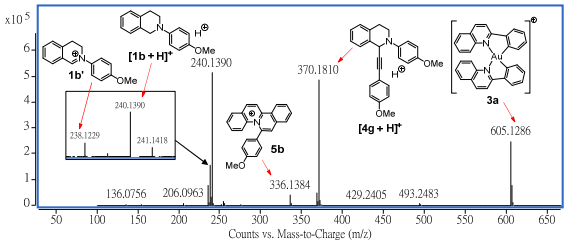
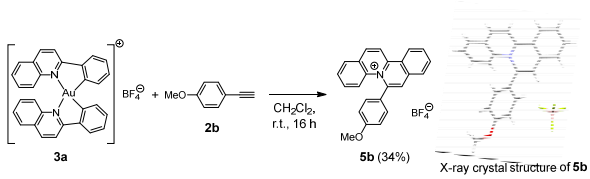


Figure 1. HRMS analysis of the crude reaction mixture of **1b** with **2b** under optimized reaction conditions.

We have been developing a novel class of fluorescent quinoliziniums with a wide range of potential applications including chemical modification of peptides and proteins, cellular imaging and fluorescent chemosensors.[63] Moreover, according to our previous studies on quinoliziniums, the quinolizinium compounds could serve as efficient photocatalysts in various visible light-induced reactions.[63a] Therefore, we reasoned that the *in situ* generated quinolizinium **5b** could function as the photosensitizer for the CDC reaction. To verify the generation of quinolizinium **5b**, we treated $[Au(C^N)_2]BF_4$ **3a** (0.05 mmol) with 4-ethynylanisole **2b** (0.5 mmol, 10 equiv.) in CH_2Cl_2 at room temperature for 16 h. To our delight, quinolizinium **5b** was obtained in 34% isolated yield (Scheme 2). The structure of quinolizinium **5b** was confirmed by ^1H NMR, ^{13}C NMR, HRMS and X-ray crystallographic analysis.[64]



Scheme 2. Formation of quinolizinium **5b**.

With the isolated quinolizinium **5b** in hand, we sought to investigate the role of quinoliziniums **5** as photocatalysts through HRMS analysis by treatment of substrate **1a** with quinolizinium **5b** and $[Au(C^N)_2]BF_4$ **3a**, respectively, under irradiation for 2 h. As shown in the MS spectra, iminium ion **1a'** (m/z 208.11) was observed in the reaction mixture of substrate **1a** with quinolizinium **5b** (Figure 2A), while **1a'** was absent in that of **1a** and gold(III) complex **3a** (Figure 2B). These results indicated that quinoliziniums **5** could serve as efficient photocatalysts for the CDC reaction.

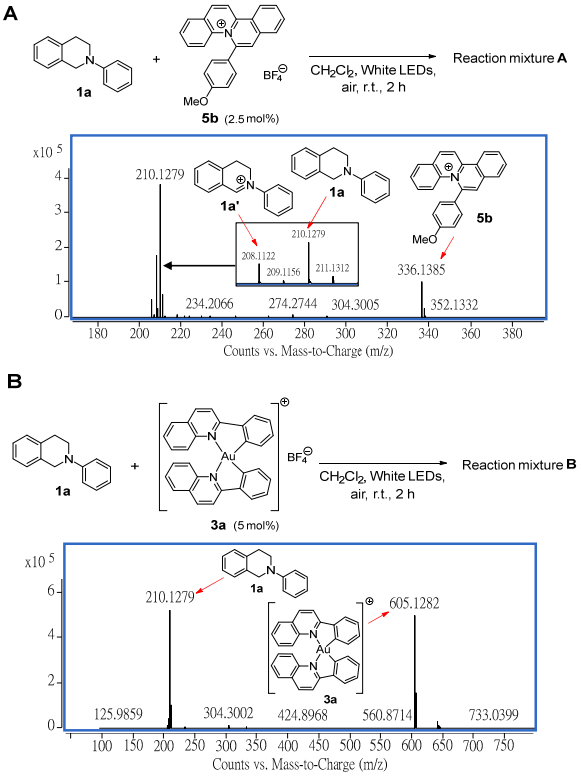
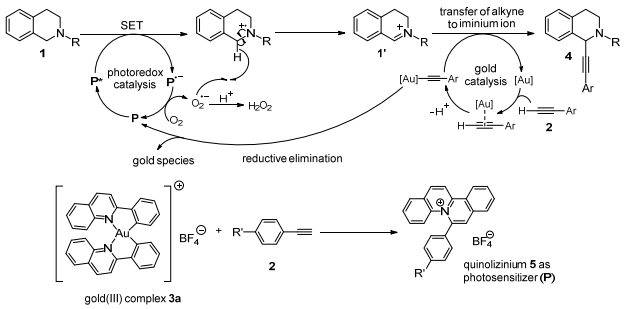


Figure 2. (A) HRMS analysis of reaction mixture **A**; (B) HRMS analysis of reaction mixture **B**.

