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Total Syntheses of Menisporphine and Daurioxoisoporphine C Enabled by Photoredox-Catalyzed Direct C–H Arylation of Isoquinoline with Aryldiazonium Salt

Jing Zhang,[†‡§] Jie Chen,[†‡§] Xiaoyun Zhang,[‡] and Xiaoguang Lei*[‡‖]

[†]School of Pharmaceutical Science and Technology, Tianjin University, Tianjin, 300072, China

[‡]National Institute of Biological Sciences (NIBS), Beijing, 102206, China

§These authors contributed equally.

‖Beijing National Laboratory for Molecular Sciences, Key Laboratory of Bioorganic Chemistry and Molecular Engineering of Ministry of Education, Department of Chemical Biology, College of Chemistry and Molecular Engineering, Synthetic and Functional Biomolecules Center, and Center for Life Sciences, Peking University, Beijing, 100871, China

xglei@pku.edu.cn

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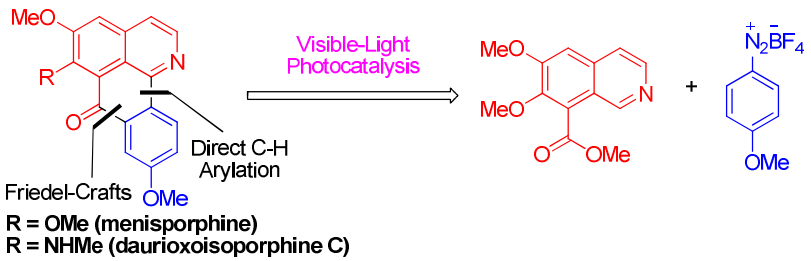


Abstract

Isoquinoline alkaloids are attractive natural products due to their diverse chemical structures as well as remarkable bioactivities. Herein, we report the concise total syntheses of two isoquinoline alkaloids menisporphine and daurioxoisoporphine C through a mild and efficient photoredox-catalyzed direct C–H arylation of isoquinoline core with aryldiazonium salt. This new

strategy is complementary to the conventional isoquinoline synthesis and would provide us a useful means to achieve a more convergent and flexible approach to access diverse isoquinoline structures.

Isoquinoline alkaloids represent one of the vastest classes of natural products with striking structural diversities as well as significant biological activities.[1] For example, papaverine (Fig. 1) is a well-known drug mainly used in the treatment of visceral spasm and vasospasm.[2] Norruffscine showed potent anti-HIV-1 activity.[3] Berberine has been used as an antibacterial drug in China since the 1950s and was identified as a good hypolipidemic drug in 2004.[4] Liriodenine exhibited a wide range of pharmacological activities, including antibacterial, antifungal, antitumoral, antiarrhythmic activities, *etc*.[5] Recently, menisporphine (**1**), originally isolated from *Menispermum dauricum* DC, was reported as a significant anti-angiogenic agent.[6] Moreover, a closely related natural product daurioxoisoporphine C (**2**) was also disclosed by Qin and coworkers in 2001.[7]

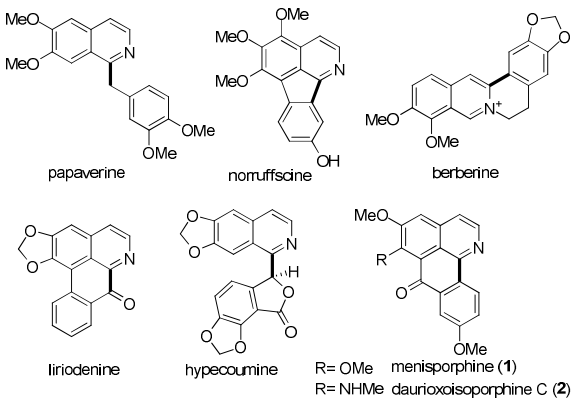


Figure1. Representative isoquinoline alkaloids.

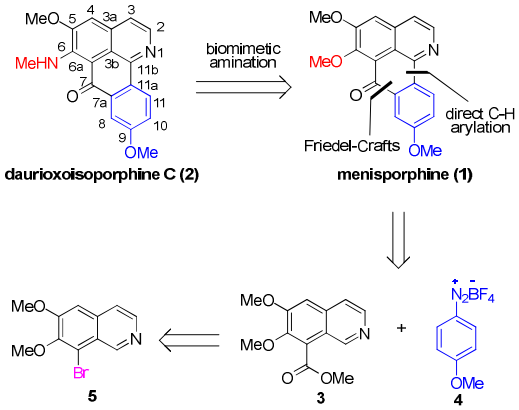
Accordingly, complex and biologically active isoquinoline alkaloids have attracted long-term and broad attention from the synthetic community and have been the subjects of numerous synthetic endeavors.[1a,8] The traditional methods for construction of isoquinoline skeletons including Pictet-Spengler,[9] Bischler-Napieralski,[10] and Pomeranz-Fritsch reactions,[11] have been extensively employed for the total syntheses of isoquinoline alkaloids. However, these

transformations typically required harsh reaction conditions, which provided poor functional group tolerance. Recently, transition metal mediated isoquinoline syntheses[12] opened new avenues in the efficient preparation of complex isoquinoline natural products. Unfortunately, when applied to the syntheses of isoquinoline alkaloids, most existing strategies involved pre-installation of the required functionalities before the construction of isoquinoline frameworks.

