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Synthesis of Benzoindolizines Through 1,5-Electrocyclization/Oxidation Cascades

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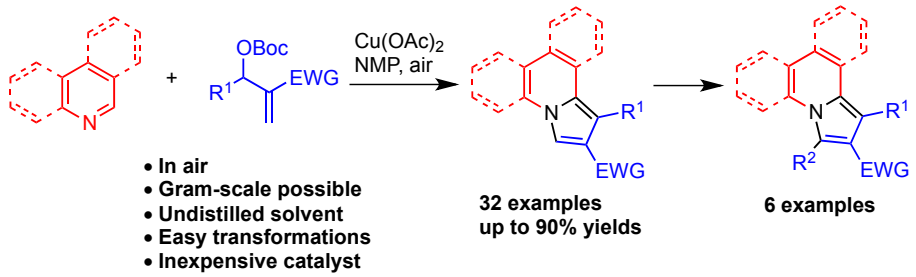


Abstract This study presents a convenient synthesis of pyrrolo[1,2-*a*]quinolines and pyrrolo[2,1-*a*]isoquinolines with simple quinolines or isoquinolines and Morita–Baylis–Hillman carbonates in the presence of copper acetate. A range of functionalized benzoindolizines could be assembled through SN2'/deprotonation/1,5-electrocyclization/oxidation cascade pathway in a one-step process.

Keywords: Pyrroloquinoline, Pyrroloisoquinoline, Electrocyclization, Quinoline, Isoquinoline

INTRODUCTION

Benzoindolizine is an important framework possessing wide occurrence in biologically active compounds

(Fig 1).[1] Furthermore, related benzoindolizine derivatives can also be used as useful building blocks and functional materials.[2] The great importance of potential applications have created a significant need for the development of convenient synthetic methods as well as structurally diversified benzoindolizines. Accordingly, a large number of attractive methodologies, including multicomponent reactions[3], 1,3-dipolar cycloadditions[4], intramolecular cyclizations[5], coupling/cyclization cascades[6], C-H activation[7], condensation/cyclization cascades[8], Michael addition/cyclization cascades[9], substitution/cyclization cascades[10], amination/C-H activation cascades[11], have been well established in past decades for the construction of benzoindolizine derivatives. From the standpoint of green and sustainable chemistry, the preparation of complex molecules bearing this privileged framework from readily available material is an interesting and longstanding topic in synthetic chemistry. Therefore, considering the great significance of structurally diversified pyrrolo[1,2-*a*]quinolines and pyrrolo[2,1-*a*]isoquinolines, the facile construction of these molecules in a straightforward fashion from simple and easily accessible material is extremely desirable.

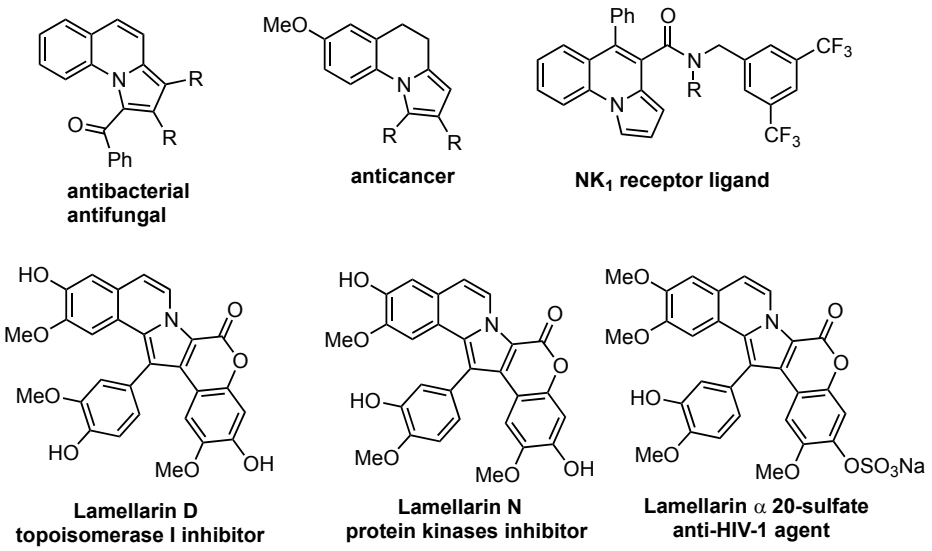
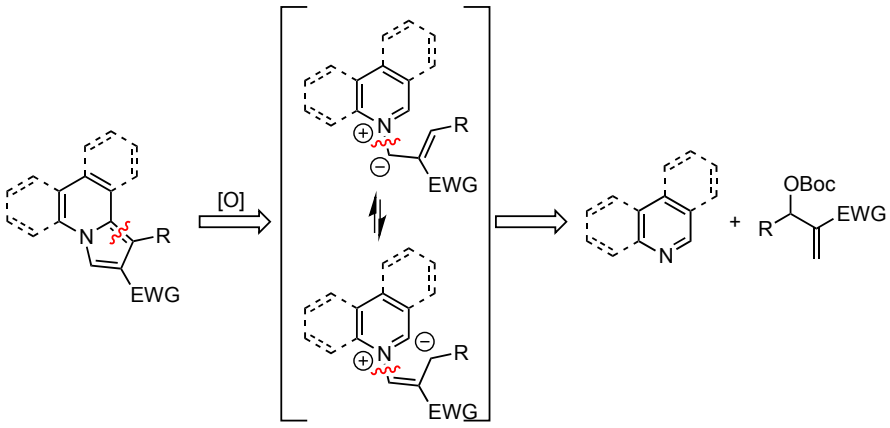


Figure 1. Representative Examples of Bioactive Pyrrolo[1,2-*a*]quinolines and Pyrrolo[2,1-*a*]isoquinolines

Cyclizations based on the formation of 1,n-dipoles (n>3) and conjugated 1,3-dipoles have been enabling the facile synthesis of highly functionalized and diversified azacycles in recent years.[12-14] Fruitful achievements in the construction of interesting nitrogen-containing molecules have been realized through this strategy. In our previous work, we have developed a catalyst-free [2+2+2] cyclization of dihydro-β-carboline and ynone allowing access to novel complex dimeric β-carboline derivatives in a single step.[15-16] The *in situ* generated 1,6-dipole was proposed as the key intermediate in this process. Based on the same 1,n-dipole cyclization strategy, we have subsequently disclosed the formal [3+2] cyclizations of dihydroisoquinoline with Morita–Baylis–Hillman (MBH) carbonates.[17-18] Electrocyclizations of *in situ* formed conjugated azomethine ylides successfully provided a range of interesting tetrahydropyrrolo[2,1-*a*]isoquinolines and tetrahydroisoquinoline fused spirooxindoles. To prepare more interesting heterocycles possessing privileged scaffold from simple material, we then tried to explore further application of 1,n-dipole cyclization strategy on the synthesis of functionalized benzoindolizines.

Inspired by the reported achievements and on the basis of retrosynthetic analysis, we envisioned that the synthesis of pyrrolo[1,2-*a*]quinoline and pyrrolo[2,1-*a*]isoquinolines could be achieved by electrocyclic closure of conjugated azomethine ylides and subsequent oxidation (Scheme 1). This retrosynthetic analysis points to commercially available quinolines, isoquinolines and simple MBH carbonates as logical precursors for synthesis. Here, we report our development of a formal [3+2] cyclization of (iso)quinolines and MBH carbonates.



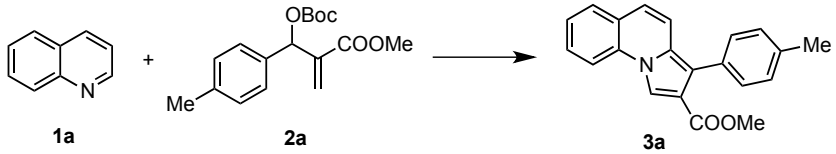
Scheme 1. Retrosynthetic Analysis.

RESULTS AND DISCUSSION

Initially, a catalyst-free reaction between quinoline **1a** and MBH carbonate **2a** in DMF was performed at 120 °C (Table 1, entry 1). We were pleased to find that the desired pyrrolo[1,2-*a*]quinoline **3a** could be detected in an encouraging 48% yield under aerobic oxidation of dioxygen in air. However, the reaction failed to run completely under the current conditions even after prolonged reaction time. As copper is an inexpensive and environment-friendly metal catalyst used extensively in aromatization by oxidation, we guessed that the employment of catalytic amount of copper salts would be helpful for the completion of

reaction. Thus, a series of copper catalysts as well as palladium salt were screened in order to improve the yield (entries 2-9). The screening of copper sources identified $Cu(OAc)_2$ as the optimal catalyst which gave a dramatically increased yield (76%). Examination of temperature and solvent led to a 98% NMR yield and 88% isolated yield of **3a** (entries 10-15). As a control experiment, a 49% isolated yield was obtained in the absence of $Cu(OAc)_2$ indicating that the use of copper salts as oxidation catalyst is critical for this process (entry 16). The role of $Cu(OAc)_2$ as oxidant was further supported by the reaction performed under Ar atmosphere, which provided 59% yield (entry 17). The use of undistilled solvent may also have influence on reaction yield. The reaction under O_2 atmosphere gave only 33% yield and more complicated byproducts could be observed compared with other cases, although reaction could be completed in a much shorter reaction time (entry 18). The reason for unexpected reaction yields obtained in these two reactions (entries 17 and 18) has not been fully understood yet.

