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Visible-light promoted α-alkylation of glycine derivatives with alkyl boronic acids†

Jiayuan Wang, Yingpeng Su, * Zhengjun Quan, * Jun Li, Jie Yang,
Yong Yuan and Congde Huo *

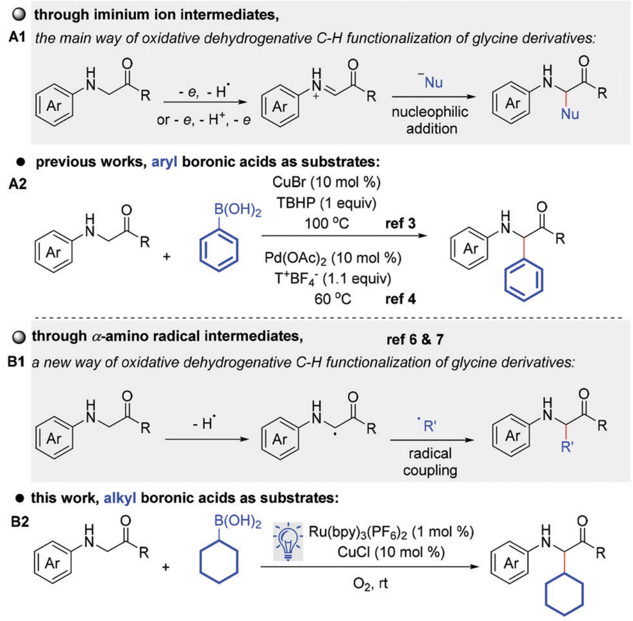
A visible-light-mediated aerobic α-alkylation reaction of glycine derivatives with alkyl boronic acids has been established in the presence of a Ru/Cu catalyst system, giving the desired radical coupling products efficiently. The transformation features mild reaction conditions and broad substrate scope, delivering a wide range of complex unnatural α-amino-acid derivatives.

Glycine is the smallest natural α-amino acid. The direct α-C–H bond modification of glycine and its derivatives is one of the most straightforward strategies to access a wide variety of complex α-amino-acid derivatives. Since the pioneering work, the C–H/C–H cross-coupling reaction of glycine amides with malonates, which was demonstrated by the Li group in 2008,[1] the oxidative dehydrogenative coupling reaction of glycine derivatives has been widely developed.[2]

In the past decade, a good deal of oxidative dehydrogenative C–C bond formation reactions of glycine derivatives have been achieved through a carbocation mechanism.[2] Iminium ions were the key intermediates in these transformations generated by one-electron oxidation and the subsequent dehydrogenation (or by one-electron oxidation, deprotonation, and second one-electron oxidation) of glycine derivatives, which were then attacked by nucleophiles to generate the C–C coupling products (Scheme 1, part A1). Using this strategy, aryl boronic acids have also been used as nucleophiles in two articles (Scheme 1, part A2). In 2009, the reaction of *N*-PMP glycine amides with aryl boronic acids was proceeded by the Li group at 100 °C under copper catalysis with TBHP as the terminal oxidant.[3] In 2015, an enantioselective version of this transformation was developed by the Yang group under palladium catalysis with a box type of chiral ligand using 2,2,6,6-tetramethylpiperidine oxoammonium salt as the oxidant.[4]

A lot of C(sp^3)–C(sp^3) bond formation reactions of glycine derivatives have been developed *via* the iminium-ion strategy. Carbonyl compounds,[5a–f] allyl compounds,[5g,h] methylquinolines,[5i] nitroalkanes,[5j] silyl enol ethers[5k] and α-angelicalactone[5l] were all suitable nucleophilic coupling reagents. However, simple alkylation without an activation group cannot be achieved by this protocol. Since 2018, the Xu group realized the alkylation of glycine derivatives *via* a radical coupling pathway (Scheme 1, part B1). NHPI esters, Katritzky salts and alkyl halides were employed as radical coupling precursors under photocatalysis.[6] In 2020, the Wang group also reported the alkylation reaction of glycine derivatives with diacyl peroxides.[7]

However, there are still deficiencies in these methods. For the first one, NHPI esters, Katritzky salts and alkyl halides are relatively un-atom-economic. In particular, alkyl halides are



Scheme 1 Methods for C–H functionalization of glycine derivatives.

