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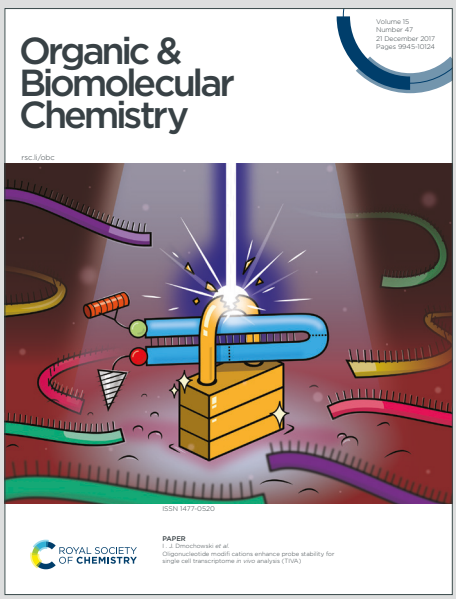

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ARTICLE

CuBr/NHPI Co-catalyzed Aerobic Oxidative [3+2] Cycloaddition-Aromatization to Access 5,6-dihydro-pyrrolo[2, 1-*a*]isoquinolines

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An efficientl and enviromental friendly CuBr /NHPI co-catalyzed aerobic oxidative [3+2] cycloaddition-aromatization cascade was realized with *N*-substituted tetrahydroisoquinolines and electron-deficient olefins. Under the mild conditions, the reaction proceeded smoothly and displayed excellent functional group tolerance, affording 5,6-dihydro-pyrrolo[2,1-a]isoquinolines in good to high yields. This protocol exhibits a broad substrate scope to both *N*-alkyl tetrahydroisoquinolines and dipolarophile substrates.

Introduction

Intricate nitrogen-containing heterocycles are widely found in numerous natural alkaloids and commercial drugs.[1] Among them, pyrrolo[2,1-*a*]isoquinoline is a privileged scaffold endowed with diverse and potent pharmacological activities.[2] Several representative compounds were listed in Fig. 1. For example, the famous lamellarin alkaloids, which were firstly isolated from marine invertebrates, exhibit excellent anti-tumor, anti-HIV and antioxidant activity. Lamellarin K and its triacetate derivative have been validated as novel potential anti-tumor drugs against various cancer cell lines with potent human topoisomerase inhibition. By down-regulating the expression of drug efflux pump-P-glycoprotein (P-gp), lamellarin G could reverse the multiple drug resistance (MDR) of tumor cell lines and improve their chemotherapeutic sensitivity. The HIV-1 integrase inhibitor, lamellarin α 20-sulfate has great potential to be clinical drug for Acquired Immune Deficiency Syndrome (AIDS). Other important structures, including (-)-trolline, compound A and B (Fig.1), also show unique biological effects, such as neuroprotective effects, antituberculous and antifungal activity.

Due to the biological importance of pyrrolo[2,1-*a*]isoquinoline moiety, numerous efforts have been made toward its construction,[3-7] and currently main three well known strategies are available. The two most widely used traditional methods for the synthesis of this important natural bioactive scaffold are 1,3-dipolar cyclization of isoquinolinium ylide and electron-deficient alkyne[4] and "one-pot multicomponent reaction".[5]

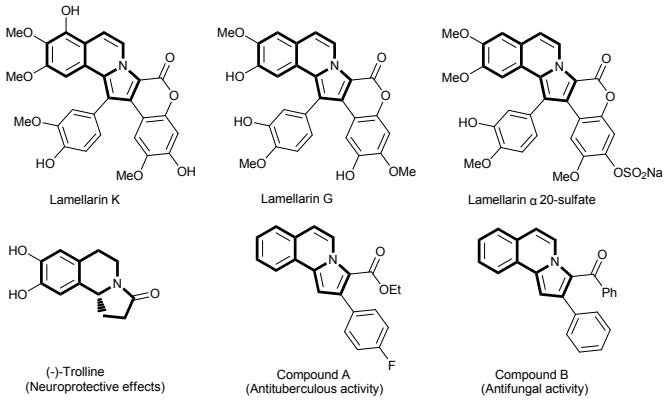

Figure 1. Representative examples of lamellarin alkaloids and their analogues.

In the past decades, direct oxidative C-H bond functionalization provided a concise approach for the construction of complex natural products with high atom- and step- economy without prior installation of activating groups since the Murahashi and Li groups' pioneering work.[8] Recently, Wang and Yu firstly developed the Cu(II)-catalyzed oxidation [3+2] cycloaddition-aromatization cascade of *N*-substituted tetrahydroisoquinoline with a series of dipolarophiles for the preparation of pyrrolo[2,1-*a*]isoquinoline analogues by using TBHP as the oxidant (Scheme 1a).[6a] After that, metal- or non-metal peroxides systems, such as $Rh_2(cap)_4$/TBHP,[6b] $Co(OAc)_2{\cdot}4H_2O$/TBHP,[6c] TBAI/TBHP,[6d] KI/H_2O_2, I_2/H_2O_2,[6e] have received extensive attention. However, all above methods suffer from the requirement of superstoichiometric amounts of hazardous peroxide to complete the final oxidative aromatization conversation. Moreover, Xiao's group reported an impressive visible-light induced dipolar cyclization strategy for the construction of pyrrolo[2,1-*a*]isoquinolines with expensive $Ru(bpy)_3Cl_2$ as photocatalyst (Scheme 1b).[7a] Since then, various of photocatalysts, such as bodipy species[7c-7e] and methylene blue,[7f] were proved to effectively promote the

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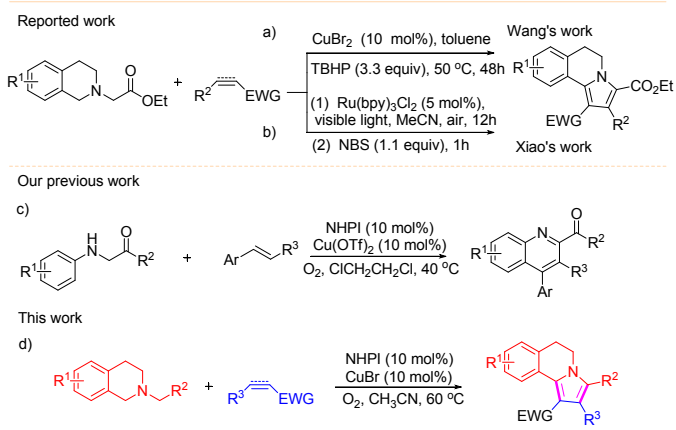
similar conversion. Yet, most photoinduced strategies still require stoichiometric NBS (1.0 eq at least) as additional oxidant to achieve the oxidative aromatization. Therefore, the economic, environmental and practical application issues for existing oxidation systems need to be improved in great demand. As part of our ongoing interest in the construction of *N*-heterocycles relying on C-H bond oxidative functionalization (Scheme 1c),[9] herein, we report a pragmatic and green protocol for the synthesis of pyrrolo[2,1-*a*]isoquinolines using molecular oxygen as the terminal oxidant (Scheme 1d).

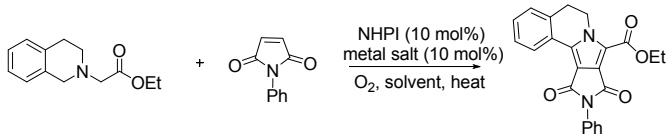


Scheme 1. The C-H bond oxidative cycloaddition reaction.

Results and discussion

Initially, we started with choosing *N*-substituted tetrahydroisoquinoline (**1a**) and *N*-phenyl maleimide (**2a**) as the model substrates to optimize the reaction conditions. Firstly, the established $Cu(OTf)_2$-NHPI(*N*-Hydroxyphthalimide)/O_2 system[9a] was employed directly and the desired pyrrolo[2,1-*a*]isoquinoline (**3a**) was obtained in 36% yield (entry 1). Then, a range of metal salts were tested to improve the yield of product. While reactions with several copper salts like CuOTf, $CuBr_2$, $CuCl_2$, $(OAc)_2$ and CuCl gave **3a** in inferior yield, CuBr was proved to be the best additive with 55% yield (entries 2-7). Other metal salt additives, such as AgOTf, $PdCl_2$, $FeCl_3$, failed to afford any target product (entries 8-10). Changing NHPI to other radical initiators, such as AIBN (2,2'-Azobis(2-methylpropionitrile)) and BPO (Benzoyl peroxide), afforded lower yields or no product respectively (entries 11-12). The screening results of DMF, EtOH, DCM, toluene and CH_3CN showed that CH_3CN was the best solvent with 65% isolated yield (entries 13-17). Furthermore, with the increasing of reaction temperature, the yield could be improved to 91% when the reaction was performed at 60 °C (entries 17-19). Finally, when the loadings of CuBr and NHPI were increased to 20 mol% respectively or together, no better result was observed (entries 20-22).

