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Iron-catalyzed Cross-Coupling of Electron-Deficient Heterocycles and Quinone with Organoboron Species via Innate C−H Functionalization: Application in Total Synthesis of Pyrazine Alkaloid Botryllazine A

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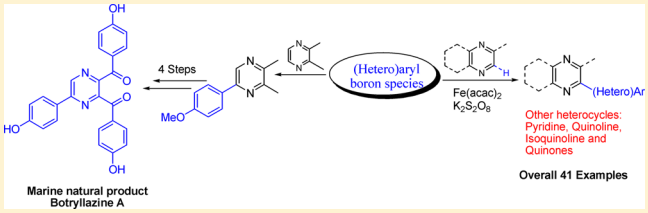
Supporting Information

ABSTRACT: Here, we report an iron-catalyzed cross-coupling reaction of electron-deficient heterocycles and quinone with organoboron species via innate C−H functionalization. Iron(II) acetylacetonate along with oxidant ($K_2S_2O_8$) and phase-transfer catalyst (TBAB) under open flask conditions efficiently catalyzed the cross-coupling of pyrazine with arylboronic acids and gave monoarylated products in good to excellent yields. Optimized conditions also worked for other heterocylces such as quinoxalines, pyridines, quinoline, and isoquinoline as well as quinones. In addition, we demonstrated as a first example its application for the synthesis of anticancer marine pyrazine alkaloid botryllazine A.



INTRODUCTION

Traditionally, a cross-coupling reaction for C−C bond formation requires two starting materials: organometallic species and organic halides. However, replacing one of the coupling partners with an appropriate C−H species offers a far more efficient and versatile alternative, and many such methods have been reported.[1−3] Most of these C−H activation mediated cross-coupling methods reported during last two decades are restricted only to the electron-rich (hetero)arenes[4] and are not suitable for electron-deficient (hetero)arenes. To address this issue, transition-metal catalysis have been employed[5−9] for cross-coupling with electron-deficient (hetero)arenes. In the past decade, many transition-metal catalysts have been employed for such cross-coupling reactions with electron-deficient heterocycles; the examples of metals include palladium[5] (coupling of electron-deficient heterocycles with aryl halides), rhodium[6] (coupling of pyridine and quinoline with arylbromide), copper[7] (coupling of heterocycles with aryl halides), nickel[8] (coupling of electron-deficient heterocycles with arylzinc reagents), and gold[9] (coupling of pyrazine and pyridine with aryl bromide). However, these transition-metal-catalyzed methods also have some limitations such as need of a large excess of heterocyclic partners, expensive ligands, and harsh reaction conditions. In a major improvement, Baran et al. recently reported a method[10] for the cross-coupling of electron-deficient (hetero)arenes and quinones with arylboronic acids under classical Minisci conditions (Ag catalyst).[11] In the last two decades, iron-based catalysts have drawn attention as cheap, nontoxic, and environmentally friendly materials for the cross-coupling reactions.[12] In the case of electron-deficient (hetero)arenes, Wen et al.[13a] reported an iron oxalate mediated coupling which required large excess of heterocycle partner and a stoichiometric amount of iron species, ligand, and high temperature. Very recently, Wang et al.[13b] reported a heterogeneous FeS-mediated cross-coupling using stoichiometric amounts of iron species. Keeping in mind the radical chemistry literature of iron and our recent interest in iron-catalyzed methods for C−C bond formation,[14] we envisioned that environmentally friendly iron catalysts could be explored for cross-coupling of electron-deficient (hetero)arenes with organometallic species. In this direction, we now report a new and efficient cross-coupling reaction of electron-deficient (hetero)arenes via functionalization of the C(sp^2)−H bond with organoboron species using a catalytic amount of iron catalyst under open-flask conditions. This method was successfully utilized for direct arylation of variety of (hetero)-arenes such as pyrazine, quinoxaline, pyridine, quinoline, isoquinoline, and quinones. In addition, we demonstrated as a first example its application for the synthesis of anticancer marine pyrazine alkaloid botryllazine A.[15a,b]

Since many biologically active natural products comprise substituted electron-deficient heterocycles such as pyrazine, quinoxaline, pyridine, quinoline, isoquinoline, pyrimidine, etc., our method offers tremendous potential for introducing functionalities into aforementioned moieties containing natural/bioactive compounds as well as their total synthesis.[15]

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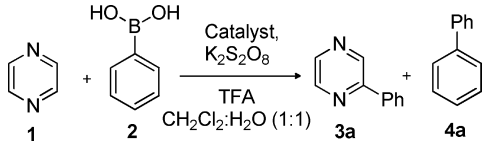
RESULTS AND DISCUSSION

We selected various iron salts to test the idea and began this study with the reaction of pyrazine with phenylboronic acid in the presence of trifluoroacetic acid using water/dichloromethane solvent system (Table 1). During our study, potassium persulfate ($K_2S_2O_8$) was used as a oxidant. When we examined the reaction of pyrazine **1** with phenylboronic acid **2** in the presence of 20 mol % of $FeSO_4$ at room temperature, the 2-phenylpyrazine **3a** was obtained with 55% yield along with biphenyl **4a** as byproduct (Table 1, entry 1). The composition of the crude product was determined by HPLC. Among the various iron salts used (Table 1, entries 2−7), iron(III) acetylacetonate [$Fe(acac)_3$] gave the desired product **3a** in 65% yield. Further, the use of iron(II) acetylacetonate [$(Fe(acac)_2$] increased the formation of 2-phenylpyrazine **3a** to 72% yield (Table 1, entry 8). To know the effective amount of iron salt required for catalysis, experiments with lower amounts (20 to 10 mol %) as well as higher amounts (20 to 30 to 100%) of $Fe(acac)_2$ did not show any improvement in the formation of desired product **3a** (Table 1, entries 9−11). Evaluation with other metals such as Mn, Ag, and Cu did not show any improvement (Table 1, entries 12−14). In the absence of iron salt, no product formation was observed (Table 1, entry 15).

Investigations toward optimization of coupling conditions such as different oxidants, solvent systems, phase-transfer catalyst, temperature, and the surrounding atmosphere were performed, and the results are summarized in Table 2. Among the various oxidants used [*tert*-butyl hydrogen peroxide (TBHP), di-*tert*-butyl hydrogen peroxide (DTBP), and Oxone], only TBHP gave 20% of the desired product **3a** (Table 2, entries 1−3). A change in the solvent system also affected the formation of 2-phenylpyrazine (Table 2, entries 4−8). As the reaction conditions involved two immiscible substances, the addition of a phase-transfer catalyst was tested (Table 2, entries 9−11), and with 5 mol % of tetrabutylammonium bromide (TBAB), formation of 2-phenylpyrazine increased to 84% (Table 2, entry 9, HPLC data provided in the Supporting Information). As observed during experiments, the addition of TBAB suppressed the emulsion formation and made the reaction mixture a very clear solution, which allowed effective coupling and yield improvement as compared to Wang's method[13b] where because of the heterogeneous nature of FeS its stoichiometric quantity was required. Moreover, a decrease in the amount of $K_2S_2O_8$ also decreased the yield of **3a** (Table 2, entries 12 and 13). In the absence of oxidant $K_2S_2O_8$, no product formation was observed (Table 2, entry 14). The presence of O_2 instead of air and an increase in the temperature did not affect the formation of desired product (Table 2, entries 15 and 16).

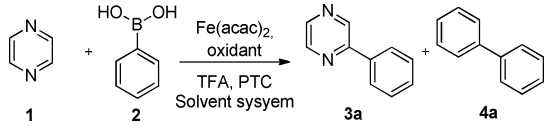
Table 1. Optimization Studies for the Cross-Coupling Reaction[a]



			product composition[b]	
entry	catalyst	qty (mol %)	3a	4a
1	$FeSO_4$	20	55	<10
2	FeO	20	50	12
3	Fe_2O_3	20	38	ND
4	$FeCl_3$	20	trace	ND
5	$FeBr_3$	20	trace	ND
6	FeF_2	20	trace	ND
7	$Fe(acac)_3$	20	65	7
8	$Fe(acac)_2$	20	72	10
9	$Fe(acac)_2$	10	65	5
10	$Fe(acac)_2$	30	70	<10
11	$Fe(acac)_2$	100	70	15
12	$Mn(OAc)_3$	20		
13	$AgNO_3$	20	55	ND
14	CuI	20	20	ND
15			0	0

[a]Reaction conditions (unless otherwise stated): pyrazine (1 mmol), TFA(1 mmol), **2** (1.1 mmol), $K_2S_2O_8$ (3.0 equiv), rt, 12 h, air. [b]Product composition was determined by HPLC. ND = denotes not detected.