Table 1 Optimization of Reaction Conditions for Synthesis of 3a.[a,b]



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

Entry	Catalyst	Solvent	T (°C)	t (h)	Yield [%][b]
1	-	DMF	120	28	48
2	$CuBr_2$	DMF	120	9	69
3	$CuCl_2$	DMF	120	12	25
4	CuCl	DMF	120	7	56
5	CuBr	DMF	120	7	64
6	$Cu(OAc)_2{\cdot}H_2O$	DMF	120	9.5	76
7	$Cu(NO_3)_2$	DMF	120	11.5	14
8	CuI	DMF	120	11.5	65
9	$Pd(OAc)_2$	DMF	120	11.5	18
10	$Cu(OAc)_2{\cdot}H_2O$	DMF	140	3	68[c]
11	$Cu(OAc)_2{\cdot}H_2O$	DMF	100	20	38[c]
12	$Cu(OAc)_2{\cdot}H_2O$	DMF	50	45	30
13	$Cu(OAc)_2{\cdot}H_2O$	DMF	rt	88	<5

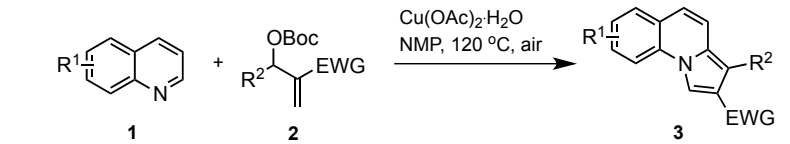
14	$Cu(OAc)_2{\cdot}H_2O$	DMSO	120	53	56
15	$Cu(OAc)_2{\cdot}H_2O$	NMP	120	35	98 (88)[c]
16	-	NMP	120	35	49
17	$Cu(OAc)_2{\cdot}H_2O$	NMP	120	35	59[c,d]
18	$Cu(OAc)_2{\cdot}H_2O$	NMP	120	12	33[c,e]

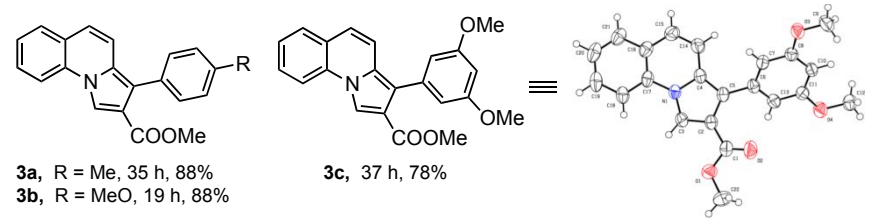
[a] **1a** (3 equiv, 0.6 mmol), **2a** (1 equiv, 0.2 mmol), catalyst (20 mol%), solvent (0.2 mL), in air. [b] Determined by ^1H NMR using CH_2Br_2 as internal standard. [c] Isolated yield. [d] Under Ar atmosphere. [e] Under O_2 atmosphere.

Next we turned our attention to the examination of substrate scope. As summarized in Table 2, aromatic MBH carbonates bearing electron-donating groups can be successfully applied in this process (**3a-3d,** 77-88%).[19] The applicability of our process was demonstrated by gram-scale reaction of quinoline **1a** and MBH carbonate **2d** (methyl 2-(((*tert*-butoxycarbonyl)oxy)(phenyl)methyl)acrylate), affording **3d** in 71% yield. However, regarding MBH carbonates with electron-withdrawing groups, steric and electronic effects played an important role in the formation of final product. Bromo substituent at the 2-position of phenyl ring (MBH carbonate **2e**) led to 16% yield likely due to steric reason (**3e**). While reactions of MBH carbonates with chloro substituents (MBH carbonates **2f** and **2g**) proceeded readily affording **3f** and **3g** in 65% and 80% yield respectively. Furfuryl group could be incorporated into benzoindolizine delivering target molecule **3h** in 30% yield by using MBH carbonate **2h**. In the case of aliphatic aldehyde-derived MBH carbonate **2i,** no reaction was observed (**3i**). We reasoned that the formation of conjugated azomethine ylides was difficult when lacking the stabilization effect of aromatic ring.[20] MBH carbonates bearing the groups of COOEt, COOBn and CN could be tolerated in this system giving **3j**, **3k** and **3l** in 58-62% yield. A range of quinolines was then submitted to this process. Electronic nature of substituted groups on the quinoline ring (Me, BocNH, MOMO, MeO and Br) has a limited effect on reaction yield, while the position of substituents significantly influenced the reaction yield. For example, quinoline with a substituent at C8 position gave no product at all. We reasoned that 8-methylquinoline is too sterically

hindered to act as nucleophile in this cascade sequence. The failure of preparation of compound **3m** is due to side reactions that involve the C4-methyl group of the quinoline precursor.[21]

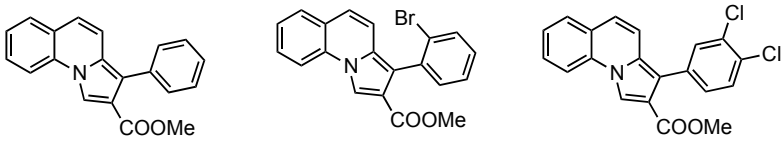
Table 2 Examination of substrate scope.[a,b]





3a, R = Me, 35 h, 88%
3b, R = MeO, 19 h, 88%

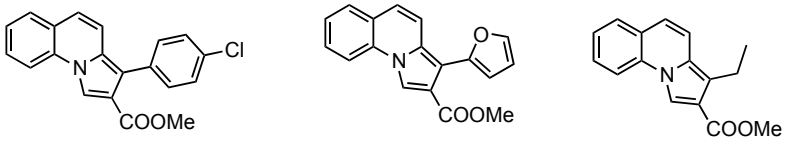
3c, 37 h, 78%



3d, 35 h, 77%
Gram-scale: 27 h, 71%

3e, 42 h, 16%

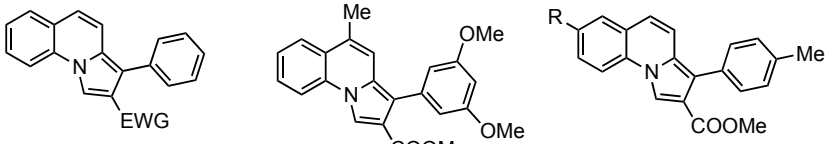
3f, 76 h, 65%



3g, 29 h, 80%

3h, 29 h, 30%

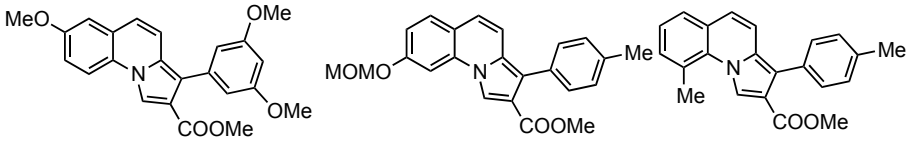
3i, 65 h, 0%



3j, EWG = COOEt, 42 h, 62%
3k, EWG = COOBn, 42 h, 60%
3l, EWG = CN, 25 h, 58%

3m, 120 h, trace

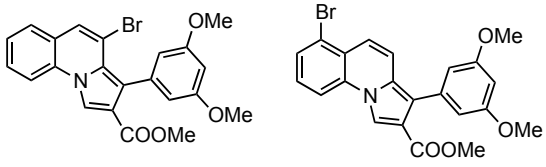
3n, R = BocNH, 26 h, 74%
3o, R = OBn, 37 h, 87%
3p, R = Me, 45 h, 70%



3q, 31 h, 63%

3r, 20 h, 58%

3s, 41 h, 0%



3t, 53 h, 62%

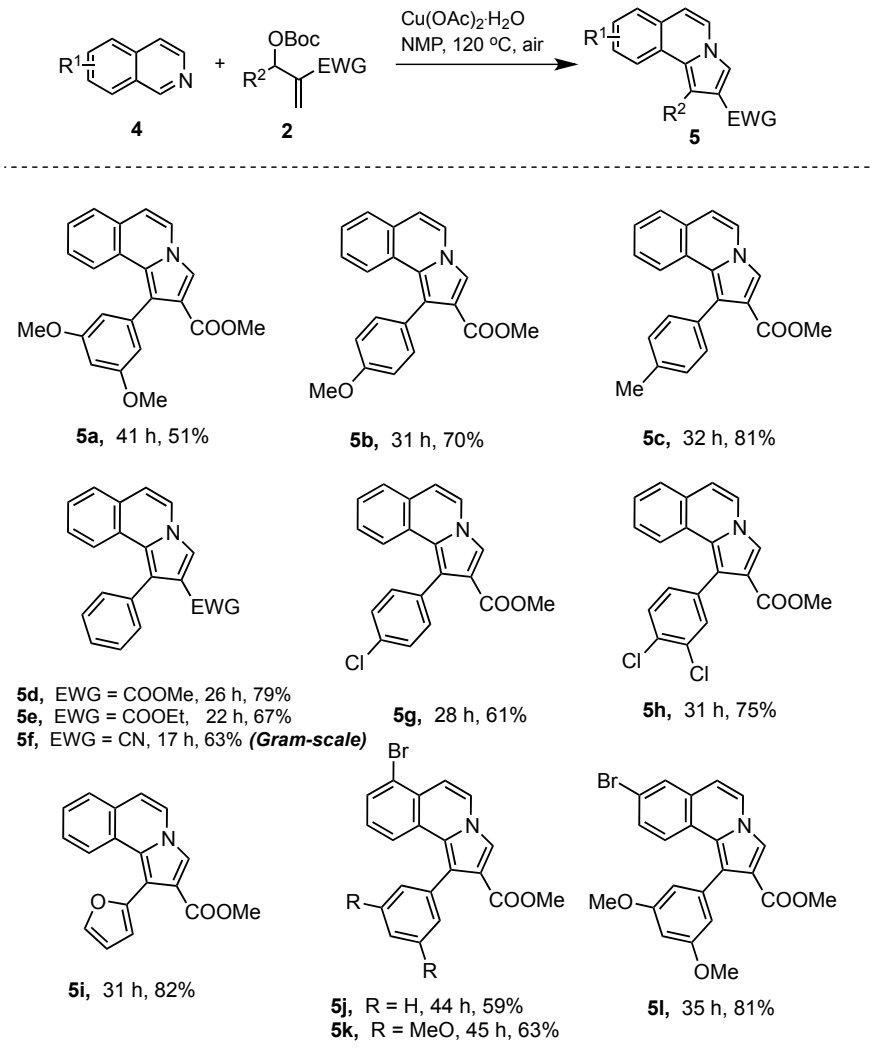
3u, 41 h, 66%

[a] **1a** (3 equiv, 0.6 mmol), **2a** (1 equiv, 0.2 mmol), $Cu(OAc)_2·H_2O$ (20 mol%), NMP (0.2 mL), in air. [b] Isolated yield.