Table 1. The Optimization of Reaction Conditions.[a]



1a **2a** **3a**

Entry	Metal Salts	Solvent	Temp	Yield[%][b]
1	$Cu(OTf)_2$	DCE	40 °C	36
2	CuOTf	DCE	40 °C	21
3	$CuBr_2$	DCE	40 °C	33
4	$CuCl_2$	DCE	40 °C	38
5	$Cu(OAc)_2$	DCE	40 °C	27
6	CuCl	DCE	40 °C	42
7	CuBr	DCE	40 °C	55
8	AgOTf	DCE	40 °C	0
9	$PdCl_2$	DCE	40 °C	0
10	$FeCl_3$	DCE	40 °C	0
11[c]	-	DCE	40 °C	0
12[d]	CuBr	DCE	40 °C	25
13[e]	CuBr	DCE	40 °C	0
14	CuBr	DMF	40 °C	trace
15	CuBr	EtOH	40 °C	37
16	CuBr	DCM	40 °C	31
17	CuBr	PhMe	40 °C	trace
18	CuBr	CH_3CN	40 °C	65
19	CuBr	CH_3CN	60 °C	91
20	CuBr	CH_3CN	80 °C	85
21[f]	CuBr	CH_3CN	60 °C	85
22[g]	CuBr	CH_3CN	60 °C	92
23[f, g]	CuBr	CH_3CN	60 °C	88

[a]General Conditions: **1a** (0.2 mmol), **2a** (0.3 mmol), NHPI (0.02 mmol), and metal salt (0.02 mmol) in anhydrous solvent (2.0 mL) under O_2 balloon atmosphere at indicated temperature overnight. [b]Isolated yield. [c]No metal salt was used. [d]0.02 mmol AIBN was used instead of NHPI. [e]0.02 mmol BPO was used instead of NHPI. [f]0.04 mmol of NHPI was employed. [g]0.04 mmol of CuBr was used.

Using the optimized reaction conditions, we turned our attention to examine the scope and limitations of this reaction, and primarily focused on the dipolarophile substrate. As shown in Table 2, reactions of **1a** with various readily available *N*-aryl maleimide with different substitution patterns on the phenyl ring underwent smoothly, giving the corresponding products in good to excellent yields (**3a**-**3h**), indicating the transformation was insensitive to electronic effect and substituent position of the aryl rings. Several other types of *N*-substituted maleimide were also proved to be suitable substrates, affording the products in 64-78% yields (**3i**-**3m**). The examination of other important dipolarophiles components had revealed that methyl acrylate, methyl propiolate, acrylonitrile, methyl crotonate, benzalacetones, cinnamaldehyde and 1,4-naphthoquinone were amenable to the reaction (**3n**-**3t**). The non-symmetric dipolarophiles **2n**-**2s** successfully provided the regioselective cycloaddition products in acceptable yields (**3n**, 35%; **3o**, 48%, **3p**, 63%, **3q**, 28%; **3r**, 40%, **3s**, 30%), which might be ascribed to their low-boiling points, low reactivity, steric hindrance or unstable properties under the existing oxidation system. Moreover, when nitroolefins bearing electronically varied groups on the aromatic ring were employed as dipolarophiles, the reaction underwent smoothly and generated the denitrative aromatization products with high regioselectivity and moderate yields (**5a**-**5c**)[6c], which could be further modified with NBS and directly used for total synthesis of lamellarin alkaloids.[7a, 10]

Table 2. The scope of dipolarophile.[a, b]

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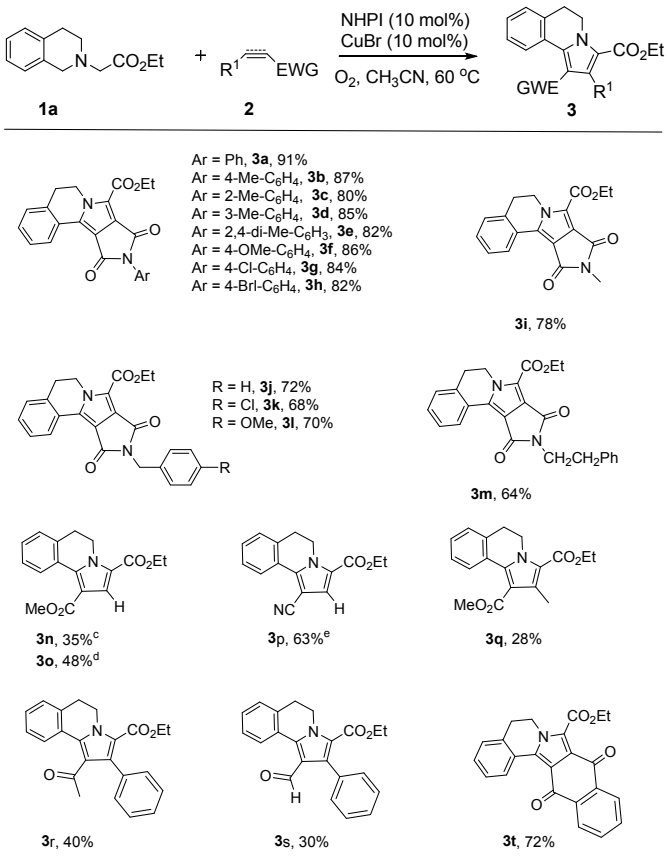
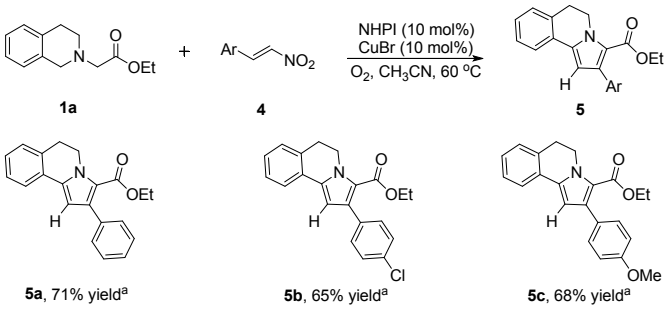


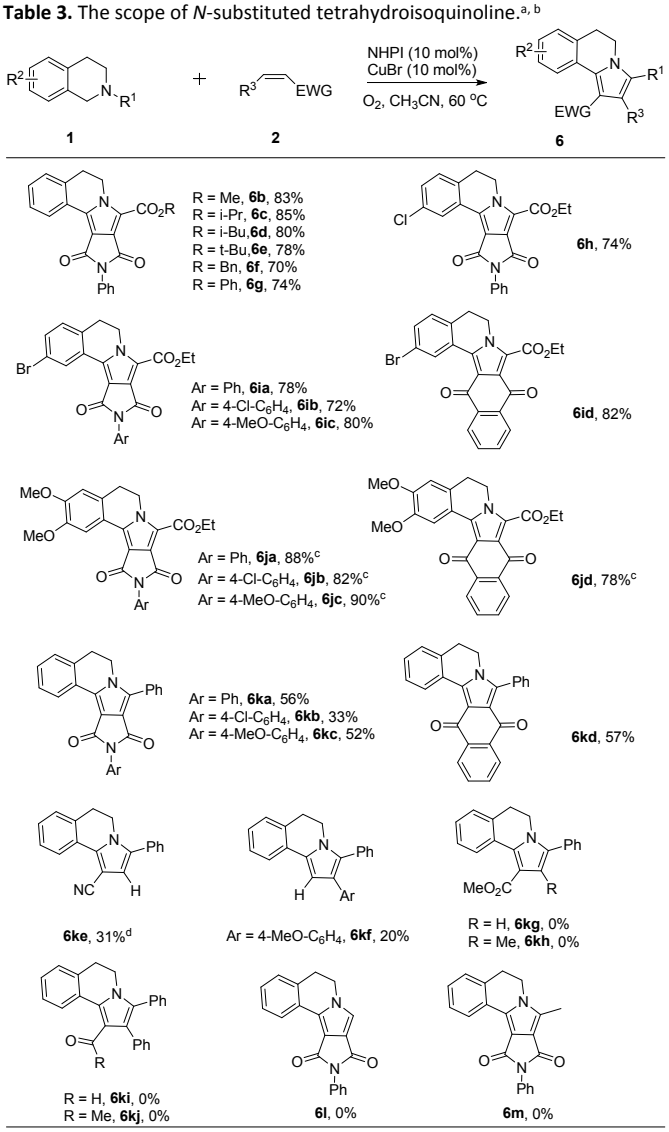
[a]General Conditions: **1a** (0.2 mmol), **2** (0.3 mmol), NHPI (0.02 mmol), and CuBr (0.02 mmol) in dried CH_3CN (2.0 mL) under O_2 balloon atmosphere at 60 °C overnight. [b]Isolated yield. [c]Reaction with methyl acrylate (0.4 mmol). [d]Reaction with methyl propiolate (0.4 mmol). [e]Reaction with acrylonitrile (0.4 mmol).



Scheme 2. Oxidative [3+2] cycloaddition with tertiary amine and nitroolefins. General Conditions: **1a** (0.2 mmol), **4** (0.3 mmol), NHPI (0.02 mmol), and CuBr (0.02 mmol) in dried CH_3CN (2.0 mL) under O_2 balloon atmosphere at 60 °C overnight. [a]Isolated yield.

