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Copper(II)-catalyzed and acid-promoted highly regioselective oxidation of tautomerizable C(sp^3)–H bonds adjacent to 3,4-dihydroisoquinolines using air (O_2) as a clean oxidant†

Yun-Gang He, Yong-Kang Huang, Qi-Qi Fan, Bo Zheng, Yong-Qiang Luo, Xing-Liang Zhu and Xiao-Xin Shi *

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A mild, efficient and eco-friendly method for the oxidation of 1-Bn-DHIQs to 1-Bz-DHIQs without concomitant excessive oxidation of 1-Bz-DHIQs to 1-Bz-IQs is very important for the syntheses of 1-Bz-DHIQ alkaloids and analogues. In this article, we developed a novel Cu(II)-catalyzed and acid-promoted highly regioselective oxidation of tautomerizable C(sp^3)–H bonds adjacent to the C-1 positions of various 1-Bn-DHIQs. It was observed that when 0.2 equiv. of $Cu(OAc)_2 \cdot 2H_2O$ was used as the catalyst, 3.0 equiv. of AcOH was used as the additive and air (O_2) was used as a clean oxidant, various 1-Bn-DHIQs could be efficiently oxidized to corresponding 1-Bz-DHIQs at 25 °C in DMSO. Especially, almost no concomitant excessive oxidation of 1-Bz-DHIQs to 1-Bz-IQs was observed during the above reaction. In addition, this method was successfully applied in the first total synthesis of the alkaloid canelillinoxine.

Introduction

Oxidation of organic compounds is a kind of fundamental transformation in organic and medicinal chemistry. Development of novel efficient and highly selective oxidation of activated or non-activated C(sp^3)–H bonds under mild reaction conditions is a challenging task for chemists due to its great importance, and it has become an exciting and promising research area in modern organic synthesis.[1] Recently, significant efforts of chemists have been devoted to solving the issues of oxidation of C(sp^3)–H bonds in a variety of substrates.[2] Although many oxidants can be used in the above oxidation of C(sp^3)–H bonds, air (O_2) is certainly the best choice in the light of its abundance, easy availability, cheapness and eco-friendliness. On the other hand, copper is a low toxic and inexpensive transition metal. Therefore, an increasing amount of copper-catalyzed aerobic oxidations of various organic compounds have been recently developed.[3]

1-Benzoyl-3,4-dihydroisoquinolines (1-Bz-DHIQs) represent an important kind of isoquinoline alkaloids, which could be isolated from numerous plants.[4] Since 1-Bz-DHIQ alkaloids and their synthetic analogues have exhibited various interesting biological activities,[5] a mild, efficient and eco-friendly method for synthesis of 1-Bz-DHIQ alkaloids might be highly desirable for organic and medicinal chemists. 1-Bz-DHIQs usually can be synthesized *via* oxidation of 1-benzyl-3,4-dihydroisoquinolines (1-Bn-DHIQs), which could be readily prepared *via* the Bischler–Napieralski cyclization[6] of corresponding amides. Some known methods for the oxidation of 1-Bn-DHIQs to 1-Bz-DHIQs have been reported.[7–14] However, these known methods usually suffered from some serious drawbacks: (a) use of poisonous and hazardous strong oxidants such as CrO_3,[7] SeO_2,[8] MnO_2,[9] CAN $[Ce(NH_4)_2(NO_3)_6]$,[10] $Pb(OAc)_4$,[11] and singlet oxygen ($^1O_2$);[8,12] (b) concomitant excessive oxidation of 1-Bz-DHIQs could not be avoided, significant amount of undesired 1-benzoyl-isoquinolines (1-Bz-IQs) were formed as by-products during the reaction;[7–13] (c) yields of 1-Bz-DHIQs as the desired products are only moderate in most instances; (d) use of precious palladium catalyst (Pd/C) in Andreu's method.[14] In order to overcome the above-mentioned drawbacks, development of a mild, efficient and eco-friendly method for the oxidation of 1-Bn-DHIQs to 1-Bz-DHIQs without concomitant excessive oxidation of 1-Bz-DHIQs to 1-Bz-IQs remains a challenge to organic chemists. Herein, we want to disclose a very mild and efficient copper(II)-catalyzed and acid-promoted highly regioselective oxidation of tautomerizable C(sp^3)–H bonds adjacent to the C-1 positions of various 1-Bn-DHIQs using air (O_2) as a clean oxidant.

Results and discussion

At first, we chose the oxidation of 1-Bn-DHIQ **1a** in dimethyl sulfoxide (DMSO) as the model reaction, and tried this model reaction under various conditions, the results are summarized

Engineering Research Center of Pharmaceutical Process Chemistry of the Ministry of Education, School of Pharmacy, East China University of Science and Technology, Shanghai 200237, People's Republic of China. E-mail: xxshi@ecust.edu.cn

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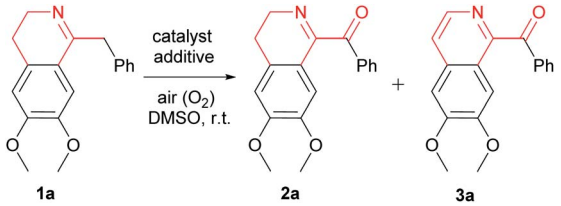
Table 1 Optimization of reaction conditions for the aerobic oxidation of 1-Bn-DHIQ **1a** in dimethyl sulfoxide (DMSO).[a]



En.	Catalyst (equiv.)	Additive (equiv.)	Time (h)	Yield %[b] (**2a**/**3a**)
1	None	None	72	25/1[c]
2	$CuCl_2 \cdot 2H_2O$ (0.2)	None	24	76/16
3	$CuBr_2 \cdot 2H_2O$ (0.2)	None	24	75/17
4	$CuSO_4 \cdot 2H_2O$ (0.2)	None	24	71/21
5	$Cu(OAc)_2 \cdot 2H_2O$ (0.1)	None	25	79/15
6	$Cu(OAc)_2 \cdot 2H_2O$ (0.2)	None	16	82/13
7	$Cu(OAc)_2 \cdot 2H_2O$ (0.5)	None	12	81/14
8	$Cu(OAc)_2 \cdot 2H_2O$ (1.0)	None	10	80/14
9	$Cu(OAc)_2 \cdot 2H_2O$ (0.2)	HCl (1.0)	15	83/1
10	$Cu(OAc)_2 \cdot 2H_2O$ (0.2)	H_2SO_4 (1.0)	18	82/1
11	$Cu(OAc)_2 \cdot 2H_2O$ (0.2)	H_3PO_4 (1.0)	14	86/1
12	$Cu(OAc)_2 \cdot 2H_2O$ (0.2)	CF_3CO_2H (1.0)	12	87/1
13	$Cu(OAc)_2 \cdot 2H_2O$ (0.2)	AcOH (1.0)	10	90/1
14	$Cu(OAc)_2 \cdot 2H_2O$ (0.2)	AcOH (2.0)	9	92/1
15	$Cu(OAc)_2 \cdot 2H_2O$ (0.2)	AcOH (3.0)	8	95/<0.5[d]
16	$Cu(OAc)_2 \cdot 2H_2O$ (0.2)	AcOH (4.0)	8	93/<0.5[d]
17	$Cu(OAc)_2 \cdot 2H_2O$ (0.2)	AcOH (5.0)	9	91/1
18	$Cu(OAc)_2 \cdot 2H_2O$ (0.2)	DBU[e] (1.0)	15	<0.5/89
19	$Cu(OAc)_2 \cdot 2H_2O$ (0.2)	Py (1.0)	15	20/72
20	$Cu(OAc)_2 \cdot 2H_2O$ (0.2)	Et_3N (1.0)	15	25/68
21	$Cu(OAc)_2 \cdot 2H_2O$ (0.2)	K_2CO_3 (1.0)	15	23/65
22	$Cu(OAc)_2 \cdot 2H_2O$ (0.2)	Na_2CO_3 (1.0)	15	23/64

[a] Reaction conditions: **1a** (2 mmol), catalyst, additive, DMSO (4.0 mL), stirred at 25 °C under an air atmosphere. [b] Isolated yields. [c] 70% of **1a** was recovered. [d] Trace amount of 1-Bz-IQ **3a** (<0.5%) was detected. [e] DBU = 1,8-Diazabicyclo[5,4,0]undec-7-ene.

