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Construction of C(sp^2)-C(sp^3) Bond between Quinoxalin-2(1*H*)-ones and *N*-Hydroxyphthalimide Esters via Photocatalytic Decarboxylative Coupling

Zhiyang Yan,[a] Bin Sun,[a] Xun Zhang,[b] Xiaohui Zhuang,[b] Jin Yang,[b] Weike Su,[a, b] and Can Jin*,[b]

Abstract: A novel visible-light-driven decarboxylative coupling of alkyl *N*-hydroxyphthalimide esters (NHP esters) with quinoxalin-2(1*H*)-ones has been developed. This C(sp^2)-C(sp^3) bond-forming transformation exhibits excellent substrate generality with respect to both the coupling partners, and of note, a series of 3-primary alkyl substituted quinoxalin-2(1*H*)-ones that were difficult to synthesize by previous methods could be obtained in moderate to excellent yields. Additionally, the mild conditions, easy availability of substrates, wide functional group tolerance and operational simplicity make this protocol practically in synthesis of 3-alkylated quinoxalin-2(1*H*)-ones.

Introduction

Construction of C(sp^2)-C(sp^3) bond is one of the most important protocols to modify the structure of heterocyclic compounds.[1] Transition-metal catalyzed cross-coupling reactions, such as Suzuki and Kumada couplings, are classical methods for C(sp^2)-C(sp^3) bond formation.[2] However, prefunctionalization, multiple steps and low atomic economy limited its further application. In recent years, direct C-H functionalization has been considered as an efficient strategy to construct C(sp^2)-C(sp^3) bond because this protocol can simplify the reaction process and increase the atomic economy.[3] However, this strategy still has several drawbacks. For example, it usually requires the use of transition-metal catalysts, excess amounts of oxidants and vigorous conditions, leading to high toxicity and energy consumption. Therefore, developing green and efficient methods for construction of C(sp^2)-C(sp^3) bonds is still of great interest.

Quinoxalin-2(1*H*)-ones, especially the 3-alkylated derivatives are widely existed in various pharmacologically active compounds (Fig 1).[4] The traditional method for synthesis of 3-alkylated quinoxalin-2(1*H*)ones was realized via the condensation between aryl-1,2-diamines and a suitable partner.[5] Recently, some progress has been made in the synthesis of 3-alkylated quinoxalin-2(1*H*)-ones via direct C-H functionalization (scheme 1).[6] For example, Qu's group successively achieved the benzylation, oxyalkylation and hydroxyalkylation of quinoxalin-2(1*H*)-ones (scheme 1, a-c).[6a-c] Additionally, Yang and co-workers described an iron-catalyzed direct C-H cyanoalkylation of quinoxalin-2(1*H*)-ones (scheme 1, d).[6d] Wang's group also achieved the oxyalkylation of quinoxalin-2(1*H*)-ones via a visible-light-inducted cross-dehydrogenative coupling reaction (scheme 1, reaction e).[6e] However, these methods all require the participation of metal catalyst or oxidant. Moreover, alkylation of quinoxalin-2(1*H*)-ones with straight-chain-alkyl group such as *n*-propyl, isopropyl, and *tert*-butyl groups is still a serious challenge.

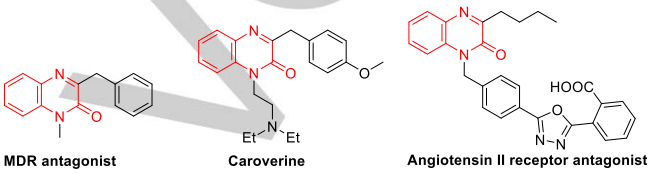
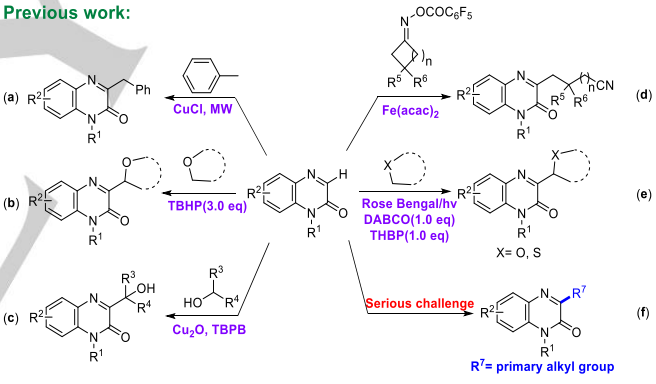


Figure 1. Representative biologically active of 3-alkyl quinoxalin-2(1*H*)-ones.



