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RESEARCH ARTICLE

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Visible Light Promoted Chan-Lam Reaction and Cycloaddition to Prepare Chromeno[4,3-c]isoxazolidines in One-pot Reaction

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Abstract. A variety of chromeno[4,3-c]isoxazolidines were prepared in good yields through visible light promoted Chan-Lam reaction and [3+2] cycloaddition cascade reaction in one pot**.** Mechanistic studies showed that visible light promoted both Chan-Lam reaction and cycloaddition. The obtained products were converted to various useful chromenone derivatives. Moreover, the reaction was easily performed at gram scales with the purification of products without column chromatography and used to efficiently synthesize estrone-derived chromeno[4,3-c]isoxazolidine.

Keywords: Visible light; Cycloaddition; Chan-Lam reaction; Nitrone; Chromeno[4,3-c]isoxazolidine

Introduction

Carbon-nitrogen bonds and nitrogen-containing heterocycles are ubiquitous in a wide range of biologically active molecules, pharmaceuticals, and natural products. In the last two decades, transition metal-catalyzed cross-coupling reactions have emerged as one of the most important synthetic tools for constructing carbon-nitrogen, carbon-oxygen and carbon-carbon bonds.[1] Since its discovery, the Chan-Lam reaction,[2] namely the cross-coupling of arylboronic acids with nucleophiles containing heteroatoms, such as amines, alcohols, or mercaptans, et al., has attracted significant attention in terms of forming carbon heteroatom bonds owing to the mild reaction conditions and open-flask chemistry (i.e., room temperature, weak base, ambient atmosphere).[3] In addition, this reaction has been successfully employed for the total synthesis of natural products.[4] Recently, the Chan-Lam reaction has been used to prepare N-aryl or N-vinyl nitrones by selective N-functionalization through the cross-coupling of oximes with aryl or alkenyl boronic acids.[5] Nitrones are ubiquitous organic intermediates in the production of heterocyclic compounds via cycloaddition.[6] In 2012 Anderson and coworkers pioneered a method to prepare N-vinyl fluorenone nitrones by cross-coupling 9-fluorenone oximes with alkenyl boronic acids in the presence of 1.0 or 2.0 equiv. of $Cu(OAc)_2$.[7] Later, the Chan-Lam reaction was used to prepare N-aryl/N-vinyl-α,β-unsaturated nitrones from α,β-unsaturated oximes and aryl or vinyl boronic acids (Scheme 1-A).[8] These findings demonstrated an elegant method for the preparation of N-substituted-α,β-unsaturated nitrones; however, these reactions often required copper salts (1.0 or 2.0 equiv.) and excess pyridine (10.0 equiv.). Although these studies have showed that adding 2.0 equivalents of 1,5-cyclooctadiene (COD) to the reaction could reduce the required amount of Cu(II) to 20 mol%, the process was still inefficient and produced excess COD waste. Several research groups have aimed to develop systems using catalytic copper salts by introducing various additives, strong oxidants, or pyridine-based N-ligands, and using recyclable heterogeneous catalysts or electrochemical catalytic methods.[9] However, these reactions were not green and sustainable enough because excess additives and complex ligands were required, or multi-step synthesis of the heterogeneous catalysts, wasted time, money, energy, and labor. Therefore, the developement of a green and sustainable system to carry out the Chan-Lam reaction is desirable.

Recently, the use of visible light as an inexhaustible source of clean energy to promote sustainable organic synthesis has attracted significant attention.[10] because it satisfies the requirements for sustainable chemistry; specifically, it avoids waste production (from ligands, additives, or by-products) after the reaction is completed.[11] However, to date, only two reports have described visible light

