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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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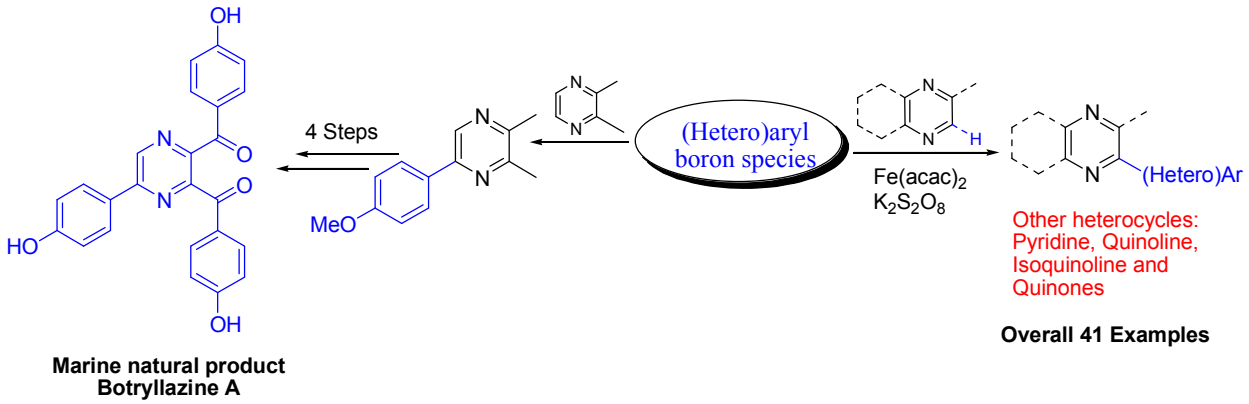


Abstract:

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 condition 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, 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 partner 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 last 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 large excess of heterocyclic partners, expensive ligands and harsh reaction condition. 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 condition (Ag catalyst).[11] In last two decades, iron based catalysts have drawn the attention as cheap, nontoxic and environmentally friendly materials for the cross-coupling reactions.[12] In the case of electron-deficient (hetero)arenes, J. Wen *et al*[13a] reported a iron-oxalate mediated coupling which required large excess of heterocycle partner and stoichiometric amount of iron species, ligand and high temperature. Very recently, J. Wang *et al*[13b] reported a heterogeneous FeS mediated cross-coupling using

stoichiometric amounts of iron species. Keeping in view 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 C(sp^2)-H bond with organoboron species using catalytic amount of iron catalyst under open-flask condition. 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]

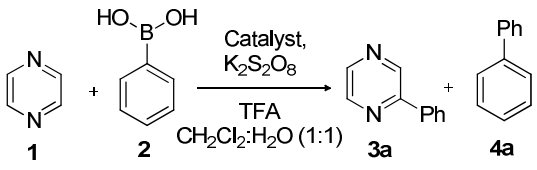
Since many biologically active natural products are comprised of substituted electron-deficient heterocycles such as pyrazine, quinoxaline, pyridine, quinoline, isoquinoline, pyrimidine *etc*., our method offers tremendous potential for introducing functionalities into aforementioned moieties containing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

Results and Discussion:

We selected various iron salts to test the idea and started this study by the reaction of pyrazine with phenylboronic acid in the presence of trifluoroacetic acid using water/dichloromethane solvent system (results summarized in 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 crude product was determined by HPLC. Among the various iron salts tried (Table 1, entries 2-7)

iron(III) acetylacetonate {$Fe(acac)_3$ gave desired product **3a** with 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 amount (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 didn't show any improvement (Table 1, entries 12-14). In the absence of iron salt, no product formation was observed (Table 1, entry 15).

Table 1: Optimization studies for the cross-coupling reaction



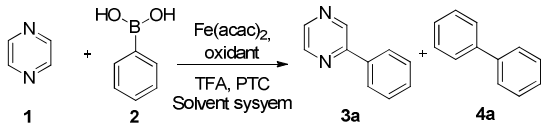
1 **2** **3a** **4a**

Entry	Catalyst	Qty (mol%)	Product composition[a]	
			3a	4a
1	$FeSO_4$	20	55	<10
2	FeO	20	50	12
3	Fe_2O_3	20	38	N.D.
4	$FeCl_3$	20	trace	N.D.
5	$FeBr_3$	20	trace	N.D.
6	FeF_2	20	trace	N.D.
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	N.D.
14	CuI	20	20	N.D.
15	–	–	0	0

