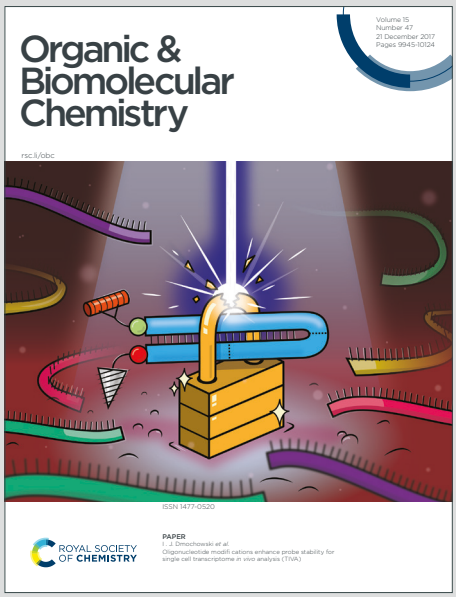
Organic & Biomolecular Chemistry

Accepted Manuscript

This article can be cited before page numbers have been issued, to do this please use: J. Wang, L. Li, Y. Guo, S. Li, S. Wang, Y. Li and Y. Zhang, *Org. Biomol. Chem.*, 2020, DOI: 10.1039/D0OB01837F.



ROYAL SOCIETY OF CHEMISTRY

rsc.li/obc

View Article Online
DOI: 10.1039/D0OB01837F

Journal Name

ARTICLE

Visible light-enabled aerobic oxidative C_{sp3}–H functionalization of glycine derivatives using an organic photocatalyst: access to substituted quinoline-2-carboxylates

Received 00th January 20xx,
Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

www.rsc.org/

Jingxin Wang, Liqi Li, Ying Guo, Shengyu Li, Shutao Wang, Ying Li and Yuan Zhang*

A practical visible light-induced aerobic oxidative dehydrogenative coupling reaction of glycine derivatives with olefins has been developed to efficiently synthesize quinoline-2-carboxylates. This metal-free process proceeds smoothly under mild conditions and exhibits good tolerance of functional groups. Given the low cost of catalyst and feedstock materials, the mild reaction conditions as well as the absence of hazardous byproducts, this protocol should find broad applications in the synthesis of quinoline-2-carboxylate derivatives.

Introduction

The quinoline-2-carboxylate (Q2C) moiety constitutes the core structure of numerous natural products[1] and pharmaceutically active molecules (Fig. 1), which typically exhibit a variety of biological activities, such as anti-inflammatory, antibacterial, anti-HIV, and anticancer activities.[2-4] Moreover, the simple Q2C structure motif also serves as the crucial intermediate for the synthesis of Quinox ligands, which have been widely used in metal-catalyzed transformations.[5, 6] Therefore, the need for step-economic and green synthetic routes to quinoline-2-carboxylates is of great interest for organic and medicinal chemists.

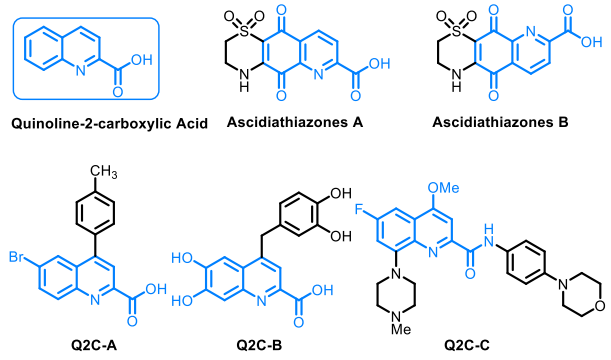


Fig. 1 Representative bioactive compounds containing quinoline-2-carboxylates.

The direct oxidative cross-dehydrogenative coupling (CDC) of two C_{sp3}–H bonds, which avoids the tedious prefunctionalization procedures, has long been considered as one of the most straightforward and atom-economical synthetic protocol for the construction of C–C bonds.[7-11] In particular, the direct cross-dehydrogenative coupling of glycine derivatives with divers nucleophiles has been applied as an effective strategy for the synthesis of α-amino acid derivatives [12-15] and azo-heterocyclic compounds.[16-18] In 2011, Mancheno et al. reported the first example of oxidative dehydrogenative coupling of glycine derivatives with olefins for the synthesis of quinoline-2-carboxylates, employing a $FeCl_3$/TEMPO oxoammonium salt catalytic system.[19, 20] Inspired by this elegant work, subsequently, the group of Jia[21-23], Huo[14, 24-26], Liu[27, 28] and Feng[29] independently explored various kinds of catalytic systems for this effective transformation. Despite the remarkable advances that have been made in this process, however, most of the reactions typically involved the use of stoichiometric amount of oxidants, and some of them were carried out at relative harsh reaction conditions. Therefore, from environmental and practical standpoints, it would be highly desirable to develop new sustainable and green catalytic versions for this type of reaction.

In this context, photoredox catalysis [30-32] has recently become an attractive protocol to initiate the CDC reaction.[33-54] However, to date, most of these studies have focused on the α-C_{sp3}–H functionalization of tertiary amines,[33-38] whereas the α-C_{sp3}–H functionalization of secondary amines (i.e. glycine derivatives) still remains far behind.[39-46] Our group has a longstanding interest in the visible light-induced CDC reactions for the C_{sp3}-H functionalization of glycine derivatives.[47-54] Recently, we have presented a visible light-induced aerobic oxidative dehydrogenative coupling/aromatization tandem reaction of glycine esters with alkenes.[47] This method provides rapid synthesis of substituted quinoline-2-carboxylates under very mild conditions. However, the practical application of this reaction is still

State Key Laboratory of Applied Organic Chemistry, College of Chemistry and Chemical Engineering, Lanzhou University, 222 Tianshui South Road, Lanzhou 730000, P. R. China. E-mail: zhangyuan@lzu.edu.cn.

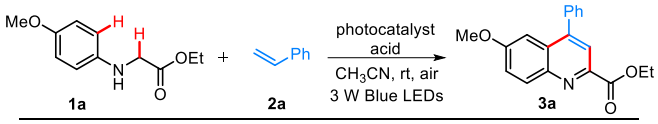
† Footnotes relating to the title and/or authors should appear here.
Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/x0xx00000x

restricted by the use of toxic and expensive ruthenium-based complex as photocatalyst. Therefore, from environmentally friendly and cost effective point of view, the use of less toxic and inexpensive organic dyes as photocatalysts, is undoubtedly a promising alternative protocol. In this regard, very recently, we have successfully demonstrated the effective synthesis of several azo-heterocyclic compounds through metal-free visible light induced α-C_{sp3}–H functionalization of glycine derivatives.[48-51] Herein, we report a metal-free visible light-induced oxidative dehydrogenative coupling/aromatization tandem reaction of glycine esters and unactivated alkenes. In comparison with previous work, the crucial innvoation of this protocol is the avoidance of the use of toxic and expensive transition metal catalyst, which means greener and cost-effective.