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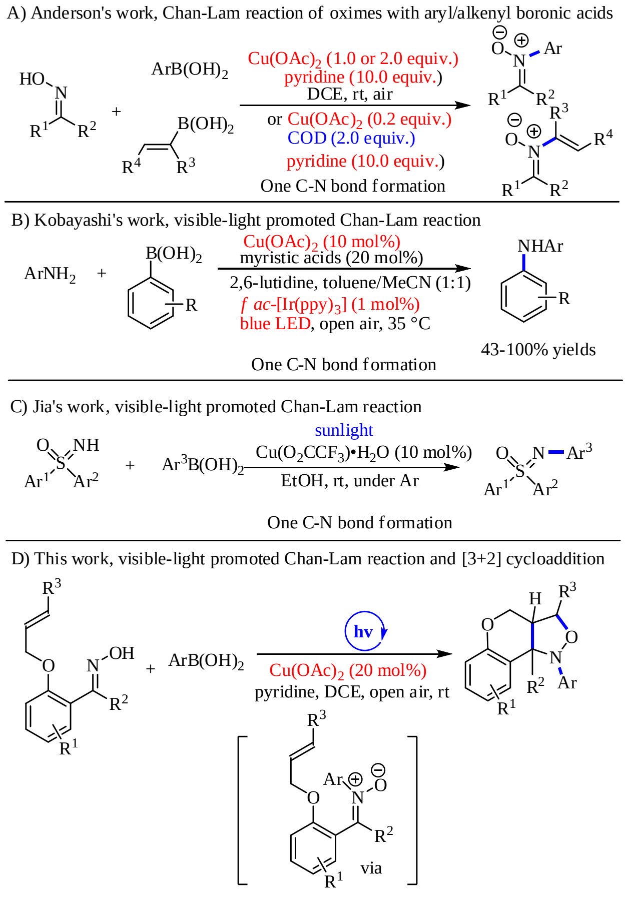
promoted Chan-Lam reactions. First, in 2015, Kobayashi and coworkers pioneered the visible-light mediated Chan-Lam coupling reaction of aniline derivatives with arylboronic acids by using a Cu(II) salt and an iridium-based photocatalyst. Importantly, they elucidated the reactivity of electron-deficient arylboronic acids in the cross-coupling reactions (Scheme 1-B).[12] Mechanistic studies revealed that the visible light likely either promoted the conversion of Cu(II) to Cu(III) intermediates or facilitated the Cu(I) to Cu(II) oxidation to complete the catalytic cycle. Then, in 2021, Jia and co-workers developed a copper-catalyzed photoredox dehydrogenative Chan-Lam coupling reaction between free diaryl sulfoximines and arylboronic acids in the presence of visible light, showing that the C-N bond coupling occurred in the absence of ligand, base and air conditions (Scheme 1-C).[13] Mechanistic studies revealed that (i) visible light promoted the oxidation of Cu(I) to Cu(II) and (ii) the ligation of N-arylated sulfoximines onto copper species enabled its capability as photocatalysts.



Scheme 1. New design for a cascade reaction of Chan-Lam reaction and cycloaddition using visible light.

Intermediates containing N-O moieties were useful as O- and N-sources to access complex building blocks, such as amines, alcohols, or 1,3-amino alcohols via N-O bond transformations.[14] Our group has developed several selective Chan-Lam reactions that are suitable for preparing nitrones or N-oxides by the cross-coupling reaction of N-O moieties with various aryl or alkenylboronic acids.[15] However, stoichiometric amounts of Cu(II) salts were also required. Recently, we developed a metal-free strategy to prepare N-aryl nitrones from oximes with diaryliodonium salts,[16] and also designed a metal-free N-arylation/[3+2] cycloaddition/[3,3]-rearrangement reaction that used alkynyl-tethered oximes and diaryliodonium salts to prepare 2,3-fused indoles.[17] However, these metal-free strategies often produced iodobenzene waste and required purification by column chromatography after the reaction was completed. Based on our group's investigations of cycloadditions powered by visible light,[18] we designed a visible light promoted Chan-Lam reaction to generate N-aryl nitrone moieties, and then catalyze the intramolecular [3+2] cycloaddition of those N-aryl nitrone moieties with internal alkenes to afford chromeno[4,3-c]isoxazolidines (Scheme 1-D). Chromenoisoxazolidines are important molecular scaffolds in drug discovery, with the properties relevant for antidepressants, antipsychotics, and antianxiolytics.[19] The few available strategies for the synthesizing these compounds rely on the intramolecular cycloaddition of alkenyl-tethered aldonitrones at high temperatures with harsh reagents were reported, and only low or moderate efficiencies were attained for alkenyl-tethered ketonitrones.[20] Therefore, developing efficient and green methods for the synthesis of chromenoisoxazolidines remains an important synthetic goal. Herein, we report a visible light promoted Chan-Lam reaction and [3+2] cycloaddition cascade to prepare a series of chromeno[4,3-c]isoxazolidines using a one pot method.