Scheme 1. Strategies for the synthesis of 3-alkylated quinoxalin-2(1*H*)-ones

Minisci reaction is a useful tool to accomplish the alkylation of *N*-heteroarenes, in which a protonated *N*-heteroarene is attacked by an alkyl radical generated through decarboxylation.[7] Generally, decarboxylation of carboxylic acids is widely used in organic synthesis.[8] In recent years, alkyl *N*-hydroxyphthalimide (NHP) esters was emerged as an efficient decarboxylation alkylation reagent because it could be reduced by photocatalyst, generating a variety of alkyl radicals via elimination of CO_2 and phthalimide.[9] For example, the regioselective alkylation of *N*-heteroarenes with alkyl NHP esters under irradiation of blue LEDs was achieved by Shang and Fu.[10] We supposed that this process also could be applied for the synthesis of 3-alkylated quinoxalin-2(1*H*)-ones. With our

[a] Dr. B. Sun, Z. Y. Yan, Prof. Dr. W. K. Su
Collaborative Innovation Center of Yangtze River Delta Region Green Pharmaceuticals
Zhejiang University of Technology
Hangzhou 310014 (P. R. China)
[b] X. Zhang, X. H. Zhuang, J. Yang, Prof. Dr. C. Jin, Prof. Dr. W. K. Su
College of Pharmaceutical Sciences
Zhejiang University of Technology
Hangzhou 310014 (P. R. China)
E-mail: jincan@zjut.edu.cn

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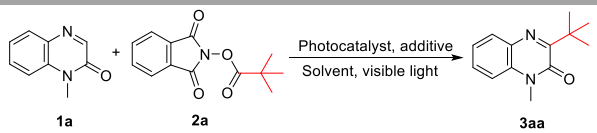
ongoing interest on developing green and efficient methods for direct C-H functionalization,[11] herein, we report a metal and oxidant free Minisci type reaction of quinoxalin-2(1*H*)one with alkyl NHP esters via a photocatalytic system promoted by visible light, leading to the synthesis of a variety of 3-alkylated quinoxaline-2(1*H*)-ones in moderate to excellent yields.

Results and Discussion

To begin our study, *N*-methylquinoxalin-2(1*H*)-one **1a** and alkyl NHP esters **2a** were chosen as model substrates to optimize the reaction conditions. The reaction was initially studied with *fac*-Ir(ppy)$_3$ (1 mol%) as a photocatalyst, trifluoroacetic acid (TFA) as an additive, and irradiated with 3 W white LEDs in DMSO under N_2 atmosphere for 40 h. Fortunately, the product **3aa** was obtained in a yield of 61% (Table 1, entry 1). When other photocatalysts such as Ru(bpy)$_3$Cl$_2$, Na$_2$-eosin Y, Rose Bengal, Methylene Blue and Rhodamine B were examined, it was delighted to find that Na$_2$-eosin Y exhibited a better efficiency and gave **3aa** in 97% yield (Table 1, entries 2-6). It could not exhibit positive effect on the yield of **3aa** when the amount of Na$_2$-eosin Y was increased to 3 mol% (Table 1, entry 7). Subsequently, other solvents such as DCE, EtOAc, DCM, MeCN were screened but none of them could give the desired product (Table 1, entries 8-11). In order to explore the effect of light source, white LEDs were replaced by blue LEDs or green LEDs, and the results revealed that the yields of **3aa** were both decreased (Table 1, entries 12, 13). Furthermore, different acids such as TfOH, AcOH were employed and both seem to be more negative than TFA, giving **3aa** in 92% and 65% yields (Table 1, entries 14-15). It was also observed that the yield of **3aa** was sharply decreased to 11%, when no additive was added (Table 1, entry 16). Contrast experiments demonstrated that visible light and photocatalyst were both essential for this decarboxylative coupling reaction (Table 1, entries 17-18). Notably, only trace product **3aa** was obtained when this progress was carried out under air atmosphere (Table 1, entries 19). After screening the reaction conditions, it was concluded that this cross-coupling transformation should be performed in the presence of Na$_2$-eosin Y (1 mol%) and TFA (0.5 equiv.) in DMSO with irradiation of 3 W white LEDs under N_2 atmosphere for 40 h.

