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Visible-Light-Driven, Copper-Catalyzed Decarboxylative C(sp^3)-H Alkylation of Glycine and Peptides

Chao Wang, Mengzhun Guo, Rupeng Qi, Qinyu Shang, Qiang Liu, Shan Wang, Long Zhao, Rui Wang,* and Zhaoqing Xu*

Abstract: Despite a well-developed and growing body of work in Cu catalysis, the potential of Cu to serve as a photocatalyst remains underexplored. We here report the first example of visible-light-induced Cu-catalyzed decarboxylative C(sp^3)-H alkylation of glycine for preparing α-alkylated unnatural α-amino acids. It merits mentioning that the mild conditions and the good functional group tolerance allow the modification of peptides using this method. The mechanistic studies revealed that a radical-radical coupling pathway was involved in the reaction.

The cross-coupling between two *sp^3* C remains a significant challenge in synthetic organic chemistry. In the past few decades, great progress has been made in transition-metal-catalyzed alkyl-alkyl cross-coupling between organometallic reagents and alkyl halides.[1] A series of significant achievements have been made by Noller, Tamura, Fu, Suzuki, Knochel, Kambe, and many others.[2] However, the frequent toxicity and limited abundance of alkyl halides restrict their applied value in alkyl-alkyl cross-couplings. Compared with alkyl halides, alkyl carboxylic acids are presented in numerous natural products and medicines. The carboxylic acids derived redox active esters, namely *N*-hydroxyphthalimide (NHP) esters or their analogues, have recently been intensively investigated as precursors for organic radical couplings.[3] In 2016, Baran's group pioneered a general alkyl-alkyl cross-coupling using alkyl NHP esters, which provided new opportunities for choosing alkyl electrophiles in *sp^3* C-C bond formations (Figure 1a).[4a] In the same year, Fu[4b] and Weix[4c] reported Ni-catalyzed decarboxylative alkene hydroalkylation and decarboxylative C(sp^2)-C(sp^3) cross-coupling using alkyl NHP esters, respectively. Although several approaches have been reported for photo activation of alkyl NHP esters, such as UV light irradiation[5a,b] and visible-light-induced photo catalysis using precious metal photocatalyst (Ru, Ir, or Pd)[5c-h, 5k-q] or organic dye catalysts[5i-j], the using of earth-abundant Cu as visible-light photosensitizer to promote the generation of alkyl radicals from alkyl NHP esters is still not easily accessible.[6]

The direct alkylation of C(sp^3)-H provide a convenient alternation for C(sp^3)-C(sp^3) cross-coupling. Very recently, the photoinduced alkylations of C(sp^3)-H have been developed by MacMillan[7] and Yu[8], using alkyl bromides or benzyl chlorides as electrophiles. MacMillan and co-workers also reported its application in alkylated modification of peptides and pharmaceutical compounds.[7] In the reactions, the precious transition-metal photocatalysts, e.g. Ir or Pd, were used to mediate the single electron transfer. Compared with Ir and Ru, the using of Cu as photoredox catalyst is uncommon.[9] In 2017, Fu reported the first visible-light-induced Cu-catalyzed intramolecular *sp^3* C-N coupling via the decarboxylation of alkyl NHP ester (Figure 1b).[6] Despite of this achievement, the visible-light-induced Cu-catalyzed intermolecular decarboxylative C(sp^3)-C(sp^3) cross-coupling, especially the C(sp^3)-H alkylation, is still not realized.

