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Synthesis of 1-Azaanthraquinone: Sequential C–N Bond Formation/Lewis Acid Catalyzed Intramolecular Cyclization Strategy

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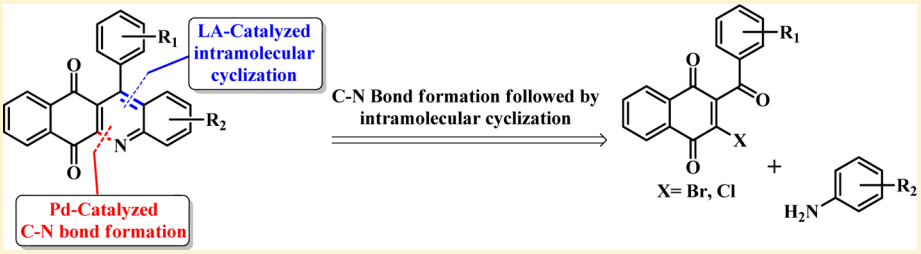
Supporting Information



ABSTRACT: A synthetic strategy has been developed for the synthesis of 1-azaanthraquinones. This synthetic protocol consists of sequential Pd-catalyzed carbon–nitrogen bond formation followed by Lewis acid catalyzed intramolecular cyclization. The Pd-catalyzed aminated intermediate was isolated and characterized. This sequential reactions strategy provides a wide range of 1-azaanthraquinones with good yields.

Anthraquinones are important class of polyaromatic compounds that have been used as critical component for many dyes, drugs, and organic materials.[1] Its derivative azaanthraquinones are found in a considerable number of natural product antibiotics and drug candidates.[2] Azaanthraquinone alkaloids are present in Annonaceous plants, and an ethanolic extract of the roots of *G. griffithii* was found to be significantly cytotoxic against a number of human cancer cell lines.[3] Scorazanone was isolated from the roots of *Goniothalamus scortechinii* and identified as 2,3-dimethoxy-4-hydroxybenzo[*g*]quinoline-9,10-dione.[4] Pixantrone is an experimental antineoplastic drug with fewer toxic effects on cardiac tissue and is now in phase III clinical trials for the treatment of aggressive non-Hodgkin's lymphoma.[5] Pyridoacridine alkaloids[6] such as cleistopholine, amphimedine, meridine, and ascidiademin are a similar type of azaanthraquinone and also possess prominent cytotoxic properties (Figure 1). On the other hand, theoretical investigations of azaanthraquinone analogues for intercalation reveals that they would be very effective intercalants and potential antitumor agents of considerable interest.[7] Therefore, there is significant interest in the synthesis of this privileged structural unit.

Several azaanthraquinones have been described in the literature,[8] and their synthetic routes have usually involved the classical Friedel–Crafts approach,[8g] introduction of the 9,10-carbonyl functions by oxidation of the corresponding hydrocarbon,[8h] cycloaddition using azadienes and azadienophiles,[9] intramolecular Michael-type addition of azadienes to 1,4-naphthoquinones,[10] 6-*exo*-*trig* radical cyclization of imine radical,[11] lithiation of 2-(2-chloro-4-pyridyl)-4,4-dimethyl-4,5-dihydro-oxazole and subsequent condensation with aromatic aldehydes,[12] and reaction of 2-acylated 3-phenoxymethyl-l,4-naphthoquinones with aqueous ammonium hydroxide.[13] Although there are several methods for the synthesis of azaanthraquinones, a few methods are reported for the synthesis of 1-azaanthraquinones.[2e] Radical couplings using 2-amino-1,4-naphthoquinones[14] and chlorocyclization of *N*-propargylaminoquinone are notable examples for the synthesis of 1-azaanthraquinones.[15] Recently, Wang et al. reported a Pd-catalyzed cascade method for the synthesis of 1-azaanthraquinones.[16] However; in all cases, limited substrate scope and side product formations are the limitations of those reported methods. Therefore, development of methods for the synthesis of 1-azaanthraquinones are important and highly desirable.

Recent reports from our laboratories have described the design of reactive substrates for metal-catalyzed carbon–carbon bond formation followed by condensation/cyclization of reactive intermediates. This strategy has been demonstrated for a variety of processes such as the synthesis of pyrimidines,[17a] polyaromatic hydrocarbons,[17b] phenanthridines, and fused quinolines.[17c] In the context of heterocycle synthesis, these synthetic strategies provide valuable heterocycles from acyclic precursors. In continuation of our research, we report here a synthetic methodology for the synthesis of 1-azaanthraquinones via a sequential palladium-catalyzed aryl

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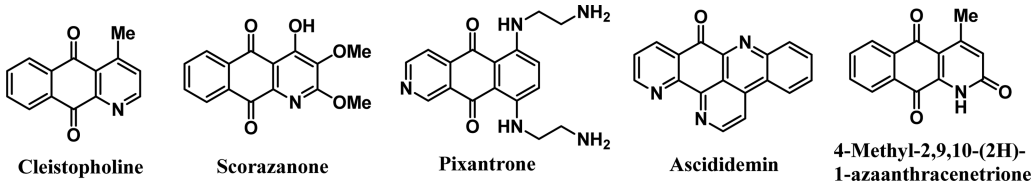


Figure 1. Representative bioactive azaanthraquinone derivatives.

Scheme 1. Synthesis of 1-Azaanthraquinones from 2-Benzoyl-3-halonaphthalene-1,4-dione and Aniline

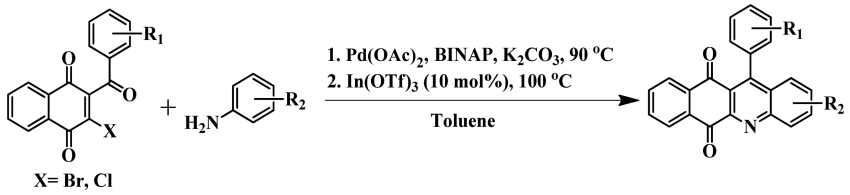
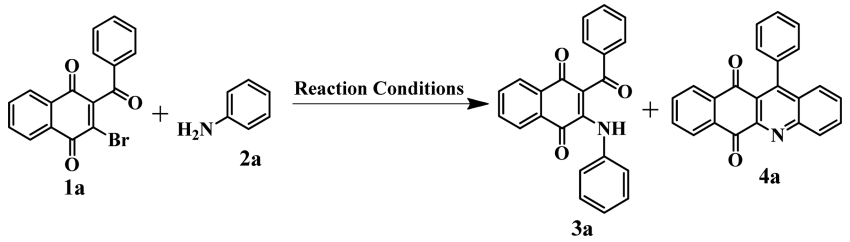


Table 1. Optimization Studies for the Synthesis of Azaanthraquinone[a]



entry	reaction conditions	yield[f] of **3a**/**4a** (%)
1	$Pd(OAc)_2$ (2 mol %), BINAP (4 mol %), Cs_2CO_3, toluene	53/trace
2	$Pd(OAc)_2$ (2 mol %), Ph_3P (8 mol %), Cs_2CO_3, toluene	47/trace
3	$Pd(OAc)_2$ (2 mol %), $^tBu_3P$ (8 mol %), Cs_2CO_3, toluene	43/trace
4	$Pd(OAc)_2$ (2 mol %), Cy_3P (8 mol %), Cs_2CO_3, toluene	49/trace
5	$Pd_2(dba)_3$ (2 mol %), BINAP (4 mol %), Cs_2CO_3, toluene	59/trace
6	$Pd(PPh_3)_4$ (2 mol %), Cs_2CO_3, toluene	50/trace
7	$Pd(OAc)_2$ (5 mol %), BINAP(10 mol %), Na_2CO_3, toluene	89/trace
8	$Pd(OAc)_2$ (5 mol %), BINAP (10 mol %), K_2CO_3, toluene	91/trace
9	$Pd(OAc)_2$ (5 mol %), BINAP (10 mol %), K_3PO_4, toluene	87/trace
10	K_2CO_3, DMF	39/trace
11[b]	$Pd(OAc)_2$ (5 mol %), BINAP (10 mol %), $In(OTf)_3$, K_2CO_3, toluene	63/trace
12[c]	$Pd(OAc)_2$ (5 mol %), BINAP (10 mol %), K_2CO_3, toluene; workup; $In(OTf)_3$, toluene	−/71
13[c,e]	$Pd(OAc)_2$ (5 mol %), BINAP (10 mol %), K_2CO_3, toluene; workup; I_2, toluene	−/35
14[c,e]	$Pd(OAc)_2$ (5 mol %), BINAP (10 mol %), K_2CO_3, toluene; workup; $AlCl_3$, toluene	−/47
15[c,d]	$Pd(OAc)_2$ (5 mol %), BINAP (10 mol %), K_2CO_3, toluene; workup; $In(OTf)_3$, DCM	−/39
16[c,e]	$Pd(OAc)_2$ (5 mol %), BINAP (10 mol %), K_2CO_3, toluene; workup; $In(OTf)_3$, xylene	−/70
17[c,e]	$Pd(OAc)_2$ (5 mol %), BINAP (10 mol %), K_2CO_3, toluene; workup; $Sc(OTf)_3$, toluene	−/50
18[c,e]	$Pd(OAc)_2$ (5 mol %), BINAP (10 mol %), K_2CO_3, toluene; workup; $Cu(OTf)_2$, toluene	−/30
19[c,e]	$Pd(OAc)_2$ (5 mol %), BINAP (10 mol %), K_2CO_3, toluene; workup; Ag(OTf), toluene	−/25
20[c,e]	$Pd(OAc)_2$ (5 mol %), BINAP (10 mol %), K_2CO_3, toluene; workup; BF_3OEt_2, toluene	−/70
21[c,e]	$Pd(OAc)_2$ (5 mol %), BINAP (10 mol %), K_2CO_3, toluene; workup; TsOH, toluene	−/65
22[c,e]	$Pd(OAc)_2$ (5 mol %), BINAP (10 mol %), K_2CO_3, toluene; workup; TFA, toluene	−/trace

