有机化学 DOI: 10.6023/cjoc202110030 研究论文
Chinese Journal of Organic Chemistry ARTICLE

可见光催化苯并噁唑与 α-酮酸合成芳基苯并噁唑

李亚东 吴鹏举 杨志勇*
(贵州理工学院化学工程学院 贵阳 550003)

摘要 发展了一种高效的可见光催化合成 2-芳基苯并噁唑的方法. 与传统合成芳基苯并噁唑的方法相比, 该方法反应条件温和, 仅需要 Eosin Y 作为光催化剂, 不需要任何其他金属催化剂. 该反应副产物仅有 CO_2, 后处理简单. 在该反应条件下, 含有不同取代基的苯并噁唑与 α-酮酸都呈现出非常好的反应活性, 能够合成一系列的芳基苯并噁唑.
关键词 可见光催化; 2-芳基苯并噁唑; α-酮酸; 自由基反应

Synthesis of 2-Aryl Benzoxazoles from Benzoxazoles and α-Ketoic Acids by Photoredox Catalysis

Li, Yadong Wu, Pengju Yang, Zhiyong*
(*Department of Chemical Engineering*, *Guizhou Institute of Technology*, *Guiyang 550003*)

Abstract An efficient protocol for the synthesis of 2-aryl benzoxazoles via visible light-initiation has been developed. Compared with the traditional method for the synthesis of arylbenzoxazole, the reaction conditions of this method are mild, and only Eosin Y is needed as photocatalyst without any other metal catalyst. The purification of the desired product is easier because only CO_2 is produced as the byproduct. Under the optimal reaction conditions, benzoxazole with different substituents and α-keto acids show very good reactivity and a series of arylbenzoxazoles can be synthesized.
Keywords photoredox catalysis; 2-aryl benzoxazole; α-keto acid; radical reaction

1 Introduction

Aryl substituted benzoxazoles, a kind of unique *N*-containing heteroaromatic compounds, have constantly been used as building blocks for the synthesis of pharmaceuticals due to their significant biological activities,[1] such as anticonvulsant,[2] antihypertensive[3] and antitumor ones.[4] Remarkable efforts have been paid to explore novel and well-organized methodologies to construct these motifs since 1887.[5] Conventionally, there are three methods to construct this motif (1) transition metal-catalyzed C—H functionalization of benzoxazoles with aryl halides,[6] aryl boronic acids,[7] carboxylic acids and derivatives;[8] (2) intramolecular cyclization of formanilides;[9] (3) condensation of 2-aminophenols/benzoxazoles with aldehydes,[10] alcohols,[11] benzylamines[12] and derivatives.[13] In the very recent years, the progress in the synthesis of 2-substituted benzothiazole was summarized by Yang and Han *et al*.[14] The strategies to form these blocks started from benzoxazoles or 2-aminophenols obviously have advantages over the method via intramolecular cyclization of formanilides because the substrates are readily available. However, the high reaction temperature and the requirement of non-reusable catalyst loading still raise serious economic and environmental concerns inevitably, especially in large-scale industrial processes. Thus, it is necessary to switch the harsh reaction conditions to a mild and practicable synthetic method for the arylation of benzoxazoles.

Recently, the visible light-driven chemical reactions for the construction of carbon-carbon (C—C) or carbon-heteroatom (C—X) bonds have attracted much attention owing to the energy issue.[15] This methodology involved in a single-electron transfer (SET) to replace the conventional two electron transfer process, and had achieved significance progress in organic synthetic chemical science.[16] With this strategy, α-keto acids, a kind of available acids has been proved to undergo direct decarboxylation to afford the corresponding radicals under photoredox

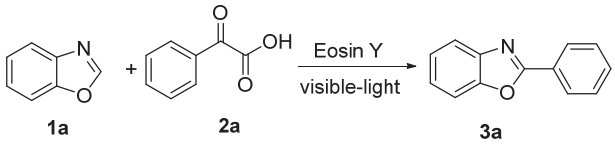
* Corresponding author. E-mail: Zhiyyang@git.edu.cn
Received October 21, 2021; revised January 4, 2022; published online February 25, 2022.
Project supported by the Scientific Research Foundation for Advanced Talents from Guizhou Institute of Technology (No. XJGC20180931) and the Science and Technology Foundation of Guizhou Province (Nos. QKHJZ20152060, QKH20167093, QKH Zhicheng [2017]2817, QKH Zhicheng [2018]2835).
贵州理工学院高层次人才启动(No. XJGC20180931)和贵州省科技厅自然科学基金(Nos. QKHJZ20152060, QKH20167093, QKH Zhicheng [2017]2817, QKH Zhicheng [2018]2835)资助项目.

catalysis conditions with a relative clean byproduct CO_2. The acyl radicals can be used as acylation or alkylation/arylation agents in many synthetic process approaching to new C—C or C—X bond formation.[17] In the context of our interest in the arylation of benzoxazoles in particular, we noticed that Lei and co-works[18] have reported a decarboxylative amidation of *α*-keto acids with amines catalyzed by $[Ru(phen)_3]Cl_2$ under the irradiation of visible light in 2013 (Scheme 1, a). And Biswas's[19] studies on the synthesis of 2-aryl benzothiazoles through condensation of 2-aminothiophenols and aldehydes by visible light-driven also proved that acyl radical can be used as arylation reagent for the synthesis of 2-aryl benzothiazoles with photoredox catalysis (Scheme 1, b). However, the arylation of benzoxazoles directly with this practical strategy has never been reported. Based on our previous exploration on the synthesis of 2-aryl benzoxazoles using phenylglyoxylic acids as the arylation reagent,[20] we wonder that the acyl radicals generated from *α*-keto acids whether react with benzoxazoles directly to afford 2-aryl benzoxazoles under a visible light-mediated condition (Scheme 1, c). With the sharp difference from the Lei's reports using ruthenium complexes as photoredox catalyst, this assumed process choosing organic dye Eosin Y as photoredox catalyst, surely has the advantages in economy and in terms of environmental friendliness.