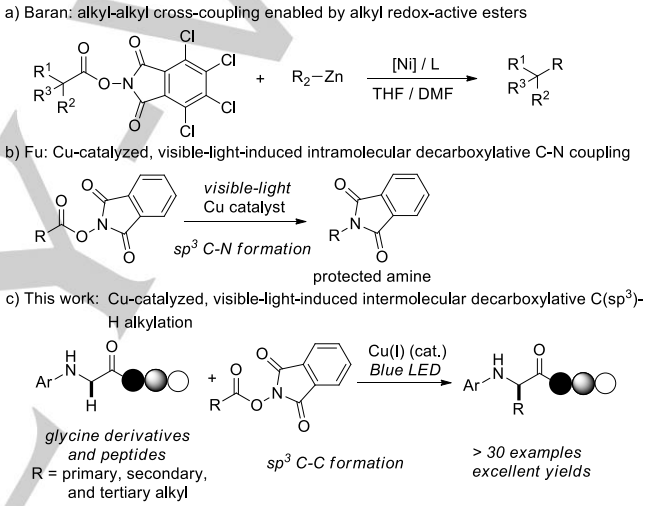

Figure 1. Decarboxylative of alkyl redox-active esters and alkylated modification of peptides.

Introduction of unnatural amino acids or modifying the residues in natural peptides are the most important strategies in peptide drug discovery.[10] Glycine possesses the basic skeleton of α-amino acids. α-C(sp^3)-H alkylation of glycine represents the most straight forward way to synthesis unnatural α-amino acid. Unfortunately, the reported methods for direct C(sp^3)-H alkylation of glycine were either merely restricted to benzylation[11] or using strong oxidants with high temperature, which led to poor regio-selectivities and functional group tolerance.[11,12] Importantly, the harsh conditions or limited substrate scopes restrict their further applications in late-stage modification of bioactive peptides.

Continued with our interest in photoinduced alkylations[13] and peptides synthesis,[14] we here report the first example of visible-light-induced Cu-catalyzed C(sp^3)-H decarboxylative alkylation (Figure 1c). The mild conditions provided good functional group tolerance and broad substrate scopes, in which the primary, secondary, and tertiary carboxylic acids, as well as amino acids and oligopeptides, all served as the alkylation reagents with uniformly good yields. It merits mentioning that peptides could also be highly site-selectively alkylated with very good yields under standard reaction conditions.

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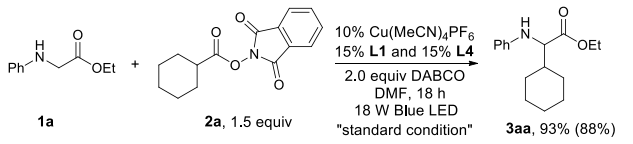
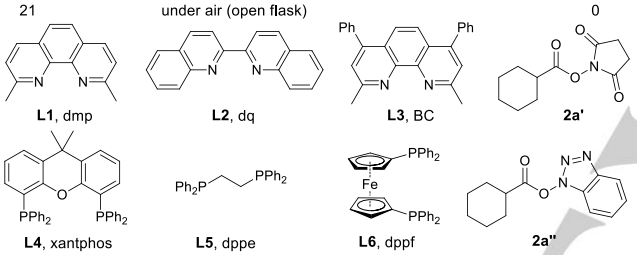
Table 1. Optimization of reaction conditions.



1a **2a**, 1.5 equiv **3aa**, 93% (88%)

entry	change from the "standard condition"	yield (%)[a]
1	no changes	93 (88)
2	without *hv*	0
3	without *hv*, and heated to 80 °C	0
4	without Cu, DABCO, **L1,** or **L4**	0
5	CuBr instead of $Cu(MeCN)_4PF_6$	70
6	CuF_2 instead of $Cu(MeCN)_4PF_6$	40
7	**L2** instead of **L1**	18
8	**L3** instead of **L1**	47
9	**L5** instead of **L4**	12
10	**L6** instead of **L4**	0
11	$Cu(dap)_2Cl$ instead of $Cu(MeCN)_4PF_6$, **L1**, and **L4**	0
12	K_2HPO_4 instead of DABCO	39
13	HMPA instead of DABCO	25
14	DCM instead of DMF	51
15	**2a'** instead of **2a**	0
16	**2a''** instead of **2a**	trace
17	white LED instead of blue LED	trace
18	1.2 equiv **2a**	75
19	10 mol% **L1** and 10 mol% **L4**	65
20	5 mol% $Cu(MeCN)_4PF_6$	52
21	under air (open flask)	0