Table 2. Optimization Studies for the Cross-Coupling Reaction of Pyrazine with Phenylboronic Acid[a]



						Product composition[c]	
entry	solvent[b]	oxidant	atm	T (°C)	PTC	3a	4a
1	DCM/ H_2O	TBHP (3 equiv)	air	rt		20	ND
2	DCM/ H_2O	DTBP (3 equiv)	air	rt			
3	DCM/ H_2O	Oxone (3 equiv)	air	rt			
4	DCM	$K_2S_2O_8$ (3 equiv)	air	rt			
5	H_2O	$K_2S_2O_8$ (3 equiv)	air	rt		40	5
6	DMSO/ H_2O	$K_2S_2O_8$ (3 equiv)	air	rt		trace	ND
7	ACN/ H_2O	$K_2S_2O_8$ (3 equiv)	air	rt		trace	ND
8	toluene/ H_2O	$K_2S_2O_8$ (3 equiv)	air	rt		45	8
9	**DCM/ H_2O**	**$K_2S_2O_8$ (3 equiv)**	**air**	**rt**	**TBAB**	**84**	**<10**
10[d]	DCM/ H_2O	$K_2S_2O_8$ (3 equiv)	air	rt	TBAB	75	<10
11	toluene/ H_2O	$K_2S_2O_8$ (3 equiv)	air	rt	TBAB	50	8
12	DCM/ H_2O	$K_2S_2O_8$ (2 equiv)	air	rt	TBAB	70	6
13	DCM/ H_2O	$K_2S_2O_8$(1 equiv)	air	rt	TBAB	65	ND
14	DCM/ H_2O		air	rt	TBAB		
15	DCM/ H_2O	$K_2S_2O_8$ (3 equiv)	O_2	rt	TBAB	80	ND
16	DCM/ H_2O	$K_2S_2O_8$ (3 equiv)	air	50	TBAB	82	10

[a]Reaction conditions (unless otherwise stated): pyrazine 1 (1 mmol), **2** (1.1 mmol), TFA (1 mmol), $Fe(acac)_2$ (20 mol %), 12 h. [b]Mixture of solvents were used in 1:1 ratio. [c]Yields were determined by HPLC. [d]Reaction was done with 20 mol % of $Fe(acac)_3$.

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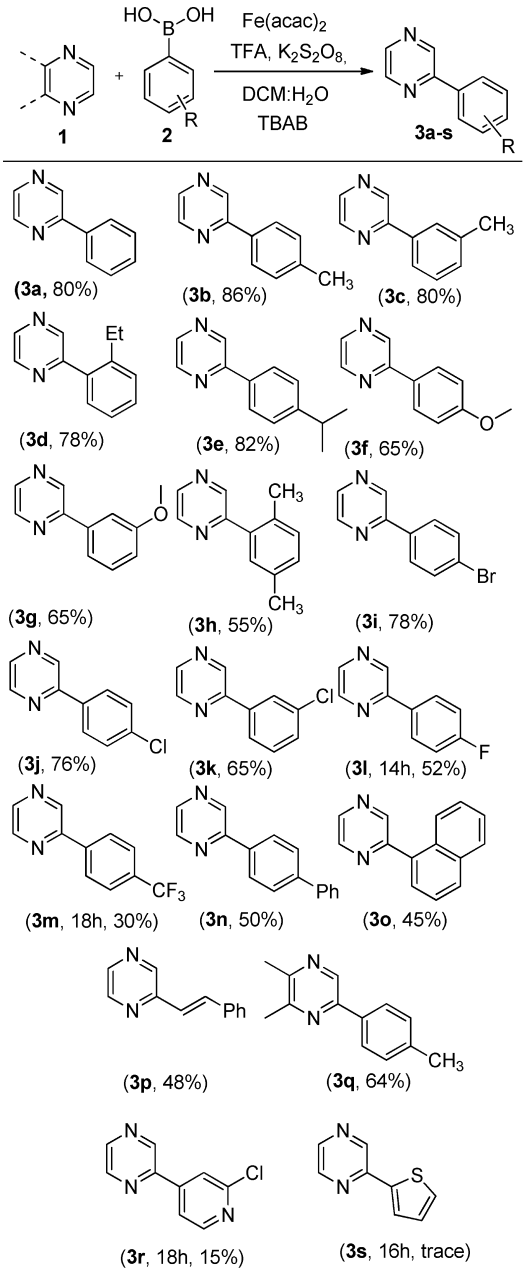
Under the optimized conditions, the reactivity of various organoboronic acids toward pyrazine was investigated, and all the results are given in Table 3. Various *ortho*-, *meta*-, and *para*-substituted organoboronic acids on reaction with pyrazine provided the desired monoarylated coupled products **3a**–**s** with varying yields. Arylboronic acids possessing electron-donating groups at the *para*, *meta*, and *ortho* position smoothly underwent cross-coupling reaction and gave good to excellent yields of the desired products **3b**–**g** while disubstituted acids such as 2,5-dimethylphenylboronic acid gave a moderate yield of coupled product **3h**. Similarly, electron-withdrawing groups possessing arylboronic acids underwent cross-coupling reaction to afford the corresponding 2-arylpyrazine derivatives **3i**–**n** in moderate to good yields. Moreover, hindered 1-napthylboronic acid underwent cross-coupling and gave 2-naphthylpyrazine **3o** in 45% yield. Vinylic boronic acids such as *trans*-2-phenylvinylboronic acid also coupled with pyrazine and afforded the corresponding coupled product **3p** in 48% yield. 2,3-Dimethylpyrazine on reaction with *p*-tolylboronic acid also underwent cross-coupling and gave 2-(*p*-tolyl)-5,6-dimethylpyrazine **3q** in 64% yield. Under optimized conditions, heteroaryl boronic acids were also used, and 2-chloropyridine-4-boronic acid underwent reaction with pyrazine and gave less than 15% of coupled product **3r** while thiophene-yl-2-boronic acid gave only a trace quantity of desired product as detected by MS analysis.

The present method under optimized conditions when performed with a benzannnulated pyrazine such as quinoxalines **5** also gave monoarylated product in moderate to good yields (Table 4). Quinoxaline on reaction with phenylboronic acid furnished 62% of 2-phenylquinoxoline **6a**. Electron-donating groups (EDGs) such as 4-methyl- and 4-methoxy-containing phenylboronic acids gave 65 and 52% of the correseponding coupled products **6b** and **6c**, respectively. Electron-withdrawing groups (EWGs) containing phenylboronic acid gave comparatively lower yield. 4-Fluoro- and 3-chlorophenylboronic acids gave 48 and 45% of **6d** and **6e**, respectively. Similarly, the reaction of 2-methylquinoxaline with *p*-tolylphenylboronic acid gave monoarylated coupled product **6f** in 45% yield.

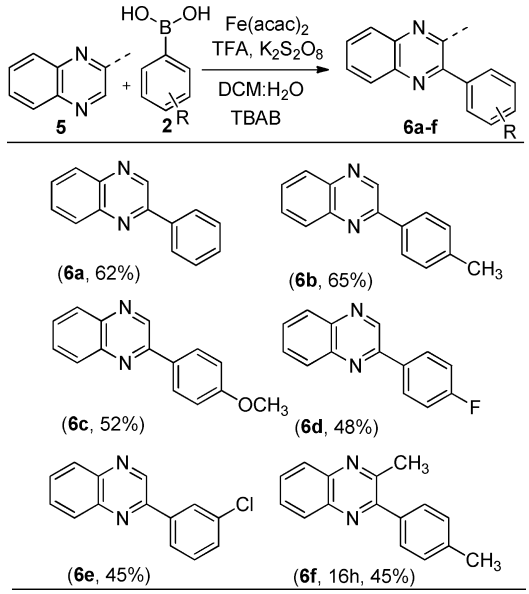
Other electron-deficient heterocycles such as un/substituted pyridines **7a**, quinoline **7b**, and isoquinoline **7c** were also explored for cross-coupling reactions. Unlike literature reports,[10a,13b] our optimized conditions gave surprisingly regioselective monoarylated coupled product (further investigation needed) but with comparatively lower yields (see Table 5). Pyridine with phenylboronic acid gave a 45% yield of **8a**. 4-

Table 3. Cross-Coupling Reaction of Pyrazines with Organoboronic Acids[a]



[a]Reaction conditions (unless otherwise stated): pyrazine **1** (1 mmol), **2** (1.1 mmol), TFA (1 mmol), $Fe(acac)_2$ (20 mol %) $K_2S_2O_8$ (3 mmol), TBAB (5 mol %), CH_2Cl_2/H_2O, 12 h, under air at rt.

Table 4. Cross-Coupling Reaction of Quinoxalines with Arylboronic Acids[a]



[a]Reaction conditions (unless otherwise stated): **5** (1 mmol), **2** (1.1 mmol), TFA (1 mmol), $Fe(acac)_2$ (20 mol %), $K_2S_2O_8$ (3 mmol), TBAB (5 mol %), CH_2Cl_2/H_2O, 12 h, under air at rt.