Next, we decided to explore the scope of *N*-substituted tetrahydroisoquinoline **1** (Table 3). At first, we studied the scope of *N*-substituted groups. The different alkyl esters including methyl **1b**, isopropyl **1c**, isobutyl **1d**, tert-butyl **1e**, benzyl **1f** and phenyl **1g** were found to be compatible with the standard conditions, giving the target compounds in moderate to good yields (**6b**-**6g**). Electronic substituent effect on the phenyl was also examined. Both electron-donating and electron-withdrawing substituents were tolerated with this oxidation system, providing the desired products in satisfying yieds (**6h**-**6jd**). Electron-rich substrate **1j** with two methoxy groups was more reactive than electron-deficient 1h and **1i**. More important, non-electron withdrawing group substituted *N*-benzyl tetrah-ydroisoquinoline **1k** also successfully reacted with various dipolarophiles, such as *N*-aryl maleimides with electron-donating and electron-withdrawing substituent on the aromatic ring, 1,4-naphthoquinone, acrylonitrile and nitroolefins (**6ka**-**6kf**). However, methyl acrylate, methyl propiolate, methyl crotonate, benzalacetones and cinnamaldehyde all falied to give any products due to their weak reactivity (**6kg**-**6kj**). The examination results of *N*-methyl and *N*-ethyl tetrahydroisoquinolines indicated that they were not the suitable substrates (**6l**, **6m**).

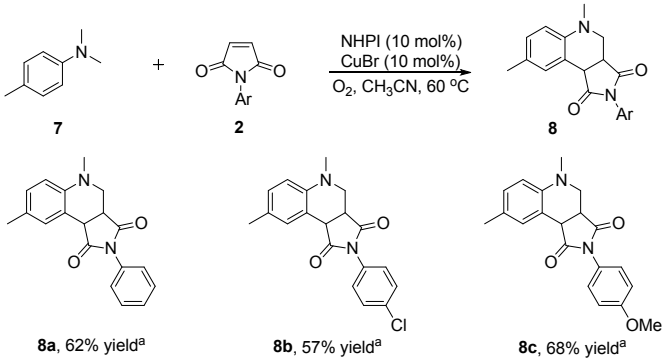
Table 3. The scope of *N*-substituted tetrahydroisoquinoline.[a, b]



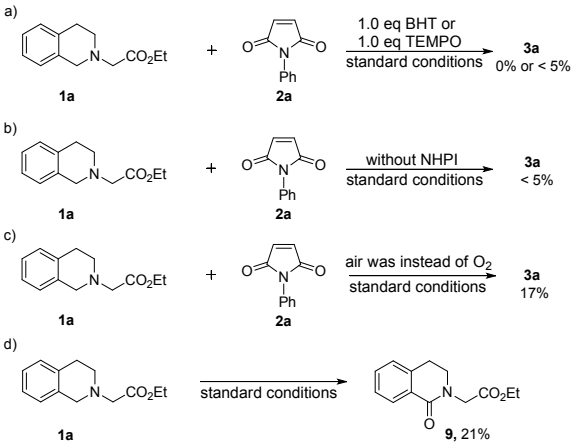
[a]General Conditions: **1** (0.2 mmol), **2** (0.3 mmol), NHPI (0.02 mmol), and CuBr (0.02 mmol) in dried CH_3CN (2.0 mL) under O_2 balloon atmosphere at 60 °C overnight. [b]Isolated yield. [c]Reaction at 50 °C. [d]Reaction with acrylonitrile (0.4 mmol).

After that, we attempted to expand other applications of this oxidation system. To our pleasure, the oxidative [4+2] cyclization[11] of *N*, *N*, 4-trimethylaniline with maleimides were also proved to be feasible and gave desired compounds in moderate yields under the mild catalytic conditions (**8a**-**8c,** scheme 3).

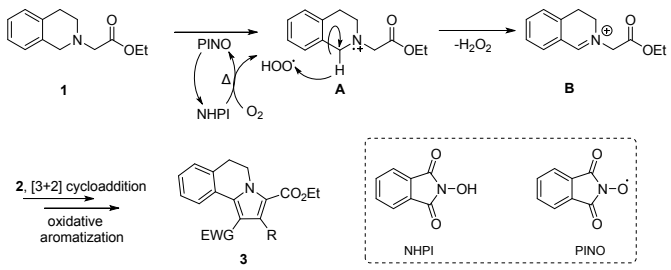
To obtain a good understanding of the reaction mechanism, some control experiments were conducted. In the presence of 1.0 equiv of radical inhibitor BHT or TEMPO, no product or only trace amount of product can be obtained (Scheme 4a), suggesting that a radical oxidative pathway might be involved. Either abandoning NHPI or replacing the oxygen atmosphere with air resulted in a drastic drop of yield, which indicated that the combination of NHPI and molecular oxygen was critical to this reaction (Scheme 4, b-c). When only 1a was subjected to the standard conditions, ethyl 2-(1-oxo-3,4-dihydroisoquinolin-2(1H)-yl) acetate **9** was obtained in 21% yield (Scheme 4d).



Scheme 3. Oxidative [4+2] cyclization reaction. General Conditions: **7** (0.2 mmol), **2** (0.3 mmol), NHPI (0.02 mmol), and CuBr (0.02 mmol) in dried CH_3CN (2.0 mL) under O_2 balloon atmosphere at 60 °C overnight. [a]Isolated yied.



Scheme 4. Control experiments.



Scheme 5. The plausible mechanism.

Based on the results of the control experiments and reported precedents,[7a] a supposed mechanism was illustrated in Scheme 5. Radical PINO was generated through the homolysis of NHPI with dioxygen,[12] which promoted the oxidation of dihydroisoquinoline esters to afford cation radical **A**. The interaction of **A** and hydroperoxyl radicl afforded the key iminium ion **B.** Then the [3+2] cycloaddition-oxidative aromatization sequence of iminium ion **B** and dipolarophiles **2** catalyzed by CuBr/NHPI was achieved adn delivered the final product **3**.

Conclusions

In summary, a facile and practical copper salt mediated oxidative [3+2] cycloaddition-aromatization cascade of tertiary amine and kinds of dipolarophiles has been developed. Dioxygen, a green and reproducible reagent, is used as the only oxidant for this complex conversion employing NHPI as co-catalyst. This novel method provides an efficient and eco-friendly approach to pyrrolo[2,1-*a*]isoquinolines based on its high atom-economy, good functional group tolerance and wide range of both reacting components.

Experimental Section

General Information. Proton (^{1}H NMR) and carbon (^{13}C NMR) nuclear magnetic resonance spectra were recorded at 400 MHz and 75 MHz, respectively. The solvent peak was used as a reference value, for ^{1}H NMR: $CDCl_3$ = 7.27 ppm, for ^{13}C NMR: $CDCl_3$ = 77.23 ppm. HRMS were carried out on an Orbitrap analyzer. All reactions were carried out with dry solvents under anhydrous conditions. DCM, DCE and CH_3CN were distilled from CaH_2. All other commercially available reagents were used as received.Analytical TLC was performed on precoated silica gel GF254 plates. Column chromatography was carried out on silica gel (200–300 mesh). *N*-substituted tetrahydroisoquinoline and dipolarophiles were synthesized according to the corresponding literatures.[7a, 13]

General procedure for the synthesis of Product 3: To a solution of the corresponding **1** (0.2 mmol, 1.0 eq) and **2** (0.3 mmol, 1.5 eq) in 2 mL anhydrous CH_3CN were added CuBr (0.02 mmol, 0.1 eq), NHPI (0.02 mmol, 0.1 eq). Then the air was replaced with dioxygen for three times and the mixture was stirred at indicated temperature under dioxygen atmosphere (dioxygen balloon, 1atm) over night. After the corresponding **1** disappeared, the reaction solvent was removed under reduced pressure and the residue was purified directedly by flash chromatography to give the pure desired product **3**.

The synthesis of ethyl 2-(1-oxo-3,4-dihydroisoquinolin-2(1H)-yl)acetate (9)： To a solution of **1a** (0.4 mmol, 1.0 eq) in 4 mL anhydrous CH_3CN were added CuBr (0.04 mmol, 0.1 eq), NHPI (0.04 mmol, 0.1 eq). Then the air was replaced with dioxygen for three times and the mixture was stirred at 60 °C under dioxygen atmosphere (dioxygen balloon, 1atm) overnight. Then, the reaction solvent was removed under reduced pressure and the residue was purified directedly by flash chromatography to give the pure **7** in 21% yield.