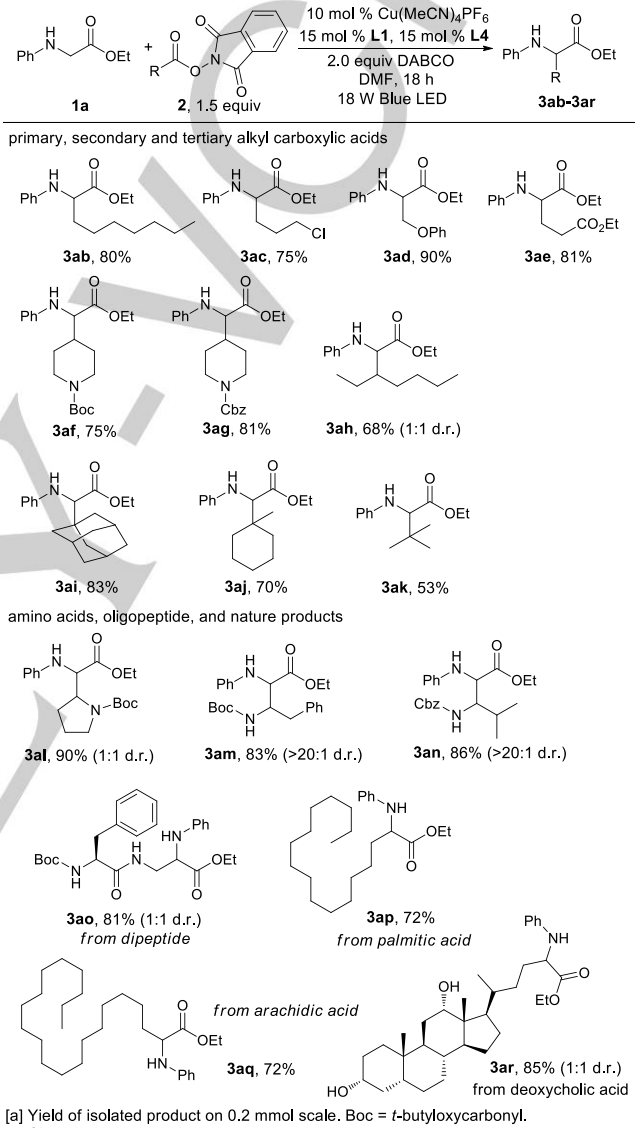
L1, dmp **L2**, dq **L3**, BC **2a'**

L4, xantphos **L5**, dppe **L6**, dppf **2a''**

[a] Yields were determined by ^1H NMR analysis using 1,3,5-trimethoxybenzene as an internal standard, the number in parentheses refer yields of isolated product. dmp = neocuproine; dq = 2,2'-biquinoline; BC = bathocuproin; xantphos = 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene; dppe = 1,2-bis(diphenylphosphino)ethane; dppf = 1,1'-bis(diphenylphosphino)ferrocene.

Our investigation was initiated by using ethyl 2-(phenylamino)acetate **1a** and cyclohexyl NHP ester **2a** as model substrates under blue LED light irradiation (Table 1). After screening of the reaction parameters (e.g. copper catalysts, ligands, basic additives, and solvents), the desired product **3aa** was obtained in 93% NMR yield (88% yield of isolated product) in the presence of 10 mol% $Cu(MeCN)_4PF_6$, 15 mol% dmp, 15 mol% xantphos, 2.0 equivalent DABCO (1,4-diazabicyclo[2.2.2]octane), and DMF (*N*,*N*-dimethylformamide, entry 1, see the SI for details). Control experiments showed that blue LED irradiation, copper catalyst, ligands, and DABCO were indispensable for the reaction (entries 2-4). Compared to cupric catalysts, cuprous catalysts furnished a better yield of the product (entries 5 and 6). When dmp and xantphos were replaced with other ligands, the reaction proceeded inefficiently (entries 7-10). $Cu(dap)_2Cl$ (dap = 2,9-bis(*p*-anisyl)-1,10-phenanthrolin) was also not effective for our reaction either under blue light or green light (530 nm) irradiation (entry 11)[15]. Replacing DABCO with other bases, including organic bases (HMPA = hexamethylphosphoric triamide) and inorganic bases, led to significantly lower yields (entries 12 and 13). Furthermore, other solvents, such as dichloromethane (DCM), could not provide a better yield than DMF (entry 14). Other NHP type esters (**2a'** and **2a''**) gave negative results (entries 15 and 16). Light sources screening showed that only blue LED light was effective for this reaction (entry 17). Reducing the amount of **2a**, $Cu(MeCN)_4PF_6$, and ligands resulted in the substantial drop of yields (entries 18-20). In addition, the coupling reaction was sensitive to the oxygen (entry 21).