2 Results and discussion

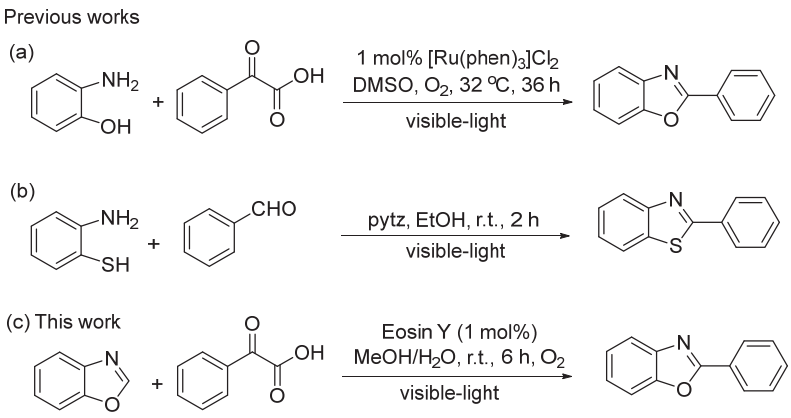
In our initial study, benzoxazole (1.0 equiv.) and phenylglyoxylic acid (2.0 equiv.) were mixed in EtOH, using Eosin Y (1 mol%) as the photoredox catalyst, and irradiated with a 5 W green LEDs (530 nm).[21] The resulting mixture was then stirred at room temperature for 12 h, affording the desired product, 2-aryl benzoxazole (**3a**), in 42% yield (Table 1, Entry 1). The arylation product was isolated in a slightly higher yield of 55% when 0.3 mL of H_2O was added into the reaction (Table 1, Entry 2). However, no desired product was found while the H_2O was sole solvent (Table 1, Entry 3). The reaction conditions were further optimized by reducing the reaction time from 12 h to 6 h (Table 1, Entry 4). Moreover, the obtained yield was increased to 60% by using MeOH instead of EtOH as the reaction solvent (Table 1, Entry 5). However, when dimethyl sulfoxide (DMSO), chlorobenzene (PhCl), MeCN or dimethylformamide (DMF) were applied, no reaction took place (Table 1, Entries 6～9), indicating MeOH was the most suitable solvent. Additional control experiments revealed that the oxidation condition was essential for this process. When the reaction atmosphere was changed from air to N_2, only 8% yield of **3a** was obtained, while the yield increased to 76% when the reaction proceeded under O_2 atmosphere (Table 1, Entries 10, 11). Details of the mechanism of the reaction proceeded under a N_2 atmosphere is still under investigation. Moreover, in the absence of visible light or Eosin Y, the transformation was completely inhibited under the optimum conditions (Table 1, Entries 12, 13). Based on these experimental results, the standard

Table 1 Optimization of the reaction conditions[a]



Entry	PC	Solvent	Time/h	Yield[b]/%
1	Eosin Y	EtOH (dry)	12	42
2	Eosin Y	EtOH/H_2O (2/0.3 mL)	12	55
3	Eosin Y	H_2O	12	0
4	Eosin Y	EtOH/H_2O (2/0.3 mL)	6	56
5	Eosin Y	MeOH/H_2O (2/0.3 mL)	6	60
6	Eosin Y	DMSO/H_2O (2/0.3 mL)	6	0
7	Eosin Y	PhCl/H_2O (2/0.3 mL)	6	0
8	Eosin Y	CH_3CN/H_2O (2/0.3 mL)	6	0
9	Eosin Y	DMF/H_2O (2/0.3 mL)	6	0
10[c]	Eosin Y	MeOH/H_2O (2/0.3 mL)	6	8
11[d]	Eosin Y	MeOH/H_2O (2/0.3 mL)	6	76
12[e]	Eosin Y	MeOH/H_2O (2/0.3 mL)	6	Trace
13	—	MeOH/H_2O (2/0.3 mL)	6	0

[a] Reaction conditions: **1a** (0.3 mmol), **2a** (0.6 mmol), Eosin Y (1 mol%), O_2, 6 h. [b] GC yield based on **1a**. [c] Reaction performed under a nitrogen atmosphere. [d] Reaction performed under an oxygen atmosphere. [e] Reaction performed in the absence of LEDs.



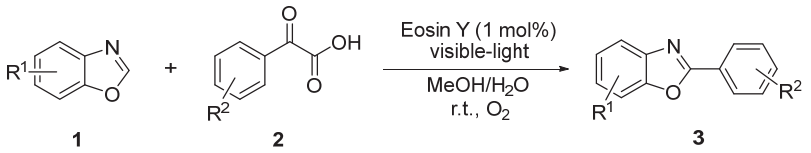
Scheme 1 Visible light-induced arylation of benzoxazoles

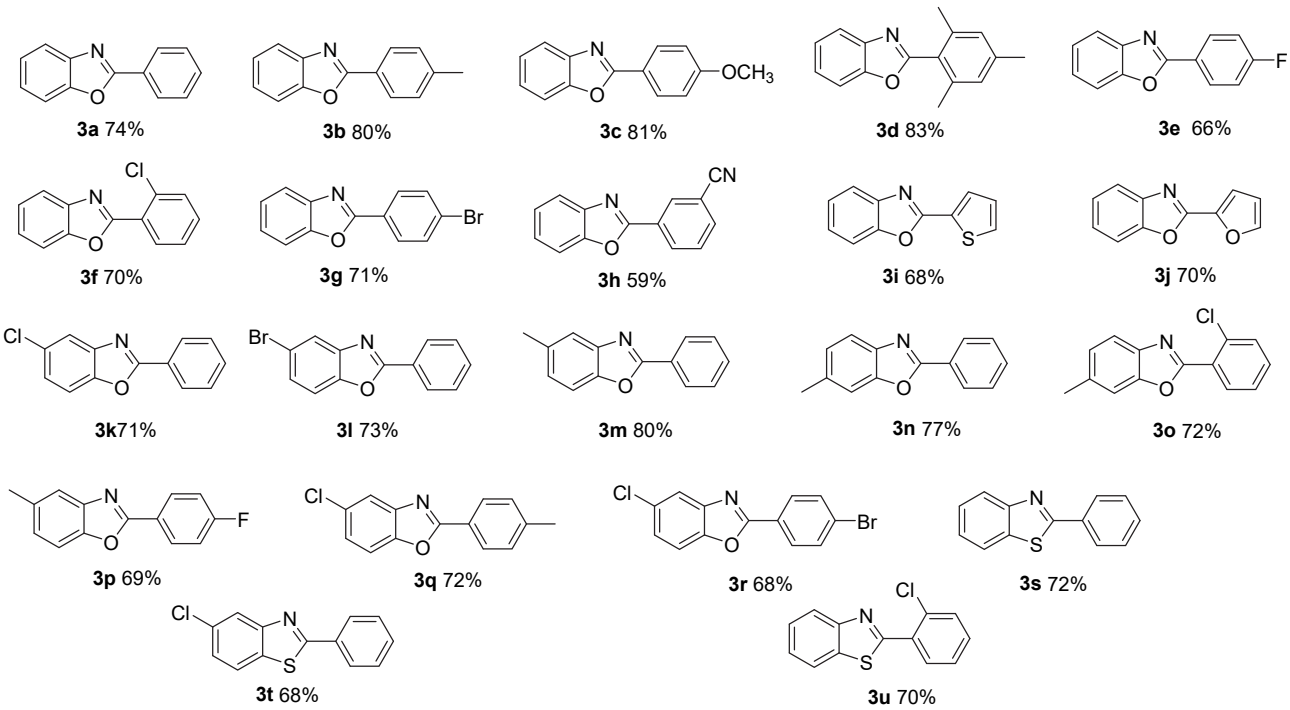
reaction conditions were determined. Specifically, benzoxazoles reacted with 2.0 equiv. of phenylglyoxylic acids in the presence of 1 mol% Eosin Y in MeOH/H_2O, while the mixture was irradiated with a 5 W green LEDs under O_2 atmosphere for 6 h.