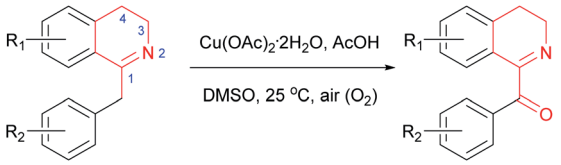
in Table 1. As can be seen from Table 1, the oxidation was sluggish in the absence of a catalyst (entry 1). The aerobic oxidation took place smoothly to give both of 1-Bz-DHIQ **2a** and 1-Bz-IQ **3a** as products in different ratios with a cupric salt as the catalyst (entries 2–22). Four cupric salts such as cupric chloride, cupric bromide, cupric sulfate and cupric acetate have been tested as the catalyst for the model reaction without additives (entries 2–8). Oxidation product 1-Bz-DHIQ **2a** was formed as the major product, but undesired excessive oxidation product 1-Bz-IQ **3a** was also formed in a significant amount.

Subsequently, we tried effects of acid and base additives on the reaction, and found that acid and base additives dramatically changed the ratios of products 1-Bz-DHIQ **2a** and 1-Bz-IQ **3a** (entries 9–22). When acids were used as additives, 1-Bz-DHIQ **2a** was formed as the major product (entries 9–17); when bases were used as additives, 1-Bz-IQ **3a** was formed as the major product (entries 18–22).[15] Especially, weak acid additive is better than strong acid (entry 13 *versus* entries 9–12), when 3.0 equiv. of acetic acid (AcOH) was used as the additive (entry 15), the desired product 1-Bz-DHIQ **2a** was obtained in the best yield (95%), and only a trace amount (<0.5%) of undesired excessive oxidation product 1-Bz-IQ **3a** was detected.

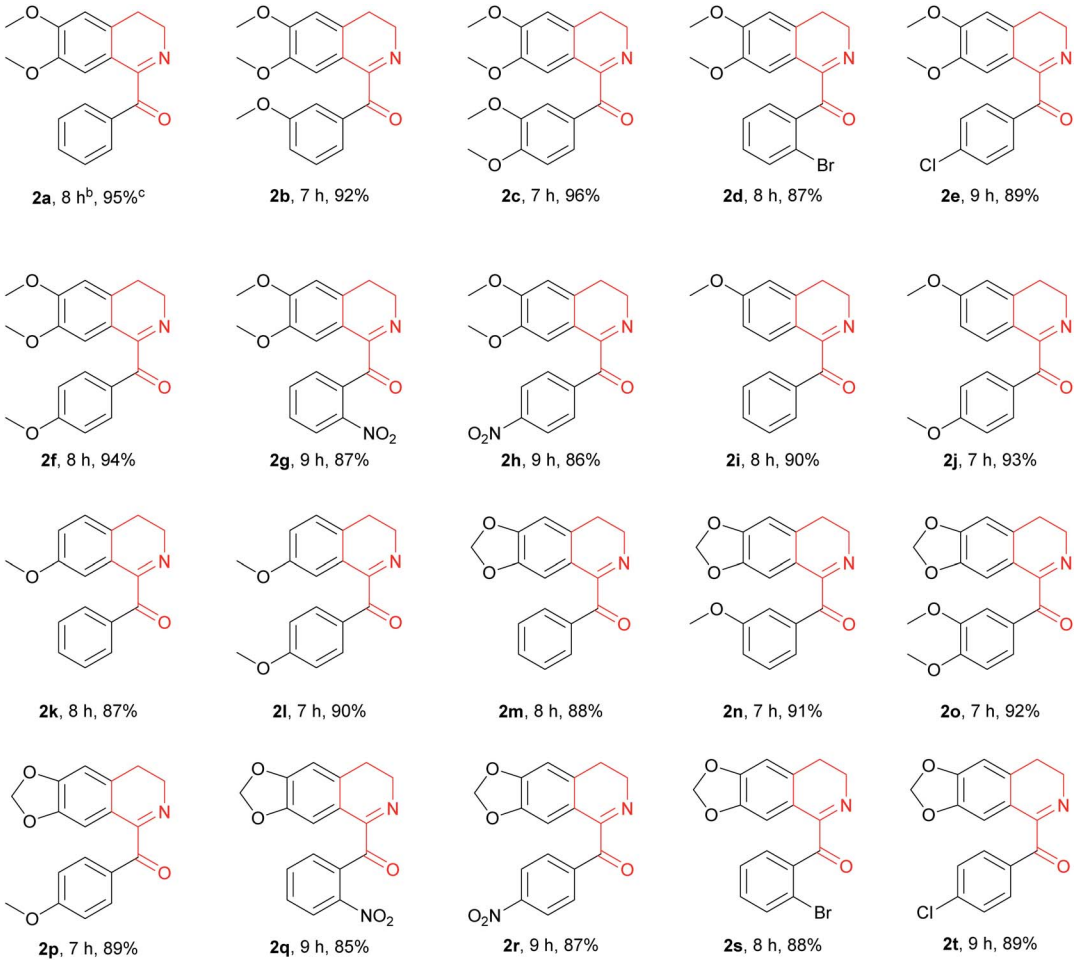
We have also tired the model reaction in different solvents, and found that the reaction is much faster in DMSO, and the yield of the desired product **2a** is higher in DMSO than in several other solvents including *N*,*N*-dimethylforamide, acetonitrile, dichloromethane, chloroform, tetrahydrofuran, ethyl acetate, acetone, 1,4-dioxane, 1,2-dimethoxyethane, isopropanol and ethanol. Consequently, we concluded that the optimized reaction conditions for the above model reaction are as follows: DMSO is the solvent, cupric salt $Cu(OAc)_2 \cdot 2H_2O$ (0.2 equiv.) is the catalyst, acid AcOH (3.0 equiv.) is the additive, and the reaction were performed under an air (O_2) atmosphere at room temperature (25 °C).

With the above optimized reaction conditions in hand, we then attempted $Cu(OAc)_2$-catalyzed oxidation of variously substituted 1-Bn-DHIQs **1**, which were prepared from corresponding amides according to the known method,[15] under the above optimized conditions to prepare 1-Bz-DHIQs **2**. As can be seen from Table 2, a total of twenty 1-Bn-DHIQs **1a–1t** have been examined for the reaction, corresponding 1-BzDHIQs **2a–2t** were thus obtained in high yields (85–96%). It is worth noting that the regioselectivity of oxidation of all tested substrates is extremely high, only tautomerizable $C(sp^3)$–H bonds adjacent to the C-1 positions of 1-Bn-DHIQs were oxidized. Although C-4 is

Table 2 $Cu(OAc)_2$-Catalyzed and acid-promoted oxidation of variously substituted 1-Bn-THIQs **1** to afford 1-Bz-DHIQs **2**.[a]