Table 2. Scope of alkyl NHP esters.[a]



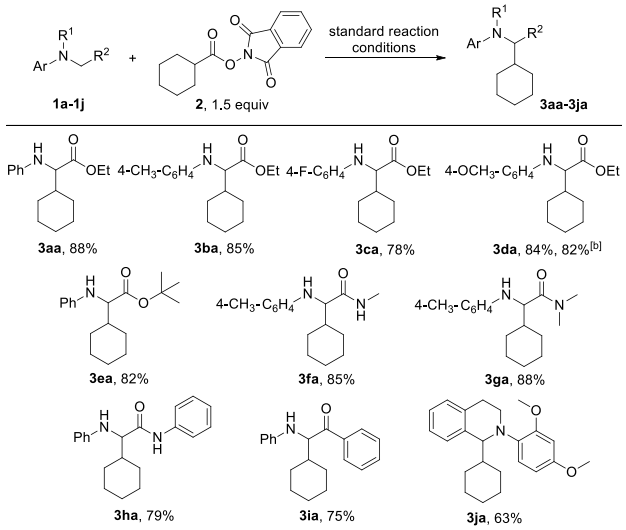
1a 2, 1.5 equiv **3ab-3ar**

[a] Yield of isolated product on 0.2 mmol scale. Boc = *t*-butyloxycarbonyl. Cbz = benzoyloxycarbonyl

To explore the substrate scopes, various alkyl NHP esters were investigated under optimal conditions. As summarized in Table 2, the strategy was successfully applied to primary, secondary, and tertiary alkyl NHP esters with good to excellent yields (**3ab**-**3ak**, 53-90%). Importantly, the substrates bearing various substituent groups, such as halogen, ester, and ether group were all tolerant (**3ac**, **3ad**, and **3ae**-**3ag**). Furthermore, NHP esters of α-amino acids (**2l**, **2m**, and **2n**) were smoothly decarboxylative coupled with **1a** in excellent yields, which provided an efficient method for the preparation of 1,2-di-amine compounds (**3al**-**3an**). Notably, dipeptide (**2o**) derived NHP

esters coupled with **1a** in 81% yield of isolated product, which rendered a versatile application of our reaction in the modification of bioactive peptides (**3ao**). Naturally occurring carboxylic acids such as palmitic acid (**2p**), arachidic acid (**2q**), and deoxycholic acid (**2r**) were also amenable to this C(sp^3)-H alkylation.

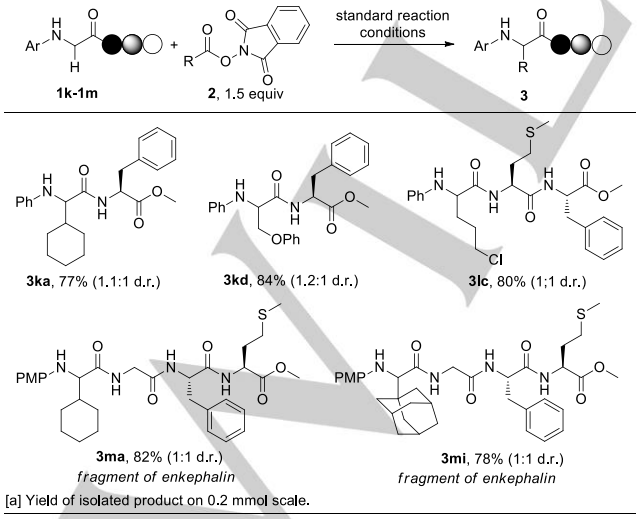
Table 3. Scope of glycine derivatives.[a]



[a] Yield of isolated product on 0.2 mmol scale. [b] Gram scale (10 mmol), 36 h.