Ethyl 9,11-dioxo-10-phenyl-6,9,10,11-tetrahydro-5*H*-pyrrolo[3',4':3,4]pyrrolo[2,1-*a*]isoquinoline-8-carboxylate (3a)： Yield 91% (88.5 mg), yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.63–8.56 (m,

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1H), 7.53–7.46 (m, 2H), 7.45–7.35 (m, 5H), 7.31 (d, *J* = 6.9 Hz, 1H), 4.79 (t, *J* = 6.9 Hz, 2H), 4.45 (q, *J* = 7.1 Hz, 2H), 3.20 (t, *J* = 6.9 Hz, 2H), 1.48 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 163.35, 161.85, 159.93, 133.72, 132.84, 132.65, 130.57, 129.16, 128.26, 128.24, 128.03, 127.89, 127.40, 125.82, 125.49, 118.92, 116.50, 61.88, 43.64, 28.61, 14.42. The data was consistent with the known literature.[7a]

Ethyl 9,11-dioxo-10-(*p*-tolyl)-6,9,10,11-tetrahydro-5*H*-pyrrolo[3',4':3,4] pyrrolo[2,1-*a*]isoquinoline-8-carboxylate (3b): Yield 87% (69.6 mg), light yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.61 (d, *J* = 7.1 Hz, 1H), 7.53-7.37 (m, 2H), 7.3-7.29 (m, 5H), 4.80 (t, *J* = 5.9 Hz, 2H), 4.45 (q, *J* = 6.7 Hz, 2H), 3.21 (t, *J* = 5.7, 2H), 2.42 (s, 3H), 1.49 (t, *J* = 6.7 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 163.29, 161.83, 159.76, 137.81, 133.42, 132.42, 130.31, 129.95, 129.63, 128.04, 127.67, 127.05, 125.65, 125.38, 118.62, 116.38, 61.66, 43.41, 28.40, 21.23, 14.19. The data was consistent with the known literature.[7a]

Ethyl 9,11-dioxo-10-(*o*-tolyl)-6,9,10,11-tetrahydro-5*H*-pyrrolo[3',4':3,4] pyrrolo[2,1-*a*]isoquinoline-8-carboxylate (3c): Yield 80% (64.0 mg), light yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.59–8.40 (m, 1H), 7.36–7.18 (m, 6H), 7.15 (d, *J* = 7.1 Hz, 1H), 4.82–4.71 (m, 1H), 4.70–4.60 (m, 1H), 4.35 (q, *J* = 7.1 Hz, 2H), 3.11 (t, *J* = 6.9 Hz, 2H), 2.18 (s, 3H), 1.38 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 163.31, 161.88, 159.87, 137.06, 133.57, 132.59, 131.82, 131.11, 130.47, 129.32, 129.29, 128.17, 128.14, 127.82, 126.88, 125.76, 125.72, 118.79, 116.63, 61.81, 43.56, 28.52, 18.22, 14.30. The data was consistent with the known literature.[6a]

Ethyl 9,11-dioxo-10-(*m*-tolyl)-6,9,10,11-tetrahydro-5*H*-pyrrolo[3',4':3,4]pyrrolo[2,1-*a*]isoquinoline-8-carboxylate (3d): Yield 85% (68.0 mg), light yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.69–8.53 (m, 1H), 7.46–7.35 (m, 3H), 7.30 (d, *J* = 6.8 Hz, 1H), 7.20 (d, *J* = 8.0 Hz, 3H), 4.79 (t, *J* = 6.9 Hz, 2H), 4.44 (q, *J* = 7.1 Hz, 2H), 3.20 (t, *J* = 6.8 Hz, 2H), 2.41 (s, 3H), 1.48 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 163.45, 161.92, 159.95, 139.08, 133.66, 132.71, 132.64, 130.53, 128.96, 128.25, 128.07, 127.87, 125.85, 125.57, 124.54, 118.88, 116.57, 61.85, 43.63, 28.61, 21.59, 14.42. The data was consistent with the known literature.[6a]

Ethyl 10-(2,4-dimethylphenyl)-9,11-dioxo-6,9,10,11-tetrahydro-5*H*-pyrrolo[3',4':3,4]pyrrolo[2,1-*a*]isoquinoline-8-carboxylate (3e): Yield 82% (67.9 mg), light yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.58 (d, *J* = 7.1 Hz, 1H), 7.48–7.35 (m, 2H), 7.30 (d, *J* = 7.0 Hz, 1H), 7.16 (s, 1H), 7.14–7.05 (m, 2H), 4.84 (dd, *J* = 13.6, 6.7 Hz, 1H), 4.75 (dd, *J* = 13.9, 6.9 Hz, 1H), 4.43 (q, *J* = 7.0 Hz, 2H), 3.20 (t, *J* = 6.7 Hz, 2H), 2.37 (s, 3H), 2.20 (s, 3H), 1.46 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 163.52, 162.12, 159.98, 139.24, 136.69, 133.56, 132.61, 131.89, 130.48, 129.18, 129.08, 128.25, 127.85, 127.68, 125.88, 118.78, 116.77, 61.85, 43.61, 28.62, 21.38, 18.15, 14.33. HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{25}H_{23}N_2O_4$: 415.1652, found 415.1647.

Ethyl 10-(4-methoxyphenyl)-9,11-dioxo-6,9,10,11-tetrahydro-5*H*-pyrrolo[3',4':3,4]pyrrolo[2,1-*a*]isoquinoline-8-carboxylate (3f): Yield 86% (71.6 mg), light yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.59 (d, *J* = 7.1 Hz, 1H), 7.48–7.35 (m, 2H), 7.31 (d, *J* = 7.1 Hz, 3H), 7.01 (d, *J* = 7.7 Hz, 2H), 4.79 (t, *J* = 6.6 Hz, 2H), 4.44 (q, *J* = 7.0 Hz, 2H), 3.85 (s, 3H), 3.20 (t, *J* = 6.6 Hz, 2H), 1.48 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 163.65, 162.21, 159.96, 159.29, 133.63, 132.63, 130.53, 128.73, 128.25, 128.23, 127.88, 125.84, 125.54, 125.29, 118.83, 116.53, 114.55, 61.87, 55.73, 43.61, 28.61, 14.40. The data was consistent with the known literature.[7e]

Ethyl 10-(4-chlorophenyl)-9,11-dioxo-6,9,10,11-tetrahydro-5*H*-pyrrolo[3',4':3,4]pyrrolo[2,1-*a*]isoquinoline-8-carboxylate (3g): Yield 84% (70.6 mg), light yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.57 (d, *J* = 7.0 Hz, 1H), 7.50-7.35 (m, 6H), 7.31 (d, *J* = 7.0 Hz, 1H), 4.79 (t, *J* = 6.7 Hz, 2H), 4.45 (q, *J* = 7.0 Hz, 2H), 3.20 (t, *J* = 6.7 Hz, 2H), 1.48 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 163.03, 161.53, 159.82, 133.89, 133.66, 132.67, 131.38, 130.69, 129.33, 128.50, 128.29, 128.19, 127.94, 125.71, 125.22, 119.09, 116.25, 61.94, 43.67, 28.57, 14.42. The data was consistent with the known literature.[7e]

Ethyl 10-(4-bromophenyl)-9,11-dioxo-6,9,10,11-tetrahydro-5*H*-pyrrol-o[3',4':3,4]pyrrolo[2,1-*a*]isoquinoline-8-carboxylate (3h): Yield 82% (76.1 mg), light yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.57 (d, *J* = 7.1 Hz, 1H), 7.62 (d, *J* = 7.8 Hz, 2H), 7.50–7.37 (m, 2H), 7.36–7.28 (m, 3H), 4.79 (t, *J* = 6.5 Hz, 2H), 4.45 (q, *J* = 7.0 Hz, 2H), 3.20 (t, *J* = 6.4 Hz, 2H), 1.48 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 162.94, 161.45, 159.81, 133.90, 132.67, 132.29, 131.90, 130.69, 128.78, 128.29, 128.19, 127.94, 125.70, 125.20, 121.67, 119.10, 116.24, 61.94, 43.67, 28.57, 14.41. The data was consistent with the known literature.[7e]

Ethyl 10-methyl-9,11-dioxo-6,9,10,11-tetrahydro-5*H*-pyrrolo[3',4':3,4]-pyrrolo[2,1-*a*]isoquinoline-8-carboxylate (3i)： Yield 78% (50.6 mg), light yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.53 (d, *J* = 7.1 Hz, 1H), 7.52–7.33 (m, 2H), 7.29 (s, 1H), 4.73 (t, *J* = 6.3 Hz, 2H), 4.43 (q, *J* = 6.8, Hz, 2H), 3.38-2.88 (m, 5H), 1.49 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 164.37, 163.05, 159.93, 133.08, 132.56, 130.37, 128.20, 128.07, 127.84, 126.08, 125.88, 118.39, 116.91, 61.74, 43.46, 28.56, 24.45, 14.41. The data was consistent with the known literature.[7a]

Ethyl 10-benzyl-9,11-dioxo-6,9,10,11-tetrahydro-5*H*-pyrrolo[3',4':3,4]-pyrrolo[2,1-*a*]isoquinoline-8-carboxylate (3j)： Yield 72% (57.6 mg), light yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.53 (d, *J* = 7.1 Hz, 1H), 7.50–7.17 (m, 8H), 4.81 (s, 2H), 4.73 (t, *J* = 6.0 Hz, 2H), 4.44 (q, *J* = 6.7 Hz, 2H), 3.15 (t, *J* = 5.6 Hz, 2H), 1.49 (t, *J* = 6.7 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 164.08, 162.52, 159.91, 137.34, 133.26, 132.56, 130.41, 128.77, 128.67, 128.18, 128.11, 127.83, 127.71, 125.89, 125.81, 118.55, 116.74, 61.79, 43.51, 42.06, 28.56, 14.48. The data was consistent with the known literature.[7a]

