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Palladium-Catalyzed Intramolecular Fujiwara-Hydroarylation: Synthesis of Benzo[*a*]phenazines Derivatives

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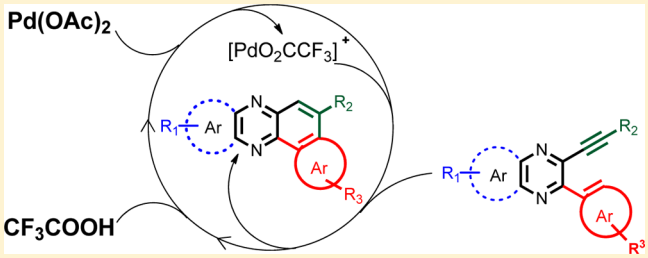
Supporting Information

ABSTRACT: An atom-economical Pd-catalyzed approach for the synthesis of benzophenazine derivatives using substituted 2-aryl-3-(aryl/alkylethynyl) quinoxaline in the presence of trifluoroacetic acid at 65 °C has been described. The chemistry involves in situ generation of cationic Pd(II) species, which functionalized the aromatic C−H bonds via electrophilic metalation followed by concomitant intramolecular trans-insertion of C−C triple bond to aryl-Pd complex. The results were supported by various control experiments including with electron−deficient arenes and deuterium labeling studies. The deuterium labeling studies supports electrophilic palladation of aromatic C−H over activation of C−C triple bond of alkyne. The structure of synthesized compounds was further confirmed by X-ray crystallography studies. This catalytic protocol has been efficiently applied for novel synthesis of highly functionalized benzo fused phenazines.



INTRODUCTION

Fused heterocycles and their analogues are pharmaceutically important scaffolds.[1] Among various heterocycles phenazines and their derivatives are significant motifs in pharmaceutical and agricultural chemistry and are used as key building blocks in natural product synthesis.[2] Some of the phenazine derivatives show antimalarial,[3] antiplasmodial activity,[4a] antibacterial,[4b] antifungal,[4c] antitumor,[4d] cancer chemopreventive,[5] neuro-protective,[6a] and anti Chagas[6b] agent (Figure 1i). The nucleus of benzophenazine derivatives (II) act as dual inhibitors of topoisomerase I and II and in the cell cycles[7] topology of DNA affected by key enzymes while some act as anticancer and antitumor agents (Figure 1ii and iii).[7a,b] The application of fluorescent phenazine derivatives has been considered as photosensitizers in photodynamic therapy (PDT)[8] in which the combination of light and photosensitizer creates highly reactive oxygen species near the tumor to selectively destroy the targeted tissue.

Metal-catalyzed hydroarylation of aryl ring has emerged as a significant tool for the construction of heterocycles and carbocycles.[9] In particular, Pd-catalyzed selective arylation for the synthesis of polyheterocycle still remain challenging. Pioneering work on hydroarylation has been reported by Fujiwara in 2000[10] using Pd-catalyst under acidic environment via C−H activation (Scheme 1i). In 2005, Tunge[11] had described the hydroarylation of arylalkynes with Pd-catalyst via electrophilic aromatic substitution. Later, Soriano[12] explained the mechanism of metal-catalyzed hydroarylation of alkynes and allenes (Scheme 1i). Further, Au/Pt/Fe were also employed for electrophilic cylization to synthesized fused heterocycles (Scheme 1ii).[13]

In 2013, Ellman group had reported the Rh-catalyzed domino approach to synthesize phenazine derivatives via amination followed by cyclization (Scheme 1iii).[14] Other groups[15] also made significant contributions for the synthesis of heterocycles in the presence of strong acids. However; the chemistry has been explored with limited substrates scope. In continuation of our interest for the construction of fused heterocyclic scaffolds from alkynes[16] herein, we report the synthesis of medicinally important functionalized benzophenazines and quinoxaline analogues by intramolecular hydroarylation from easily accessible 2-aryl 3-ethynylquinoxalines and pyrazines, respectively (Scheme 1iv).

RESULTS AND DISCUSSION

To find the optimal reaction condition, 2-phenyl-3-(phenylethynyl)quinoxaline **1a** was chosen as model substrate with different catalysts in various solvents (Table 1). We commenced our study with Fujiwara's conditions[10] of Pd(OAc)$_2$ (3 mol%) in TFA/DCM at 25 °C for 5 h, and the desired product **2a** was obtained in 40% yield (entry 1). On further increasing the reaction temperature from 45 to 65 °C for 24 h, the product **2a** was formed in 52 and 60% yield, respectively (entries 2−3). Interestingly, when the reaction was performed in TFA without cosolvent at 65 °C for 24 h, 70% yield of the desired product was obtained (entry 4). Lower yield was obtained at elevated temperature (entries 5−6). However, on decreasing the catalyst loading from 3 to 2 mol%, **2a** was obtained in best yield (entry 7). While, further decreasing the catalyst loading, **2a** was observed in 64% yield in

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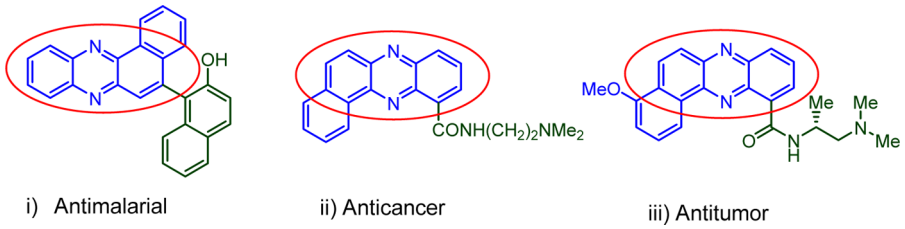


Figure 1. Biologically active phenazine derivatives.

Scheme 1. Previous Synthetic Approaches

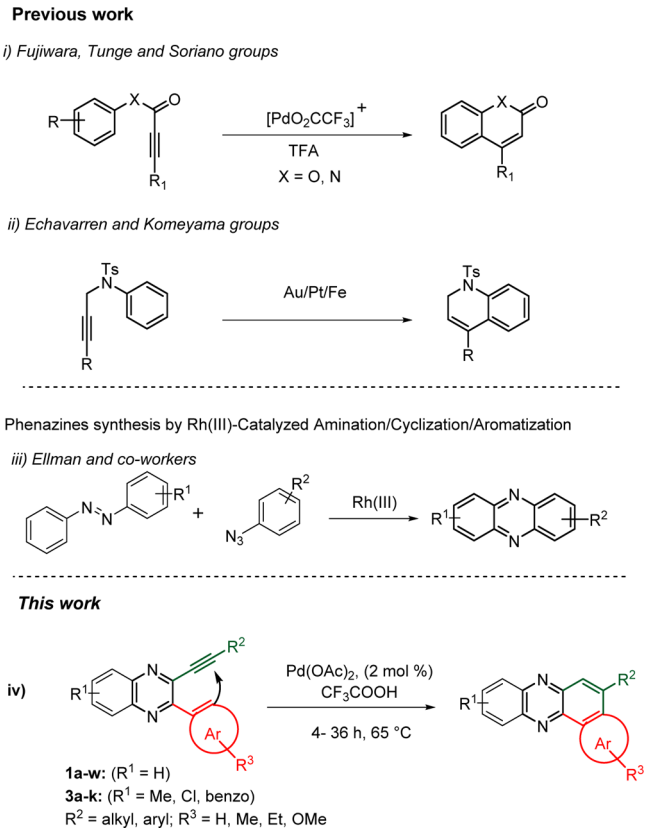
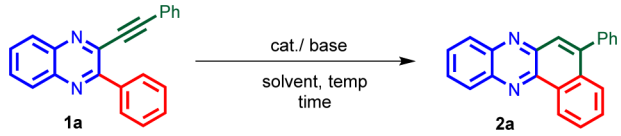


Table 1. Optimization of Reaction Conditions[a]



entry	catalyst/mol%	solvent	temp(°C)/time (h)	yield (%)
1	$Pd(OAc)_2$/3	TFA/DCM (4:1)	25/5	40
2	$Pd(OAc)_2$/2	TFA	45/24	52
3	$Pd(OAc)_2$/3	TFA/DCM (4:1)	65/24	60
4	$Pd(OAc)_2$/3	TFA	65/24	70
5	$Pd(OAc)_2$/3	TFA	70/24	65
6	$Pd(OAc)_2$/2	TFA	85/24	62
7	**$Pd(OAc)_2$/2**	**TFA**	**65/24**	**70**
8	$Pd(OAc)_2$/1	TFA	65/36	64
9	$Pd(OAc)_2$/5	TFA	65/24	61
10	$Pd(OAc)_2$/10	TFA	65/24	56
11	$Pd(OCOCF_3)_2$/2	TFA	65/24	68
12	$PdCl_2$/2	TFA	65/24	30
13	$Pd(CH_3CN)_4(BF_4)_2$/2	TFA	65/24	28
14	$Pd_2(dba)_2$/2	TFA	65/24	20
15	$Pd(OAc)_2$/2	CH_3COOH	65/24	NR
16	$Pd(OAc)_2$/2	DCE	65/28	NR
17	$Pd(OAc)_2$/2	DMF	65/28	NR
18	$Pd(OAc)_2$/2	DMSO	65/48	NR
19	$Fe(OTf)_3$/10	DCE	80/24	20
20	$Fe(OAc)_3$/10	TFA	65/24	NR
21	$Cu(OAc)_2$/10	TFA	65/24	NR
22		TFA	65/24	NR

[a]Reactions were performed using 0.5 mmol of o-alkynylaryls **1a**, catalyst in 4.0 mL of solvent. N.R. = no reaction, TFA = trifluoroacetic acid, DCE = 1,2-dichloroethane.

36 h (entry 8). No significant results were obtained with high catalyst loading (entries 9−10). The reaction with $Pd(OCOCF_3)_2$ afforded the 68% yield of desired product **2a** (entry 11). Inferior results were obtained with other Pd catalyst like $PdCl_2$, $Pd(CH_3CN)_4(BF_4)_2$, and $Pd_2(dba)_2$ (entry 12−14). No product formation was observed when CH_3COOH, DCE, DMF, and DMSO were used as solvent (entries 15−18). When reaction was performed using Komeyama[13b] condition, i.e., 10 mol% of $Fe(OTf)_3$ in DCE at 80 °C for 24 h, only 20% yield of the desired product was achieved (entry 19). After screening various conditions, we next examined other acetate salts of Fe and Cu in TFA at 65 °C for 24 h, however we failed to obtained the desired product (entries 20−21). In order to understand the role of metal, we performed the reaction in the absence of catalyst, no reaction was observed (entry 22).

We next examined the scope and efficacy of the reaction by employing a wide range of 2-aryl-3-(aryl/alkylethynyl)-quinoxalines **1a−w** with different electronic properties at aryl as well as alkyne substituents (Scheme 2). Reaction of 2-phenyl-3-(phenylethynyl) quinoxaline **1a** provided the fused cyclized product **2a** in 70% yield. Substrates **1b** bearing *p*-NMe_2 group to the triple bonded phenyl ring afforded the corresponding desired product **2b** in 65% yield. The reaction was well tolerated with aryl as well heteroaryl alkynes (**2c−e**). 3,5-Dimethoxy arenes having aromatic and aliphatic alkynes afforded the product **2f−i** in 96−82% yields. Quinoxalines **1j−r** with electron rich and electron deficient alkynes gave the corresponding product **2j−r** in good to excellent yields. The structure of phenazine **2j** was further supported by X-ray crystallographic analysis (see, Supporting Information). It is noteworthy, that the 3-thienyl substituted quinoxalines were also capable to give corresponding thienophenazine **2s−w** in 75−88% yields.

We further extended the scope of the reaction with 6-methyl/chloro substituted alkynyl quinoxaline **3a−j** (Scheme 3). The reaction was compatible with aryl and alkyl substituent on quinoxaline and afforded the corresponding single regioisomers **4a−j** in 73−88% yield. Both electron-rich and electron-deficient alkyne substituted quinoxalines afforded the

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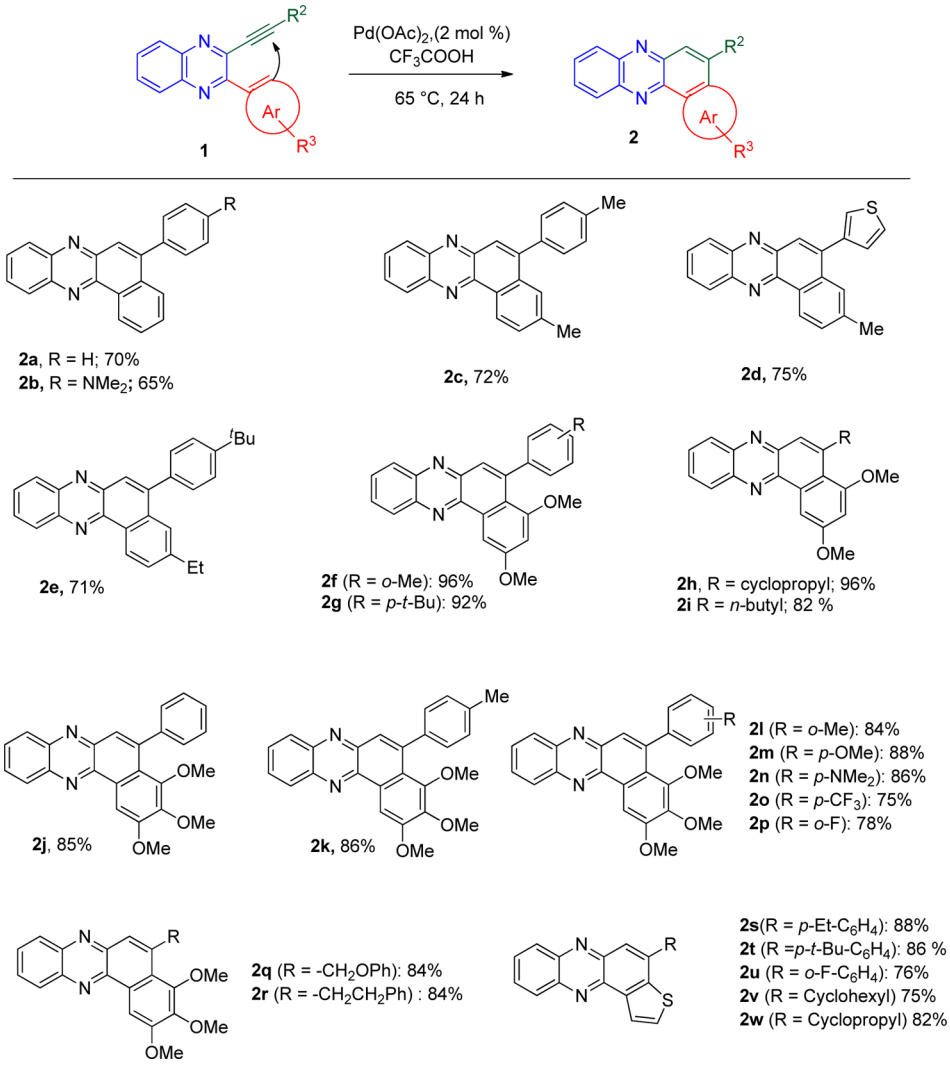
Scheme 2. Scope of 2-Aryl-3-(alkynyl)quinoxalines[a]



[a]Using optimized conditions (entry 7, Table 1).

corresponding product in good yields. The formation of regioselective product was confirmed by the X-ray crystallographic analysis of **4c** (see, Supporting Information). The reaction condition was also successful with benzo-fused quinoxaline **3k** and afforded the desired product **4k** in 86% yield.