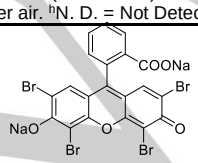
Table 1. Optimization of the Reaction Conditions



1a 2a 3aa

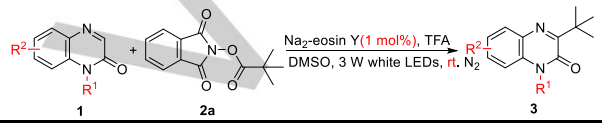
Entry	Photocatalyst	Solvent	Additive	Yield(%)
1	*fac*-Ir(ppy)$_3$	DMSO	TFA	61
2	Ru(bpy)$_3$Cl$_2$	DMSO	TFA	61
3	Na$_2$-Eosin Y	DMSO	TFA	97
4	Rose Bengal	DMSO	TFA	50
5	Methylene Blue	DMSO	TFA	N. D.
6	Rhodamine B	DMSO	TFA	N.D.
7[c]	Na$_2$-Eosin Y	DMSO	TFA	97
8	Na$_2$-Eosin Y	DCE	TFA	N. D.
9	Na$_2$-Eosin Y	EtOAc	TFA	N. D.
10	Na$_2$-Eosin Y	DCM	TFA	N. D.
11	Na$_2$-EosinY	MeCN	TFA	N. D.
12[d]	Na$_2$-Eosin Y	DMSO	TFA	75
13[e]	Na$_2$-Eosin Y	DMSO	TFA	49
14	Na$_2$-Eosin Y	DMSO	TfOH	92
15	Na$_2$-Eosin Y	DMSO	AcOH	65
16	Na$_2$-Eosin Y	DMSO	-	11
17	-	DMSO	TFA	N. D.
18[f]	Na$_2$-Eosin Y	DMSO	TFA	N. D.
19[g]	Na$_2$-Eosin Y	DMSO	TFA	trace

[a]Reaction conditions: **1a** (1.0 mmol), **2a** (1.2 mmol), catalyst (0.01 mmol), additive (0.5 mmol), solvent (3.0 mL), rt, 3 W white lights, 40 h. [b]Isolated yield base on **1a**. [c]Na$_2$-Eosin Y (0.03 mmol). [d]3 W Blue LEDs. [e]3 W Green LEDs. [f]without light. [g]under air. [h]N. D. = Not Detected