In order to achieve more convergent and flexible synthesis, we envisioned that direct C–H functionalization of the isoquinoline core might offer a promising alternative means to access complex isoquinoline alkaloids. Over the past decade, a number of remarkable synthetic methods have been developed for the direct C–H functionalization of heterocycles.[13] Recently, König group,[14] and Martín and Carrillo group[15] reported two elegant photocatalytic approaches[16,17] for direct C–H arylation of electron-rich (hetero)arenes with aryldiazonium salts or anilines nitrosated in situ. With regard to electron-deficient N-heterocycles, direct C–H arylation was still a synthetic challenge. Very recently, Xue et al disclosed the direct C–H arylation of pyridines with good functional group tolerance utilizing aryldiazonium salts, but the reactivity of isoquinoline was undiscussed.[17j] As reported by Baran et al, although a number of N-heterocycles showed excellent reactivity, only 33% yield was obtained when isoquinoline was used to react with arylboronic acids.[18] All of these previous landmark works inspired us to further develop a more efficient method to achieve the direct C-H arylation of isoquinoline, which should ultimately enable us to accomplish the efficient synthesis of diverse isoquinoline natural products. Here, we report our endeavors in developing a mild and efficient photoredox-catalyzed direct C–H arylation of isoquinoline core with aryldiazonium salt as well as the concise total syntheses of menisporphine (**1**) and daurioxoisoporphine C (**2**) applying this newly developed chemistry.

Our synthetic plan for **1** and **2** is depicted in Scheme 1. We envisioned that the methylamino group of **2** could be installed through a biomimetic amination of **1**. The C11a–C11b and C7a–C7 bonds of **1** could be derived through a Minisci-type[19] direct C–H arylation of methyl ester **3** with 4-methoxybenzenediazonium tetrafluoroborate **4** and an intramolecular Friedel-Crafts acylation reaction, respectively. The methyl ester **3** could be prepared from the known bromide **5**.[20]

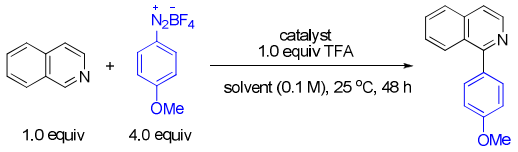
Scheme 1. Retrosynthetic analysis.



We first examined the crucial direct C–H arylation of isoquinoline **6** with aryldiazonium salt **4**. Several metal catalysts and solvents were carefully investigated, and the results were displayed in Table 1. The control reaction suggested a catalyst was required for this reaction system (Table 1, entry 1). Through the screen of various catalysts, we were pleased to find that the photoredox catalyst $Ru(bpy)_3Cl_2•6H_2O$ gave us the best results (38% yield, entry 12) when the reaction was conducted in DMSO utilizing a 40W compact fluorescent bulb. Among other non-photoreaction catalysts, 20% CuCl gave the highest yield (35%) in DMSO (entry 4). Trifluoroacetic acid was required for this reaction (entry 4, 5), most likely because it could protonate the heterocycles and increase their reactivities. Further screening of different solvent showed that the yield was

improved to 55% when MeOH was employed (entry 14). Other commonly used photoredox catalysts like eosin Y and $Ir(ppy)_3$ reduced the yield of the arylated product **7** (entry 11, 16). Remarkably, we observed that the photoredox-catalyzed reaction could proceed smoothly at room-temperature, which provided us a very mild reaction condition to facilitate the synthesis of highly functionalized isoquinolines.

Table 1. Initial reaction screening[a]



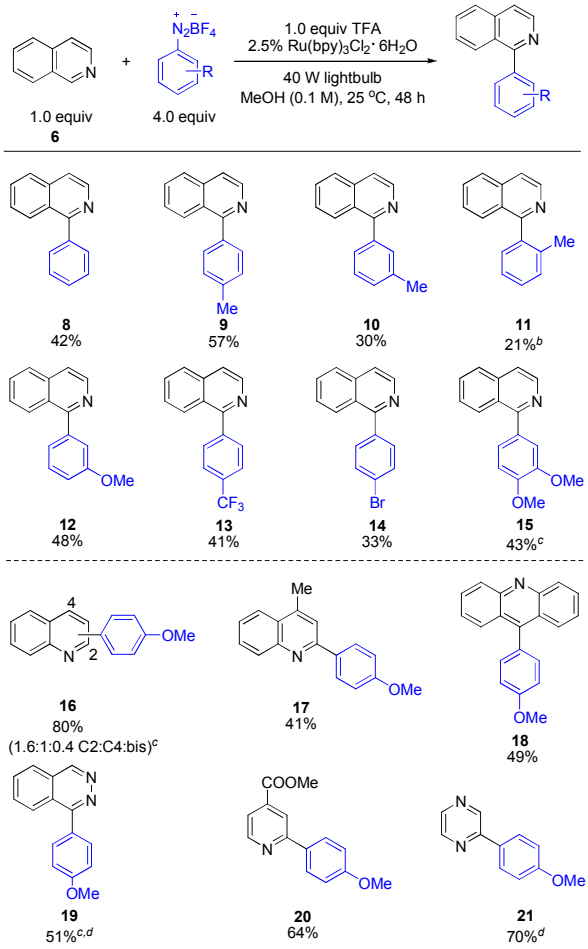
Entry	Catalyst	Solvent	Yield[b]
1	none	DMSO	trace
2	20% $AgNO_3$	DMSO	trace
3	20% $CoCl_2$	DMSO	12%
4	20% CuCl	DMSO	35%
5	20% CuCl	DMSO	20%[c]
6	20% CuBr	DMSO	25%
7	20% CuI	DMSO	24%
8	20% $FeCl_2$	DMSO	13%
9	20% $Fe(OAc)_2$	DMSO	27%
10	20% $Mn(OAc)_3$	DMSO	11%
11	1% Eosin Y	DMSO	5%[d]
12	2.5% $Ru(bpy)_3Cl_2 \cdot 6H_2O$	DMSO	38%[e]