Results and discussion

Our initial reaction screening focused on the photocatalyzed coupling reaction of glycine ester **1a** and styrene **2a** with a variety of organic-dyes and $BF_3{\cdot}Et_2O$ under the irradiation of a 3 W blue LED lamp (Table 1, for details, see the ESI†). To our delight, the reaction proceeded smoothly with Rhodamine 6G (Rh-6G) as the photocatalyst and afforded the desired product **3a** in 11% yield (Table 1, entry 1). Encouraged by this result, we then screened different acids to improve the yield (Table 1, entries 4–6). Gratifyingly, **3a** could be obtained in 60% yield when 15 mol% of $HClO_4$ was employed (Table 1, entry 6). When a 23 W blue LED strip was used as the light source, the yield of **3a** was improved to 68% (Table 1, entry 7). The product yield could be further improved to 75% in a lower concentration (Table 1, entry 9). We also used green LEDs as light source (Table S3, entry 6), however, no improvement of the efficiency was afforded (51% yield). In addition, trace oxanilate byproduct from **1a** was observed in this reaction. Finally, control experiments indicated that photocatalyst, acid, air and visible light are all essential for this reaction (Table 1, entries 11–14).

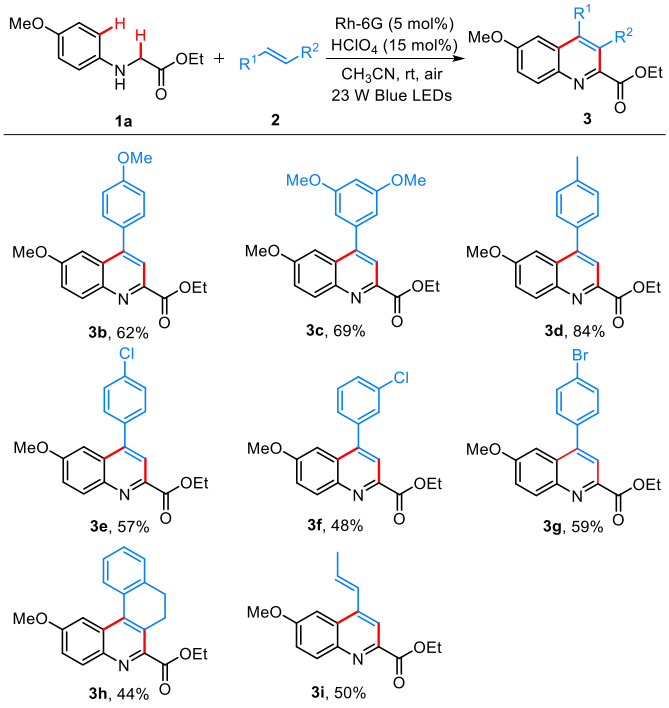
Table 1 Optimization of the reaction conditions[a]



Entry	Photocatalyst	Acid	Yield (%)[b]
1	Rh-6G	$BF_3{\cdot}Et_2O$	11
2	Rose Bengal	$BF_3{\cdot}Et_2O$	10
3	Methylene blue	$BF_3{\cdot}Et_2O$	—
4	Rh-6G	TsOH	33
5[c]	Rh-6G	TfOH	53
6[c]	Rh-6G	$HClO_4$	60
7[c,d]	Rh-6G	$HClO_4$	68
8[d,e]	Rh-6G	$HClO_4$	64
9[c,d,f]	Rh-6G	$HClO_4$	75
10[c,d,g]	Rh-6G	$HClO_4$	71
11[c,d,f]	—	$HClO_4$	19
12[c,d,f]	Rh-6G	—	—
13[c,d,f,h]	Rh-6G	$HClO_4$	trace
14[c,d,f,i]	Rh-6G	$HClO_4$	32

[a] Unless otherwise noted, all reactions were run under the following conditions: **1a** (0.1 mmol), **2a** (0.5 mmol), photocatalyst (5 mol%), acid (10 mol%), CH_3CN (1.0 mL), 3 W blue LED light irradiation under air at room temperature. [b] Yields of isolated products are given. [c] 15 mol% of acid was used. [d] Under the irradiation of a 23 W blue LED strip. [e] 20 mol% $HClO_4$ was used. [f] 2.0 mL CH_3CN was used. [g] 3.0 mL CH_3CN was used. [h] Reaction was carried out under Ar. [i] Reaction was carried out in the dark.

Table 2 Scope of the olefin component



Reaction conditions: **1a** (0.1 mmol), **2** (0.5 mmol), Rh-6G (5 mol%), $HClO_4$ (15 mol%), CH_3CN (2.0 mL), 23 W blue LED light irradiation in air at rt. Yield of the isolated product.

Having established the optimized reaction conditions, we next explored the scope of this photocatalytic aerobic oxidative coupling reaction. Firstly, a variety of alkenes were investigated. As shown in Table 2, the reaction of substituted styrenes **2** bearing either electron-donating or electron-withdrawing groups at the para- and meta-positions of the phenyl ring proceeded smoothly with **1a** to afford the desired coupling products in 48–84% yields (**3b**–**3g**). The use of disubstituted alkene as the substrates gave similar results (**3h**). In addition, besides styrenes, aliphatic alkene is also a suitable substrate for this tandem reaction (**3i**). Specifically, potentially reactive chloro- and bromo- substituents are well tolerated with this mild catalytic system (**3e**–**3g**), which afford handles for further modifications.