[a]Reaction conditions: **1a** (1.0 mmol), aniline **2a** (1.2 mmol), catalyst, ligand, base (2 mmol), in solvent(3 mL), at 90 °C for 12 h. [b]$In(OTf)_3$ (10 mol %). [c]Workup followed by $In(OTf)_3$ (10 mol %), in representative solvent (3 mL) at 100 °C for 36 h. [d]40 °C for 48 h;trace: less than 10% yield. [e]Lewis acid/Bronsted acid (10 mol %). [f]Isolated yield.

aminations[18] of 2-benzoyl-3-halonaphthalene-1,4-diones followed by Lewis acid catalyzed intramolecular cyclization (Scheme 1). This methodology allows direct access to 1-azaanthraquinones.

Our initial attempt was cascade C−N and C−C bond formation reactions between 2-benzoyl-3-bromonaphthalene-1,4-diones (**1a**) and aniline (**2a**) utilizing catalytic conditions similar to the method used for the synthesis of pyrimidines from *β*-halo-*α*,*β*-unsaturated aldehydes [2 mol % of $Pd(OAc)_2$ and 4 mol % of BINAP, Cs_2CO_3, toluene, 90 °C][17a] provided the desired 1-azaanthraquinone **4a**, albeit in only <10% yield (Table 1, entry 1). The major product isolated was 2-benzoyl-3-(phenylamino)naphthalene-1,4-dione (**3a**) in 53% yield, resulting from the initial coupling reaction of aniline with halide group of the 2-benzoyl-3-bromonaphthalene-1,4-diones. Changing reaction conditions including ligand, solvent, and

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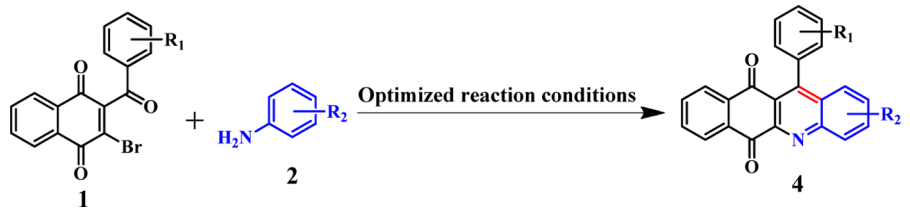
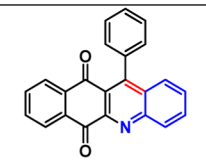
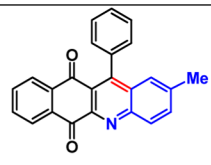
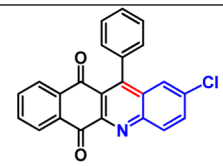
Table 2. Synthesis of 1-Azaanthraquinones[a]



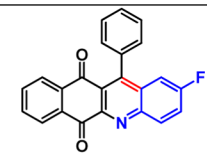

4a (71%)



4b (77%)



4c (70%)



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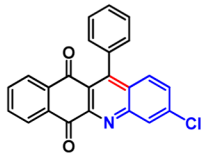
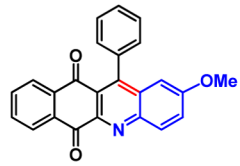
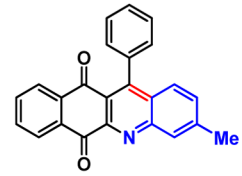


4e (46%)



4f (79%)



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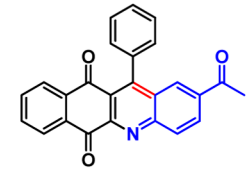
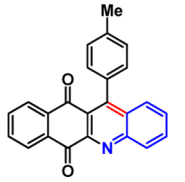
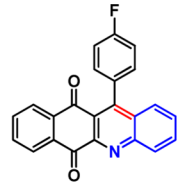


4h (52%)



4i (69%)



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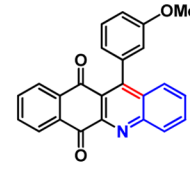

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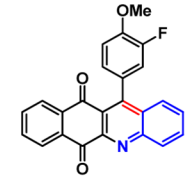

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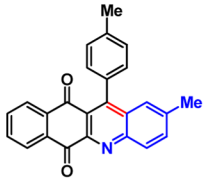
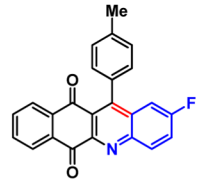


4m (71%)



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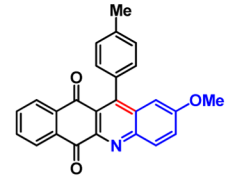

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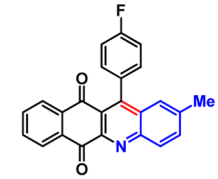
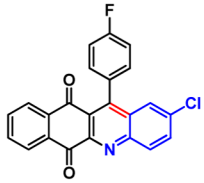
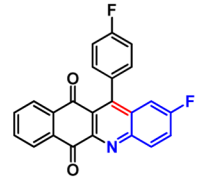


4p (77%)



4q (62%)



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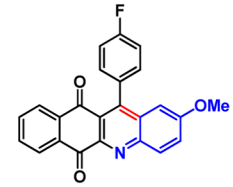
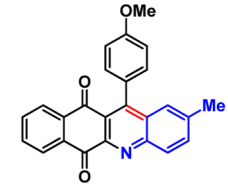


4s (75%)



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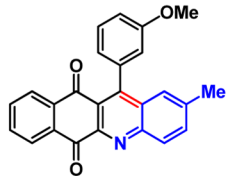
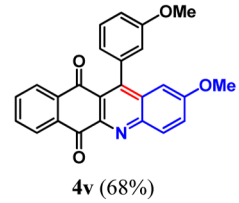
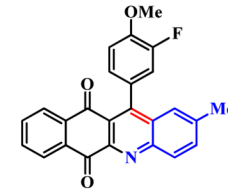


4u (67%)



4v (68%)



4w (63%)

[a]Reaction conditions: **1** (1.0 mmol), aniline **2** (1.2 mmol), $Pd(OAc)_2$ (5 mol %), BINAP (10 mol %), K_2CO_3 (2 mmol),toluene (3 mL) at 90 °C for 12 h; workup followed by $In(OTf)_3$ (10 mol %), toluene at 100 °C for 36 h.

base did not improve the yield of **4a**. However, the yield of initial coupled product **3a** was improved by increasing the catalyst and ligand loading (Table 1, entries 7 and 8). Other bases like Na_2CO_3, K_2CO_3, or K_3PO_4 gave results more or less similar to those of Cs_2CO_3. As a control experiment, the reaction was performed in the absence of Pd catalyst, and no desired product **4a** was observed. However, the product **3a** was obtained in 39% yield, which might be the addition/elimination substitution reaction (Table 1, entry 10). A combination of Pd catalyst with Lewis acid $In(OTf)_3$ (10 mol %) was used in a single reaction vessel for the synthesis of **4a**; however, no significant improvement was observed (Table 1, entry 11).