With the optimal experimental conditions in hand, the scope and limitations of this reaction were explored. As shown in Table 2, the decarboxylative arylation of benzoxazoles was initially examined by treating a variety of substituted *α*-keto acids with **1a**. The results demonstrated that the *α*-keto acids bearing either electron-donating, neutral, or electron-withdrawing groups on the benzene ring, readily reacted with benzoxazole with moderate to good yields ranging from 59% to 83%. Comparatively, the substrates bearing an electron-donating group led to slightly higher arylation yields, such as the *α*-keto acid with a nitrile substrate exhibited less reactivity to this transformation and resulted in lower yields compared to electron-donating groups. It should be emphasized that 2-furylglyoxylic acid was also a suitable partner, as it could afford the corresponding product in 68% yield. Next, a series of benzoxazoles bearing diverse substituents were also explored, affording the arylation products in yields ranging from 61% to 77%. However, the benzoxazoles with a strong electron-withdrawing groups on the 5-position almost could not participate in the reaction, such as the nitryl group, only afforded yields less than 5%. The synthesis of corresponding products using the benzothiazole substrate and phenylglyoxylic acid was not successful under the same reaction conditions, maybe the thiazole ring is more stable than the oxazole ring. To address this problem, a stoichiometric amount of iodine was added in the photoredox system. Surprisingly, the desired 2-aryl benzothiazole product was isolated in 72% yield. It was demonstrated that iodine, as a strong oxidant, promoted the thiazole ring-opening, leading ultimately to the arylation product.

To suggest a preliminary mechanism of the transformation, a series of control experiments were performed (Scheme 2). First, analogue **3a** could also be formed by treating 2-aminophenol with phenylglyoxylic acid under the standard conditions in 80% yield (Scheme 2, a). However, 2-aminophenol was not detected when benzoxazole was employed under the standard conditions in the absence of phenylglyoxylic acid, while benzoxazole remained intact (Scheme 2, b), indicating that no ring-opening occurred before the acylation. To find out whether the transformation of this reaction really involved in a radical process, a radical scavenger, 2,2,6,6-tetramethylpiperidin-1-oxyl (TEMPO), was added to the reaction mixture under the optimized reaction conditions, resulting in complete

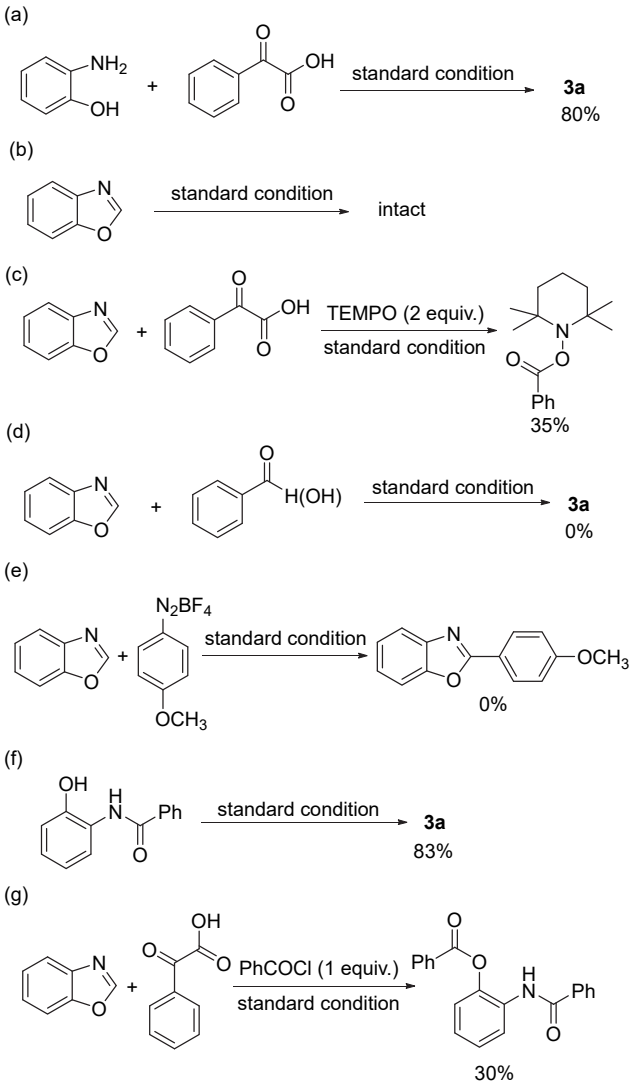
Table 2 Arylation of benzoxazoles with various *α*-keto acids[a]