Gansu International Scientific and Technological Cooperation Base of Water-Retention Chemical Functional Materials, College of Chemistry and Chemical Engineering, Northwest Normal University, Lanzhou, Gansu 730070, China. E-mail: huocongde1978@hotmail.com

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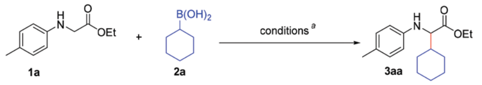
also less environment-friendly. In the second one, peroxides are potentially explosive and rather expensive. Meanwhile, the peroxide scope was limited. Therefore, given the economic and environmental factors, the development of a more atom-economic and environment-friendly method using more readily available and safer radical coupling reagents for the alkylation of glycine derivatives is highly desired.

Radical reactions involving organoboron compounds have emerged after entering the 21st century.[8] This chemistry actually has a long history. For example, the auto-oxidation of organoboranes was reported in 1862 by Frankland.[9] In the past decade, the application of organoboronic acids as radical precursors appeared to construct C–C bonds. In this field, a few alkylation reactions were reported using alkyl boronic acids as alkyl radical sources.[10] In 2011, a Ag(I)/$K_2S_2O_8$ induced alkylation of quinones with alkyl boronic acids was developed by the Baran group.[10a] Subsequently, a manganese promoted alkylation of arenes and a photoredox mediated alkylation of N-hetero arenes using alkyl boronic acids as alkyl radical sources were reported by the Rodriguez group[10b] and the Chen group[10c] respectively in 2016. Then, the Liu group demonstrated an auto-oxidation of organoboronic acid to generate alkyl radicals to react with heteroaromatics in 2017.[10d] In 2019, the Chen group reported a visible-light induced radical addition of α-keto acids with alkyl boronic acid.[10e]

Herein, we report a visible-light-promoted aerobic C(sp^3)–H alkylation of glycine derivatives with alkyl boronic acids under Ru/Cu co-catalysis (Scheme 1, part B2). The reaction can also proceed under single Ru or Cu catalysis or even under auto-oxidation conditions without metal catalyst in lower yields. A radical–radical coupling mechanism was proposed.