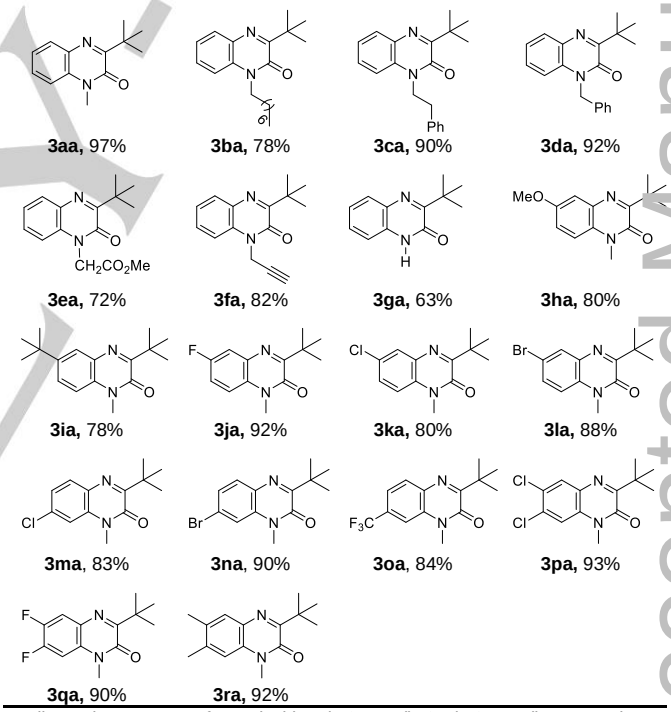


Na$_2$-Eosin Y

Table 2. Substrate Scope of Quinoxalin-2(1*H*)-ones



1 2a 3

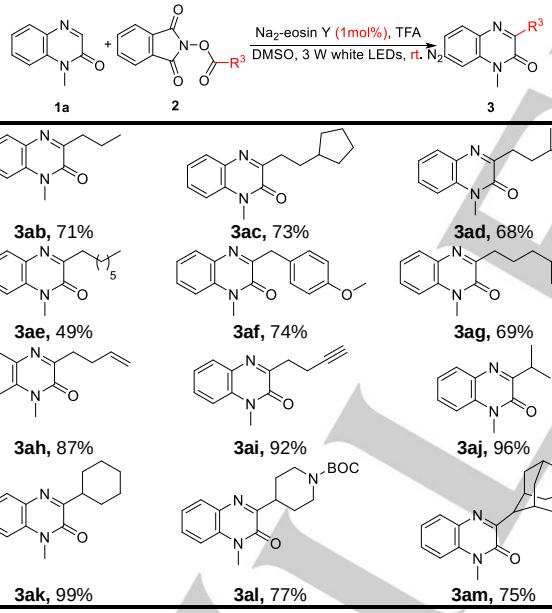


[a]All reactions were performed with **1** (1.0 mmol), **2a** (1.2 mmol), Na$_2$-eosin Y (0.01 mmol) and TFA (0.5 mmol) in DMSO (3.0 mL) at room temperatur with irradiation by white LEDs under N_2 atmosphere for 40 h.

With the optimized conditions in hand, the scope of the quinoxalin-2(1*H*)-ones was then investigated. As show in table 2, a series of *N*-alkylated quinoxalin-2(1*H*)-ones were examined, and the results revealed that these substrates were all suitable for this transformation, providing the corresponding products in moderate to good yields (**3aa-3fa**). Initially, when the methyl

group was changed into the *n*-octyl group, the corresponding product **3ba** could be obtained in satisfied yield. In addition, primary alkyl with phenyl, ester or alkynyl group was also tolerated in this reaction and gave the corresponding products in moderate to good yields (**3ca**-**3fa**). Delightfully, the quinoxalin-2(1*H*)-ones without *N*-substituted also displayed good tolerance for this transformation and gave the product **3ga** in 63% yield. Subsequently, the quinoxalin-2(1*H*)-ones with different substituents on the benzene ring were also investigated under the optimized conditions, providing the corresponding products **3ha-3ra** in good to excellent yields. For example, quinoxalin-2(1*H*)-ones bearing electron-donating groups at 6-position of aromatic ring, such as methoxy and *t*-butyl, provided corresponding products in 80% and 78% yields (**3ha, 3ia**). Notably, substrates bearing electron-withdrawing substituents such as fluoro, chloro, bromo at 6-position of benzene ring showed excellent tolerance for this reaction, and provided the corresponding products in good yields (**3ja-3la**). Subsequently, quinoxalin-2(1*H*)-ones with substituents at 7-positions were examined, and the corresponding product **3ma**, **3na** was obtained in 83% and 90% yields, respectively. Remarkably, it was worth noting that quinoxalin-2(1*H*)-ones bearing strong electron-withdrawing group (trifluoromethyl) at 7-position, could also undergo this transformation smoothly, and provided the target product **3oa** in a yield of 84%. It was noted that the disubstituted quinoxalin-2(1*H*)-ones containing two electron-withdrawing groups (**1p**, **1q**) or electron-donating groups (**1r**) in the 6- and 7- positions, also could undergo this decarboxylative coupling process well, and gave the corresponding products in good yields (**3pa**-**3ra**).