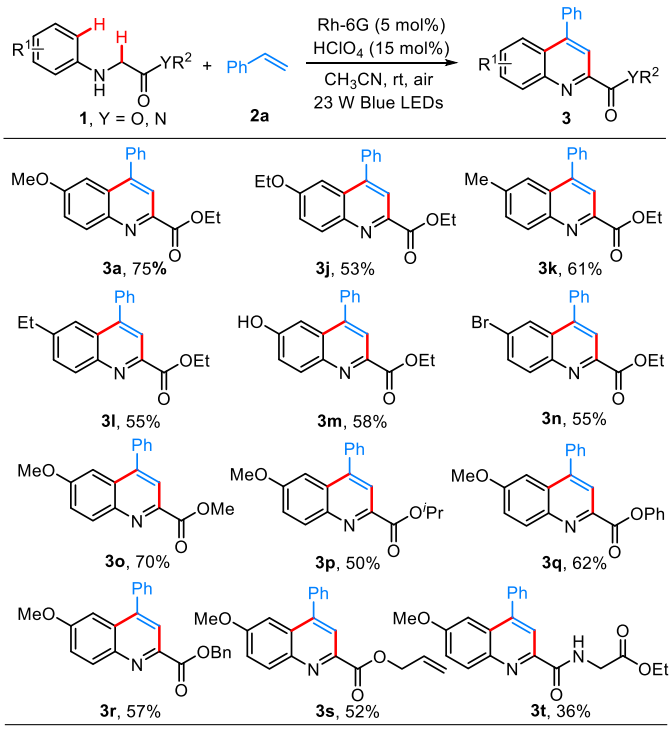
The scope of this reaction in terms of the glycine ester partner was also investigated (Table 3). A variety of electron-donating substituents at the benzene rings are well tolerated under these mild reaction conditions, affording the corresponding quinoline-2-carboxylates (**3a**, **3j**-**3m**) in 53% to 75% yields. Notably, bromo-substituent was also tolerated using this mild protocol (**3n**). We also performed the reaction with glycine ester bearing strong electron-withdrawing group (ester), however, only trace product could be observed. The reaction is also amenable to a range of ester substrates, such as methyl ester, isopropyl ester, phenyl ester, benzyl

View Article Online
DOI: 10.1039/D0OB01937F

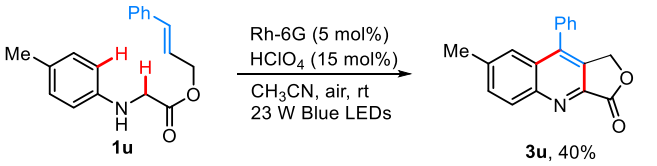
ester, and allyl ester, affording the corresponding products **3o**-**3s** with 50-70% yield. Specifically, in addition to glycine esters, a glycine derived dipeptide can also be utilized in this transformation (**3t**).

We then turned our focus toward the intramolecular variant of this visible light-induced reaction. To our delight, the intramolecular reaction occurred smoothly under our standard conditions, giving quinoline fused lactone **3u** with 40% yield in one step (Scheme 1). This reaction may open a new avenue for the rapid construction of quinoline fused lactone skeletons, which are widely spread in natural products. Furthermore, to evaluate the synthetic utility of this protocol, a gram scale reaction of **1a** (5 mmol) and **2a** was conducted (Scheme 2). The target product **3a** was obtained in 72% yield.

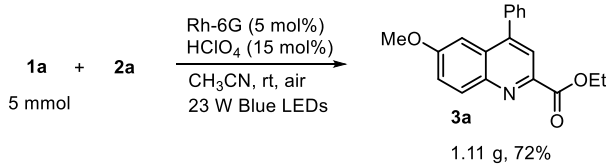
Table 3 Scope of the glycine ester component



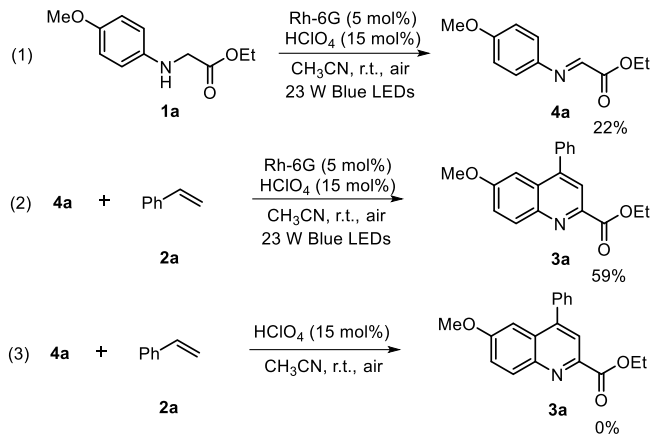
Reaction conditions: **1** (0.1 mmol), **2a** (0.5 mmol), Rh-6G (5 mol%), $HClO_4$ (15 mol%), CH_3CN (2.0 mL), 23 W blue LED light irradiation in air at rt. Yield of the isolated product.



Scheme 1 Visible light-mediated intramolecular reaction of glycine ester **1u**.



Scheme 2 Large scale synthesis of **3a.**



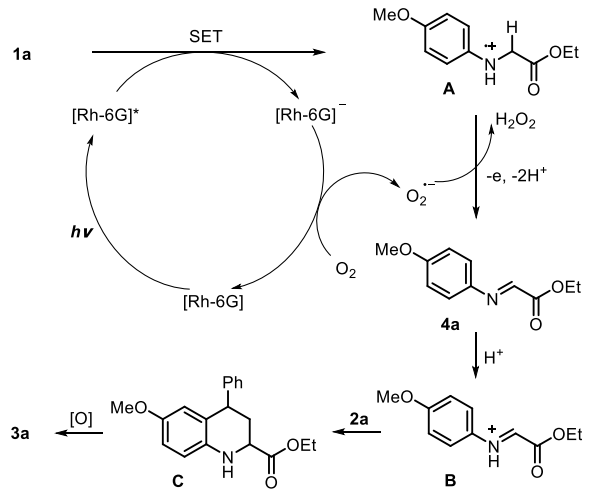
Scheme 3 Control Experiments.

The interaction between **1a** and Rh-6G was studied by photoluminescence investigations (for details, see Fig. S2†). The fluorescence intensity of Rh-6G was quenched obviously upon the addition of **1a** with a rate constant of 35.11 L mol^{-1}, which should be attributed to the formation of the radical anion of Rh-6G via photoinduced electron transfer. We further performed electron paramagnetic resonance (EPR) studies to detect the active species of oxygen in this photocatalytic reaction (for details, see Fig. S3†). When the solution of **1a**, Rh-6G and 5,5-dimethyl-1-pyrroline-*N*-oxide (DMPO) in air-saturated CH_3CN was irradiated with blue LED, a signal of the trapping radical of $O_2^{\cdot-}$ was captured (Fig. S3a†). By contrast, only very weak EPR signal could be detected when 2,2,6,6-tetramethylpiperidine (TEMP), an $^1O_2$ scavenger, was used as a probe in the same air-saturated CH_3CN solution (Fig. S3b†). These results illustrate that $O_2^{\cdot-}$ generated from O_2 is the main active species in this photocatalytic oxidative reaction.