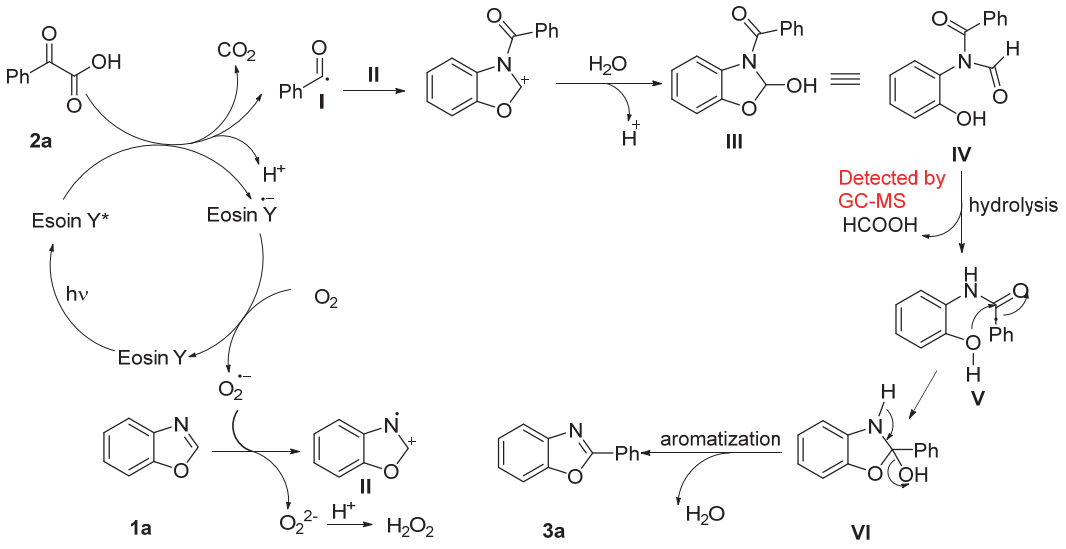
[a] Reaction conditions: **1** (0.3 mmol), **2** (0.6 mmol), Eosin Y (1 mol%), MeOH/H_2O (2/0.3 mL), 5 W green LEDs, r.t., O_2, 6 h. [b] Isolated yield based on **1**.

inhibition of the **3a** formation. The corresponding product of radical trapping TEMPO-benzoyl moiety, was observed by GC-MS analysis, implying that the reaction proceeded via a radical-free pathway (Scheme 2, c). When benzaldehyde or benzoic acid was used instead of phenylglyoxylic acid, the target compound (**3a**) was not formed (Scheme 2, d). According to König's[22] report, aryl radical can be formed by SET from the excited state of Eosin Y to aryl diazonium salt in MeOH solvent. Benzoxazole was then treated with 4-methoxybenzene diazonium salts and phenylglyoxylic acid under the standard conditions. No 4-methoxyl-2-phenylbenzoxazolel was found in the reaction mixture (Scheme 2, e), indicating that the C-2 position of benzoxazole would also not react with aryl radical directly. Thus, the reaction mainly took place through a ring-opening and closure pathway. According to the previous studies,[13] it was believed that a ring-opening-closing process would occurred after a single-electron oxidation at the nitrogen atom of benzoxazole instead of reacting with aryl radical on C-2 position directly. To prove this hypothesis, a further control experiment conducted by treating 0.5 equiv. of *N*-(2-hydroxyphenyl)benzamide under the standard reaction conditions. Analysis of the reaction mixture by GC revealed that the target product 2-aryl benzoxazole was actually formed in 83% yield (Scheme 2, f). The exist of intermediate analogue *N*-(2-hydroxyphenyl)benzamide could be obtained by adding an amount of benzoyl chloride into the reaction mixture (Scheme 2, g).



Scheme 2 Control experiments

Although the exact reaction mechanism was not completely clarified regarding the 2-aryl benzoxazole formation, a plausible reaction pathway could be suggested based on the control experiments and previous reports (Scheme 3).[13,21] Specifically, Eosin Y that served as the photoredox catalyst, could be excited by visible light, leading to the formation of a benzoyl radical **I** from phenylglyoxylic acid via a single-electron transfer (SET), along



Scheme 3 Proposed mechanism for arylation of benzoxazoles with α-keto acids

with the formation of Eosin Y$^{\bullet-}$. Eosin Y$^{\bullet-}$ is a powerful reducing agent (Eosin Y$^{\bullet-}$ to Eosin Y is −1.06 V) quenched by molecular oxygen to accomplish the photoredox cycle by generating the hydroperoxyl radical $O_2^{\bullet-}$.[21] At the meantime, a one-electron oxidation take place at the nitrogen atom of benzoxazole with the hydroperoxyl radical anion $O_2^{\bullet-}$, producing benzoxazole radical cation **II** and O_2^{2-}.[21d] Benzoxazole radical cation **II** subsequently reacts with the benzoyl radical, affording the intermediate **III** which may transform to the unstable intermediate acylformimide **IV**. The acylformimide **IV** could be hydrolyzed to the intermediate **V** along with the HCOOH (detected by GC-MS). This step was also proved in Cheng's report.[13d] The intermediate **V** then undergoes cyclisation to generate the intermediate **VI**. Finally, the desired arylation product 2-phenylbenzoxazole (**3a**) is formed from the intermediate **VI** trough a dehydration-aromatization reaction.

3 Conclusions

In summary, an efficient way to synthesizing 2-aryl benzoxazoles was developed, while the visible light-initiated direct arylation of benzoxazoles was reported for the first time. With this mild and metal-free protocol, a variety of 2-aryl benzoxazoles can be synthesized with yields ranging from 59% to 83%. Unlike the transition metal-catalyzed processes and traditional condensation reactions that lead to similar products, this methodology employs mild reaction conditions. It is more efficient in cases where substituted benzoxazoles are readily available. Furthermore, the expansion of the reaction scope is currently under investigation.

4 Experimental section

4.1 General information

All the solvents and commercially available reagents were purchased from commercial sources and used directly. ^{1}H NMR and ^{13}C NMR were recorded in $CDCl_3$ at room temperature on the Bruker avance 400 M spectrometer. The chemical-shifts scale is based on internal TMS. Mass spectroscopy data were collected on an Aglient 7250 HRMS-ESI instrument. Products were purified by flash column chromatography on 200～300 mesh silica gel, SiO_2.

4.2 Typical procedure for the preparation of α-keto acids

Phenylglyoxylic acid was purchased commercially and used without further purification. Other α-keto acids were prepared from oxidation of corresponding methyl ketones with SeO_2 according to the reported procedure.[23]

4.3 Typical procedure for the arylation of benzoxazoles with α-keto acids

A 25 mL flask was charged with benzoxazole (**1a**, 0.3 mmol), phenylglyoxylic acid (**2a**, 0.6 mmol) and Eosin Y (1 mol%). Then the mixture of MeOH (2 mL) and H_2O (0.3 mL) was added. The reaction mixture was stirred at room temperature for 6 h exposed under the 5W green LEDs. After the reaction was completed, aqueous (10 mL) and CH_2Cl_2 (10 mL) were added successively to the cooled reaction mixture. The organic phase was separated, and the aqueous phase was further extracted with CH_2Cl_2 (30 mL×3). The combined organic layers were dried over anhydrous $MgSO_4$ and concentrated under vacuum. The crude product was purified with flash chromatography column on silica gel (eluent: petroleum ether/ethyl acetate, V∶V=50∶1) to yield the pure 2-phenylbenzoxazole (**3a**) as a white solid. This procedure was also applied for the synthesis of **3b**～**3u**.