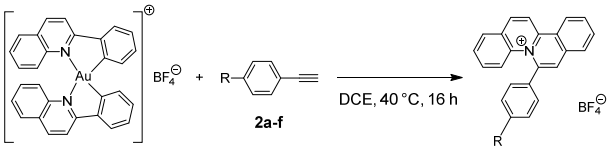


Scheme 3. Proposed reaction mechanism.

On the basis of the aforementioned findings and literature reports,[56,58] a reaction mechanism supporting our design of dual visible light-induced gold(III) catalysis was proposed (Scheme 3). As reported in our previous study on the bis-cyclometalated gold(III) complexes, **3a** consisted of a distorted square planar geometry with elongated bond lengths, which facilitated the ligand dissociation to generate a reactive gold(III) reaction center for alkyne activation.[65] By treatment of catalyst **3a** with terminal alkynes, quinolizinium **5** was generated *in situ* as the photosensitizer (**P**). This visible light-excited *in situ* generated **5** oxidized the tetrahydroisoquinolines **1** by a single electron transfer (SET) process and the reduced photosensitizer was further oxidized by oxygen in air. A hydrogen atom on the oxidized tetrahydroisoquinoline was abstracted by the superoxide formed, resulting in the formation of iminium ion **1'**. Then, iminium ion **1'** could react with terminal alkyne **2** to form product **4**.

We also examined the photophysical properties of the *in situ* generated quinolizinium-based photocatalysts. Treatment of $[Au(C^N)_2]BF_4$ **3a** with alkynes **2a-f**, respectively, in DCE at 40 °C for 16 h afforded quinoliziniums **5a-f** as confirmed by HRMS analysis (Figure S1). UV–Vis and fluorescence measurement was conducted in DCE. Quinoliziniums **5a-e** possessed the absorption maxima in the visible light region (λ_{abs} = 419 – 440 nm) with a wide range of emission maxima between 500 and 594 nm, which was comparable with the reported quinolizinium compounds (Table 3, Figure 3A-B).[63a] The absorption and emission maxima of the *in situ* generated **5b** was also found similar to those of the isolated quinolizinium **5b** (Figure 3C-D). On the other hand, it was observed that the emission maxima of **5a-e** were influenced by the electronic effect brought by the substituents. Particularly, compared with the λ_{em} of **5a** at 521 nm, the introduction of electron-withdrawing CF_3 in **5d** leads to the hypsochromic shift of emission to 500 nm, while that of electron-donating OMe in **5b** results in the bathochromic shift of emission to 594 nm. For quinolizinium **5f**, fluorescence was quenched by the amine group *via* intramolecular photo-induced electron transfer (PET) contributed by the amine substituent as the electron donor towards quinolizinium. This observation was consistent with the properties of the PET-based pH fluorescent probes previously reported by us, which were non-fluorescent without protonation of the aniline moiety.[63b] As a result, quinolizinium **5f** lost the ability for the SET process and could not function as the photosensitizer in the CDC reaction.

Table 3. Photophysical properties of *in situ* generated quinolizinium compounds **5a-f**.[a]



Quino-lizinium	R	λ_{abs} (nm)	λ_{em} (nm)	Stokes Shift (cm^{-1})
5a	H	423	521	4447
5b	OMe	440	594	5892
5c	F	422	516	4317
5d	CF_3	419	500	3866
5e	CN	434	517	3699
5f	NH_2	-	-	-

[a] Absorption and emission properties were measured in DCE at the concentration of 0.01 mM.