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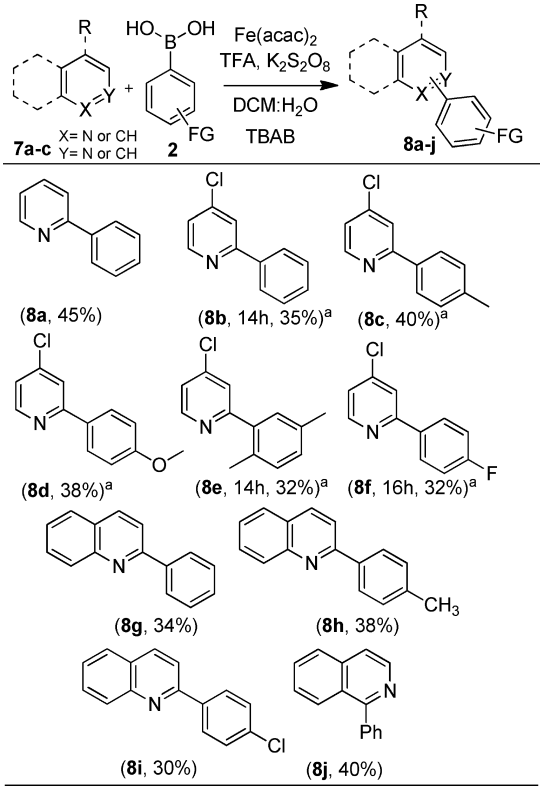
Table 5. Cross-Coupling Reaction of Pyridines, Quinoline, and Isoquinoline with Arylboronic Acids[b]

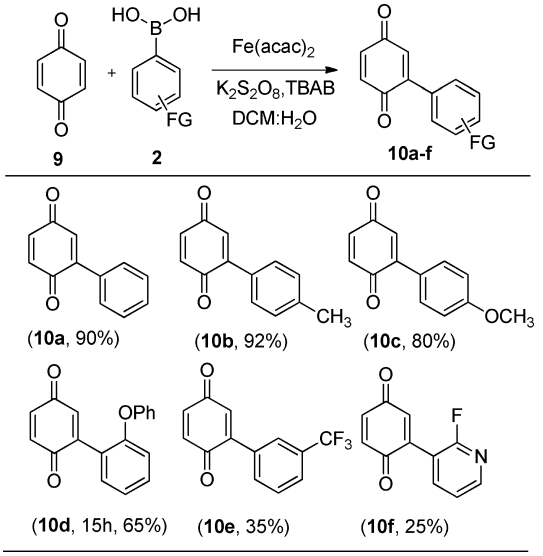


[a]4-Chloropyridine hydrochloride was used and without TFA. [b]Reaction conditions (unless otherwise stated): **7** (1 mmol), **2** (1.1 mmol), TFA (1 mmol), $Fe(acac)_2$ (20 mol %), $K_2S_2O_8$ (3 mmol), TBAB (5 mol %), CH_2Cl_2/H_2O, 12 h, under air at rt.

Chloropyridine as hydrochloride salt on reaction with phenylboronic acid gave monoarylated coupled product 2-phenyl-4-chloro-pyridine **8b** in 35% yield. 4-Chloropyridine hydrochloride with EDGs such as 4-methyl- and 4-methoxy-containing phenylboronic acids gave corresponding 40 and 38% yields of monoarylated coupled products **8c** and **8d**, respectively. In the case of the reaction of 4-chloropyridine hydrochloride with 2,5-dimethylphenylboronic acid, 32% of the desired monoarylated **8e** was obtained. On the other hand, 4-chloropyridine hydrochloride on coupling with 4-fluorophenylboronic acid gave 32% of the desired monoarylated product **8f**. Quinoline on reaction with phenyl-, *p*-tolyl-, and 4-chlorphenylboronic acids gave 34, 38, and 30% of the corresponding mono-2-arylated products **8g**, **8h**, and **8i**, respectively. Similarly, isoquinoline under optimized conditions coupled with phenylboronic acid and gave a moderate 40% yield of monoarylated 1-phenylisoquinoline **8j**.

The present optimized method also worked very well with quinone **9**. Quinone underwent coupling with various unsubstituted organoboronic acids to give monoarylated cross-coupled products **10a–f** (Table 6). Phenyl as well as EDGs (4-Me, 4-OMe) containing arylboronic acids gave coupled products **10a–c** in excellent yields. Bulky substituted arylboronic acid such as 2-phenoxyphenylboronic acid also reacted and gave a good yield (65%) of coupled product **10d**. EWG (3-CF_3) containing phenylboronic acid smoothly underwent cross-coupling and gave 35% of coupled product **10e**. Likewise, heteroarylboronic acid such as 2-fluoropyridine-3-

Table 6. Cross-Coupling Reaction of Quinone with Organoboronic Acids[a]



[a]Reaction conditions (unless otherwise stated): **9** (1 mmol), **2** (1.1 mmol), $Fe(acac)_2$(20 mol %), $K_2S_2O_8$ (3 mmol), TBAB (5 mol %), CH_2Cl_2/H_2O, 12 h, under air at rt.

boronic acid also coupled with quinone but gave a comparatively lower yield of **10f** (25%).

In order to see the compatibility of other organoboron species, potassium organotrifluoroborate salts and arylboronic acid pinacol ester were used (Figure 1). Potassium organotrifluoroborate salt, i.e., phenyltrifluoroborate **11**, underwent cross-coupling smoothly with pyrazine and gave 2-phenylpyrazine in 78% yield; on the other hand, arylboronic acid pinacol ester **12** gave a comparatively lower yield of 2-phenylpyrazine (30%).

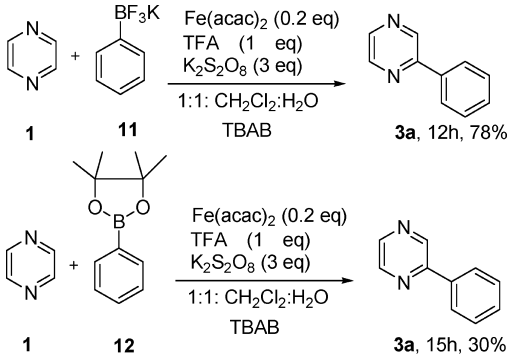


Figure 1. Cross-coupling reaction of pyrazine with potassium organotrifluoroborate salts and arylboronic acid pinacol ester.

Efforts to understand the mechanism were made (Figure 2). Addition of free radical scavenger such as (2,2,6,6-tetramethylpiperidin-1-yl)oxyl (TEMPO) in the reaction mixture drastically suppressed the formation of 2-phenylpyrazine **3a**, suggesting the involvement of free-radical intermediates. Furthermore, when the optimized reaction was performed with $ArB(OH)_2$ in the absence of heterocycle (Figure 2), GC–MS studies showed the formation of phenol and biphenyl and also suggested that the Fe^{2+}/SO_4^{2-} system activates the arylboronic acid. On the basis of a literature precedent[10,11]

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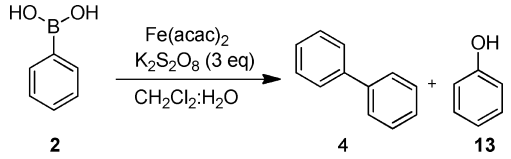


Figure 2. Exploration of present method toward free-radical mechanism.

and the present experimental findings, the plausible mechanism seemed to be similar as reported by Baran et al.[10]

After exploring the versatility and diversity of the present iron-catalyzed cross-coupling reaction of N-heterocycles with hetero(aryl)boron reagent, its application toward the synthesis of bioactive natural product was explored. In this direction, we successfully developed a new and more concise (five steps as compared to the seven-step literature reported method[15b]) and an effective route for the synthesis of a pyrazine alkaloid botryllazine A, isolated from marine red ascidian *Botryllus leachi* (Figure 3).[15a,b] As per strategy 1, we first tried the synthesis of

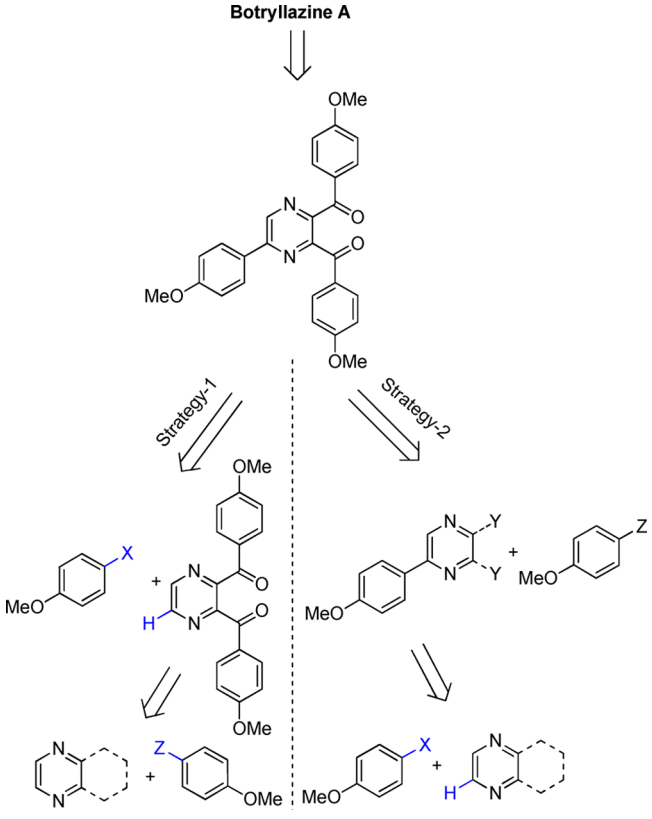
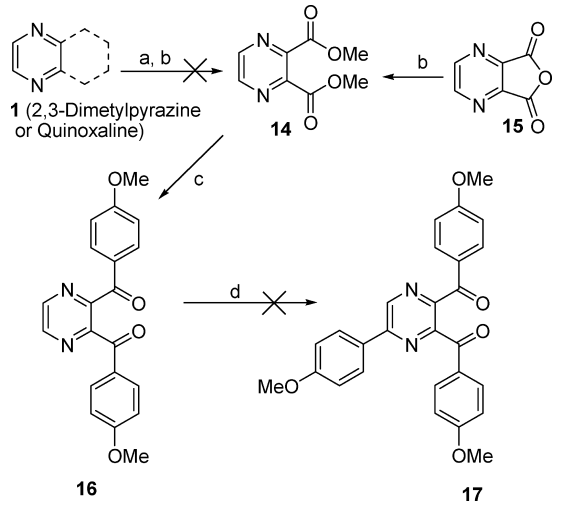