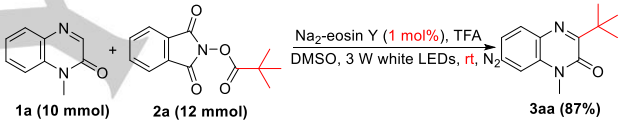
Table 3. Substrate Scope of Alkyl NHP Esters[a]



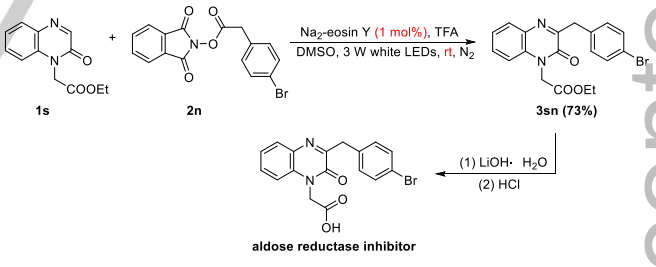
[a]All reactions were performed with **1a** (1.0 mmol), **2** (1.2 mmol), Na_2-eosin Y (0.01 mmol) and TFA (0.5 mmol) in DMSO (3.0 mL) at room temperature with irradiation by white LEDs under N_2 atmosphere for 40 h.

After the scope of quinoxalin-2(1*H*)-ones was explored, a variety of alkyl NHP esters were then examined via the decarboxylative coupling reaction with *N*-methylquinoxalin-2(1*H*)-one **1a**. The experimental results indicated that different types of alkyl (primary, secondary and tertiary) NHP esters were found to be suitable for this reaction (**3ab-3am**). Initially, primary alkyl NHP esters bearing *n*-propyl, 2-cyclopentyl-ethyl, 3-methyl-butyl, *n*-heptyl were tested and the corresponding products were obtained in only moderate yields (**3ab-3ae**), which mainly due to the lower reactivity of primary alkyl radical compared with tertiary alkyl radicals. In addition, primary alkyl group bearing additional benzyl, alkenyl or alkynyl group was also well tolerated for this transformation, providing the desired alkylated products **3af-3ai** in 69-92% yields. However, no methylated product was detected when methyl NHP ester was applied to react with *N*-methylquinoxalin-2(1*H*)-one under standard condition. Subsequently, the secondary alkyl NHP esters were also explored, and the results showed that alkyl NHP esters bearing isopropyl, cyclohexyl, pyridyl were all adapt to this reaction and the desired products **3aj**, **3ak**, **3al** were obtained in 96%, 99% and 77% yields. Furthermore, adamantyl NHP ester also survived in this procedure and gave the desired product **3am** in 75% yield.

To evaluate the potential synthetic utility of this decarboxylative coupling reaction, the reaction between *N*-methylquinoxalin-2(1*H*)-one **1a** and *t*-butyl NHP esters **2a** was carried out on a gram-scale under the optimized conditions, and gave the desired product **3aa** in the yield of 87% (Scheme 2). In addition, an aldose reductase inhibitor precursor **3sn** was obtained by this transformation in a yield of 73% (Scheme 3). Ethyl 2-(2-oxoquinoxalin-1(2*H*)-yl)acetate **1s** was coupled with alkyl NHP ester **2n** under the optimized standard conditions to give the product **3sn**, which could be used for synthesis of a aldose reductase inhibitor after hydrolysis and acidification.



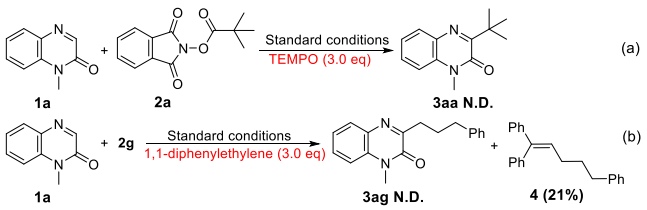
Scheme 2. Large-scale experiment



Scheme 3. Application of the coupling strategy to the synthesis of the aldose reductase inhibitor.