13	2.5% $Ru(bpy)_3Cl_2•6H_2O$	MeCN	29%[e]
14	**2.5% $Ru(bpy)_3Cl_2•6H_2O$**	**MeOH**	**55%**[e]
15	2.5% $Ru(bpy)_3Cl_2•6H_2O$	MeOH	NR[f]
16	2.5% $Ir(ppy)_3$	MeOH	28%[e]

[a] General conditions: isoquinoline (0.1 mmol), **4** (0.4 mmol), TFA (0.1 mmol), solvent (1 mL), 25 °C, 48 h. [b] Isolated yields. [c] The reaction was conducted without TFA. [d] König's conditions[14]: isoquinoline (1.0 mmol), **4** (0.1 mmol), 530 nm, 1 W LED bulb as the light source. [e] A 40 W compact fluorescent light bulb was used as the light source. [f] no light. DMSO = dimethylsulfoxide, TFA = trifluoroacetic acid, bpy = 2,2'-bipyridine, NR = no reaction, ppy = 2-phenylpyridinato-C^2,*N*.

We then examined the scope of aryldiazonium salts for the arylation of isoquinoline **6** under the optimal conditions, and the results were summarized in Scheme 2. In general, the electron-rich aryldiazonium salts showed better reactivity than the electron-deficient ones. The reaction system tolerated several functional groups including OMe, CF_3 and Br (**12**–**15**). However, we also observed that the reactivities of single-substituted aryldiazonium salts unfortunately decreased as follows: *para*- > *meta*- > *ortho*-substitution (e.g., **9**–**11**), which was probably attributed to the steric hindrance effect. As a result, nearly half of the starting material was recovered when 2-methylbenzenediazonium tetrafluoroborate (**11**) was used for this reaction. Interestingly, we found that some other types of heterocycles also exhibited good reactivity. Quinolines (**16**, **17**), acridine (**18**), phthalazine (**19**), pyridine (**20**) and pyrazine (**21**) could be directly C–H arylated using this method in moderate to good yields. The regio-selectivity for quinolines tended to favor the 2-position over the 4-position.

Scheme 2. Substrate scope[a]

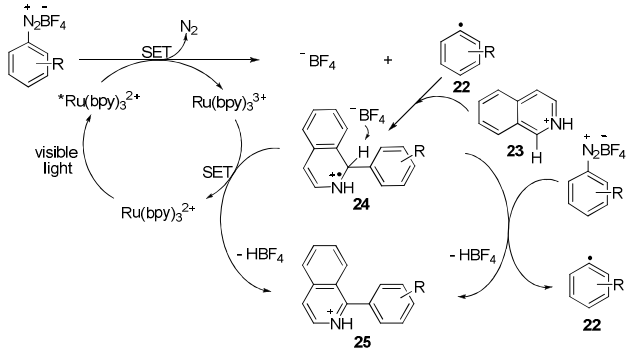


[a] Reactions were conducted at 0.4 mmol scale under the reaction conditions in Table 1, entry 13. Yields are of the isolated products. [b] 42% starting material was recovered. [c] The reaction was conducted at 0.1 mmol scale. [d] 2.0 equiv of TFA was added to the reaction mixture.

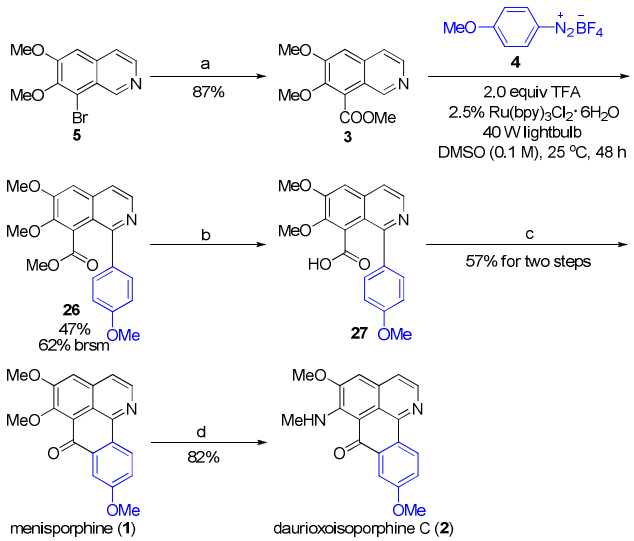
Our proposed mechanism for the ruthenium-catalyzed photoreaction is described in Scheme 3 which is based on our experimental results and the known catalytic cycle.[14,17j,21] The photocatalyst Ru(Ⅱ) first turns to the excited state with the visible light, followed by single electron transfer (SET) from the excited state of Ru(Ⅱ) to aryldiazonium salt, which would afford the aryl radical **22**. Subsequently the aryl radical **22** adds to the protonated isoquinoline **23** to give the radical