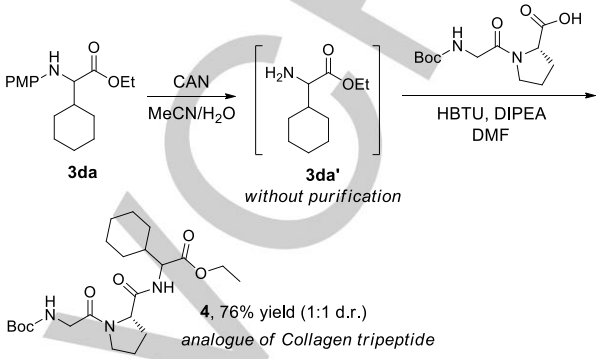
Further expansion of the substrate scopes was focused on glycine derivatives (Table 3). The esters of glycine bearing both electron-rich and electron-poor groups on the aromatic ring were well tolerated (**3aa**-**3ea**, 78-88%). In addition, the yield of **3da** was maintained when the reaction was conducted on a gram scale (82%, 10 mmol scale and 36 h). Besides esters, the amides of glycine with *N*-mono-substituent and *N*-bis-substituents all went smoothly (**3fa**-**3ha**). Furthermore, α-amino ketone **1i** and *N*-aryl tetrahydroisoquinoline **1j** were also suitable substrates for this transformation.

Table 4. Site-selective modification of peptides.[a]



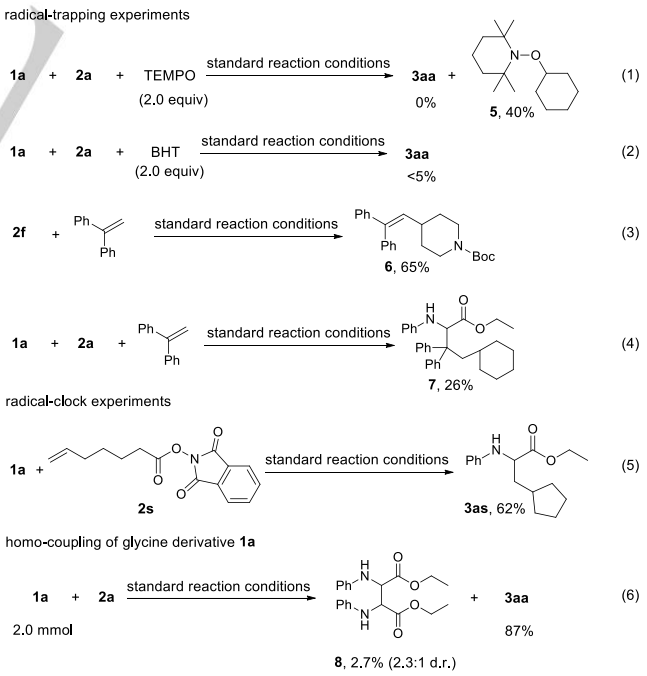
[a] Yield of isolated product on 0.2 mmol scale.

The applied value of our reaction was demonstrated by alkylated modification of peptides (Table 4). The *N*-phenyl protected dipeptide **1k** was successfully coupled with primary and secondary alkyl NHP esters in excellent yields (**3ka** and **3kd**). For the alkylation of tripeptide and tetrapeptide (fragment of enkephalin) bearing sensitive functional group (-CH_2SCH_3), the reactions absolutely selective proceeded at α-position of glycine carbonyl, rather than α-position of thiomethyl (**3lc**, **3ma**, and **3mi**, PMP = *p*-methoxyphenyl).



Scheme 1. Synthetic application of product **3da**.