1 **2**

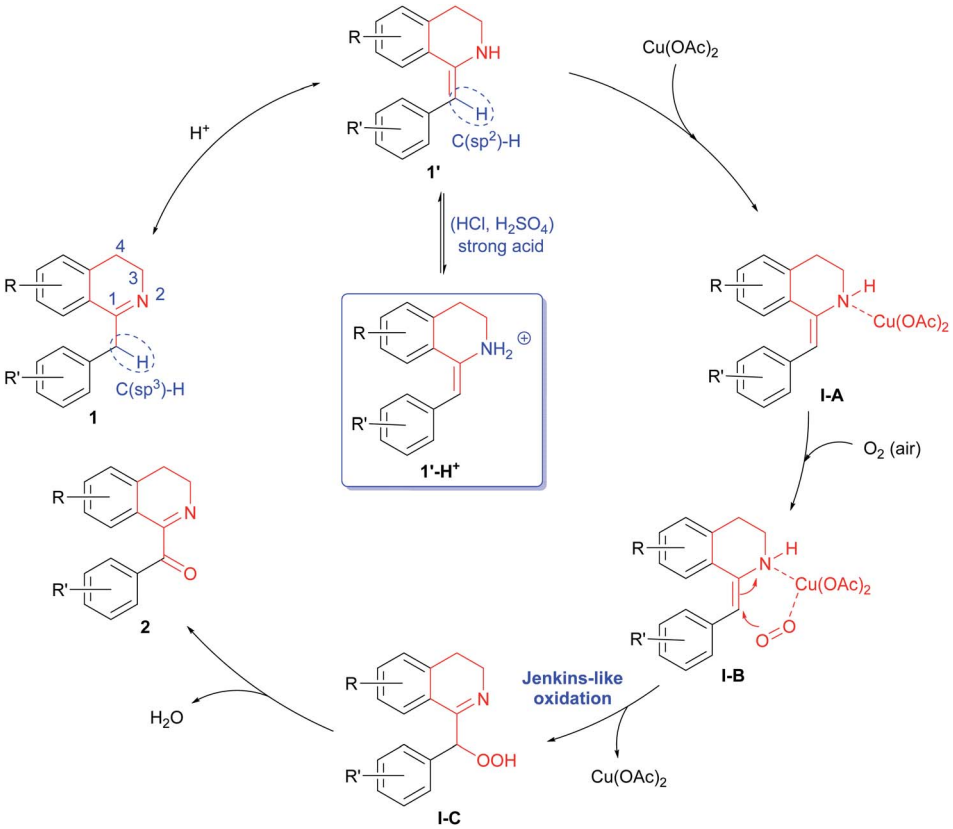


[a] Reaction conditions: 1-Bn-DHIQ **1** (2 mmol), $Cu(OAc)_2 \cdot 2H_2O$ (0.4 mmol), AcOH (6 mmol), DMSO (4 mL), 25 °C, air (O_2). [b] Reaction time. [c] Isolated yields.

also a benzylic position, almost none of oxidation of C(sp^3)–H bond at the C-4 position happened.

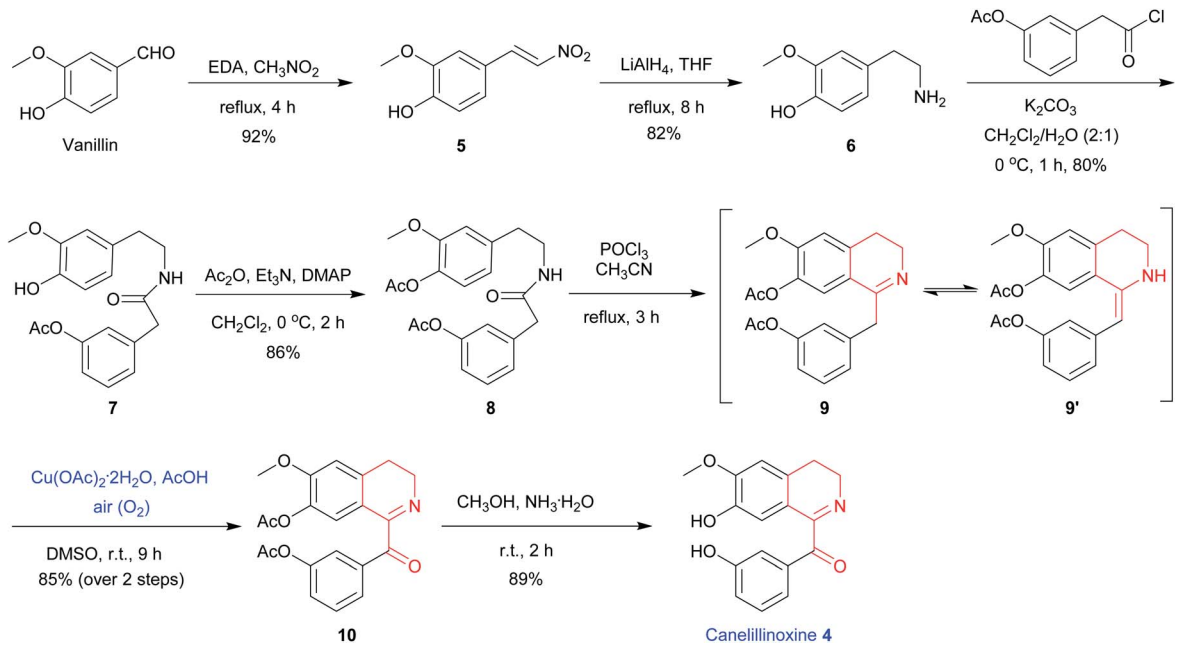
A possible mechanism for the above $Cu(OAc)_2$-catalyzed and acid promoted aerobic oxidation of 1-Bn-DHIQs **1** was proposed in Scheme 1. 1-Bn-DHIQs **1** would first undergo acid-promoted tautomerization[16] to form enamines **1′**. Enamines **1′** would then coordinate with $Cu(OAc)_2$ to produce Cu-complex **I-A**, which would further coordinate with molecule O_2 (in air) to give more reactive Cu-complex **I-B**.[17] Next, complex **I-B** would undergo intramolecular Jenkins-like oxidation[18] to furnish an unstable perhydroxide compound **I-C**. Finally, decomposition[19] of **I-C** would afford 1-Bz-DHIQs **2**. Although acids can speed up tautomerization of imines **1** to enamines **1′**, strong acids (HCl, H_2SO_4, *etc.*) would also react with imines **1** to form ammonium **1′-H**$^+$ reversibly, which could not coordinate with $Cu(OAc)_2$ to form **I-A**, and that would retard the oxidation (Table 1, entries 9–12).

To demonstrate the utility of above-described methodology, we have applied the protocol to an efficient total synthesis of 1-Bz-DHIQ canelillinoxine **4**. The alkaloid canelillinoxine **4** was isolated from the stem bark of *Aniba canelilla* H.B.K. (Lauraceae) in 1993.[20] Herein we would like to report the first total synthesis of canelillinoxine **4** starting from vanillin by using the above mild $Cu(OAc)_2$-catalyzed and acid-promoted oxidation of as the key step. As depicted in the Scheme 2, EDA-catalyzed condensation of vanillin with nitromethane produced nitroalkene **5** in



Scheme 1 Possible mechanism for the $Cu(OAc)_2$-catalyzed and acid-promoted aerobic oxidation of $C(sp^3)$–H bonds adjacent to the C-1 positions of 1-Bn-DHIQs **1**.

92% yield.[21] Compound **5** was then treated with 5.0 equiv. of $LiAlH_4$, simultaneous reduction of the double bond and nitro group took place to give amine **6** in 82% yield. When compound **6** was exposed to 1.1 equiv. of freshly prepared 2-(3-acetoxyphenyl) acetyl chloride and 3.0 equiv. of K_2CO_3, amide **7** was obtained in 80% yield. Treatment of compound **7** with 3.0 equiv. of Ac_2O, 3.0 equiv. of Et_3N and 0.1 equiv. of *N*,*N*-dimethylaminopyridine (DMAP) gave compound **8** in 86% yield. Next, exposure



Scheme 2 The first total synthesis of canelillinoxine **4** from vanillin.

of amide **8** to 3.0 equiv. of $POCl_3$, Bischler–Napieralski cyclization[6] took place smoothly to produce the tautomeric mixture of imine **9** and enamine **9′**, which were then treated with 0.2 equiv. of $Cu(OAc)_2 \cdot 2H_2O$ and 3.0 equiv. of AcOH in DMSO under an air atmosphere at 25 °C to furnish compound **10** in 85% yield (over 2 steps from **8**). Finally, when compound **10** was treated with excessive $NH_3 \cdot H_2O$, protecting groups (two Ac groups) were removed to afford 1-Bz-DHIQ canelillinoxine **4** in 89% yield.