[a]Product composition was determined by HPLC
Reaction conditions (unless otherwise stated):Pyrazine (1mmol), TFA (1 mmol), **2** (1.1 mmol), $K_2S_2O_8$ (3.0 equiv.), rt, 12 h, air.
N.D. denotes Not detected

Investigation towards optimization of coupling conditions such as different oxidants, solvent systems, phase transfer catalyst, temperature and surrounding atmosphere were tried and all the results summarized in Table 2. Among the various oxidants tried {*ter*-butyl hydrogen peroxide (TBHP), Di-*ter*-butyl hydrogen peroxide (DTBP) and oxone}, only TBHP gave 20% of desired product **3a** (Table 2, entries 1-3). Change in the sovlent system also affected the formation of 2-phenylpyrazine (Table 2, entries 4-8). As the reaction conditions involved two immiscible substances, the addition of 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 supporting information). As observed during experiment the addition of TBAB supressed the emulsion formation and made the reaction mixture a very clear solution which allowed effective coupling and yield improvement as compared to J. wang method[13b] where because of heterogenous nature of FeS, its stoichiometric quantity was required. Moreover, decrease in the amount of $K_2S_2O_8$ also decreased the yield of **3a** (Table 2, entries 12-13). 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 increase in the temperature did not affect the formation of desired product (Table 2, entries 15-16).

Table 2: Optimization studies for the cross-coupling reaction of pyrazine with phenylboronic acid



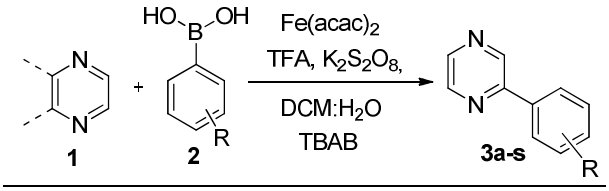
1 2 3a 4a

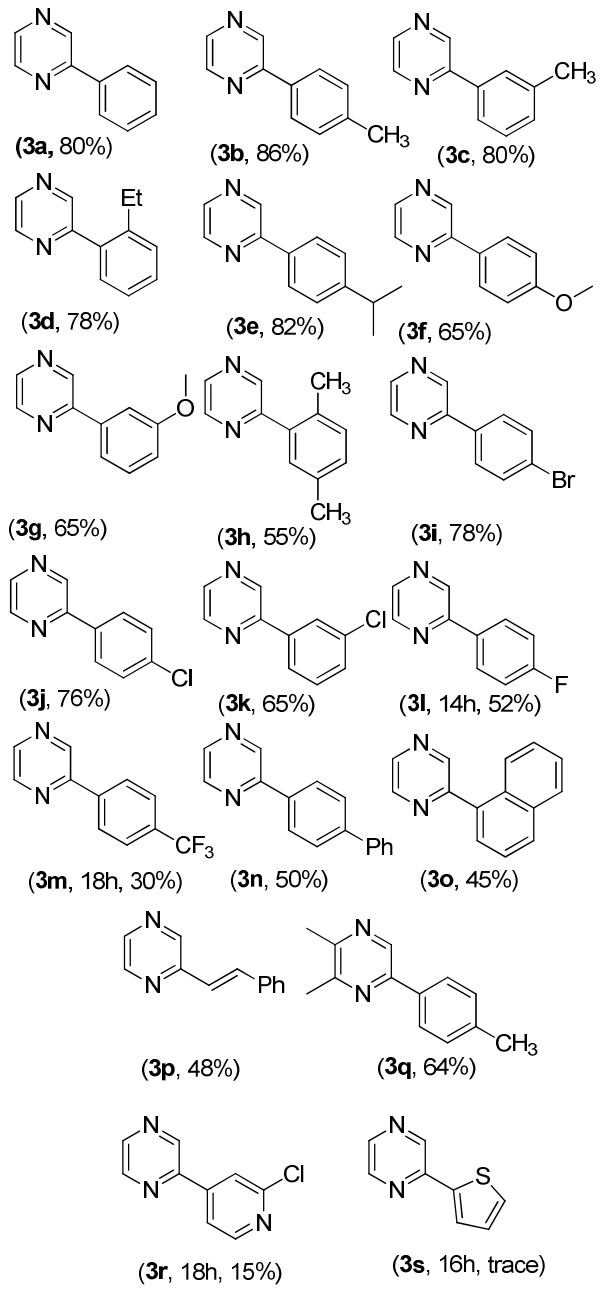
Entry	Solvent[a]	Oxidant	Atm	Temp (°C)	PTC	Product composition[b] 3a	4a
1	DCM:H_2O	TBHP (3 eq.)	Air	rt	–	20	N.D.
2	DCM:H_2O	DTBP (3 eq.)	Air	rt	–	–	–
3	DCM:H_2O	Oxone (3 eq.)	Air	rt	–	–	–
4	DCM	$K_2S_2O_8$ (3 eq.)	Air	rt	–	–	–
5	H_2O	$K_2S_2O_8$ (3 eq.)	Air	rt	–	40	5
6	DMSO:H_2O	$K_2S_2O_8$ (3 eq.)	Air	rt	–	trace	N.D.
7	ACN:H_2O	$K_2S_2O_8$ (3 eq.)	Air	rt	–	trace	N.D.
8	Toluene:H_2O	$K_2S_2O_8$ (3 eq.)	Air	rt	–	45	8
9	**DCM:H_2O**	**$K_2S_2O_8$ (3 eq.)**	**Air**	**rt**	**TBAB**	**84**	**<10**
10[c]	DCM:H_2O	$K_2S_2O_8$ (3 eq.)	Air	rt	TBAB	75	<10
11	Toluene:H_2O	$K_2S_2O_8$ (3 eq.)	Air	rt	TBAB	50	8
12	DCM:H_2O	$K_2S_2O_8$ (2 eq.)	Air	rt	TBAB	70	6
13	DCM:H_2O	$K_2S_2O_8$ (1 eq.)	Air	rt	TBAB	65	N.D.
14	DCM:H_2O	–	Air	rt	TBAB	–	–
15	DCM:H_2O	$K_2S_2O_8$ (3 eq.)	O_2	rt	TBAB	80	N.D.
16	DCM:H_2O	$K_2S_2O_8$ (3 eq.)	Air	50	TBAB	82	10