We also conducted several control experiments to provide insights into the reaction mechanisms of this transformation (Scheme 3). Upon irradiation of **1a** with blue LEDs under the standard conditions, the imine intermediate **4a** was isolated in 22% yield, which reacted readily with **2a** under the standard conditions, giving **3a** in 59% yield; however, in the absence of photocatalyst and light, no **3a** was obtained. These control reactions revealed that the cyclization could not happen spontaneously along with possible spontaneous autooxidation, and imine **4a** should be the key intermediate of this reaction.

On the basis of these control experiments and the precedent literatures,[47] a plausible mechanism for this photocatalytic oxidative dehydrogenative coupling/aromatization tandem reaction was

proposed (Scheme 4). Firstly, the excited state of Rh-6G (Rh-6G*, $E^{ox}_{1/2}$=1.29 V vs. SCE)[55] would readily accept a single electron from **1a** (0.74 V vs. SCE)[37] to produce the radical cation **A** and [Rh-6G]$^{-}$. Rh-6G may be regenerated by the oxidation of O_2; meanwhile, an active species $O_2^{\cdot-}$ is formed during this process, which may abstract an electron and two protons from **A** to generate the imine intermediate **4a**. **4a** subsequently forms the active iminium intermediate **B** under the action of acid. Finally, trapping of **B** with **2a** would form the tetrahydroquinoline **C**, which may be further dehydrogenated via photocatalysis to afford **3a**. Alternatively, an α-amino radical is also likely to be generated from radical cation **A**, which may directly react with alkenes. In addition, excited state Rh-6G may act as a triplet energy transfer catalyst to oxygen, producing $^1O_2$ which could undergo alternative product forming pathways (hydrogen atom transfer followed by electron transfer processes).[56]



Scheme 4 Proposed Mechanism.

Conclusions

In summary, we have disclosed a metal-free visible light-mediated oxidative dehydrogenative coupling/aromatization tandem reaction of glycine esters and unactivated alkenes employing an organic-dye/acid catalytic system, which provides a straightforward access to diverse quinoline-2-carboxylates. This mild and efficient protocol tolerates a range of functional groups. Given the cheap catalysts and starting materials, as well as the mild and operationally simple reaction conditions, this reaction should find broad applications in the synthesis of quinoline-2-carboxylates. Further research towards the application of this protocol for the synthesis of pharmaceutically active molecules is underway in our laboratory.

Experimental

General procedure for the metal-free visible light-induced oxidative dehydrogenative coupling/aromatization tandem reaction of glycine esters and alkenes

To a solution of *N*-arylglycine ester **1a** (20.9 mg, 0.1 mmol, 1 eq) and Rhodamine 6G (2.4 mg, 0.005 mmol, 5 mol%) in dry CH_3CN (2.0 mL, 0.05 M) were added $HClO_4$ (the $HClO_4$ used in this study was purchased as neat; 1.5 mg, 0.015 mmol, 15 mol%) and styrene **2a** (52.1 mg, 57.3 μL, 0.5 mmol, 5 eq). The mixed solution was irradiated with blue LED (3 W in optimization, 23 W in scope) under air atmosphere at room temperature. After completion of the reaction as monitored by TLC, the solvent was removed under vacuo, and the residue was separated by silica gel column chromatography (with petroleum ether/EtOAc = 8/1 as eluent) to afford the product **3a**.

Ethyl 6-methoxy-4-phenylquinoline-2-carboxylate (3a).[47] Purified by flash column chromatography (silica gel, petroleum ether/EtOAc = 8/1 as eluent). White solid, 23.1 mg, 75% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.28 (d, J = 9.3 Hz, 1H), 8.10 (s, 1H), 7.61 – 7.47 (m, 5H), 7.44 (dd, J = 9.3, 2.8 Hz, 1H), 7.22 (d, J = 2.7 Hz, 1H), 4.56 (q, J = 7.1 Hz, 2H), 3.81 (s, 3H), 1.49 (t, J = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 165.6, 159.5, 148.0, 145.4, 144.3, 137.9, 132.7, 129.3, 129.2, 128.8, 128.6, 122.8, 121.8, 103.3, 62.1, 55.5, 14.4.

Ethyl 6-methoxy-4-(4-methoxyphenyl)quinoline-2-carboxylate (3b).[47] Purified by flash column chromatography (silica gel, petroleum ether/EtOAc = 8/1 as eluent). White solid, 20.9 mg, 62% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.26 (d, J = 9.3 Hz, 1H), 8.08 (s, 1H), 7.50 (d, J = 8.7 Hz, 2H), 7.43 (dd, J = 9.2, 2.8 Hz, 1H), 7.27 (d, J = 3.2 Hz, 1H), 7.09 (d, J = 8.7 Hz, 2H), 4.55 (q, J = 7.1 Hz, 2H), 3.92 (s, 3H), 3.83 (s, 3H), 1.49 (t, J = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 165.9, 160.1, 159.6, 148.0, 145.5, 144.6, 132.9, 130.8, 130.3, 129.5, 122.9, 121.9, 114.4, 103.5, 62.3, 55.7, 55.6, 14.6.

Ethyl 4-(3,5-dimethoxyphenyl)-6-methoxyquinoline-2-carboxylate (3c).[47] Purified by flash column chromatography (silica gel, petroleum ether/EtOAc = 8/1 as eluent). White solid, 25.3 mg, 69% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.26 (d, J = 9.3 Hz, 1H), 8.10 (s, 1H), 7.43 (dd, J = 9.3, 2.8 Hz, 1H), 7.28 (d, J = 3.5 Hz, 1H), 6.67 (d, J = 2.3 Hz, 2H), 6.61−6,59 (m, 1H), 4.55 (q, J = 7.1 Hz, 2H), 3.85 (s, 6H), 3.83 (s, 3H), 1.49 (t, J = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 165.6, 161.0, 159.5, 147.9, 145.3, 144.3, 139.8, 132.7, 129.1, 122.8, 121.5, 107.4, 103.3, 100.6, 62.1, 55.6, 55.5, 14.4.