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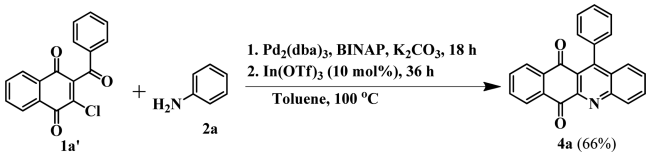
Finally, the intermediate **3a** was separated from the reaction mixture by a simple workup followed by independent treatment with Lewis acid for the synthesis of **4a** (Table 1, entry 12). In this regard, a variety of Lewis acids including various organic solvents were also tested for the final intramolecular cyclization of **3a** (Table 1, entries 13−20). In addition to that, few Bronsted acids were also tested for the cyclization of intermediate **3a** (Table 1, entries 21 and 22). Among them, the Lewis acid catalysts $In(OTf)_3$ and $BF_3{\cdot}OEt_2$ in toluene were found to be efficient for this reaction. However, the catalyst $In(OTf)_3$ was exclusively used for the generalization of our synthetic protocol due to its mild nature.

The optimized sequential reaction strategy was applied for the synthesis of various substituted 1-azaanthraquinones, and the results are summarized in Table 2. This initial C−N bond formation followed by intramolecular cyclization took place smoothly, affording good yields of our desired azaanthraquinones. To find the substrate scope leading to azaanthraquinones, a variety of substituted anilines were sequentially coupled with 2-benzoyl-3-bromonaphthalene-1,4-diones (**1a**) followed by cyclization and afforded the corresponding products **4** in good yields in spite of the electronic nature of aniline (**4a−h**, Table 2). Interestingly, when 3-chloroaniline and 3-methylaniline were treated with **1a** under the optimized reaction conditions, the products **4e** and **4g** were obtained regioselectivity. This regioselective cyclization could be due to steric reasons. Next, a variety of benzoyl-substituted 2-bromonaphthalene-1,4-diones were also examined as substrates for our sequential reaction strategy and gave 1-azaanthraquinones in good yields. The reaction conditions are mild and notably compatible with alkyl, methoxy, chloro, fluoro, and acetyl groups on the aryl ring (**4e−j**, Table 2). In addition, 4-aminobenzonitrile was treated with **1a** under the optimized reaction conditions for the synthesis of nitrile-substituted 1-azaanthraquinone; however, the reaction did not take place. The requisite 2-benzoyl-3-bromonaphthalene-1,4-diones were efficiently synthesized using silver-catalyzed decarboxylative benzoylation of 2-bromonaphthalene-1,4-dione.[19]

To demonstrate the versatility of our synthetic strategy, 2-benzoyl-3-chloronaphthalene-1,4-dione **1a′** was also used as substrate for our sequential C−N bond formation followed by intramolecular cyclization reactions under the optimized reaction conditions (Scheme 2). The desired product **4a** was obtained in 66% yield; however, it took more reaction time in comparison to the 2-benzoyl-3-bromonaphthalene-1,4-dione **1a**.

Scheme 2. Synthesis of Azaanthraquinones 4a from 2-Benzoyl-3-chloronaphthalene-1,4-dione 1a′ and Aniline



A plausible reaction mechanism for the synthesis of 1-azaanthraquinone is proposed in Figure 2. Regarding the mechanism, it is presumed that the reaction proceeds via the generation of Pd(0) species in situ from $Pd(OAc)_2$ in the presence of ligand and base, which catalyzes the coupling of halide with amine functionalities. This cross-coupling reaction is probably facilitated by the intramolecular coordination of the neighboring carbonyl oxygen to the palladium to form an intermediate **I**[17] during the oxidative addition step (Figure 2). The intermediate **I** undergoes anion exchange followed by reductive elimination to form intermediate **3** and regenerates Pd(0) species. Finally the intermediate **3** undergoes intramolecular cyclization in the presence of Lewis acid as shown in Figure 2. The intermediate **3** was isolated and characterized by ^1H and ^{13}C NMR and HRMS analysis. In an independent experiment, the intermediate **3a** was treated with Lewis acid at 100 °C for overnight. The desired 1-azaanthraquinone **4a** was obtained in 88% yield (Scheme 3).

CONCLUSION

In conclusion, we have developed a sequential reaction strategy for the synthesis of 1-azaanthraquinones. This synthetic protocol consists of sequential Pd-catalyzed carbon−nitrogen bond formation followed by Lewis acid catalyzed intramolecular cyclization. The Pd-catalyzed aminated intermediate was isolated and characterized by NMR and HRMS analysis. This reactions strategy provides a wide range of 1-azaanthraquinones with good yields. Additionally, this synthetic strategy will definitely help in academic as well as drug discovery program in near future.

EXPERIMENTAL SECTION

General Information. All reactions involving oxygen- or moisture-sensitive compounds were carried out under argon atmosphere using oven-dried or flame-dried glassware. Reactions were monitored by thin-layer chromatography (TLC) using aluminum-backed silica gel plates (0.2 mm thickness); the chromatograms were visualized first with ultraviolet light (254 nm) and then by immersion in solutions of *p*-anisaldehyde followed by heating. Flash column chromatography was performed with silica gel 60 (100−200 mesh). HRMS data were recorded by electron spray ionization with a Q-TOF mass analyzer.

General Procedure for the Synthesis of 2-Benzoyl-3-halonaphthalene-1,4-diones 1.[19] A reaction vessel was charged with $AgNO_3$ (3.4 mg, 10 mol %), 2-halo-1,4-naphthoquinone (2 mmol, 1.0 equiv), and $K_2S_2O_8$ (540 mg, 4.2 mmol, 2.0 equiv). The reaction vessel was evacuated and backfilled with argon (three times). Arylglyoxylic acid (3 mmol, 1.5 equiv) in CH_3CN/H_2O (1:1) (12 mL) was added via syringe. The whole reaction mixture was stirred at 50 °C under argon atmosphere for 24 h at room temperature. Upon completion of the reaction, the mixture was diluted with EtOAc and filtered through a pad of Celite, and the filtrate was then removed in vacuo. The residue was purified with chromatography column on silica gel using EtOAc/hexanes as eluent.

2-Benzoyl-3-bromonaphthalene-1,4-dione, ***1a.*** Flash chromatography on silica gel (20% ethyl acetate/hexanes) gave **1a** (0.414 g; yield: 61%) as a yellow solid: mp 130−131 °C; ^1H NMR (500 MHz, $CDCl_3$): δ 8.20−8.27 (m, 1H), 8.07−8.13 (m, 1H), 7.95 (d, J = 1.1 Hz, 1H), 7.93 (d, J = 1.3 Hz, 1H), 7.83 (d, J = 3.3 Hz, 1H), 7.82 (d, J = 3.3 Hz, 1H), 7.66 (t, J = 7.4 Hz, 1H), 7.52 (t, J = 7.8 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 190.3, 180.7, 177.2, 148.1, 136.1, 134.9, 134.8, 134.6, 134.1, 131.2, 130.8, 129.4 × 2, 129.2 × 2, 127.9, 127.2; IR ($CHCl_3$) 1682, 1655, 1595, 1319, 1272, 1221, 1151, 772 cm^{-1}; HRMS (ESI-TOF) calcd for $C_{17}H_{10}BrO_3$ $[M + H]^+$ 340.9813, found 340.9815.

2-Benzoyl-3-chloronaphthalene-1,4-dione, ***1a′.***[19] Flash chromatography on silica gel (20% ethyl acetate/hexanes) gave **1a′** (0.385 g; yield: 65%) as a yellow solid: mp 147−150 °C; ^1H NMR (500 MHz, $CDCl_3$) δ 8.21−8.26 (s, 1H), 8.08−8.14 (s, 1H), 7.90−7.95 (m, 2H), 7.81−7.86 (m, 2H), 7.63−7.68 (m, 1H), 7.47−7.55 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 189.5, 181.2, 177.3, 144.1, 141.5, 134.9 × 2, 134.6, 134.5, 131.2, 131.1, 129.3 × 2, 129.1 × 2, 127.6, 127.1; IR ($CHCl_3$) 1683, 1656, 1593, 1449, 1321, 1276, 1226, 1156, 772 cm^{-1}; HRMS (ESI-TOF) calcd for $C_{17}H_{10}ClO_3$ $[M + H]^+$ 297.0318, found 297.0328.