Ethyl 10-(4-chlorobenzyl)-9,11-dioxo-6,9,10,11-tetrahydro-5*H*-pyrrolo[3',4':3,4]pyrrolo[2,1-*a*]isoquinoline-8-carboxylate (3k)： Yield 68% (59.0 mg), light yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.51 (d, *J* = 7.3 Hz, 1H), 7.49–7.33 (m, 4H), 7.29 (s, 2H), 4.82-4.65 (m, 4H), 4.44 (q, *J* = 7.1 Hz, 2H), 3.15 (t, *J* = 6.7 Hz, 2H), 1.48 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 163.97, 162.42, 159.83, 135.81, 133.62, 133.39, 132.58, 130.50, 130.17, 128.92, 128.20, 128.08, 127.87, 125.75, 125.73, 118.67, 116.56, 61.83, 43.53, 41.38, 28.54, 14.47. The data was consistent with the known literature.[7e]

Ethyl 10-(4-methoxybenzyl)-9,11-dioxo-6,9,10,11-tetrahydro-5*H*-pyrr-olo[3',4':3,4]pyrrolo[2,1-*a*]isoquinoline-8-carboxylate (3l): Yield 70% (60.2 mg), light yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.53 (d, *J* = 7.4 Hz, 1H), 7.55–7.33 (m, 5H), 6.84 (d, *J* = 8.6 Hz, 2H), 4.78–4.67 (m, 4H), 4.44 (q, *J* = 7.1 Hz, 2H), 3.78 (s, 3H), 3.15 (t, *J* = 6.8 Hz, 2H), 1.49 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 164.13, 162.55, 159.93, 159.23, 133.21, 132.56, 130.39, 130.19,

129.69, 128.18, 128.13, 127.83, 125.99, 125.86, 118.51, 116.84, 114.13, 61.77, 55.47, 43.51, 41.51, 28.58, 14.49. The data was consistent with the known literature.[7e]

Ethyl 9,11-dioxo-10-phenethyl-6,9,10,11-tetrahydro-5*H*-pyrrolo[3',4':-3,4]pyrrolo[2,1-*a*]isoquinoline-8-carboxylate (3m): Yield 64% (53.0 mg), light yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.53 (d, *J* = 7.3 Hz, 1H), 7.49–7.28 (m, 6H), 7.27–7.16 (m, 2H), 4.74 (t, *J* = 6.6 Hz, 2H), 4.45 (q, *J* = 7.0 Hz, 2H), 3.86 (t, *J* = 7.8 Hz, 2H), 3.17 (t, *J* = 6.4 Hz, 2H), 2.98 (t, *J* = 7.8 Hz, 2H), 1.50 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 164.12, 162.71, 159.97, 138.71, 133.17, 132.58, 130.41, 129.13, 128.75, 128.22, 128.10, 127.86, 126.69, 125.98, 125.90, 118.45, 116.83, 61.79, 43.53, 39.92, 35.16, 28.60, 14.49. HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{25}H_{23}N_2O_4$: 415.1652, found 415.1658.

Ethyl 1-methyl 5,6-dihydropyrrolo[2,1-*a*]isoquinoline-1,3-dicarboxylate (3n): Yield 35% (20.9 mg), light yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.40 (d, *J* = 7.3 Hz, 1H), 7.46 (s, 1H), 7.30–7.19 (m, 3H), 4.57 (t, *J* = 5.4 Hz , 2H), 4.29 (q, *J* = 6.7 Hz, 2H), 3.83 (s, 3H), 3.00 (d, *J* = 5.3 Hz, 2H), 1.35 (t, *J* = 6.7 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 165.19, 161.18, 138.08, 134.29, 129.14, 128.71, 127.52, 127.35, 127.20, 121.59, 121.42, 112.18, 60.57, 51.63, 42.59, 29.71, 14.61. The data was consistent with the known literature.[7f]

Ethyl 1-cyano-5,6-dihydropyrrolo[2,1-a]isoquinoline-3-carboxylate (3p): Yield 63% (33.5 mg), white solid.^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.30–8.14 (m, 1H), 7.43–7.32 (m, 2H), 7.32–7.27 (m, 2H), 4.67 (t, *J* = 6.7 Hz,, 2H), 4.34 (q, *J* = 7.1 Hz, 2H), 3.10 (t, *J* = 6.8 Hz, 2H), 1.39 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 160.43, 139.58, 132.83, 129.83, 128.22, 128.08, 126.23, 125.03, 122.79, 121.76, 116.92, 89.12, 60.94, 42.82, 28.89, 14.53. The data was consistent with the known literature.[7f]

3-ethyl 1-methyl 2-methyl-5,6-dihydropyrrolo[2,1-a]isoquinoline-1,3-dicarboxylate (3q): Yield 28% (17.5 mg), light yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.73–7.64 (m, 1H), 7.29 (s, 1H), 7.27–7.22 (m, 2H), 4.52 (t, *J* = 6.6 Hz, 2H), 4.36 (q, *J* = 7.1 Hz, 2H), 3.87 (s, 3H), 3.01 (t, *J* = 6.6 Hz, 2H), 2.51 (s, 3H), 1.41 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 166.84, 162.22, 135.80, 134.27, 131.26, 128.53, 127.63, 127.41, 127.38, 126.92, 120.11, 113.02, 60.44, 51.54, 42.93, 29.72, 14.63, 12.59. HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{18}H_{20}NO_4$: 314.1387, found 314.1382.

Ethyl 1-acetyl-2-phenyl-5,6-dihydropyrrolo[2,1-a]isoquinoline-3-carboxylate (3r): Yield 40% (28.7 mg), light yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.67–7.57 (m, 1H), 7.37–7.25 (m, 3H), 7.23–7.15 (m, 5H), 4.51 (t, *J* = 5.6 Hz, 2H), 4.03–3.84 (m, 2H), 3.01 (t, *J* = 5.8 Hz, 2H), 1.94 (s, 3H), 0.82 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 200.55, 161.73, 135.73, 134.16, 133.57, 132.97, 130.30, 128.71, 127.87, 127.49, 127.32, 126.86, 124.02, 119.53, 60.30, 42.85, 32.37, 29.64, 13.71. HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{23}H_{22}NO_3$: 360.1594, found 360.1596.

Ethyl 1-formyl-2-phenyl-5,6-dihydropyrrolo[2,1-a]isoquinoline-3-carboxylate (3s): Yield 30% (20.7 mg), light yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 9.67 (s, 1H), 8.68–8.47 (m, 1H), 7.53–7.27 (m, 8H), 4.65 (t, *J* = 6.6 Hz, 2H), 4.04 (q, *J* = 7.1 Hz, 2H), 3.11 (t, *J* = 6.6 Hz, 2H), 0.89 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 187.17, 161.54, 138.25, 137.42, 134.33, 133.85, 130.71, 129.90, 128.79, 127.73, 127.67, 127.55, 127.54, 126.92, 120.35, 120.09, 60.48, 42.95, 29.48, 13.66. HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{22}H_{20}NO_3$: 346.1438, found 346.1440.

Ethyl 2-bromo-9,14-dioxo-5,6,9,14-tetrahydrobenzo[5,6]isoindolo[1,2-*a*]isoquinoline-8-carboxylate (3t): Yield 72% (53.4 mg), light yellow solid. H NMR (400 MHz, $CDCl_3$) δ = 9.30 (s, 1H), 8.35 (d, *J* = 6.7 Hz, 1H), 8.23 (d, *J* = 6.6 Hz, 1H), 7.74 (s, 2H), 7.53 (d, *J* = 7.7 Hz, 1H), 7.17 (d, *J* = 7.9 Hz, 1H), 4.56 (dd, *J* = 13.9, 6.9 Hz, 2H), 4.41–4.17 (m, 2H), 3.21–2.97 (m, 2H), 1.51 (t, *J* = 7.0 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 179.73, 179.38, 161.34, 135.54, 134.64, 133.95, 133.44, 133.15, 132.76, 132.28, 131.53, 128.92, 128.25, 127.46, 126.66, 126.36, 123.32, 121.28, 118.01, 62.63, 43.06, 28.70, 14.03. The data was consistent with the known literature.[6f]

Ethyl 2-phenyl-5,6-dihydropyrrolo[2,1-*a*]isoquinoline-3-carboxylate (5a): Yield 71% (45.0 mg), light yellow solid. ^{1}H NMR (400 MHz, CDCl3) δ = 7.57 (d, *J* = 7.4 Hz, 1H), 7.43 (d, *J* = 7.2 Hz, 2H), 7.39–7.21 (m, 6H), 6.57 (s, 1H), 4.64 (t, *J* = 6.3 Hz, 2H), 4.13 (q, *J* = 7.0 Hz, 2H), 3.11 (t, *J* = 6.4 Hz, 2H), 1.06 (t, *J* = 7.0 Hz, 3H) ; ^{13}C NMR (101 MHz, CDCl3) δ = 162.11, 137.06, 134.92, 134.59, 132.15, 129.81, 128.32, 128.04, 127.72, 127.65, 127.40, 126.85, 123.82, 118.92, 107.12, 60.07, 42.90, 29.24, 14.02. The data was consistent with the known literature.[5b]

Ethyl 2-(4-chlorophenyl)-5,6-dihydropyrrolo[2,1-*a*]isoquinoline-3-carboxylate (5b): Yield 65% (45.6 mg), light yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.52 (d, *J* = 6.8 Hz, 1H), 7.39–7.28 (m, 3H), 7.24–7.15 (m, 4H), 6.49 (s, 1H), 4.59 (t, *J* = 5.5 Hz, 2H), 4.11 (q, *J* = 6.9 Hz, 2H), 3.07 (m, t, *J* = 5.5 Hz, 2H), 1.06 (t, *J* = 6.9 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 161.88, 135.58, 135.10, 133.28, 132.78, 132.16, 131.16, 128.16, 128.09, 127.88, 127.80, 127.46, 123.85, 118.91, 107.02, 60.19, 42.98, 29.21, 14.15. HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{21}H_{19}ClNO_2$: 352.1099, found 352.1106.