2-Phenylbenzoxazole (**3a**): White solid (43 mg, 74%); m.p. 104～105 ℃ (lit.[6g] 102～103 ℃); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.35～7.37 (m, 2H), 7.53～7.60 (m, 4H), 7.77～7.80 (m, 1H), 8.27～8.28 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 110.6, 120.0, 124.6, 125.1, 127.2, 127.6, 128.9, 131.5, 142.1, 150.8, 161.0.

2-(4-Methylphenyl)benzoxazole (**3b**): White solid (51 mg, 80%); m.p. 112～114 ℃ (lit.[6g] 113～114 ℃); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.36 (s, 3H), 7.24～7.28 (m, 4H), 7.49～7.51 (m, 1H), 7.70～7.72 (m, 1H), 8.09 (d, J=8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 21.5, 110.4, 119.7, 124.3, 124.4, 124.8, 127.5, 129.5, 141.9, 142.1, 150.6, 163.2.

2-(4-Methoxyphenyl)benzoxazole (**3c**): White solid (55 mg, 81% yield); m.p. 105～106 ℃ (lit.[10f] 103～104 ℃); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 3.58 (s, 3H), 7.03 (s, 2H), 7.32～7.34 (m, 2H), 7.547.32～7.57 (m, 1H), 7.737.32～7.75 (m, 1H), 8.20 (d, J=8.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 111.8, 117.3, 123.0, 126.7, 127.8, 128.1, 129.0, 131.9, 143.7, 149.8, 164.1.

2-(2,4,6-Trimethylphenyl)benzoxazole (**3d**): White solid (60 mg, 83% yield); m.p. 63～65 ℃ (lit.[6a] 63～65 ℃); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.29 (s, 6H), 2.35 (s, 3H), 6.98 (s, 2H), 7.37～7.39 (m, 2H), 7.58～7.60 (m, 1H), 7.81～7.83 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 20.3, 21.3, 110.6, 120.1, 124.2, 124.9, 125.0, 128.6, 138.5, 140.3, 141.6, 150.6.

2-(4-Fluorophenyl)benzoxazole (**3e**): White solid (42 mg, 66% yield); m.p. 100～102 ℃ (lit.[10f] 99 ℃); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.17 (t, J=8.8 Hz, 2H), 7.26～7.35 (m, 2H), 7.52～7.55 (m, 1H), 7.73～7.76 (m, 1H), 8.20～8.24 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 110.5, 116.1 (d, $J_{C\text{-}F}$=22.0 Hz), 119.9, 123.4 (d, $J_{C\text{-}F}$=3.0 Hz), 124.6, 125.0, 129.7 (d, $J_{C\text{-}F}$=9.0 Hz), 142.0, 150.7, 162.8, 164.7 (d, $J_{C\text{-}F}$=252.0 Hz).

2-(2-Chlorophenyl)benzoxazole (**3f**): White solid (48 mg, 70% yield); m.p. 100～102 ℃ (lit.[10f] 100～102 ℃); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.39～7.43 (m, 4H), 7.55～7.63 (m, 2H), 7.84～7.87 (m, 1H), 8.14 (d, J=7.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 110.7, 120.5, 124.6, 125.5, 126.2, 126.9, 131.4, 131.8, 131.9, 133.4, 141.7, 150.5, 160.9.

2-(4-Bromophenyl)benzoxazole (**3g**): White solid (58 mg, 71% yield); m.p. 158～159 ℃ (lit.[6g] 157～158 ℃);

^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.33～7.37 (m, 2H), 7.55～7.62 (m, 1H), 7.63 (d, J=8.4 Hz, 2H), 7.74～7.77 (m, 1H), 8.08 (d, J=7.6 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 110.6, 120.1, 124.7, 125.3, 126.0, 126.2, 128.9, 132.1, 141.9, 150.7, 162.0.

3-(Benzoxazol-2-yl)benzonitrile (**3h**): White solid (38 mg, 59% yield); m.p. 143～144 ℃ (lit.[10f] 143～144 ℃); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.40～7.42 (m, 2H), 7.61～7.68 (m, 2H), 7.79～7.82 (m, 2H), 7.49 (d, J=8.0 Hz, 1H), 8.55 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 110.8, 113.6, 117.9, 120.5, 125.1, 126.0, 128.6, 129.9, 131.0, 131.4, 134.4, 141.8, 150.9, 160.7.

2-(Thiophen-2-yl)benzoxazole (**3i**): White solid (43 mg, 68% yield); m.p. 80～82 ℃ (lit.[11b] 81～82 ℃); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.19 (t, J=8.4 Hz, 1H), 7.32 (d, J=8.0 Hz, 1H), 7.38 (t, J=7.6 Hz, 1H), 7.46 (t, J=8.0 Hz, 1H), 7.62 (d, J=5.2 Hz, 1H), 7.79 (d, J=8.0 Hz, 1H), 8.43 (d, J=3.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 116.2, 125.7, 128.6, 128.9, 130.5, 131.6, 132.5, 133.4, 138.6, 145.6, 146.0, 151.5.

2-(Furan-2-yl)benzoxazole (**3j**): White solid (34 mg, 63% yield); m.p. 88～90 ℃ (lit.[11b] 89～90 ℃); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 6.58～6.60 (m, 1H), 7.25～7.27 (m, 1H), 7.32～7.35 (m, 2H), 7.53～7.56 (m, 1H), 7.65 (s, 1H), 7.73～7.76 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 110.5, 112.2, 114.2, 120.1, 124.8, 125.2, 141.6, 142.6, 145.7, 150.1, 155.2.

5-Chloro-2-phenylbenzoxazole (**3k**): White solid (49 mg, 71% yield); m.p. 103～105 ℃ (lit.[10f] 102～104 ℃); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.24 (d, J=7.2 Hz, 1H), 7.40 (d, J=8.8 Hz, 1H), 7.46～7.50 (m, 3H), 7.69 (s, 1H), 8.16 (d, J=7.2 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 111.1, 119.8, 125.2, 126.5, 127.6, 128.8, 129.9, 131.8, 143.1, 164.2.

5-Bromo-2-phenylbenzoxazole (**3l**): White solid (60 mg, 73% yield); m.p. 100～102 ℃ (lit.[9c] 101～103 ℃); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.46 (s, 2H), 7.51～7.56 (m, 3H), 7.90 (s, 1H), 8.23 (d, J=7.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 111.8, 117.2, 117.3, 123.0, 126.7, 127.8, 128.1, 129.0, 131.9, 143.7, 149.8, 164.2.