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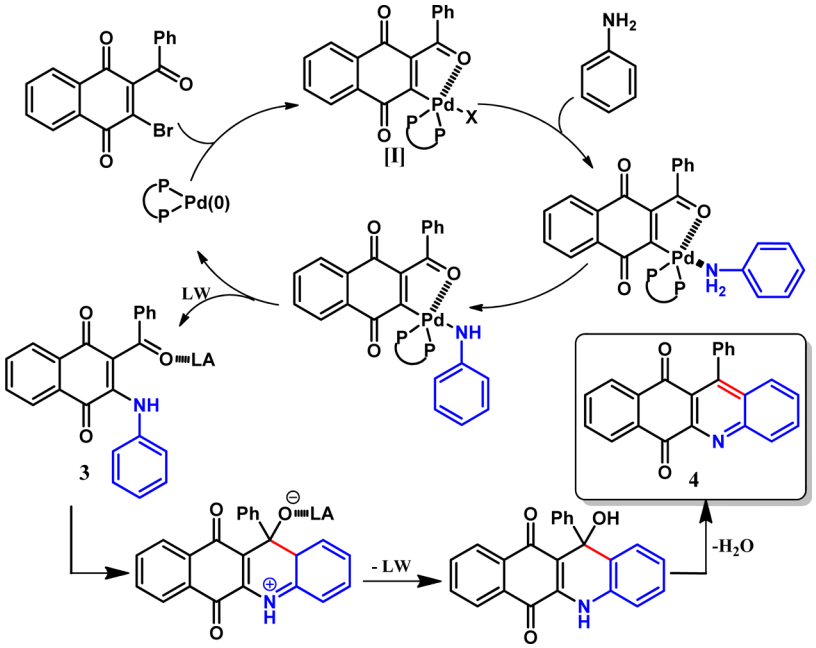
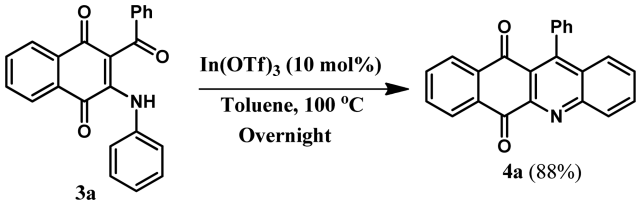


Figure 2. Proposed mechanism for the synthesis of 1-azaanthraquinones.

Scheme 3. Synthesis of 4a from 2-Benzoyl-3-(phenylamino)naphthalene-1,4-dione 3a



2-Bromo-3-(4-methylbenzoyl)naphthalene-1,4-dione, ***1b.*** Flash chromatography on silica gel (20% ethyl acetate/hexanes) gave **1b** (0.418 g; yield: 59%) as a yellow solid: mp 197−199 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.23 (dd, J_1 = 3.4 Hz, J_2 = 5.5 Hz, 1H), 8.10 (dd, J_1 = 3.3 Hz, J_2 = 5.7 Hz, 1H), 7.80−7.85 (m, 4H), 7.30 (d, J = 8.0 Hz, 2H), 2.43 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 189.9, 180.7, 177.2, 148.1, 146.1, 135.9, 134.7, 134.5, 131.5, 131.1, 130.7, 129.8, 129.5, 127.8, 127.2, 21.9; IR ($CHCl_3$) 1681, 1655, 1603, 1306, 1273, 1230, 1180, 1150, 771 cm^{-1}; HRMS (ESI-TOF) calcd for $C_{18}H_{12}BrO_3$ $[M + H]^+$ 354.9907, found 354.9905.

2-Bromo-3-(4-fluorobenzoyl)naphthalene-1,4-dione, ***1c.*** Flash chromatography on silica gel (20% ethyl acetate/hexanes) gave **1c** (0.415 g; yield: 58%) as a yellow solid: mp 189−192 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.23 (dd, J_1 = 3.3 Hz, J_2 = 5.7 Hz, 1H), 8.10 (dd, J_1 = 3.3 Hz, J_2 = 5.7 Hz, 1H), 7.97 (dd, J_1 = 5.3 Hz, J_2 = 8.9 Hz, 2H), 7.82 (dd, J_1 = 3.3 Hz, J_2 = 5.7 Hz, 2H), 7.16−7.22 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 188.7, 180.8, 177.1, 166.7 (d, J = 258.1 Hz), 147.6, 136.2, 134.8, 134.7, 132.2 (d, J = 9.7 Hz), 127.8, 127.2, 131.1, 130.7, 130.5 (d, J = 2.7 Hz), 116.5 (d, J = 22.4 Hz); IR ($CHCl_3$) 1680, 1655, 1595, 1310, 1273, 1233, 1149, 771 cm^{-1}; HRMS (ESI-TOF) calcd for $C_{17}H_9BrFO_3$ $[M + H]^+$ 358.9719, found 358.9723.

2-Bromo-3-(3-methoxybenzoyl)naphthalene-1,4-dione, ***1d.*** Flash chromatography on silica gel (15% ethyl acetate/hexanes) gave **1d** (0.222 g; yield: 60%) as a light brown solid: mp 130−133 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.19−8.31 (m, 1H), 8.11 (dd, J_1 = 3.1 Hz, J_2 = 5.9 Hz, 1H), 7.78−7.89 (m, 2H), 7.33−7.58 (m, 3H), 7.14−7.23 (m, 1H), 3.87 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 190.2, 180.8, 177.2, 160.2, 147.9, 136.1, 135.3, 134.8, 134.6, 131.1, 130.8, 130.2, 127.9, 127.2, 122.6, 121.6, 112.6, 55.5; IR ($CHCl_3$) 2938, 1680, 1656, 1594, 1273, 1142 cm^{-1}; HRMS (ESI-TOF) calcd for $C_{18}H_{12}BrO_4$ $[M + H]^+$ 370.9919, found 370.9943.

2-Bromo-3-(3-fluoro-4-methoxybenzoyl)naphthalene-1,4-dione, ***1e.*** Flash chromatography on silica gel (15% ethyl acetate/hexanes) gave **1e** (0.419 g; yield: 54%) as light brown solid: mp 168−170 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.24 (dd, J_1 = 3.3 Hz, J_2 = 5.7 Hz, 1H), 8.11 (dd, J_1 = 3.3 Hz, J_2 = 5.7 Hz, 1H), 7.84 (dd, J_1 = 3.3 Hz, J_2 = 5.7 Hz, 2H), 7.79−7.88 (m, 2H), 7.03 (t, J = 8.3 Hz, 1H), 3.91(s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 188.1, 180.8, 177.2, 153.4 (d, J = 19.7 Hz), 152.3 (d, J = 258.3 Hz), 147.6, 136.3, 134.8, 134.7, 131.1, 130.8, 127.9, 127.4 (d, J = 3.1 Hz), 127.3 (d, J = 5.5 Hz), 127.2, 116.4 (d, J = 19.2 Hz), 112.8, 56.4; IR ($CHCl_3$) 2924, 1680, 1608, 1518, 1437, 1273, 1118, 771 cm^{-1}; HRMS (ESI-TOF) calcd for $C_{18}H_{11}BrFO_3$ $[M + H]^+$ 388.9825, found 388.9846.

2-Bromo-3-(4-methoxybenzoyl)naphthalene-1,4-dione, ***1f.*** Flash chromatography on silica gel (20% ethyl acetate/hexanes) gave **1f** (0.450 g; yield: 61%) as a yellow solid: mp 183−184 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.22 (dd, J_1 = 3.4 Hz, J_2 = 5.7 Hz, 1H), 8.09 (dd, J_1 = 3.2 Hz, J_2 = 5.8 Hz, 1H), 7.90 (d, J = 8.9 Hz, 2H), 7.81 (dd, J_1 = 3.3 Hz, J_2 = 5.7 Hz, 2H), 6.97 (d, J = 8.9 Hz, 2H), 3.88 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 188.7, 180.8, 177.3, 164.8, 148.1, 135.8, 134.7, 134.5, 131.8, 131.1, 130.7, 127.8, 127.1, 127.11, 114.4, 55.6; IR ($CHCl_3$) 2923, 1677, 1593, 1310, 1266, 1149, 1024 cm^{-1}; HRMS (ESI-TOF) calcd for $C_{18}H_{12}BrO_4$ $[M + H]^+$ 370.9919, found 370.9951.