Results and Discussion

Initially, alkenyl-tethered oxime **1a** and phenylboronic acid **2a** were selected as the model substrates. As shown in Table 1, chromeno[4,3-c]isoxazolidine **3aa** was generated in 84% yield when **1a** and **2a** reacted under the standard conditions: $Cu(OAc)_2$ (20 mol%), methylene blue (5 mol%), and pyridine (pyr) (3.0 equiv.) in DCE (3.0 mL), using a 17 W white LED open to air at room temperature (Table 1, entry 1). The structure of **3aa** was determined by X-ray diffraction analysis.[21] No reaction occurred in the absence of $Cu(OAc)_2$ after 72 h (Table 1, entry 2). Nitrone **4aa** was the only product obtained (35% yield; 10:1 E/Z isomers) in the absence of 17 W white LED light, and **3aa** was not observed, suggesting that visible light promoted both the Chan-Lam reaction and the [3+2] cycloaddition (Table 1, entry 3). Next, various copper species were evaluated in the presence of visible light. Other Cu(II) salts, such as $CuCl_2$, $CuBr_2$, and $Cu(OTf)_2$, all catalyzed the reaction smoothly to afford **3aa** in yields ranging from 29% to 45%, whereas the addition of CuCl afforded **3aa** in only

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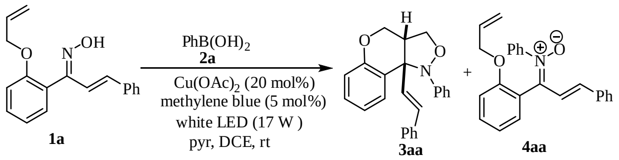
6% yield (Table 1, entries 4-7). Interestingly, using CuBr and CuI as catalysts gave **3aa** in 15% and 30% yields, respectively (Table 1, entries 8-9). These results showed that the anion of Cu(I) salt had an impact on the yield of **3aa**. Product **3aa** was not obtained without methylene blue and that reaction only afforded nitrone **4aa** in 41% yield (Table 1, entry 10). However, when methylene blue was replaced with the photoredox catalyst, Eosin Y, the reaction generated **3aa** in 62% yield (Table 1, entry 11). Decreasing the amount of methylene blue to 1 mol% afforded **3aa** in 65% yield (Table 1, entry 12). When the 17 W white LED was replaced with an 11 or 4 W white LED, the yield of **3aa** was in 71% and 55%, respectively (Table1, entries 13-14). Solvent screening revealed that the reaction proceeded smoothly in DCM, MeCN, THF, MeOH, and DMF, affording **3aa** in good yields (Table 1, entries 15-19). Changing the amount of $Cu(OAc)_2$ to 10 mol% generated **3aa** in 57% yield (Table 1, entry 20). When the loading amounts of phenylboronic acid **2a** were reduced to 1.5 equiv. and 1.0 equiv., the yield of **3aa** was dropped to 59% and 45% yield, respectively (Table 1, entries 21-22). Therefore, the optimal conditions for synthesizing chromeno[4,3-c]isoxazolidine **3aa** in a one pot reaction were: $Cu(OAc)_2$ (20 mol%), methylene blue (5 mol%), and pyridine (3.0 equiv.) in DCE at room temperature, open to air under 17 W white LED light.

Table 1. Optimization of reaction conditions.[a]