Ethyl 6-methoxy-4-(p-tolyl)quinoline-2-carboxylate (3d).[57] Purified by flash column chromatography (silica gel, petroleum ether/EtOAc = 4/1 as eluent). White solid, 27.1 mg, 84% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.26 (d, J = 9.3 Hz, 1H), 8.08 (s, 1H), 7.47 – 7.29 (m, 5H), 7.24 (d, J = 2.8 Hz, 1H), 4.55 (q, J = 7.2 Hz, 2H), 3.82 (s, 3H), 2.48 (s, 3H), 1.48 (t, J = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 165.7, 159.4, 148.1, 145.4, 144.3, 138.6, 134.9, 132.7, 129.5, 129.2, 122.7, 121.7, 103.4, 62.1, 55.5, 21.3, 14.4.

Ethyl 4-(4-chlorophenyl)-6-methoxyquinoline-2-carboxylate (3e).[47] Purified by flash column chromatography (silica gel, petroleum ether/EtOAc = 8/1 as eluent). White solid, 19.5 mg, 57% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.27 (d, J = 9.3 Hz, 1H), 8.07 (s, 1H), 7.54 (d, J = 8.5 Hz, 2H), 7.49 (d, J = 8.5 Hz, 2H), 7.44 (dd, J = 9.3, 2.8 Hz, 1H), 7.13 (d, J = 2.7 Hz, 1H), 4.55 (q, J = 7.1 Hz, 2H), 3.82 (s, 3H), 1.48 (t, J = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 165.7, 159.8, 146.8, 145.3, 144.3, 136.3, 134.8, 132.8, 130.6, 129.0, 128.9, 122.9, 121.7, 102.9, 62.1, 55.5, 14.4.

View Article Online DOI: 10.1039/D0OB01837F

Ethyl 4-(3-chlorophenyl)-6-methoxyquinoline-2-carboxylate (3f).[47] Purified by flash column chromatography (silica gel, petroleum ether/EtOAc = 4/1 as eluent). White solid, 16.4 mg, 48% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.27 (d, J = 9.3 Hz, 1H), 8.05 (s, 1H), 7.58 (m, 1H), 7.48 – 7.37 (m, 4H), 7.13 (d, J = 2.8 Hz, 1H), 4.55 (q, J = 7.1 Hz, 2H), 3.82 (s, 3H), 1.48 (t, J = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 165.4, 159.7, 146.3, 145.3, 144.3,139.6, 134.8, 132.8, 130.0, 129.3, 128.8, 128.7, 127.5, 122.9, 121.7, 102.9, 62.1, 55.5, 14.4.

Ethyl 4-(4-bromophenyl)-6-methoxyquinoline-2-carboxylate (3g).[57] Purified by flash column chromatography (silica gel, petroleum ether/EtOAc = 4/1 as eluent). White solid, 22.9 mg, 59% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.28 (d, J = 9.3 Hz, 1H), 8.06 (s, 1H), 7.70 (d, J = 8.4 Hz, 2H), 7.44 (d, J = 8.0 Hz, 3H), 7.13 (s, 1H), 4.58-4.53 (m, 2H), 3.83 (s, 3H), 1.49 (t, J = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 165.5, 159.7, 146.7, 145.4, 144.3, 136.8, 132.9, 132.1, 130.9, 128.9, 123.1, 123.0, 121.7, 102.9, 102.8, 62.2, 55.6, 14.4.

Ethyl 2-methoxy-7,8-dihydrobenzo[k]phenanthridine-6-carboxylate (3h).[47] Purified by flash column chromatography (silica gel, petroleum ether/EtOAc = 8/1 as eluent). Pale yellow solid, 14.7 mg, 44% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.14 (d, J = 9.2 Hz, 1H), 8.00 – 7.94 (m, 1H), 7.78 (d, J = 2.7 Hz, 1H), 7.44-7.36 (m, 4H), 4.53 (q, J = 7.1 Hz, 2H), 3.92 (s, 3H), 3.15 – 3.06 (m, 2H), 2.87 – 2.79 (m, 2H), 1.48 (t, J = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.1, 159.4, 146.8, 143.6, 140.5, 140.4, 132.5, 132.2, 130.7, 129.1, 128.6, 128.3, 126.5, 126.5, 121.7, 103.6, 62.2, 55.7, 29.0, 25.9, 14.5.

Ethyl (E)-6-methoxy-4-(prop-1-en-1-yl)quinoline-2-carboxylate (3i).[47] Purified by flash column chromatography (silica gel, petroleum ether/EtOAc = 8/1 as eluent). Pale White solid, 14.7 mg, 50% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.18 (t, J = 4.6 Hz, 2H), 7.41 (dd, J = 9.3, 2.7 Hz, 1H), 7.31 – 7.28 (m, 1H), 7.02 (d, J = 15.6 Hz, 1H), 6.68 – 6.56 (m, 1H), 4.55 (q, J = 7.1 Hz, 2H), 3.99 (s, 3H), 2.07 (dd, J = 6.7, 1.8 Hz, 3H), 1.49 (t, J = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 165.9, 159.1, 145.5, 144.1, 143.2, 133.7, 132.8, 128.4, 125.6, 122.6, 117.7, 101.1, 62.0, 55.6, 19.2, 14.4.

Ethyl 6-ethoxy-4-phenylquinoline-2-carboxylate (3j).[23b] Purified by flash column chromatography (silica gel, petroleum ether/EtOAc = 8/1 as eluent). White solid, 17.0 mg, 53% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.27 (d, J = 9.3 Hz, 1H), 8.09 (s, 1H), 7.61 – 7.47 (m, 5H), 7.43 (dd, J = 9.3, 2.7 Hz, 1H), 7.20 (d, J = 2.7 Hz, 1H), 4.56 (q, J = 7.1 Hz, 2H), 4.01 (q, J = 7.0 Hz, 2H), 1.49 (t, J = 7.1 Hz, 3H), 1.42 (t, J = 7.0 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 165.9, 159.1, 148.1, 144.4, 138.2, 132.9, 129.5, 129.4, 128.9, 128.8, 123.2, 122.0, 104.2, 64.0, 62.3, 14.8, 14.6.

Ethyl 6-methyl-4-phenylquinoline-2-carboxylate (3k).[47] Purified by flash column chromatography (silica gel, petroleum ether/EtOAc = 8/1 as eluent). White solid, 17.7 mg, 61% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.28 (d, J = 8.7 Hz, 1H), 8.11 (s, 1H), 7.71 (s, 1H), 7.63 (dd, J = 8.7, 1.9 Hz, 1H), 7.60 – 7.48 (m, 5H), 4.57 (q, J = 7.1 Hz, 2H), 2.50 (s, 3H), 1.49 (t, J = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 165.6, 148.9, 146.82, 146.75, 139.0, 137.7, 132.3, 130.9, 129.5, 128.62, 128.56, 127.8, 124.3, 121.4, 62.2, 22.0, 14.4.