cation intermediate **24**, which is further transformed to the protonated target molecule **25** by two possible pathways: (a) oxidation of the radical cation intermediate **24** by the Ru(III) and followed by deprotonation to yield **25** or (b) oxidation of **24** by aryldiazonium salt and then deprotonation to afford **25** to complete the catalytic cycle of SET. However, no reaction occurred without light according to the light "on/off" experiment (Table 1, entry 14, 15), indicating that pathway b, a radical chain propagation pathway, was less possible.

Scheme 3. The proposed mechanism for the photocatalytic direct C–H arylation of isoquinoline.



Scheme 4. Total syntheses of menisporphine and daurioxoisoporphine C[a]



[a] Reagents and conditions: (a) CO (45 atm), MeOH, Et_3N, 1,3-DPPP, $Pd(OAc)_2$, DMSO, 80 °C, 18 h; (b) KOH, $EtOH/H_2O$, microwave, 100 °C, 2 h; (c) TFAA, 80 °C, 13 h; (d) $MeNH_2$, CH_2Cl_2,

sealed tube, 100 ^{o}C, 8 h. 1,3-DPPP = 1,3-bis(diphenylphosphino)propane, TFAA = trifluoroacetic anhydride.

After establishing the key C–H arylation reaction, we then set out to investigate its synthetic application in the total syntheses of isoquinoline alkaloids **1** and **2** (Scheme 4). The readily available bromide **5** was converted into the methyl ester **3** in 87% yield through a palladium-catalyzed methoxycarbonylation[22] utilizing carbon monoxide and methanol. Then **3** was subjected to the newly developed direct C–H arylation condition. It was interesting to find that in this case higher yield of compound **26** (47%, 62% brsm) was obtained when DMSO was employed as the solvent than methanol was used as the solvent previously. After extensive screening of reaction conditions, hydrolysis of the ester **26** under a basic and microwave condition afforded the acid **27**, which was subsequently cyclized by the treatment of trifluoroacetic anhydride through an intramolecular Friedel-Crafts acylation reaction to furnish the desired natural product menisporphine (**1**) in 57% yield over two steps. Compared with the classic approaches for isoquinoline syntheses, the current strategy offered us a more concise (only 4 steps) and convergent synthetic route with good total yield (23%, 31% brsm). With menisporphine (**1**) in hand, we further investigated the biomimetic transformation from menisporphine to daurioxoisoporphine C (**2**). To our delight, the direct amination was smoothly realized by the treatment of **1** with methylamine[23] to complete the first total synthesis of daurioxoisoporphine C (**2**) in good yield (82%). The spectroscopic data of the synthetic compounds **1** and **2** fully matched the data reported previously for the natural products.

In conclusion, we have accomplished the concise total syntheses of two isoquinoline alkaloids menisporphine and daurioxoisoporphine C (4 and 5 steps, respectively). The synthesis featured a

newly developed photoredox-catalyzed direct C–H arylation of isoquinoline core with aryldiazonium salts and a late stage biomimetic amination of menisporphine. The direct C–H arylation of isoquinoline proceeds at room temperature and can also be applied to other electron-deficient heteroarenes with good functional group tolerance. Further investigations of its synthetic application in other complex isoquinoline natural product synthesis are currently underway and will be reported in due course.

EXPERIMENTAL SECTION

General Methods. Organic solutions were concentrated under reduced pressure on a Büchi rotary evaporator (R-3). Dimethylsulfoxide (DMSO) were distilled from anhydrous $CaSO_4$/calcium hydride; acetonitrile were distilled from calcium hydride; trifluoroacetic acid (TFA) were distilled from trifluoroacetic anhydride; methanol were distilled from magnesium; acetone were distilled from K_2CO_3/$KMnO_4$ prior to use. Analytical thin layer chromatography (TLC) was performed using 0.25 mm silica gel 60-F plates and the visualization was accomplished with short wave UV light (254 nm) and phosphomolybdic acid. Chromatographic purification of products was accomplished using force-flow chromatography on basic aluminum oxide (200-300 mesh) or silica gel (200-400 mesh). ^{1}H NMR spectra were recorded on a 400 MHz spectrometer at ambient temperature with $CDCl_3$ as the solvent unless otherwise stated. ^{13}C NMR spectra were recorded on a 100 MHz spectrometer (with complete proton decoupling) at ambient temperature. Chemical shifts are reported in parts per million relative to chloroform (^{1}H, δ7.26; ^{13}C, δ77.0). Data for ^{1}H NMR are reported as follows: chemical shift(ppm), integration, multiplicity (s = singlet, d = doublet, t = triplet, q =quartet, dd = double-doublet, dq = double quartet, ddd= double double doublet, sept = septet, m = multiplet, br = broad, and app = apparent) and coupling constants (Hz). High resolution mass spectra (HRMS) were recorded by FTMS spectrometer. All reactions were carried out in oven-dried glassware under an argon atmosphere unless otherwise noted.