Figure 3. Retro-synthetic strategies for the synthesis of pyrazine alkaloid−botryllazine A.

pyrazine 2,3-dicarboxylate **14** from 2,3-dimethylpyrazine or quinoxaline **1** on oxidation with aqueous $KMNO_4$ or HNO_3, but in our case we did not get the expected pyrazine-2,3-dicarboxylate under all of the tried conditions (Scheme 1). However, the synthesis of **14** was successfully achieved from commercially available pyrazine anhydride **15**, which was further converted into 2,3-dibenzoylpyrazine **16**, but the subsequent arylation with 4-anisylboronic acid under optimized conditions did not give the expected methylated botryllazine A (**17**) (Scheme 1). Then, as per strategy 2, quinoxaline **1** under optimized conditions was converted into 2-(*p*-methoxyphenyl)-

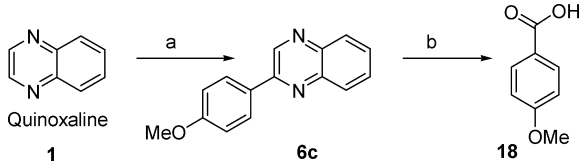
Scheme 1. Studies toward the Synthesis of Pyrazine Alkaloid−Botryllazine A[a]



[a]Reagents and conditions: (a) aq $KMnO_4$ or 60% HNO_3 reflux, 18 h; (b) PTSA, MeOH rt, 12 h; (c) 4-anisyl-MgBr, dry THF, −70 °C; (d) 4-anisyl-$B(OH)_2$, TFA, $Fe(acac)_2$, $K_2S_2O_8$, TBAB, CH_2Cl_2/H_2O, 12 h.

quinoxaline **6c** which on oxidation under aq $KMNO_4$ or HNO_3 conditions underwent decomposition of the pyrazine ring and gave *p*-methoxybenzoic acid **18** as the sole product (Scheme 2).

Scheme 2. Studies toward the Synthesis of Pyrazine Alkaloid−Botryllazine A[a]



[a]Reagents and conditions: (a) 4-anisyl-$B(OH)_2$, TFA, $Fe(acac)_2$ $K_2S_2O_8$, TBAB, CH_2Cl_2/H_2O, 12 h; (b) aq $KMnO_4$ or 60% HNO_3 reflux, 18 h.

Next, 2,3-dimethylpyrazine under optimized conditions was converted into 2-(*p*-methoxyphenyl)-5,6-dimethylpyrazine **19** (Scheme 3). 2-(*p*-Methoxyphenyl)-5,6-dimethylpyrazine **19** was converted into dialdehyde **20** on treatment with SeO_2. Further, dialdehyde **20** when treated with 4-anisylmagnesium bromide at −70 °C gave botryllazine skeleton **21** which on oxidation with PCC gave methylated botryllazine A **17**. The methylated botryllazine A **17** on demethylation with pyridinehydrochloride[15b] gave final botryllazine A (**22**) (Scheme 3). This reaction has opened new opportunities to iron-catalyzed functionalization of electron-deficient heterocycles as well as toward the synthesis of these heterocycles containing natural products.

■ CONCLUSIONS

In summary, an iron-catalyzed cross-coupling reaction for the electron-deficient heterocycles and quinone with organoboron species via innate C−H functionalization has been developed. Iron(II) acetylacetonate along with oxidant ($K_2S_2O_8$) and phase-transfer catalyst (TBAB) in dichloromethane/water under open flask conditions efficiently catalyzed the cross-coupling reaction of pyrazine with arylboronic acids and gave

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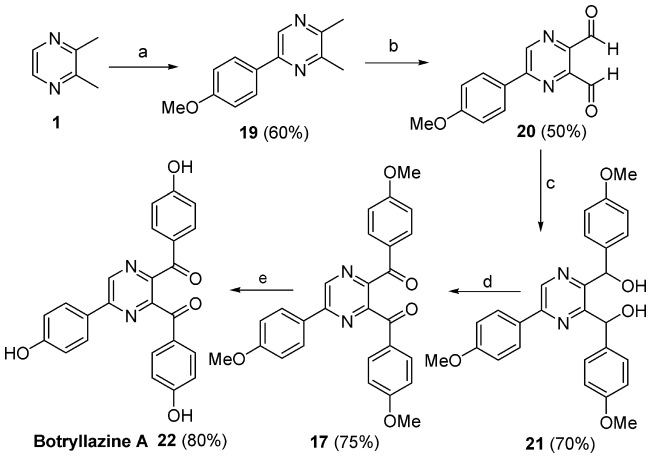
Scheme 3. Studies toward the Synthesis of Pyrazine Alkaloid−Botryllazine A[a]



[a]Reagents and conditions: (a) 4-anisyl-B(OH)$_2$, TFA, Fe(acac)$_2$ $K_2S_2O_8$, TBAB, CH_2CI_2/H_2O, 12 h; (b) SeO_2, dioxane, reflux, 24 h; (c) 4-anisyl-MgBr, dry THF, −70 °C; (d) PCC, DCM, rt; (e) pyridine hydrochloride, 220 °C, 1 h.

monoarylated products in good to excellent yields. These optimized conditions worked with other N-heterocylces such as quinoxaline, pyridine, quinoline, isoquinoline, as well as quinones. The present methodology was successfully utilized for the synthesis of botryllazine A, a marine-derived natural product. Moreover, heteroarylboronic acids also worked under optimized conditions but gave less yield of coupled product. Further extension of the present method to other (hetero)-arenes and studies toward yield improvement/regio-selectivity wherever noted are underway and will be reported in due course.

EXPERIMENTAL SECTION

General Methods. All reactions were performed under air atmosphere. Analytical thin-layer chromatography was performed using TLC precoated silica gel 60 F_{254} (20 × 20 cm). TLC plates were visualized by exposing UV light or by iodine vapors or immersion in an acidic staining solution of *p*-anisaldehyde followed by heating on hot plate. Organic solvents were concentrated by rotary evaporation. Flash column chromatography was performed on flash silica gel 230−400 mesh size. ^{1}H NMR spectra were recorded with 400 and 500 MHz NMR instruments. Chemical data for protons are reported in parts per million (ppm, scale) downfield from tetramethylsilane and are referenced to the residual proton in the NMR solvent ($CDCl_3$: δ 7.26, or other solvents as mentioned). Mass spectra were recorded with an LCMS-QTOF instrument. HPLC were performed on an instrument equipped with a DAD VL detector using a 5 μm, 4.6 × 250 mm column.

General Procedure for Cross-Coupling (Hetero)arene with Organoboron Species. To a solution of (hetero)arene (1 mmol) in dichloromethane (8 mL) was added trifluoroacetic acid (80 μL, 1 mmol) followed by arylboronic acid (1.1 mmol). Water (8 mL) was then added, followed by iron(II) acetylacetonate (0.2 mmol) and potassium persulfate (3 mmol). TBAB was then added [5 mol % with respect to (hetero)arenes], and the solution was stirred vigorously at room temperature until completion as monitored by TLC. Then reaction mixture was diluted with dichloromethane and washed with saturated sodium bicarbonate solution. The layers were separated, and the aqueous layer was extracted with dichloromethane. Organic layers were compiled, dried over sodium sulfate, and evaporated in vacuo. Purification was performed by silica gel chromatography to get pure product and characterized by NMR and HRMS.

Note: Trifluoroacetic acid was not added in the case of 4-chloropyridine hydrochloride and quinone.

*2-Phenylpyrazine (Table 3, **3a**).*[16] Column chromatography (flash silica gel, hexane/EtOAc): R_f = 0.50 (hexane/EtOAc, 8:2); yield 80% (125 mg); light yellow solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 9.02 (d, J = 1.4 Hz, 1H), 8.62 (dd, J = 2.4, 1.6 Hz, 1H), 8.49 (d, J = 2.5 Hz, 1H), 8.02−7.99 (m, 2H), 7.52−7.46 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 152.8, 144.1, 142.8, 142.2, 136.3, 129.9, 129.0, 126.9; HRMS (ESI-TOF) calcd for $C_{10}H_8N_2$ $[M + H]^+$ 157.0766, found 157.0750.

*2-(p-Tolyl)pyrazine (Table 3, **3b**).*[9] Column chromatography (flash silica gel, hexane/EtOAc): R_f = 0.55 (hexane/EtOAc, 8:2); yield 86% (147 mg); pale yellow solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.99 (s, 1H), 8.59 (dd, J = 3.1, 1.6 Hz, 1H), 8.45 (t, J = 2.3 Hz, 1H), 7.90 (dd, J = 8.1, 1.7 Hz, 2H), 7.30 (d, J = 7.8 Hz, 2H), 2.41 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 152.8, 144.1, 142.5, 142.0, 140.1, 133.5, 129.8, 126.8, 21.3; HRMS (ESI-TOF) calcd for $C_{11}H_{10}N_2$ $[M + H]^+$ 171.0917, found 171.0912.