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

Under optimized conditions, the reactivity of various organoboronic acids towards pyrazine was investigated, and all the reults are given in Table 3. Various *ortho-, meta- and para-* substituted organoboronic acids on reaction with pyrazine provided the desired mono-arylated coupled products **3a-s** with varying yields. Arylboronic acids possessing electron-donating groups at *para*, *meta* and *ortho* position smoothly underwent cross-coupling reaction and gave good to excellent yields of desired products **3b-g** while di-substituted such as 2,5-dimethylphenylboronic acid gave moderate yield of coupled product **3h**. Similarly, electron-withdrawing groups possessing arylboronic acids underwent cross-coupling reaction to afford corresponding 2-arylpyrazine derivatives **3i-n** in moderate to good yields. Moreover, hindered

Table 3: Cross-coupling reaction of pyrazines with organoboronic acids



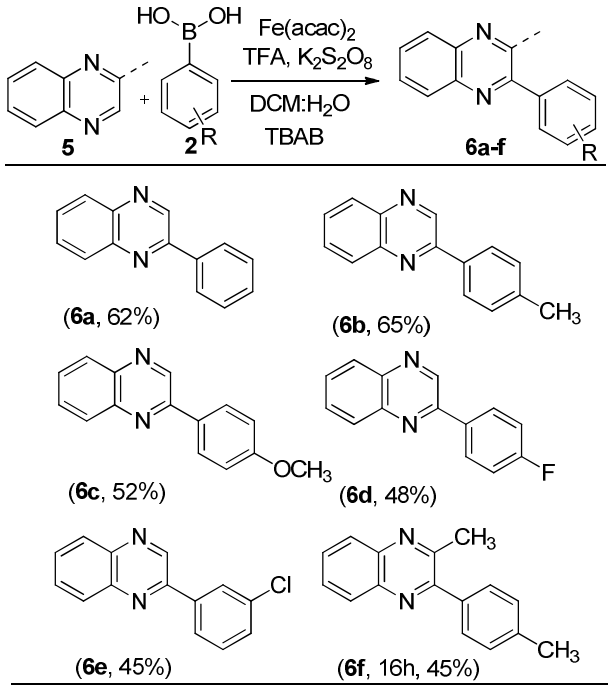


Reaction conditions (unless otherwise stated): Pyrazine **1** (1 mmol), **2** (1.1 mmol), TFA (1 mmol), $Fe(acac)_2$ (20 mol%), $K_2S_2O_8$ (3 mmol), TBAB (5mol%), CH_2Cl_2:H_2O, 12h, under air at rt.