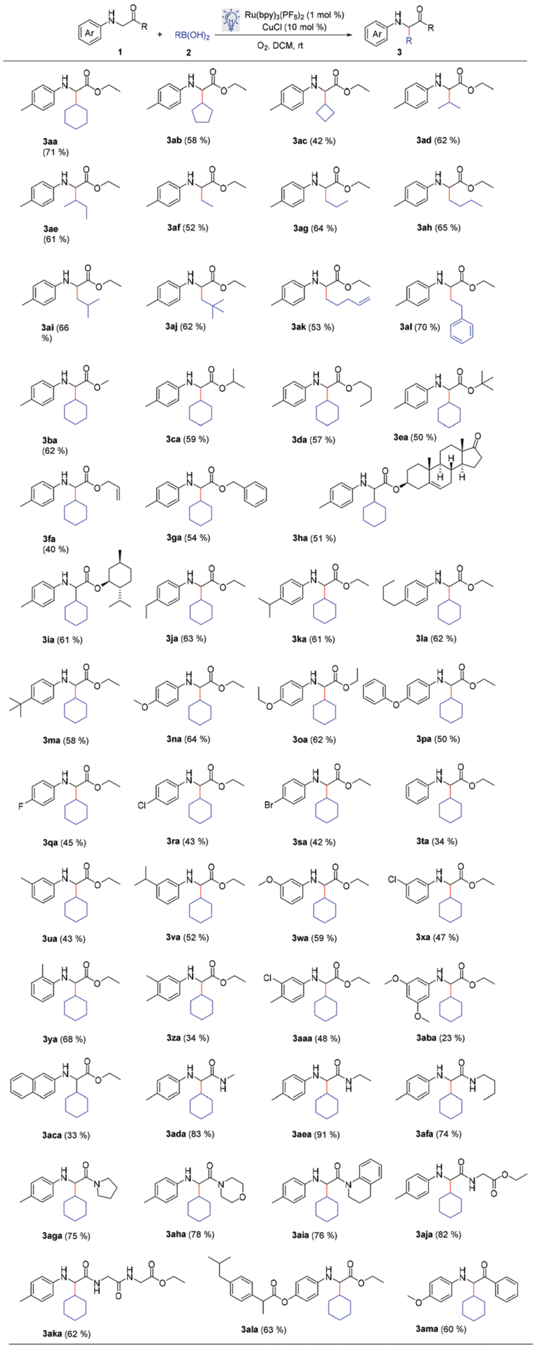
We commenced the investigation of the reaction using glycine ester **1a** and cyclohexyl boronic acid **2a** as the template substrates. After extensive screening of the reaction parameters, we defined the use of $Ru(bpy)_3(PF_6)_2$ (1 mol%) and CuCl (10 mol%) as catalysts and O_2 (balloon) as the terminal oxidant in dichloromethane under irradiation of a 6 W blue LED as the optimized reaction conditions, affording the desired alkylated product **3aa** in 71% yield (Scheme 2, entry 9). The selection of catalyst systems is essential for this transformation. Other photosensitizers such as EosinY, Rose bengal, $Ir[dF(CF_3)bpy]_2(dtbpy)PF_6$, and $RuCl_2(bpy)_3$ proved to be inferior to $Ru(bpy)_3(PF_6)_2$ for this reaction (Scheme 2, entries 1–7). The use of other copper or iron salts could usually mediate the reaction with lower yields than CuCl (Scheme 2, entries 8–17). And white light or green light led to lower yields too (Scheme 2, entries 18 and 19). The reaction gave lower yields of **3aa** in DCE, MeCN and toluene, while no desired product **3aa** was observed in other solvents such as DMSO and THF (Scheme 2, entries 20–24). The replacement of oxygen gas with argon led to no formation of **3aa** (Scheme 2, entry 25). A slightly lower yield was obtained when air (open flask) was utilized instead of an O_2 balloon (Scheme 2, entry 26).