*2-(m-Tolyl)pyrazine (Table 3, **3c**).*[9] Column chromatography (flash silica gel, hexane/EtOAc): R_f = 0.53 (hexane/EtOAc, 8:2); yield 80% (136 mg); light yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 9.02 (d, J = 1.5 Hz, 1H), 8.63 (dd, J = 2.5, 1.6 Hz, 1H), 8.50 (d, J = 2.5 Hz, 1H), 7.85 (s, 1H), 7.79 (d, J = 7.8 Hz, 1H), 7.41 (t, J = 7.6 Hz, 1H), 7.30 (d, J = 7.6 Hz, 1H), 2.46 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 153.0, 144.1, 142.8, 142.3, 138.8, 136.3, 130.7, 128.9, 127.6, 124.0, 21.5; HRMS (ESI-TOF) calcd for $C_{11}H_{10}N_2$ $[M + H]^+$ 171.0917, found 171.0912.

*2-(2-Ethylphenyl)pyrazine (Table 3, **3d**).* Column chromatography (flash silica gel, hexane/EtOAc): R_f = 0.55 (hexane/EtOAc, 8:2); yield 78% (144 mg); light yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.71 (d, J = 1.5 Hz, 1H), 8.66 (dd, J = 2.5, 1.6 Hz, 1H), 8.54 (d, J = 2.5 Hz, 1H), 7.44−7.29 (m, 4H), 2.73 (q, J = 7.5 Hz, 2H), 1.13 (t, J = 7.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 155.9, 145.1, 143.8, 142.6, 142.5, 136.4, 129.9, 129.4, 129.3, 126.0, 26.0, 15.6; HRMS (ESI-TOF) calcd for $C_{12}H_{12}N_2$ $[M + H]^+$ 185.1079, found 185.1065.

*2-(4-Isopropylphenyl)pyrazine (Table 3, **3e**).* Column chromatography (flash silica gel, hexane/EtOAc): R_f = 0.56 (hexane/EtOAc, 8:2); yield 82% (163 mg); light yellow solid; mp 52−54 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 9.01 (d, J = 1.5 Hz, 1H), 8.61 (dd, J = 2.5, 1.6 Hz, 1H), 8.47 (d, J = 2.5 Hz, 1H), 7.97−7.94 (m, 2H), 7.39−7.37 (m, 2H), 2.98 (septet, J = 6.9 Hz, 1H), 1.30 (d, J = 6.9 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 152.9, 151.0, 144.1, 142.5, 142.0, 133.9, 127.2, 126.9, 34.0, 23.8; HRMS (ESI-TOF) calcd for $C_{13}H_{14}N_2$ $[M + H]^+$ 199.1230, found 199.1226.

*2-(4-Methoxyphenyl)pyrazine (Table 3, **3f**).*[16] Column chromatography (flash silica gel, hexane/EtOAc): R_f = 0.40 (hexane/EtOAc, 8:2); yield 65% (121 mg); colorless solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.98 (d, J = 1.5 Hz, 1H), 8.58 (dd, J = 2.5, 1.6 Hz, 1H), 8.44 (d, J = 2.5 Hz, 1H), 8.00−7.97 (m, 2H), 7.05−7.02 (m, 2H), 3.88 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 161.2, 152.5, 144.0, 142.1, 141.6, 128.8, 128.3, 114.5, 55.4; HRMS (ESI-TOF) calcd for $C_{11}H_{10}N_2O$ $[M + H]^+$ 187.0866, found 187.0862.

*2-(3-Methoxyphenyl)pyrazine (Table 3, **3g**).*[16] Column chromatography (flash silica gel, hexane/EtOAc): R_f = 0.40 (hexane/EtOAc, 8:2); yield 65% (121 mg); pale yellow solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 9.02 (d, J = 1.4 Hz, 1H), 8.63 (dd, J = 2.4, 1.6 Hz, 1H), 8.51 (d, J = 2.5 Hz, 1H), 7.60−7.56 (m, 2H), 7.42 (t, J = 7.9 Hz, 1H), 7.03 (ddd, J = 8.2, 2.6, 0.9 Hz, 1H), 3.90 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 160.3, 152.6, 144.1, 142.9, 142.3, 137.7, 130.0, 119.2, 116.0, 112.1, 55.4; HRMS (ESI-TOF) calcd for $C_{11}H_{10}N_2O$ $[M + H]^+$ 187.0866, found 187.0861.

*2-(2,5-Dimethylphenyl)pyrazine (Table 3, **3h**).* Column chromatography (flash silica gel, hexane/EtOAc): R_f = 0.55 (hexane/EtOAc, 8:2); yield 55% (102 mg); light yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.72 (d, J = 1.5 Hz, 1H), 8.66 (dd, J = 2.4, 1.6 Hz, 1H), 8.52 (d, J = 2.5 Hz, 1H), 7.25 (s, 1H), 7.19 (q, J = 7.8 Hz, 2H), 2.38 (s, 3H), 2.36 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 155.7, 145.2, 143.8, 142.4, 136.5, 135.7, 133.0, 131.0, 130.4, 129.9, 20.9, 19.8; HRMS (ESI-TOF) calcd for $C_{12}H_{12}N_2$ $[M + H]^+$ 185.1073, found 185.1067.

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*2-(4-Bromophenyl)pyrazine (Table 3, **3i**).*[17] Column chromatography (flash silica gel, hexane/EtOAc); R_f = 0.50 (hexane/EtOAc, 8:2); yield 78% (182 mg); light yellow solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 9.02 (d, J = 1.4 Hz, 1H), 8.63 (dd, J = 2.3, 1.7 Hz, 1H), 8.53 (d, J = 2.4 Hz, 1H), 7.92−7.90 (m, 2H), 7.65 (dd, J = 8.8, 2.0 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 151.7, 144.3, 143.2, 141.9, 135.2, 132.3, 128.4, 124.6; HRMS (ESI-TOF) calcd for $C_{10}H_7BrN_2$ $[M + H]^+$ 234.9865, found 234.9839.

*2-(4-Chlorophenyl)pyrazine (Table 3, **3j**).*[17] Column chromatography (flash silica gel, hexane/EtOAc): R_f = 0.45 (hexane/EtOAc, 8:2); yield 76% (145 mg); pale yellow solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 9.01 (d, J = 1.5 Hz, 1H), 8.63 (dd, J = 2.2, 1.8 Hz, 1H), 8.53 (d, J = 2.5 Hz, 1H), 7.99−7.97 (m, 2H), 7.51−7.48 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 151.7, 144.2, 143.2, 141.9, 136.2, 134.7, 129.3, 128.2; HRMS (ESI-TOF) calcd for $C_{10}H_7ClN_2$ $[M + H]^+$ 191.0371, found 191.0361.

*2-(3-Chlorophenyl)pyrazine (Table 3, **3k**).*[18] Column chromatography (flash silica gel, hexane/EtOAc): R_f = 0.45 (hexane/EtOAc, 8:2); yield 65% (124 mg); light yellow solid, ^{1}H NMR (400 MHz, $CDCl_3$) δ = 9.02 (d, J = 1.5 Hz, 1H), 8.65 (dd, J = 2.4, 1.6 Hz, 1H), 8.55 (d, J = 2.5 Hz, 1H), 8.05−8.04 (m, 1H), 7.93−7.87 (m, 1H), 7.46−7.44 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 151.4, 144.3, 143.4, 142.0, 138.0, 135.2, 130.3, 129.9, 127.1, 124.9; HRMS (ESI-TOF) calcd for $C_{10}H_7ClN_2$ $[M + H]^+$ 191.0371, found 191.0363.

*2-(4-Fluorophenyl)pyrazine (Table 3, **3l**).*[17] Column chromatography (flash silica gel, hexane/EtOAc): R_f = 0.40 (hexane/EtOAc, 8:2); yield 52% (91 mg); brownish solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 9.02 (s, 1H), 8.64 (d, J = 1.5 Hz, 1H), 8.52 (d, J = 2.3 Hz, 1H), 8.06−8.02 (m, 2H), 7.22 (t, J = 8.5 Hz, 2H); ^{19}F NMR (376 MHz, $CDCl_3$) δ = −111.17 (m, 1F); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 164.0 (d, J = 250.3 Hz), 151.8, 144.1, 142.8, 141.8, 132.5 (d, J = 3.2 Hz), 128.8 (d, J = 8.5 Hz), 116.1 (d, J = 21.8 Hz); HRMS (ESI-TOF) calcd for $C_{10}H_7FN_2$ $[M + H]^+$ 175.0666, found 175.0659.

*2-(4-(Trifluoromethyl)phenyl)pyrazine (Table 3, **3m**).*[19] Column chromatography (flash silica gel, hexane/EtOAc): R_f = 0.35 (hexane/EtOAc, 8:2); yield 30% (68 mg); pale yellow solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 9.10 (d, J = 1.4 Hz, 1H), 8.71 (dd, J = 2.4, 1.6 Hz, 1H), 8.61 (d, J = 2.4 Hz, 1H), 8.18 (d, J = 8.1 Hz, 2H), 7.81 (d, J = 8.2 Hz, 2H); ^{19}F NMR (376 MHz, $CDCl_3$) δ = −63.20 (s, 3F); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 151.3, 144.3, 143.8, 142.3, 139.7, 132.1 (q, J = 32.6 Hz), 127.2, 126.6 (q, J = 272.4 Hz), 126.0 (q, J = 3.8 Hz); HRMS (ESI-TOF) calcd for $C_{11}H_7F_3N_2$ $[M + H]^+$ 225.0635, found 225.0646.