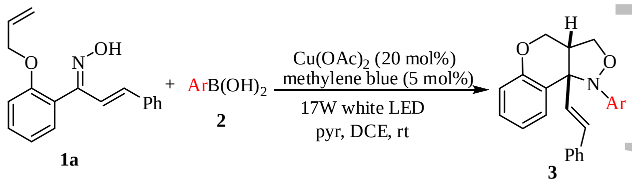


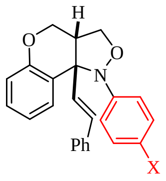
entry	conditions	3aa%[b]	4aa%[b]
1	The standard conditions	84	-
2	Without $Cu(OAc)_2$	-	-
3	Without 17 W white LED	<5	35
4	$CuCl_2$ instead of $Cu(OAc)_2$	45	-
5	$CuBr_2$ instead of $Cu(OAc)_2$	31	-
6	$Cu(OTf)_2$ instead of $Cu(OAc)_2$	29	-
7	CuCl instead of $Cu(OAc)_2$	6	-
8	CuBr instead of $Cu(OAc)_2$	15	-
9	CuI instead of $Cu(OAc)_2$	30	-
10	Without methylene blue	<5	41
11	Using Eosin Y as photosensor	62	-
12	Using methylene blue (1 mol%)	65	-
13	11 W instead of 17 W	71	-
14	4 W instead of 17 W	55	-
15	DCM instead of DCE	62	-
16	MeCN instead of DCE	79	-
17	THF instead of DCE	61	-
18	MeOH instead of DCE	69	-
19	DMF instead of DCE	65	-
20	Using 10 mol% of $Cu(OAc)_2$	57	-
21	Using 1.5 equiv of **2a**	59	
22	Using 1.0 equiv of **2a**	45	

[a] The standard conditions: **1a** (0.3 mmol), **2a** (0.6 mmol), $Cu(OAc)_2$ (20 mol%), methylene blue (5 mol%), DCE (3.0 mL), pyr (0.9 mmol, 3.0 equiv.), 17 W white LED, in air, 30 ˚C, 36-72 h;[b] isolated yield.

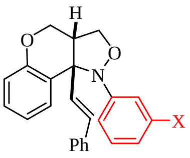
With the standard conditions in hand, various arylboronic acids **2** were evaluated to determine the scope of the reaction for preparing chromeno[4,3-c]isoxazolidines via the visible light promoted cascade. As shown in Table 2, various arylboronic acids with electron-donating and electron-withdrawing groups at the *para*-, *meta*-, and *ortho*-positions proceeded smoothly to produce the corresponding chromeno[4,3-c]isoxazoles **3ac-3ap** in moderate to good yields. The one exception was 4-methoxyphenylboronic acid **2b,** which afforded **3ab** in only 26% yield likely because of the facile decomposition of **2b** to 4-methoxyphenol under the visible light conditions. In general, arylboronic acids tolerated the strongly electron-withdrawing CF_3 and CO_2Me groups at the *para*-positions, to give products **3ai** and **3aj** in 54% and 55% yields, respectively. Interestingly, arylboronic acid **2n** with an *ortho*-bromo substituted group afforded **3an** in 51% yield. This product was more difficult to prepare using the developed method compared with conventional Chan-Lam reaction conditions without visible light. Carbazole-derived boronic acids **2o** and **2p** both delivered the desired products **3ao** and **3ap** in 76% and 63% yields, respectively. This visible light promoted cascade strategy tolerated halides, ethers, thioether, esters and carbazoles.

Table 2. Substrate scope of arylboronic acids **2**. [a,b]

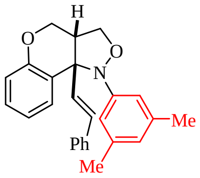




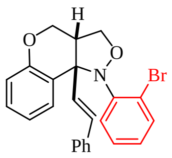
X = OMe, **3ab**, 26%
X = OPh, **3ac**, 62%
X = SMe, **3ad**, 56%
X = Me, **3ae**, 70%
X = Cl, **3af**, 71%
X = Br, **3ag**, 68%
X = F, **3ah**, 61%
X = CF_3, **3ai**, 54%
X = CO_2Me, **3aj**, 55%



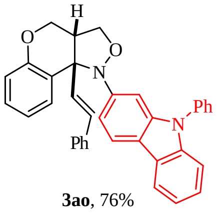
X = OMe, **3ak**, 66%
X = Br, **3al**, 73%



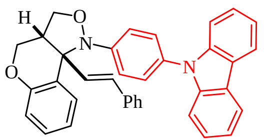
3am, 68%



3an, 51%



3ao, 76%



3ap, 63%

[a] Reaction conditions: **1a** (0.3 mmol), **2** (0.6 mmol), $Cu(OAc)_2$ (20 mol%), methylene blue (5 mol%), DCE (3.0