entry	photosensitizer	additive	light source	solvent	atmosphere	yield (%)
1	EosinY (1 mol%)	$Cu(OTf)_2$ (10 mol%)	blue LED	DCM	O_2	29
2	Rose bengal (1mol%)	$Cu(OTf)_2$ (10 mol%)	blue LED	DCM	O_2	44
3	$Ir[dF(CF_3)bpy)]_2(dtbpy)PF_6$ (1 mol%)	$Cu(OTf)_2$ (10 mol%)	blue LED	DCM	O_2	27
4	$RuCl_2(bpy)_3.6H_2O$ (1 mol%)	$Cu(OTf)_2$ (10 mol%)	blue LED	DCM	O_2	48
5	$Ru(bpy)_3(PF_6)_2$ (1 mol%)	$Cu(OTf)_2$ (10 mol%)	blue LED	DCM	O_2	68
6	$Ru(bpy)_3(PF_6)_2$ (0.5 mol%)	$Cu(OTf)_2$ (10 mol%)	blue LED	DCM	O_2	57
7	$Ru(bpy)_3(PF_6)_2$ (1.5 mol%)	$Cu(OTf)_2$ (10 mol%)	blue LED	DCM	O_2	64
8	$Ru(bpy)_3(PF_6)_2$ (1 mol%)	Cu(OTf) (10 mol%)	blue LED	DCM	O_2	70
9	$Ru(bpy)_3(PF_6)_2$ (1 mol%)	CuCl (10 mol%)	blue LED	DCM	O_2	**71**
10	$Ru(bpy)_3(PF_6)_2$ (1 mol%)	CuBr (10 mol%)	blue LED	DCM	O_2	60
11	$Ru(bpy)_3(PF_6)_2$ (1 mol%)	CuI (10 mol%)	blue LED	DCM	O_2	64
12	$Ru(bpy)_3(PF_6)_2$ (1 mol%)	$Cu(MeCN)_4PF_6$ (10 mol%)	blue LED	DCM	O_2	67
13	$Ru(bpy)_3(PF_6)_2$ (1 mol%)	$Fe(OTf)_2$ (10 mol%)	blue LED	DCM	O_2	27
14	$Ru(bpy)_3(PF_6)_2$ (1 mol%)	$Fe(OAc)_2$ (10 mol%)	blue LED	DCM	O_2	70
15	$Ru(bpy)_3(PF_6)_2$ (1 mol%)	$FeCl_2$ (10 mol%)	blue LED	DCM	O_2	66
16	$Ru(bpy)_3(PF_6)_2$ (1 mol%)	CuCl (5 mol%)	blue LED	DCM	O_2	55
17	$Ru(bpy)_3(PF_6)_2$ (1 mol%)	CuCl (15 mol%)	blue LED	DCM	O_2	65
18	$Ru(bpy)_3(PF_6)_2$ (1 mol%)	CuCl (10 mol%)	white LED	DCM	O_2	48
19	$Ru(bpy)_3(PF_6)_2$ (1 mol%)	CuCl (10 mol%)	green LED	DCM	O_2	35
20	$Ru(bpy)_3(PF_6)_2$ (1 mol%)	CuCl (10 mol%)	blue LED	DCE	O_2	26
21	$Ru(bpy)_3(PF_6)_2$ (1 mol%)	CuCl (10 mol%)	blue LED	MeCN	O_2	14
22	$Ru(bpy)_3(PF_6)_2$ (1 mol%)	CuCl (10 mol%)	blue LED	DMSO	O_2	0
23	$Ru(bpy)_3(PF_6)_2$ (1 mol%)	CuCl (10 mol%)	blue LED	THF	O_2	0
24	$Ru(bpy)_3(PF_6)_2$ (1 mol%)	CuCl (10 mol%)	blue LED	tuluene	O_2	36
25	$Ru(bpy)_3(PF_6)_2$ (1 mol%)	CuCl (10 mol%)	blue LED	DCM	Ar	0
26	$Ru(bpy)_3(PF_6)_2$ (1 mol%)	CuCl (10 mol%)	blue LED	DCM	air	64

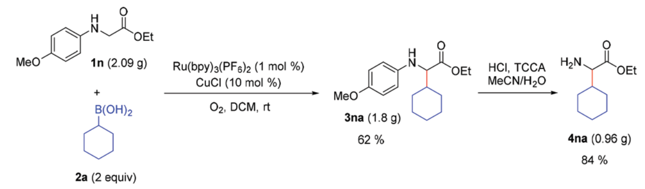
Scheme 2 Screening of reaction conditions. [a] Reaction conditions: **1a** (0.2 mmol), **2a** (2 equiv.), solvent (2 mL), O_2 balloon, 6 h, rt. [b] Isolated yields.

With the optimal reaction conditions in hand, we turned to evaluating the substrate-scope of this visible-light induced aerobic transformation. The reaction exhibits broad substrate scope with good functional group tolerance (Scheme 3). Initially, with respect to the alkyl boronic acid part, a wide range of secondary and primary aliphatic boronic acids are all suitable substrates in this oxidative C–H functionalization reaction of glycine derivatives (Scheme 3, **3a–3l**). Next, we explored the scope of glycine derivatives for this complex α-amino-acid-forming reaction. First, the reaction tolerates various glycine esters (R = MeO, EtO, i-PrO, *n*-BuO, *t*-BuO, allylO, BnO). It is worth noting that **1h** derived from dehydroisoandrosterone (DHEA) and **1i** derived from menthol were also good substrates for this reaction under standard reaction conditions, affording the desired products **3ha** and **3ia** in high isolated yields. Then, *para*-substituted *N*-aromatic glycine esters with electron-donating and electron-withdrawing groups were all tolerated well to give the C–C cross-coupled products in high yields (Scheme 3, **3ja–3sa**). *meta-*, *ortho-* and multi-Substituted *N*-aromatic glycine ester derivatives are also suitable substrates for this reaction (Scheme 3, **3ua–3aba**). Notably, *N*-phenyl glycine ester **1t** was also transformed to the corresponding product **3ta** smoothly. Glycine esters (**1q–1s**, **1x**, **1aa**) with halogen atoms (F, Cl, and Br) were all tolerated using this photocatalytic protocol, leaving halides as chemical handles for further elaboration. *N*-Naphthyl derivative **1ac** could also be converted to the desired product in moderate yield. Note that glycine amides could be applied to the standard reaction conditions to achieve the corresponding alkylated products in synthetically useful yields (**3ada–3aia**). Moreover, dipeptide **1aj** and tripeptide **1ak** participated in this reaction smoothly to deliver the C–H functionalized products **3aja** and **3aka**. Finally, Ibuprofen derivative **1al** and amino ketone compound **1am** showed good reactivity too. The corresponding products **3ala** and **3ama** were obtained in high yields.