*2-([1,1′-Biphenyl]-4-yl)pyrazine (Table 3, **3n**).*[20] Column chromatography (flash silica gel, hexane/EtOAc); R_f = 0.45 (hexane/EtOAc, 8:2); yield 50% (116 mg); light yellow solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 9.09 (d, J = 1.8 Hz, 1H), 8.66−8.65 (m, 1H), 8.52 (dd, J = 6.1, 2.6 Hz, 1H), 8.12−8.10 (m, 2H), 7.78−7.74 (m, 2H), 7.69−7.66 (m, 2H), 7.51−7.46 (m, 2H), 7.41−7.25 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 152.5, 144.3, 142.8, 142.7, 142.1, 140.2, 135.1, 128.9, 128.7, 128.3, 127.8, 127.7 127.3, 127.1, 126.7; HRMS (ESI-TOF) calcd for $C_{16}H_{12}N_2$ $[M + H]^+$ 233.1073, found 233.1064.

*2-(Naphthalen-1-yl)pyrazine (Table 3, **3o**).*[9] Column chromatography (flash silica gel, hexane/EtOAc): R_f = 0.50 (hexane/EtOAc, 8:2); yield 45% (93 mg); light yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.90 (s, 1H), 8.77−8.76 (m, 1H), 8.64−8.63 (m, 1H), 8.09 (d, J = 7.0 Hz, 1H), 8.10−7.92 (m, 2H), 7.63−7.53 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 155.1, 145.8, 144.1, 142.8, 134.6, 133.9, 134.0, 130.0, 128.6, 128.2, 127.0, 126.3, 125.3,124.9; HRMS (ESI-TOF) calcd for $C_{14}H_{10}N_2$ $[M + H]^+$ 207.0917, found 207.0912.

*(E)-2-Styrylpyrazine (Table 3, **3p**).*[16] Column chromatography (flash silica gel, hexane/EtOAc): R_f = 0.35 (hexane/EtOAc, 8:2); yield 48% (88 mg); light yellow solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.65 (d, J = 1.4 Hz, 1H), 8.55−8.54 (m, 1H), 8.40 (d, J = 2.5 Hz, 1H), 7.76 (d, J = 16.1 Hz, 1H), 7.61−7.59 (m, 2H), 7.42−7.33 (m, 3H), 7.16 (d, J = 16.1 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 151.3, 144.3, 143.7, 142.7, 136.0, 135.2, 129.0, 128.8, 127.3, 124.0; HRMS (ESI-TOF) calcd for $C_{12}H_{10}N_2$ $[M + H]^+$ 183.0917, found 183.0907.

*2,3-Dimethyl-5-(p-tolyl)pyrazine (Table 3, **3q**).* Column chromatography (flash silica gel, hexane/EtOAc): R_f = 0.60 (hexane/EtOAc, 8:2); yield 64% (127 mg); colorless solid; mp 109−111 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.68 (s, 1H), 7.89−7.87 (m, 2H), 7.28 (d, J = 7.9 Hz, 2H), 2.60 (s, 3H), 2.56 (s, 3H), 2.41 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 151.6, 150.0, 149.4, 139.2, 138.0, 134.0, 129.6, 126.5, 22.2, 21.7, 21.3; HRMS (ESI-TOF) calcd for $C_{13}H_{14}N_2$ $[M + H]^+$ 199.1230, found 199.1223.

*2-(2-Chloropyridin-4-yl)pyrazine (Table 3, **3r**).* Column chromatography (flash silica gel, hexane/EtOAc): R_f = 0.30 (hexane/EtOAc, 8:2); yield 15% (29 mg); light yellow solid; mp 111−112 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 9.10 (d, J = 1.3 Hz, 1H), 8.72−8.67 (m, 1H), 8.67 (d, J = 2.4 Hz, 1H), 8.56 (d, J = 5.2 Hz, 1H), 8.01 (d, J = 0.7 Hz, 1H), 7.85 (dd, J = 5.2, 1.4 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 152.8, 150.5, 148.9, 146.6, 145.3, 144.7, 142.3, 121.7, 119.5; HRMS (ESI-TOF) calcd for $C_9H_6ClN_3$ $[M + H]^+$ 192.0328, found 192.0322.

*2-Phenylquinoxaline (Table 4, **6a**).*[21] Column chromatography (flash silica gel, hexane/EtOAc): R_f = 0.50 (hexane/EtOAc, 8:2); yield 62% (128 mg); light yellow solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 9.33 (s, 1H), 8.21−8.12 (m, 4H), 7.81−7.73 (m, 2H), 7.60−7.51 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 151.8, 143.3, 142.3, 141.6, 136.8, 130.2, 130.1, 129.6, 129.5, 129.1, 127.5; HRMS (ESI-TOF) calcd for $C_{14}H_{10}N_2$ $[M + H]^+$ 207.0917, found 207.0912.

*2-(p-Tolyl)quinoxaline (Table 4, **6b**).*[21] Column chromatography (flash silica gel, hexane/EtOAc): R_f = 0.55 (hexane/EtOAc, 8:2); yield 65% (143 mg); light yellow solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 9.31 (s, 1H), 8.15−8.09 (m, 4H), 7.75 (dddd, J = 14.9, 8.4, 6.9, 1.6 Hz, 2H), 7.37 (d, J = 8.0 Hz, 2H), 2.45 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 151.8, 143.3, 142.3, 141.4, 140.5, 133.9, 130.2, 129.9, 129.5, 129.3, 129.1, 127.4, 21.4; HRMS (ESI-TOF) calcd for $C_{15}H_{12}N_2$ $[M + H]^+$ 221.1073, found 221.1068.

*2-(4-Methoxyphenyl)quinoxaline (Table 4, **6c**).*[21] Column chromatography (flash silica gel, hexane/EtOAc): R_f = 0.40 (hexane/EtOAc, 8:2); yield 52% (123 mg); colorless solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 9.29 (s, 1H), 8.19−8.13 (m, 2H), 8.11 (ddd, J = 9.8, 8.4, 1.3 Hz, 2H), 7.74 (dddd, J = 21.2, 8.4, 6.9, 1.5 Hz, 2H), 7.10−7.06 (m, 2H), 3.90 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 161.4, 151.5, 143.1, 142.3, 141.2, 130.2, 129.4, 129.3, 129.0, 128.9, 114.6, 55.4; HRMS (ESI-TOF) calcd for $C_{15}H_{12}N_2O$ $[M + H]^+$ 237.1022, found 237.1017.

*2-(4-Fluorophenyl)quinoxaline (Table 4, **6d**).*[21] Column chromatography (flash silica gel, hexane/EtOAc): R_f = 0.40 (hexane/EtOAc, 8:2); yield 48% (108 mg); light yellow solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 9.30 (s, 1H), 8.23−8.19 (m, 2H), 8.15−8.12 (m, 2H), 7.83−7.73 (m, 2H), 7.28−7.24 (m, 2H); ^{19}F NMR (376 MHz, $CDCl_3$) δ = −110.56 (m, 1F); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 164.2 (d, J = 250.8 Hz), 150.7, 142.9, 142.2, 141.5, 132.9 (d, J = 3.2 Hz), 130.4, 129.5, 129.5, 129.5 (d, J = 8.3 Hz), 129.1, 116.2 (d, J = 21.8 Hz); HRMS (ESI-TOF) calcd for $C_{14}H_9FN_2$ $[M + H]^+$ 225.0823, found 225.0813.

*2-(3-Chlorophenyl)quinoxaline (Table 4, **6e**).*[22] Column chromatography (flash silica gel, hexane/EtOAc): R_f = 0.45 (hexane/EtOAc, 8:2); yield 45% (108 mg); light yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 9.31 (s, 1H), 8.24 (d, J = 0.9 Hz, 1H), 8.18−8.13 (m, 2H), 8.08−8.06 (m, 1H), 7.84−7.76 (m, 2H), 7.51−7.50 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 150.3, 142.9, 142.2, 141.8, 138.5, 135.3, 130.5, 130.4, 130.2, 130.0, 129.7, 129.1, 127.7, 125.5; HRMS (ESI-TOF) calcd for $C_{14}H_9ClN_2$ $[M + H]^+$ 241.0527, found 241.0518.

*2-Methyl-3-(p-tolyl)quinoxaline (Table 4, **6f**).*[10a] Column chromatography (flash silica gel, hexane/EtOAc): R_f = 0.60 (hexane/EtOAc, 8:2); yield 45% (106 mg); pale yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.12−8.10 (m, 1H), 8.05−8.03 (m, 1H), 7.73−7.70 (m, 2H), 7.56 (d, J = 8.1 Hz, 2H), 7.34 (d, J = 8.3 Hz, 2H), 2.79 (s, 3H), 2.45 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 154.9, 152.6, 141.1, 141.0, 139.0, 136.1, 129.6, 129.2, 129.2, 129.1, 128.9, 128.2, 24.4, 21.3; HRMS (ESI-TOF) calcd for $C_{16}H_{14}N_2$ $[M + H]^+$ 235.1235, found 235.1223.

*2-Phenylpyridine (Table 5, **8a**).*[23] Column chromatography (flash silica gel, hexane/EtOAc): R_f = 0.60 (hexane/EtOAc, 8:2); yield 45% (70 mg); colorless solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.70−8.69 (m, 1H), 8.00−7.98 (m, 2H), 7.75−7.73 (m, 2H), 7.52−7.38 (m, 3H),

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7.25−7.21 (m, 1H); HRMS (ESI-TOF) calcd for $C_{11}H_9N$ [M + H]$^+$ 156.0813, found 156.0815.