Then we focused on the synthesis of pyrrolo[2,1-*a*]isoquinolines using isoquinolines. MBH carbonates

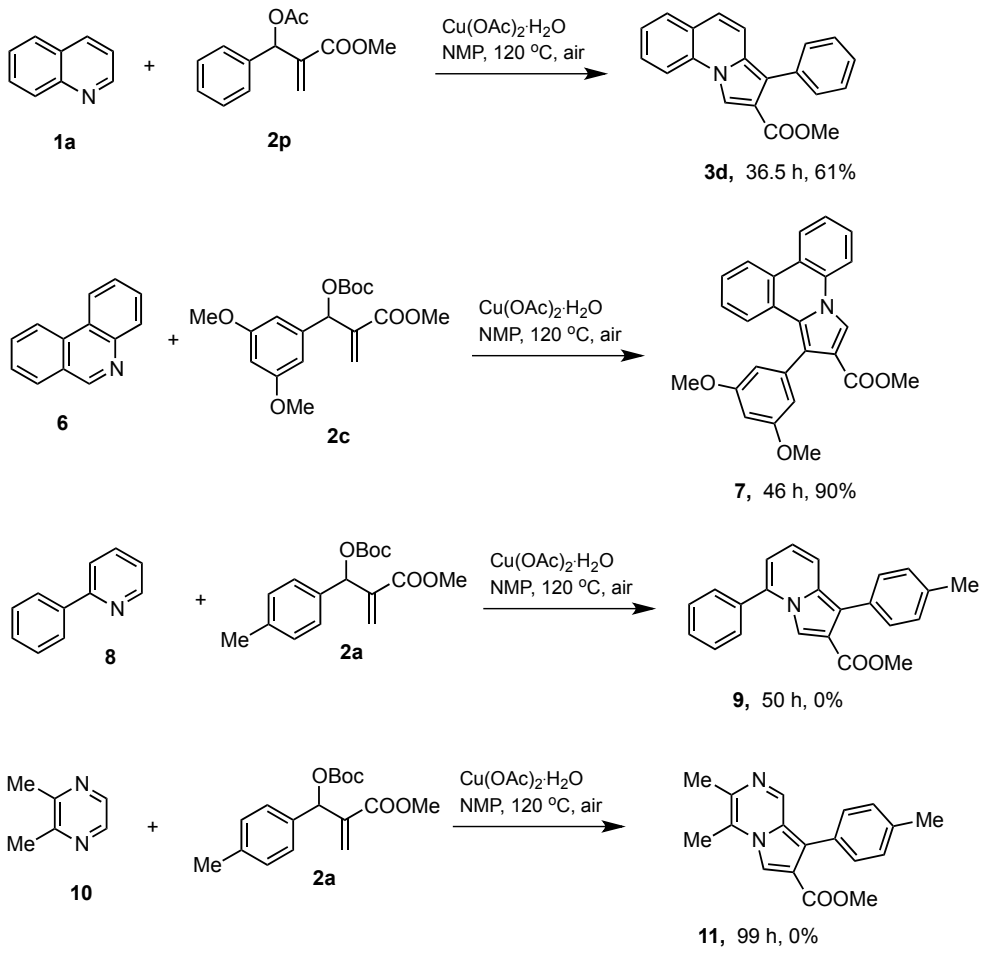
bearing electron-donating groups and electron-withdrawing groups could be tolerant in this process, providing corresponding pyrroloisoquinolines in moderate to good yields (51-81%, Table 3, compounds **5a-5h**). It's worthy of note that the gram-scale reaction of isoquinoline **2a** with MBH carbonate **2l** (*tert*-butyl (2-cyano-1-phenylallyl) carbonate) was successful providing compound **5f** in 63% yield. Furan moiety can also be successfully incorporated into pyrroloisoquinoline in 82% yield. Substituted isoquinolines reacted with MBH carbonates smoothly giving the desired products in 59-81% yield (**5j, 5k** and **5l**).

Table 3 Examination of substrate scope.[a,b]



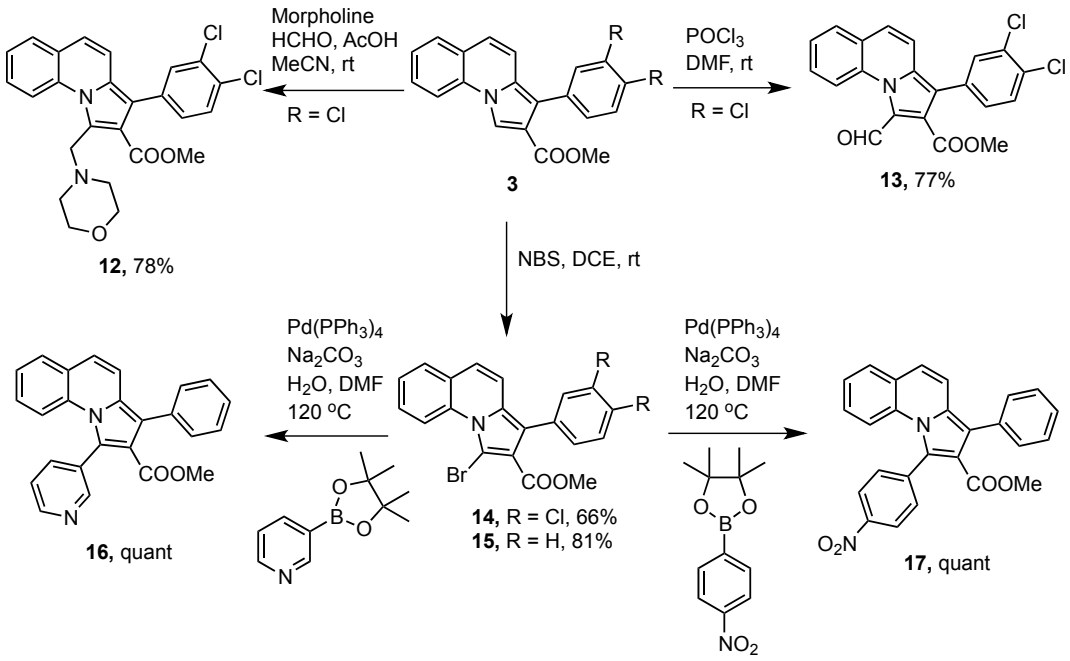
[a] **1a** (3 equiv, 0.6 mmol), **2a** (1 equiv, 0.2 mmol), $Cu(OAc)_2·H_2O$ (20 mol%), NMP (0.2 mL), in air. [b] Isolated yield.

We tried to further extend this methodology to other MBH adducts and nitrogen-containing aromatic ring. As shown in Scheme 2, the reaction of MBH acetate **2p** proceeded smoothly affording **3d** in 61% yield. Phenanthridine **6** is also a suitable candidate for this process, giving corresponding pyrrolo[1,2-*f*]phenanthridine **7** in excellent yield (90%). 2-Phenylpyridine and 2,3-dimethylpyrazine failed to deliver the desired azacycles **9** and **11,** probably due to side reactions.



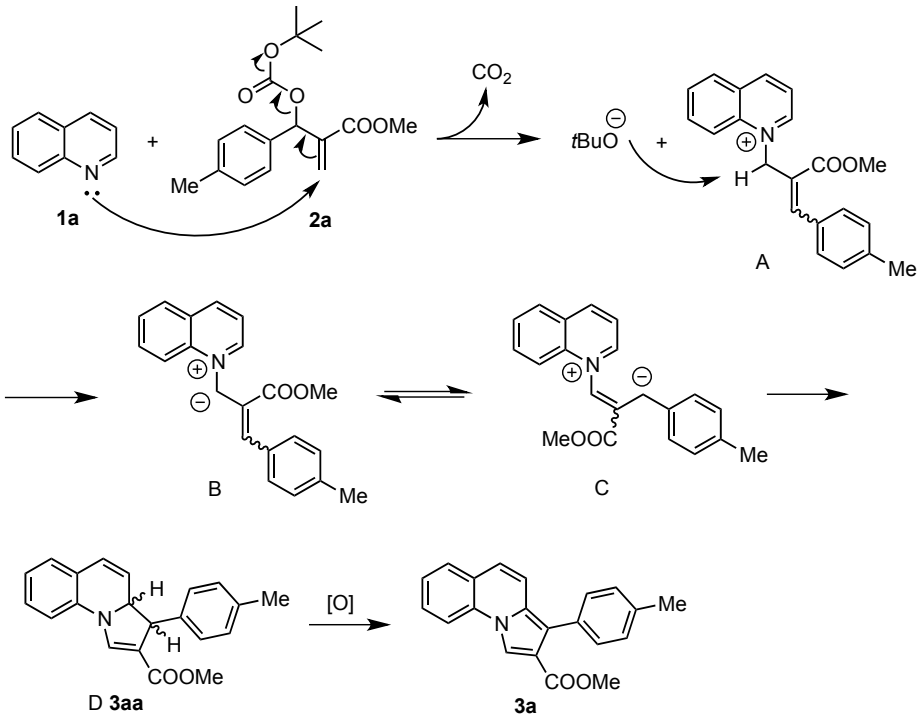
Scheme 2. Attempts of further extension of substrate scope.

The synthetic application of the obtained pyrrolo[1,2-*a*]quinolines **3** was successfully demonstrated by easy transformation to highly functionalized molecules **12-17** (Scheme 3). Mannich reaction of **3a** at room temperature gave tertiary amine **12** in 78% yield, while Vilsmeier-Haack reaction led to the formation of compound **13** in 77% yield. Bromination of pyrrolo[1,2-*a*]quinolines **3d** and **3f** with NBS proceeded readily providing compound **14** and **15** (66% and 81% yields respectively). The subsequent Suzuki coupling of **15** afforded highly fused heterocycles **16** and **17** respectively in excellent yields.



Scheme 3. Transformations of pyrrolo[1,2-*a*]quinoline 3

Based on these results and previous reports[4c-4f,12,14,17,18], we proposed a possible mechanism (Scheme 4). MBH carbonate **2a** can be attacked by quinoline **1a** giving intermediate A. The subsequent deprotonation by the *in situ* generated *tert*-butoxide anion[17,22] affords intermediates B and C. Electrocyclization of conjugated azomethine ylide and a final oxidation of intermediate D[23] provide pyrrolo[1,2-*a*]quinolone **3a.** Both copper acetate and oxygen in air play an important role in the final oxidative aromatization of intermediate D.[24] The possible intermolecular allylic alkylation reaction of intermediate A may be the reason for the low yield observed in the case of **3m.**[17] While the lack of aromatic ring resulted poor stability of intermediate B and C should be responsible for the failure of compound **3i.**



Scheme 4. Proposed mechanism

CONCLUSION

In summary, we have established a convenient method for the construction of pyrrolo[1,2-*a*]quinolines and pyrrolo[2,1-*a*]isoquinolines with simple quinolines or isoquinolines and MBH carbonates as starting material in the presence of copper acetate in air. A variety of benzoindolizines could be accessed in moderate to good yields (up to 90% yield) through a S_N2'/deprotonation/electrocyclization/oxidation pathway. The utility of this synthetic methodology has been demonstrated by easy transformations to highly functionalized azacycles.