General procedure for the preparation of aryl diazonium tetrafluoroborates.[24] The

appropriate aniline (10 mmol) was dissolved in a mixture of 50% hydrofluoroboric acid (3.4 mL) and distilled water (4 mL). After cooling to 0 °C with ice bath. Sodium nitrite (0.69 g) in distilled water (1.5 mL) was added dropwise in a period of 5 minutes. The resulting mixture was stirred for a period of 30 minutes and the precipitate was collected by filtration and redissolved in minimum amount of acetone. Diethyl ether was added until the precipitation of diazonium tetrafluoroborate, which was filtered, washed with diethyl ether several times and dried under vacuum.

General procedure for the reaction of heterocycle with aryl diazonium tetrafluoroborate. An oven-dried 10 mL vial equipped with a magnetic stir bar was taken into the glove box. To the vial was added $Ru(bpy)_3Cl_2•6H_2O$ (7.5 mg, 0.01 mmol), aryl diazonium tetrafluoroborate (1.6 mmol) and MeOH (2 mL). A solution of heterocycle (0.4 mmol) and trifluoroacetic acid (30.6 μL, 0.4 mmol) in MeOH (2 mL) was added into the reaction vial. The vial was sealed with a septum before removed from the glove box and placed approximately 2 cm from a 40 W compact fluorescent light bulb. The reaction mixture was stirred at room temperature for 48 h. Then the solution was evaporated to remove MeOH and the resulting residue was dissolved in CH_2Cl_2 (4 mL) and washed with saturated aqueous sodium bicarbonate (2 mL). The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (3×4 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated in vacuum. Purification of the crude product was performed by aluminum oxide or silica gel chromatography with petroleum ether/ethyl acetate or dichloromethane/methanol (depending on different substrates) as the eluent.

1-(4-Methoxyphenyl)isoquinoline (7). The General Procedure was followed but at 0.1 mmol scale to afford 1-(4-methoxyphenyl)isoquinoline (**7**) as a light yellow solid (13.0 mg, 55%). The spectroscopic data for this compound were identical to those reported in the literature.[25]

1-Phenylisoquinoline (8). The General Procedure was followed to afford 1-phenylisoquinoline (**8**) as a yellow oil (34.4 mg, 42%). The spectroscopic data for this compound were identical to those reported in the literature.[26]

1-(p-Tolyl)isoquinoline (9). The General Procedure was followed to afford 1-(p-tolyl)isoquinoline (**9**) as a yellow oil (50.0 mg, 57%). The spectroscopic data for this compound were identical to those reported in the literature.[26]

1-(m-Tolyl)isoquinoline (10). The General Procedure was followed to afford 1-(m-tolyl)isoquinoline (**10**) as a white solid (26.0 mg, 30%): mp 76.9 – 78.7 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.61 (d, *J* = 5.7 Hz, 1H), 8.15 – 8.10 (m, 1H), 7.88 (d, *J* = 8.2 Hz, 1H), 7.69 (ddd, *J* = 8.2, 6.9, 1.2 Hz, 1H), 7.64 (dd, *J* = 5.7, 0.7 Hz, 1H), 7.57 – 7.51 (m, 2H), 7.48 (d, *J* = 7.6 Hz, 1H), 7.44 – 7.39 (m, 1H), 7.31 (d, *J* = 7.5 Hz, 1H), 2.46 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.9, 142.2, 139.5, 138.1, 136.8, 130.5, 129.9, 129.3, 128.1, 127.7, 127.1, 127.0, 126.9, 126.7, 119.8, 21.5; IR (neat) ν = 3047, 2918, 1619, 1581, 1555, 1498, 1384, 1354, 1275, 1162, 1137, 872, 826, 781, 751, 707, 633 cm^{-1}; HRMS (ESI) $[M + H]^+$ calculated for $C_{16}H_{14}N$: 220.1121, found: 220.1118.

1-(o-Tolyl)isoquinoline (11). The General Procedure was followed to afford 1-(o-tolyl)isoquinoline (**11**) as a light yellow oil (18.4 mg, 21%) and the starting material isoquinoline as a colorless oil (21.6 mg, 42%) . The spectroscopic data for this compound were identical to those reported in the literature.[27]

1-(3-Methoxyphenyl)isoquinoline (12). The General Procedure was followed to afford 1-(3-methoxyphenyl)isoquinoline (**12**) as a yollow oil (47.0 mg, 48%). The spectroscopic data for this compound were identical to those reported in the literature.[28]