*4-Chloro-2-phenylpyridine (Table 5, **8b**).*[23] Column chromatography (flash silica gel, hexane/EtOAc): R_f = 0.50 (hexane/EtOAc, 8:2); yield 35% (67 mg); light yellow semisolid; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.57 (d, J = 5.3 Hz, 1H), 7.96 (dt, J = 8.4, 2.1 Hz, 2H), 7.72 (d, J = 1.9 Hz, 1H), 7.48−7.43 (m, 3H), 7.23 (dd, J = 5.3, 1.9 Hz, 1H); HRMS (ESI-TOF) calcd for $C_{11}H_8ClN$ [M + H]$^+$ 190.0424, found 190.0418.

*4-Chloro-2-(p-tolyl)pyridine (Table 5, **8c**).*[10a] Column chromatography (flash silica gel, hexane/EtOAc): R_f = 0.60 (hexane/EtOAc, 8:2); yield 40% (82 mg); colorless semisolid; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.55 (d, J = 5.3 Hz, 1H), 7.87 (d, J = 8.1 Hz, 2H), 7.70 (d, J = 1.9 Hz, 1H), 7.29−7.25 (m, 2H), 7.20 (dd, J = 5.3 Hz, 1.9, 1H), 2.41 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 159.0, 150.4, 144.6, 139.7, 135.3, 129.5, 126.8, 121.9, 120.4, 21.2; HRMS (ESI-TOF) calcd for $C_{12}H_{10}ClN$ [M + H]$^+$ 204.0580, found 204.0574.

*4-Chloro-2-(4-methoxyphenyl)pyridine (Table 5, **8d**).*[24] Column chromatography (flash silica gel, hexane/EtOAc): R_f = 0.50 (hexane/EtOAc, 8:2); yield 38% (84 mg); light yellow semisolid; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.51 (d, J = 5.3 Hz, 1H), 7.93−7.90 (m, 2H), 7.63 (d, J = 1.8 Hz, 1H), 7.14 (dd, J = 5.3, 1.9 Hz, 1H), 6.99−6.95 (m, 2H), 3.83 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 160.9, 158.6, 150.3, 144.6, 130.8, 128.3, 121.5, 119.9, 114.2, 55.3; HRMS (ESI-TOF) calcd for $C_{12}H_{10}ClNO$ [M + H]$^+$ 220.0529; found 220.0529.

*4-Chloro-2-(2,5-dimethylphenyl)pyridine (Table 5, **8e**).* Column chromatography (flash silica gel, hexane/EtOAc): R_f = 0.60 (hexane/EtOAc, 8:2); yield 32% (70 mg); colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ = 8.58 (d, J = 5.4 Hz, 1H), 7.42 (d, J = 1.9 Hz, 1H), 7.26 (dd, J = 5.3, 2.0 Hz, 1H), 7.20−7.12 (m, 3H), 2.35 (s, 3H), 2.32 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 161.7, 150.0, 144.0, 138.9, 135.5, 132.6, 130.8, 130.1, 129.5, 124.4, 121.9, 20.8, 19.7; HRMS (ESI-TOF) calcd for $C_{13}H_{12}ClN$ [M + H]$^+$ 218.0737, found 218.0734.

*4-Chloro-2-(4-fluorophenyl)pyridine (Table 5, **8f**).*[24] Column chromatography (flash silica gel, hexane/EtOAc): R_f = 0.50 (hexane/EtOAc, 8:2); yield 32% (67 mg); light yellow solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.55 (d, J = 5.3 Hz, 1H), 7.98−7.94 (m, 2H), 7.67 (d, J = 1.7 Hz, 1H), 7.26−7.13 (m, 3H); ^{19}F NMR (376 MHz, $CDCl_3$) δ = −111.89 (m, 1F); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 163.8 (d, J = 249.6 Hz), 157.9, 150.5, 144.7, 134.3 (d, J = 3.1 Hz), 128.8 (d, J = 8.5 Hz), 122.2, 120.5, 115.8 (d, J = 21.7 Hz); HRMS (ESI-TOF) calcd for $C_{11}H_7ClFN$ [M + H]$^+$ 208.0329, found 208.0327.

*2-Phenylquinoline (Table 5, **8g**).*[25] Column chromatography (flash silica gel, hexane/EtOAc): R_f = 0.60 (hexane/EtOAc, 8:2); yield 34% (70 mg); colorless solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.22 (d, J = 8.6 Hz, 1H), 8.18−8.16 (m, 3H), 7.88 (d, J = 8.6 Hz, 1H), 7.83 (d, J = 8.1, 1H), 7.75−7.71 (m, 1H), 7.55−7.51 (m, 3H), 7.49−7.45 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 156.9, 147.8, 139.2, 136.3, 129.2, 129.1, 128.8, 128.3, 127.1, 127.0, 126.7, 125.8, 118.5; HRMS (ESI-TOF) calcd for $C_{15}H_{11}N$ [M + H]$^+$ 206.0970, found 206.0970.

*2-(p-Tolyl)quinoline (Table 5, **8h**).*[25] Column chromatography (flash silica gel, hexane/EtOAc): R_f = 0.60 (hexane/EtOAc, 8:2); yield 38% (84 mg); colorless solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.17 (dd, J = 12.9, 8.6 Hz, 2H), 8.08−8.06 (m, 2H), 7.83 (dd, J = 19.5, 8.4 Hz, 2H), 7.73−7.67 (m, 1H), 7.52−7.48 (m, 1H), 7.33 (d, J = 8.0 Hz, 2H), 2.43 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 157.3, 148.3, 139.4, 136.9, 136.6, 129.6, 129.5, 127.4, 127.4, 127.1, 126.0, 118.8, 21.3; HRMS (ESI-TOF) calcd for $C_{16}H_{13}N$ [M + H]$^+$ 220.1126, found 220.1126.

*2-(4-Chlorophenyl)quinoline (Table 5, **8i**).*[25] Column chromatography (flash silica gel, hexane/EtOAc): R_f = 0.55 (hexane/EtOAc, 8:2); yield 30% (72 mg); colorless solid; ^{1}H NMR (500 MHz, $CDCl_3$) δ = 8.22 (d, J = 8.6 Hz, 1H), 8.15 (d, J = 8.5 Hz, 1H), 8.12 (d, J = 8.4 Hz, 2H), 7.83 (dd, J = 8.3, 4.6 Hz, 2H), 7.76−7.71 (m, 1H), 7.54 (t, J = 7.5 Hz, 1H), 7.50−7.48 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 156.0, 148.2, 138.0, 136.9, 135.5, 129.8, 129.6, 129.0, 128.8, 127.4, 127.2, 126.5, 118.5; HRMS (ESI-TOF) calcd for $C_{15}H_{10}ClN$ [M + H]$^+$ 240.0580, found 240.0575.

*1-Phenylisoquinoline (Table 5, **8j**).*[25] Column chromatography (flash silica gel, hexane/EtOAc): R_f = 0.60 (hexane/EtOAc, 8:2); yield 40% (82 mg); light yellow solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.64−8.60 (m, 1H), 8.10 (d, J = 8.5 Hz, 1H), 7.88 (d, J = 8.1 Hz, 1H), 7.71−7.63 (m, 4H), 7.55−7.49 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 160.7, 142.1, 139.5, 136.8, 129.9, 129.8, 128.5, 128.3, 127.5, 127.1, 126.9, 126.6, 119.9; HRMS (ESI-TOF) calcd for $C_{15}H_{11}N$ [M + H]$^+$ 206.0970, found 206.0970.

*2-Phenyl-1,4-benzoquinone (Table 6, **10a**).*[10b] Column chromatography (flash silica gel, hexane/EtOAc): R_f = 0.60 (hexane/EtOAc, 8:2); yield 90% (166 mg); yellow solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.49−7.44 (m, 5H), 6.89−6.82 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 187.6, 186.6, 145.9, 137.0, 136.2, 132.7, 130.1, 129.2, 128.5; HRMS (ESI-TOF) calcd for $C_{12}H_8O_2$ [M + H]$^+$ 185.0603, found 185.0602.

*2-(4-Methylphenyl)-1,4-benzoquinone (Table 6, **10b**).*[10b] Column chromatography (flash silica gel, hexane/EtOAc): R_f = 0.70 (hexane/EtOAc, 8:2); yield 92% (183 mg); yellow solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.39 (d, J = 8.1 Hz, 2H), 7.27−7.25 (m, 2H), 6.87−6.80 (m, 3H), 2.40(s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 187.7, 186.8, 145.8 140.6, 137.0, 136.2, 132.0, 129.8, 129.3, 129.2, 21.4; HRMS (ESI-TOF) calcd for $C_{13}H_{10}O_2$ [M + H]$^+$ 199.0759, found 199.0749.

*2-(4-Methoxyphenyl)-1,4-benzoquinone (Table 6, **10c**).*[10b] Column chromatography (flash silica gel, hexane/EtOAc): R_f = 0.60 (hexane/EtOAc, 8:2); yield 80% (172 mg); red solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.50−7.46 (m, 2H), 6.99−6.95 (m, 2H), 6.86−6.79 (m, 3H), 3.86 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 187.7, 187.1, 161.4, 145.2, 137.0, 136.2, 131.1, 130.9, 124.9, 114.1, 55.4; HRMS (ESI-TOF) calcd for $C_{13}H_{10}O_3$ [M + H]$^+$ 215.0708, found 215.0697.