General Procedure for the Synthesis of 1-Azaanthraquinone. A reaction vessel was charged sequentially with aniline (1.2 mmol), $Pd(OAc)_2$ (0.05 mmol), BINAP (0.1 mmol), K_2CO_3 (2.0 mmol), and anhydrous toluene (distilled over Na; 3 mL) under an argon atmosphere. The reaction mixture was stirred for 5 min at room temperature, and then a solution of 2-benzoyl-3-bromonaphthalene-1,4-dione (1.0 mmol) in anhydrous toluene (3.0 mL) was added. The whole reaction mixture was vigorously stirred at 90 °C (preheated oil-bath) for 12 h and then allowed to cool to room temperature. Water (10 mL) was added to the reaction mixture, and the organic layer was extracted with ethyl acetate (2 × 20 mL). The combined organic phases were washed with brine and dried over anhydrous sodium sulfate. The solvent was removed, and the residue was dissolved in freshly distilled toluene (5 mL) followed by addition of $In(OTf)_3$ (0.01 mmol). The reaction mixture was stirred at 100 °C for 36 h and then allowed to cool to room temperature. A saturated solution of ammonium chloride (15 mL) was added to the reaction mixture, and the organic layer was extracted with ethyl acetate (2 × 20 mL). The combined organic phases were washed with brine and dried over anhydrous sodium sulfate. The solvent was removed, and the residue

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was purified by column chromatography on silica gel using hexane/ethyl acetate as eluent.

2-Benzoyl-3-(phenylamino)naphthalene-1,4-dione, ***3a***.[20] Flash chromatography on silica gel (25% ethyl acetate/hexanes) gave **3a** (0.321 g; yield: 91%) as a brown gummy solid: ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.14 (d, J = 7.7 Hz, 1H), 8.10 (d, J = 7.7 Hz, 1H), 7.91(s, 1H), 7.77 (t, J = 7.6 Hz, 1H), 7.69 (t, J = 7.6 Hz, 1H), 7.54 (d, J = 8.2 Hz, 2H), 7.44 (m, 1H), 7.27 (t, J = 7.7 Hz, 2H), 6.92−7.03 (m, 3H), 6.83 (d, d, J = 7.8 Hz, 2H); ^{13}CNMR (125 MHz, $CDCl_3$) δ 193.6, 182.1, 181.9, 143.6, 137.3, 136.7, 135.3, 132.9, 132.8, 132.6, 129.8, 128.7, 128.6, 128.1, 126.9, 126.5, 126.4, 125.9, 113.3; IR ($CHCl_3$) 3298, 2916, 1673, 1591, 1339, 1288, 1222, 772 cm^{-1}; HRMS (ESI-TOF) calcd for $C_{23}H_{16}NO_3$ [M + H]$^+$ 354.1130, found 354.1150.

12-Phenylbenzo[b]acridine-6,11-dione, ***4a***.[16] Flash chromatography on silica gel (35% ethyl acetate/hexanes) gave **4a** (0.238 g; yield: 71%) as a brown solid: mp 215−217 °C (lit. mp 219−220 °C);[14] ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.45 (d, J = 8.4 Hz, 1H), 8.38 (dd, J_1 = 1.4 Hz, J_2 = 7.6 Hz, 1H), 8.10 (dd, J_1 = 1.7 Hz, J_2 = 7.3 Hz, 1H), 7.79−7.88 (m, 1H), 7.67−7.78 (m, 2H), 7.47−7.56 (m, 5H), 7.19−7.23 (m, 2H); ^{13}CNMR (125 MHz, $CDCl_3$) δ 182.7, 182.1, 152.9, 149.4, 148.4, 137.2, 134.9, 134.8, 134.2, 133.6, 132.7, 131.6, 129.9, 129.6, 128.5, 128.2, 128.1, 127.9, 127.7, 127.6, 124.1; IR ($CHCl_3$) 2923, 2853, 1683, 1330, 1220, 770 cm^{-1}; HRMS (ESI-TOF) calcd for $C_{23}H_{14}NO_2$ [M + H]$^+$ 336.1025, found 336.1026.

2-Methyl-12-phenylbenzo[b]acridine-6,11-dione, ***4b***. Flash chromatography on silica gel (40% ethyl acetate/hexanes) gave **4b** (0.269 g; yield: 77%) as a reddish brown solid: mp 280−282 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.42 (d, J = 7.3 Hz, 1H), 8.39 (d, J = 8.6 Hz, 1H), 8.15 (d, J = 7.1 Hz, 1H), 7.74−7.83 (m, 2H), 7.71 (d, J = 8.2 Hz, 1H), 7.54−7.66 (m, 3H), 7.21−7.34 (m, 3H), 2.44 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 182.7, 181.9, 151.8, 147.9, 147.4, 140.2, 137.2, 135.0, 134.7, 134.5, 134.0, 133.4, 131.1, 129.7, 128.3, 127.8, 127.7, 127.5, 126.7, 123.9, 22.0; IR ($CHCl_3$) 3405, 2922, 1685, 1372, 1305, 1247, 772 cm^{-1}; HRMS (ESI-TOF) calcd for $C_{24}H_{16}NO_2$ [M + H]$^+$ 350.1181, found 350.1182.

2-Chloro-12-phenylbenzo[b]acridine-6,11-dione, ***4c***. Flash chromatography on silica gel (40% ethyl acetate/hexanes) gave **4c** (0.258 g; yield: 70%) as a yellow solid: mp 284−286 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.38−8.49 (m, 2H), 8.15 (dd, J_1 = 1.6 Hz, J_2 = 7.2 Hz, 1H), 7.74−7.85 (m, 3H), 7.56−7.65 (m, 3H), 7.52 (d, J = 2.2 Hz, 1H), 7.22−7.29 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 182.3, 181.6, 151.9, 148.3, 147.6, 136.3, 136.0, 134.8, 134.5, 134.3, 133.6, 133.4, 132.9, 130.5, 128.6, 128.3, 127.7, 127.6, 126.7, 124.5; IR ($CHCl_3$) 3408, 2919, 1686, 1477, 1307, 1243, 772 cm^{-1}; HRMS (ESI-TOF) calcd for $C_{23}H_{13}ClNO_2$ [M + H]$^+$ 370.0635, found 370.0637.

2-Fluoro-12-phenylbenzo[b]acridine-6,11-dione, ***4d***. Flash chromatography on silica gel (40% ethyl acetate/hexanes) gave **4d** (0.237 g; yield: 67%) as a brown solid: mp 285−288 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.52 (dd, J_1 = 5.5 Hz, J_2 = 9.3 Hz, 1H), 8.43 (dd, J_1 = 1.4 Hz, J_2 = 7.5 Hz, 1H), 8.16 (dd, J_1 = 1.0 Hz, J_2 = 7.4 Hz, 1H), 7.74−7.87 (m, 2H), 7.57−7.71 (m, 4H), 7.22−7.31 (m, 2H), 7.17 (dd, J_1 = 2.7 Hz, J_2 = 9.7 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 182.5, 181.7, 162.2 (d, J = 254.1 Hz), 152.2, 152.1, 147.7 (d, J = 2.8 Hz), 146.4, 136.6, 134.8, 134.5, 134.3, 134.2 (d, J = 9.3 Hz), 133.4, 131.2 (d, J = 9.9 Hz), 128.6, 128.3, 127.7, 124.3, 123.3 (d, J = 26.4 Hz), 111.4 (d, J = 23.7 Hz); IR ($CHCl_3$) 3395, 2924, 2855, 1685, 1307, 1221, 772 cm^{-1}; HRMS (ESI-TOF) calcd for $C_{23}H_{13}FNO_2$ [M + H]$^+$ 354.0930, found 354.0932.

3-Chloro-12-phenylbenzo[b]acridine-6,11-dione, ***4e***. Flash chromatography on silica gel (40% ethyl acetate/hexanes) gave **4e** (0.170 g; yield: 46%) as a light brown solid: mp 271−273 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.50 (s, 1H), 8.42 (d, J = 7.4 Hz, 1H), 8.16 (dd, J_1 = 1.6 Hz, J_2 = 7.2 Hz, 1H), 7.71−7.87 (m, 2H), 7.47−7.62 (m, 5H), 7.23−7.30 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): 182.3, 181.6, 152.9, 149.5, 149.1, 139.2, 134.8, 134.2, 134.5, 133.3, 130.5, 130.0, 129.4, 128.4, 128.2, 127.7, 127.6, 127.5, 123.9 (one peak is missing due to overlap); IR ($CHCl_3$) 3407, 2992, 2851, 1688, 1593, 1309, 1263, 722 cm^{-1}; HRMS (ESI-TOF) calcd for $C_{23}H_{13}ClNO_2$ [M + H]$^+$ 370.0635, found 370.0641.