EXPERIMENTAL SECTION

General methods ^1H NMR and ^{13}C NMR spectra were recorded at Bruker Avance 400. Chemical shifts are reported in ppm downfield from $CDCl_3$ (δ = 7.26 ppm) for ^1H NMR and relative to the central $CDCl_3$

resonance (δ = 77.0 ppm) for ^{13}C NMR spectroscopy. Coupling constants are given in Hz. ESI-MS analysis was performed using a LTQ Orbitrap mass spectrometer.

All reagents and solvents were obtained from commercial sources and used without further purification. Substituted quinolines **1** and MBH carbonates **2** were prepared according to reported procedure. [22,25]

General procedure for the synthesis of compounds 3, 5 and 7

A mixture of quinoline **1 (**or **4**, **6)** (0.6 mmol), MBH carbonate **2** (0.2 mmol), $Cu(OAc)_2{\cdot}H_2O$ (0.04 mmol) and NMP (0.2 mL) was stirred at 120 °C in air. Upon the consumption of MBH carbonate **2** (monitored by TLC), the mixture was concentrated and the residue was purified by a silica gel flash chromatography (PE/EtOAc) to afford **3 (**or **5**, **7)**.

Methyl 3-(p-tolyl)pyrrolo[1,2-a]quinoline-2-carboxylate ***(3a).*** Purified by flash column chromatography (PE/EA = 200:3); 56.0 mg, 88% yield, yellow solid; m.p. 108-111℃. ^1H NMR (400 MHz, $CDCl_3$) δ 8.46 (s, 1H), 7.94 (d, *J* = 8.4 Hz, 1H), 7.62 (dd, *J* = 0.8, 7.6 Hz, 1H), 7.56-7.51 (m, 1H), 7.41-7.36 (m, 3H), 7.27-7.25 (m, 3H), 6.98 (d, *J* = 9.6 Hz, 1H), 3.81 (s, 3H), 2.43 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 165.2, 136.5, 132.8, 130.7, 130.5, 129.5, 128.74, 128.65, 128.2, 125.0, 124.7, 120.3, 119.2, 118.2, 116.65, 116.61, 114.4, 51.2, 21.3; IR (CH_2Cl_2, cm^{-1}) υ 1697, 1607, 1561, 1539, 1518, 1503, 1463, 1452, 1436, 1235, 1140, 793, 735; ESI-HRMS: calcd. for $C_{21}H_{18}NO_2^+$ $(M+H)^+$ 316.1332, found 316.1337.

Methyl 3-(4-methoxyphenyl)pyrrolo[1,2-a]quinoline-2-carboxylate ***(3b).*** Purified by flash column chromatography (PE/EA = 50:1); 58.4 mg, 88% yield, yellow solid; m.p. 166-170℃. ^1H NMR (400 MHz, $CDCl_3$) δ 8.46 (s, 1H), 7.94 (d, *J* = 8.4 Hz, 1H), 7.63 (d, *J* = 8.0 Hz, 1H), 7.56-7.52 (m, 1H), 7.43-7.36 (m, 3H), 7.26-7.24 (m, 1H), 7.01-6.97 (m, 3H), 3.87 (s, 3H), 3.81 (s, 3H), $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ

165.1, 159.2, 135.1, 132.8, 129.6, 128.8, 128.3, 125.0 124.7, 123.3, 120.5, 118.9, 118.2, 116.8, 116.7, 116.4, 114.4, 112.5, 55.3, 51.2; IR (CH_2Cl_2, cm^{-1}) υ 1714, 1606, 1548, 1515, 1498, 1482, 1450, 1217, 1175, 792, 756; ESI-HRMS: calcd. for $C_{21}H_{18}NO_3^+$ $(M+H)^+$ 332.1281, found 332.1285.

Methyl 3-(3,5-dimethoxyphenyl)pyrrolo[1,2-a]quinoline-2-carboxylate ***(3c).*** Purified by flash column chromatography (PE/EA = 100:3); 56.7 mg, 78% yield, yellow solid; m.p. 140-144℃. ^1H NMR (400 MHz, $CDCl_3$) δ 8.46 (s, 1H), 7.95-7.92 (m, 1H), 7.63 (d, *J* = 7.6 Hz, 1H), 7.57-7.53 (m, 1H), 7.39 (t, *J* = 7.6 Hz, 1H), 7.32 (d, *J* = 9.6 Hz, 1H), 7.01 (d, *J* = 9.6 Hz, 1H), 6.66 (d, *J* = 2.4 Hz, 2H), 6.49 (t, *J* = 2.0 Hz, 1H), 3.85 (s, 6H), 3.84 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 165.1, 160.2, 135.7, 132.8, 129.6, 128.8, 128.3, 125.0, 124.7, 120.6, 118.9, 118.2, 116.8, 116.7, 114.4, 109.0, 107.3, 99.3, 55.4, 51.3; IR (CH_2Cl_2, cm^{-1}) υ 1715, 1594, 1456, 1427, 1401, 1205, 1153, 840; ESI-HRMS: calcd. for $C_{22}H_{20}NO_4^+$ $(M+H)^+$ 362.1387, found 362.1390.

Methyl 3-phenylpyrrolo[1,2-a]quinoline-2-carboxylate ***(3d).*** Purified by flash column chromatography (PE/EA = 80:1); 46.6 mg, 77% yield, yellow solid; m.p. 138-141℃. ^1H NMR (400 MHz, $CDCl_3$) δ 8.35 (s, 1H), 7.81 (d, *J* = 8.4 Hz, 1H), 7.50 (d, *J* = 8.0 Hz, 1H), 7.43-7.39 (m, 3H), 7.37-7.33 (m, 2H), 7.26 (t, *J* = 7.2 Hz, 2H), 7.16-713 (m, 1H), 6.87 (d, *J* = 9.6 Hz, 1H), 3.71 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 165.2, 133.8, 132.8, 130.7, 129.6, 128.8, 128.3, 127.9, 126.8, 125.0, 124.7, 120.5, 119.2, 118.1, 116.7, 116.7, 114.4, 51.2; IR (CH_2Cl_2, cm^{-1}) υ 1700, 1645, 1599, 1562, 1539, 1506, 1479, 1453, 1434, 1209, 727; ESI-HRMS: calcd. for $C_{20}H_{16}NO_2^+$ $(M+H)^+$ 302.1176, found 302.1178.

Methyl 3-(2-bromophenyl)pyrrolo[1,2-a]quinoline-2-carboxylate ***(3e).*** Purified by flash column chromatography (PE/EA = 90:1); 12.5 mg, 16% yield, yellow solid; m.p. 157-158℃. ^1H NMR (400 MHz, $CDCl_3$) δ 8.49 (s, 1H), 7.97 (d, *J* = 8.0 Hz, 1H), 7.71 (d, *J* = 8.0 Hz, 1H), 7.65 (dd, *J* = 0.8, 7.6 Hz, 1H),

7.59-7.54 (m, 1H), 7.42-7.36 (m, 3H), 7.27-7.23 (m, 1H), 7.03 (d, *J* = 9.6 Hz, 1H), 6.99 (d, *J* = 9.2 Hz, 1H), 3.76 (s, 3H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 163.9, 134.3, 131.8, 131.53, 131.51, 128.6, 127.85, 127.77, 127.4, 125.8, 124.8, 124.0, 123.5, 119.7, 116.9, 116.7, 116.6, 115.0, 113.4, 50.3; IR (CH_2Cl_2, cm^{-1}) υ 1699, 1607, 1561, 1514, 1468, 1435, 1208, 1147, 747; ESI-HRMS: calcd. for $C_{20}H_{15}BrNO_2^+$ $(M+H)^+$ 380.0281, found 380.0284.

Methyl 3-(3,4-dichlorophenyl)pyrrolo[1,2-a]quinoline-2-carboxylate ***(3f).*** Purified by flash column chromatography (PE/EA = 120:1); 48.3 mg, 65% yield, yellow solid; m.p. 173-175℃. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.47 (s, 1H), 7.95 (d, *J* = 8.4 Hz, 1H), 7.66 (d, *J* = 7.6 Hz, 1H), 7.59-7.55 (m, 2H), 7.50 (d, *J* = 8.4 Hz, 1H), 7.42 (t, *J* = 7.6 Hz, 1H), 7.35-7.33 (m, 1H), 7.21 (d, *J* = 9.2 Hz, 1H), 7.07 (d, *J* = 9.2 Hz, 1H), 3.82 (s, 3H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 164.9, 133.9, 132.7, 132.3, 131.8, 130.9, 130.3, 129.8, 129.7, 128.9, 128.6, 125.3, 124.6, 121.5, 117.3, 117.0, 116.6, 116.4, 114.5, 51.4; IR (CH_2Cl_2, cm^{-1}) υ 1716, 1613, 1595, 1566, 1537, 1502, 1471, 1453, 1439, 1209, 1143, 744; ESI-HRMS: calcd. for $C_{20}H_{14}Cl_2NO_2^+$ $(M+H)^+$ 370.0396, found 370.0398.

Methyl 3-(4-chlorophenyl)pyrrolo[1,2-a]quinoline-2-carboxylate ***(3g).*** Purified by flash column chromatography (PE/EA = 100:1); 53.8 mg, 80% yield, yellow solid; m.p. 178-179℃. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.48 (s, 1H), 7.95 (d, *J* = 8.4 Hz, 1H), 7.65 (d, *J* = 8.0 Hz, 1H), 7.58-7.54 (m, 1H), 7.44-7.39 (m, 5H), 7.22 (d, *J* = 9.6 Hz, 1H), 7.03 (d, *J* = 9.2 Hz, 1H), 3.81 (s, 3H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 165.0, 132.8, 132.3, 132.0, 129.6, 128.8, 128.4, 128.1, 125.1, 124.6, 120.9, 117.8, 117.7, 116.8, 116.6, 114.4, 51.3; IR (CH_2Cl_2, cm^{-1}) υ 1721, 1561, 1540, 1500, 1478, 1451, 1440, 1407, 1397, 1210, 1139, 740; ESI-HRMS: calcd. for $C_{20}H_{15}ClNO_2^+$ $(M+H)^+$ 336.0786, found 336.0788.