1-napthylboronic acid underwent cross-coupling and gave 2-napthylpyrazine **3o** in 45% yield. Vinylic boronic acid such as trans-2-phenylvinylboronic acid also coupled with pyrazine and afforded 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 acid were also tried where 2-chloropyridine-4-boronic acid underwent reaction with pyrazine and gave very less yield 15% of coupled product **3r** while thiophenyl-2-boronic acid gave only trace quantity of desired product as detected by MS analysis.

The present method under optimized conditions when tried with benzannnulated pyrazine such as quinoxalines **5** also gave mono-arylated product in moderate to good yields (results summmarized in Table 4). Quinoxaline on reaction with phenylboronic acid furnished 62% of 2-

Table 4: Cross-coupling reaction of quinoxalines with arylboronic acids



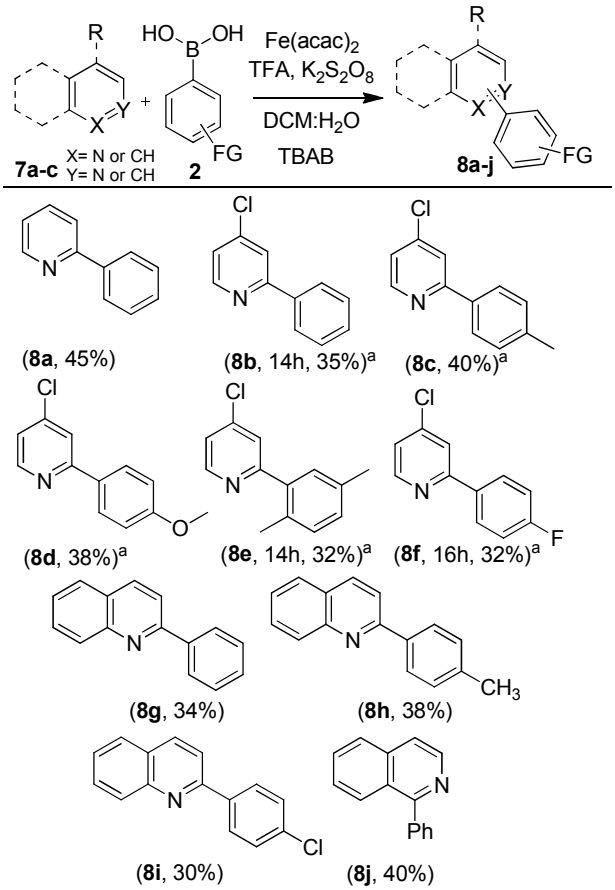
Reaction conditions (unless otherwise stated): **5** (1 mmol), **2** (1.1 mmol), TFA (1 mmol), $Fe(acac)_2$ (20 mol%), $K_2S_2O_8$ (3 mmol), TBAB (5mol%), CH_2Cl_2:H_2O, 12h, under air at rt.

phenyl quinoxoline **6a**. Electron-donating groups (EDGs) such as 4-methyl and 4-methoxy

containing phenyl-boronic acids gave 65 and 52% of corresponding coupled products **6b** and **6c** respectively. Electron-withdrawing groups (EWGs) containing phenylboronic acid gave comparatively lower yield. 4-fluoro and 3-chloro phenyl boronic acids gave 48 and 45% of **6d** and **6e** respectively. Similarly, the reaction of 2-methylquinoxaline with *p*-tolylphenyl boronic acid gave mono-arylated coupled product **6f** of 45% yield.

Other electron-deficient heterocycles such as un/substitued pyridines **7a**, quinoline **7b** and isoquinoline **7c** were also explored for cross-coupling reaction. Unlikely literature reports,[10a,13b] our optimized condition gave surprisingly regio-selective mono-arylated coupled product (need further investigation) but with comparatively lower yields (all the results given in Table 5). Pyridine with phenylboronic acid gave 45% yield of **8a**. 4-Chloropyridine as hydrochloride salt on reaction with phenylboronic acid gave monoarylated coupled product, 2-phenyl-4-chloro-pyridine **8b** with 35% yield. 4-Chloropyridine hydrochloride with EDGs such as 4-methyl and 4-methoxy containing phenylboronic acids gave corresponding 40 and 38% of mono-arylated coupled product **8c** and **8d** respectively. In case of reaction of 4-chloropyridine hydrochloride with 2,5-dimethylphenyl boronic acid also underwent and gave 32% of desired mono-arylated **8e**. On the other hand, 4-chloropyridine hydrochloride on coupling with 4-fluorophenylboronic acid gave 32% of desired mono-arylated product **8f**. Quinoline on reaction with phenyl, *p*-tolyl and 4-chlorphenyl boronic acids gave 34, 38 and 30% of corresponding mono-2-arylated products **8g**, **8h** and **8i** respectively. Similarly, isoquinoline under optimized conditions coulpled with phenylboronic acid and gave moderate 40% of mono-arylated 1-phenylisoquinoline **8j.**