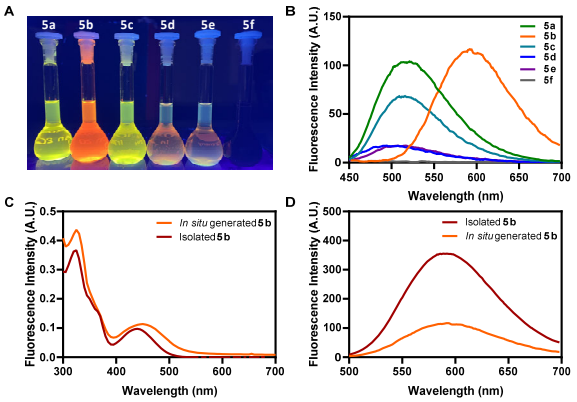


Figure 3. (A) Fluorescence images of the *in situ* generated quinoliziniums **5a-f** under a 365 nm UV lamp (1 mM in DCE); (B) Emission spectra of *in situ* generated quinoliziniums **5a-f**; (C) Absorption spectra of **5b**; (D) Emission spectra of **5b**.

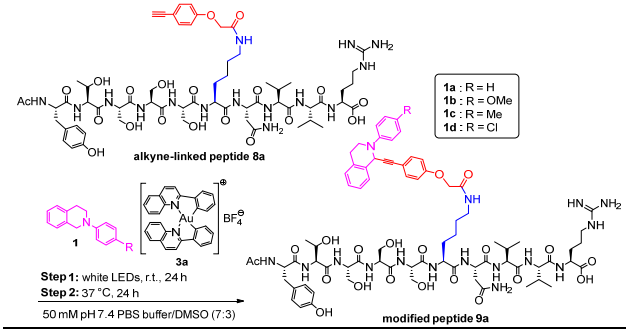
With the promising findings of the visible light-induced gold(III)-catalyzed alkynylation of tetrahydroisoquinoline **1** under mild reaction conditions, we envision that the present reaction could be applied as a novel method for selective modification of alkyne-linked peptides. The alkyne

handle was first incorporated into a model peptide Ac-YTSSSKNVVR **6a** with 2-(4-ethynylphenoxy)acetic acid N-hydroxysuccinimide ester **7a** (6 equiv.) to obtain alkyne-linked Ac-YTSSSKNVVR **8a** in 77% conversion. The reaction conditions were then screened by treatment of alkyne-linked Ac-YTSSSKNVVR **8a** (0.05 mM) with substrate **1a** (10-20 equiv.) and gold(III) complex **3a** (5 equiv.) in 50 mM pH 7.4 PBS buffer/DMSO (7:3) under white LEDs irradiation for 48 h. The corresponding modified peptide **9a** was observed in trace amount. (Table 4, entries 1-2). LC-MS analysis of the reaction mixture indicated that the generation of iminium ion **1a'** was efficient under light irradiation for 24 h (Figure S4), but the transfer of alkyne-linked peptide to **1a'** was relatively slow at room temperature. To further facilitate the alkynylation, the reaction was conducted in two steps. After the generation of iminium ion **1a'** (Step 1), the reaction temperature was increased to 37 °C with the removal of light source (Step 2). Using this two-step approach, treatment of alkyne-linked peptide **8a** with **1a** (5 equiv.) and **3a** (3-5 equiv.) in 50 mM pH 7.4 PBS buffer/DMSO (7:3) afforded modified peptide **9a** in 24-50% conversion (entries 3-4). As confirmed by LC-MS/MS analysis, the modification was on the alkyne-linked lysine residue with other residues on the peptide remained intact (Figure S12). Increasing the loading of **1a** from 5 equivalents to 10 equivalents resulted in an improvement of conversion to 60% (entry 5). Changing the reaction time of Step 2 from 24 h to 30 h gave the highest conversion in 67% (entry 6).

Control experiment was performed by treatment of alkyne-linked peptide **8a** with gold(III) complex **3a** (5 equiv.) under the optimized reaction conditions. LC-MS analysis revealed that quinolizinium **5g** was generated *in situ* by the reaction between gold(III) complex **3a** and 2-(4-ethynylphenoxy)acetic acid originated from the hydrolyzed reagent **7a** (Figure S5-6), which served as the photosensitizer for the bioconjugation.

With the optimized reaction conditions, substrates **1b-d** bearing different substituents (including -OMe, -Me and -Cl) were used for the modification, affording the corresponding modified peptides **9b-d** with 39-51% conversion (Table 4, entries 7-9). To our knowledge, we are the first to combine photoredox catalysis and gold(III) catalysis for alkynylation of tetrahydroisoquinolines and peptide modification.