Conclusions

In conclusion, we have studied the $Cu(OAc)_2$-catalyzed and acid-promoted highly regioselective oxidation of tautomerizable $C(sp^3)$–H bonds adjacent to C-1 positions of 1-Bn-DHIQs, and found that $Cu(OAc)_2 \cdot 2H_2O$ is the most effective catalyst, DMSO is the best solvent, weak acid AcOH is the best additive, and air (O_2) is the suitable oxidant. The reaction is highly controlled by acid/base additives, acid additives led to formation of 1-Bz-DHIQ as the major product, while base additives led to formation of 1-Bz-IQ as the major product. The reaction is applicable for a variety of substituted 1-Bn-DHIQs to afford 1-Bz-DHIQs in high yields. The present method is superior to the known methods[7–14] due to some advantages such as mildness, high regioselectivity, high yields, good practicability and eco-friendliness. In addition, the methodology was successfully applied to the first total synthesis of 1-Bz-DHIQ alkaloid canelillinoxine, it was synthesized from vanillin *via* 7 steps in 39% overall yield.

Experimental

General methods

^1H and ^{13}C NMR spectra were acquired on a Bruker AM-400 magnetic resonance instrument. Chemical shifts were given on the delta scale as parts per million (ppm) with tetramethylsilane (TMS) as the internal standard. IR spectra were recorded on a Nicolet Magna IR-550 spectrometer. MS spectra were recorded on a Mariner mass spectrum equipment. Melting points were determined on a Mei-TEMP II apparatus. Column chromatography was performed on silica gel (Qingdao Chemical Factory). All chemicals are analytically pure, and were used as such as received from the chemical suppliers.

Preparation of 1-Bn-DHIQs 1 (ref. 15). A corresponding amide (5 mmol) was dissolved in anhydrous acetonitrile (40 mL), and phosphorus oxychloride (2.350 g, 15.33 mmol) was slowly added into the mixture. The resulting solution was then heated and stirred at reflux for 2 h. After the reaction was complete (checked by TLC, eluent: CH_2Cl_2/hexane = 3 : 1), the solution was concentrated under vacuum to dryness, the residue was dissolved in CH_2Cl_2 (50 mL). An aqueous solution of K_2CO_3 (20 mL, 15% w/w) was added. After the mixture was vigorously stirred for 5 min, two phases were separated, and the aqueous phase was extracted twice with CH_2Cl_2 (2 × 25 mL). Organic extracts were combined, dried over anhydrous $MgSO_4$, and then concentrated under vacuum to give crude product 1-Bn-DHIQ **1** in an almost quantitative yield, which was used as such for the next step.

General procedure for the $Cu(OAc)_2$-catalyzed and acid-promoted oxidation of 1-Bn-DHIQs 1 into 1-Bz-DHIQs 2. 1-Bn-DHIQ **1** (2.000 mmol) was dissolved in DMSO (4 mL). $Cu(OAc)_2 \cdot 2H_2O$ (87.10 mg, 0.4002 mmol) and CH_3COOH (360.5 mg, 6.003 mmol) were added. The resulting solution was stirred at room temperature under an atmosphere of air. After the reaction was complete (checked by TLC, EtOAc/hexane = 1 : 1), a dilute ammonia aqueous solution (5% w/w, 20 mL) and EtOAc (20 mL) were added into the mixture. After the mixture was vigorously stirred for 5 min, two phases were separated. The aqueous phase was twice extracted with EtOAc (20 mL × 2). The organic extracts were combined, and dried over anhydrous $MgSO_4$. Removal of solvent by vacuum distillation gave crude product, which was purified by flash chromatography (eluent: CH_2Cl_2/EtOAc = 20 : 1 to 5 : 1) to afford 1-Bz-DHIQ **2** in 85–96% yields. Characterization data of compounds **2a–t** are as follows:

(6,7-Dimethoxy-3,4-dihydroisoquinolin-1-yl)(phenyl)methanone ***2a***: pale yellow crystals, m.p. 78–79 °C (lit.[22] m.p. 78.8–79.4 °C). ^1H NMR (400 MHz, $CDCl_3$) δ 8.04 (d, J = 7.3 Hz, 2H), 7.59 (t, J = 7.4 Hz, 1H), 7.47 (dd, J_1 = 7.3 Hz, J_2 = 7.4 Hz, 2H), 6.95 (s, 1H), 6.76 (s, 1H), 3.99–3.87 (m, 2H), 3.92 (s, 3H), 3.78 (s, 3H), 2.88–2.77 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 193.97, 164.39, 151.72, 147.62, 135.57, 133.85, 131.17, 130.43, 128.54, 119.30, 110.57, 109.59, 56.07, 56.02, 47.31, 25.37. IR (KBr film) ν 3080, 2936, 2907, 2844, 1656, 1586, 1516, 1485, 1265, 1239, 1146, 1024, 929, 865, 752 cm^{-1}.

(6,7-Dimethoxy-3,4-dihydroisoquinolin-1-yl)(3-methoxyphenyl)-methanone ***2b***: pale yellow crystals, m.p. 98–100 °C. ^1H NMR (400 MHz, $CDCl_3$) δ 7.59 (s, 1H), 7.57 (d, J = 7.8 Hz, 1H), 7.37 (dd, J_1 = 7.8 Hz, J_2 = 7.9 Hz, 1H), 7.15 (d, J = 7.9 Hz, 1H), 6.93 (s, 1H), 6.76 (s, 1H), 3.98–3.89 (m, 2H), 3.94 (s, 3H), 3.86 (s, 3H), 3.79 (s, 3H), 2.88–2.77 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 193.82, 164.54, 159.73, 151.77, 147.66, 136.85, 131.15, 129.58, 123.63, 120.63, 119.30, 113.96, 110.54, 109.58, 56.11, 56.05, 55.48, 47.21, 25.40. IR (KBr film) ν 3070, 2921, 2852, 1666, 1596, 1592, 1569, 1515, 1461, 1425, 1135, 1072, 1033, 935, 807, 754, 709 cm^{-1}. HRMS (ESI) m/z calcd for $C_{19}H_{19}NO_4Na$ $[M + Na]^+$: 348.1212, found: 348.1211.

(6,7-Dimethoxy-3,4-dihydroisoquinolin-1-yl)(3,4-dimethoxy-phenyl)methanone ***2c***: pale yellow crystals, m.p. 188–189 °C (lit.[23] m.p. 188–190 °C). ^1H NMR (400 MHz, $CDCl_3$) δ 7.68 (s, 1H), 7.61 (d, J = 8.4 Hz, 1H), 6.91 (s, 1H), 6.89 (d, J = 8.4 Hz, 1H), 6.76 (s, 1H), 3.96 (s, 3H), 3.95–3.88 (m, 2H), 3.95 (s, 3H), 3.94 (s, 3H), 3.79 (s, 3H), 2.89–2.76 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 192.76, 164.63, 154.16, 151.67, 149.16, 147.64, 131.08, 128.59, 126.61, 119.49, 111.21, 110.50, 110.02, 109.61, 56.16, 56.11, 56.04, 56.02, 47.25, 25.43. IR (KBr film) ν 3013, 2935, 2833, 2604, 1659, 1583, 1514, 1461, 1278, 1133, 1023, 866, 791, 755 cm^{-1}.