Ethyl 6-ethyl-4-phenylquinoline-2-carboxylate (3l). Purified by flash column chromatography (silica gel, petroleum ether/EtOAc = 8/1 as eluent). White solid, 16.8 mg, 55% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.30 (d, J = 8.7 Hz, 1H), 8.11 (s, 1H), 7.73 (s, 1H), 7.67 (dd, J = 8.7, 1.8 Hz, 1H), 7.59 – 7.50 (m, 5H), 4.57 (q, J = 7.1 Hz, 2H), 2.79 (q, J = 7.6 Hz, 2H), 1.49 (t, J = 7.1 Hz, 3H), 1.27 (t, J = 7.6 Hz, 4H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 165.7, 149.1, 147.0, 145.1, 137.8, 131.2, 131.1, 129.6, 128.7, 128.6, 127.8, 123.2, 121.4, 62.2, 29.3, 15.4, 14.4. HRMS (ESI): calculated $[C_{20}H_{19}NO_2+H]^+$: 306.1489, found: 306.1487.

Ethyl 6-hydroxy-4-phenylquinoline-2-carboxylate (3m).[47] Purified by flash column chromatography (silica gel, petroleum ether/EtOAc = 8/1 as eluent). White solid, 17.0 mg, 58% yield. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.42 (s, 1H), 8.11 (d, J = 9.2 Hz, 1H), 7.87 (s, 1H), 7.61 – 7.54 (m, 5H), 7.43 (dd, J = 9.1, 2.7 Hz, 1H), 7.16 (d, J = 2.7 Hz, 1H), 4.40 (q, J = 7.1 Hz, 2H), 1.37 (t, J = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 165.0, 158.0, 146.6, 144.2, 142.8, 137.4, 132.3, 129.2, 128.9, 128.8, 128.7, 123.2, 120.8, 105.9, 61.3, 14.3.

Ethyl 6-bromo-4-phenylquinoline-2-carboxylate (3n).[47] Purified by flash column chromatography (silica gel, petroleum ether/EtOAc = 4/1–2/1 as eluent). White solid, 19.6 mg, 55% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.25 (d, J = 9.0 Hz, 1H), 8.15 (s, 1H), 8.11 (d, J = 2.1 Hz, 1H), 7.86 (dd, J = 9.0, 2.2 Hz, 1H), 7.63 – 7.49 (m, 5H), 4.57 (q, J = 7.1 Hz, 2H), 1.49 (t, J = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 165.4, 149.2, 148.3, 147.0, 137.1, 133.9, 133.0, 129.7, 129.3, 129.1, 128.1, 123.5, 122.3, 62.6, 14.6.

Methyl 6-methoxy-4-phenylquinoline-2-carboxylate (3o).[47] Purified by flash column chromatography (silica gel, petroleum ether/EtOAc = 8/1–4/1 as eluent). White solid, 20.5 mg, 70% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.27 (d, J = 9.3 Hz, 1H), 8.12 (s, 1H), 7.60 – 7.47 (m, 5H), 7.44 (dd, J = 9.3, 2.8 Hz, 1H), 7.23 (d, J = 2.7 Hz, 1H), 4.08 (s, 3H), 3.81 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.2, 159.6, 148.1, 145.0, 144.3, 137.8, 132.6, 129.3, 129.3, 128.8, 128.7, 122.9, 121.9, 103.3, 55.5, 53.1.

Isopropyl 6-methoxy-4-phenylquinoline-2-carboxylate (3p).[47] Purified by flash column chromatography (silica gel, petroleum ether/EtOAc = 8/1–4/1 as eluent). Pale yellow solid, 16.1 mg, 50% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.28 (d, J = 9.3 Hz, 1H), 8.05 (s, 1H), 7.57-7.50 (m, 5H), 7.43 (dd, J = 9.3, 2.8 Hz, 1H), 7.20 (d, J = 2.8 Hz, 1H), 5.44-5.35 (m, 1H), 3.81 (s, 3H), 1.46 (d, J = 6.3 Hz, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 165.0, 159.4, 147.9, 145.7, 144.4, 138.0, 132.9, 129.4, 129.1, 128.8, 128.6, 122.7, 121.8, 103.2, 69.7, 55.5, 22.0.

Phenyl 6-methoxy-4-phenylquinoline-2-carboxylate (3q).[47] Purified by flash column chromatography (silica gel, petroleum ether/EtOAc = 8/1 as eluent). Pale yellow solid, 22.1 mg, 62% yield. ^{1}H NMR (400 MHz, DMSO-*d6*) δ 8.24 (d, J = 9.3 Hz, 1H), 8.08 (s, 1H), 7.69 – 7.57 (m, 6H), 7.51 (dd, J = 8.8, 7.1 Hz, 2H), 7.35 (d, J = 7.9 Hz, 3H), 7.26 (d, J = 2.9 Hz, 1H), 3.81 (s, 3H); ^{13}C NMR (101 MHz, DMSO-*d6*) δ 163.7, 159.6, 150.8, 147.5, 143.8, 137.0, 132.4, 129.8, 129.4, 129.13, 129.07, 128.6, 126.3, 123.3, 122.0, 121.8, 103.3, 55.6.

Benzyl 6-methoxy-4-phenylquinoline-2-carboxylate (3r).[47] Purified by flash column chromatography (silica gel, petroleum ether/EtOAc = 8/1–4/1 as eluent). Pale yellow solid, 21.0 mg, 57% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.28 (d, J = 9.3 Hz, 1H), 8.08

(s, 1H), 7.56 – 7.50 (m, 7H), 7.44 (dd, *J* = 9.3, 2.8 Hz, 1H), 7.40 – 7.30 (m, 3H), 7.21 (d, *J* = 2.8 Hz, 1H), 5.53 (s, 2H), 3.81 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 165.4, 159.6, 148.0, 145.0, 144.4, 137.9, 135.8, 132.8, 129.3, 129.2, 128.8, 128.7, 128.6, 128.6, 128.4, 122.9, 121.9, 103.2, 67.6, 55.6.