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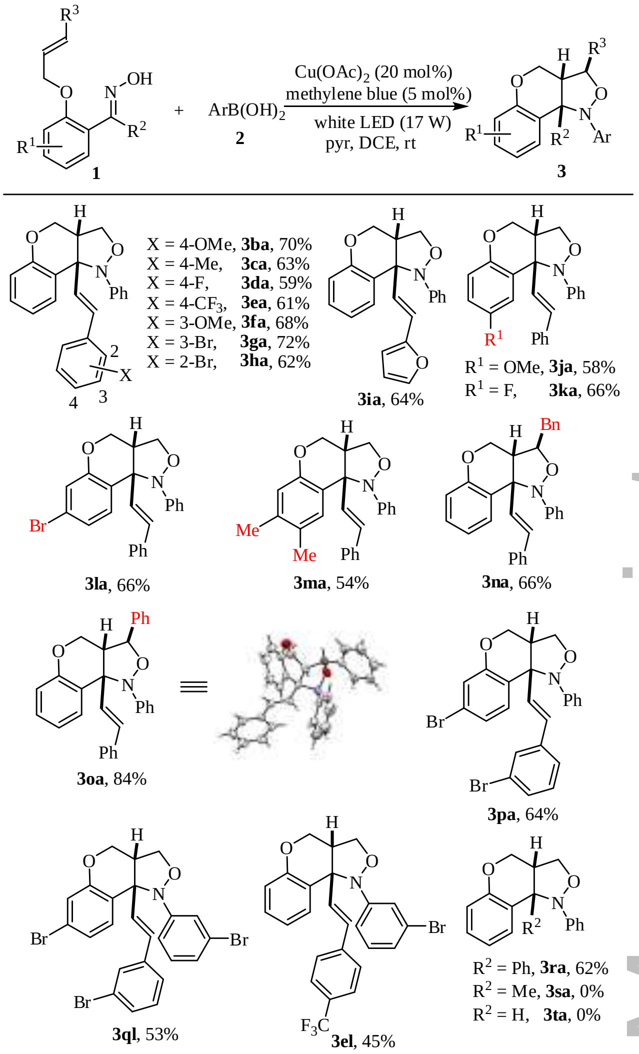
mL), pyr (0.9 mmol, 3.0 equiv.), 17 W white LED, in air, 30 ˚C, 36-72 h; [b)] isolated yield.

Alkenyl-tethered oximes **1** were also studied to further explore the scope of this cascade process. As shown in Table 3, a variety of alkenyl-tethered oximes reacted with **2a** to afford the desired chromeno[4,3-c]isoxazoles **3** in good yields. When the R^2 group comprised an aryl group bearing electron-donating or electron-withdrawing groups at the *para*, *meta*, or *ortho*-positions, the products **3ba-3ha** were obtained in good yields. Even the oxime **1i,** which had a furanyl substituent, gave the corresponding product **3ia** in 64% yield. The R^1 group in the aryloxy moieties was not only compatible with methoxy, fluoro, and bromo groups but also with two methyl groups affording the products **3ja-3ma** in good yields. The R^3 group at the terminal position of the alkene in the oxime could be a benzyl or phenyl group, which provided **3na** and **3oa** bearing three continuous stereocenters in 66% and 84% yields as single isomers, respectively. The structure of compound **3oa** was determined by X-ray diffraction, which indicated that it was a *cis*-isomer based on the relative configuration of its styrenyl, proton, and phenyl groups.[21] The reaction also tolerated various functional groups present in both oxime and arylboronic acid and delivered the desired cycloadducts **3pa**, **3ql**, and **3el** in good yields. In addition to the R^2 group bearing styrenyl groups, the R^2 group could also be present with phenyl group and afford **3ra** in 62% yield. However, when oximes **1s** with a methyl and **1t** with a hydrogen at the R^2 group, compounds **3sa** and **3ra** were not observed because the Chan-Lam reaction of these types of oximes with phenylboronic acid **2a** did not occur.[22]

Table 3. Substrate scope of oximes **1**.[a,b]



[a)] Reaction conditions: **1** (0.3 mmol), **2** (0.6 mmol), $Cu(OAc)_2$ (20 mol%), methylene blue (5 mol%), DCE (3.0 mL), pyr (0.9 mmol, 3.0 equiv.), 17 W white LED, in air, 30 ˚C, 36−72 h; [b)] isolated yield.