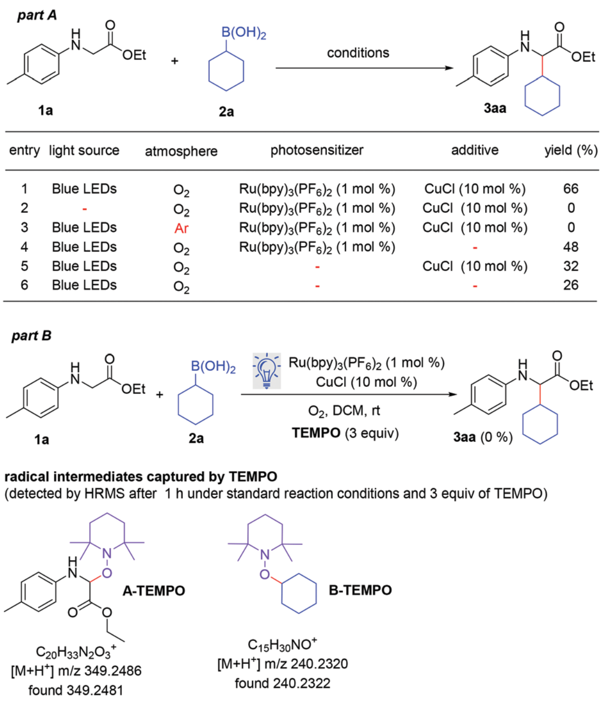
Scheme 3 Visible-light promoted C–H alkylation of glycine derivatives with alkyl boronic acids.[a,b] [a] Reaction conditions: **1** (0.2 mmol), **2** (2 equiv.), $Ru(bpy)_3(PF_6)_2$ (1 mol%), CuCl (10 mol%), blue LED (6 W), DCM (2 mL), O_2 balloon, 6–14 h, rt. [b] Isolated yields.

To demonstrate the scalability and practicality of this visible-light mediated aerobic radical cross coupling reaction, a gram-scale experiment was proceeded using the compounds **1n** and **2a**, giving the desired alkylated product **3na** in 62% yield. Furthermore, the *N*-PMP protecting group could be efficiently removed to afford the α-amino ester **4na** in 84% yield (Scheme 4).



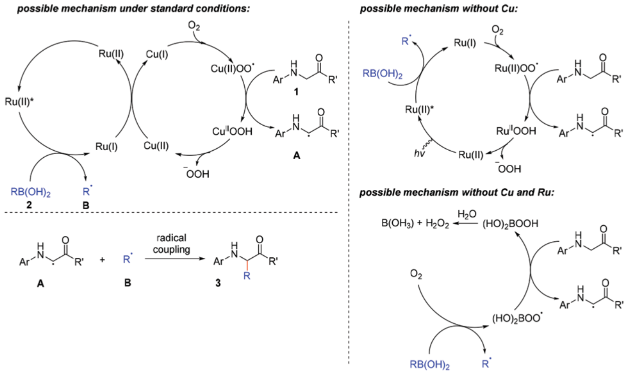
Scheme 4 Scalability of the reaction to the gram scale.