Methyl 3-(furan-2-yl)pyrrolo[1,2-a]quinoline-2-carboxylate ***(3h).*** Purified by flash column

chromatography (PE/EA = 130:1); 17.3 mg, 30% yield, yellow solid; m.p. 91-92℃. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.45 (s, 1H), 7.93 (d, *J* = 8.0 Hz, 1H), 7.82 (d, *J* = 5.6 Hz, 1H), 7.66 (d, *J* = 5.6 Hz, 1H), 7.57-7.53 (m, 2H), 7.40 (t, *J* = 5.6 Hz, 1H), 7.10 (d, *J* = 2.0 Hz, 1H), 7.05 (d, *J* = 3.2 Hz, 1H), 6.55-6.54 (m, 1H), 3.90 (m, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 164.8, 148.6, 141.2, 132.6, 129.8, 128.7, 128.4, 125.2, 124.6, 121.1, 119.4, 117.6, 115.6, 114.4, 111.2, 109.5, 108.3, 51.5; IR (CH_2Cl_2, cm^{-1}) υ 1714, 1590, 1561, 1502, 1471, 1434, 1407, 1260, 1206, 1127, 763; ESI-HRMS: calcd. for $C_{18}H_{14}NO_3^+$ $(M+H)^+$ 292.0968, found 292.0972.

Ethyl 3-phenylpyrrolo[1,2-a]quinoline-2-carboxylate ***(3j).*** Purified by flash column chromatography (PE/EA = 100:1); 38.8 mg, 62% yield, yellow solid; m.p. 93-94℃. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.47 (s, 1H), 7.94 (d, *J* = 8.4 Hz, 1H), 7.62 (d, *J* = 8.0 Hz, 1H), 7.55-7.48 (m, 3H), 7.43 (t, *J* = 7.6 Hz, 2H), 7.39-7.33 (m, 2H), 7.26-7.24 (m, 1H), 6.98 (d, *J* = 9.6 Hz, 1H), 4.27 (q, *J* = 7.2 Hz, 2H), 1.26 (t, *J* = 7.2 Hz, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 164.8, 133.9, 132.8, 130.8, 129.6, 128.7, 128.3, 127.8, 126.8, 124.9, 124.7, 120.4, 119.2, 118.1, 117.2, 116.6, 114.4, 60.0, 14.2; IR (CH_2Cl_2, cm^{-1}) υ 1696, 1597, 1558, 1538, 1503, 1477, 1451, 1442, 1235, 758; ESI-HRMS: calcd. for $C_{21}H_{18}NO_2^+$ $(M+H)^+$ 316.1332, found 316.1337.

Benzyl 3-phenylpyrrolo[1,2-a]quinoline-2-carboxylate ***(3k).*** The mixture was passed through a pad of silica gel eluted with PE/EA (80/1). The eluate was concentrated and the residue was recrystallized with PE/EA affording **3k** as yellow solid, 45.5 mg, 60% yield; m.p. 144-147℃. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.43 (s, 1H), 7.86 (d, *J* = 8.4 Hz, 1H), 7.56 (d, *J* = 8.0 Hz, 1H), 7.48-7.42 (m, 3H), 7.36 (t, *J* = 7.2 Hz, 2H), 7.33-7.25 (m, 5H), 7.22-7.17 (m, 3H), 6.92 (d, *J* = 9.6 Hz, 1H), 5.22 (s, 2H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 164.6, 136.3, 133.8, 132.8, 130.8, 129.7, 128.8, 128.4, 128.3, 128.1, 127.9, 126.8, 125.0, 124.7,

120.5, 118.1, 116.9, 116.8, 114.5, 65.8; IR (CH_2Cl_2, cm^{-1}) υ 1693, 1645, 1601, 1558, 1547, 1514, 1495, 1477, 1452, 1232, 1154, 750; ESI-HRMS: calcd. for $C_{26}H_{20}NO_2^+$ $(M+H)^+$ 378.1489, found 378.1489.

3-Phenylpyrrolo[1,2-a]quinoline-2-carbonitrile ***(3l).*** Purified by flash column chromatography (PE/EA = 120:1); 31.1 mg, 58% yield, white solid; m.p. 147-150℃. ^1H NMR (400 MHz, $CDCl_3$) δ 8.30 (s, 1H), 7.89 (d, *J* = 8.4 Hz, 1H), 7.69 (d, *J* = 8.0 Hz, 1H), 7.64-7.62 (m, 2H), 7.58 (d, *J* = 8.0 Hz, 1H), 7.53-7.49 (m, 2H), 7.47-7.37 (m, 3H), 7.14 (d, *J* = 9.6 Hz, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 132.4, 132.3, 129.0, 128.9, 128.8, 128.1, 127.5, 125.6, 124.5, 122.0, 120.4, 118.0, 117.4, 116.1, 114.4, 96.7; IR (CH_2Cl_2, cm^{-1}) υ 2219, 1739, 1645, 1599, 1560, 1542, 1500, 1476, 1452, 1443, 1402, 1195, 743; ESI-HRMS: calcd. for $C_{19}H_{13}N_2^+$ $(M+H)^+$ 269.1073, found 269.1075.

Methyl 7-((tert-butoxycarbonyl)amino)-3-(p-tolyl)pyrrolo[1,2-a]quinoline-2-carboxylate ***(3n).*** Performed at 0.05 mmol scale; Purified by flash column chromatography (PE/EA = 25:1); 16.0 mg, 74% yield, yellow solid; m.p. 154-158℃. ^1H NMR (400 MHz, $CDCl_3$) δ 8.39 (s, 1H), 7.84 (d, *J* = 8.8 Hz, 1H), 7.75 (s, 1H), 7.45 (dd, *J* = 2.4, 9.2 Hz, 1H), 7.38 (d, *J* = 8.0 Hz, 2H), 7.26-7.23 (m, 3H), 6.93 (d, *J* = 9.6 Hz, 1H), 6.63 (s, 1H), 3.80 (s, 3H), 2.41 (s, 3H), 1.55 (s, 9H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 165.2, 152.8, 136.4, 135.4, 130.7, 130.5, 129.3, 128.7, 128.6, 125.4, 120.2, 119.5, 119.3, 119.2, 119.2, 118.8, 116.4, 115.0, 51.2, 28.4, 21.3, 14.1; IR (CH_2Cl_2, cm^{-1}) υ 1700, 1570, 1548, 1532, 1506, 1444, 1418, 1397, 1213, 1154, 1137, 812; ESI-HRMS: calcd. for $C_{26}H_{27}N_2O_4^+$ $(M+H)^+$ 431.1965, found 431.1967.

Methyl 7-(benzyloxy)-3-(p-tolyl)pyrrolo[1,2-a]quinoline-2-carboxylate ***(3o).*** The mixture was passed through a pad of silica gel eluted with Hexane/EA (40/1). The eluate was concentrated and the residue was recrystallized with PE/EA affording **3o** as yellow solid, 73.2 mg, 87% yield; m.p. 155-157℃. ^1H NMR (400 MHz, $CDCl_3$) δ 8.38 (s, 1H), 7.85 (d, *J* = 8.8 Hz, 1H), 7.47 (d, *J* = 7.2 Hz, 2H), 7.43-7.33 (m, 5H),

7.26-7.24 (m, 3H), 7.20 (dd, J = 2.8, 9.2 Hz, 1H), 7.14 (d, J = 2.4 Hz, 1H), 6.90 (d, J = 9.6 Hz, 1H), 5.15 (s, 2H), 3.80 (s, 3H), 2.42 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 165.2, 155.9, 136.6, 136.4, 130.8, 130.5, 129.2, 128.7, 128.6, 128.2, 127.5, 125.8, 120.0, 119.3, 118.8, 117.1, 116.3, 116.2, 115.7, 111.9, 100.0, 70.5, 51.2, 21.3; IR (CH_2Cl_2, cm^{-1}) υ 1695, 1614, 1564, 1518, 1492, 1466, 1434, 1402, 1206, 1138, 1023, 729; ESI-HRMS: calcd. for $C_{28}H_{24}NO_3^+$ $(M+H)^+$ 422.1751, found 422.1752.

Methyl 7-methyl-3-(p-tolyl)pyrrolo[1,2-a]quinoline-2-carboxylate ***(3p).*** Purified by flash column chromatography (PE/EA = 80:1); 45.4 mg, 70% yield, yellow solid; m.p. 184-185℃. ^1H NMR (400 MHz, $CDCl_3$) δ 8.40 (s, 1H), 7.79 (d, J = 8.4 Hz, 1H), 7.40-7.38 (m, 3H), 7.33-7.31 (m, 1H), 7.26-7.21 (m, 3H), 6.90 (d, J = 9.2 Hz, 1H), 3.80 (s, 3H), 2.45 (s, 3H), 2.42 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 165.2, 136.3, 134.6, 130.9, 130.8, 130.5, 129.5, 129.4, 128.6, 128.6, 127.4, 120.2, 119.1, 118.2, 116.4, 116.4, 114.2, 51.1, 21.3, 21.0; IR (CH_2Cl_2, cm^{-1}) υ 1705, 1642, 1563, 1492, 1434, 1233, 1209, 767; ESI-HRMS: calcd. for $C_{22}H_{20}NO_2^+$ $(M+H)^+$ 330.1489, found 330.1490.

Methyl 3-(3,5-dimethoxyphenyl)-7-methoxypyrrolo[1,2-a]quinoline-2-carboxylate ***(3q).*** Purified by flash column chromatography (PE/EA = 10:1); 49.2 mg, 63% yield, yellow solid; m.p. 150-155℃. ^1H NMR (400 MHz, $CDCl_3$) δ 8.38 (s, 1H), 7.86 (d, J = 9.2 Hz, 1H), 7.31 (d, J = 9.6 Hz, 1H), 7.14 (dd, J = 2.4, 9.2 Hz, 1H), 7.07 (d, J = 2.8 Hz, 1H), 6.95 (d, J = 9.6 Hz, 1H), 6.66 (s, 1H), 6.65 (s, 1H), 6.48 (m, 1H), 3.90 (s, 3H), 3.83 (s, 6H), 3.81 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 165.1, 160.2, 156.8, 135.8, 129.3, 127.2, 125.8, 120.4, 118.8, 118.7, 116.6, 116.4, 116.3, 115.7, 110.6, 108.9, 99.2, 55.7, 55.4, 51.3; IR (CH_2Cl_2, cm^{-1}) υ 1700, 1586, 1566, 1456, 1425, 1292, 1153, 1134, 809; ESI-HRMS: calcd. for $C_{23}H_{22}NO_5^+$ $(M+H)^+$ 392.1493, found 392.1494.