2-Methoxy-12-phenylbenzo[b]acridine-6,11-dione, ***4f***. Flash chromatography on silica gel (40% ethyl acetate/hexanes) gave **4f** (0.288 g; yield: 79%) as a brown solid: mp 226−228 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.36 (d, J = 7.5 Hz, 1H), 8.33 (d, J = 9.3 Hz, 1H), 8.08 (dd, J_1 = 1.1 Hz, J_2 = 7.6 Hz, 1H), 7.57−7.82 (m, 2H), 7.29−7.59 (m, 4H), 7.20 (dd, J_1 = 1.6 Hz, J_2 = 7.8 Hz, 2H), 6.67 (d, J = 2.7 Hz, 1H), 3.63 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 182.9, 181.9, 160.1, 150.4, 146.1, 145.7, 137.4, 134.6, 134.4, 134.0, 133.5, 132.9, 131.5, 128.5, 127.9, 127.6, 127.5, 125.7, 124.2, 105.2, 55.4; IR ($CHCl_3$) 2923, 2851, 1684, 1612, 1491, 1304, 1242 cm^{-1}; HRMS (ESI-TOF) calcd for $C_{24}H_{16}NO_3$ [M + H]$^+$ 366.1130, found 366.1131.

3-Methyl-12-phenylbenzo[b]acridine-6,11-dione, ***4g***. Flash chromatography on silica gel (35% ethyl acetate/hexanes) gave **4g** (0.220 g; yield: 63%) as a brown solid: mp 298−300 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.38−8.44 (m, 1H), 8.27 (s, 1H), 8.12−8.18 (m, 1H), 7.74−7.82 (m, 2H), 7.56−7.62 (m, 3H), 7.38−7.48 (m, 2H), 7.26−7.30 (m, 2H), 2.59 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 182.6, 181.9, 152.5, 149.4, 148.3, 143.8, 137.3, 134.6, 134.5, 134.0, 133.4, 131.9, 130.3, 128.3, 127.9, 127.8, 127.7, 127.6, 127.5, 123.4, 21.9 one peak is missing due to overlap; IR ($CHCl_3$) 2923, 1686, 1594, 1485, 1271, 1247, 721 cm^{-1}; HRMS (ESI-TOF) calcd for $C_{24}H_{16}NO_2$ [M + H]$^+$ 350.1181, found 350.1183.

2-Acetyl-12-phenylbenzo[b]acridine-6,11-dione, ***4h***. Flash chromatography on silica gel (40% ethyl acetate/hexanes) gave **4h** (0.196 g; yield: 52%) as a brown solid: mp 294−297 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.58 (d, J = 8.8 Hz, 1H), 8.09−8.24 (m, 2H), 8.19 (d, J = 7.6 Hz, 1H), 8.16 (s, 1H), 7.79−7.87 (m, 2H), 7.65 (m, 2H), 7.20−7.36 (m, 3H), 2.53 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 196.8, 182.3, 181.7, 154.5, 150.9, 149.8, 136.9, 136.3, 135.0, 134.4, 133.5, 132.1, 130.6, 129.7, 129.3, 128.6, 128.5, 127.9, 127.8, 127.7, 124.5, 113.7, 26.5; IR ($CHCl_3$) 2923, 2847, 1650, 1617, 666 cm^{-1}; HRMS (ESI-TOF) calcd for $C_{25}H_{16}NO_3$ [M + H]$^+$ 378.1130, found 378.1132.

12-(p-Tolyl)benzo[b]acridine-6,11-dione, ***4i***. Flash chromatography on silica gel (40% ethyl acetate/hexanes) gave **4i** (0.241 g; yield: 69%) as a yellow solid: mp 266−268 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.49 (d, J = 8.5 Hz, 1H), 8.43 (dd, J_1 = 1.5 Hz, J_2 = 7.4 Hz, 1H), 8.17 (dd, J_1 = 1.3 Hz, J_2 = 7.5 Hz, 1H), 7.89 (m, 1H), 7.75−7.83 (m. 2H), 7.55−7.64 (m, 2H), 7.40 (d, J = 7.8 Hz, 2H), 7.16 (d, J = 7.8 Hz, 2H), 2.53 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 182.8, 182.1, 153.2, 149.2, 148.3, 137.7, 134.8, 134.7, 134.1, 134.0, 133.5, 132.6, 131.4, 130.0, 129.4, 129.1, 128.2, 127.7, 127.6, 124.1, 21.5; IR ($CHCl_3$) 2921, 2851, 1684, 1488, 1331, 1248, 768 cm^{-1}; HRMS (ESI-TOF) calcd for $C_{24}H_{16}NO_2$ [M + H]$^+$ 350.1181, found 350.1184.

12-(4-Fluorophenyl)benzo[b]acridine-6,11-dione, ***4j***. Flash chromatography on silica gel (40% ethyl acetate/hexanes) gave **4j** (0.258 g; yield: 73%) as a brown solid: mp 265−268 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.50 (d, J = 8.5 Hz, 1H), 8.42 (d, J = 7.4 Hz, 1H), 8.16 (d, J = 7.8 Hz, 1H), 7.86−7.97 (m, 1H), 7.75−7.87 (m, 2H), 7.53−7.68 (m, 2H), 7.22−7.38 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 182.7, 181.8, 162.5 (d, J = 247.6 Hz), 151.8, 149.2, 148.2, 134.7, 134.6, 134.3, 133.4, 132.8, 132.7, 131.5, 129.8, 129.7, 129.6 (d, J = 8.1 Hz), 127.8, 127.7 (d, J = 3.3 Hz), 127.6, 124.1, 115.6 (d, J = 21.6 Hz); IR ($CHCl_3$) 3015, 2921, 2852, 1684, 1591, 1330, 1221, 987, 763 cm^{-1}; HRMS (ESI-TOF) calcd for $C_{23}H_{13}FNO_2$ [M + H]$^+$ 354.0930, found 354.0932.

12-(3-Methoxyphenyl)benzo[b]acridine-6,11-dione, ***4k***. Flash chromatography on silica gel (40% ethyl acetate/hexanes) gave **4k** (0.259 g; yield: 71%) as a brown solid: mp 259−261 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.52 (dd, J_1 = 0.6 Hz, J_2 = 8.5 Hz, 1H), 8.45 (dd, J_1 = 1.4 Hz, J_2 = 7.4 Hz, 1H), 8.18 (dd, J_1 = 1.6 Hz, J_2 = 7.0 Hz, 1H), 7.76−7.95 (m, 3H), 7.57−7.64 (m, 2H), 7.51 (t, J = 7.9 Hz, 1H), 7.11 (dd, J_1 = 2.5 Hz, J_2 = 8.4 Hz, 1H), 6.86 (dd, J_1 = 0.6 Hz, J_2 = 7.4 Hz, 1H), 6.81 (s, 1H), 3.86 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 182.6, 182.1, 159.6, 152.6, 149.3, 148.3, 138.5, 134.8, 134.2, 133.6, 132.8, 134.8, 131.5, 129.8, 129.7, 129.6, 128.3, 127.8, 127.7, 123.9, 120.3, 113.3, 55.3; IR ($CHCl_3$) 2920, 2850, 1684, 1586, 1307, 1250, 1031, 763 cm^{-1}; HRMS (ESI-TOF) calcd for $C_{24}H_{16}NO_3$ [M + H]$^+$ 366.1130, found 366.1132.

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12-(3-Fluoro-4-methoxyphenyl)benzo[b]acridine-6,11-dione, ***4l.*** Flash chromatography on silica gel (45% ethyl acetate/hexanes) gave **4l** (0.257 g; yield: 67%) as a dark brown solid: mp 239−241 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.50 (dd, J_1 = 0.6 Hz, J_2 = 8.5 Hz, 1H), 8.43 (dd, J_1 = 1.8 Hz, J_2 = 6.8 Hz, 1H), 8.17 (d, J = 7.2 Hz, 1H), 7.86−7.97 (m, 1H), 7.75−7.86 (m, 2H), 7.63 (s, 1H), 7.62 (s, 1H), 7.18 (t, J = 8.4 Hz, 1H), 7.04 (dd, J_1 = 2.0 Hz, J_2 = 11.4 Hz, 1H), 6.99 (d, J = 8.2 Hz, 1H), 4.03 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 182.7, 181.9, 152.2 (d, J = 247.6 Hz), 151.2, 149.2, 148.2, 147.5 (d, J = 10.5 Hz), 134.8, 134.6, 134.3, 133.5, 132.7, 131.6, 129.9, 129.8, 129.4 (d, J = 6.9 Hz), 127.9, 127.7, 127.6, 124.1, 123.9 (d, J = 3.4 Hz), 116.3 (d, J = 19.7 Hz), 113.1 (d, J = 1.5 Hz), 56.1; IR ($CHCl_3$) 3399, 2922, 2855, 1683, 1217, 771 cm^{-1}; HRMS (ESI-TOF) calcd for $C_{24}H_{15}FNO_3$ [M + H]$^+$ 384.1036, found 384.1038.