Ethyl 2-(4-methoxyphenyl)-5,6-dihydropyrrolo[2,1-*a*]isoquinoline-3-carboxylate (5c): Yield 68% (47.2 mg), light yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.49 (d, *J* = 7.6 Hz, 1H), 7.31 (s, 1H), 7.25–7.04 (m, 4H), 6.84 (d, *J* = 8.7 Hz, 2H), 6.47 (s, 1H), 4.56 (t, *J* = 6.7 Hz, 2H), 4.09 (q, *J* = 7.1 Hz, 2H), 3.78 (s, 3H), 3.04 (t, *J* = 6.7 Hz, 2H), 1.05 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 162.16, 158.81, 134.93, 134.35, 132.17, 130.91, 129.46, 128.37, 128.04, 127.69, 127.39, 123.83, 118.82, 113.15, 107.13, 60.04, 55.52, 42.95, 29.28, 14.20. HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{22}H_{22}NO_3$: 348.1594, found 348.1588.

Methyl 9,11-dioxo-10-phenyl-6,9,10,11-tetrahydro-5*H*-pyrrolo[3',-4':3, 4]pyrrolo[2,1-*a*]isoquinoline-8-carboxyl-ate (6b): Yield 83% (61.8 mg), light yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.55 (d, *J* = 7.1 Hz, 1H), 7.45 (t, *J* = 7.1 Hz, 2H), 7.40–7.30 (m, 4H), 7.26–7.18 (m, 2H), 4.75 (t, *J* = 6.3 Hz, 2H), 3.96 (s, 3H), 3.16 (t, *J* = 6.0 Hz, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 163.20, 161.84, 160.29, 133.86, 132.77, 132.63, 130.60, 129.05, 128.23, 128.21, 127.94, 127.87, 127.24, 125.71, 125.55, 118.37, 116.49, 52.52, 43.64, 28.52. The data was consistent with the known literature.[6f]

Isopropyl 9,11-dioxo-10-phenyl-6,9,10,11-tetrahydro-5*H*-pyrrolo [3',4':3,4]pyrrolo[2,1-*a*]isoquinoline-8-carboxylate (6c): Yield 85% (68.0 mg), light yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.60 (d, *J* = 7.0 Hz, 1H), 7.62–7.28 (m, 8H), 5.34-5.20 (m, 1H), 4.79 (t, *J* = 6.9 Hz, 2H), 3.20 (t, *J* = 6.9 Hz, 2H), 1.45 (d, *J* = 6.2 Hz, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 163.40, 161.70, 159.48, 133.49, 132.89, 132.62, 130.47, 129.16, 128.21, 128.00, 127.86, 127.45, 125.86, 125.33, 119.43, 116.44, 69.91, 43.60, 28.61, 22.09. HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{24}H_{21}N_2O_4$: 401.1496, found 401.1499.

Isobutyl 9,11-dioxo-10-phenyl-6,9,10,11-tetrahydro-5*H*-pyrrolo[3',

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4':3, 4]pyrrolo[2,1-*a*]isoquinoline-8-carboxylate (6d): Yield 80% (66.3 mg), light yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.57 (d, *J* = 7.0 Hz, 1H), 7.49–7.30 (m, 7H), 7.27–7.19 (m, 1H), 4.76 (t, *J* = 6.4 Hz, 2H), 4.13 (d, *J* = 6.4 Hz, 2H), 3.16 (t, *J* = 6.4 Hz, 2H), 2.26-2.06 (m, 1H), 1.03 (d, *J* = 6.5 Hz, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 163.35, 161.62, 160.10, 133.69, 132.85, 132.65, 130.52, 129.13, 128.21, 127.98, 127.85, 127.41, 125.80, 125.35, 118.77, 116.57, 72.06, 43.68, 28.60, 28.04, 19.39. HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{25}H_{23}N_2O_4$: 415.1652, found 415.1659.

Tert-butyl 9,11-dioxo-10-phenyl-6,9,10,11-tetrahydro-5*H*-pyrrolo [3', 4':3,4]pyrrolo[2,1-*a*]isoquinoline-8-carboxylate (6e): Yield 78% (64.6 mg), light yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.59 (d, *J* = 7.1 Hz, 1H), 7.50 (t, *J* = 7.7 Hz, 2H), 7.44–7.32 (m, 5H), 7.30 (d, *J* = 7.0 Hz, 1H), 4.77 (t, *J* = 6.8 Hz, 2H), 3.18 (t, *J* = 6.8 Hz, 2H), 1.67 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 163.46, 161.80, 159.24, 133.24, 132.94, 132.64, 130.37, 129.16, 128.18, 128.16, 127.98, 127.83, 127.49, 125.95, 124.90, 120.45, 116.26, 83.66, 43.53, 28.64, 28.52. The data was consistent with the known literature.[6f]

Benzyl 9,11-dioxo-10-phenyl-6,9,10,11-tetrahydro-5*H*-pyrrolo[3',4': 3,4]pyrrolo[2,1-*a*]isoquinoline-8-carboxylate (6f): Yield 70% (62.7 mg), light yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.65–8.55 (m, 1H), 7.60 (d, *J* = 7.3 Hz, 2H), 7.54–7.47 (m, 2H), 7.46-7.27 (m, 9H), 5.46 (s, 2H), 4.78 (t, *J* = 6.9 Hz, 2H), 3.18 (t, *J* = 6.9 Hz, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 163.28, 161.66, 159.67, 135.72, 133.89, 132.85, 132.65, 130.60, 129.12, 128.79, 128.59, 128.50, 128.24, 128.00, 127.86, 127.39, 125.73, 118.46, 116.62, 67.26, 43.70, 28.55. HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{28}H_{21}N_2O_4$: 449.1496, found 449.1502.

Phenyl 9,11-dioxo-10-phenyl-6,9,10,11-tetrahydro-5*H*-pyrrolo[3',4' :3,-4]pyrrolo[2,1-*a*]isoquinoline-8-carboxylate (6g): Yield 74% (64.3 mg), light yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.64 (d, *J* = 7.0 Hz, 1H), 7.78–7.27 (m, 13H), 4.83 (t, *J* = 6.7 Hz, 2H), 3.24 (t, *J* = 6.6 Hz, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 163.23, 161.65, 158.01, 150.61, 134.57, 132.78, 132.71, 130.83, 129.65, 129.14, 128.39, 128.34, 128.06, 127.96, 127.33, 126.65, 126.29, 125.66, 121.65, 117.82, 116.94, 43.73, 28.55. HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{27}H_{19}N_2O_4$: 435.1339, found 435.1343.

Ethyl 2-chloro-9,11-dioxo-10-phenyl-6,9,10,11-tetrahydro-5*H*-pyrrolo-[3',4':3,4]pyrrolo[2,1-*a*]isoquinoline-8-carboxylate (6h): Yield 74% (62.2 mg), light yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.75 (s, 1H), 7.58–7.43 (m, 3H), 7.43–7.32 (d, *J* = 8.5 Hz, 2H), 7.27 (d, *J* = 2.4 Hz, 1H, overlapped in $CDCl_3$), 7.18 (d, *J* = 8.1 Hz, 1H), 4.79 (t, *J* = 6.8 Hz, 2H), 4.45 (q, *J* = 7.0 Hz, 2H), 3.16 (t, *J* = 6.8 Hz, 2H), 1.48 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 162.87, 161.33, 159.69, 133.85, 133.46, 132.18, 131.26, 131.21, 130.73, 129.52, 129.40, 128.52, 127.46, 125.20, 121.96, 119.50, 116.87, 62.07, 43.52, 28.15, 14.39. HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{23}H_{18}ClN_2O_4$: 421.0950, found 421.0954.