Allyl 6-methoxy-4-phenylquinoline-2-carboxylate (3s).[47] Purified by flash column chromatography (silica gel, petroleum ether/EtOAc = 8/1 as eluent). White solid, 16.6 mg, 52% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.28 (d, *J* = 9.3 Hz, 1H), 8.11 (s, 1H), 7.59-7.50 (m, 5H), 7.44 (dd, *J* = 9.3, 2.8 Hz, 1H), 7.22 (d, *J* = 2.8 Hz, 1H), 6.18 – 6.07 (m, 1H), 5.47 (dd, *J* = 17.2, 1.5 Hz, 1H), 5.33 (d, *J* = 10.4, 1H), 4.99 (d, *J* = 5.8 Hz, 2H), 3.81 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 165.5, 159.8, 148.2, 145.2, 144.6, 138.0, 132.9, 132.1, 129.5, 129.4, 129.0, 128.8, 123.1, 122.1, 119.4, 103.4, 66.9, 55.7.

Ethyl (6-methoxy-4-phenylquinoline-2-carbonyl)glycinate (3t).[47] Purified by flash column chromatography (silica gel, petroleum ether/EtOAc = 8/1 as eluent). White solid, 13.1 mg, 36% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.69 (t, *J* = 5.7 Hz, 1H), 8.19 (s, 1H), 8.09 (d, *J* = 9.2 Hz, 1H), 7.56 – 7.48 (m, 5H), 7.43 (dd, *J* = 9.3, 2.8 Hz, 1H), 7.24 (d, *J* = 2.8 Hz, 1H), 4.33 (t, *J* = 5.9 Hz, 2H), 4.28 (q, *J* = 7.1Hz, 2H), 3.81 (s, 3H), 1.33 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.1, 165.3, 159.3, 148.5, 146.6, 143.4, 138.2, 131.9, 129.6, 129.3, 128.9, 128.8, 122.9, 119.7, 103.6, 61.7, 55.7, 41.7, 14.4.

7-Methyl-9-phenylfuro[3,4-b]quinolin-3(1H)-one (3u).[21] Purified by flash column chromatography (silica gel, petroleum ether/EtOAc = 4/1 as eluent). Pale yellow solid, 11.0 mg, 40% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.32 (d, *J* = 8.7 Hz, 1H), 7.69 (dd, *J* = 8.7, 1.6 Hz, 1H), 7.66 – 7.52 (m, 4H), 7.45 (dd, *J* = 7.8, 1.5 Hz, 2H), 5.37 (s, 2H), 2.52 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.9, 148.3, 142.3, 141.8, 139.0, 132.7, 132.1, 131.5, 130.0, 128.4, 128.3, 127.8, 126.9, 123.3, 66.8, 21.1.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

We gratefully acknowledge the National Natural Science Foundation of China (Nos. 22071092, 21572092 and 21772079) and Natural Science Foundation of Gansu Province (18JR4RA003) for financial support.

Notes and references

1 A. N. Pearce, E. W. Chia, M. V. Berridge, G. R. Clark, J. L. Harper, L. Larsen, E. W. Maas, M. J. Page, N. B. Perry, V. L. Webb and B. R. Copp, *J. Nat. Prod.*, 2007, **70**, 936-940.
2 C. N. Carrigan, R. D. Bartlett, C. S. Esslinger, K. A. Cybulski, P. Tongcharoensirikul, R. J. Bridges and C. M. Thompson, *J. Med. Chem.*, 2002, **45**, 2260-2276.
3 C. L. Horchler, J. P. McCauley, Jr., J. E. Hall, D. H. Snyder, W. Craig Moore, T. J. Hudzik and M. J. Chapdelaine, *Bioorg. Med. Chem.*, 2007, **15**, 939-950.
4 Y.-F. Zhu, X.-C. Wang, P. Connors, K. Wilcoxen, Y. Gao, R. Gross, N. Strack, T. Gross, J. R. McCarthy, Q. Xie, N. Ling and G. Chen, *Bioorg. Med. Chem. Lett.*, 2003, **13**, 1931-1934.
5 B. W. Michel, J. R. McCombs, A. Winkler and M. S. Sigman, *Angew. Chem., Int. Ed.,* 2010, **49**, 7312-7315.
6 T. Volker, F. Dempwolff, P. L. Graumann and E. Meggers, *Angew. Chem., Int. Ed.,* 2014, **53**, 10536-10540.
7 S. A. Girard, T. Knauber and C. J. Li, *Angew. Chem., Int. Ed.,* 2014, **53**, 74-100.
8 C. S. Yeung and V. M. Dong, *Chem. Rev.*, 2011, **111**, 1215-1292.
9 C. Liu, H. Zhang, W. Shi and A. Lei, *Chem. Rev.*, 2011, **111**, 1780-1824. 4-3484.
10 C. Zhang, C. Tang and N. Jiao, *Chem. Soc. Rev.*, 2012, **41**, 3464-3484.
11 Y. Qin, L. Zhu and S. Luo, *Chem. Rev.*, 2017, 117, 9433-9520.
12 L. Zhao and C. J. Li, *Angew. Chem., Int. Ed.,* 2008, **47**, 7075-7078.
13 J. Xie and Z. Z. Huang, *Angew. Chem., Int. Ed.,* 2010, **49**, 10181-10185.
14 C. Huo, Y. Yuan, M. Wu, X. Jia, X. Wang, F. Chen and J. Tang, *Angew. Chem., Int. Ed.,* 2014, **53**, 13544-13547.
15 Z. Xie, X. Liu and L. Liu, *Org. Lett.*, 2016, **18**, 2982-2985.
16 Y. J. Li, X. Li, S. X. Zhang, Y. L. Zhao and Q. Liu, *Chem. Commun.*, 2015, **51**, 11564-11567.
17 (a) X. Bao, W. Jiang, J. Liang and C. Huo, *Org. Chem. Front.*, 2020,**7**, 2107-2144; (b) H. Li, S. Huang, Y. Wang and C. Huo, *Org. Lett.*, 2018, **20**, 92-95.
18 J. Xie, Y. Huang, H. Song, Y. Liu and Q. Wang, *Org. Lett.*, 2017, **19**, 6056-6059.
19 H. Richter and O. Garcia Mancheno, *Org. Lett.*, 2011, **13**, 6066-6069.
20 R. Rohlmann, T. Stopka, H. Richter and O. Garcia Mancheno, *J. Org. Chem.*, 2013, **78**, 6050-6064.
21 X. Jia, F. Peng, C. Qing, C. Huo and X. Wang, *Org. Lett.*, 2012, **14**, 4030-4033.
22 X. Jia, Y. Wang, F. Peng, C. Huo, L. Yu, J. Liu and X. Wang, *J. Org. Chem.*, 2013, **78**, 9450-9456.
23 (a) J. Liu, Y. Wang, L. Yu, C. Huo, X. Wang and X. Jia, *Adv. Synth. Catal.*, 2014, **356**, 3214-3218; (b) X. Liu, Y. Shao, P. Li, H. Ji, Y. Yuan and X. Jia, *Tetrahedron Lett.*, 2018, **59**, 637-640.
24 W. Jiang, Y. Wang, P. Niu, Z. Quan, Y. Su and C. Huo, *Org. Lett.*, 2018, **20**, 4649-4653.
25 C. D. Huo, H. S. Xie, M. X. Wu, X. D. Jia, X. C. Wang, F. J. Chen and J. Tang, *Chem. – Eur. J.*, 2015, **21**, 5723-5726.
26 C. Huo, Y. Yuan, F. Chen and Y. Wang, *Adv. Synth. Catal.*, 2015, **357**, 3648-3654.
27 G. Liu, J. Qian, J. Hua, F. Cai, X. Li and L. Liu, *Org. Biomol. Chem.*, 2016, **14**, 1147-1152.
28 Z. Xie, J. Jia, X. Liu and L. Liu, *Adv. Synth. Catal.*, 2016, **358**, 919-925.
29 M. Ni, Y. Zhang, T. Gong and B. Feng, *Adv. Synth. Catal.*, 2017, **359**, 824-831.
30 J. Xuan and W. J. Xiao, *Angew. Chem., Int. Ed.,* 2012, **51**, 6828-6838.
31 C. K. Prier, D. A. Rankic and D. W. MacMillan, *Chem. Rev.*, 2013, **113**, 5322-5363.
32 L. Shi and W. Xia, *Chem. Soc. Rev.*, 2012, **41**, 7687-7697.
33 A. G. Condie, J. C. Gonzalez-Gomez and C. R. Stephenson, *J. Am. Chem. Soc.*, 2010, **132**, 1464-1465.
34 M. Rueping, C. Vila, R. M. Koenigs, K. Poscharny and D. C. Fabry, *Chem. Commun.*, 2011, **47**, 2360-2362.
35 Q. Y. Meng, J. J. Zhong, Q. Liu, X. W. Gao, H. H. Zhang, T. Lei, Z. J. Li, K. Feng, B. Chen, C. H. Tung and L. Z. Wu, *J. Am. Chem. Soc.*, 2013, **135**, 19052-19055.
36 X. Liu, X. Ye, F. Bures, H. Liu and Z. Jiang, *Angew. Chem., Int. Ed.,* 2015, **54**, 11443-11447.
37 Q. Yang, L. Zhang, C. Ye, S. Luo, L.-Z. Wu and C.-H. Tung, *Angew. Chem., Int. Ed.,* 2017, **56**, 3694-3698.