Next, we explored the scope of the developed protocol for the synthesis of benzo[*f*]quinoxaline **6a**–**b** from pyrazines **5a**–**b** in 12 h, probably due to the electronic effect of the substrate (Scheme 4). The reaction afforded 85% yield of quinoxaline **6a** with trimethoxy substituted ethynylpyrazine **5a**. While pyrazine **5b** (R = *p*-Et) gave the desired hydroarylated product **6b** in 82% yield.

Encouraged by the above results, we next examined the scope of hydroarylation via elctrophilic metalation on electron-deficient aryl substrate **1x**–**z** (Scheme 5). Interestingly, an uncyclized enolic form of quinoxalines **7a**–**c** were obtained in 86–90% yields via hydration of C–C triple bonds of alkynes to ketones[17] which tautomerize to furnished enolic products. The product has been confirmed by X-ray crystallography (Scheme 5a).

The probable reason might be due to the nature of electron-poor arenes which restrain electrophilic metalation on aromatic C–H bond. Later, we performed a reaction on 3-chloroquinoxaline **1′** and surprisingly we observed a cyclized product **3′** rather than **2′** which may be through the electrophilic attack of Pd-TFA complex at C-3 position of quinoxaline **1′** followed by coordination with alkyne to generate cyclized compound **3′** (Scheme 5b).

To further validate the reaction mechanism, when quinoxaline **1** was treated with TFA under optimized reaction condition followed by work up via D_2O, no deuterium incorporation was observed in product **2a** (Scheme 6). This suggested that the exchange of proton occur *in situ* in the reaction. It is interesting to note that, when deuterated TFA was used as a solvent; products **8a**–**b** were obtained in 64–65% yields with 84–90% incorporation of deuterium. This is probably due to electron-rich aromatic rings in compound **1p** and **1i** which favor deuteration at more than one position. Even in the products, this may occur due to a highly acidic TFA solvent under the reaction conditions. As from the past decade deuterated drugs have gained importance due to their medicinal value and application in the study of reaction mechanism.[18]

On the basis of the above preliminary results and literature information, a plausible mechanism showing two routes was proposed in Scheme 7. The deuterium isotopic experiments

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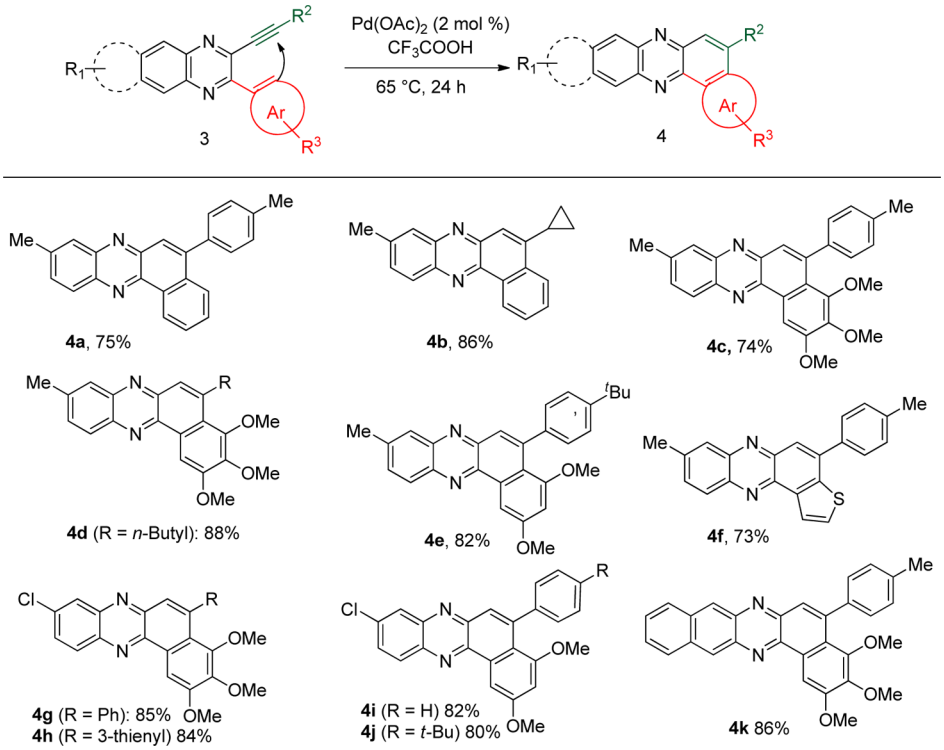
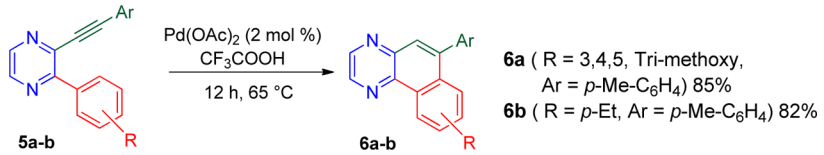
Scheme 3. Scope of Substituted Quinoxalines[a]



[a]Using optimized conditions (entry 7, Table 1).

Scheme 4. Synthesis of Benzo[f]quinoxaline



shown in Scheme 6 revealed that vinyl and aromatic H or D in all adducts results from the protonation of vinyl-Pd complex[10a,b] **S** by deuterated TFA or TFA (Scheme 7). The facile formation of complex **Q** through electrophilic metalation of the aromatic C−H bond from cationic Pd(II) species has been well documented.[10] This reaction required TFA for the protonation of a vinyl-Pd intermediate **S** as reaction failed in other solvents like acetic acid.

Thus, the electrophilic attack of the aromatic C−H bond by cationic Pd(II) species to generate **Q** followed by coordination of alkyne to give **R**. Then, trans insertion[19] of C−C triple bonds to the aryl-Pd bond results in species **S**, and later, 1/6 aryl-Pd adduct (**S**) releases Pd(II) to give 1,6-D-benzo[a]phenazines. Alternatively, the reaction may proceed via coordination of Pd(II) cationic species with alkyne **P′** to generate vinyl palladium species **Q′** which forms Wheland intermediate[10] **R′** through electrophilic cylization. The intermediate **R′** then undergoes aromatization followed by protodemetalation to give product **8** as shown in path **B**.

In conclusion, we have described an intramolecular alkyne-hydroarylation reaction in the presence of Pd-catalyst under strong acidic condition. The reaction was well tolerated with electron-rich and electron-neutral groups and provided the intriguing benzophenazines and quinoxalines in good yields, while new enolic compounds were obtained with electron−withdrawing substitutents. Various preliminary studies involving deuterium-labeling experiments were performed to support the mechanistic pathway via electrophilic metalation on aromatic C−H bond over alkyne activation. Further the structure of benzophenazine derivatives were confirmed by the X-ray crystallographic studies.

EXPERIMENTAL SECTION

General Information and Method. Nuclear magnetic resonance spectra were recorded in $CDCl_3$, ^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz), at ambient temperature. Chemical shifts (δ) for all protons are reported in parts per million (ppm) and were measured relative to the residual $CHCl_3$ resonance as an internal reference in the deuterated solvent. Chemical shifts were reported as parts per million (δ in ppm) using tetramethylsilane (TMS) as internal standard or by reference to proton resonances resulting from incomplete deuteration of the NMR solvent. The following abbreviations were used to describe the multiplicities: when appropriate s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, dd = doublet of doublet. Reactions were monitored using thin-layer chromatography on commercially prepared silica gel plates and visualized by either UV irradiation or by staining with I_2. Chemical yields are referred to the pure isolated substances. Chromatographic purification of the label compounds was accomplished by column chromatography using 100−200 mesh size silica gels.

General Procedure for the Synthesis of Starting Substrate. *General Experimental Procedure for Sequential Sonogashira/*

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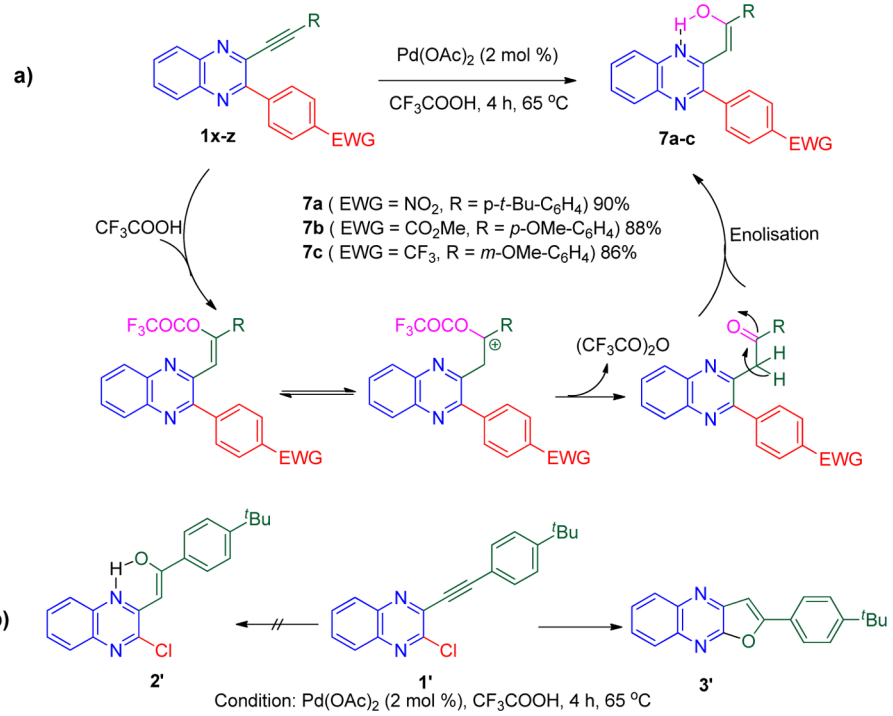
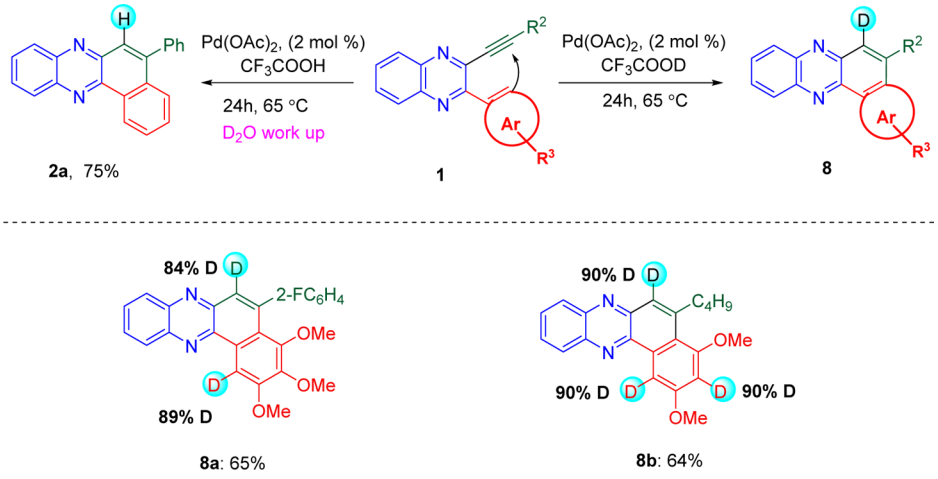
Scheme 5. Unusual Hydroxylation



Scheme 6. Deuterium Labeling Experiments



*Suzuki Coupling Reaction and Analytic Data of **1a–z, 3a–k, and 5a–b**.* To a solution of substituted 2,3-dichloroquinoxaline/2,3-dichloropyrazine (0.5 mmol) in DMF (2 mL), 2 mol% of $Pd(PPh_3)_2Cl_2$ was added. The reaction vial was then sealed and flushed with nitrogen. Then, 1.5 equiv of Et_3N and 0.51 mmol of alkyne 2 were added to the reaction mixture. The reaction was then stirred at 70 °C until TLC revealed complete conversion of the starting material. After the completion of the first coupling reaction (monitored by TLC) 3 mol% of $Pd(PPh_3)_2Cl_2$, 0.5 mmol of boronic acid, 1.5 equiv of Et_3N was added under nitrogen atmosphere. The reaction was then stirred at 80 °C until TLC revealed complete conversion of the starting material. The reaction mixture was then allowed to cool, was diluted with H_2O, and was extracted with EtOAc (3 × 10 mL). The combined organic layers were dried over Na_2SO_4, concentrated under vacuum, and purified by column chromatography using 100–200 mesh size silica gels (hexane: ethyl acetate) to afford the corresponding product.

*2-Phenyl-3-(phenylethynyl)quinoxaline (**1a**).* The product was obtained as a yellow needles (110.2 mg, 72%): mp 108–112 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.16–8.09 (m, 4H), 7.78–7.74 (m, 2H), 7.59–7.54 (m, 3H), 7.50–7.47 (m, 2H), 7.39–7.30 (m, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 155.1, 141.0, 140.7, 138.1, 137.6, 132.1, 130.6, 130.3, 129.7, 129.3, 128.7, 128.4, 128.1, 121.7, 95.0, 88.3; HRMS (ESI) calcd for $[C_{22}H_{14}N_2]$ requires $[M+H]^+$ 307.1235, found 307.1224.

*N,N-Dimethyl-4-((3-phenylquinoxalin-2-yl)ethynyl)aniline.(**1b**).* The product was obtained as a yellow needles (132.7 mg, 76%): mp 120–124 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.11–8.07 (m, 4H), 7.74–7.67 (m, 2H), 7.57–7.50 (m, 3H), 7.34 (d, J = 8.7 Hz, 2H), 6.60 (d, J = 9.3 Hz, 2H), 2.97 (s, 6H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 154.8, 150.8, 141.0, 140.2, 138.9, 137.8, 133.5, 130.0, 129.8, 129.6, 129.4, 129.1, 128.4, 127.9, 111.5, 107.7, 98.0, 87.6, 39.9; HRMS (ESI) calcd for $[C_{24}H_{19}N_3]$ requires $[M+Na]^+$ 372.1477, found 372.1474.