Ethyl 2-bromo-9,11-dioxo-10-phenyl-6,9,10,11-tetrahydro-5*H*-pyrrolo[3',4':3,4]pyrrolo[2,1-*a*]isoquinoline-8-carboxylate (6ia): Yield 78% (72.4 mg), light yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.78 (s, 1H), 7.63-7.35 (m, 6H), 7.17 (d, *J* = 8.1 Hz, 1H), 4.79 (t, *J* = 6.9 Hz, 2H), 4.44 (q, *J* = 7.1 Hz, 2H), 3.15 (t, *J* = 6.8 Hz, 2H), 1.48 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 163.21, 161.64, 159.80, 133.35, 132.70, 132.01, 131.24, 130.76, 129.47, 129.24, 128.20, 127.57, 127.43, 125.47, 121.95, 119.34, 117.13, 62.01, 43.49, 28.18, 14.39. The data was consistent with the known literature.[7a]

Ethyl 2-bromo-10-(4-chlorophenyl)-9,11-dioxo-6,9,10,11-tetrahydro-5*H*-pyrrolo[3',4':3,4]pyrrolo[2,1-*a*]isoquinoline-8-carboxylate (6ib): Yield 72% (71.7 mg), light yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.63 (d, *J* = 1.9 Hz, 1H), 7.54–7.47 (m, 2H), 7.41 (d, *J* = 7.9 Hz, 2H), 7.35 (dd, *J* = 8.1, 2.0 Hz, 1H), 7.24 (d, *J* = 8.1 Hz, 1H), 4.79 (t, *J* = 6.9 Hz, 2H), 4.45 (q, *J* = 7.1 Hz, 2H), 3.18 (t, *J* = 6.9 Hz, 2H), 1.48 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 163.20, 161.66, 159.80, 134.18, 132.67, 132.19, 130.75, 130.44, 129.23, 128.19, 127.87, 127.40, 127.24, 125.45, 119.31, 117.10, 62.01, 43.55, 28.11, 14.39. HRMS (ESI): m/z $[M+Na]^+$ calcd for $C_{23}H_{16}BrClN_2NaO_4$: 520.9874, found 520.9869.

Ethyl 2-bromo-10-(4-methoxyphenyl)-9,11-dioxo-6,9,10,11-tetrahydro-5*H*-pyrrolo[3',4':3,4]pyrrolo[2,1-*a*]isoquinoline-8-carboxylate (6ic): Yield 80% (79.0 mg), light yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.76 (s, 1H), 7.48 (d, *J* = 8.0 Hz, 1H), 7.30 (d, *J* = 8.8 Hz, 2H), 7.16 (d, *J* = 8.1 Hz, 1H), 7.01 (d, *J* = 8.8 Hz, 2H), 4.77 (t, *J* = 6.9 Hz, 2H), 4.43 (q, *J* = 7.1 Hz, 2H), 3.85 (s, 3H), 3.14 (t, *J* = 6.8 Hz, 2H), 1.46 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 163.50, 161.98, 159.80, 159.41, 133.29, 131.91, 131.22, 130.72, 129.45, 128.74, 127.57, 125.51, 125.34, 121.90, 119.24, 117.12, 114.63, 61.98, 55.75, 43.45, 28.16, 14.37. HRMS (ESI): m/z $[M+Na]^+$ calcd for $C_{24}H_{19}BrN_2NaO_5$: 517.0370, found 517.0377.

Ethyl 2-bromo-9,14-dioxo-5,6,9,14-tetrahydrobenzo[5,6]isoindolo-[1,2-*a*]isoquino-line-8-carboxylate (6id): Yield 82% (73.6 mg), light yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 9.30 (s, 1H), 8.35 (d, *J* = 6.7 Hz, 1H), 8.23 (d, *J* = 6.6 Hz, 1H), 7.74 (s, 2H), 7.53 (d, *J* = 7.7 Hz, 1H), 7.17 (d, *J* = 7.9 Hz, 1H), 4.56 (dd, *J* = 13.9, 6.9 Hz, 2H), 4.41–4.17 (m, 2H), 3.21–2.97 (m, 2H), 1.51 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 179.92, 179.57, 161.53, 135.74, 134.84, 134.14, 133.63, 133.34, 132.95, 132.48, 131.73, 129.11, 128.45, 127.66, 126.85, 126.56, 123.52, 121.48, 118.21, 62.82, 43.26, 28.90, 14.22. HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{23}H_{17}BrNO_4$: 450.0335, found 450.0338.

Ethyl 2,3-dimethoxy-9,11-dioxo-10-phenyl-6,9,10,11-tetrahydro-5 *H*-pyrrolo[3',4':3,4]pyrrolo[2,1-*a*]isoquinoline-8-carboxylate (6ja): Yield 88% (78.5 mg), light yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.27 (s, 1H), 7.57–7.47 (m, 2H), 7.45–7.33 (m, 3H), 6.77 (s, 1H), 4.76 (t, *J* = 7.0 Hz, 2H), 4.43 (q, *J* = 7.1 Hz, 2H), 3.99 (s, 3H), 3.95 (s, 3H), 3.14 (t, *J* = 7.0 Hz, 2H), 1.47 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 163.82, 161.97, 159.96, 150.95, 148.89, 134.36, 132.84, 129.32, 128.20, 127.61, 125.84, 125.37, 118.61, 118.44, 115.08, 110.79, 110.53, 61.80, 56.46, 56.28, 43.74, 28.17, 14.41. The data was consistent with the known literature.[7a]

Ethyl 10-(4-chlorophenyl)-2,3-dimethoxy-9,11-dioxo-6,9,10,11-tetrahydro-5*H*-pyrrolo[3',4':3,4]pyrrolo[2,1-*a*]isoquinoline-8-carboxylate (6jb): Yield 82% (78.7 mg), light yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.23 (s, 1H), 7.46 (d, *J* = 8.5 Hz, 2H), 7.36 (d, *J* = 8.5 Hz, 2H), 6.77 (s, 1H), 4.76 (t, *J* = 6.8 Hz, 2H), 4.43 (q, *J* = 7.0 Hz, 2H), 4.19–3.74 (m, 6H), 3.14 (t, *J* = 6.7 Hz, 2H), 1.47 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 163.49, 161.64, 159.84, 151.00, 148.84, 134.54, 133.85, 131.32, 129.47, 128.71, 125.88, 125.06, 118.77, 118.26, 114.78, 110.68,110.49, 61.85, 56.43, 56.27, 43.75, 28.11, 14.40. HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{25}H_{22}ClN_2O_6$: 481.1161, found 481.1167.

Ethyl 2,3-dimethoxy-10-(4-methoxyphenyl)-9,11-dioxo-6,9,10,11-tetrahydro-5*H*-pyrrolo[3',4':3,4]pyrrolo[2,1-*a*]isoquinoline-8-carb-

oxylate (6jc): Yield 90% (85.7 mg), light yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.26 (s, 1H), 7.29 (d, *J* = 8.7 Hz, 2H), 7.01 (d, *J* = 8.7 Hz, 2H), 6.76 (s, 1H), 4.75 (t, *J* = 6.9 Hz, 2H), 4.42 (q, *J* = 7.0 Hz, 2H), 4.10–3.88 (m, 6H), 3.84 (s, 3H), 3.13 (t, *J* = 6.8 Hz, 2H), 1.46 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 164.13, 162.30, 159.96, 159.41, 150.88, 148.84, 134.26, 128.92, 125.78, 125.47, 125.41, 118.51, 118.43, 115.07, 114.73, 110.73, 110.48, 61.77, 56.43, 56.25, 55.72, 43.69, 28.14, 14.38. HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{26}H_{25}N_2O_7$: 477.1656, found 477.1664.

Ethyl 2,3-dimethoxy-9,14-dioxo-5,6,9,14-tetrahydrobenzo[5,6]isoindolo[1,2-*a*]isoquinoline-8-carboxylate (6jd): Yield 78% (67.3 mg), light yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.95 (s, 1H), 8.39–8.28 (m, 1H), 8.24–8.11 (m, 1H), 7.81–7.63 (m, 2H), 6.77 (s, 1H), 4.55 (q, *J* = 7.1 Hz, 2H), 4.29 (t, *J* = 6.7 Hz, 2H), 4.12 (s, 3H), 3.96 (s, 3H), 3.07 (t, *J* = 6.6 Hz, 2H), 1.51 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 179.94, 179.79, 161.84, 150.50, 148.00, 136.53, 136.13, 134.96, 133.42, 133.05, 127.54, 127.20, 126.77, 126.20, 123.28, 119.41, 116.64, 112.67, 110.50, 62.69, 56.55, 56.22, 43.54, 28.85, 14.24. The data was consistent with the known literature.[6f]

8,10-diphenyl-5*H*-pyrrolo[3',4':3,4]pyrrolo[2,1-*a*]isoquinoline-9,11(6H, 10H)-dione (6ka): Yield 56% (43.7 mg), light yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.59 (d, *J* = 7.3 Hz, 1H), 7.69 (d, *J* = 6.8 Hz, 2H), 7.59–7.25 (m, 11H), 4.31 (s, 2H), 3.16 (s, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 163.91, 163.74, 133.29, 132.98, 132.09, 130.59, 129.75, 129.59, 129.46, 129.06, 128.95, 128.38, 128.31, 127.79, 127.63, 127.56, 127.20, 126.97, 118.26, 115.77, 43.38, 29.26. HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{26}H_{19}N_2O_2$: 391.1441, found 391.1440.