(2-Bromophenyl)(6,7-dimethoxy-3,4-dihydroisoquinolin-1-yl) methanone ***2d***: pale yellow crystals, m.p. 159–161 °C. ^1H NMR (400 MHz, $CDCl_3$) δ 7.64 (d, J = 7.8 Hz, 1H), 7.58 (d, J = 7.6 Hz, 1H),7.44 (dd, J_1 = 7.8 Hz, J_1 = 7.7 Hz, 1H), 7.36 (dd, J_1 = 7.7 Hz, J_2 = 7.7 Hz, 1H), 7.32 (s, 1H), 6.74 (s, 1H), 3.94 (s, 3H), 3.89 (s, 3H), 3.88–3.80 (m, 2H), 2.83–2.62 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 195.75, 163.67, 151.61, 147.54, 140.23, 133.14, 132.51, 131.68, 131.11, 127.51, 120.75, 119.16, 110.32, 110.28, 56.15,

56.02, 48.19, 25.12. IR (KBr film) ν 3054, 2942, 2899, 2844, 1681, 1587, 1499, 1478, 1460, 1381, 1315, 1266, 1032, 924, 868 cm^{-1}. HRMS (ESI) *m/z* calcd for $C_{18}H_{16}NO_3Na$ $[M + Na]^+$: 396.0211, found: 396.0215.

(4-Chlorophenyl)(6,7-dimethoxy-3,4-dihydroisoquinolin-1-yl) methanone ***2e***: white crystals, m.p. 132–133 °C (lit.[24] m.p. 130–131 °C). ^1H NMR (400 MHz, $CDCl_3$) δ 7.99 (d, J = 8.6 Hz, 2H), 7.45 (d, J = 8.6 Hz, 2H), 6.96 (s, 1H), 6.75 (s, 1H), 3.97–3.89 (m, 2H), 3.94 (s, 3H), 3.80 (s, 3H), 2.86–2.76 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 192.56, 163.93, 151.83, 147.69, 140.35, 134.01, 131.87, 131.22, 128.85, 119.17, 110.55, 109.61, 56.12, 56.06, 47.38, 25.38.

(6,7-Dimethoxy-3,4-dihydroisoquinolin-1-yl)(4-methoxyphenyl)-methanone ***2f***: pale yellow crystals, m.p. 92–93 °C (lit.[25] m.p. 91–92 °C). ^1H NMR (400 MHz, $CDCl_3$) δ 8.03 (d, J = 8.9 Hz, 2H), 6.96 (d, J = 8.9 Hz, 2H), 6.92 (s, 1H), 6.75 (s, 1H), 3.96–3.89 (m, 2H), 3.94 (s, 3H), 3.88 (s, 3H), 3.78 (s, 3H), 2.87–2.77 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 192.73, 164.67, 164.26, 151.61, 147.62, 132.91, 131.10, 128.50, 119.48, 113.87, 110.47, 109.61, 56.12, 55.56, 47.27, 29.72, 25.45.

(6,7-Dimethoxy-3,4-dihydroisoquinolin-1-yl)(2-nitrophenyl)-methanone ***2g***: pale yellow crystals, m.p. 98–100 °C. ^1H NMR (400 MHz, $CDCl_3$) δ 8.09 (d, J = 7.8 Hz, 1H), 7.78 (dd, J_1 = 7.8 Hz, J_2 = 7.9 Hz, 1H), 7.71–7.61 (m, 3H), 6.70 (s, 1H), 3.97 (s, 3H), 3.94 (s, 3H), 3.74–3.62 (m, 2H), 2.70–2.56 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 192.66, 163.10, 151.69, 147.81, 147.56, 136.08, 134.17, 131.81, 131.04, 130.19, 123.57, 119.03, 110.97, 109.92, 56.17, 56.00, 47.84, 25.20. IR (KBr film) ν 3072, 2964, 2919, 2851, 1697, 1600, 1562, 1529, 1512, 1468, 1405, 1346, 1280, 1197, 1147, 1047, 906, 877, 800, 750, 707 cm^{-1}. HRMS (ESI) *m/z* calcd for $C_{18}H_{17}N_2O_5$ $[M + H]^+$: 341.1137, found: 341.1135.

(6,7-Dimethoxy-3,4-dihydroisoquinolin-1-yl)(4-nitrophenyl)-methanone ***2h***: white crystals, m.p. 160–161 °C. ^1H NMR (400 MHz, $CDCl_3$) δ 8.31 (d, J = 8.8 Hz, 2H), 8.20 (d, J = 8.8 Hz, 2H), 7.07 (s, 1H), 6.77 (s, 1H), 4.00–3.92 (m, 2H), 3.95 (s, 3H), 3.84 (s, 3H), 2.89–2.76 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 191.71, 163.27, 152.06, 150.42, 147.75, 140.75, 131.53, 131.43, 123.49, 118.87, 110.58, 109.68, 56.16, 56.12, 47.57, 25.32. IR (KBr film) ν 3003, 2924, 2853, 1674, 1637, 1606, 1564, 1519, 1458, 1347, 1200, 1043, 906, 859, 800, 781 cm^{-1}. HRMS (ESI) *m/z* calcd for $C_{18}H_{17}N_2O_5$ $[M + H]^+$: 341.1137, found: 341.1143.

(6-Methoxy-3,4-dihydroisoquinolin-1-yl)(phenyl)methanone ***2i***: pale yellow crystals, m.p. 89–90 °C (lit.[26] m.p. 88–90 °C). ^1H NMR (400 MHz, $CDCl_3$) δ 8.03 (d, J = 7.4 Hz, 2H), 7.58 (t, J = 7.5 Hz, 1H), 7.45 (dd, J_1 = 7.4 Hz, J_2 = 7.5 Hz, 2H), 7.31 (d, J = 8.5 Hz, 1H), 6.76 (s, 1H), 6.73 (d, J = 8.5 Hz, 1H), 3.99–3.88 (m, 2H), 3.81 (s, 3H), 2.91–2.79 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 194.09, 164.86, 162.02, 139.57, 135.56, 133.86, 130.37, 128.56, 128.50, 120.16, 113.47, 112.13, 55.42, 47.13, 26.19.

(6-Methoxy-3,4-dihydroisoquinolin-1-yl)(4-methoxyphenyl)-methanone ***2j***: white crystals, m.p. 156–157 °C. ^1H NMR (400 MHz, $CDCl_3$) δ 8.02 (d, J = 9.0 Hz, 2H), 7.29 (d, J = 8.5 Hz, 1H), 6.94 (d, J = 9.0 Hz, 2H), 6.76 (s, 1H), 6.72 (d, J = 8.5 Hz, 1H), 3.97–3.87 (m, 2H), 3.85 (s, 3H), 3.82 (s, 3H), 2.90–2.80 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 192.81, 165.11, 164.24, 161.93, 139.53, 132.77, 128.53, 128.50, 120.28, 113.87, 113.40, 112.09, 55.56, 55.38, 47.05, 26.20. HRMS (ESI) *m/z* calcd for $C_{18}H_{18}NO_3$ $[M + H]^+$: 296.1287, found: 296.1292.