Methyl 8-(methoxymethoxy)-3-(p-tolyl)pyrrolo[1,2-a]quinoline-2-carboxylate ***(3r).*** Performed at 0.045

mmol scale; Purified by flash column chromatography (PE/EA = 10:1); 9.8 mg, 58% yield, yellow solid; m.p. 150-151℃. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.37 (s, 1H), 7.60 (d, *J* = 1.6 Hz, 1H), 7.54 (d, *J* = 8.8 Hz, 1H), 7.38 (d, *J* = 8.0 Hz, 2H), 7.26-7.24 (m, 2H), 7.16 (d, *J* = 9.6 Hz, 1H), 7.08 (dd, *J* = 2.0, 8.8 Hz, 1H), 6.94 (d, *J* = 9.6 Hz, 1H), 5.32 (s, 2H), 3.81 (s, 3H), 3.55 (s, 3H), 2.42 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 165.2, 157.5, 136.4, 133.8, 130.8, 130.5, 129.9, 129.7, 128.6, 120.0, 119.3, 118.8, 116.8, 116.4, 116.0, 114.5, 101.3, 94.7, 56.2, 51.2, 21.3; IR (CH_2Cl_2, cm^{-1}) υ 1721, 1624, 1607, 1552, 1492, 1440, 1142, 817; ESI-HRMS: calcd. for $C_{23}H_{22}NO_4^+$ $(M+H)^+$ 376.1543, found 376.1545.

Methyl 4-bromo-3-(3,5-dimethoxyphenyl)pyrrolo[1,2-a]quinoline-2-carboxylate ***(3t).*** Performed at 0.26 mmol scale; Purified by flash column chromatography (PE/EA = 10:1); 71.0 mg, 62% yield, yellow solid; m.p. 132-133℃. 1H NMR (400 MHz, $CDCl_3$) δ 8.47 (s, 1H), 7.93 (d, *J* = 8.4 Hz, 1H), 7.58-7.55 (m, 2H), 7.41-7.37 (m, 1H), 7.30 (s, 1H), 6.55 (d, *J* = 2.4 Hz, 2H), 6.51 (t, *J* = 2.0 Hz, 1H), 3.81 (s, 6H), 3.74 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 164.4, 159.3, 136.4, 131.9, 128.7, 127.9, 125.7, 125.4, 124.6, 124.1, 121.7, 118.5, 116.8, 114.4, 112.1, 110.5, 105.5, 99.7, 55.3, 51.4; IR (CH_2Cl_2, cm^{-1}) υ 1693, 1588, 1509, 1496, 1455, 1434, 1410, 1204, 1136, 745; ESI-HRMS: calcd. for $C_{22}H_{19}BrNO_4^+$ $(M+H)^+$ 440.0492, found 440.0498.

Methyl 6-bromo-3-(3,5-dimethoxyphenyl)pyrrolo[1,2-a]quinoline-2-carboxylate ***(3u).*** The mixture was passed through a pad of silica gel eluted with PE/EA/DCM (200/3/2). The eluate was concentrated and the residue was recrystallized with PE/EA affording **3u** as yellow solid, 57.7 mg, 66% yield; m.p. 139-141℃. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.45 (s, 1H), 7.90 (d, *J* = 8.4 Hz, 1H), 7.64 (d, *J* = 8.0 Hz, 1H), 7.37 (t, *J* = 7.6 Hz, 3H), 6.65 (s, 1H), 6.64 (s, 1H), 6.50 (t, *J* = 2.0 Hz, 1H), 3.81 (s, 6H), 3.78 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 164.9, 160.3, 135.2, 133.8, 129.4, 129.2, 128.6, 124.1, 123.5, 119.7, 119.4, 119.2,

117.5, 117.2, 113.9, 108.9, 99.4, 55.4, 51.4; IR (CH_2Cl_2, cm^{-1}) υ 1729, 1593, 1537, 1502, 1464, 1446, 1433, 1422, 1402, 1113, 1134, 1154, 757; ESI-HRMS: calcd. for $C_{22}H_{19}BrNO_4^+$ $(M+H)^+$ 440.0492, found 440.0498.

Methyl 1-(3,5-dimethoxyphenyl)pyrrolo[2,1-a]isoquinoline-2-carboxylate ***(5a).*** Purified by flash column chromatography (PE/EA = 80:1); 36.8 mg, 51% yield, yellow solid; m.p. 144-146℃. ^1H NMR (400 MHz, $CDCl_3$) δ 7.84 (s, 1H), 7.67 (d, *J* = 7.2 Hz, 1H), 7.49 (d, *J* = 8.0 Hz, 1H), 7.45 (d, *J* = 8.0 Hz, 1H), 7.31-7.27 (m, 1H), 7.18 (t, *J* = 8.0 Hz, 1H), 6.80 (d, *J* = 7.6 Hz, 1H), 6.60-6.57 (m, 3H), 3.80 (s, 6H), 3.72 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 164.8, 160.8, 138.2, 127.7, 127.5, 127.1, 126.8, 126.2, 126.2, 124.0, 123.3, 119.6, 118.9, 117.2, 113.7, 108.4, 100.0, 55.4, 51.2; IR (CH_2Cl_2, cm^{-1}) υ 1715, 1592, 1520, 1453, 1422, 1398, 1146, 776; ESI-HRMS: calcd. for $C_{22}H_{20}NO_4^+$ $(M+H)^+$ 362.1387, found 362.1389.

Methyl 1-(4-methoxyphenyl)pyrrolo[2,1-a]isoquinoline-2-carboxylate ***(5b).*** Purified by flash column chromatography (PE/EA = 200:3); 46.2 mg, 70% yield, yellow solid; m.p. 182-185℃. ^1H NMR (400 MHz, $CDCl_3$) δ 7.84 (s,1 H), 7.67 (d, *J* = 7.2 Hz, 1H), 7.49 (d, *J* = 7.6 Hz, 1H), 7.43 (d, *J* = 8.0 Hz, 1H), 7.35 (d, *J* = 8.4 Hz, 2H), 7.29-7.26 (m, 1H), 7.17-7.13 (m, 1H), 7.04 (d, *J* = 8.4 Hz, 2H), 6.79 (d, *J* = 7.2 Hz, 1H), 3.91 (s, 3H), 3.72 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 165.0, 158.9, 131.6, 128.2, 127.6, 127.5, 127.1, 127.0, 126.5, 126.1, 124.1, 122.9, 119.6, 118.9, 117.3, 114.0, 113.6, 55.2, 51.1; IR (CH_2Cl_2, cm^{-1}) υ 1711, 1646, 1598, 1508, 1462, 1436, 1398, 1177, 1028, 765; HRMS (ESI) m/z calcd for $C_{21}H_{18}NO_3^+$ $(M+H)^+$ 332.1281, found 332.1284.

Methyl 1-(p-tolyl)pyrrolo[2,1-a]isoquinoline-2-carboxylate ***(5c).*** Purified by flash column chromatography (PE/EA = 110:1); 51.1 mg, 81% yield, yellow solid; m.p. 100-103℃. ^1H NMR (400 MHz, $CDCl_3$) δ 7.76 (s, 1H), 7.58 (d, *J* = 7.2 Hz, 1H), 7.41 (d, *J* = 7.6 Hz, 1H), 7.36-7.34 (m, 1H), 7.26-7.18 (m,

5H), 7.09-7.05 (m, 1H), 6.71 (d, *J* = 7.2 Hz, 1H), 3.64 (s, 3H), 2.40 (s, 3H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 164.9, 136.9, 133.0, 130.4, 129.3, 127.6, 127.5, 127.1, 127.0, 126.1, 124.1, 123.0, 120.0, 118.9, 117.2, 113.6, 51.1, 21.5; IR (CH_2Cl_2, cm^{-1}) υ 1716, 1644, 1604, 1496, 1460, 1438, 1399, 1022, 950, 826; HRMS (ESI) m/z calcd for $C_{21}H_{18}NO_2^+$ $(M+H)^+$ 316.1332, found 316.1334.

Methyl 1-phenylpyrrolo[2,1-a]isoquinoline-2-carboxylate ***(5d).*** Purified by flash column chromatography (PE/EA = 120:1); 47.4 mg, 79% yield, yellow solid; m.p. 177-179℃. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86 (s, 1H), 7.68 (d, *J* = 7.6 Hz, 1H), 7.51-7.43 (m, 6H), 7.35 (d, *J* = 8.4 Hz, 1H), 7.29-7.26 (m, 1H), 7.15-7.11 (m, 1H), 6.80 (d, *J* = 7.2 Hz, 1H), 3.70 (s, 3H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 164.9, 136.2, 130.6, 128.5, 127.6, 127.5, 127.4, 127.1, 126.9, 126.3, 126.1, 124.1, 122.9, 119.9, 119.0, 117.2, 113.7, 51.1; IR (CH_2Cl_2, cm^{-1}) υ 1706, 1604, 1512, 1496, 1459, 1439, 1398, 1096, 772; HRMS (ESI) m/z calcd for $C_{20}H_{16}NO_2^+$ $(M+H)^+$ 302.1176, found 302.1179.

Ethyl 1-phenylpyrrolo[2,1-a]isoquinoline-2-carboxylate ***(5e).*** Purified by flash column chromatography (PE/EA = 60:1); 42.1 mg, 67% yield, yellow solid; m.p. 105-107℃. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 (s, 1H), 7.68 (d, *J* = 7.6 Hz, 1H), 7.50-7.42 (m, 6H), 7.36 (d, *J* = 8.0 Hz, 1H), 7.29-7.25 (m, 1H), 7.14-7.10 (m, 1H), 6.79 (d, *J* = 7.2 Hz, 1H), 4.14 (q, *J* = 7.2 Hz, 2H), 1.12 (t, *J* = 7.2 Hz, 3H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 164.7, 136.5, 130.6, 128.4, 127.6, 127.5, 127.3, 127.1, 127.0, 126.2, 126.1, 124.1, 122.9, 119.8, 119.0, 117.8, 113.6, 59.8, 14.0; IR (CH_2Cl_2, cm^{-1}) υ 1702, 1645, 1604, 1513, 1459, 1434, 1208, 779; HRMS (ESI) m/z calcd for $C_{21}H_{18}NO_2^+$ $(M+H)^+$ 316.1332, found 316.1335.