5-Methyl-2-phenylbenzoxazole (**3m**): White solid (51 mg, 80% yield); m.p. 138～139 ℃ (lit.[6g] 138～139 ℃); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.48 (s, 3H), 7.15 (d, J=8.4 Hz, 1H), 7.44～7.56 (m, 5H), 8.24～8.25 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 21.5, 109.9, 119.9, 126.2, 127.3, 127.5, 128.8, 131.3, 134.3, 142.3, 149.0, 163.1.

6-Methyl-2-phenylbenzoxazole (**3n**): White solid (48 mg, 77% yield); m.p. 94～95 ℃ (lit.[13d] 93 ℃); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.50 (s, 3H), 7.16 (d, J=8 Hz, 1H), 7.37 (s, 1H), 7.51～7.52 (m, 3H), 7.64 (d, J=8 Hz, 1H), 8.23～8.25 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 21.8, 110.7, 119.3, 125.8, 127.3, 127.4, 128.8, 131.2, 135.5, 139.9, 151.0, 162.5.

6-Methyl-2-(2-chlorophenyl)benzoxazole (**3o**): White solid (52 mg, 72% yield); m.p. 123～125 ℃ (lit.[10f] 124～125 ℃); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.50 (s, 3H), 7.19 (d, J=8.0 Hz, 1H), 7.37～7.44 (m, 3H), 7.53～7.56 (m, 1H), 7.10～7.30 (m, 1H), 8.11～8.14 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 21.8, 110.8, 119.8, 125.9, 126.4, 126.8, 131.3, 131.6, 133.3, 136.0, 139.5, 150.8, 160.4.

5-Methyl-2-(4-fluorophenyl)benzoxazole (**3p**): White solid (47 mg, 69% yield); m.p. 170～172 ℃ (lit.[10g] 170 ℃); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.44 (s, 3H), 7.09～7.16 (m, 3H), 7.37 (d, J=8.4 Hz, 1H), 7.50 (s, 1H), 8.15～8.19 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 21.4, 109.8, 116.0 (d, $J_{C\text{-}F}$=22.0 Hz), 119.8, 123.5, 126.1, 129.6 (d, $J_{C\text{-}F}$=9.0 Hz), 134.3, 142.1, 148.9, 162.1, 164.6 (d, $J_{C\text{-}F}$=251.0 Hz).

5-Chloro-2-(4-methylphenyl)benzoxazole (**3q**): White solid (52 mg, 72% yield); m.p. 148～150 ℃ (lit.[10f] 148～150 ℃); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.42 (s, 3H), 7.25～7.31 (m, 3H), 7.44 (d, J=8.4 Hz, 1H), 7.69 (s, 1H), 8.08 (d, J=7.6 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 21.6, 110.1, 119.7, 123.8, 125.0, 127.6, 129.6, 129.8, 142.5, 143.3, 149.2, 164.5.

5-Chloro-2-(4-bromophenyl)benzoxazole (**3r**): White solid (63 mg, 68% yield); m.p. 191～193 ℃ (lit.[10g] 191～192 ℃); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.34 (d, J=8.6 Hz, 1H), 7.49 (d, J=8.4 Hz, 1H), 7.67 (d, J=7.2 Hz, 2H), 7.74 (s, 1H), 8.09 (d, J=7.2 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 111.3, 120.1, 125.7, 126.7, 129.1, 130.3, 132.3, 143.1, 149.3, 163.4.

2-Phenylbenzothiazole (**3s**): White solid (45 mg, 72% yield); m.p. 111～113 ℃ (lit.[10f] 111～113 ℃); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.39 (t, J=7.2 Hz, 1H), 7.48～7.52 (m, 4H), 7.91 (d, J=8.0 Hz, 1H), 8.08～8.11 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 121.6, 123.1, 125.2, 126.2, 127.5 , 128.9, 130.9, 133.5, 134.9, 154.0, 168.0.

5-Chloro-2-phenylbenzothiazole (**3t**): White solid (50 mg, 68% yield); m.p. 111～113 ℃ (lit.[6a] 111～113 ℃); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.47～7.51 (m, 4H), 7.73 (d, J=8.4 Hz, 1H), 8.05～8.08 (m, 2H), 8.21 (s,1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 119.9, 122.6, 126.1, 127.6, 128.2, 129.1, 131.3, 133.2, 133.8, 169.7.

2-(2-Chlorophenyl)benzothiazole (**3u**): White solid (48 mg, 70% yield); m.p. 84～85 ℃ (lit.[10f] 84～86 ℃); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.41～7.46 (m, 3H), 7.51～7.56 (m, 2H), 7.95 (d, J=8.0 Hz, 1H), 8.14 (d, J=8.4 Hz, 1H), 8.21～8.23 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 121.4, 123.5, 125.4, 126.3, 127.1, 130.8, 131.1, 131.8, 132.3, 132.8, 136.1, 152.6, 164.2.

4.4 Synthesis of 2-benzamidophenyl benzoate

A 25 mL flask was charged with benzoxazole (0.3 mmol), phenylglyoxylic acid (0.6 mmol), benzoyl chloride (0.3 mmol) and Eosin Y (1% yield mol). Then MeOH/H_2O (2/0.3 mL) was added. The reaction mixture was stirred at room temperature for 6 h. The concentrated reaction mixture was purified with flash chromatography column on silica gel (eluent: petroleum ether/ethyl acetate, V∶V=4∶1) to yield the pure 2-benzamidophenyl benzoate as a yellow solid (28 mg, 30% yield). m.p. 155～157 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.29～7.32 (m, 4H), 7.39～

7.52 (m, 7H), 7.65 (t, J=8.0 Hz, 1H), 8.10 (d, J=7.6 Hz, 2H), 9.40 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 123.7, 126.3, 127.9, 128.3, 128.6, 128.7, 129.2, 129.8, 129.9, 130.1, 132.5, 132.6, 134.0, 146.1, 162.6, 163.5, 171.1. HRMS (ESI) calcd for $C_{20}H_{15}NO_3$ 317.1052, found 317.1049.

Supporting Information ^{1}H NMR and ^{13}C NMR spectra of compounds **3**. The Supporting Information is available free of charge via the Internet at http://sioc-journal.cn.