View Article Online
DOI: 10.1039/D0OB01837F

38 L. Niu, S. Wang, J. Liu, H. Yi, X. A. Liang, T. Liu and A. Lei, *Chem. Commun.*, 2018, **54**, 1659-1662.
39 Z. Q. Wang, M. Hu, X. C. Huang, L. B. Gong, Y. X. Xie and J. H. Li, *J. Org. Chem.*, 2012, **77**, 8705-8711.
40 S. Zhu and M. Rueping, *Chem. Commun.*, 2012, **48**, 11960-11962.
41 X.-W. Gao, Q.-Y. Meng, M. Xiang, B. Chen, K. Feng, C.-H. Tung and L.-Z. Wu, *Adv. Synth. Catal.*, 2013, **355**, 2158-2164.
42 X.-W. Gao, Q.-Y. Meng, J.-X. Li, J.-J. Zhong, T. Lei, X.-B. Li, C.-H. Tung and L.-Z. Wu, *ACS Catal.*, 2015, **5**, 2391-2396.
43 Q. Y. Meng, X. W. Gao, T. Lei, Z. Liu, F. Zhan, Z. J. Li, J. J. Zhong, H. Xiao, K. Feng, B. Chen, Y. Tao, C. H. Tung and L. Z. Wu, *Sci. Adv.*, 2017, **3**, e1700666.
44 W. Dong, B. Hu, X. Gao, Y. Li, X. Xie and Z. Zhang, *J. Org. Chem.*, 2016, **81**, 8770-8776.
45 Y.-H. He, Y. Xiang, D.-C. Yang and Z. Guan, *Green Chem.*, 2016, **18**, 5325-5330.
46 C. Wang, M. Guo, R. Qi, Q. Shang, Q. Liu, S. Wang, L. Zhao, R. Wang and Z. Xu, *Angew. Chem., Int. Ed.,* 2018, **57**, 15841-15846.
47 X. Yang, L. Li, Y. Li and Y. Zhang, *J. Org. Chem.*, 2016, **81**, 12433-12442.
48 S. Li, X. Yang, Y. Wang, H. Zhou, B. Zhang, G. Huang, Y. Zhang and Y. Li, *Adv. Synth. Catal.*, 2018, **360**, 4452-4456.
49 Y. Zhang, X. Yang, H. Zhou, S. Li, Y. Zhu and Y. Li, *Org. Chem. Front.*, 2018, **5**, 2120-2125.
50 Y. He, B. Yan, H. Tao, Y. Zhang and Y. Li, *Org. Biomol. Chem.*, 2018, **16**, 3816-3823.
51 H. Zhou, X. Yang, S. Li, Y. Zhu, Y. Li and Y. Zhang, *Org. Biomol. Chem.*, 2018, **16**, 6728-6734.
52 X. R. Yang, Z. X. Xie, Y. Li and Y. Zhang, *Chem. Sci.*, 2020, **11**, 4741-4746.
53 X. Yang, Y. Zhu, Z. Xie, Y. Li and Y. Zhang, *Org. Lett.*, 2020, **22**, 1638-1643.
54 Y. Zhang, S. L. Li, Y. Zhu, X. R. Yang, H. Zhou and Y. Li, *J. Org. Chem.*, 2020, **85**, 6261-6270.
55 N. A. Romero and D. A. Nicewicz, *Chem. Rev.*, 2016, **116**, 10075–10166.
56 F. Stracke, Ma. Heupel, E. Thiel, *J. Photochem. Photobiol. A: Chem.,* 1999, **126**, 51−58.
57 J. McNulty, R. Vemula, C. Bordón, R. Yolken and L. Jones-Brando, *Org. Biomol. Chem.*, 2014, **12**, 255-260.