2-Methyl-12-(p-tolyl)benzo[b]acridine-6,11-dione, ***4m.*** Flash chromatography on silica gel (40% ethyl acetate/hexanes) gave **4m** (0.258 g; yield: 71%) as a brown solid: mp 240−242 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.42 (dd, J_1 = 1.3 Hz, J_2 = 7.5 Hz, 1H), 8.38 (d, J = 8.6 Hz, 1H), 8.16 (dd, J_1 = 1.3 Hz, J_2 = 7.5 Hz, 1H), 7.73−7.82 (m, 2H), 7.71 (dd, J_1 = 1.7 Hz, J_2 = 8.6 Hz, 1H), 7.40 (d, J = 7.7 Hz, 2H), 7.33 (s, 1H), 7.16 (d, J = 7.9 Hz, 2H), 2.5 (s, 3H), 2.44 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 182.8, 182.1, 152.2, 147.9, 147.5, 140.1, 137.5, 134.9, 134.7, 134.5, 134.1, 133.9, 133.5, 131.1, 129.9, 129.1, 127.7, 127.5, 126.7, 124.1, 22.0, 21.5; IR ($CHCl_3$) 3395, 2920, 2851, 1685, 1594, 1303, 1220, 772 cm^{-1}; HRMS (ESI-TOF) calcd for $C_{25}H_{18}NO_2$ [M + H]$^+$ 364.1338, found 364.1339.

2-Fluoro-12-(p-tolyl)benzo[b]acridine-6,11-dione, ***4n.*** Flash chromatography on silica gel (40% ethyl acetate/hexanes) gave **4n** (0.257 g; yield: 70%) as a reddish brown solid: mp 227−229 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.52 (dd, J_1 = 5.5 Hz, J_2 = 9.2 Hz, 1H), 8.44 (dd, J_1 = 1.0 Hz, J_2 = 7.5 Hz, 1H), 8.18 (dd, J_1 = 1.3 Hz, J_2 = 7.5 Hz, 1H), 7.73−7.86 (m, 2H), 7.60−7.70 (m, 1H), 7.41 (d, J = 7.7 Hz, 2H), 7.21 (dd, J_1 = 2.8 Hz, J_2 = 9.8 Hz, 1H), 7.15 (d, J = 7.9 Hz, 2H), 2.54 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 182.7, 181.8, 162.2 (d, J = 253.8 Hz), 152.5, 152.4, 147.8 (d, J = 2.8 Hz), 146.5, 138.1, 134.8, 134.7, 134.3, 134.2 (d, J = 9.9 Hz), 133.5, 133.4, 131.5 (d, J = 10.1 Hz), 129.4, 127.7, 127.6, 124.4, 123.3 (d, J = 26.4 Hz), 111.5 (d, J = 23.8 Hz), 21.5; IR ($CHCl_3$) 3399, 2923, 2855, 1683, 1492, 1307, 1223, 772 cm^{-1}; HRMS (ESI-TOF) calcd for $C_{24}H_{15}FNO_2$ [M + H]$^+$ 368.1087, found 368.1085.

2-Methoxy-12-(p-tolyl)benzo[b]acridine-6,11-dione, ***4o.*** Flash chromatography on silica gel (40% ethyl acetate/hexanes) gave **4o** (0.243 g; yield: 64%) as a brown solid: mp 270−272 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.43 (dd, J_1 = 1.2 Hz, J_2 = 7.5 Hz, 1H), 8.40 (d, J = 9.3 Hz, 1H), 8.16 (dd, J_1 = 1.2 Hz, J_2 = 7.5 Hz, 1H), 7.72−7.84 (m, 2H), 7.53 (dd, J_1 = 2.8 Hz, J_2 = 9.3 Hz, 1H), 7.41 (d, J = 7.7 Hz, 2H), 7.16 (d, J = 8.0 Hz, 2H), 6.80 (d, J = 2.8 Hz, 1H), 3.73 (s, 3H), 2.53 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 183.0, 182.0, 160.0, 150.8, 146.1, 145.6, 137.5, 134.6, 134.4, 134.3, 133.9, 133.5, 132.9, 131.6, 129.3, 127.6, 127.5, 127.4, 125.6, 105.3, 55.5, 21.5; IR ($CHCl_3$) 2923, 2852, 1683, 1497, 1304, 1241, 1031, 722 cm^{-1}; HRMS (ESI-TOF) calcd for $C_{25}H_{18}NO_3$[M + H]$^+$ 380.1287, found 380.1286.

12-(4-Fluorophenyl)-2-methylbenzo[b]acridine-6,11-dione, ***4p.*** Flash chromatography on silica gel (40% ethyl acetate/hexanes) gave **4p** (0.283 g; yield: 77%) as a light brown solid: mp 162−164 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.42 (d, J = 6.3 Hz, 1H), 8.38 (d, J = 8.5 Hz, 1H), 8.15 (d, J = 6.5 Hz, 1H), 7.57−7.94 (m, 3H), 7.08−7.44 (m, 5H), 2.46 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 182.8, 181.8, 162.4 (d, J = 247.3 Hz), 150.6, 147.9, 147.4, 140.4, 135.1, 134.6, 134.1, 133.4, 132.9 (d, J = 3.6 Hz), 131.1, 129.7, 129.6, 129.5, 127.4 (d, J = 9.3 Hz), 126.4, 115.6 (d, J = 21.6 Hz), 124.1, 22.0; IR ($CHCl_3$) 3398, 2852, 1648, 1025, 994, 766 cm^{-1}; HRMS (ESI-TOF) calcd for $C_{24}H_{15}FNO_2$ [M + H]$^+$ 368.1087, found 368.1085.

2-Chloro-12-(4-fluorophenyl)benzo[b]acridine-6,11-dione, ***4q.*** Flash chromatography on silica gel (35% ethyl acetate/hexanes) gave **4q** (0.240 g; yield: 62%) as a brown solid: mp 254−256 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.39−8.51 (m, 2H), 8.16 (dd, J_1 = 0.9 Hz, J_2 = 7.3 Hz, 1H), 7.75−7.88 (m, 3H), 7.52 (d, J = 2.2 Hz, 1H), 7.32 (t, J = 8.5 Hz, 2H), 7.22−7.27 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 182.6, 181.6, 162.7 (d, J = 248.2 Hz), 150.9, 148.4, 147.7, 136.3, 134.9, 134.6, 134.5, 133.8, 133.5, 133.1, 132.1 (d, J = 3.5 Hz), 130.6, 129.7 (d, J = 8.1 Hz), 126.5, 124.7, 115.9 (d, J = 21.7 Hz) (two peaks are missing due to overlap) ; IR ($CHCl_3$) 3395, 2920, 1686, 1597, 1304, 1221, 771 cm^{-1}; HRMS (ESI-TOF) calcd for $C_{23}H_{12}FClNO_2$ [M + H]$^+$ 388.0541, found 388.0541.