References

[1] Wei, C.-X.; Guan, L.-P.; Jia, J.-H.; Cha, K.-Y.; Quan, Z.-S. *Arch. Pharmacal Res.* **2009**, *32*, 23.
(b) Gerova, M.-S.; Stateva, S.-R.; Radonova, E.-M.; Kalenderska, R.-B.; Rusew, R.-I.; Nikolova, R.-P.; Chanev, C.-D.; Shivachev, B.-L.; Apostolova, M.-D.; Petrov, O.-I. *Eur. J. Med. Chem.* **2016**, *120*, 121.

[2] (a) Seth, K.; Garg, S.-K.; Kumar, R.; Purohit, P.; Meena, V.-S.; Goyal, R.; Banerjee, U.-C.; Chakraborti, A.-K. *ACS Med. Chem. Lett.* **2014**, *5*, 512.
(b) Chanda, K.; Rajasekhar, S.; Maiti, B. *Synlett* **2017**, *28*, 521.

[3] (a) Abdeen, S.; Kunkle, T.; Salim, N.; Ray, A.-M.; Mammadova, N.; Summers, C.; Stevens, M.; Ambrose, A.-J.; Park, Y.; Schultz, P.-G.; Horwich, A.-L.; Hoang, Q.-Q.; Chapman, E.; Johnson, S.-M. *J. Med. Chem.* **2018**, *61*, 7345.
(b) Wu, Z.; Bao, X.-L.; Wang, Y.-H.; Anh, N.-T.-P.; Wu, X.-F.; Yan, Y.-J.; Chen, Z.-L. *ACS Med. Chem. Lett.* **2019**, *10*, 40.

[4] (a) Zhang, W.; Liu, J.; Macho, J.-M.; Jiang, X.; Xie, D.; Jiang, F.; Liu, W.; Fu, L. *Eur. J. Med. Chem.* **2017**, *126*, 7.
(b) Dementiev, A.; Joachimiak, A.; Nguyen, H.; Gorelik, A.; Illes, K.; Shabani, S.; Gelsomino, M.; Gelsomino, E.-Y.; Ahn, E.; Nagar, B.; Doan, N. *J. Med. Chem.* **2019**, *62*, 987.

[5] Hantzsch, A.-R.; Weber, J.-H. *Eur. J. Inorg. Chem.* **187**, *20*, 3118.

[6] (a) Do, H.-Q.; Daugulis, O. *J. Am. Chem. Soc.* **2007**, *129*, 12404.
(b) Canivet, J.; Yamaguchi, J.; Ban, I.; Itami, K. *Org. Lett.* **2009**, *11*, 1733.
(c) Yamamoto, T.; Muto, K.; Komiyama, M.; Canivet, J.; Yamaguchi, J.; Itami, K. *Chem.-Eur. J.* **2011**, *17*, 10113.
(d) Shibahara, F.; Yamaguchi, E.; Murai, T. *Chem. Commun.* **2010**, *46*, 2471.
(e) Gao, F.; Kim, B.-S.; Walsh, P.-J. *Chem. Commun.* **2014**, *50*, 10661.
(f) Abdellaoui, F.; Youssef, C.; Ammar, H.-B.; Roisnel, T.; Soulé, J.-F.; Doucet, H. *ACS Catal.* **2016**, *6*, 4248.
(g) WangYang, D.; Yu, X.; Fu, H.; Zheng, X.; Chen, H.; Li, R. *Chin. J. Org. Chem.* **2019**, *39*, 482 (in Chinese).
(汪洋点点, 余晓军, 付海燕, 郑学丽, 陈华, 李瑞祥, 有机化学, **2019**, *39*, 482.)

[7] (a) Ranjit, S.; Liu, X. *Chem.-Eur. J.* **2011**, *17*, 1105.
(b) Xu, Z.; Wang, Z.; Yu, Z.; Wang, R. *Chem.-Eur. J.* **2011**, *17*, 6321.
(c) Phan, N.-T.-S.; Nguyen, C.-K.; Nguyen, T.-T.; Truong, T. *Catal. Sci. Technol.* **2014**, *4*, 369.

[8] (a) Xie, K.; Yang, Z.-Y.; Zhou, X.-J.; Li, X.-J.; Wang, S. Z.; Tan, Z.; An, X.-Y.; Guo, C.-C. *Org. Lett.* **2010**, *12*, 1564.
(b) Yang, K.; Chen, X.; Wang, Y.; Li, W.; Kadi, A.; Fun, H.; Sun, H.; Zhang, Y.; Li, G.; Lu, H. *J. Org. Chem.* **2015**, *80*, 11065.
(c) Li, Y.; Qian, F.; Wang, M.; Lu, H.; Li, G. *Org. Lett.* **2017**, *19*, 5589.
(d) Tian, W.-F.; Hu, C.-H.; He, K.-H.; He, X.-Y.; Li, Y. *Org. Lett.* **2019**, *21*, 6930.
(e) Rouchet, J.-B.-E.-Y.; Hachem, M.; Schneider, C.; Hoarau, C. *ACS Catal.* **2017**, *7*, 5363.

[9] (a) Ueda, S.; Nagasawa, H. *Angew. Chem., Int. Ed.* **2008**, *47*, 6411.
(b) Bonnamour, J.; Bolm, C. *Org. Lett.* **2008**, *10*, 2665.
(c) Ueda, S.; Nagasawa, H. *J. Org. Chem.* **2009**, *74*, 4272.
(d) Guru, M.-M.; Ali, M.-A.; Punniyamurthy, T. *J. Org. Chem.* **2011**, *76*, 5295.
(e) Maleki, B.; Baghayeri, M.; Vahdat, S.-M.; Mohammadzadeh, A.; Akhoondi, S. *RSC Adv.* **2015**, *5*, 46545.

[10] (a) Chen, Y.-X.; Qian, L.-F.; Zhang, W.; Han, B. *Angew. Chem.* **2008**, *47*, 9330.
(b) Cho, Y.-H.; Lee, C.-Y.; Ha, D.-C.; Cheon, C.-H. *Adv. Synth. Catal.* **2012**, *354*, 2992.
(c) Liu, S.; Chen, R.; Guo, X.; Yang, H.; Deng, G.; Li, C.-J. *Green Chem.* **2012**, *43*, 1577.
(d) Yang, Z.; Chen, X.; Wang, S.; Liu, J.; Xie, K.; Wang, A.; Tan, Z. *J. Org. Chem.* **2012**, *77*, 7086.
(e) Patra, A.; James, A.; Das, T.-K.; Biju, A.-T. *J. Org. Chem.* **2018**, *83*, 14820.
(f) Nguyen, T. T.; Nguyen, X. T.; Nguyen, T. H.; Tran, P. H. *ACS Omega* **2019**, *4*, 368.
(g) Nguyen, Q. T.; Hang, A.-H. T.; Nguyen, T.-L. H.; Chaua, D.-K. N.; Tran, P. H. *RSC Adv.* **2018**, *8*, 11834.