To better understand the mechanism, control experiments were performed (Scheme 2). Nitrone **4aa** could not be converted to **3aa** in the presence of $Cu(OAc)_2$ without 17 W white LED light whereas **3aa** was obtained in 82% yield without $Cu(OAc)_2$ in the presence of 17 W white LED light (Scheme 2-1 and 2-2). These results indicated that visible light did promote the cycloaddition while the copper additive did not catalyze the cycloaddition. As shown in Scheme 2-3, 20 mol% of $Cu(OAc)_2$ delivered **4aa** in 35% yield, although a 73% yield was obtained using 1.0 equiv. of $Cu(OAc)_2$ and no white LED. Combining $Cu(OAc)_2$ with visible light afforded **3aa** in 80% yield. These results suggested that visible light promoted both the Chan-Lam reaction and the cycloaddition step. When **1a** and **2a** were subjected to the standard conditions in the presence of N_2, **4aa** and **3aa** were not detected, and only **1a** was recovered, demonstrating that the air played an important role (Scheme 2-4). When 1.0 equiv. of 9,10-dimethylanthracene was added, the yield of **3aa** dropped to 56%, and the trapped product 9,10-

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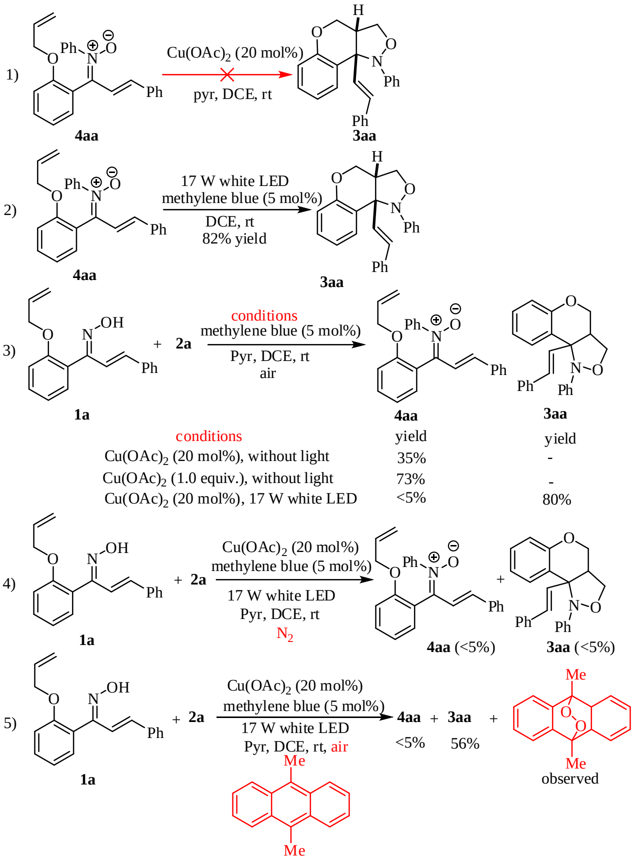
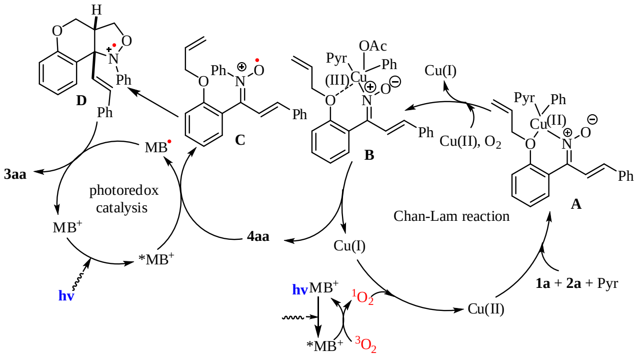
dimethyl-9,10-dihydro-9,10-epidioxgeanthracene was observed (Scheme 2-5). Because 9,10-dimethylanthracene is a typical singlet oxygen quencher, we proposed that singlet oxygen was the key species promoting the oxidation of Cu(I) to Cu(II) to finish the catalytic cycle.