Some control experiments were carried out to pursue the mechanism of this transformation (Scheme 5). When the template reaction was carried out without blue LEDs (Scheme 5, entry 2) or under an argon atmosphere (Scheme 5, entry 3), no desired product can be observed, which means that visible-light irradiation and an oxygen atmosphere are critical to the success of this transformation. When Ru catalyst, Cu catalyst, or even both of them were omitted, the same transformation also proceeds with the yield of **3aa** gradually reduced. A free radical scavenging experiment of the template reaction was then performed. The formation of **3aa** was totally suppressed. Moreover, TEMPO trapped adducts **TEMPO-A** and **TEMPO-B** were detected by HRMS (high-resolution mass spectrometry). These results suggest that a radical coupling process might be involved and α-amino alkyl radical intermediates **A** and alkyl radical intermediates **B** might exist in this process. Luminescence quenching experiments were conducted (Scheme 5, part C). Alkyl boronic acid **2a** showed a strong quenching effect to the excited Ru photocatalyst. Glycine ester **1a** showed no significant quenching effect to the excited photocatalyst. This observation provides evidence that the reaction proceeds *via* interaction of Ru photosensitizer and the alkyl boronic acid. A light on–off experiment was also carried out with **1a** and **2a** (Scheme 5, part D). These results



entry	light source	atmosphere	photosensitizer	additive	yield (%)
1	Blue LEDs	O_2	$Ru(bpy)_3(PF_6)_2$ (1 mol %)	CuCl (10 mol %)	66
2	-	O_2	$Ru(bpy)_3(PF_6)_2$ (1 mol %)	CuCl (10 mol %)	0
3	Blue LEDs	Ar	$Ru(bpy)_3(PF_6)_2$ (1 mol %)	CuCl (10 mol %)	0
4	Blue LEDs	O_2	$Ru(bpy)_3(PF_6)_2$ (1 mol %)	-	48
5	Blue LEDs	O_2	-	CuCl (10 mol %)	32
6	Blue LEDs	O_2	-	-	26

Scheme 5 Control experiments.



Scheme 6 Proposed mechanism.

and the low quantum yield (0.011) for product formation indicated that the transformation underwent a catalytic radical pathway instead of a radical chain process.[11]

On the basis of the control experimental results and the literature reports, a plausible mechanism is depicted for this alkylation reaction of glycine derivatives (Scheme 6). Initially, the Ru(II) is irradiated to the excited state. Then, the reaction of alkyl boronic acid **2** with excited *Ru(II) generates the alkyl radical species **A** *via* a single electron transfer (SET) process. At the same time, the *Ru(II) was one-electron reduced to generate Ru(I). Subsequently, Ru(I) was one-electron oxidized by Cu(II) to regenerate Ru(II). At the same time, Cu(II) was one-electron reduced to generate Cu(I). Then, a Cu(II) peroxide radical generated by a combination of Cu(I) with O_2 abstracts a H-atom of glycine derivatives **1** to form radical intermediate **B** stabilized by the captodative effect. Finally, the alkyl–alkyl radical cross coupling of **A** and **B** occurred to deliver the alkylation product **3**. Tentative mechanisms under single metal catalysis or auto-oxidation conditions were also proposed in Scheme 6.

In summary, we for the first-time report herein an aerobic oxidative alkylation of glycine derivatives with alkyl boronic acids using an Ru/Cu co-catalyst system under visible-light irradiation. We also disclosed that under single Ru or Cu catalysis or even under auto-oxidation conditions without a metal catalyst, the same transformation also proceeds with lower yields. A large library of complex amino-acid derivatives was successfully achieved with a broad substrate scope and pronounced functional-group tolerance under mild reaction conditions. Mechanistic investigations revealed the importance of radical intermediates. Further investigations of asymmetric variants and other cross coupling reactions of glycine derivatives *via* α-amino alkyl radical intermediates are currently underway in our laboratory.

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Conflicts of interest

There are no conflicts to declare.

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