2-Fluoro-12-(4-fluorophenyl)benzo[b]acridine-6,11-dione, ***4r.*** Flash chromatography on silica gel (35% ethyl acetate/hexanes) gave **4r** (0.223 g; yield: 60%) as a brown solid: mp 290−293 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.46 (dd, J_1 = 5.4 Hz, J_2 = 9.3 Hz, 1H), 8.37 (dd, J_1 = 1.1 Hz, J_2 = 7.4 Hz, 1H), 8.09 (dd, J_1 = 1.0 Hz, J_2 = 6.6 Hz, 1H), 7.77−7.80 (m, 2H), 7.57−7.64 (m, 1H), 7.24 (t, J = 8.6 Hz, 2H), 7.14−7.21 (m, 2H), 7.09 (dd, J_1 = 2.7 Hz, J_2 = 9.7 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 182.6, 181.6, 162.7 (d, J = 248.2 Hz), 162.3 (d, J = 254.3 Hz), 151.1, 151.0, 147.7 (d, J = 3.0 Hz), 146.5, 134.9, 134.5, 134.4, 134.3 (d, J = 9.3 Hz), 133.4, 132.8 (d, J = 9.6 Hz), 132.3 (d, J = 3.7 Hz), 131.2 (d, J = 10.2 Hz), 129.6, 129.5, 127.7, 127.6, 125.6, 124.5, 123.5 (d, J = 26.4 Hz), 115.9 (d, J = 21.8 Hz), 115.6 (d, J = 21.9 Hz), 111.2 (d, J = 23.8 Hz); IR ($CHCl_3$) 3407, 2920, 1684, 1492, 1222, 771 cm^{-1}; HRMS (ESI-TOF) calcd for $C_{23}H_{12}F_2NO_2$ [M + H]$^+$ 372.0836, found 372.0837.

12-(4-Fluorophenyl)-2-methoxybenzo[b]acridine-6,11-dione, ***4s.*** Flash chromatography on silica gel (35% ethyl acetate/hexanes) gave **4s** (0.287 g; yield: 75%) as a brown solid: mp 270−272 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.42 (d, J = 7.3 Hz, 1H), 8.38 (d, J = 9,2 Hz, 1H), 8.15(d, J = 7.4 Hz, 1H), 7.64−7.90 (m, 2H), 7.52 (dd, J_1 = 2.6 Hz, J_2 = 9.2 Hz, 1H), 7.14−7.36 (m, 4H), 6.71 (d, J = 2.4 Hz, 1H), 3.73 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 183.1, 181.8, 262.4 (d, J = 246.9 Hz), 160.3, 149.4, 146.1, 145.7, 134.6, 134.5, 134.2, 133.5, 133.2 (d, J = 3.6 Hz), 133.1, 131.5, 129.5 (d, J = 7.9 Hz), 127.6, 127.5, 125.9, 124.4, 115.8 (d, J = 21.1), 104.9, 55.5; IR ($CHCl_3$) 3399, 2922, 1669, 1613, 1305, 1241, 721 cm^{-1}; HRMS (ESI-TOF) calcd for $C_{24}H_{15}FNO_3$ [M + H]$^+$ 384.1036, found 384.1048.

12-(4-Methoxyphenyl)-2-methylbenzo[b]acridine-6,11-dione, ***4t.*** Flash chromatography on silica gel (40% ethyl acetate/hexanes) gave **4t** (0.269 g; yield: 71%) as a yellow solid: mp 236−238 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.41 (d, J = 7.2 Hz, 1H), 8.38 (d, J = 8.6 Hz, 1H), 8.16 (d, J = 7.5 Hz, 1H), 7.74−7.85 (m 2H), 7.71 (dd, J_1 = 1.6 Hz, J_2 = 8.6 Hz, 1H), 7.36 (s, 1H), 7.20 (d, J = 8.5 Hz, 2H), 7.13 (d, J = 8.3 Hz, 2H), 3.95 (s, 3H), 2.45 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 182.9, 182.1, 159.2, 151.9, 147.9, 147.5, 140.1, 134.9, 134.8, 134.5, 134.5, 133.9, 133.4, 131.1, 130.2, 129.2 × 2, 129.1, 127.5 × 2, 126.7, 113.8 × 2, 55.2, 22.1; IR ($CHCl_3$) 3582, 2916, 1684, 1373, 1304, 1244, 1032, 726 cm^{-1}; HRMS (ESI-TOF) calcd for $C_{25}H_{18}NO_3$ [M + H]$^+$ 380.1287, found 380.1286.

12-(3-Methoxyphenyl)-2-methylbenzo[b]acridine-6,11-dione, ***4u.*** Flash chromatography on silica gel (40% ethyl acetate/hexanes) gave **4u** (0.254 g; yield: 67%) as a yellow solid: mp 265−268 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.43 (dd, J_1 = 1.1 Hz, J_2 = 7.0 Hz, 1H), 8.38 (d, J = 8.6 Hz, 1H), 8.16 (dd, J_1 = 8.2 Hz, J_2 = 7.4 Hz, 1H), 7.65−7.85 (m, 3H), 7.51 (t, J = 7.9 Hz, 1H), 7.33 (s, 1H), 7.11 (dd, J_1 = 2.5 Hz, J_2 = 8.4 Hz, 1H), 6.85 (dd, J_1 = 0.8 Hz, J_2 = 7.5 Hz, 1H), 6.80 (br s, 1H), 3.87 (s, 3H), 2.45 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 182.6, 182.1, 159.5, 151.5, 147.9, 147.5, 140.3, 138.6, 135.2, 134.7, 134.6, 134.1, 133.5, 131.2, 129.7, 129.5, 127.6, 126.7, 123.9, 120.2, 113.6, 113.1, 55.2, 22.1; IR ($CHCl_3$) 3062, 2923, 2853, 1682, 1591, 1306, 1249, 1037 cm^{-1}; HRMS (ESI-TOF) calcd for $C_{25}H_{18}NO_3$ [M + H]$^+$ 380.1287, found 380.1289.

2-Methoxy-12-(3-methoxyphenyl)benzo[b]acridine-6,11-dione, ***4v.*** Flash chromatography on silica gel (40% ethyl acetate/hexanes) gave **4v** (0.268 g; yield: 68%) as a dark brown solid: mp 236−240 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.41 (dd, J_1 = 1.3 Hz, J_2 = 7.5 Hz, 1H), 8.37 (d, J = 9.3 Hz, 1H), 8.15 (dd, J_1 = 1.4 Hz, J_2 = 7.6 Hz, 1H), 7.70−7.82 (m, 2H), 7.44−7.56 (m, 2H), 7.09 (ddd, J_1 = 0.7 Hz, J_2 = 2.5 Hz, J_3 = 8.4 Hz, 1H), 6.86 (d, J = 7.5 Hz, 1H), 8.80 (br s, 1H), 6.77 (d, J = 2.7 Hz, 1H), 3.86 (s, 3H), 3.71 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 182.7, 181.9, 160.1, 159.7, 150.2, 146.1, 145.6, 138.8, 134.6, 134.5, 134.1, 133.5, 132.9, 131.4, 129.7, 127.5, 125.8, 124.1, 120.0, 113.4, 113.3, 105.2, 55.5, 55.2; IR ($CHCl_3$) 2925, 1682, 1614, 1592, 1241, 1029 cm^{-1}; HRMS (ESI-TOF) calcd for $C_{25}H_{18}NO_4$ [M + H]$^+$ 396.1236, found 396.1237.

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12-(3-Fluoro-4-methoxyphenyl)-2-methylbenzo[b]acridine-6,11-dione, **4w**. Flash chromatography on silica gel (35% ethyl acetate/hexanes) gave **4w** (0.250 g; yield: 63%) as a brown solid: mp 273−275 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.40 (dd, J_1 = 1.4 Hz, J_2 = 7.5 Hz, 1H), 8.37 (d, J = 8.6 Hz, 1H), 8.14 (dd, J_1 = 1.4 Hz, J_2 = 7.5 Hz, 1H), 7.73−7.83 (m, 2H), 7.71 (dd, J_1 = 1.7 Hz, J_2 = 8.7 Hz, 1H), 7.31 (s, 1H), 7.16 (t, J = 8.4 Hz, 1H), 7.00 (dd, J_1 = 1.9 Hz, J_2 = 11.4 Hz, 1H), 6.94 (d, J = 8.4 Hz, 1H), 4.02 (s, 3H), 2.45 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 182.8, 181.9, 152.2 (d, J = 246.9 Hz), 150.1, 147.9, 147.4, 147.3 (d, J = 10.5 Hz), 140.5, 135.2, 134.6, 134.5, 134.2, 133.4, 131.2, 129.8, 129.5 (d, J = 7.1 Hz), 127.6, 127.5, 126.5, 124.2, 123.9 (d, J = 3.4 Hz), 116.2 (d, J = 19.6 Hz), 113.1, 56.1, 22.1; IR ($CHCl_3$) 3399, 2920, 2847, 1684, 1221, 722 cm^{-1}; HRMS (ESI-TOF) calcd for $C_{25}H_{17}FNO_3$ $[M + H]^+$ 398.1192, found 398.1195.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.7b01427.

^{1}H NMR, ^{13}C NMR, and HRMS spectra of all azaanthraquinone products (PDF)

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Notes

The authors declare no competing financial interest.

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