*2-(p-Tolyl)-3-(p-tolylethynyl)quinoxaline (**1c**).* The product was obtained as a yellow needles (128.7 mg, 77%): mp 113–117 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.20–8.17 (m, 2H), 8.13 (d, J = 7.6 Hz, 2H), 7.81–7.79 (m, 2H), 7.50 (d, J = 7.6 Hz, 2H), 7.44 (d, J = 8.4 Hz, 2H), 7.23 (d, J = 7.6 Hz, 2H), 2.54 (s, 3H), 2.42 (s, 3H); $^{13}C\{^1H\}$

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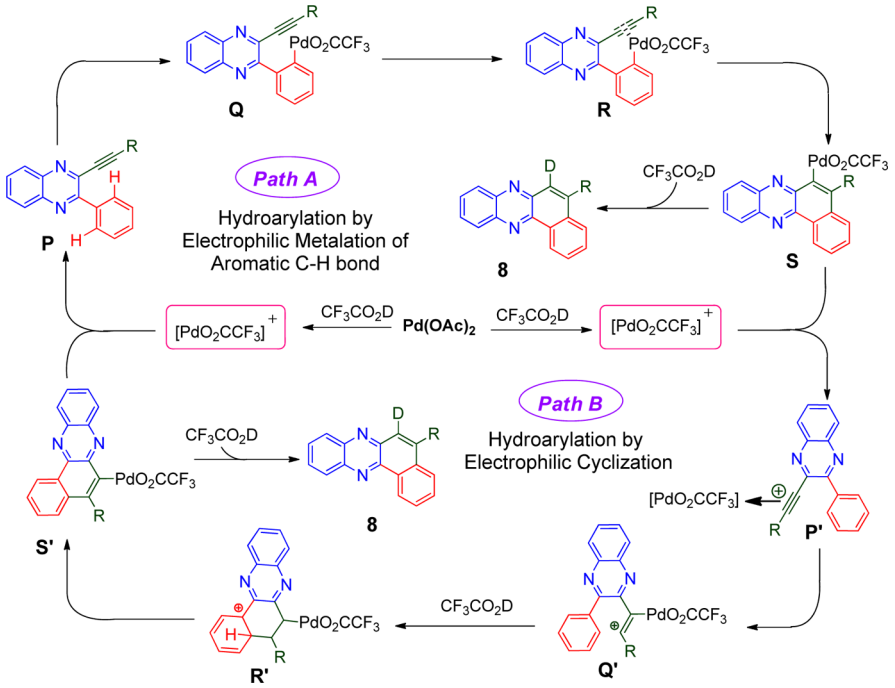
Scheme 7. Plausible Mechanism



NMR (100 MHz, $CDCl_3$) δ 154.6, 140.7, 140.5, 139.8, 139.6, 138.0, 134.6, 131.9, 130.3, 129.9, 129.5, 129.1, 128.7, 128.5, 118.6, 95.1, 88.0, 21.5, 21.4; HRMS (ESI) calcd for $[C_{24}H_{18}N_2]$ requires $[M+Na]^+$ 357.1368, found 357.1354.

*2-(Thiophen-3-ylethynyl)-3-(p-tolyl)quinoxaline (**1d**).* The product was obtained as a yellow needles (120.7 mg, 74%): mp 144−149 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 8.11−8.06 (m, 2H), 8.0 (d, J = 7.6 Hz, 2H), 7.74−7.69 (m, 2H), 7.58 (d, J = 3.0 Hz, 1H), 7.33 (d, J = 8.4 Hz, 2H), 7.28−7.24 (m, 1H), 7.15 (d, J = 3.8 Hz, 1H), 2.44 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 154.7, 140.8, 140.7, 139.8, 137.9, 134.6, 131.2, 130.5, 130.0, 129.65, 129.56, 129.2, 128.8, 128.6, 125.7, 120.9, 90.3, 88.2, 21.4; HRMS (ESI) calcd for $[C_{21}H_{14}N_2S]$ requires $[M+Na]^+$ 349.0775, found 349.0768.

*2-((4-tert-Butyl)phenyl)ethynyl)-3-(4-ethylphenyl)quinoxaline (**1e**).* The product was obtained as a yellow oil (138.6 mg, 71%); ^1H NMR (400 MHz, $CDCl_3$) δ 8.05−8.03 (m, 2H), 7.97 (d, J = 7.6 Hz, 2H), 7.69−7.65 (m, 2H), 7.38−7.36 (m, 2H), 7.32−7.29 (m, 4H), 2.70 (q, J = 7.6 Hz, 2H), 1.26−1.23(m, 12H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 155.1, 153.1, 146.1, 140.9, 140.7, 138.3, 135.0, 131.9, 130.5, 130.1, 129.7, 128.6, 127.7, 125.5, 118.7, 115.2, 95.4, 88.1, 34.9, 31.1, 28.9, 15.6; HRMS (ESI) calcd for $[C_{28}H_{26}N_2]$ requires $[M+H]^+$ 391.2174, found 391.2168.

*2-(3,5-Dimethoxyphenyl)-3-(o-tolylethynyl)quinoxaline (**1f**).* The product was obtained as a yellow needles (155.9 mg, 82%): mp 125−129 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 8.22−8.16 (m, 2H), 7.85−7.80 (m, 2H), 7.59−7.57 (m, 1H), 7.34−7.30 (m, 1H), 7.25−7.22 (m, 4H), 6.67 (t, J = 2.4 Hz, 1H), 3.89 (s, 6H), 2.38 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 160.6, 155.0, 141.20, 141.16, 140.4, 139.5, 138.3, 132.8, 130.6, 130.3, 129.6, 129.2, 128.7, 125.6, 121.4, 107.6, 101.9, 94.4, 91.6, 55.5, 20.3; HRMS (ESI) calcd for $[C_{25}H_{20}N_2O_2]$ requires $[M+Na]^+$ 403.1422, found 403.1415.

*2-((4-(tert-Butyl)phenyl)ethynyl)-3-(3,5-dimethoxyphenyl)-quinoxaline (**1g**).* The product was obtained as a yellow needles (179.5 mg, 85%): mp 133−137 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 8.14−8.10 (m, 2H), 7.78−7.73 (m, 2H), 7.45 (d, J = 8.4 Hz, 2H), 7.36 (d, J = 8.4 Hz, 2H), 7.24−7.23 (m, 2H), 6.65−6.64 (m, 1H), 3.85 (s, 6H), 1.30 (s, 9H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 160.6, 154.9, 153.1, 146.4, 141.1, 138.3, 132.0, 130.5, 128.7, 128.1, 127.6, 126.9, 125.6, 118.7, 107.8, 102.3, 95.9, 87.9, 55.54, 55.49, 34.9, 31.1; HRMS (ESI) calcd for $[C_{28}H_{26}N_2O_2]$ requires $[M+H]^+$ 423.2073, found 423.2066.

*2-(Cyclopropylethynyl)-3-(3,5-dimethoxyphenyl)quinoxaline (**1h**).* The product was obtained as a yellow needles (165.1 mg, 81%): mp 115−121 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 8.09−8.03 (m, 2H), 7.73−7.70 (m, 2H), 7.185−7.154 (m, 2H), 6.60−6.59 (m, 1H), 3.87 (s, 6H), 1.51−1.44 (m, 1H), 0.92−0.84 (m, 4H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 159.9, 154.0, 140.3, 139.7, 138.8, 137.7, 129.74, 129.67, 128.6, 127.9, 107.1, 101.5, 100.9, 74.5, 55.0, 54.9, 8.4, 0.0; HRMS (ESI) calcd for $[C_{21}H_{18}N_2O_2]$ requires $[M+Na]^+$ 353.1266, found 353.1261.

*2-(3,5-Dimethoxyphenyl)-3-(hex-1-yn-1-yl)quinoxaline (**1i**).* The product was obtained as a yellow oil (118.6 mg, 82%); ^1H NMR (400 MHz, $CDCl_3$) δ 8.20−8.13 (m, 2H), 7.84−7.79 (m, 2H), 7.24−7.23 (m, 2H), 6.68 (s, 1H), 3.94 (s, 6H), 2.54 (t, J = 6.7 Hz, 2H), 1.67−1.60 (m, 2H), 1.49−1.40 (m, 2H), 0.96 (t, J = 6.7 Hz, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 160.4, 154.6, 140.9, 140.3, 139.4, 138.3, 130.3, 130.1, 129.1, 128.5, 107.6, 101.8, 98.0, 79.7, 55.4, 29.9, 22.0, 19.5, 13.5; HRMS (ESI) calcd for $[C_{22}H_{22}N_2O_2]$ requires $[M+H]^+$ 347.1760, found 347.1741.

*2-(Phenylethynyl)-3-(3,4,5-trimethoxyphenyl)quinoxaline (**1j**).* The product was obtained as a yellow needles (176.4 mg, 89%): mp 189−193 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 7.99 (s, 2H), 7.63 (s, 2H), 7.35 (s, 2H), 7.24 (s, 5H), 3.82 (s, 3H), 3.77 (s, 6H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 154.4, 152.8, 140.7, 140.3, 139.2, 137.6, 132.7, 131.9, 130.6, 130.1, 129.5, 129.0, 128.5, 128.4, 121.3, 106.9, 95.1, 88.3, 60.8, 56.0; HRMS (ESI) calcd for $[C_{25}H_{20}N_2O_3]$ requires $[M+Na]^+$ 419.1372, found 419.1368.

*2-(p-Tolylethynyl)-3-(3,4,5-trimethoxyphenyl)quinoxaline (**1k**).* The product was obtained as a yellow needles (184.7 mg, 90%): mp 148−152 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 8.01−7.99 (m, 2H), 7.65−7.63 (m, 2H), 7.27−7.24 (m, 4H), 7.03 (d, J = 7.6 Hz, 2H), 3.82 (s, 3H), 3.78 (s, 6H), 2.24 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 154.5, 152.9, 140.9, 140.2, 139.3, 138.0, 132.9, 132.0, 130.6, 130.2, 129.3, 129.1, 128.6, 118.4, 106.9, 104.5, 95.8, 87.9, 60.9, 56.2, 21.6; HRMS (ESI) calcd for $[C_{26}H_{22}N_2O_3]$ requires $[M+Na]^+$ 433.1528, found 433.1536.

*2-(o-Tolylethynyl)-3-(3,4,5-trimethoxyphenyl)quinoxaline (**1l**).* The product was obtained as a yellow needles (164.1 mg, 80%): mp 152−156 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 8.07−8.04 (m, 2H), 7.71−7.69 (m, 2H), 7.41 (d, J = 6.8 Hz, 1H), 7.21−7.18 (m, 3H), 7.12−7.07 (m, 2H), 3.85 (s, 3H), 3.80 (s, 6H), 2.26 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 154.5, 152.8, 140.8, 140.7, 140.1, 139.1,

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J. Org. Chem. 2016, 81, 9912−9923

137.9, 132.9, 130.4, 130.0, 129.4, 128.9, 128.4, 125.4, 121.0, 106.8, 94.1, 91.6, 60.6, 55.9, 20.1; HRMS (ESI) calcd for $[C_{26}H_{22}N_2O_3]$ requires $[M+Na]^+$ 433.1528, found 433.1540.

*2-((4-Methoxyphenyl)ethynyl)-3-(3,4,5-trimethoxyphenyl)-quinoxaline (**1m**).* The product was obtained as a yellow needles (187.6 mg, 88%): mp 132−136 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00−7.98 (m, 2H), 7.64−7.62 (m, 2H), 7.31 (d, J = 9.1 Hz, 2H), 7.24 (s, 2H), 6.74 (d, J = 8.4 Hz, 2H), 3.83 (s, 3H), 3.79 (s, 6H), 3.69 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 160.7, 154.4, 152.9, 140.9, 140.3, 139.2, 138.1, 133.7, 132.9, 130.4, 130.1, 129.1, 128.6, 114.2, 113.4, 106.9, 95.9, 87.6, 60.9, 56.1, 55.3; HRMS (ESI) calcd for $[C_{26}H_{22}N_2O_4]$ requires $[M+Na]^+$ 449.1477, found 449.1469.

*N,N-Dimethyl-4-((3-(3,4,5-trimethoxyphenyl)quinoxalin-2-yl)-ethynyl) aniline (**1n**).* The product was obtained as a yellow needles (184.5 mg, 84%): mp 183−187 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.07−8.05 (m, 2H), 7.70−7.69 (m, 2H), 7.33−7.31 (m, 4H), 6.58 (d, J = 8.4 Hz, 2H), 3.92 (s, 3H), 3.89 (s, 6H), 2.96 (s, 6H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 154.6, 153.0, 151.0, 141.2, 140.2, 139.3, 138.8, 133.7, 133.3, 130.2, 130.1, 129.2, 128.6, 111.7, 107.7, 107.1, 98.5, 87.8, 61.1, 56.3, 40.1; HRMS (ESI) calcd for $[C_{27}H_{25}N_3O_3]$ requires $[M+Na]^+$ 462.1794, found 462.1785.

*2-((4-(Trifluoromethyl)phenyl)ethynyl)-3-(3,4,5-trimethoxyphenyl) quinoxaline (**1o**).* The product was obtained as a yellow needles (176.4 mg, 76%): mp 182−186 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.04 (s, 2H), 7.69 (s, 2H), 7.51 (s, 4H), 7.25 (s, 2H), 3.86 (s, 3H), 3.82 (s, 6H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 154.6, 153.0, 140.8, 140.6, 139.5, 137.0, 132.6, 132.2, 131.1, 130.4, 129.1, 128.7, 125.41 (q, $^1J_{C-F}$ = 15.2 Hz, 1C), 125.2, 124.9, 122.1, 106.9, 93.0, 90.1, 60.9, 56.2; HRMS (ESI) calcd for $[C_{26}H_{19}F_3N_2O_3]$ requires $[M+Na]^+$ 487.1245, found 487.1243.

*2-((2-Fluorophenyl)ethynyl)-3-(3,4,5-trimethoxyphenyl)-quinoxaline (**1p**).* The product was obtained as a yellow needles (155.4 mg, 75%): mp 162−166 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.16−8.13 (m, 2H), 7.81−7.78 (m, 2H), 7.54−7.50 (m, 1H), 7.34−7.33 (m, 1H), 7.26−7.25 (m, 1H), 7.16−7.08 (m, 2H), 6.71(s, 1H), 3.94−3.92 (m, 9H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 163.3 (d, $^1J_{C-F}$ = 253.9 Hz, $1^{13}C$), 154.6, 153.0, 140.9, 140.6, 137.4, 133.9, 133.8, 132.6, 131.6−131.4 (m, $1^{13}C$), 130.9, 129.1, 128.8, 124.2−124.0 (m, $1^{13}C$), 115.9−115.5 (m, $1^{13}C$), 110.3 (d, $^2J_{C-F}$ = 15.3 Hz, $1^{13}C$), 107.0, 106.9, 104.6, 92.7, 88.3, 60.8, 56.2; HRMS (ESI) calcd for $[C_{25}H_{19}FN_2O_3]$ requires $[M+H]^+$ 415.1458, found 415.1487.

*2-(3-Phenoxyprop-1-yn-1-yl)-3-(3,4,5-trimethoxyphenyl)-quinoxaline (**1q**).* The product was obtained as a yellow needles (153.5 mg, 72%): mp 100−104 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.12−8.08 (m, 2H), 7.80−7.74 (m, 2H), 7.27−7.24 (m, 4H), 6.99−6.91 (m, 3H), 4.93 (s, 2H), 3.90 (s, 9H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 157.5, 154.2, 153.0, 140.76, 140.67, 139.5, 136.6, 132.3, 131.1, 130.3, 129.5, 129.1, 128.7, 121.7, 114.6, 106.8, 89.8, 85.5, 60.9, 56.4, 56.1; HRMS (ESI) calcd for $[C_{26}H_{22}N_2O_4]$ requires $[M+Na]^+$ 449.1477, found 449.1479.