Table 4. Visible light-induced gold(III)-catalyzed peptide modification.[a]



Entry	**1** (equiv.)	**3a** (equiv.)	Conversion [%][d]
1[b]	**1a** (10)	5	trace
2[b]	**1a** (20)	5	trace
3	**1a** (5)	3	24
4	**1a** (5)	5	50
5	**1a** (10)	5	60
6[c]	**1a** (10)	5	67
7[c]	**1b** (10)	5	44
8[c]	**1c** (10)	5	51
9[c]	**1d** (10)	5	39

[a] Reaction conditions: Treatment of alkyne-linked peptide **8a** (0.05 mM), different concentrations of **1** and **3a** in 50 mM pH 7.4 PBS buffer/DMSO (7:3) under white LEDs at room temperature for 24 h followed by heating at 37 °C for 24 h.

[b] The reaction was performed with Step 1 for 48 h only.

[c] The reaction time for Step 2 was 30 h.

[d] Conversion was determined by LC–MS analysis.

Conclusion

In summary, we have developed a new approach of dual visible light-mediated gold(III)-catalyzed CDC reaction of tetrahydroisoquinolines with terminal alkynes. With the dual roles of the bis-cyclometalated gold(III) complex **3a**, the quinolizinium-based photosensitizers were generated *in situ* for the oxidation of tetrahydroisoquinolines, while **3a** itself worked as the metal catalyst for the alkynylation. Under the optimized conditions, alkynylated products were afforded in good yields up to 73%. This newly developed visible light-induced gold(III)-catalyzed alkynylation was successfully applied in selective modification of alkyne-linked peptides, giving the corresponding modified peptides in up to 67% conversion.

Experimental Section

General procedure for visible light-induced gold(III)-catalyzed alkynylation of tetrahydroisoquinolines 1

A mixture of tetrahydroisoquinolines **1** (0.1 mmol), terminal alkynes **2a-f** (0.5 mmol, 5 equiv.), $[Au(C\hat{}N)_2]BF_4$ **3a** (5 mol%) and 2 mL of CH_2Cl_2 was added into a 4-mL vial. The vial was capped with a screw cap and the vial containing the reaction mixture was irradiated with 5 W white LEDs at

room temperature for 48 h. After the reaction completed, the mixture was concentrated under reduced pressure. The residues were purified by flash column chromatography using EtOAc/hexane as eluent to give the desired products.

General procedure for synthesis of fluorescent quinolizinium 5b

A mixture of $[Au(C^N)_2]BF_4$ **3a** (0.05 mmol), terminal alkynes **2b** (0.5 mmol, 10 equiv.) and 2 mL of CH_2Cl_2 was added into a 4-mL vial. The vial was capped with a screw cap and the vial containing the reaction mixture was stirred at room temperature for 16 h. After the reaction completed, the mixture was concentrated under reduced pressure. The residues were purified by flash column chromatography using CH_2Cl_2/MeOH as eluent to give the desired product.

Modification of peptide using 2-(4-ethynylphenoxy)acetic acid-NHS ester 7a

A mixture of 200 μL of peptide Ac-YTSSSKNVR **6a** (1 mM in H_2O), 20 μL of **7a** (60 mM in DMSO), 20 μL of DMSO and 160 μL of 50 mM pH 7.4 PBS buffer was treated in a 1.5-mL Eppendorf tube at 25 °C for 16 h. The modified product **8a** was characterized by LC–MS and LC–MS/MS analysis.

Modification of alkyne-linked peptide 8a by visible light-induced gold(III)-catalyzed alkynylation

A mixture of 10 μL of alkyne-linked peptide **8a** (0.5 mM in 50 mM pH 7.4 PBS buffer/DMSO 9:1), 5 μL of **1** (10 mM in DMSO), 5 μL of **3a** (5 mM in DMSO), 20 μL of DMSO and 60 μL of 50 mM pH 7.4 PBS buffer was treated in a 1.5-mL Eppendorf tube at room temperature under irradiation of white LEDs for 24 h, followed by heating at 37 °C for 30 h. The modified product **9** was characterized by LC–MS and LC–MS/MS analysis.

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Notes

Graphic abstract and Scheme 1 were created with Biorender (BioRender—biorender.com).

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In situ Generation of Quinoliziniums as Photocatalysts for Dual Visible Light-induced Gold(III)-catalyzed Alkynylation and Peptide Modification

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