(7-Methoxy-3,4-dihydroisoquinolin-1-yl)(phenyl)methanone ***2k***: pale yellow crystals, m.p. 130–131 °C. ^1H NMR (400 MHz, $CDCl_3$) δ 8.03 (d, J = 7.7 Hz, 2H), 7.60 (t, J = 7.8 Hz, 1H), 7.48 (dd, J_1 = 7.7 Hz, J_2 = 7.8 Hz, 2H), 7.17 (d, J = 8.2 Hz, 1H), 6.97 (d, J = 8.2 Hz, 1H), 6.92 (s, 1H), 4.03–3.89 (m, 2H), 3.73 (s, 3H), 2.87–2.76 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 193.80, 165.11, 158.55, 135.49, 133.94, 130.41, 129.19, 128.74, 128.60, 127.16, 117.68, 111.67, 55.49, 47.77, 24.78. IR (KBr film) ν 3058, 2973, 2946, 2836, 1664, 1598, 1575, 1498, 1475, 1448, 1353, 1311, 1259, 1222, 1199, 1112, 1031, 921, 879, 858, 740, 698 cm^{-1}. HRMS (ESI) *m/z* calcd for $C_{17}H_{15}NO_2Na$ $[M + Na]^+$: 288.1000, found: 288.1005.

(7-Methoxy-3,4-dihydroisoquinolin-1-yl)(4-methoxyphenyl)-methanone ***2l***: white crystals, m.p. 58–60 °C. ^1H NMR (400 MHz, $CDCl_3$) δ 8.02 (d, J = 9.0 Hz, 2H), 7.16 (d, J = 8.2 Hz, 1H), 6.95 (d, J = 8.2 Hz, 1H), 6.94 (d, J = 9.0 Hz, 2H), 6.90 (s, 1H), 3.98–3.91 (m, 2H), 3.87 (s, 3H), 3.73 (s, 3H), 2.86–2.76 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 192.53, 165.38, 164.32, 158.54, 132.82, 129.17, 128.69, 128.42, 117.60, 113.91, 113.76, 111.69, 55.57, 55.48, 47.67, 24.80. IR (KBr film) ν 3037, 2947, 2924, 2833, 1652, 1603, 1572, 1499, 1468, 1422, 1357, 1317, 1259, 1222, 1209, 1169, 1126, 1040, 1019, 948, 926, 881, 819, 767 cm^{-1}. HRMS (ESI) *m/z* calcd for $C_{18}H_{17}NO_3Na$ $[M + Na]^+$: 318.1106, found: 318.1102.

(7,8-Dihydro-[1,3]dioxolo[4,5-g]isoquinolin-5-yl)(phenyl)-methanone ***2m***: pale yellow crystals, m.p. 76–77 °C. ^1H NMR (400 MHz, $CDCl_3$) δ 7.93 (d, J = 8.0 Hz, 2H), 7.50 (t, J = 8.1 Hz, 1H), 7.37 (dd, J_1 = 8.0 Hz, J_2 = 8.1 Hz, 2H), 6.76 (s, 1H), 6.62 (s, 1H), 5.85 (s, 2H), 3.88–3.74 (m, 2H), 2.74–2.63 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 193.80, 164.41, 149.91, 146.51, 135.42, 133.88, 132.99, 130.34, 128.55, 120.37, 108.29, 106.88, 101.48, 47.19, 25.85. IR (KBr film) ν 3054, 2921, 2846, 1664, 1621, 1581, 1502, 1483, 1461, 1058, 1037, 991, 931, 869, 730, 688 cm^{-1}. HRMS (ESI) *m/z* calcd for $C_{17}H_{13}NO_3Na$ $[M + Na]^+$: 302.0793, found: 302.0800.

(7,8-Dihydro-[1,3]dioxolo[4,5-g]isoquinolin-5-yl)(3-methoxyphenyl)methanone ***2n***: pale yellow crystals, m.p. 70–72 °C. ^1H NMR (400 MHz, $CDCl_3$) δ 7.58 (s, 1H), 7.55 (d, J = 7.9 Hz, 1H), 7.36 (dd, J_1 = 7.9 Hz, J_2 = 8.0 Hz, 1H), 7.14 (d, J = 8.0 Hz, 1H), 6.83 (s, 1H), 6.72 (s, 1H), 5.96 (s, 2H), 3.93–3.85 (m, 2H), 3.86 (s, 3H), 2.83–2.74 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 193.77, 164.53, 159.76, 149.94, 146.54, 136.71, 132.99, 129.59, 123.59, 120.71, 120.45, 113.82, 108.31, 106.98, 101.49, 55.51, 47.23, 25.92. IR (KBr film) ν 3077, 2941, 2903, 2837, 1677, 1592, 1568, 1481, 1459, 1429, 1375, 1318, 1264, 1191, 1104, 1038, 992, 935, 872, 751, 679 cm^{-1}. HRMS (ESI) *m/z* calcd for $C_{18}H_{15}NO_4Na$ $[M + Na]^+$: 332.0899, found: 332.0907.

(7,8-Dihydro-[1,3]dioxolo[4,5-g]isoquinolin-5-yl)(3,4-dimethoxyphenyl)methanone ***2o***: pale yellow crystals, m.p. 154–155 °C (lit.[5d] m.p. 153–154 °C). ^1H NMR (400 MHz, $CDCl_3$) δ 7.56 (s, 1H), 7.50 (d, J = 8.4 Hz, 1H), 6.80 (d, J = 8.4 Hz, 1H), 6.74 (s, 1H), 6.64 (s, 1H), 5.88 (s, 2H), 3.88 (s, 3H), 3.86 (s, 3H), 3.85–3.76 (m, 2H), 2.76–2.65 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 192.72, 164.68, 154.19, 149.87, 149.20, 146.52, 132.93, 128.47, 126.55, 120.64, 111.07, 110.01, 108.27, 107.04, 101.46, 56.18, 56.06, 47.18, 25.93.

(7,8-Dihydro-[1,3]dioxolo[4,5-g]isoquinolin-5-yl)(4-methoxyphenyl)methanone ***2p***: pale yellow crystals, m.p. 131–132 °C. ^1H NMR (400 MHz, $CDCl_3$) δ 8.01 (d, J = 8.9 Hz, 2H), 6.94 (d, J = 8.9 Hz, 2H), 6.83 (s, 1H), 6.71 (s, 1H), 5.95 (s, 2H), 3.94–3.82 (m, 2H), 3.86 (s, 3H), 2.84–2.73 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$)

δ 192.60, 164.70, 164.27, 149.83, 146.49, 132.95, 132.80, 128.33, 120.57, 113.88, 108.26, 107.04, 101.45, 55.59, 47.17, 25.93. IR (KBr film) ν 3069, 2920, 2841, 1650, 1599, 1505, 1486, 1257, 1171, 1038, 932, 849, 768 cm^{-1}. HRMS (ESI) *m/z* calcd for $C_{18}H_{16}NO_4$ $[M + H]^+$: 310.1079, found: 310.1073.

(7,8-Dihydro-[1,3]dioxolo[4,5-g]isoquinolin-5-yl)(2-nitrophenyl)-methanone ***2q***: pale yellow crystals, m.p. 180–181 °C (lit.[7] m.p. 180–183 °C). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01 (d, J = 7.8 Hz, 1H), 7.70 (dd, J_1 = 7.8 Hz, J_2 = 7.9 Hz, 1H), 7.63–7.54 (m, 2H), 7.48 (s, 1H), 6.60 (s, 1H), 5.94 (s, 2H), 3.62–3.50 (m, 2H), 2.56–2.44 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 192.38, 163.19, 149.90, 147.77, 146.52, 136.00, 134.21, 133.78, 131.08, 130.26, 123.61, 120.01, 108.49, 107.70, 101.47, 47.78, 25.79.

(7,8-Dihydro-[1,3]dioxolo[4,5-g]isoquinolin-5-yl)(4-nitrophenyl)-methanone ***2r***: white crystals, m.p. 160–161 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.31 (d, J = 8.9 Hz, 2H), 8.18 (d, J = 8.9 Hz, 2H), 6.96 (s, 1H), 6.75 (s, 1H), 6.00 (s, 2H), 4.01–3.81 (m, 2H), 2.88–2.60 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 191.55, 163.31, 150.44, 150.25, 146.66, 140.56, 133.33, 131.46, 123.51, 119.95, 108.37, 106.99, 101.62, 47.47, 25.81. HRMS (ESI) *m/z* calcd for $C_{17}H_{13}N_2O_5$ $[M + H]^+$: 325.0824, found: 325.0821.