*2-(4-Phenylbut-1-yn-1-yl)-3-(3,4,5-trimethoxyphenyl)quinoxaline (**1r**).* The product was obtained as a yellow needles (144.3 mg, 68%): mp 94−98 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.10−8.07 (m, 2H), 7.75−7.73 (m, 2H), 7.27−7.22 (m, 4H), 7.19−7.13 (m, 3H), 3.91 (s, 6H), 3.89 (s, 3H), 2.90 (t, J = 6.8 Hz, 2H), 2.75 (t, J = 7.6 Hz, 2H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 154.2, 152.9, 140.7, 140.4, 139.8, 139.3, 137.8, 132.8, 130.5, 130.1, 129.0, 128.5, 128.4, 128.2, 126.4, 106.9, 96.4, 80.4, 60.9, 56.1, 34.3, 22.0; HRMS (ESI) calcd for $[C_{27}H_{24}N_2O_3]$ requires $[M+Na]^+$ 447.1685, found 447.1702.

*((4-Ethylphenyl)ethynyl)-3-(thiophen-3-yl)quinoxaline (**1s**).* The product was obtained as a yellow needles (129.3 mg, 76%): mp 86−91 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.39−8.37 (m, 1H), 8.03−7.99 (m, 2H), 7.95−7.94 (m, 1H), 7.68−7.63 (m, 2H), 7.47 (d, J = 8.2 Hz, 2H), 7.39−7.37 (m, 1H), 7.18−7.15 (m, 2H), 2.61 (q, J = 7.8 Hz, 2H), 1.18 (t, J = 7.8 Hz, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 149.5, 146.4, 140.6, 139.0, 137.4, 132.2, 130.6, 130.0, 129.1, 128.9, 128.6, 128.2, 128.0, 125.3, 118.8, 95.4, 88.2, 29.0, 15.2; HRMS (ESI) calcd for $[C_{22}H_{16}N_2S]$ requires $[M+H]^+$ 341.1112, found 341.1109.

*2-((4-(tert-Butyl)phenyl)ethynyl)-3-(thiophen-3-yl)quinoxaline (**1t**).* The product was obtained as a yellow needles (130.8 mg, 71%): mp 88−93 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.44−8.42 (m, 1H), 8.08−8.03 (m, 2H), 8.00−7.98 (m, 1H), 7.74−7.69 (m, 2H), 7.56−7.53 (m, 2H), 7.45−7.42 (m, 1H), 7.41−7.39 (m, 2H), 1.39 (s, 9H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 153.3, 149.6, 140.73, 140.68, 137.5, 132.0, 130.6, 130.0, 129.1, 128.9, 128.7, 128.0, 125.6, 125.3, 118.6, 95.4, 88.3, 35.0, 31.1; HRMS (ESI) calcd for $[C_{24}H_{20}N_2S]$ requires $[M+H]^+$ 369.1425, found 369.1428.

*2-((2-Fluorophenyl)ethynyl)-3-(thiophen-3-yl)quinoxaline (**1u**).* The product was obtained as a yellow needles (120.5 mg, 73%): mp 122−126 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.60−8.59 (m, 1H), 8.09−8.04 (m, 3H), 7.76−7.69 (m, 2H), 7.66−7.62 (m, 1H), 7.45−7.41 (m, 1H), 7.40−7.36 (m, 1H), 7.18−7.11 (m, 2H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 163.3 (d, $^1J_{C-F}$ = 253.9 Hz, 1C), 149.2, 140.8, 140.5, 138.5, 136.6, 134.0, 131.5 (d, J = 7.6, 1C), 130.8, 130.0, 129.0, 128.8, 128.7, 128.37, 128.35, 125.3, 124.2 (d, $^4J_{C-F}$ = 3.8 Hz, $1^{13}C$), 115.7 (d, $^2J_{C-F}$ = 20.1 Hz, 1C), 110.3 (d, $^3J_{C-F}$ = 14.3 Hz, 1C), 93.1, 88.2; HRMS (ESI) calcd for $[C_{20}H_{11}FN_2S]$ requires $[M+H]^+$ 331.0705, found 331.0728.

*2-(Cyclohexylethynyl)-3-(thiophen-3-yl)quinoxaline (**1v**).* The product was obtained as a yellow oil (106.6 mg, 67%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.34 (s, 1H), 7.98−7.96 (s, 2H), 7.89 (d, J = 4.56 Hz, 1H), 7.64−7.62 (m, 2H), 7.35−7.33 (m, 1H), 2.69−2.62 (m, 1H), 1.91−1.89 (m, 2H), 1.72−1.65 (m, 2H), 1.58−1.48 (m, 2H), 1.33−1.17 (m, 4H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 149.4, 140.50, 140.47, 139.03, 137.6, 130.3, 129.8, 129.0, 128.9, 128.5, 127.9, 125.0, 101.1, 80.2, 31.8, 30.0, 25.7, 24.9; HRMS (ESI) calcd for $[C_{20}H_{18}N_2S]$ requires $[M+Na]^+$ 341.1088, found 341.1095.

*2-(Cyclopropylethynyl)-3-(thiophen-3-yl)quinoxaline (**1w**).* The product was obtained as a yellow needles (88.4 mg, 64%): mp 78−82 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.29−8.28 (m, 1H), 7.94−7.90 (m, 2H), 7.85 (d, J = 5.3 Hz, 1H), 7.60−7.56 (m, 2H), 7.32−7.30 (m, 1H), 1.52−1.46 (m, 1H), 0.88−0.86 (m, 4H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 149.1, 140.4, 140.3, 138.9, 137.4, 130.1, 129.7, 128.9, 128.7, 128.3, 127.7, 125.0, 100.6, 75.6, 8.8, 0.5; HRMS (ESI) calcd for $[C_{17}H_{12}N_2S]$ requires $[M+Na]^+$ 299.0619, found 299.0622.

*2-((4-(tert-Butyl)phenyl)ethynyl)-3-(4-nitrophenyl)quinoxaline (**1x**).* The product was obtained as a yellow needles (107.9 mg, 53%): mp 111−116 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.42−8.39 (m, 2H), 8.32−8.30 (m, 2H), 8.15−8.11 (m, 2H), 7.84−7.79 (m, 2H), 7.42−7.37 (m, 4H), 1.31 (s, 9H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 153.7, 152.4, 148.4, 143.8, 141.4, 140.5, 137.7, 131.9, 131.2, 131.0, 130.8, 129.4, 128.8, 125.7, 123.3, 118.0, 96.4, 87.1, 35.0, 31.0; HRMS (ESI) calcd for $[C_{26}H_{21}N_3O_2]$ requires $[M+H]^+$ 408.1712, found 408.1700.

*Methyl 4-(3-((4-Methoxyphenyl)ethynyl)quinoxalin-2-yl)-benzoate (**1y**).* The product was obtained as a yellow needles (116.3 mg, 59%): mp 150−155 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.17−8.15 (m, 4H), 8.07−8.05 (m, 2H), 7.73−7.69 (m, 2H), 7.36−7.33 (m, 2H), 6.81−6.79 (m, 2H), 3.91 (s, 3H), 3.75 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 166.8, 160.8, 153.7, 142.0, 141.2, 140.5, 138.1, 133.8, 130.9, 130.7, 130.6, 129.8, 129.3, 128.7, 114.3, 113.4, 96.1, 87.2, 55.3, 52.3; HRMS (ESI) calcd for $[C_{25}H_{18}N_2O_3]$ requires $[M+H]^+$ 395.1396, found 395.1384.

*3-((3-Methoxyphenyl)ethynyl)-6-methyl-2-(4-(trifluoromethyl)-phenyl)quinoxaline (**1z**).* The product was obtained as a yellow needles (115.2 mg, 57%): mp 109−112 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.15 (d, J = 7.6 Hz, 2H), 8.09−8.03 (m, 2H), 7.76−7.71 (m, 4H), 7.20−7.16 (m, 1H), 6.97 (d, J = 7.6 Hz, 1H), 6.88−6.86 (m, 2H), 3.70 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 159.3, 153.5, 141.3, 140.6, 137.6, 131.0, 130.9, 130.2, 130.1, 129.6, 129.4, 129.3, 125.04 (q, $^1J_{C-F}$ = 15.2 Hz, 1C), 124.6, 122.2, 117.0, 116.5, 116.2, 95.6, 87.5, 55.3; HRMS (ESI) calcd for $[C_{24}H_{15}F_3N_2O]$ requires $[M+H]^+$ 405.1215, found 405.1209.

*2-((4-(tert-Butyl)phenyl)ethynyl)-3-chloroquinoxaline (**1′**).* The product was obtained as a yellow needles (137.9 mg, 86%): mp 111−116 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.10−8.07 (m, 1H), 8.00−7.96 (m, 1H), 7.78−7.74 (m, 2H), 7.64 (d, J = 8.4 Hz, 2H), 7.43 (d, J = 8.4 Hz, 2H), 1.33 (s, 9H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 153.7, 148.1, 140.2, 138.8, 132.3, 131.2, 130.6, 128.9, 128.7, 125.5,

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118.1, 97.8, 85.1, 35.0, 31.0; HRMS (ESI) calcd for $[C_{20}H_{17}ClN_2]$ requires $[M+H]^+$ 321.1159, found 321.1163.

*6-Methyl-2-phenyl-3-(p-tolylethynyl)quinoxaline (**3a**).* The product was obtained as a yellow needles (135.4 mg, 81%): mp 130−134 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01−8.00 (m, 2H), 7.92 (d, J = 9.1 Hz, 1H), 7.80 (s, 1H), 7.51−7.44 (m, 4H), 7.29 (d, J = 7.6 Hz, 2H), 7.06 (d, J = 7.6 Hz, 2H), 2.51 (s, 3H), 2.27 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 154.1, 141.2, 141.0, 140.7, 139.8, 139.1, 138.0, 137.7, 132.8, 131.9, 129.6, 129.1, 128.7, 128.0, 127.4, 118.6, 95.2, 88.0, 21.8, 21.5; HRMS (ESI) calcd for $[C_{24}H_{18}N_2]$ requires $[M+H]^+$ 335.1548, found 335.1572

*3-(Cyclopropylethynyl)-6-methyl-2-phenylquinoxaline (**3b**).* The product was obtained as a yellow needles (96.6 mg, 68%): mp 111−116 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00−7.93 (m, 3H), 7.86−7.82 (m, 1H), 7.58−7.49 (m, 4H), 2.58 (s, 3H), 1.50−1.42 (m, 1H), 0.89−0.82 (m, 4H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 153.5, 140.4, 140.2, 138.4, 137.3, 132.1, 129.0, 128.8, 128.2, 127.5, 127.4, 126.8, 100.2, 74.8, 21.4, 8.3, 0.00; HRMS (ESI) calcd for $[C_{20}H_{16}N_2]$ requires $[M+H]^+$ 285.1392, found 285.1391.

*6-Methyl-3-(p-tolylethynyl)-2-(3,4,5-trimethoxyphenyl)-quinoxaline (**3c**).* The product was obtained as a yellow needles (186.7 mg, 88%): mp 124−128 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01 (d, J = 8.4 Hz, 1H), 7.89 (s, 1H), 7.61 (d, J = 8.4 Hz, 1H), 7.39−7.34 (m, 3H), 7.26 (s, 2H), 7.17−7.15 (m, 1H), 3.94 (s, 3H), 3.91 (s, 6H), 2.61 (s, 3H), 2.37 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 153.3, 152.9, 141.0, 140.9, 140.1, 139.2, 139.0, 133.1, 133.0, 132.0, 129.3, 128.6, 127.4, 118.5, 107.0, 104.6, 95.5, 88.1, 60.9, 56.3, 56.2, 21.9, 21.6; HRMS (ESI) calcd for $[C_{27}H_{24}N_2O_3]$ requires $[M+H]^+$ 425.1865, found 425.1882.

*3-(Hex-1-yn-1-yl)-6-methyl-2-(3,4,5-trimethoxyphenyl)-quinoxaline (**3d**).* The product was obtained as a yellow oil (160.0 mg, 82%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91−7.88 (m, 1H), 7.96−7.76 m, 1H), 7.50 (d, J = 8.5 Hz, 1H), 7.20−7.19 (m, 2H), 3.88 (s, 6H), 3.85 (s, 3H), 2.50 (s, 3H), 2.39 (t, J = 7.6 Hz, 2H), 1.53−1.45 (m, 2H), 1.34−1.25 (m, 2H), 0.81 (t, J = 7.2 Hz, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 153.6, 152.9, 140.9, 140.7, 139.2, 138.8, 133.2, 132.8, 128.6, 128.1, 127.3, 106.9, 97.4, 80.0, 60.9, 56.2, 30.1, 22.0, 21.9, 19.5, 13.5; HRMS (ESI) calcd for $[C_{24}H_{26}N_2O_3]$ requires $[M+H]^+$ 391.2022, found 391.2021.

*3-((4-tert-Butyl)phenyl)ethynyl)-2-(3,5-dimethoxyphenyl)-6-methylquinoxaline (**3e**).* The product was obtained as a yellow semisolid (200.8 mg, 92%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01 (d, J = 8.4 Hz, 1H), 7.90−7.89 (m, 1H), 7.60 (d, J = 8.4 Hz, 1H), 7.46−7.44 (m, 2H), 7.38−7.36 (m, 2H), 7.24−7.23 (m, 2H), 6.65−6.64 (m, 1H), 3.86(s, 6H), 2.61(s, 3H), 1.31 (s, 9H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 160.5, 154.0, 153.0, 141.2, 140.9, 139.6, 139.0, 132.9, 131.9, 128.8, 128.1, 127.5, 125.5, 118.7, 107.7, 102.2, 95.6, 88.0, 55.54, 55.50, 34.9, 31.1, 21.9; HRMS (ESI) calcd for $[C_{29}H_{28}N_2O_2]$ requires $[M+H]^+$ 437.2229, found 437.2229.

*6-Methyl-2-(thiophen-3-yl)-3-(p-tolylethynyl)quinoxaline (**3f**).* The product was obtained as a yellow needles (129.3 mg, 76%): mp 129−134 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.48−844 (m, 1H), 8.05−8.03 (m, 1H), 8.00−7.97 (m, 1H), 7.87 (s, 1H), 7.60−7.53 (m, 3H), 7.49−7.47 (m, 1H), 7.23 (d, J = 7.6 Hz, 2H), 2.61(s, 3H), 2.41 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 148.7, 141.3, 140.7, 140.5, 140.0, 139.1, 137.1, 132.9, 132.0, 129.3, 128.8, 128.5, 127.6, 127.4, 125.1, 118.6, 95.0, 88.3, 21.8, 21.6; HRMS (ESI) calcd for $[C_{22}H_{16}N_2S]$ requires $[M+H]^+$ 341.1112, found 341.1121.

*6-Chloro-3-(phenylethynyl)-2-(3,4,5-trimethoxyphenyl)-quinoxaline (**3g**).* The product was obtained as a yellow needles (172.3 mg, 80%): mp 155−159 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.106−8.103 (m, 1H), 8.05 (d, J = 9.1 Hz, 1H), 7.70 (dd, J = 2.3 and 9.1 Hz, 1H), 7.50−7.48 (m, 2H), 7.40−7.34 (m, 5H), 3.94 (s, 3H), 3.89 (s, 6H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 154.7, 153.0, 141.1, 139.6, 139.0, 138.7, 136.1, 132.4, 132.1, 131.7, 130.3, 129.9, 128.6, 127.5, 121.3, 106.9, 96.1, 88.2, 61.0, 56.2; HRMS (ESI) calcd for $[C_{25}H_{19}ClN_2O_3]$ requires $[M+H]^+$ 431.1162, found 431.1183.