*2-(2-Phenoxyphenyl)-1,4-benzoquinone (Table 6, **10d**).* Column chromatography (flash silica gel, hexane/EtOAc): R_f = 0.50 (hexane/EtOAc, 8:2); yield 65% (180 mg); yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.38−7.26 (m, 4H), 7.18−7.05 (m, 2H), 7.02 (t, J = 11.0 Hz, 2H), 6.95−6.75 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 187.5, 185.4, 156.5, 155.3, 145.4, 137.0, 136.2, 134.5, 131.2, 130.9, 129.8, 124.7, 123.8, 123.2, 119.3, 118.3; HRMS (ESI-TOF) calcd for $C_{18}H_{12}O_3$ [M − H]$^-$ 275.0714; found 275.0717.

*2-(3-Trifluoromethylphenyl)-1,4-benzoquinone (Table 6, **10e**).*[26] Column chromatography (flash silica gel, hexane/EtOAc); R_f = 0.50 (hexane/EtOAc, 8:2); yield 35% (89 mg); yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.73 (d, J = 9.2 Hz, 2H), 7.68 (d, J = 7.8 Hz, 1H), 7.59 (t, J = 7.7 Hz, 1H), 6.93−6.86 (m, 3H); ^{19}F NMR (376 MHz, $CDCl_3$) δ = −62.75 (s, 3F); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 187.2, 186.0, 144.6, 137.0, 136.4, 133.4, 133.3, 132.5, 131.1 (q, J = 32.6 Hz), 129.1, 126.7 (q, J = 3.6 Hz), 126.1 (q, J = 3.8 Hz), 123.7 (q, J = 272.5 Hz); HRMS (ESI-TOF) calcd for $C_{13}H_7F_3O_2$ [M + H]$^+$ 253.0476, found 253.0472.

*2-(2-Fluoropyridin-3-yl)-1,4-benzoquinone (Table 6, **10f**).* Column chromatography (flash silica gel, hexane/EtOAc): R_f = 0.40 (hexane/EtOAc, 8:2); yield 25% (51 mg); brown solid; mp 124−125 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.32−8.30 (m, 1H), 7.80 (ddd, J = 9.4, 7.5, 1.9 Hz, 1H), 7.31 (ddd, J = 7.3 Hz, 4.9, 1.7, 1H), 6.97−6.87 (m, 3H); ^{19}F NMR (376 MHz, $CDCl_3$) δ = −66.85 (s, 1F); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 186.6, 184.6, 160.3 (d, J = 241.2 Hz), 148.8 (d, J = 15.0 Hz), 142.0 (d, J = 3.1 Hz), 140.1 (d, J = 5.2 Hz), 136.8, 136.5, 135.5 (d, J = 3.1 Hz), 121.3 (d, J = 4.4 Hz), 115.5 (d, J = 29.4 Hz); HRMS (ESI-TOF) calcd for $C_{11}H_6FNO_2$ [M + H]$^+$ 204.0461, found 204.0449.

General Procedures and Spectral Data for the Synthesis of Botryllazine A. *5-(4-Methoxyphenyl)-2,3-dimethylpyrazine (Scheme 3, **19**).* To a solution of 2,3-dimethylpyrazine (324 mg, 3 mmol) in dichloromethane (20 mL) was added trifluoroacetic acid (250 μL, 3 mmol) followed by 4-methoxyphenylboronic acid (500 mg, 3.3 mmol). Water (20 mL) was then added, followed by iron(II) acetylacetonate (150 mg, 0.6 mmol), and potassium persulfate (2.5 g, 9 mmol). TBAB was then added (48 mg), and the solution was stirred vigorously at room temperature. Upon consumption of heterocycle, the reaction mixture was diluted with dichloromethane and washed with saturated sodium bicarbonate solution. The layers were separated, and the aqueous layer was extracted with dichloromethane. Organic

layers were compiled, dried over sodium sulfate, and evaporated in vacuo. Purification was performed by silica gel chromatography eluting with hexane/ethyl acetate to get 386 mg (60%) of pure product **19** as a colorless solid: R_f = 0.5 (hexane/EtOAc, 7:3); mp 76−78 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.65 (s, 1H), 7.96−7.92 (m, 2H), 7.02−6.99 (m, 2H), 3.86 (s, 3H), 2.59 (s, 3H), 2.56 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 160.6, 151.5, 149.5, 149.1, 137.6, 129.4, 127.9, 114.3, 55.3, 22.2, 21.6; HRMS (ESI-TOF) calcd for $C_{13}H_{14}N_2O$ $[M + H]^+$ 215.1184, found 215.1179.

*5-(4-Methoxyphenyl)pyrazine-2,3-dicarbaldehyde (Scheme 3, **20**).* To a solution of compound **19** (215 mg, 1 mmol) in dioxane (4 mL) was added SeO_2 (1.1 g, 10 mmol), and the reaction mixture was heated to reflux for 24 h. After completion, reaction mixture was filtered, and the filtrate was concentrated in vacuo. The crude was purified by flash chromatography eluting with hexane/ethyl acetate to give 140 mg (50%) of **20** as a light yellow solid: R_f = 0.45 (MeOH/CH_2Cl_2, 1:19); mp 142−143 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 10.50 (s, 1H), 10.44 (s, 1H), 9.21 (s, 1H), 8.14−8.11 (m, 2H), 7.03−6.99 (m, 2H), 3.84 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 191.0, 189.5, 161.8, 153.3, 146.2, 143.2, 142.3, 128.6, 125.4, 113.9, 54.5; HRMS (ESI-TOF) calcd for $C_{13}H_{10}N_2O_3$ $[M + H]^+$ 243.0770, found 243.0763.

*(5-(4-Methoxyphenyl)pyrazine-2,3-diyl)bis((4-methoxyphenyl)-methanol) (Scheme 3, **21**).* To a solution of pyrazine dialdehyde **20** (140 mg, 0.5 mmol) in anhydrous THF (2 mL) was added a solution of 4-methoxyphenylmagnesium bromide (0.5 M solution in THF, 2.5 mL, 1.25 mmol) at −78 °C, and the reaction mixture was stirred at the same temperature for 1 h under Ar atmosphere. The reaction was quenched with a saturated solution of NH_4Cl, and the reaction mixture was extracted with diethyl ether twice. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo to give the crude. Silica gel column chromatography (hexane/ethyl acetate) provided the product **21** (185 mg, 70%) as a yellow solid: R_f = 0.55 (hexane/EtOAc, 5:5); mp 126−127 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.91 (s, 1H), 8.01 (d, J = 8.9 Hz, 2H), 7.07−7.00 (m, 6H), 6.81 (dd, J = 8.7, 1.2 Hz, 4H), 5.33 (s, 2H), 3.84 (s, 3H), 3.73 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 160.5, 158.7, 158.7, 150.8, 149.3, 148.0, 136.4, 132.0, 131.8, 128.2, 128.1, 127.3, 126.7, 113.6, 113.5, 113.4, 69.9, 54.4, 54.3, 54.3; HRMS (ESI-TOF) calcd for $C_{27}H_{26}N_2O_5$ $[M + H]^+$ 459.1920, found 459.1906.

*(5-(4-Methoxyphenyl)pyrazine-2,3-diyl)bis((4-methoxyphenyl)-methanone) (Scheme 3, **17**).* To a stirred solution of PCC (107 mg, 0.5 mmol) in anhydrous CH_2Cl_2 (2 mL) was added a solution of diol **21** (90 mg, 0.2 mmol), and the reaction mixture was stirred at room temperature for 2 h under N_2 atmosphere. After completion, reaction mixture was concentrated in vacuo, and the crude was purified by flash chromatography eluting with MeOH/CH_2Cl_2 to give 80 mg (75%) of **17** as a yellow solid: R_f = 0.60 (hexane/EtOAc, 5:5); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 9.09 (s, 1H), 8.10−8.00 (m, 6H), 7.04 (d, J = 8.7 Hz, 2H), 6.97 (d, J = 8.4 Hz, 4H), 3.89 (s, 9H); HRMS (ESI-TOF) calcd for $C_{27}H_{22}N_2O_5$ $[M + H]^+$ 455.1607, found 455.1595.

*Botryllazine A (Scheme 3, **22**).* A mixture of pyridine hydrochloride (1 g, 8.93 mmol) and **17** (20 mg, 0.04 mmol) was stirred at 220 °C for 1 h and then poured onto ice. The solution was extracted with ether (3 × 10 mL), and the combined organic layers were then dried on Na_2SO_4 and concentrated in vacuo. The crude was purified by flash chromatography eluting with ether to give 15 mg (80%) of botryllazine A (**22**) as a yellow solid: R_f = 0.30 (hexane/EtOAc, 4:6); ^{1}H NMR (500 MHz, CD_3OD) δ = 9.12 (s, 1H), 7.98 (d, J = 8.7 Hz, 2H), 7.79 (d, J = 8.7 Hz, 2H), 7.75 (d, J = 8.7 Hz, 2H), 6.84 (d, J = 8.7 Hz, 2H), 6.76 (dd, J = 8.7, 6.9 Hz, 4H); HRMS (ESI-TOF) calcd for $C_{24}H_{16}N_2O_5$ $[M + H]^+$ 413.1137, found 413.1115.

■ ASSOCIATED CONTENT

Supporting Information

Copies of NMR, HRMS spectra, and HPLC analysis graph of optimized conditions. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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