1-(4-(Trifluoromethyl)phenyl)isoquinoline (13). The General Procedure was followed to afford 1-(4-(trifluoromethyl)phenyl)isoquinoline (**13**) as a white solid (44.0 mg, 41%): mp 130.4 – 132.4 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.64 (d, *J* = 5.7 Hz, 1H), 8.03 (dd, *J* = 8.5, 0.9 Hz, 1H), 7.92 (d, *J* = 8.2 Hz, 1H), 7.86 – 7.78 (m, 4H), 7.75 – 7.69 (m, 2H), 7.57 (ddd, *J* = 8.3, 6.9, 1.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.1, 143.1, 142.3, 136.9, 130.7 (q, *J* = 32.5 Hz), 130.3, 130.3, 127.6, 127.2, 126.9, 126.5, 125.3 (q, *J* = 3.7 Hz), 124.2 (q, *J* = 270.6 Hz), 120.6; IR (neat) ν = 3058, 1618, 1582, 1555, 1404, 1332, 1158, 1114, 1070, 839, 831, 756, 681, 610 cm^{-1}; HRMS (ESI) $[M + H]^+$ calculated for $C_{16}H_{11}F_3N$: 274.0838, found: 274.0839.

1-(4-Bromophenyl)isoquinoline (14). The General Procedure was followed to afford 1-(4-bromophenyl)isoquinoline (**14**) as a yellow solid (37.3 mg, 33%). The spectroscopic data for this compound were identical to those reported in the literature.[29]

1-(3,4-Dimethoxyphenyl)isoquinoline (15). The General Procedure was followed but at 0.1 mmol scale to afford 1-(3,4-dimethoxyphenyl)isoquinoline (**15**) as a light yellow solid (11.5 mg, 43%). The spectroscopic data for this compound were identical to those reported in the literature.[30]

2-(4-Methoxyphenyl)quinoline (16-C2), 4-(4-methoxyphenyl)quinoline (16-C4), 2,4-bis(4-methoxyphenyl)quinoline (16-C2C4). The General Procedure was followed but at 0.1 mmol scale to afford 2-(4-methoxyphenyl)quinoline (**16-C2**) as a light yellow solid (10.0 mg, 43%), 4-(4-methoxyphenyl)quinoline (**16-C4**) as a yellow oil (6.3 mg, 27%), and 2,4-bis(4-methoxyphenyl)quinoline (**16-C2C4**) as a light yellow oil (3.5 mg, 10%). For **16-C2** and **16-C4**, the spectroscopic data were identical to those reported in the literature.[31] For **16-C2C4**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.23 – 8.13 (m, 3H), 7.92 (dd, *J* = 8.4, 1.0 Hz, 1H), 7.75 (s, 1H), 7.71 (ddd, *J* = 8.4, 6.8, 1.4 Hz, 1H), 7.54 – 7.48 (m, 2H), 7.45 (ddd, *J* = 8.2, 6.8, 1.3 Hz, 1H), 7.12 –

7.02 (m, 4H), 3.92 (s, 3H), 3.89 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.8, 159.8, 156.4, 148.9, 148.7, 132.3, 130.8, 130.8, 129.9, 129.3, 128.9, 125.8, 125.7, 125.6, 118.8, 114.2, 114.0, 55.4, 55.4; IR (neat) ν = 3000, 2932, 2835, 2360, 2342, 1607, 1516, 1497, 1462, 1401, 1359, 1291, 1248, 1178, 1032, 833, 766 cm^{-1}; HRMS (ESI) $[M + H]^+$ calculated for $C_{23}H_{20}NO_2$: 342.1489, found: 342.1481.

2-(4-Methoxyphenyl)-4-methylquinoline (17). The General Procedure was followed to afford 2-(4-methoxyphenyl)-4-methylquinoline (**17**) as a yellow oil (40.3 mg, 41%). The spectroscopic data for this compound were identical to those reported in the literature.[32]

9-(4-Methoxyphenyl)acridine (18). The General Procedure was followed with the exception of the way of work up: the solution of the reaction was evaporated to remove MeOH and the resulting residue was diluted with CH_2Cl_2 (10 mL) and dry sodium bicarbonate solid (500 mg) was added to the residue. The resulting mixture was stirred for 1 hour, filtered and the sodium bicarbonate solid was washed with CH_2Cl_2 several times. The CH_2Cl_2 solutions were combined and concentrated in vacuum. Purification of the crude product was performed by aluminum oxide chromatography with petroleum ether/ethyl acetate as the eluent to afford 9-(4-methoxyphenyl)acridine (**18**) as a yellow solid (55.3 mg, 49%). The spectroscopic data for this compound were identical to those reported in the literature.[33]

1-(4-Methoxyphenyl)phthalazine (19). The General Procedure was followed but at 0.1 mmol scale and with the addition of 2.0 equiv of TFA to afford 1-(4-methoxyphenyl)phthalazine (**19**) as a white solid (12.0 mg, 51%): mp 124.0 – 126.0 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.49 (s, 1H), 8.14 – 8.11 (m, 1H), 8.04 – 7.96 (m, 1H), 7.88 (tdd, J = 9.6, 7.0, 1.4 Hz, 2H), 7.77 – 7.70 (m, 2H), 7.14 – 7.04 (m, 2H), 3.91 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.7, 159.4, 150.2, 132.4,

132.0, 131.5, 128.5, 127.1, 126.6, 126.2, 125.4, 114.0, 55.4; IR (neat) ν = 3052, 2961, 2932, 2838, 2359, 2341, 1722, 1611, 1518, 1489, 1367, 1253, 1176, 1034, 840, 738, 703 cm^{-1}; HRMS (ESI) $[M + H]^+$ calculated for $C_{15}H_{13}N_2O$: 237.1022, found: 237.1023.