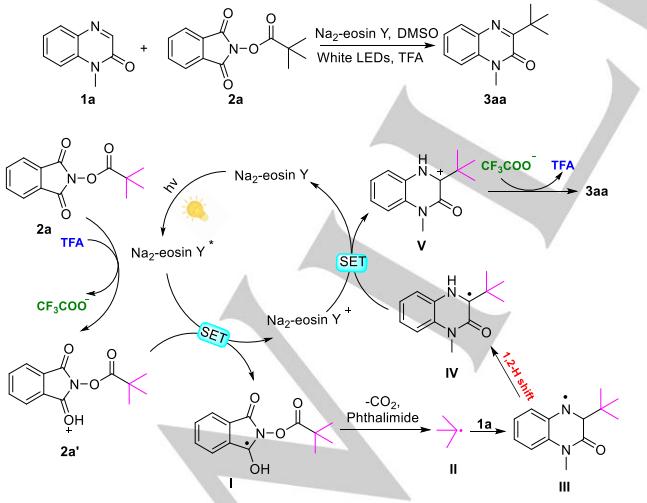
To unambiguously clarify this reaction mechanism, several control experiments were conducted. As show in scheme 4, when TEMPO (2,2,6,6-tetramethyl-1-piperidinyl-oxy) (3.0 equiv.) was added into the model reaction, the transformation was completely suppressed, which might indicate that this reaction proceeded via a radical process. To confirm the formation of alkyl radical, another radical scavenger 1,1-

diphenylethylene (3.0 equiv.) was introduced into the coupling reaction between *N*-methyl-quinoxalin-2(1*H*)-one **1a** and aryl-propyl NHP ester **2i**. Expectedly, the adduct **4** of 3-phenylpropyl radical and 1,1-diphenylethylene was isolated in a yield of 21%, while the corresponding product **3ai** was not observed. Furthermore, the Stern-Volmer experiment demonstrated that Na_2-eosin Y* could be quenched by alkyl NHP esters rather than quinoxalin-2(1*H*)-ones. Finally, the quantum yield (Φ) of the reaction was estimated by chemical actinometry and a low value was observed (Φ = 0.225) (for more details, see Supporting Information).



Scheme 4. Control experiments

On the basis of control experiments and previous reports, a plausible mechanism for this decarboxylative coupling reaction was proposed in Scheme 4. Under visible light irradiation, the photocatalyst Na_2-eosin Y was turned into its excited form Na_2-eosin Y*. Through the comparision of the redox potential of Na_2-eosin Y (PC^+/PC^*: -1.44 V vs. SCE) and alkyl NHP esters (-1.26 to -1.37 V vs. SCE),[12] it could be concluded that Na_2-eosin Y* can be quenched by alkyl NHP ester **2a'** that was protonated by TFA via a single-electron transfer (SET) process to generate radical **I** and Na_2-eosin Y^+. After the elimination of CO_2 and phthalimide, radical **I** was change into *tert*-butyl radical **II**. Subsequently, the radical **II** regioselectively attacked quinoxalin-2(1*H*)-ones **1a** to produce nitrogen radical **III**. After a hydrogen transfer process, nitrogen radical **III** was turned into carbon radical **IV**, which could be further oxidized by Na_2-eosin Y^+ to provide carbocation **V** via another SET process. Finally, **3aa** was generated through a deprotonation process of intermediate **V**.



Scheme 5. Proposed mechanism

Conclusions

In summary, we have developed a green and efficient method for construction of C(sp^2)-C(sp^3) bonds via decarboxylative coupling reaction between various quinoxalin-2(1*H*)-ones and alkyl NHP esters. A wide scope of linear alkyl NHP esters and a variety of quinoxalin-2(1*H*)-ones bearing various functional groups were demonstrated to be suitable for this transformation, providing a novel avenue to synthesize C-3 alkylated quinoxalin-2(1*H*)-ones. This protocol was featured by its mild conditions, easy availability of substrates, wide functional group tolerance and operational simplicity.

Experimental Section

General Information. Melting points were determined using a digital melting point apparatus and uncorrected. ^{1}H NMR spectra were recorded at 400 MHz using TMS as internal standard, ^{13}C NMR spectra were recorded at 100 MHz using TMS as internal standard. ^{19}F NMR spectra were recorded at 376 MHz using TMS as internal standard. All chemical shifts were reported as δ values (ppm) relative to TMS and observed coupling constants (*J*) are given in Hertz (Hz). Mass spectra were measured with a HRMS-ESI instrument. Cyclic voltammetry were measured by CHI660E (Chenhua, China) electrochemical workstation. Unless otherwise indicated, all reactions were carried out under N_2 atmosphere at room temperature with magnetic stirring. Quinoxalin-2(1*H*)-ones and *N*-acyloxyphthalimides were prepared according to literatures. All reagents were purchased from commercial source and without prior purification. Column chromatography was performed on silica gel (200-300 mesh) and the elution was performed with hexane/ethyl acetate.