*6-Chloro-3-(thiophen-3-ylethynyl)-2-(3,4,5-trimethoxyphenyl)-quinoxaline (**3h**).* The product was obtained as a yellow needles (181.3 mg, 83%): mp 157−161 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.06−7.97(m, 2H), 7.67−7.63 (m, 1H), 7.58−7.57 (m, 1H), 7.34−7.27 (m, 3H), 7.12 (d, J = 5.0 Hz, 1H), 3.92 (s, 3H), 3.88 (s, 6H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 153.0, 141.1, 139.6, 139.0, 138.7, 136.1, 132.4, 131.7, 131.6, 130.6, 129.6, 127.5, 126.1, 120.5, 107.0, 99.2, 91.6, 88.0, 61.0, 56.3, 56.2; HRMS (ESI) calcd for $[C_{23}H_{17}ClN_2O_3S]$ requires $[M+H]^+$ 437.0727, found 437.0743.

*6-Chloro-2-(3,5-dimethoxyphenyl)-3-(phenylethynyl)quinoxaline (**3i**).* The product was obtained as a yellow needles (170.3 mg, 85%): mp 176−181 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96−7.95 (m, 1H), 7.64−7.62 (m, 3H), 7.52−7.50 (m, 1H), 7.38−7.31 (m, 3H), 6.42−6.41 (m, 2H), 6.35−6.34 (m, 1H), 3.74 (s, 6H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 160.5, 154.9, 141.2, 139.0, 138.9, 136.2, 132.2, 131.6, 130.5, 129.8, 128.5, 127.5, 121.4, 107.6, 102.4, 96.2, 88.0, 55.5; HRMS (ESI) calcd for $[C_{24}H_{17}ClN_2O_2]$ requires $[M+H]^+$ 401.1057, found 401.1038.

*3-((4-(tert-Butyl)phenyl)ethynyl)-6-chloro-2-(3,5-dimethoxyphenyl)quinoxaline (**3j**).* The product was obtained as a yellow needles (187.3 mg, 82%): mp 171−175 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.11 (d, J = 2.3 Hz, 1H), 8.06 (d, J = 9.1 Hz, 1H), 7.70 (dd, J = 2.2 and 9.1 Hz, 1H), 7.46 (d, J = 9.1 Hz, 2H), 7.38 (m, J = 8.4 Hz, 2H), 7.23 (d, J = 1.5 Hz, 2H), 6.66 (t, J = 2.2 Hz, 1H), 3.87 (s, 6H), 1.32 (s, 9H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 160.5, 154.9, 153.4, 141.3, 139.1, 139.0, 138.9, 136.1, 132.1, 131.4, 130.5, 127.4, 125.5, 118.3, 107.7, 102.4, 96.8, 87.7, 55.6, 35.0, 31.1; HRMS (ESI) calcd for $[C_{28}H_{25}ClN_2O_2]$ requires $[M+H]^+$ 457.1683, found 457.1701.

*2-(p-Tolylethynyl)-3-(3,4,5-trimethoxyphenyl)benzo[g]-quinoxaline (**3k**).* The product was obtained as a yellow needles (177.3 mg, 77%): mp 185−200 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.74−8.73 (m, 2H), 8.19−8.14 (m, 2H), 7.65−7.61 (m, 2H), 7.47−7.46 (m, 3H), 7.23 (d, J = 7.6 Hz, 2H), 6.77−6.76 (m, 1H), 4.02−3.99 (m, 9H), 2.43 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 154.5, 153.3, 152.9, 140.4, 139.4, 137.6, 136.9, 134.3, 134.0, 133.0, 132.1, 129.4, 128.7, 128.4, 127.4, 127.1, 126.9, 118.3, 107.0, 104.5, 96.6, 88.5, 61.0, 56.2, 21.7; HRMS (ESI) calcd for $[C_{30}H_{24}N_2O_3]$ requires $[M+H]^+$ 461.1865, found 461.1876.

*2-(p-Tolylethynyl)-3-(3,4,5-trimethoxyphenyl)pyrazine (**5a**).* The product was obtained as a yellow needles (147.7 mg, 82%): mp 99−105 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.62 (d, J = 2.2 Hz, 1H), 8.59 (d, J = 2.2 Hz, 1H), 7.46 (s, 1H), 7.44 (s, 3H), 7.22 (d, J = 8.4 Hz, 2H), 4.01 (s, 3H), 3.96 (s, 6H), 2.44 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 154.9, 152.9, 142.2, 142.0, 140.0, 139.4, 137.2, 132.3, 131.8, 129.3, 118.6, 106.7, 95.3, 87.1, 60.9, 56.2, 56.1, 21.6; HRMS (ESI) calcd for $[C_{22}H_{20}N_2O_3]$ requires $[M+H]^+$ 361.1552, found 361.1559.

*2-(4-Ethylphenyl)-3-(p-tolylethynyl)pyrazine (**5b**).* The product was obtained as a yellow needles (113.3 mg, 76%): mp 89−94 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.54−8.48 (m, 2H), 8.02 (d, J = 8.2 Hz, 2H), 7.39−7.33 (m, 4H), 7.15 (d, J = 8.2 Hz, 2H), 2.74 (q, J = 7.8 Hz, 2H), 2.35 (s, 3H), 1.29 (t, J = 7.5 Hz, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 155.3, 146.1, 142.1, 142.0, 139.7, 137.3, 134.4, 131.8, 139.3, 129.2, 127.6, 118.8, 94.8, 87.1, 28.7, 21.6, 15.4; HRMS (ESI) calcd for $[C_{21}H_{18}N_2]$ requires $[M+H]^+$ 299.1548, found 299.1545.

*General Procedure for the Synthesis of Benzophenazine **2a**−**w**.* In a oven-dried RBF, a solution of *o*-alkynylaryls derivatives (**1**) (0.5 mmol) in 4 mL of CF_3COOH as a solvent and $Pd(OAc)_2$ (2 mol%), were added. The resulting reaction mixture was heated at 65 °C for 24 h. Progression of the reaction was monitored by TLC, while noticing complete consumption of *o*-alkynylaryls, reaction was brought to room temperature. The reaction mixture was diluted with ethyl acetate (10 mL) and water (15 mL) and then filtered through a plug of Celite. The layers were separated, and the organic layer was washed with aqueous saturated brine solution, dried over Na_2SO_4. Organic layer was concentrated under reduced pressure. The crude material so obtained was purified by column chromatography on silica gel (hexane:ethyl acetate) and DCM:hexane was used for crystallization. The structure and purity of known starting materials were confirmed by comparison of their physical and spectral data (^{1}H NMR, ^{13}C NMR, and HRMS).

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J. Org. Chem. 2016, 81, 9912−9923

*5-Phenylbenzo[a]phenazine (**2a**).* The product was obtained as a yellow needles (107.2 mg, 70%): mp 138−142 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.44 (d, J = 7.8 Hz, 1H), 8.31−8.27 (m, 1H), 8.21−8.16 (m, 1H), 7.84−7.82 (m, 2H), 7.78−7.75 (m, 2H), 7.74−7.70 (m, 1H), 7.63−7.59 (m, 1H), 7.54−7.52 (m, 2H), 7.49−7.42 (m, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 145.2, 143.1, 143.0, 142.3, 142.0, 139.3, 132.7, 131.4, 130.0, 129.7, 129.64, 129.59, 129.1, 128.5, 128.1, 127.8, 127.2, 127.0, 125.7; HRMS (ESI) calcd for $[C_{22}H_{14}N_2]$ requires $[M+H]^+$ 307.1235, found 307.1247.

*4-(Benzo[a]phenazin-5-yl)-N,N-dimethylaniline (**2b**).* The product was obtained as a brown needles (113.5 mg, 65%): mp 175−179 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.44 (d, J = 7.6 Hz, 1H), 8.29−8.27 (m, 1H), 8.19−8.16 (m, 1H), 8.01 (d, J = 8.4 Hz, 1H), 7.83 (s, 1H), 7.77−7.70 (m, 3H), 7.63 (t, J = 8.4 Hz, 1H), 7.46 (d, J = 8.4 Hz, 2H), 6.81 (d, J = 8.4 Hz, 2H), 2.99 (s, 6H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 150.3, 145.6, 143.5, 143.1, 142.3, 141.7, 133.1, 131.5, 130.6, 129.9, 129.7, 129.45, 129.36, 129.0, 127.6, 127.2, 126.9, 126.4, 125.6, 112.1, 40.5; HRMS (ESI) calcd for $[C_{24}H_{19}N_3]$ requires $[M+H]^+$ 350.1657, found 350.1674.

*3-Methyl-5-(p-tolyl)benzo[a]phenazine (**2c**).* The product was obtained as a yellow needles (120.3 mg, 72%): mp 184−189 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.29 (d, J = 7.6 Hz, 1H), 8.29−8.24 (m, 1H), 8.18−8.13 (m, 1H), 7.78 (s, 1H), 7.76−7.73 (m, 2H), 7.62 (s, 1H), 7.52 (d, J = 8.4 Hz, 1H), 7.43−7.41 (m, 2H), 7.29−7.27 (m, 2H), 2.41 (s, 6H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 145.2, 143.1, 142.9, 142.4, 141.9, 139.9, 137.9, 136.5, 132.9, 129.7, 129.6, 129.5, 129.2, 129.0, 127.2, 126.9, 125.6, 22.0, 21.3; HRMS (ESI) calcd for $[C_{24}H_{18}N_2]$ requires $[M+H]^+$ 335.1548, found 335.1535.

*3-Methyl-5-(thiophen-3-yl)benzo[a]phenazine (**2d**).* The product was obtained as a yellow needles (122.4 mg, 75%): mp 192−196 °C; ^{1}H NMR (400 MHz, CF_3COOD) δ 9.63−9.57 (m, 1H), 8.91−8.86 (m, 1H), 8.53−8.37 (m, 4H), 8.19 (s, 1H), 8.11 (t, J = 7.6 Hz, 1H), 8.04−7.99 (m, 1H), 7.84−7.81 (m, 1H), 7.67−7.66 (m, 1H), 2.82 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, CF_3COOD) δ 153.7, 145.5, 143.1, 138.3, 137.1, 133.5, 133.4, 133.1, 132.9, 131.0, 129.7, 129.4, 128.6, 128.2, 127.8, 127.6, 126.5, 119.8, 115.5, 21.1; HRMS (ESI) calcd for $[C_{21}H_{14}N_2S]$ requires $[M+H]^+$ 327.0956, found 327.0950.

*5-(4-(tert-Butyl)phenyl)-3-ethylbenzo[a]phenazine (**2e**).* The product was obtained as a yellow needles (138.6 mg, 71%): mp 173−177 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 (d, J = 7.6 Hz, 1H), 7.75 (d, J = 8.3 Hz, 2H), 7.68 (d, J = 8.3 Hz, 2H), 7.55−7.50 (m, 2H), 7.45−7.42 (m, 2H), 7.40−7.37 (m, 2H), 7.26 (s, 1H), 2.77 (q, J = 7.6 Hz, 2H), 1.33 (s, 9H), 1.20 (t, J = 6.8 Hz, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 157.1, 154.4, 147.3, 146.2, 137.0, 134.7, 131.7, 130.5, 129.2, 128.8, 128.2, 126.5, 125.6, 125.4, 119.1, 34.9, 31.2, 28.8, 15.5; HRMS (ESI) calcd for $[C_{28}H_{26}N_2]$ requires $[M+H]^+$ 391.2174, found 391.2163.

*2,4-Dimethoxy-5-(o-tolyl)benzo[a]phenazine (**2f**).* The product was obtained as a yellow needles (182.6 mg, 96%): mp 179−183 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.60 (d, J = 2.4 Hz, 1H), 8.30−8.27 (m, 1H), 8.17−8.15 (m, 1H), 7.76−7.73 (m, 2H), 7.49 (s, 1H), 7.19−7.14 (m, 4H), 6.44 (d, J = 2.4 Hz, 1H), 4.04 (s, 3H), 3.36 (s, 3H), 1.98 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 160.1, 158.5, 144.1, 143.6, 143.5, 143.4, 141.7, 141.6, 135.3, 134.5, 130.1, 129.7, 129.4, 129.0, 128.5, 127.6, 126.5, 125.4, 124.8, 118.1, 102.0, 99.1, 55.8, 20.0; HRMS (ESI) calcd for $[C_{25}H_{20}N_2O_2]$ requires $[M+H]^+$ 381.1603, found 381.1600.

*5-(4-(tert-Butyl)phenyl)-2,4-dimethoxybenzo[a]phenazine (**2g**).* The product was obtained as a brown needles (194.3 mg, 92%): mp 186−190 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.64−8.63 (m, 1H), 8.35−8.33 (m, 1H), 8.23−8.21 (m, 1H), 7.82−7.80 (m, 2H), 7.65 (s, 1H), 7.43−7.41 (m, 2H), 7.37−7.35 (m, 2H), 6.73−6.72 (m, 1H), 4.11 (s, 3H), 3.46 (s, 3H), 1.41 (s, 9H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 160.2, 158.5, 149.4, 144.0, 143.5, 143.4, 141.7, 141.2, 134.9, 130.1, 129.8, 129.4, 129.1, 127.8, 126.1, 124.0, 117.8, 102.4, 99.2, 55.9, 55.7, 34.7, 31.6; HRMS (ESI) calcd for $[C_{28}H_{26}N_2O_2]$ requires $[M+H]^+$ 423.2073, found 423.2065.

*5-Cyclopropyl-2,4-dimethoxybenzo[a]phenazine (**2h**).* The product was obtained as a yellow needles (158.5 mg, 96%): mp 178−182 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.48 (d, J = 2.7 Hz, 1H), 8.21−8.18 (m, 1H), 8.13−8.10 (m, 1H), 7.71−7.67 (m, 2H), 7.44 (s, 1H), 6.73 (d, J = 2.2 Hz, 1H), 4.0 (s, 3H), 3.87 (s, 3H), 2.85−2.78 (m, 1H), 0.98−0.93 (m, 2H), 0.85−0.81(m, 2H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 159.7, 159.6, 146.2, 143.9, 143.3, 141.7, 141.5, 134.8, 130.1, 129.8, 129.0, 128.8, 121.3, 119.3, 102.2, 99.1, 56.0, 55.8, 18.8, 8.3; HRMS (ESI) calcd for $[C_{21}H_{18}N_2O_2]$ requires $[M+H]^+$ 331.1447, found 331.1434.

*5-Butyl-2,4-dimethoxybenzo[a]phenazine (**2i**).* The product was obtained as a yellow needles (122.3 mg, 82%): mp 177−181 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.53−8.52 (m, 1H), 8.22−8.20 (m, 1H), 8.12 (d, J = 7.6 Hz, 1H), 7.76−7.73 (m, 2H), 7.46 (s, 1H), 6.71−6.70 (m, 1H), 4.0 (s, 3H), 3.87 (s, 3H), 3.20 (t, J = 8.0 Hz, 2H), 1.66−1.58 (m, 2H), 1.45−1.35(m, 2H), 0.89 (t, J = 7.6 Hz, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 159.4, 158.8, 145.8, 143.6, 143.2, 141.5, 141.3, 135.0, 129.9, 129.7, 128.8, 128.7, 124.2, 118.2, 101.8, 99.2, 55.7, 55.5, 38.3, 33.7, 22.9, 14.1; HRMS (ESI) calcd for $[C_{22}H_{22}N_2O_2]$ requires $[M+H]^+$ 347.1760, found 347.1765.