Methyl 2-(4-methoxyphenyl)isonicotinate (20). The General Procedure was followed to afford methyl 2-(4-methoxyphenyl)isonicotinate (**20**) as a light yellow solid (62.0 mg, 64%): mp 68.5 – 70.5 ^oC; ^1H NMR (400 MHz, $CDCl_3$) δ 8.78 (dd, *J* = 5.0, 0.8 Hz, 1H), 8.23 (dd, *J* = 1.4, 0.9 Hz, 1H), 8.04 – 8.00 (m, 2H), 7.70 (dd, *J* = 5.0, 1.5 Hz, 1H), 7.04 – 6.99 (m, 2H), 3.98 (d, *J* = 1.9 Hz, 3H), 3.87 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.9, 160.9, 158.1, 150.3, 138.0, 131.1, 128.3, 120.3, 118.9, 114.2, 55.4, 52.7; IR (neat) ν = 2953, 2838, 1731, 1606, 1556, 1515, 1435, 1303, 1251, 1176, 1111, 1031, 972, 836, 764, 684 cm^{-1}; HRMS (ESI) $[M + H]^+$ calculated for $C_{14}H_{14}NO_3$: 244.0968, found: 244.0967.

2-(4-Methoxyphenyl)pyrazine (21). The General Procedure was followed with the addition of 2.0 equiv of TFA to afford 2-(4-methoxyphenyl)pyrazine (**21**) as a yellow solid (52.0 mg, 70%). The spectroscopic data for this compound were identical to those reported in the literature.[34]

Procedures for the syntheses of menisporphine and daurioxoisoporphine C

Methyl 6,7-dimethoxyisoquinoline-8-carboxylate (3). A mixture of bromide **5** (525 mg, 1.96 mmol), triethylamine (396 mg , 3.92 mmol), 1,3-bis(diphenylphosphino)propane (143 mg, 0.35 mmol) and palladium acetate (78 mg, 0.35 mmol) in DMSO (2 mL) and MeOH (20 mL) was placed in a pressure reactor and pressurized with carbon monoxide (45 atm).[22] The mixture was heated to 80 °C with stirring for 18 h, then cooled, filtered through a short-pad of celite (eluting with ethyl acetate), and concentrated in *vacuo*. The residue was diluted with ethyl acetate (20 mL),

and then washed with water (15 mL). The organic layer was dried over anhydrous Na_2SO_4 and concentrated in *vacuo*. The residue was purified by aluminum oxide chromatography (eluting with petroleum ether/ethyl acetate = 3:1) to afford **3** as a white solid (421 mg, 87% yield): mp 78.2 – 80.2 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.07 (s, 1H), 8.46 (d, *J* = 5.7 Hz, 1H), 7.52 (dd, *J* = 5.7, 0.7 Hz, 1H), 7.15 (s, 1H), 4.07 (s, 3H), 4.02 (s, 3H), 3.97 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.5, 155.3, 148.5, 147.9, 143.2, 134.1, 124.2, 121.2, 119.3, 107.1, 62.0, 56.0, 52.7; IR (neat) ν = 2948, 1729, 1616, 1472, 1426, 1336, 1303, 1249, 1212, 1045, 1014, 858, 757, 637 cm^{-1}; HRMS (ESI) $[M + H]^+$ calculated for $C_{13}H_{14}NO_4$: 248.0917, found: 248.0913.

Methyl 6,7-dimethoxy-1-(4-methoxyphenyl)isoquinoline-8-carboxylate (26). An oven-dried 10 mL vial equipped with a magnetic stir bar was taken into the glove box. To the vial was added $Ru(bpy)_3Cl_2$•$6H_2O$ (9.2 mg, 0.0123 mmol), 4-methoxybenzenediazonium tetrafluoroborate **4** (431 mg, 1.94 mmol) and DMSO (2.45 mL). A solution of **3** (120 mg, 0.49 mmol) and trifluoroacetic acid (73 μL, 0.98 mmol) in DMSO (2.45 mL) was added into the reaction vial. The vial was sealed with a septum before removed from the glove box and placed approximately 2 cm from a 40 W compact fluorescent light bulb. The reaction mixture was stirred at room temperature for 48 h. Then the solution was diluted with CH_2Cl_2 (8 mL) and washed with saturated aqueous sodium bicarbonate (5 mL). The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (3×6 mL). The combined organic layers were washed with water (3×10 mL), dried over anhydrous Na_2SO_4, filtered and concentrated in *vacuo*. The residue was purified by aluminum oxide chromatography (eluting with petroleum ether/ethyl acetate = 19:1 to 9:1) to afford **26** as a yellow solid (81 mg, 47%, 62% b.r.s.m.), together with the recovered starting material **3** (28 mg). Compound **26**: mp 154.7 – 156.7 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.49 (d, *J* = 5.2 Hz, 1H), 7.50