conditions	4aa yield	3aa yield
Cu(OAc)$_2$ (20 mol%), without light	35%	-
Cu(OAc)$_2$ (1.0 equiv.), without light	73%	-
Cu(OAc)$_2$ (20 mol%), 17 W white LED	<5%	80%

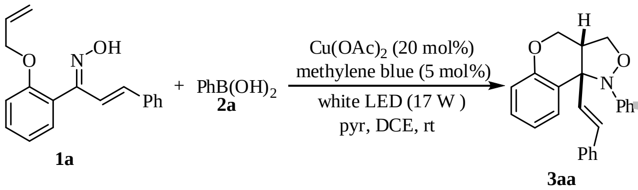
Scheme 2. Mechanistic studies.

Although the mechanism was not definitely elucidated, a reasonable mechanism for the formation of **3aa** from **1a** and **2a** was proposed (Scheme 3). Initially, the Cu(II) catalyst undergoes ligand exchange and transmetalation between oxime **1a** and phenylboronic acid **2a** with pyridine (pyr) as base and N-ligand to generate intermediate **A**. Disproportionation of the Cu(II) intermediate **A** in the presence of air affords Cu(III) species **B** and releases Cu(I) species, which undergoes reductive elimination to give nitrone **4aa** and a Cu(I) species.[12, 23] The Cu(I) species can then be reoxidized to a Cu(II) species by the singlet oxygen ($^1O_2$) produced by the photosensitization with the excited state of methylene blue *MB$^+$. Concurrently, photoirradiation of ground state methylene blue MB$^+$ generates the triplet excited state *MB$^+$, which is reductively quenched by nitrone **4aa**, generating a radical cation **C** and a semi-reduced MB radical (MB$^\cdot$).[24] Then, **C** undergoes intramolecular radical addition to form the chromenoisoxazolidine radical cation **D**, which rapidly undergoes single electron transfer reduction to produce **3aa** and return the MB$^\cdot$ radical to the ground state (i.e., MB$^+$).



Scheme 3. Proposed mechanism.

The operational simplicity of the one-pot Chan-Lam reaction and cycloaddition cascade has significant potenial for preparing chromenoisoxazolidines with an economic and green protocol, particularly if it could be scaled up. As shown in Scheme 4, 1.0 mol of **1a** (0.279 g) reacted with **2a** under the optimized conditions after 36 h. Pure **3aa** was obtained in 86% yield (0.305 g) following extraction and recrystallization procedures without requiring flash column chromatography. When 9 mmol of oxime **1a** (2.5 g) was allowed to react with **2a** under the standard conditions, 2.099 g of **3aa** was obtained (66% yield) after purification by the same method. This simple operation avoided conventional purification procedures and provided a green approach to reduce waste.



1a		3aa
0.279 g, 1 mmol	extraction and recrystallization	0.305 g, 86% yield
2.500 g, 9 mmol	extraction and recrystallization	2.099 g, 66% yield

Scheme 4. Gram-scale preparation and purification of product **3aa**

To study the utility of chromenoisoxazolidines, several reductive conditions were evaluated. As shown in Scheme 5-1, treating **3aa** with Fe/HOAc in DCM at 40 °C afforded compound **5aa** in 46% yield, whereas compounds **6aa** and **7aa** were obtained in 72% and 12% yields, respectively, after treating **3aa** with Zn/HOAc instead. Additionally, **3la** and **3oa** were converted to the corresponding products **6la** (78% yield) and **7la** (21% yield), and **6oa** (54% yield) and **7oa** (25% yield), respectively. It is known that estrone-derived arylboronic acid **2q** can be easily prepared by Lee's method in three steps.[25] When