Methyl 1-(4-chlorophenyl)pyrrolo[2,1-a]isoquinoline-2-carboxylate ***(5g).*** Purified by flash column chromatography (PE/EA = 120:1); 40.7 mg, 61% yield, yellow solid; m.p. 130-134℃. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85 (s, 1H), 7.68 (d, *J* = 7.2 Hz, 1H), 7.51 (d, *J* = 7.6 Hz, 1H), 7.48-7.46 (m, 2H), 7.39-7.35 (m,

3H), 7.32-7.29 (m, 1H), 7.20-7.15 (m, 1H), 6.81 (d, J = 7.2 Hz, 1H), 3.72 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 164.8, 134.8, 133.3, 132.1, 128.7, 127.7, 127.6, 127.3, 126.7, 126.3, 124.0, 122.8, 119.2, 118.4, 117.2, 113.8, 100.0, 51.1; IR (CH_2Cl_2, cm^{-1}) υ 1712, 1603, 1545, 1515, 1490, 1472, 1460, 1439, 1185, 770; HRMS (ESI) m/z calcd for $C_{20}H_{15}ClNO_2^+$ $(M+H)^+$ 336.0786, found 336.0789.

Methyl 1-(3,4-dichlorophenyl)pyrrolo[2,1-a]isoquinoline-2-carboxylate ***(5h).*** Purified by flash column chromatography (PE/EA = 50:1); 55.7 mg, 75% yield, yellow solid; m.p. 134-138℃. ^1H NMR (400 MHz, $CDCl_3$) δ 7.76 (s, 1H), 7.59 (d, J = 7.6 Hz, 1H), 7.49-7.43 (m, 3H), 7.29-7.20 (m, 3H), 7.17-7.11 (m, 1H), 6.74 (d, J = 7.6 Hz, 1H), 3.64 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 164.6, 136.5, 132.7, 132.4, 131.5, 130.41, 130.37, 127.9 127.7, 127.4, 126.6, 126.5, 126.4, 124.0, 122.8, 119.3, 117.1, 116.9, 113.9, 51.2; IR (CH_2Cl_2, cm^{-1}) υ 1713, 1605, 1518, 1486, 1466, 1458, 1438, 1186, 773; HRMS (ESI) m/z calcd for $C_{20}H_{14}Cl_2NO_2^+$ $(M+H)^+$ 370.0396, found 370.0399.

Methyl 1-(furan-2-yl)pyrrolo[2,1-a]isoquinoline-2-carboxylate ***(5i).*** The mixture was passed through a pad of silica gel eluted with PE/EA (200:3). The eluate was concentrated and the residue was recrystallized with PE/EA affording **5i** as yellow solid, 48.0 mg, 82% yield; m.p. 145-148℃. ^1H NMR (400 MHz, $CDCl_3$) δ 7.85 (s, 1H), 7.69-7.66 (m, 2H), 7.54 (d, J = 7.6 Hz, 1H), 7.41 (d, J = 8.0 Hz, 1H), 7.38-7.35 (m, 1H), 7.33-7.29 (m, 1H), 6.85 (d, J = 7.2 Hz, 1H), 6.64-6.63 (m, 1H), 6.53 (d, J = 2.8 Hz, 1H), 3.78 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 164.5, 147.4, 142.2, 129.3, 128.1, 127.8, 127.2, 126.8, 126.1, 123.9, 123.2, 119.4, 118.5, 114.1, 111.3, 110.5, 107.4, 51.4; IR (CH_2Cl_2, cm^{-1}) υ 1704, 1625, 1517, 1495, 1458, 1439, 1183, 1126, 748; HRMS (ESI) m/z calcd for $C_{18}H_{14}NO_3^+$ $(M+H)^+$ 292.0968, found 292.0969.

Methyl 7-bromo-1-phenylpyrrolo[2,1-a]isoquinoline-2-carboxylate ***(5j).*** The mixture was passed through a pad of silica gel eluted with PE/EA (120:1). The eluate was concentrated and the residue was

recrystallized with PE/EA affording **5j** as yellow solid, 44.5 mg, 59% yield; m.p. 142-145℃. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88 (s, 1H), 7.75 (d, *J* = 7.6 Hz, 1H), 7.53-7.45 (m, 4H), 7.41-7.39 (m, 2H), 7.32 (d, *J* = 8.0 Hz, 1H), 7.28-7.26 (m, 1H), 6.94 (t, *J* = 8.0 Hz, 1H), 3.70 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 164.7, 135.9, 130.4, 130.1, 128.6, 128.6, 128.2, 127.6, 126.6, 125.5, 125.3, 122.3, 122.1, 120.6, 119.1, 117.9, 112.1, 51.2; IR (CH_2Cl_2, cm^{-1}) υ 1710, 1592, 1510, 1469, 1441, 1108, 783; HRMS (ESI) m/z calcd for $C_{20}H_{15}BrNO_2^+$ $(M+H)^+$ 380.0281, found 380.0286.

Methyl 7-bromo-1-(3,5-dimethoxyphenyl)pyrrolo[2,1-a]isoquinoline-2-carboxylate ***(5k).*** The mixture was passed through a pad of silica gel eluted with PE/EA (120:1). The eluate was concentrated and the residue was recrystallized with PE/EA affording **5k** as yellow solid, 55.4 mg, 63% yield; m.p. 168-170℃. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89 (s, 1H), 7.77 (d, *J* = 7.6 Hz, 1H), 7.56 (d, *J* = 8.0 Hz, 1H), 7.45 (d, *J* = 7.6 Hz, 1H), 7.31-7.26 (m, 1H), 7.03 (t, *J* = 8.0 Hz, 1H), 6.59-6.56 (m, 3H), 3.83 (s, 6H), 3.75 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 164.5, 160.9, 137.8, 130.1, 128.5, 128.4, 126.6, 125.4, 125.3, 122.6, 122.0, 120.4, 119.0, 117.9, 112.1, 108.3, 100.0, 55.4, 51.3; IR (CH_2Cl_2, cm^{-1}) υ 1702, 1587, 1509, 1453, 1434, 1224, 1152, 780; HRMS (ESI) m/z calcd for $C_{22}H_{19}BrNO_4^+$ $(M+H)^+$ 440.0492, found 440.0498.

Methyl 8-bromo-1-(3,5-dimethoxyphenyl)pyrrolo[2,1-a]isoquinoline-2-carboxylate ***(5l).*** Purified by flash column chromatography (PE/EA = 50:1); 71.0 mg, 81% yield, yellow solid; m.p. 148-150℃. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79 (s, 1H), 7.63 (d, *J* = 7.2 Hz, 1H), 7.58 (d, *J* = 1.6 Hz, 1H), 7.24-7.21 (m, 2H), 6.66 (d, *J* = 7.2 Hz, 1H), 6.51 (s, 3H), 3.75 (s, 6H), 3.67 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 164.6, 160.9, 137.8, 130.7, 129.3, 129.2, 125.7, 125.5, 125.1, 124.8, 120.0, 119.8, 119.2, 117.6, 112.5, 108.3, 100.0, 55.4, 51.2; IR (CH_2Cl_2, cm^{-1}) υ 1716, 1611, 1582, 1538, 1512, 1461, 1428, 1202, 1162, 763; HRMS (ESI) m/z calcd for $C_{22}H_{19}BrNO_4^+$ $(M+H)^+$ 440.0492, found 440.0500.

Methyl 1-(3,5-dimethoxyphenyl)pyrrolo[1,2-f]phenanthridine-2-carboxylate ***(7).*** The mixture was passed through a pad of silica gel eluted with PE/EA/DCM (200:3:2). The eluate was concentrated and the residue was recrystallized with PE/EA affording **7** as yellow solid, 73.9 mg, 90% yield; m.p. 206-208℃. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.44 (s, 1H), 8.34 (d, *J* = 8.0 Hz, 1H), 8.23 (d, *J* = 8.0 Hz, 1H), 7.95 (d, *J* = 8.0 Hz, 1H), 7.56 (t, *J* = 7.2 Hz, 1H), 7.49-7.43 (m, 2H), 7.36 (t, *J* = 7.2 Hz, 1H), 7.19 (t, *J* = 7.6 Hz, 1H), 6.60-6.58 (m, 3H), 3.81 (s, 6H), 3.75 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 164.7, 160.9, 138.3, 132.3, 128.9, 128.1, 126.5, 126.3, 125.7, 125.2, 124.2, 124.0, 122.4, 121.3, 117.8, 117.3, 115.2, 108.3, 100.0, 55.4, 51.2; IR (CH_2Cl_2, cm^{-1}) υ 1710, 1609, 1584, 1516, 1504, 1492, 1473, 1453, 1427, 1404, 1201, 1021, 716; HRMS (ESI) m/z calcd for $C_{26}H_{22}NO_4^+$ $(M+H)^+$ 412.1543, found 412.1547.

Gram-scale reaction of quinoline 1a and MBH carbonate 2d (Synthesis of compound 3d)

A mixture of quinoline **1a** (3 eq, 10.2 mmol, 1.2 mL), MBH carbonate **2d** (1 eq, 3.4 mmol, 1.0 g), $Cu(OAc)_2{\cdot}H_2O$ (0.2 eq, 0.68 mmol, 0.136 g) and NMP (3.4 mL) was stirred at 120 °C in air. Upon the consumption of **2d** (monitored by TLC), the mixture was passed through a pad of silica gel eluted with PE/EtOAc (25/1). The eluate was concentrated and the residue was recrystallized with PE/EtOAc affording **3d** as yellow solid (0.727 g, 71% yield).