(2-Bromophenyl)(7,8-dihydro-[1,3]dioxolo[4,5-g]isoquinolin-5-yl) methanone ***2s***: pale yellow crystals, m.p. 147–148 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62 (d, J = 7.7 Hz, 1H), 7.56 (d, J = 7.9 Hz, 1H), 7.43 (dd, J_1 = 7.7 Hz, J_2 = 7.8 Hz, 1H), 7.35 (dd, J_1 = 7.8 Hz, J_2 = 7.9 Hz, 1H), 7.25 (s, 1H), 6.71 (s, 1H), 6.00 (s, 2H), 3.91–3.73 (m, 2H), 2.77–2.63 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 195.61, 163.63, 149.79, 146.43, 140.24, 133.04, 132.46, 131.05, 127.53, 120.66, 120.22, 108.02, 107.81, 101.46, 48.20, 25.70. HRMS (ESI) *m/z* calcd for $C_{17}H_{12}BrNO_3Na$ $[M + Na]^+$: 379.9898, found: 379.9895.

(4-Chlorophenyl)(7,8-dihydro-[1,3]dioxolo[4,5-g]isoquinolin-5-yl)methanone ***2t***: pale yellow crystals, m.p. 133–134 °C (lit.[5d] m.p. 132–133 °C). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97 (d, J = 8.2 Hz, 2H), 7.45 (d, J = 8.2 Hz, 2H), 6.86 (s, 1H), 6.73 (s, 1H), 5.97 (s, 2H), 3.99–3.83 (m, 2H), 2.87–2.72 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 192.36, 164.05, 150.10, 146.60, 140.45, 133.82, 133.14, 131.79, 128.90, 120.24, 108.33, 107.01, 101.53, 47.20, 25.88. IR (KBr film) ν 3004, 2923, 2852, 1668, 1622, 1587, 1502, 1484, 1462, 1208, 1089, 1041, 936, 899, 821, 769 cm^{-1}.

Preparation of (*E*)-2-methoxy-4-(2-nitrovinyl)phenol (5). Vanillin (9.902 g, 65.08 mmol) was dissolved in nitromethane (100 mL). Ethylenediamine (78.10 mg, 1.300 mmol) was added. The resulting solution was then heated to reflux, and stirring was continued at reflux for around 4 h. After the reaction was complete (TLC: EtOAc/hexane = 1 : 2), the nitromethane was removed by vacuum distillation to give a crude yellowish solid product, which was then triturated in aqueous methanol (CH_3OH/H_2O = 2 : 1, 20 mL). Pale yellow crystals were collected on a Buchner funnel by suction, and rinsed twice with aqueous methanol (CH_3OH/H_2O = 1 : 1, 2 × 10 mL). After being dried overnight under a warm air, compound **5** (11.68 g, 59.84 mmol) was obtained as yellow crystals in 92% yield, m.p. 164–165 °C (lit.[27] m.p. 162–164 °C). ^{1}H NMR (400 MHz, acetone-d_6) δ 8.58 (brs, 1H, *OH*), 8.02 (d, J = 13.5 Hz, 1H), 7.91 (d, J = 13.5 Hz, 1H), 7.49 (s, 1H), 7.32 (d, J = 8.2 Hz, 1H), 6.94 (d, J = 8.2 Hz, 1H), 3.94 (s, 3H). ^{13}C NMR (100 MHz, acetone-d_6) δ 151.85, 149.02, 140.44, 136.03, 126.41, 123.18, 116.47, 112.21, 56.42.

Preparation of 4-(2-aminoethyl)-2-methoxyphenol (6). A solution of compound **5** (5.856 g, 30.00 mmol) in THF (60 mL) was dropwise added into a stirred suspension of $LiAlH_4$ (5.693 g, 150.0 mmol) in THF (60 mL) at 0 °C over 20 min. After the addition was finished, the mixture was then heated and stirred at reflux for 8 h. The mixture was cooled to 0 °C by an ice-bath. While the mixture was vigorously stirred, water (20 mL) was dropwise added into the reaction mixture over 30 min, and $NaHCO_3$ (12.60 g, 150.0 mmol) was then slowly added into the mixture at 0 °C. The ice-bath was removed, and the mixture was further stirred at reflux for 3 h. After cooled to room temperature, the mixture was filtered through a thin layer of celite, and the filter cake was washed twice with EtOH (2 × 30 mL). The filtrates were combined and dried over anhydrous $MgSO_4$. The solution was concentrated under vacuum to give crude product as a viscous oil, which was purified by flash chromatography (eluent: CH_2Cl_2/CH_3OH = 1 : 1) to afford pure compound **6** (4.115 g, 24.61 mmol) as white crystals in 82% yield, m.p. 158–160 °C (lit.[28] m.p. 158.5–160.5 °C). ^{1}H NMR (400 MHz, DMSO-d_6) δ 6.83 (s, 1H), 6.76 (d, J = 8.0 Hz, 1H), 6.63 (d, J = 8.0 Hz, 1H), 3.76 (s, 3H), 3.02–2.91 (m, 2H), 2.81 (t, J = 7.9 Hz, 2H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 147.51, 145.24, 128.02, 120.71, 115.47, 112.74, 55.52, 55.47, 32.61.

Preparation of 3-(2-((4-hydroxy-3-methoxyphenethyl)amino)-2-oxoethyl)phenyl acetate (7). 2-(3-Acetoxyphenyl)acetic acid (3.841 g, 19.78 mmol) was dissolved in CH_2Cl_2 (25 mL), and $SOCl_2$ (4.706 g, 39.56 mmol) was added. The resulting solution was then heated and stirred at reflux for 4 h. The reaction solution was concentrated under vacuum to dryness, oily residue was then dissolved in dry CH_2Cl_2 (10 mL), the solution was immediately used bellow. Compound **6** (3.006 g, 17.98 mmol) was dissolved in CH_2Cl_2 (50 mL), and an aqueous solution of K_2CO_3 (7.456 g, 53.95 mmol) in water (30 mL) was added. The biphasic mixture was cooled by an ice-bath, and was stirred at 0 to 5 °C. The above freshly prepared solution of 2-(3-acetoxyphenyl)acetyl chloride was added slowly into the reaction mixture over 2 min. After the addition was finished, stirring was continued at 0–5 °C for 1 h. When the reaction was completed, the reaction mixture was transferred into a separatory funnel. Two phases were separated, and the aqueous phase was extracted again with CH_2Cl_2 (20 mL). The organic extracts were combined, dried over anhydrous $MgSO_4$, and then concentrated under vacuum to give crude product, which was purified by flash chromatography (eluent: EtOAc/hexane = 1 : 2) to afford pure compound **7** (4.945 g, 14.40 mmol) as white crystals in 80% yield, m.p. 108–110 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30 (dd, J_1 = 7.9 Hz, J_2 = 7.8 Hz, 1H), 7.02 (d, J = 7.8 Hz, 1H), 7.00 (d, J = 7.9 Hz, 1H), 6.94 (s, 1H), 6.77 (d, J = 8.0 Hz, 1H), 6.60 (s, 1H), 6.51 (d, J = 8.0 Hz, 1H), 5.70 (brs, 1H, N*H*), 3.79 (s, 3H), 3.49 (s, 2H), 3.47–3.36 (m, 2H), 2.66 (t, J = 6.9 Hz, 2H), 2.29 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.55, 169.52, 150.95, 146.76, 144.30, 136.41, 130.37, 129.88, 126.83, 122.60, 121.28, 120.51, 114.50, 111.23, 55.84, 43.37, 40.97, 35.02, 21.10. IR (KBr film) ν 3378, 3301, 3079, 2935, 2848, 1762, 1736, 1653, 1607, 1512, 1449, 1371, 1278, 1206, 1147, 1124, 1032, 963, 933, 861, 791, 693 cm^{-1}. HRMS (ESI) *m/z* calcd for $C_{19}H_{21}NO_5Na$ $[M + Na]^+$: 366.1317, found: 366.1313.