The α-alkylated product was easily converted to α-unnatural amino acid via removing *N*-protecting group (Scheme 1, **3da**). The PMP protection could be removed by CAN (ammonium cerium nitrate, 6 equiv) and used in peptide synthesis without further purifications. Collagen tripeptides are important skin care products. With our strategy, the condensation of the deprotected intermediate **3da'** and dipeptide proceeded smoothly and provided the analogue of collagen tripeptide **4** in 76% overall yield (1:1d.r.).

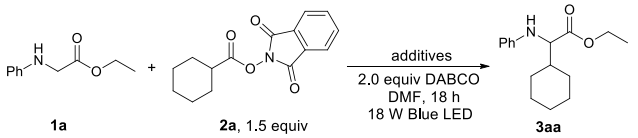


Scheme 2. Mechanistic studies.

To gain some information of the reaction mechanism, radical trapping experiments and radical clock experiments were

conducted (Scheme 2). When 2.0 equiv of TEMPO (2,2,6,6-tetramethylpiperidin-1-oxyl) or BHT (2,6-di-*tert*-butyl-4-methylphenol) was added, the reaction was shut down, respectively (eq 1 and 2). The TEMPO trapping product **5** was isolated in 40% yield (eq 1). When ethene-1,1-diyldibenzene was added instead of **1a**, Heck-type product **6** was obtained in 65% yield (eq 3). In the presence of **1a**, **2a**, and ethene-1,1-diyldibenzene, the product of three-component reaction was observed (eq 4). Furthermore, the radical clock experiment with 6-heptenoic acid derived NHP ester **2s** led to the formation of cyclization product **3as** in 62% yield (eq 5). In addition, the homo-coupling product **8** from glycine derivative **1a** was obtained in 2.7% yield of isolated product (eq 6). These results suggested that the alkyl radical and the glycine derivative radical were generated in the reaction system.

Table 5. Control experiments.



1a **2a**, 1.5 equiv **3aa**

entry	additives	yield (%)[a]
1	10% $Cu(MeCN)_4PF_6$	0
2	10% $Cu(MeCN)_4PF_6$ and 15% dmp	0
3	10% $Cu(MeCN)_4PF_6$ and 15% xantphos	0
4	10% $Cu(MeCN)_4PF_6$, 15% dmp and 15% xantphos	93
5	5% Cu(dmp)(xantphos)PF_6	75
6	10% Cu(dmp)(xantphos)PF_6	92

[a] Yield was determined by ^1H NMR analysis using 1,3,5-trimethoxybenzene as an internal standard.

To further understand the interactional manners between copper salt and ligands, control experiments were carried out (Table 5). In the absence of dmp and xantphos, or either of them, the reaction was not proceeded (entries 1-3). The results suggested that a heteroleptic copper(I)-based complex might formed in the system and acted as the photosensitizer. When Cu(dmp)(xantphos)PF_6 was prefabricated[16] and employed in the reaction (10 mol %), a similar result was obtained to the using of in situ generated catalyst (entries 4-6). Furthermore, HRMS analysis of the mixture in the standard reaction (Table 1, entry 1) indicated the formation of Cu(dmp)(xantphos)BF_6 in the reaction system.[17]

In UV-Vis absorption experiments, the absorption spectrum of the in situ generated Cu catalyst ($Cu(MeCN)_4PF_6$:dmp:xantphos = 1:1.5:1.5) was consistent with the prefabricated [Cu(dmp)(xantphos)]PF_6 (see the SI for details, Figure S3). When cyclohexyl NHP ester **2a** was combined with Cu salt and ligands, an obvious bathochromic-shift and broader absorption region were observed (Figure S4). The results indicated that the Cu complex might also increase the reactivity of NHP ester under blue light irradiation. In addition, Stern-Volmer plot results indicated that the alkyl NHP ester **2a** quenched the excited state of Cu(dmp)(xantphos)PF_6, where it presumably engaged in SET event in the reaction (Figure 2). Finally, the quantum yield Φ = 0.74 indicated a radical chain process might not involve in the reaction (see the SI for details)