[11] (a) Foot, J.-S.; Kanno, H.; Giblin, G.-M.-P.; Taylor, R.-J.-K. *Synlett* **2002**, 1291.
(b) Blacker, A.-J.; Farah, M.-M.; Hall, M.-I.; Marsden, S.-P.; Saidi, O.; Williams, J.-M.-J. *Org. Lett.* **2009**, *11*, 2039.
(c) Wu, M.; Hu, X.; Liu, J.; Liao, Y.; Deng, G.-J. *Org. Lett.* **2012**, *14*, 2722.

[12] (a) Altenhoff, G.; Glorius, F. *Adv. Synth. Catal.* **2004**, *346*, 1661.
(b) Viirre, R.-D.; Evindar, G.; Batey, R.-A. *J. Org. Chem.* **2008**, *73*, 3452.
(c) Yang, Z.; Wang, A.; Chen, X.; Gui, Q.; Liu, J.; Tan, Z.; Wang, H.; Shi, J.-C. *Synlett* **2013**, *24*, 1549.
(d) Endo, Y.; Backvall, J.-E. *Chem.-Eur. J.* **2012**, *18*, 13609.
(e) Nale, D.-B.; Bhanage, B. M. *Synlett* **2015**, *26*, 2835.
(f) Zhang, R.; Qin, Y.; Zhang, L. *Org. Lett.* **2017**, *19*, 5629.

[13] (a) Hein, D.-M.; Alheim, R. J.; Leavitt, J. J. *J. Am. Chem. Soc.* **1957**, *79*, 427.
(b) Bastug, G.; Eviolitte, C.; Markó, I.-E. *Org. Lett.* **2012**, *14*, 3502.
(c) Song, Q.; Feng, Q.; Zhou, M. *Org. Lett.* **2013**, *15*, 5990.
(d) Wang, L.; Ren, X.; Yu, J.; Jiang, Y.; Cheng, J. *J. Org. Chem.* **2013**, *78*, 12076.
(e) Wang, S.-S.; Fu, H.; Shen, Y.; Sun, M.; Li, Y.-M. *J. Org. Chem.* **2016**, *81*, 2920.

[14] Yang, Z.; Cheng, Y.; Zhou, L. *Chin. J. Synth. Chem.* **2020**, *28*, 84 (in Chinese).
(杨志勇, 成园园, 周亮, 合成化学, **2020**, *28*, 84.)

[15] (a) Prier, C.-K.; Rankic, D.-A.; MacMillan, D.-W.-C. *Chem. Rev.* **2013**, *113*, 5322.
(b) Ravelli, D.; Protti, S.; Fagnoni, M. *Chem. Rev.* **2016**, *116*, 9850.
(c) Marzo, L.; Pagire, S. K.; Reiser, O.; König, B. *Angew. Chem., Int. Ed.* **2018**, *57*, 10034.
(d) Wang, Z.; Li, C.; Domen, K. *Chem. Soc. Rev.* **2019**, *48*, 2109.

[16] (a) Qin, Y.; Zhu, L.; Luo, S. *Chem. Rev.* **2017**, *117*, 9433.
(b) Wang, C.-S.; Dixneuf, P.-H.; Soulé, J.-F. *Chem. Rev.* **2018**, *118*, 7532.
(c) Festa, A.-A.; Voskressensky, L.-G.; Eycken, E.-V.-V. *Chem. Soc. Rev.* **2019**, *48*, 4401.

[17] (a) Shi, Q.; Li, P.; Zhu, X.; Wang, L. *Green Chem.* **2016**, *18*, 4916.
(b) Xu, W.-T.; Huang, B.; Dai, J.-J.; Xu, J.; Xu, H.-J. *Org. Lett.* **2016**, *18*, 3114.
(c) Guo, L.-N.; Wang, H.; Duan, X.-H. *Org. Biomol. Chem.* **2016**, *14*, 7380.
(d) Wang, L.; Wang, Y.; Chen, Q.; He, M. *Tetrahedron Lett.* **2018**, *59*, 1489.
(e) Raviola, C.; Protti, S.; Ravelli, D.; Fagnoni, M. *Green Chem.* **2019**, *21*, 748.
(f) Penteado, F.; Lopes, E.-F.; Alves, D.; Perin, G.; Jacob, R. G.; Lenardao, E. J. *Chem. Rev.* **2019**, *119*, 7113.

[18] Liu, J.; Liu, Q.; Yi, H.; Qin, C.; Bai, R.; Qi, X.; Lan, Y.; Lei, A.

Angew. Chem., *Int. Ed.* **2014**, *53*, 502.
[19] (a) Das, S.; Samanta, S.; Maji, S.-K.; Samanta, P.-K.; Dutta, A.-K.; Srivastava, D. N.; Adhikary, B.; Biswas, P. *Tetrahedron Lett.* **2012**, *54*, 1090.
(b) Samanta, S.; Das, S.; Biswas, P. *J. Org. Chem.* **2013**, *78*, 11184.
[20] Yang, Z.; Zhou, L.; Liu, Y.; Lu, H.; Wu, F.; Xie, Y.; Liu, J. *ChemistrySelect* **2019**, *4*, 13788.
[21] (a) Majek, M.; Filace, F.; Wangelin, A. J. V. *Beilstein J. Org. Chem.* **2014**, *10*, 981.
(b) Zhou, C.; Li, P.; Zhu, X.; Wang, L. *Org. Lett.* **2015**, *17*, 6198.
(c) Yan, D.; Chen, J.; Xiao, W. *Angew. Chem.*, *Int. Ed.* **2019**, *58*, 378.
(d) Wang, B.; Li, P.; Miao, T.; Zou, L.; Wang, L. *Org. Biomol. Chem.* **2019**, *17*, 115.
(e) Bosveli, A.; Montagnon, T.; Kalaitzakis, D.; Vassilikogiannakis, G. *Org. Biomol. Chem.* **2021**, *19*, 3303.
[22] Hari, D.-P.; Schroll, P.; König, B. *J. Am. Chem.Soc.* **2012**, *134*, 2958.
[23] Wadhwa, C.; Yang, P. R.; West, K. C.; Deming, S. R. *Synth. Commun.* **2008**, *38*, 4434.

(Zhao, C.)