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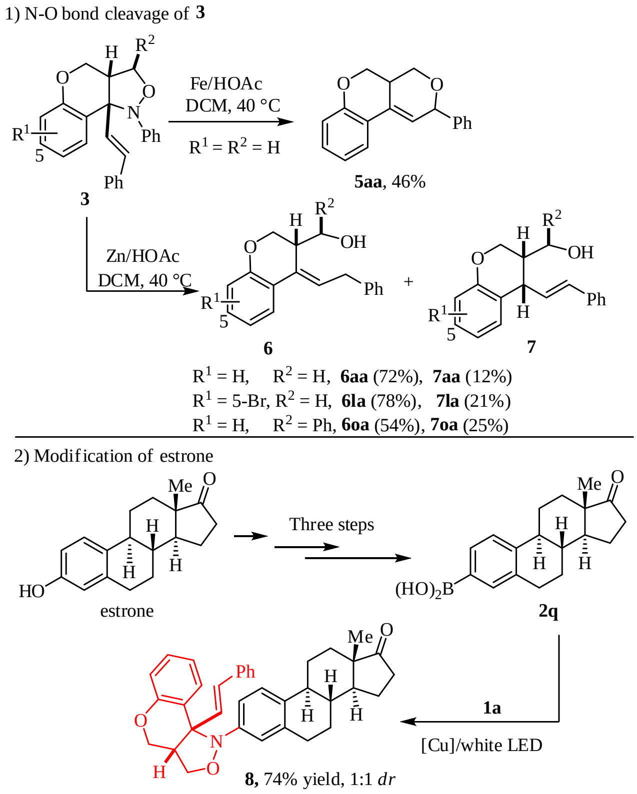
arylboronic acid **2q** and oxime **1a** reacted under the optimized conditions, the desired estrone-derived chromenoisoxazolidine **8** was afforded in 74% yield with 1:1 diastereoselectivity (Scheme 5-2).



Scheme 5. Applications of chromenoisoxazolidines.

Conclusion

We have identified a visible light promoted cascade reaction that was suitable for the preparation of various chromenoisoxazolidines in good yields. These reactions proceeded through a Chan-Lam reaction and subsequent [3+2] cycloaddition under mild reaction conditions starting with alkenyl-tethered oximes and arylboronic acids. The developed method tolerated a variety of substrates with various functional groups. The use of visible light promoted a catalytic Chan-Lam reaction and enabled metal-free cycloaddition. Overall, this method featured mild reaction conditions, minimized waste and could be scaled up without losing significant performance, avoided stoichiometric amounts of copper salts, and accommodated diverse chromenones and late-stage modifications.

Experimental Section

General procedure for the synthesis of chromeno[4,3-c]isoxazoles 3: A 25 mL reaction flask was charged with oxime **1** (0.3 mmol), arylboronic acid **2** (0.6 mmol, 2.0 equiv.), $Cu(OAc)_2$ (20 mol%), methylene blue (5 mol%), pyridine (0.9 mmol, 3.0 equiv.), and DCE (3 mL) in air. Then, the reaction mixture was stirred and irradiated (17 W white LED) at room temperature for 36−72 h (monitored by TLC). At this time, the solvent was removed under reduced pressure and the crude product was purified by flash column chromatography (the crude residue was dry loaded with silica gel, 1/20 to 1/10, ethyl acetate/petroleum ether as the eluent) to afford chromeno[4,3-c]isoxazole **3**.

Acknowledgements

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[22] Although oximes **1s** and **1t** did not work in the Chan-Lam reaction conditions, compound **3sa** and **3ta** were obtained in 77% and 70% yields, respectively, from other synthetic methods in the 17W white LED light. Please see more details for the preparation of **3sa** and **3ta** in the Supporting Information.

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RESEARCH ARTICLE

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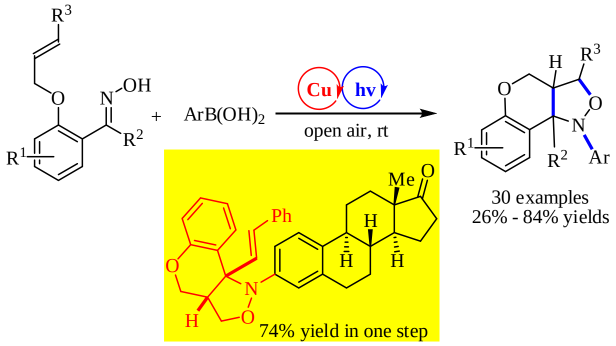
Jie Zhao, Bing-Qing Huang, Bin-Can Zhu, Xiao-Pan Ma*, and Dong-Liang Mo*



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