General procedure for the synthesis of 1.[13] Ethyl 2-oxoacetate (1.1 equiv.) was added to a suspension of *o*-arylenediamine (4 mmol, 1 equiv.) in ethanol (1 mol/L). The reaction mixture was stirred and heated at reflux in an oil bath for 1 h, then at room temperature for 16 h. Upon completion (as monitored by TLC), the precipitate was filtered and washed with ethanol, then dried to give quinoxalinone. For alkylation, the corresponding halogenoalkane (1.6 equiv.) was added to a suspension of quinoxalinone (1 equiv.) and potassium carbonate (1.2 equiv.) in DMF (16 mL). The mixture was stirred at room temperature for 16 h. Upon completion (as monitored by TLC), the reaction mixture was washed with saturated solution of ammonium chloride (5 mL), ethyl acetate (10 mL) and water (10 mL). The organic layer was separated and the aqueous layer was extracted with ethyl acetate (2 × 10 mL). The combined organic layers were dried with anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The resulting organic residue was purified by flash chromatography column over silica gel (SiO_2) to afford the desired substrate **1**.

General procedure for the synthesis of 2.[9c] In a 50 mL round bottom flask equipped with magnetic stir bar was added *N*-hydroxyphthalimide (1.63 g, 10 mmol, 1.0 equiv), 4-dimethylaminopyridine (61mg, 0.5 mmol), dicyclohexylcarbodiimide (2.47 g, 12 mmol, 1.2 equiv), CH_2Cl_2 (20 mL) and carboxylic acid (12 mmol, 1.2 equiv). The mixture was stirred at room temperature for 0.5-3 h, during which time the reaction mixture became cloudy and a white solid precipitated from the solution. The white solid was removed via vacuum filtration and the filtrate was removed under reduced pressure. The crude product was purified by chromatography on a silica gel column (0→20% ethyl acetate/hexane) to afford the desired substrate **2**.

General procedure for the synthesis of 3 (3aa as an example). To a 10 mL Schlenk-tube was charged with *N*-methylquinoxalin-2(1*H*)-one **1a** (160 mg, 1.0 mmol), *N*-(acyloxy)-phthalimide **2a** (296 mg, 1.2 mmol), Na_2-eosin Y (7 mg, 0.01 mmol), DMSO (1.5 mL) and TFA (57 mg, 0.5 mmol). The tube was evacuated and backfilled with N_2 for three times.

The mixture was then irradiated by 3 W white LEDs for 40 h. The reaction mixture was then quenched with water (20 mL) and extracted with DCM (10 mL × 3). The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel column (ethyl acetate/hexane, 1:12) to afford **3aa** as a white solid.

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Keywords: C(sp^2)-C(sp^3) • metal and oxidant free • quinoxalin-2(1*H*)-ones • NHP esters • photoredox catalysis

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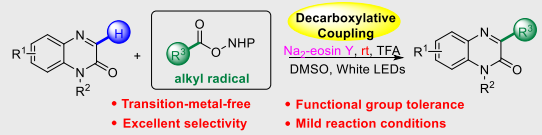

A metal and oxidant free decarboxylative coupling of quinoxalin-2(1*H*)-ones with NHP esters via a photocatalytic system promoted by visible light has been developed.

Zhiyang Yan, Bin Sun, Xun Zhang, Xiaohui Zhuang, Jin Yang, Jiayang Wang, and Can Jin*,

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Construction of C(sp^2)-C(sp^3) Bond between Quinoxalin-2(1*H*)-ones and *N*-Hydroxyphthalimide Esters via Photocatalytic Decarboxylative Coupling

[c] Z. Yan, X. Zhang, X. Zhuang, J. Yang, J. Wang, Prof. [illegible] C.
College of Pharmaceutical Sciences
Zhejiang University of Technology
Hangzhou 310014 (P. R. China)
E-mail: jincan@zjut.edu.cn
[b] Dr. B. Sun
Collaborative Innovation Center of Yangtze River Delta Reg
Green Pharmaceuticals
Zhejiang University of Technology
Hangzhou 310014 (P. R. China)

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