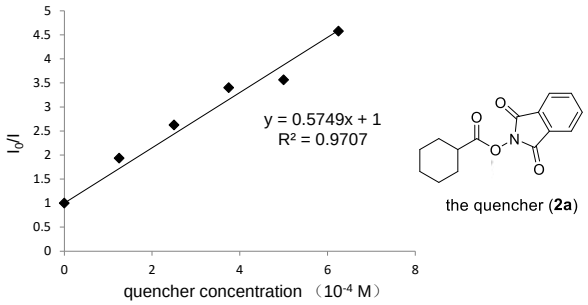
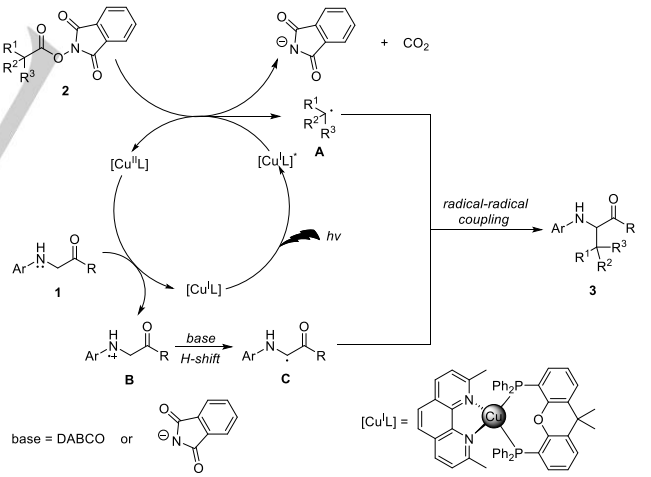


Figure 2. Stern-Volmer plot for the emission quenching of Cu(dmp)(xantphos)PF_6 by various concentrations of quencher **2a**.

On the basis of above investigations and previous reports,[16] a possible reaction mechanism was proposed in Scheme 3. Under blue LED light irradiation, cuprous-based complex [Cu^IL] was excited to its excited state [Cu^IL]* ($E_{1/2}[Cu^{II}/Cu^{I*}]$ = -1.86 V versus SCE (saturated calomel electrode) in MeCN), which underwent a single electron transfer (SET) process with alkyl NHP ester **2** ($E_p^{0/-1}$(**2**) = -1.28 to -1.37 V versus SCE in MeCN)[16c,18], followed by the generation of alkyl radical **A**, CO_2, phthalimide anion, and [Cu^{II}L]. [Cu^{II}L] ($E_{1/2}[Cu^{II}/Cu^I]$ = 0.38 V versus SCE in MeCN) oxidized glycine derivatives **1** ($E_p^{0/+1}$(**1a**) = 0.31 V versus SCE in MeCN) to form radical cation intermediate **B**, along with regeneration of [Cu^IL]. On the other hand, intermediate **B** was deprotonated and followed by a 1,2-H shift process under basic conditions (DABCO or phthalimide anion) to provide a stable α-carbon radical **C**. Finally, the radical-radical cross-coupling between alkyl radical **A** and α-carbon radical **C** was proposed and provided alkyl-alkyl cross-coupling product **3**.



Scheme 3. Proposed mechanism.

In summary, we disclosed the first photo-induced Cu-catalyzed site-selective alkylation of C(sp^3)-H via decarboxylative of alkyl NHP esters. A series of glycine derivatives and *N*-aryl tetrahydroisoquinoline were tolerant with uniformly good yields. A variety of alkyl NHP esters proceeded the alkyl-alkyl cross-coupling in good to excellent yields. The strategy was successfully applied in the preparation of unnatural α-amino acids and the alkylated modification of peptides. Furthermore, with a simple operation, the α-alkylated unnatural amino acid could be directly used for the preparation peptide-

based bioactive molecules, such as the analogue of collagen tripeptide.

Acknowledgements

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Keywords: alkylation • decarboxylative • C(sp^3)-C(sp^3) cross-coupling • copper • peptide

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