Gram-scale reaction of isoquinoline 4a and MBH carbonate 2l (Synthesis of compound 5f)

A mixture of isoquinoline **1a** (3 eq, 12.0 mmol, 1.55g), MBH carbonate **2l** (1 eq, 4.0 mmol, 1.04 g), $Cu(OAc)_2{\cdot}H_2O$ (0.2 eq, 0.8 mmol, 0.160 g) and NMP (4.0 mL) was stirred at 120 °C in air. Upon the consumption of **2l** (monitored by TLC), the mixture was passed through a pad of silica gel eluted with PE/EtOAc (6/1). The eluate was concentrated and the residue was recrystallized with EtOH affording **5f** as yellow solid (0.453 g). The mother liquid was concentrated and the residue was purified by flash

chromatography to give 0.227 g of **5f** as yellow solid (63% yield totally).[14e]

Synthesis of compound 12

To a solution of **3f** in acetonitrile (0.5 mL) was added a mixture of morpholine (0.12 mmol, 1.2 eq, 10.5 μL), paraformaldehyde (4.5 eq, 0.45 mmol, 13.4 mg) and acetic acid (87.6 μL). After the mixture was stirred at rt for 39 h (monitored by TLC), it was diluted with DCM and washed with sat aq K_2CO_3 and brine. The organic phase was dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was purified by a silica gel flash chromatography (PE/DCM/EtOAc = 50:20:3) to give compound **12** (*Methyl 3-(3,4-dichlorophenyl)-1-(morpholinomethyl)pyrrolo [1,2-a]quinoline-2-carboxylate*, 36.7 mg, 78% yield, yellow solid, m.p. 75-76℃); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.04 (d, *J* = 8.4 Hz, 1H), 7.65 (d, *J* = 6.8 Hz, 1H), 7.56-7.52 (m, 1H), 7.50-7.48 (m, 2H), 7.42 (t, *J* = 7.6 Hz, 1H), 7.21-7.17 (m, 2H), 7.07 (d, *J* = 9.6 Hz, 1H), 4.32 (s, 2H), 3.75-3.72 (m, 7H), 2.72 (t, *J* = 4.4 Hz, 4H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 166.3, 135.0, 134.8, 132.04, 131.97, 130.7, 130.4, 129.9, 129.8, 128.7, 128.3, 127.9, 126.1, 124.9, 122.0, 120.3, 119.2, 117.2, 115.6, 77.2, 67.2, 52.5, 51.4; IR (CH_2Cl_2, cm^{-1}) υ 1707, 1591, 1557, 1510, 1468, 1436, 1369, 1246, 1113, 751; ESI-HRMS: calcd. for $C_{25}H_{23}Cl_2N_2O_3^+$ $(M+H)^+$ 469.1080, found 469.1085

Synthesis of compound 13

$POCl_3$ (0.3 mmol, 3 eq, 27.5 μL) was added to 1 mL of DMF and the mixture was stirred at rt for 10 min before a solution of compound **3f** (0.1 mmol, 1 eq, 37.0 mg) in DMF (1 mL) was added. The resulting mixture was stirred at rt until the reaction was complete (monitored by TLC). The reaction was then quenched by addition of water and extracted with DCM. The organic phase was washed with water and brine, dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was purified by a silica gel flash chromatography (PE/DCM/EtOAc = 4:3:1) to give compound **13** (*Methyl*

3-(3,4-dichlorophenyl)-1-formylpyrrolo[1,2-a]quinoline-2-carboxylate, 30.5 mg, 77% yield, yellow solid; m.p. 155-156℃); ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.31 (s, 1H), 8.84 (d, *J* = 8.8 Hz, 1H), 7.77 (d, *J* = 8.0 Hz, 1H), 7.70-7.86 (m, 1H), 7.58-7.52 (m, 4H), 7.34 (d, *J* = 9.6 Hz, 1H), 7.29-7.26 (m, 1H), 3.83 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 178.4, 164.8, 136.2, 133.8, 132.7, 132.6, 132.0, 131.9, 130.6, 130.4, 129.6, 128.8, 128.6, 128.1, 128.0, 126.4, 125.9, 121.2, 118.4, 116.0, 52.5; IR (CH_2Cl_2, cm^{-1}) υ 1704, 1646, 1553, 1476, 1465, 1447, 1436, 1242, 1131, 808, 732; ESI-HRMS: calcd. for $C_{21}H_{14}Cl_2NO_3^+$ $(M+H)^+$ 398.0345, found 398.0349**.**

Synthesis of compound 14 or 15

A mixture of compound **3** (1 eq, 0.1 mmol), NBS (1.2 eq, 0.12 mmol, 21.4 mg), in DCE (0.1M, 1.0 mL) was stirred at rt. Upon the consumption of **3** (monitored by TLC), the mixture was purified directly by a silica gel flash chromatography (PE/ EtOAc) to afford compound **14** or **15**.

Methyl 1-bromo-3-phenylpyrrolo[1,2-a]quinoline-2-carboxylate ***(14).*** Purified by flash column chromatography (PE/EA = 120:1); 29.6 mg, 66% yield, yellow solid; m.p. 174-176℃. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.53 (d, *J* = 8.4 Hz, 1H), 7.65 (dd, *J* = 0.8, 7.6 Hz, 1H), 7.55 (td, *J* = 1.2, 7.2 Hz, 1H), 7.51-7.48 (m, 2H), 7.46-7.42 (m, 1H), 7.21 (dd, *J* = 2.0, 8.4 Hz, 1H), 7.14 (d, *J* = 9.2 Hz, 1H), 7.07 (d, *J* = 9.6 Hz, 1H), 3.76 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 163.5, 133.5, 132.9, 131.1, 131.0, 130.4, 130.2, 129.0, 128.8, 127.8, 126.2, 125.2, 124.5, 121.2, 118.5, 116.4, 116.0, 115.9, 98.9, 50.7; IR (CH_2Cl_2, cm^{-1}) υ 1706, 1659, 1632, 1594, 1557, 1536, 1493, 1467, 1442, 1246, 1190, 748; ESI-HRMS: calcd. for $C_{20}H_{15}BrNO_2^+$ $(M+H)^+$ 380.0281, found 380.0284.

Methyl 1-bromo-3-(3,4-dichlorophenyl)pyrrolo[1,2-a]quinoline-2-carboxylate ***(15).*** Purified by flash column chromatography (PE/EA = 100:3); 30.6 mg, 81% yield, yellow solid; m.p. 187-189℃. ^{1}H NMR

(400 MHz, $CDCl_3$) δ 8.46 (s, 1H), 8.05 (dd, *J* = 1.2, 8.0 Hz, 1H), 7.92 (d, *J* = 8.4 Hz, 1H), 7.63-7.58 (m, 2H), 7.49-7.44 (m, 5H), 7.42-7.36 (m, 1H), 3.80 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 164.8, 133.1, 133.0, 130.6, 129.5, 129.3, 128.9, 128.0, 127.2, 125.6, 123.3, 121.5, 119.4, 117.13, 117.05, 114.8, 114.5, 51.4; IR (CH_2Cl_2, cm^{-1}) υ 1696, 1597, 1559, 1532, 1497, 1475, 1436, 1235, 1144, 750; ESI-HRMS: calcd. for $C_{20}H_{13}BrCl_2NO_2^+$ $(M+H)^+$ 447.9501 found 447.9508.

Synthesis of compound 16

A mixture of compound **15** (1 eq, 0.1 mmol, 38.0 mg), 3-(4,4,5,5-tetramethyl -1,3,2-dioxaborolan-2-yl)pyridine (2 eq, 0.2 mmol, 21.2 mg), $Pd(PPh_3)_4$ (0.1 eq, 0.01 mmol, 11.6 mg) and Na_2CO_3 (2 eq, 0.2 mmol, 21.2 mg) in DMF (0.8 mL) and H_2O (0.2 mL) was stirred at 120 °C. Upon the consumption of **15** (monitored by TLC), the reaction mixture was then cooled to rt, diluted with EtOAc, washed with sat Na_2CO_3 and brine, dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was purified by a silica gel flash chromatography (PE/EtOAc = 9:1) to give compound **16** (*Methyl 1-(4-nitrophenyl)-3-phenylpyrrolo[1,2-a]quinoline-2-carboxylate*, 42.6 mg, quant, yellow solid; m.p. 150-151 ℃); 1H NMR (400 MHz, $CDCl_3$) δ 8.70-8.65 (m, 2H), 8.54 (s, 1H), 8.05 (d, *J* = 8.0 Hz, 1H), 7.77-7.75 (m, 1H), 7.63-7.33 (m, 9H), 7.21 (s, 1H), 3.82 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 165.0, 150.3, 148.9, 137.1, 134.8, 133.4, 132.9, 130.6, 129.0, 128.9, 128.8, 128.0, 127.0, 127.0, 125.1, 123.8, 123.3, 120.2, 118.9, 117.2, 116.9, 114.9, 51.4; IR (CH_2Cl_2, cm^{-1}) υ 1695, 1601, 1560, 1536, 1508, 1496, 1479, 1455, 1445, 1433, 1244, 1235, 1194, 752; ESI-HRMS: calcd. for $C_{25}H_{19}N_2O_2^+$ $(M+H)^+$ 379.1441, found 379.1445.

Synthesis of compound 17

A mixture of compound **15** (1 eq, 0.1 mmol, 38.0 mg), 4,4,5,5-tetramethyl-2-(4-nitrophenyl)

-1,3,2-dioxaborolane (2 eq, 0.1 mmol, 49.8 mg), $Pd(PPh_3)_4$ (0.1 eq, 0.01 mmol, 11.6 mg) and Na_2CO_3 (2 eq, 0.2 mmol, 21.2 mg) in DMF (0.8 mL) and H_2O (0.2 mL) was stirred at 120 °C. Upon the consumption of **15** (monitored by TLC), the reaction mixture was cooled to rt, diluted with DCM, washed with sat Na_2CO_3 and brine, dried over anhydrous Na_2SO_4, filtered and concentrated. The mixture was passed through a pad of silica gel and eluted with PE/EtOAc (25/2). The eluate was concentrated and recrystallized from PE/EtOAc affording **17** (*Methyl 3-phenyl-1-(pyridin-3-yl)pyrrolo[1,2-a]quinoline-2-carboxylate,* 42.4 mg, quant, red solid; m.p. 209-211℃); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.55 (s, 1H), 8.32 (d, J = 8.4 Hz, 2H), 8.06 (d, J = 8.4 Hz, 1H), 7.64-7.57 (m, 4H), 7.51-7.49 (m, 2H), 7.44 (t, J = 7.2 Hz, 2H), 7.39-7.34 (m, 2H), 7.22 (s, 1H), 3.82 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 164.9, 147.3, 145.9, 133.3, 132.9, 130.63, 130.55, 130.4, 129.0, 128.7, 128.0, 127.1, 126.9, 125.2, 123.8, 123.3, 120.8, 118.9, 117.4, 117.1, 115.0, 51.4; IR (CH_2Cl_2, cm^{-1}) υ 1693, 1646, 1592, 1510, 1494, 1469, 1435, 1409, 1342, 1087, 759; ESI-HRMS: calcd. for $C_{26}H_{19}N_2O_4^+$ $(M+H)^+$ 423.1339, found 423.1336

Conflict of interest The authors declare that they have no conflict of interest.

Supporting Information Available: ^{1}H NMR and ^{13}C NMR spectra for all new compounds, X-ray crystallography data of compound **3c** and CIF data for **3c** (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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