*2,3,4-Trimethoxy-5-phenylbenzo[a]phenazine (**2j**).* The product was obtained as a brown needles (168.4 mg, 85%): mp 188−192 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.83 (s, 1H), 8.31−8.27 (m, 1H), 8.18−8.15 (m, 1H), 7.79−7.74 (m, 2H), 7.59 (s, 1H), 7.42−7.40 (m, 2H), 7.38−7.31 (m, 3H), 4.15 (s, 3H), 3.89 (s, 3H), 3.23 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 153.8, 151.0, 144.9, 143.4, 143.2, 143.0, 142.5, 141.7, 141.4, 129.8, 129.5, 129.0, 128.7, 128.2, 127.4, 127.1, 126.6, 121.6, 102.9, 61.0, 60.9, 56.2; HRMS (ESI) calcd for $[C_{25}H_{20}N_2O_3]$ requires $[M+Na]^+$ 419.1372, found 419.1384.

*2,3,4-Trimethoxy-5-(p-tolyl)benzo[a]phenazine (**2k**).* The product was obtained as a brown needles (176.4 mg, 86%): mp 168−172 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.86 (s, 1H), 8.34−8.30 (m, 1H), 8.22−8.18 (m, 1H), 7.81−7.78 (m, 2H), 7.64 (s, 1H), 7.38 (d, J = 7.6 Hz, 2H), 7.23 (d, J = 7.6 Hz, 2H), 4.19 (s, 3H), 3.96 (s, 3H), 3.30 (s, 3H), 2.44 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 153.8, 151.1, 145.0, 143.5, 143.1, 142.6, 141.7, 141.5, 140.3, 136.1, 129.7, 129.5, 129.4, 129.0, 128.7, 128.1, 127.8, 127.4, 121.8, 103.0, 61.1, 61.0, 56.2, 21.3; HRMS (ESI) calcd for $[C_{26}H_{22}N_2O_3]$ requires $[M+Na]^+$ 433.1528, found 433.1523.

*2,3,4-Trimethoxy-5-(o-tolyl)benzo[a]phenazine (**2l**).* The product was obtained as a brown needles (172.3 mg, 84%): mp 160−164 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.08 (s, 1H), 8.27−8.25 (m, 1H), 8.15−8.13 (m, 1H), 7.73−7.71 (m, 2H), 7.52 (s, 1H), 7.25−7.22 (m, 2H), 7.20−7.14 (m, 2H), 4.11 (s, 3H), 3.58 (s, 3H), 3.17 (s, 3H), 2.0 (s, 3H) ; ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 153.8, 150.9, 144.8, 143.2, 143.0, 142.7, 141.8, 141.4, 135.9, 129.8, 129.5, 129.0, 128.7, 128.4, 127.7, 126.8, 126.6, 124.7, 122.1, 102.9, 61.0, 60.8, 56.2, 20.2; HRMS (ESI) calcd for $[C_{26}H_{22}N_2O_3]$ requires $[M+Na]^+$ 433.1528, found 433.1546.

*2,3,4-Trimethoxy-5-(4-methoxyphenyl)benzo[a]phenazine (**2m**).* The product was obtained as a brown needles (187.6 mg, 88%): mp 181−185 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.83 (s, 1H), 8.30−8.28 (m, 1H), 8.18−8.16 (m, 1H), 7.78−7.75 (m, 2H), 7.59 (s, 1H), 7.36 (d, J = 8.4 Hz, 2H), 6.90 (d, J = 8.4 Hz, 2H), 4.15 (s, 3H), 3.91 (s, 3H), 3.83 (s, 3H), 3.25 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 158.5, 153.8, 151.2, 145.0, 143.2, 143.1, 142.7, 141.7, 141.4, 139.2, 135.6, 129.9, 129.5, 129.0, 128.8, 127.5, 121.8, 114.0, 112.5, 103.1, 61.2, 61.1, 56.2, 55.3; HRMS (ESI) calcd for $[C_{26}H_{22}N_2O_4]$ requires $[M+Na]^+$ 449.1477, found 449.1470.

*N,N-Dimethyl-4-(2,3,4-trimethoxybenzo[a]phenazin-5-yl)aniline (**2n**).* The product was obtained as a yellow needles (188.9 mg, 86%): mp 195−199 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.83 (s, 1H), 8.29−8.26 (m, 1H), 8.17−8.15 (m, 1H), 7.76−7.73 (m, 2H), 7.61 (s, 1H), 7.35−7.33 (m, 2H), 6.73 (d, J = 9.2 Hz, 2H), 4.14 (s, 3H), 3.92 (s, 3H), 3.26 (s, 3H), 2.96 (s, 6H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 153.6, 151.3, 149.5, 145.0, 143.9, 143.1, 142.9, 141.6, 131.1, 129.7, 129.5, 129.4, 129.2, 129.0, 127.2, 121.9, 111.2, 103.1, 61.3, 61.2, 56.2, 40.7; HRMS (ESI) calcd for $[C_{27}H_{25}N_3O_3]$ requires $[M+Na]^+$ 462.1794, found 462.1785.

*2,3,4-Trimethoxy-5-(4-(trifluoromethyl)phenyl)benzo[a]-phenazine (**2o**).* The product was obtained as a brown needles (174.1 mg, 75%): mp 198−202 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.80 (s,

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J. Org. Chem. 2016, 81, 9912−9923

1H), 8.26−8.24 (m, 1H), 8.14−8.12 (m, 1H), 7.76−7.71 (m, 2H), 7.61 (d, J = 7.8 Hz, 2H), 7.51 (t, J = 5.0 Hz, 3H), 4.12 (s, 3H), 3.88 (s, 3H), 3.20 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 154.1, 150.6, 147.0, 144.9, 143.1, 142.3, 141.9, 141.7, 141.4, 130.0, 129.8, 129.6, 129.1, 128.7, 128.5, 127.5, 125.8, 124.10 (q, $^1J_{C-F}$ = 15.2 Hz, $1^{13}C$), 123.1, 121.1, 103.1, 61.0, 60.7, 56.2; HRMS (ESI) calcd for $[C_{26}H_{19}F_3N_2O_3]$ requires $[M+H]^+$ 465.1426, found 465.1426.

*5-(2-Fluorophenyl)-2,3,4-trimethoxybenzo[a]phenazine (**2p**).* The product was obtained as a yellow needles (161.6 mg, 78%): mp 187−191 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 8.82 (s, 1H), 8.32−8.29 (m, 1H), 8.20−8.17 (m, 1H), 7.79−7.77 (m, 2H), 7.646−7.643 (m, 1H), 7.44−7.40 (m, 1H), 7.36−7.30 (m, 1H), 7.22−7.15 (m, 1H), 7.07 (t, J = 9.1 Hz, 1H), 4.15 (s, 3H), 3.91 (s, 3H), 3.29 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 158.8, 152.9 (d, $^1J_{C-F}$ = 208.0 Hz, $1^{13}C$), 150.9, 144.7, 143.1, 142.6, 142.0, 141.7, 139.3, 137.3, 130.0, 129.8, 129.7, 129.6, 129.1, 128.8, 128.7, 128.0, 123.5, 123.3 (d, $^4J_{C-F}$ = 3.8 Hz, $1^{13}C$), 121.7, 115.9, 114.4 (d, $^2J_{C-F}$ = 21.1 Hz, 1H), 114.1, 102.9, 61.1, 61.0, 56.3; HRMS (ESI) calcd for $[C_{25}H_{19}FN_2O_3]$ requires $[M+H]^+$ 415.1458, found 415.1460.

*2,3,4-Trimethoxy-5-(phenoxymethyl)benzo[a]phenazine (**2q**).* The product was obtained as a brown needles (179.1 mg, 84%): mp 159−162 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 8.75 (s, 1H), 8.23−8.21 (m, 1H), 8.14−8.10 (m, 2H), 7.73−7.71 (m, 2H), 7.27−7.23 (m, 2H), 7.02 (d, J = 7.9 Hz, 2H), 6.90 (t, J = 7.3 Hz, 1H), 5.66 (s, 2H), 4.11 (s, 3H), 4.0 (s, 3H), 3.96 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 158.7, 153.5, 150.9, 144.6, 142.9, 142.8, 141.7, 141.3, 138.4, 129.8, 129.5, 129.4, 129.0, 128.6, 122.7, 120.9, 120.2, 114.8, 103.2, 69.3, 61.6, 61.0, 56.2; HRMS (ESI) calcd for $[C_{26}H_{22}N_2O_4]$ requires $[M+Na]^+$ 449.1477, found 449.1483.

*2,3,4-Ttrimethoxy-5-phenethylbenzo[a]phenazine (**2r**).* The product was obtained as a brown needles (169.7 mg, 80%): mp 123−127 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 8.81 (s, 1H), 8.25−8.21 (m, 1H), 8.15−8.10 (m, 1H), 7.74−7.69 (m, 2H), 7.57 (s, 1H), 7.24 (d, J = 4.6 Hz, 4H), 7.16−7.11 (m, 1H), 4.12 (s, 3H), 3.98 (s, 3H), 3.96 (s, 3H), 3.49−3.45 (m, 2H), 3.02−2.98 (m, 2H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 153.4, 151.4, 145.0, 143.7, 143.0, 142.9, 142.3, 141.6, 141.5, 129.8, 129.5, 129.2, 128.9, 128.5, 128.4, 125.9, 125.7, 121.6, 103.4, 61.6, 61.0, 56.2, 39.7, 37.8; HRMS (ESI) calcd for $[C_{27}H_{24}N_2O_3]$ requires $[M+Na]^+$ 447.1685, found 447.1684.

*4-(4-Ethylphenyl)thieno[3,2-a]phenazine (**2s**).* The product was obtained as a yellow needles (149.7 mg, 88%): mp 162−166 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 8.59 (d, J = 5.3 Hz, 1H), 8.36−8.33 (m, 1H), 8.29−8.26 (m, 1H), 8.06 (s, 1H), 7.88−7.81 (m, 3H), 7.75(d, J = 5.3 Hz, 1H), 7.41 (d, J = 8.4 Hz, 2H), 7.25 (s, 1H), 2.79 (q, J = 7.6 Hz, 2H), 1.35 (t, J = 7.6 Hz, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 145.5, 143.0, 142.5, 142.3, 141.3, 140.9, 140.1, 139.3, 137.4, 136.5, 130.0, 129.5, 129.0, 128.6, 128.3, 127.7, 124.8, 123.6, 28.7, 15.4; HRMS (ESI) calcd for $[C_{22}H_{16}N_2S]$ requires $[M+H]^+$ 341.1112, found 341.1141.

*4-(4-(tert-Butyl)phenyl)thieno[3,2-a]phenazine (**2t**).* The product was obtained as a brown needles (158.4 mg, 86%): mp 166−170 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 8.60−8.58 (m, 1H), 8.36−8.32 (m, 1H), 8.29−8.26 (m, 1H), 8.07 (s, 1H), 7.87−7.83 (m, 4H), 7.76−7.74 (m, 1H), 7.61−7.59 (m, 2H), 1.43 (s, 9H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 152.2, 143.4, 142.9, 142.2, 141.1, 140.4, 139.9, 137.4, 136.2, 129.9, 129.8, 129.5, 129.4, 128.0, 127.5, 126.0, 124.7, 124.0, 34.8, 31.3; HRMS (ESI) calcd for $[C_{24}H_{20}N_2S]$ requires $[M+H]^+$ 369.1425, found 369.1430.

*4-(2-Fluorophenyl)thieno[3,2-a]phenazine (**2u**).* The product was obtained as a brown needles (125.5 mg, 76%): mp 169−173 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 8.49 (d, J = 5.3 Hz, 1H), 8.28−8.26 (m, 1H), 8.21−8.19 (m, 1H), 8.0 (s, 1H), 7.81−7.77 (m, 2H), 7.66−7.63 (m, 2H), 7.47−7.41 (m, 1H), 7.28−7.20 (m, 2H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 159.7(d, $^1J_{C-F}$ = 249.2 Hz, $1^{13}C$), 142.84, 142.82, 142.6, 142.4, 141.6, 140.1, 137.2, 134.3, 130.9, 130.8, 130.3, 129.9, 129.5 (d, $^4J_{C-F}$ = 3.8 Hz, $1^{13}C$), 129.4, 127.6, 126.2, 124.6, 124.5, 116.6 (d, $^2J_{C-F}$ = 22.4 Hz, $1^{13}C$); HRMS (ESI) calcd for $[C_{20}H_{11}FN_2S]$ requires $[M+H]^+$ 331.0705, found 331.0708.

*4-Cyclohexylthieno[3,2-a]phenazine (**2v**).* The product was obtained as a brown needles (119.4 mg, 75%): mp 139−143 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 8.44 (d, J = 5.3 Hz, 1H), 8.25−8.23 (m, 1H), 8.19−8.16 (m, 1H), 7.81 (s, 1H), 7.78−7.74 (m, 2H), 7.62 (d, J = 5.3 Hz, 1H), 2.95−2.87 (m, 1H), 2.25−2.15 (m, 2H), 1.98−1.77 (m, 4H), 1.69−1.59 (m, 2H), 1.54−1.43 (m, 2H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 146.4, 143.6, 142.5, 142.2, 142.0, 139.8, 136.6, 129.6, 129.4, 129.2, 126.2, 124.9, 120.6, 44.0, 33.2, 29.7, 26.8; HRMS (ESI) calcd for $[C_{20}H_{18}N_2S]$ requires $[M+H]^+$ 319.1269, found 319.1282.

*4-Cyclopropylthieno[3,2-a]phenazine (**2w**).* The product was obtained as a brown needles (113.3 mg, 82%): mp 131−135 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 8.41 (d, J = 5.3 Hz, 1H), 8.22−8.20 (m, 1H), 8.14−8.11 (m, 1H), 7.75−7.72 (m, 2H), 7.62 (d, J = 7.6 Hz, 1H), 7.51 (s, 1H), 2.23−2.16 (m, 1H), 1.15−1.11 (m, 2H), 1.00−0.96 (m, 2H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 143.5, 143.3, 142.4, 141.8, 139.8, 136.2, 129.62, 129.57, 129.4, 129.2, 126.6, 124.7, 119.2, 15.0, 8.4; HRMS (ESI) calcd for $[C_{17}H_{12}N_2S]$ requires $[M+H]^+$ 277.0799, found 277.0810.

*General Procedure for the Synthesis of Substituted Benzophenazine **4a−k** and Benzoquinoxaline (**6a−b**).* In a oven-dried RBF, a solution of *o*-alkynylaryls derivatives (**3** and **5**) (0.5 mmol) in 4 mL of CF_3COOH as a solvent and $Pd(OAc)_2$ (2 mol%), were added. The resulting reaction mixture was heated at 65 °C for 24 h. Progression of the reaction was monitored by TLC, while noticing complete consumption of *o*-alkynylaryls, reaction was brought to room temperature. The reaction mixture was diluted with ethyl acetate (10 mL) and water (15 mL) and then filtered through a plug of Celite. The layers were separated, and the organic layer was washed with aqueous saturated brine solution and dried over Na_2SO_4. Organic layer was concentrated under reduced pressure. The crude material so obtained was purified by column chromatography on silica gel (hexane: ethyl acetate) and DCM:hexane was used for crystallization. The structure and purity of known starting materials were confirmed by comparison of their physical and spectral data (^1H NMR, ^{13}C NMR, and HRMS).