(d, J = 5.2 Hz, 1H), 7.43 (d, J = 8.1 Hz, 2H), 7.20 (s, 1H), 6.96 (d, J = 8.1 Hz, 2H), 4.04 (s, 3H), 3.91 (s, 3H), 3.86 (s, 3H), 3.26 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.6, 159.8, 158.5, 155.1, 148.5, 141.9, 136.3, 133.3, 130.9, 125.9, 119.3, 118.6, 113.2, 107.4, 62.1, 56.0, 55.4, 52.0; IR (neat) ν = 2945, 1733, 1608, 1469, 1412, 1273, 1249, 1178, 1125, 1046, 1017, 837, 777 cm^{-1}; HRMS (ESI) $[M + H]^+$ calculated for $C_{20}H_{20}NO_5$: 354.1336, found: 354.1332.

Menisporphine (1). Compound **26** (22.8 mg, 0.065 mmol) was added to a solution of KOH (5 N) in 2.2 mL of EtOH/H_2O (1:10). The vial was capped and heated in the microwave reactor at 100 ^oC for 2 h, and then the alkaline solution was cooled to room temperature, neutralized to pH 7 with 1 N HCl, and extracted with *n*-BuOH (4×10 mL). The organic layers were dried over Na_2SO_4, filtered and concentrated in *vacuo* to afford the crude acid **27**, which was dissolved in 4 mL of TFAA in a sealed tube. The tube was capped then stirred at 80 ^oC for 13 h. The reaction solution was cooled to room temperature, added dropwise to ice-cold water (15 mL), neutralized to pH 7 with saturated aqueous $NaHCO_3$ and extracted with CH_2Cl_2 (3×20 mL). The organic layers were dried over Na_2SO_4, filtered and concentrated in *vacuo*. The residue was purified by aluminum oxide chromatography (eluting with petroleum ether/ethyl acetate = 9:1) to afford menisporphine **1** as a yellow solid (11.8 mg, 57% over 2 steps): mp 205.3 – 206.8 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.79 (d, J = 8.8 Hz, 1H), 8.66 (d, J = 5.5 Hz, 1H), 7.86 (d, J = 2.8 Hz, 1H), 7.56 (d, J = 5.5 Hz, 1H), 7.40 (s, 1H), 7.33 (dd, J = 8.8, 2.8 Hz, 1H), 4.15 (s, 3H), 4.08 (s, 3H), 3.98 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 182.6, 161.3, 156.4, 155.5, 147.3, 143.6, 134.8, 133.3, 129.7, 126.9, 122.0, 120.5, 119.0, 118.4, 111.5, 108.9, 61.5, 56.3, 55.7; IR (neat) ν = 2923, 2851, 2358, 1656, 1603, 1472, 1413, 1349, 1279, 1242, 1139, 1014, 839, 805, 627 cm^{-1}; HRMS (ESI) $[M + H]^+$ calculated for $C_{19}H_{16}NO_4$: 322.1074, found: 322.1071.

Daurioxoisoporphine C (2). To a solution of **1** (8.4 mg, 0.026 mmol) in CH_2Cl_2 (1 mL) was added methylamine (27.0~32.0% in alcohol, 1 mL). The resulting mixture was stirred at 100 ^oC in a sealed tube for 8 h, before cooled to room temperature.[23] Then the reaction mixture was diluted with water (3 mL), and extracted with CH_2Cl_2 (3×5 mL). The organic layers were dried over Na_2SO_4 and concentrated in *vacuo*. The residue was purified by aluminum oxide chromatography (eluting with petroleum ether/ethyl acetate = 9:1) to afford daurioxoisoporphine C **2** as a yellow solid (6.9 mg, 82%): mp 221.5 – 223.5 ºC; ^1H NMR (400 MHz, $CDCl_3$) δ 12.83 (br s, 1H), 8.96 (d, J = 8.8 Hz, 1H), 8.62 (d, J = 5.2 Hz, 1H), 8.02 (d, J = 2.8 Hz, 1H), 7.45 (d, J = 5.2 Hz, 1H), 7.38 (dd, J = 8.8, 2.8 Hz, 1H), 7.06 (s, 1H), 4.01 (s, 3H), 3.99 (s, 3H), 3.57 (d, J = 5.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 181.5, 160.5, 153.2, 151.6, 142.3, 141.8, 134.4, 129.7, 126.5, 121.2, 118.9, 118.6, 110.5, 106.9, 105.9, 55.6, 34.0; IR (neat) ν = 2921, 2851, 1730, 1574, 1532, 1496, 1355, 1279, 1204, 1141, 845, 810, 742 cm^{-1}; HRMS (ESI) $[M + H]^+$ calculated for $C_{19}H_{17}N_2O_3$: 321.1234, found: 321.1233.

ASSOCIATED CONTENT

Supporting Information

Comparisons of natural and synthetic menisporphine and daurioxoisoporphine C, copies of NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

AUTHOR INFORMATION

Corresponding Author

*E-mail: xglei@pku.edu.cn

Notes

The authors declare no competing financial interest.

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