Preparation of 3-(2-((4-acetoxy-3-methoxyphenethyl)amino)-2-oxoethyl)phenyl acetate (8). Compound 7 (4.005 g, 11.66 mmol) was dissolved in CH_2Cl_2 (100 mL). After the solution was cooled to triethylamine (3.540 g, 34.98 mmol), DMAP (142.5 mg, 1.166 mmol) and acetic anhydride (3.571 g, 34.98 mmol) and were added in turn. The mixture was further stirred at 0 °C for 2 h. After the reaction was complete (checked by TLC, EtOAc/hexane = 1 : 1), an aqueous solution of hydrochloric acid (1 N, 50 mL) was added. After the mixture was vigorously stirred for 5 min, two phases were separated, and organic layer was washed with an aqueous solution of potassium carbonate (15% w/w, 30 mL). The aqueous phase was extracted again with CH_2Cl_2 (30 mL). The organic extracts were combined, dried over anhydrous $MgSO_4$, and then concentrated under vacuum to give crude product, which was purified by flash chromatography (eluent: EtOAc/hexane = 1 : 3) to afford pure compound **8** (3.866 g, 10.03 mmol) as white crystals in 86% yield, m.p. 95–97 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32 (dd, J_1 = 7.8 Hz, J_2 = 7.9 Hz, 1H), 7.04 (d, J = 7.8 Hz, 1H), 7.00 (d, J = 7.9 Hz, 1H), 6.96 (s, 1H), 6.89 (d, J = 8.0 Hz, 1H), 6.71 (s, 1H), 6.61 (d, J = 8.0 Hz, 1H), 5.71 (brs, 1H, N*H*), 3.76 (s, 3H), 3.50 (s, 2H), 3.48–3.40 (m, 2H), 2.72 (t, J = 6.9 Hz, 2H), 2.30 (s, 3H), 2.29 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.46, 169.46, 169.23, 151.01, 150.95, 138.25, 137.73, 136.44, 129.94, 126.82, 122.69, 122.60, 120.79, 120.51, 112.78, 55.85, 43.39, 40.69, 35.36, 21.13, 20.67. IR (KBr film) ν 3300, 3037, 2938, 2854, 1769, 1649, 1601, 1540, 1448, 1424, 1373, 1267, 1206, 1151, 1120, 1028, 967, 905, 807, 790, 690 cm^{-1}. HRMS (ESI) *m/z* calcd for $C_{21}H_{23}NO_6Na$ $[M + Na]^+$: 408.1423, found: 408.1425.

Preparation of 3-(7-acetoxy-6-methoxy-3,4-dihydroisoquinoline-1-carbonyl)phenyl acetate (10). Amide **8** (3.002 g, 7.789 mmol) was dissolved in anhydrous acetonitrile (30 mL), and phosphorus oxychloride (3.583 g, 23.37 mmol) was slowly added into the mixture. The resulting solution was then heated and stirred at reflux for 3 h. After the reaction was complete, the solution was concentrated under vacuum to dryness, the residue was dissolved in EtOAc (60 mL). An aqueous solution of K_2CO_3 (35 mL, 20% w/w) was added. After the mixture was vigorously stirred for 5 min, two phases were separated, and the aqueous phase was extracted twice with EtOAc (20 mL × 2). The organic extracts were combined, dried over anhydrous $MgSO_4$, and then concentrated under vacuum to give crude solid as a tautomeric mixture of 3,4-dihydroisoquinoline **9** and enamine **9′**, which was used as such for the next step.

The above tautomeric mixture of 3,4-dihydroisoquinoline **9** and enamine **9′** were dissolved in DMSO (15 mL). $Cu(OAc)_2 \cdot 2H_2O$ (339.0 mg, 1.557 mmol) and CH_3COOH (1.400 g, 23.31 mmol) were added. The resulting solution was then stirred at room temperature for 9 h under an atmosphere of air. After the reaction was completed (checked by TLC, EtOAc/hexane = 1 : 1), a dilute ammonia aqueous solution (5% w/w, 60 mL) and EtOAc (60 mL) were added. After the mixture was vigorously stirred for 5 min, two phases were separated, and the aqueous phase was extracted again with EtOAc (50 mL). The organic extracts were combined, and dried over anhydrous $MgSO_4$. Removal of solvent by vacuum distillation gave crude product, which was purified by flash chromatography (eluent: EtOAc/hexane = 1 : 3) to afford pure compound **10** (2.525 g, 6.621 mmol) as pale yellow crystals in 85% yield, m.p. 80–82 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88 (d, J = 8.0 Hz, 1H), 7.78 (s, 1H), 7.47 (dd, J_1 = 8.0 Hz, J_2 = 7.9 Hz, 1H), 7.34 (d, J = 7.9 Hz, 1H), 7.16 (s, 1H), 6.83 (s, 1H), 4.01–3.94 (m, 2H), 3.88 (s, 3H), 2.92–2.79 (m, 2H), 2.31 (s, 3H), 2.27 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 192.12, 169.11, 168.90, 163.37, 153.78, 150.74, 138.18, 137.11, 136.82, 129.54, 128.14, 127.25, 123.21, 121.52, 119.38, 111.55, 56.10, 47.10, 25.71, 21.13, 20.54. IR (KBr film) ν 3072, 2923, 2849, 1763, 1673, 1608, 1585, 1563, 1512, 1438, 1367, 1282, 1200, 1127, 1068, 1045, 1008, 912, 886, 808, 756, 701 cm^{-1}. HRMS (ESI) *m/z* calcd for $C_{21}H_{20}NO_6$ $[M + H]^+$: 382.1291, found: 382.1291.

Preparation of (7-hydroxy-6-methoxy-3,4-dihydroisoquinolin-1-yl)(3-hydroxyphenyl)methanone (canelillinoxine 4). Compound **10** (1.003 g, 2.630 mmol) was dissolved in methanol (15 mL), and concentrated aqueous ammonia (25%, w/w, 2 mL) was slowly added. After the addition was finished, the mixture was further stirred at room temperature for about 2 h. After the reaction was complete (checked by TLC, EtOAc/hexane = 1 : 1), solvents were removed by vacuum distillation to give crude product, which was then purified by flash chromatography (eluent: CH_2Cl_2/CH_3OH = 10 : 1) to afford pure compound **4** (696.0 mg, 2.341 mmol) as pale yellow crystals in 89% yield, m.p. 120–122 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 (d, J = 7.9 Hz, 1H), 7.20 (s, 1H), 7.17 (dd, J_1 = 7.9 Hz, J_2 = 8.0 Hz, 1H), 6.89 (s, 1H), 6.87 (d, J = 8.0 Hz, 1H), 6.70 (s, 1H), 3.93 (s, 3H), 3.87–3.80 (m, 2H), 2.81–2.73 (m, 2H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 194.03, 164.32, 157.60, 150.45, 144.86, 136.16, 129.99, 128.87, 121.44, 120.80, 118.63, 115.64, 112.52, 111.46, 55.63, 46.65, 24.46. IR (KBr film) ν 3391, 3072, 2928, 2847, 1672, 1600, 1585, 1513, 1452, 1374, 1286, 1133, 1048, 1024, 1000, 880, 826, 762 cm^{-1}. HRMS (ESI) *m/z* calcd for $C_{17}H_{16}NO_4$ $[M + H]^+$: 298.1079, found: 298.1075.

Conflicts of interest

There are no conflicts to declare.

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