10-(4-chlorophenyl)-8-phenyl-5H-pyrrolo[3',4':3,4]pyrrolo[2,1-a]isoquinoline-9,11(6H,10H)-dione (6kb): Yield 33% (28.0 mg), light yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.56 (d, *J* = 7.6 Hz, 1H), 7.67 (d, *J* = 7.2 Hz, 2H), 7.61–7.48 (m, 3H), 7.48–7.27 (m, 7H), 4.31 (t, *J* = 6.7 Hz, 3H), 3.16 (t, *J* = 6.4 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 163.59, 163.43, 133.20, 133.10, 132.11, 131.81, 130.80, 129.95, 129.71, 129.59, 129.11, 129.10, 128.33, 128.28, 128.25, 127.84, 127.58, 126.83, 117.98, 115.47, 43.37, 29.21. HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{26}H_{18}ClN_2O_2$: 425.1051, found 425.1054.

10-(4-methoxyphenyl)-8-phenyl-5H-pyrrolo[3',4':3,4]pyrrolo[2,1-a]isoquinoline-9,11(6H,10H)-dione (6kc): Yield 52% (43.7 mg), light yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.57 (d, *J* = 7.6 Hz, 1H), 7.68 (d, *J* = 7.3 Hz, 2H), 7.60–7.27 (m, 8H), 6.99 (d, *J* = 8.4 Hz, 2H), 4.30 (t, *J* = 6.1 Hz, 2H), 3.85 (s, 3H), 3.15 (t, *J* = 5.9 Hz, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 164.20, 164.04, 158.94, 132.86, 132.06, 130.46, 129.72, 129.54, 129.40, 129.04, 128.50, 128.39, 128.29, 127.78, 127.59, 126.98, 126.02, 118.26, 115.78, 114.35, 55.70, 43.33, 29.25. HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{27}H_{21}N_2O_3$: 421.1547, found 421.1544.

8-phenyl-5,6-dihydrobenzo[5,6]isoindolo[1,2-a]isoquinoline-9,14-dione (6kd): Yield 57% (42.8 mg), light yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 9.11 (d, *J* = 7.6 Hz, 1H), 8.33 (d, *J* = 7.0 Hz, 1H), 8.15 (d, *J* = 7.0 Hz, 1H), 7.88–7.43 (m, 8H), 7.36 (t, *J* = 7.1 Hz, 1H), 7.25 (d, *J* = 6.4 Hz, 1H), 3.959 (t, *J* = 5.4 Hz, 2H), 3.00 (s, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 180.38, 180.34, 138.08, 136.45, 135.51, 134.53, 134.00, 133.14, 132.95, 130.68, 129.71, 128.81, 128.64, 127.65, 127.57, 127.46, 127.33, 126.59, 119.73, 117.68, 42.51, 29.76. HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{26}H_{18}NO_2$: 376.1332, found 376.1336.

3-phenyl-5,6-dihydropyrrolo[2,1-a]isoquinoline-1-carbonitrile (6ke): Yield 31% (16.7 mg), light yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.21 (d, *J* = 7.7 Hz, 1H), 7.51–7.44 (m, 2H), 7.44–7.34 (m, 4H), 7.29 (s, 2H), 6.56 (s, 1H), 4.13 (t, *J* = 6.6 Hz, 2H), 3.05 (t, *J* = 6.6 Hz, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 135.93, 134.79, 132.04, 131.02, 129.22, 128.97, 128.43, 128.41, 128.17, 128.10, 127.56, 124.38, 118.15, 112.62, 88.64, 42.50, 29.54. HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{19}H_{15}N_2$: 271.1230, found 271.1233.

2-(4-methoxyphenyl)-3-phenyl-5,6-dihydropyrrolo[2,1-a]isoquinoline (6kf): Yield 20% (14.0 mg), light yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.48–7.43 (m, 5H), 7.41–7.30 (m, 3H), 7.24–7.19 (m, 1H), 7.07 (dd, *J* = 16.7, 8.1 Hz, 2H), 6.94 (d, *J* = 8.6 Hz, 2H), 6.36 (s, 1H), 4.14 (t, *J* = 6.3 Hz, 2H), 3.87 (s, 3H), 3.05 (t, *J* = 6.2 Hz, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 158.49, 133.61, 132.77, 132.57, 130.40, 130.28, 130.02, 129.23, 128.95, 128.68, 127.88, 127.19, 126.78, 125.68, 124.57, 122.70, 114.15, 111.27, 55.50, 42.68, 30.63. HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{25}H_{22}NO$: 352.1696, found 352.1698.

5,8-dimethyl-2-phenyl-3a,4,5,9b-tetrahydro-1*H*-pyrrolo[3,4-*c*]quinoline-1,3(2*H*)-dione (8a): Yield 62% (38.0 mg), light yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.36 (t, *J* = 7.5 Hz, 2H), 7.31–7.25 (m, 2H), 7.24–7.17 (m, 2H), 6.96 (dd, *J* = 15.6, 8.7 Hz, 1H), 6.59 (d, *J* = 8.3 Hz, 1H), 4.05 (d, *J* = 9.6 Hz, 1H), 3.52 (dd, *J* = 11.4, 2.6 Hz, 1H), 3.48–3.42 (m, 1H), 2.99 (dd, *J* = 11.4, 4.3 Hz, 1H), 2.73 (s, 3H), 2.23 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 177.95, 176.04, 146.43, 132.24, 131.04, 129.47, 129.36, 129.19, 128.70, 126.59, 118.76, 112.86, 51.15, 43.71, 42.37, 39.84, 20.65. The data was consistent with the known literature.[11b]

2-(4-chlorophenyl)-5,8-dimethyl-3a,4,5,9b-tetrahydro-1*H*-pyrrolo-[3,4-*c*]quinoline-1,3(2*H*)-dione (8b): Yield 57% (38.8 mg), light yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39–7.30 (m, 2H), 7.23–7.10 (m, 3H), 7.03–6.94 (m, 1H), 6.61 (d, *J* = 8.3 Hz, 1H), 4.06 (d, *J* = 9.6 Hz, 1H), 3.52 (dd, *J* = 11.4, 2.6 Hz, 1H), 3.49-3.42 (m, 1H), 3.00 (dd, *J* = 11.4, 4.3 Hz, 1H), 2.74 (s, 3H), 2.24 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 177.68, 175.77, 146.36, 134.46, 131.01, 130.69, 130.37, 129.58, 129.38, 127.80, 118.61, 112.98, 51.11, 43.70, 42.35, 39.87, 20.66. The data was consistent with the known literature.[11b]

3-(4-methoxyphenyl)-5,8-dimethyl-3a,4,5,9b-tetrahydro-1*H*-pyrrolo[3,4-*c*]quinoline-1,3(2*H*)-dione (8c): Yield 68% (45.7 mg), light yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.36 (s, 1H), 7.22–7.13 (m, 2H), 7.05 (dd, *J* = 8.2, 1.6 Hz, 1H), 6.99–6.86 (m, 2H), 6.67 (d, *J* = 8.3 Hz, 1H), 4.12 (d, *J* = 9.5 Hz, 1H), 3.81 (s, 3H), 3.59 (dd, *J* = 11.4, 2.7 Hz, 1H), 3.55–3.47 (m, 1H), 3.07 (dd, *J* = 11.4, 4.4 Hz, 1H), 2.81 (s, 3H), 2.31 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 178.18, 176.25, 159.63, 146.38, 131.06, 129.44, 129.39, 127.81, 124.91, 118.87, 114.52, 112.88, 55.69, 51.17, 43.61, 42.30, 39.88, 20.67. The data was consistent with the known literature.[11b]

Ethyl 2-(1-oxo-3,4-dihydroisoquinolin-2(1*H*)-yl)acetate (9): Yield 21% (19.5 mg), light yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.09 (d, *J* = 7.7 Hz, 1H), 7.44 (t, *J* = 7.5, 1.2 Hz, 1H), 7.35 (t, *J* = 7.5 Hz, 1H), 7.20 (d, *J* = 7.5 Hz, 1H), 4.35 (s, 2H), 4.23 (q, *J* = 7.1 Hz, 2H), 3.67 (t, *J* = 6.6 Hz, 2H), 3.08 (t, *J* = 6.6 Hz, 2H), 1.29 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 169.51, 165.21, 138.64, 132.15, 129.05, 128.68, 127.26, 127.20, 61.49, 49.40, 47.62, 28.27, 14.40. HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{13}H_{15}NO_3$: 233.1052, found 233.1055. The data was consistent with the known literature.[14]

Conflicts of interest

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There are no conflicts to declare.

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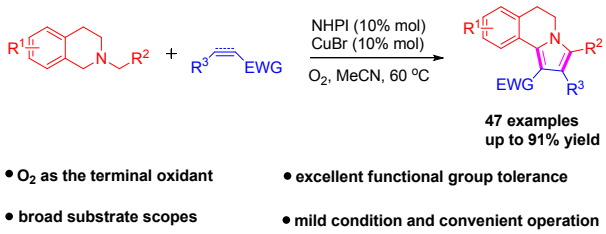

- O_2 as the terminal oxidant
- broad substrate scopes
- excellent functional group tolerance
- mild condition and convenient operation

An efficient and enviromental friendly copper(I)/NHPI co-catalyzed aerobic oxidative [3+2] cycloaddition-aromatization cascade was realized with tertiary amine and dipolarophiles.