*9-Methyl-5-(p-tolyl)benzo[a]phenazine (**4a**).* The product was obtained as a yellow needles (125.4 mg, 75%): mp 161−165 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 9.36−9.33 (m, 1H), 8.10 (d, J = 8.7 Hz, 1H), 7.87 (s, 1H), 7.81 (d, J = 8.4 Hz, 1H), 7.77 (s, 1H), 7.66−7.62 (m, 1H), 7.56−7.51 (m, 2H), 7.40−7.38 (m, 2H), 7.25−7.23 (m, 2H), 2.51 (s, 3H), 2.37 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 144.9, 143.1, 142.5, 141.5, 140.5, 140.2, 137.8, 136.5, 132.6, 132.5, 132.3, 131.5, 129.6, 129.1, 128.5, 127.53, 127.45, 127.1, 126.9, 125.4, 22.1, 21.3;HRMS (ESI) calcd for $[C_{24}H_{18}N_2]$requires $[M+H]^+$ 335.1548, found 335.1568.

*5-Cyclopropyl-9-methylbenzo[a]phenazine (**4b**).* The product was obtained as a yellow needles (122.2 mg, 86%): mp 142−146 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 9.39−9.29 (m, 1H), 8.35−8.33 (m, 1H), 8.10 (d, J = 8.7 Hz, 1H), 7.87 (s, 1H), 7.73−7.67 (m, 2H), 7.59 (s, 1H), 7.56−7.52 (m, 1H), 2.54 (s, 3H), 2.32−2.27 (m, 1H), 1.10−1.05 (m, 2H), 0.88−0.84 (m, 2H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 144.7, 143.5, 142.9, 141.6, 140.4, 133.8, 132.1, 131.0, 129.4, 129.1, 128.4, 127.5, 127.4, 125.3, 124.7, 123.6, 22.1, 13.9, 6.9, 1.0; HRMS (ESI) calcd for $[C_{20}H_{16}N_2]$ requires $[M+H]^+$ 285.1392, found 285.1391.

*2,3,4-Trimethoxy-9-methyl-5-(p-tolyl)benzo[a]phenazine (**4c**).* The product was obtained as a brown needles (157.0 mg, 74%): mp 147−152 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 8.79−8.77 (m, 1H), 8.14 (d, J = 9.2 Hz, 1H), 8.04−8.02 (m, 1H), 7.90 (s, 1H), 7.58−7.56 (m, 2H), 7.30 (d, J = 7.6 Hz, 2H), 7.17−7.14 (m, 1H), 4.12 (s, 3H), 3.88 (s, 3H), 3.23 (s, 3H), 2.58 (s, 3H), 2.37 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 153.7, 151.1, 144.7, 143.2, 142.5, 140.8, 140.5, 140.4, 140.3, 136.1, 132.6, 132.3, 129.0, 128.5, 128.1, 127.8, 127.5, 127.4, 121.6, 102.7, 61.1, 60.1, 56.2, 22.1, 21.3; HRMS (ESI) calcd for $[C_{27}H_{24}N_2O_3]$ requires $[M+H]^+$ 425.1865, found 425.1881.

*5-Butyl-2,3,4-trimethoxy-9-methylbenzo[a]phenazine (**4d**).* The product was obtained as a brown needles (171.8 mg, 88%): mp 90−94 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 8.72−8.70 (m, 1H), 8.05 (d, J = 8.7 Hz, 1H), 7.83 (s, 1H), 7.50−7.46 (m, 2H), 4.07 (s, 3H), 3.93−3.92 (m, 6H), 3.15 (t, J = 7.3 Hz, 2H), 2.51 (s, 3H), 1.68−1.64 (m, 2H), 1.43−1.38 (m, 2H), 0.91−0.87 (m, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 153.13, 153.07, 151.5, 144.6, 144.5, 144.0, 142.9, 141.5,

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140.7, 140.2, 131.7, 128.9, 127.2, 125.1, 121.6, 102.9, 61.4, 60.9, 56.1, 36.9, 33.2, 22.9, 22.0, 14.0; HRMS (ESI) calcd for $[C_{24}H_{26}N_2O_3]$ requires $[M+H]^+$ 391.2022, found 391.2021.

*5-(4-(tert-Butyl)phenyl)-2,4-dimethoxy-9-methylbenzo[a]-phenazine (**4e**).* The product was obtained as a brown needles (178.9 mg, 82%): mp 149−153 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.56−8.54 (m, 1H), 8.15 (d, J = 8.4 Hz, 1H), 8.05−8.03 (m, 1H), 7.91 (s, 1H), 7.57 (m, 1H), 7.35−7.33 (m, 2H), 7.29−7.27 (m, 2H), 6.65 (s, 1H), 4.05 (s, 3H), 3.39(s, 3H), 2.56 (s, 3H), 1.33 (s, 9H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 160.0, 158.3, 149.2, 143.6, 143.5, 143.1, 141.2, 140.7, 134.9, 132.8, 132.1, 129.1, 127.7, 127.4, 126.1, 123.8, 117.5, 102.0, 98.8, 55.7, 55.5, 34.5, 31.5, 22.1; HRMS (ESI) calcd for $[C_{29}H_{28}N_2O_2]$ requires $[M+H]^+$ 437.2229, found 437.2230.

*8-Methyl-4-(p-tolyl)thieno[3,2-a]phenazine (**4f**).* The product was obtained as a yellow needles (124.2 mg, 73%): mp 135−140 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.38−8.36 (m, 1H), 8.04−7.95 (m, 1H), 7.90−7.81 (m, 2H), 7.65−7.63 (m, 1H), 7.59−7.55 (m, 1H), 7.50−7.47 (m, 2H), 7.26−7.21 (m, 2H), 2.50 (s, 3H), 2.35 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 143.1, 142.6, 140.8, 140.3, 139.3, 138.9, 138.2, 137.4, 136.4, 132.6, 129.6, 129.4, 128.8, 128.1, 127.5, 125.2, 124.5, 123.8, 22.1, 21.3; HRMS (ESI) calcd for $[C_{22}H_{16}N_2S]$ requires $[M+H]^+$ 341.1112, found 341.1108.

*9-Chloro-2,3,4-trimethoxy-5-phenylbenzo[a]phenazine (**4g**).* The product was obtained as a brown needles (183.1 mg, 85%): mp 210−215 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.72 (s, 1H), 8.15 (d, J = 8.4 Hz, 1H), 8.10 (d, J = 2.2 Hz, 1H), 7.64 (dd, J = 2.3 and 9.1 Hz, 1H), 7.51 (s, 1H), 7.40−7.31 (m, 5H), 4.11 (s, 3H), 3.88 (s, 3H), 3.22 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 154.0, 151.1, 145.1, 144.3, 143.12, 143.08, 141.5, 140.1, 135.7, 130.73, 130.69, 128.5, 128.1, 127.6, 127.2, 126.7, 121.7, 103.0, 61.1, 61.0, 56.2; HRMS (ESI) calcd for $[C_{25}H_{19}ClN_2O_3]$ requires $[M+H]^+$ 431.1162, found 431.1185.

*9-Chloro-2,3,4-trimethoxy-5-(thiophen-3-yl)benzo[a]phenazine (**4h**).* The product was obtained as a brown needles (183.5 mg, 84%): mp 218−222 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.75 (s, 1H), 8.20 (d, J = 9.1 Hz, 1H), 8.16−8.15 (m, 1H), 7.69 (dd, J = 2.2 Hz, and 9.1 Hz, 1H), 7.64 (s, 1H), 7.32 (s, 1H), 7.28−7.26 (m, 1H), 7.19−7.18 (m, 1H), 4.13 (s, 3H), 3.93 (s, 3H), 3.31 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 154.0, 151.1, 145.3, 143.2, 143.1, 141.7, 140.2, 139.9, 139.2, 135.8, 130.8, 129.9, 128.5, 127.7, 127.5, 123.3, 121.9, 121.5, 103.1, 61.21, 61.16, 56.3; HRMS (ESI) calcd for $[C_{23}H_{17}ClN_2O_3S]$ requires $[M+H]^+$ 437.0727, found 437.0719.

*9-Chloro-2,4-dimethoxy-5-phenylbenzo[a]phenazine (**4i**).* The product was obtained as a brown needles (164.3 mg, 82%): mp 201−205 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97−7.96 (m, 1H), 7.83 (d, J = 9.1 Hz, 1H), 7.55 (dd, J = 1.8 and 8.7 Hz, 1H), 7.38−7.37(m, 2H), 7.31−7.25 (m, 3H), 7.04 (s, 1H), 6.719−6.713 (m, 1H), 6.23−6.22 (m, 1H), 3.79 (s, 3H), 3.25 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 162.7, 159.2, 158.9, 157.3, 146.1, 142.9, 141.7, 138.6, 135.0, 130.8, 129.3, 128.1, 127.8, 127.6, 126.4, 126.3, 98.8, 98.0, 55.8, 55.6; HRMS (ESI) calcd for $[C_{24}H_{17}ClN_2O_2]$ requires $[M+H]^+$ 401.1057, found 401.1037.

*5-(4-(tert-Butyl)phenyl)-9-chloro-2,4-dimethoxybenzo[a]-phenazine (**4j**).* The product was obtained as a brown needles (182.7 mg, 80%): mp 107−111 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.42 (d, J = 2.7 Hz, 1H), 8.12 (d, J = 9.1 Hz, 1H), 8.08 (d, J = 2.3 Hz, 1H), 7.61−7.58 (m, 1H), 7.48 (s, 1H), 7.32 (d, J = 8.2 Hz, 2H), 7.25 (d, J = 8.2 Hz, 2H), 6.61 (d, J = 2.3 Hz, 1H), 3.99 (s, 3H), 3.36 (s, 3H), 1.31 (s, 9H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 160.2, 158.4, 149.4, 144.7, 143.7, 143.4, 141.5, 140.9, 139.9, 135.8, 134.6, 130.8, 130.6, 127.60, 127.56, 125.7, 123.8, 117.6, 102.4, 99.1, 55.7, 55.5, 34.6, 31.5; HRMS (ESI) calcd for $[C_{28}H_{25}ClN_2O_2]$ requires $[M+H]^+$ 457.1683, found 457.1710.

*2,3,4-Trimethoxy-5-(p-tolyl)dibenzo[a,i]phenazine (**4k**).* The product was obtained as a brown needles (230.2 mg, 86%): mp 217−222 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.99 (s, 1H), 8.93 (s, 1H), 8.85 (s, 1H), 8.18−8.14 (m, 2H), 7.60 (s, 1H), 7.58−7.55 (m, 2H), 7.40 (d, J = 7.6 Hz, 2H), 7.27−7.25 (m, 2H), 4.24 (s, 3H), 3.98 (s, 3H), 3.32 (s, 3H), 2.46 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 153.9, 151.4, 145.4, 144.4, 144.1, 142.9, 140.2, 139.9, 138.6, 136.4, 134.1, 133.9, 128.8, 128.5, 128.4, 128.0, 127.9, 127.7, 127.5, 126.9, 126.54, 126.47, 121.7, 103.8, 61.18, 61.16, 56.3, 21.3; HRMS (ESI) calcd for $[C_{30}H_{24}N_2O_3]$ requires $[M+H]^+$ 461.1865, found 461.1864.

*7,8,9-Trimethoxy-6-(p-tolyl)benzo[f]quinoxaline (**6a**).* The product was obtained as a brown needles (153.1 mg, 85%): mp 87−91 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.84 (dd, J = 10.5 and 1.8 Hz, 2H), 8.64 (s, 1H), 7.62 (s, 1H), 7.34 (d, J = 7.8 Hz, 2H), 7.23(d, J = 7.8 Hz, 2H), 4.14 (s, 3H), 3.95 (s, 3H), 3.30 (s, 3H), 2.44 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 153.8, 150.6, 144.6, 144.5, 142.5, 142.1, 141.7, 140.4, 140.2, 136.1, 128.9, 128.3, 127.7, 127.3, 122.2, 101.2, 61.10, 60.96, 56.1, 21.3; HRMS (ESI) calcd for $[C_{22}H_{20}N_2O_3]$ requires $[M+H]^+$ 361.1552, found 361.1559.

*8-Ethyl-6-(p-tolyl)benzo[f]quinoxaline (**6b**).* The product was obtained as a brown needles (122.3 mg, 82%): mp 76−80 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.14 (d, J = 8.2 Hz, 1H), 8.79−8.77 (m, 2H), 7.76 (s, 1H), 7.68 (s, 1H), 7.55 (d, J = 8.7 Hz, 1H), 7.38 (d, J = 7.7 Hz, 2H), 7.27−7.24 (m, 2H), 2.71 (q, J = 7.3 Hz, 2H), 2.39 (s, 3H), 1.19 (t, J = 7.7 Hz, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 145.4, 144.3, 143.9, 142.9, 142.0, 141.3, 137.7, 136.6, 132.7, 129.7, 129.2, 128.0, 126.9, 125.1, 124.8, 29.3, 21.3, 15.7; HRMS (ESI) calcd for $[C_{21}H_{18}N_2]$ requires $[M+H]^+$ 299.1548, found 299.1540.

*Unusual Hydroxylation. (Z)-1-(4-(tert-Butyl)phenyl)-2-(3-(4-nitrophenyl)quinoxalin-2-yl)ethenol (**7a**).* The product was obtained as a brown needles (191.4 mg, 90%): mp 191−196 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 15.69 (br s, 1H), 8.41(d, J = 9.1 Hz, 2H), 7.94 (d, J = 8.4 Hz, 2H), 7.88−7.85 (m, 1H), 7.83−7.79 (m, 1H), 7.70 (d, J = 8.4 Hz, 2H), 7.64−7.57 (m, 2H), 7.47−7.42 (m, 2H), 6.20 (s, 1H), 1.32 (s, 9H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 180.7, 154.8, 154.2, 148.5, 147.3, 143.6, 137.1, 134.8, 132.9, 131.6, 130.1, 129.4, 126.3, 125.6, 123.9, 120.2, 90.5, 34.9, 31.1; HRMS (ESI) calcd for $[C_{26}H_{23}N_3O_3]$ requires $[M+H]^+$ 426.1818, found 426.1801.

*(Z)-Methyl 4-(3-(2-hydroxy-2-(4-methoxyphenyl)vinyl)-quinoxalin-2-yl)benzoate (**7b**).* The product was obtained as a yellow needles (181.4 mg, 88%): mp 210−215 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 15.6 (br s, 1H), 8.16 (d, J = 8.4 Hz, 2H), 7.77 (t, J = 8.4 Hz, 3H), 7.67 (d, J = 9.1 Hz, 2H), 7.52−7.48 (m, 1H), 7.44−7.41 (m, 1H), 7.32 (t, J = 7.6 Hz, 1H), 6.83 (d, J = 9.1 Hz, 2H), 6.15 (s, 1H), 3.92(s, 3H), 3.77 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 182.4, 166.6, 162.1, 156.1, 146.7, 141.7, 136.6, 131.9, 131.2, 130.8, 130.6, 130.0, 129.3, 128.9, 128.5, 125.6, 118.9, 113.7, 90.1, 55.4, 52.4; HRMS (ESI) calcd for $[C_{25}H_{20}N_2O_4]$ requires $[M+H]^+$ 413.1501, found 413.1485.

*(Z)-1-(3-Methoxyphenyl)-2-(3-(4-(trifluoromethyl)phenyl)-quinoxalin-2-yl)ethanol (**7c**).* The product was obtained as a brown needles (181.6 mg, 86%): mp 154−157 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 15.82 (br s, 1H), 7.90−7.88 (m, 3H), 7.84−7.80 (m, 3H), 7.62−7.52 (m, 2H), 7.48−7.46 (m, 1H), 7.39 (s, 1H), 7.32−7.29 (m, 2H), 6.28 (s, 1H), 3.85 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 181.2, 159.8, 155.2, 147.2, 139.3, 137.1, 132.3, 131.3, 130.2, 129.5, 129.3, 126.2, 125.75 (q, $^1J_{C-F}$ = 15.2 Hz, 1C), 119.7, 119.0, 117.0, 111.5, 90.9, 55.3; HRMS (ESI) calcd for $[C_{24}H_{17}F_3N_2O_2]$ requires $[M+H]^+$ 423.1320, found 423.1352.

*2-(4-(tert-Butyl)phenyl)furo[2,3-b]quinoxaline (**3′**).* The product was obtained as a brown needles (111.8 mg, 74%): mp 226−231 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.19−8.15 (m, 1H), 8.12−8.09 (m, 1H), 7.96 (d, J = 8.2 Hz, 2H), 7.75−7.70 (m, 2H), 7.56 (d, J = 8.6 Hz, 2H), 7.24(s, 1H), 1.38 (s, 9H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 164.3, 155.0, 154.4, 144.7, 142.2, 138.6, 128.7, 128.62, 128.56, 128.2, 126.1, 126.0, 125.7, 100.0, 35.1, 31.1; HRMS (ESI) calcd for $[C_{20}H_{18}N_2O]$ requires $[M+H]^+$ 303.1497, found 303.1490.

*Deuterium Labeling Experiments. 5-(2-Fluorophenyl)-2,3,4-trimethoxy-1,6-di-[D]benzo[a]phenazine (**8a**).* The product was obtained as a yellow needles (174.9 mg, 84%): mp 179−183 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.88 (s, 0.16H), 8.37−8.34 (m, 1H), 8.26−8.23 (m, 1H), 7.87−7.83 (m, 2H), 7.72 (s, 0.1H), 7.52−7.47 (m, 1H), 7.43−7.37 (m, 1H), 7.26−7.22 (m, 1H), 7.17−7.12 (m, 1H), 4.22 (s, 3H), 3.98 (s, 3H), 3.37 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 160.0 (d, $^1J_{C-F}$ = 245.4 Hz, ^{13}C), 158.8, 152.4 (d, $^1J_{C\text{-}D}$ = 300 Hz, ^{13}C), 144.7, 142.8, 142.3, 142.0, 141.7, 137.3, 131.2 (d, $^2J_{C-F}$ = 16.2 Hz, ^{13}C), 130.0, 129.8, 129.6, 129.0, 128.8 (d, $^3J_{C-F}$ = 8.6 Hz, ^{13}C), 128.4, 123.3 (d, $^4J_{C-F}$ = 2.8 Hz, ^{13}C), 121.6 114.4 (d, $^1J_{C\text{-}D}$ =

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J. Org. Chem. 2016, 81, 9912−9923

21.0 Hz, $1^{13}C$), 102.9, 61.1, 60.9, 56.2; HRMS (ESI) calcd for $[C_{25}H_{17}D_2FN_2O_3]$ requires $[M+H]^+$ 417.1583, found 417.1573.

*2,3,4-Trimethoxy-5-(4-methoxyphenyl)benzo[a]phenazine (**8b**).* The product was obtained as a yellow needles (111.8 mg, 64%): mp 170−175 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 8.50 (s, 56.0mH), 8.20 (d, J = 8.4 Hz, 1H), 8.11 (d, J = 8.4 Hz, 1H), 7.73−7.66 (m, 2H), 7.45 (s, 82.3mH), 6.69 (s, 52.5mH), 4.0 (s, 3H), 3.85 (s, 3H), 3.19 (t, J = 8.0 Hz, 2H), 1.65−1.58 (m, 2H), 1.44−1.35 (m, 2H), 0.89 (t, J = 7.6 Hz, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 159.3, 158.7, 145.6, 143.5, 143.2, 141.5, 141.3, 134.9, 129.9, 129.6, 128.8, 128.7, 123.8 (t, J = 122.0 Hz 1C),118.2, 101.5 (t, J = 83.9 Hz, 1C), 98.91 (t, J = 99.1 Hz, 1C), 55.7, 55.5, 38.1, 33.6, 22.9, 14.1; HRMS (ESI) calcd for $[C_{22}H_{19}D_3N_2O_2]$ requires $[M+H]^+$ 350.1948, found 350.1938.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b02096.

Data and spectral copies of ^1H, ^{13}C NMR, and HRMS for target compounds (PDF)
X-ray crystallography data of **2j** (CIF; 1495030)
X-ray crystallography data of **4c** (CIF; 1469810)
X-ray crystallography data of **7a** (CIF; 1504986)

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) (a) Ackermann, L. *Org. Lett.* **2005**, *7*, 439. (b) Fan, H.; Peng, J.; Hamann, M. T.; Hu, J.-F. *Chem. Rev.* **2008**, *108*, 264. (c) Bailly, C. *Curr. Med. Chem.: Anti-Cancer Agents* **2004**, *4*, 363. (d) Yao, B.; Prinsep, M. R.; Nicholson, B. K.; Gordon, D. P. *J. Nat. Prod.* **2003**, *66*, 1074.

(2) (a) Cimmino, A.; Evidente, A.; Mathieu, V.; Andolfi, A.; Lefranc, F.; Kornienko, A.; Kiss, R. *Nat. Prod. Rep.* **2012**, *29*, 487. (b) Laursen, J. B.; Nielsen, J. *Chem. Rev.* **2004**, *104*, 1663. (c) Motohashi, N.; Mitscher, L. A.; Meyer, R. *Med. Res. Rev.* **1991**, *11*, 239. (d) Martins, M. A. P.; Frizzo, C. P.; Moreira, D. N.; Buriol, L.; Machado, P. *Chem. Rev.* **2009**, *109*, 4140.

(3) Hussain, H.; Specht, S.; Sarite, S. R.; Saeftel, M.; Hoerauf, A.; Schulz, B.; Krohn, K. *J. Med. Chem.* **2011**, *54*, 4913.

(4) (a) Makgatho, M. E.; Anderson, R.; O'Sullivan, J. F.; Egan, T. J.; Freese, J. A.; Cornelius, N.; van Rensburg, C. E. J. *Drug Dev. Res.* **2000**, *50*, 195. (b) Borrero, N. V.; Bai, F.; Perez, C.; Duong, B. Q.; Rocca, J. R.; Jin, S.; Huigens, R. W., III *Org. Biomol. Chem.* **2014**, *12*, 881. (c) Kerr, J. R.; Taylor, G. W.; Rutman, A.; Hoiby, N.; Cole, P. J.; Wilson, R. *J. Clin. Pathol.* **1999**, *52*, 385. (d) Mimoun, H.; Seree de Roch, I.; Sajus, L. *Bull. Soc.Chim. Fr.* **1969**, 1481.

(5) (a) Conda-Sheridan, M.; Marler, L.; Park, E.-J.; Kondratyuk, T. P.; Jermihov, K.; Mesecar, A. D.; Pezzuto, J. M.; Asolkar, R. N.; Fenical, W.; Cushman, M. *J. Med. Chem.* **2010**, *53*, 8688.

(6) (a) Shinya, K.; Shimizu, S.; Kunigami, T.; Furihata, K.; Hayakawa, Y.; Seto, H. *J. Antibiot.* **1995**, *48*, 1378. (b) Neves-Pinto, C.; Malta, V. R. S.; Pinto, M. C. F. R.; Santos, R. H. A.; De Castro, S. L.; Pinto, A. V. *J. Med. Chem.* **2002**, *45*, 2112.

(7) (a) Vicker, N.; Burgess, L.; Chuckowree, I. S.; Dodd, R.; Folkes, A. J.; Hardick, D. J.; Hancox, T. C.; Miller, W.; Milton, J.; Sohal, S.; Wang, S.; Wren, S. P.; Charlton, P. A.; Dangerfield, W.; Liddle, C.; Mistry, P.; Stewart, A. J.; Denny, W. A. *J. Med. Chem.* **2002**, *45*, 721. (b) Gamage, S. A.; Spicer, J. A.; Rewcastle, G. W.; Milton, J.; Sohal, S.; Dangerfield, W.; Mistry, P.; Vicker, N.; Charlton, P. A.; Denny, W. A. *J. Med. Chem.* **2002**, *45*, 740. (c) Rewcastle, G. W.; Denny, W. A.; Baguley, B. C. *J. Med. Chem.* **1987**, *30*, 843. (d) Funayama, S.; Eda, S.; Komiyama, K.; Omura, S.; Tokunaga, T. *Tetrahedron Lett.* **1989**, *30*, 3151. (e) Wang, S.; Miller, W.; Milton, J.; Vicker, N.; Stewart, A.; Charlton, P.; Mistry, P.; Hardick, D.; Denny, W. A. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 415.

(8) (a) Fischer, B. B.; Krieger-Liszkay, A.; Eggen, R. I. L. *Environ. Sci. Technol.* **2004**, *38*, 6307. (b) Khurana, J. M.; Chaudhary, A.; Lumb, A.; Nand, B. *Green Chem.* **2012**, *14*, 2321. (c) Singh, P.; Baheti, A.; Thomas, K. R. J. *J. Org. Chem.* **2011**, *76*, 6134. (d) Bunz, U. H. F.; Engelhart, J. U.; Lindner, B. D.; Schaffroth, M. *Angew. Chem., Int. Ed.* **2013**, *52*, 3810.

(9) (a) Kakiuchi, F.; Murai, S. *Acc. Chem. Res.* **2002**, *35*, 826. (b) Nevado, C.; Echavarren, A. M. *Synthesis* **2005**, *2005*, 167. (c) Kakiuchi, F.; Kochi, T. *Synthesis* **2008**, *2008*, 3013. (d) Kitamura, T. *Eur. J. Org. Chem.* **2009**, *2009*, 1111. (e) Yamamoto, Y. *Chem. Soc. Rev.* **2014**, *43*, 1575.

(10) (a) Jia, C.; Piao, D.; Oyamada, J.; Lu, W.; Kitamura, T.; Fujiwara, Y. *Science* **2000**, *287*, 1992. (b) Jia, C.; Piao, D.; Kitamura, T.; Fujiwara, Y. *J. Org. Chem.* **2000**, *65*, 7516. (c) Jia, C.; Kitamura, T.; Fujiwara, Y. *Acc. Chem. Res.* **2001**, *34*, 633. (d) Jia, C.; Lu, W.; Oyamada, J.; Kitamura, T.; Matsuda, K.; Irie, M.; Fujiwara, Y. *J. Am. Chem. Soc.* **2000**, *122*, 7252.

(11) Tunge, J. A.; Foresee, L. N. *Organometallics* **2005**, *24*, 6440.

(12) Soriano, E.; Marco-Contelles, J. *Organometallics* **2006**, *25*, 4542.

(13) (a) Nevado, C.; Echavarren, A. M. *Chem. - Eur. J.* **2005**, *11*, 3155. (b) Komeyama, K.; Igawa, R.; Takaki, K. *Chem. Commun.* **2010**, *46*, 1748.

(14) Lian, Y.; Hummel, J. R.; Bergman, R. G.; Ellman, J. A. *J. Am. Chem. Soc.* **2013**, *135*, 12548.

(15) (a) Ding, D.; Mou, T.; Feng, M.; Jiang, X. *J. Am. Chem. Soc.* **2016**, *138*, 5218. (b) Nakamura, K.; Furumi, S.; Takeuchi, M.; Shibuya, T.; Tanaka, K. *J. Am. Chem. Soc.* **2014**, *136*, 5555. (c) Kang, D.; Kim, J.; Oh, S.; Lee, P. H. *Org. Lett.* **2012**, *14*, 5636. (d) Jung, Y.; Kim, I. *Org. Lett.* **2015**, *17*, 4600. (e) Seth, K.; Raha Roy, S.; Chakraborti, A. K. *Chem. Commun.* **2016**, *52*, 922.

(16) (a) Verma, A. K.; Danodia, A. K.; Saunthwal, R. K.; Patel, M.; Choudhary, D. *Org. Lett.* **2015**, *17*, 3658. (b) Saunthwal, R. K.; Patel, M.; Danodia, A. K.; Verma, A. K. *Org. Biomol. Chem.* **2015**, *13*, 1521. (c) Saunthwal, R. K.; Patel, M.; Kumar, S.; Danodia, A. K.; Verma, A. K. *Chem. - Eur. J.* **2015**, *21*, 18601. (d) Aggarwal, T.; Kumar, S.; Dhaked, D. K.; Tiwari, R. K.; Bharatam, P. V.; Verma, A. K. *J. Org. Chem.* **2012**, *77*, 8562. (e) Kumar, S.; Cruz-Hernandez, C.; Pal, S.; Saunthwal, R. K.; Patel, M.; Tiwari, R. K.; Juaristi, E.; Verma, A. K. *J. Org. Chem.* **2015**, *80*, 10548. (f) Aggarwal, T.; Jha, R. R.; Tiwari, R. K.; Kumar, S.; Kotla, S. K. R.; Kumar, S.; Verma, A. K. *Org. Lett.* **2012**, *14*, 5184.

(17) Simonetta, M.; Gavezzotti, A. In *The Chemistry of the Carbon-Carbon Triple Bond*; Patai, S., Ed.; John Wiley & Sons: New York, 1978; Part 1, pp 1−73.

(18) (a) Harbeson, S. L.; Tung, R. D. *Annu. Rep. Med. Chem.* **2011**, *46*, 403. (b) Meanwell, N. A. *J. Med. Chem.* **2011**, *54*, 2529. (c) Phillips, D. H.; Potter, G. A.; Horton, M. N.; Hewker, A.; Crofton-Sleigh, C.; Jarman, M.; Venitt, S. *Carcinogenesis* **1994**, *15*, 1487. (d) Jarman, M.; Poon, G. K.; Rowlands, M. G.; Grimshaw, R. M.; Horton, M. N.; Potter, G. A.; McCague, R. *Carcinogenesis* **1995**, *16*, 683. (e) Mutlib, A. E.; Gerson, R. J.; Meunier, P. C.; Haley, P. J.; Chen, H.; Gan, L. S.; Davies, M. H.; Gemzik, B.; Christ, D. D.; et al. *Toxicol. Appl. Pharmacol.* **2000**, *169*, 102.

(19) (a) Van der Zeijden, A.; Bosch, H. W.; Berke, H. *Organometallics* **1992**, *11*, 563. (b) Boese, W. T.; Goldman, A. S. *Organometallics* **1991**, *10*, 782. (c) Lu, X.; Zhu, G.; Ma, S. *Tetrahedron Lett.* **1992**, *33*, 7205. (d) Yanagihara, N.; Lambert, C.; Iritani, K.; Utimoto, K.; Nozaki, H. *J. Am. Chem. Soc.* **1986**, *108*, 2753.

DOI: 10.1021/acs.joc.6b02096
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