Table 5: Cross-coupling reaction of pyridines, quinoline and isoquinoline with arylboronic acids

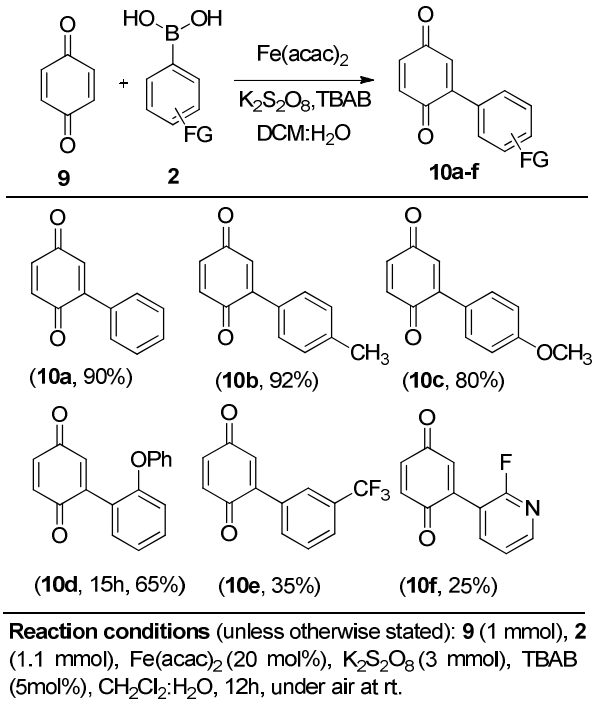


Reaction conditions (unless otherwise stated): **7** (1 mmol), **2** (1.1 mmol), TFA (1 mmol), $Fe(acac)_2$ (20 mol%), $K_2S_2O_8$ (3 mmol), TBAB (5mol%), CH_2Cl_2:H_2O, 12h, under air at rt. [a]4-Chloropyridine hydrochloride was used and without TFA

Present optimized method also worked very well with quinone **9**. Quinone underwent coupling with various un/substituted organoboronic acids gave mono-arylated cross-coupled products **10a-f** and all the results were summarized in Table 6. Phenyl as well as EDGs- (4-Me, 4-OMe) containing arylboronic acids gave coupled product **10a-c** in excellent yields. Bulky substituted arylboronic acid such as 2-Phenoxyphenylboronic acid also reacted and gave good yield (65%) of coupled product **10d**. EWG (3-CF_3) containing phenyl boronic acid smoothly underwent cross-coupling and gave 35% of coupled product **10e.** Likewise, heteroarylboronic

acid such as 2-fluoropyridine-3-boronic acid also coupled with quinone but gave comparatively lower yield of **10f** (25%).

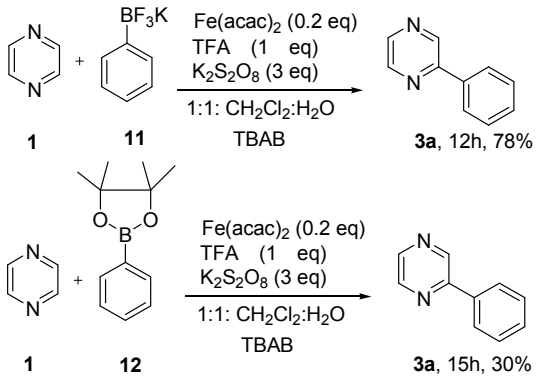
Table 6: Cross-coupling reaction of quinone with organoboronic acids



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

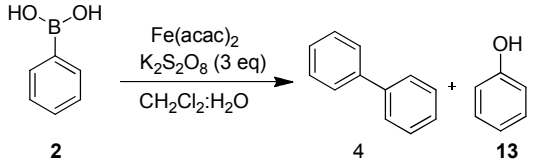
In order to see the compatibility of other organoboron species, potassium organotrifluoroborate salts and arylboronic acid pinacol ester was tried (shown in Fig 1). Potassium organotrifluoroborate salt *i.e.* phenyltrifluoroborate **11** underwent cross-coupling smoothly with pyrazine and gave 2-phenyl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

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



Efforts to understand the mechanism were made (Fig. 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**, suggested the involvement of free radical intermediates (Fig 2). Furthermore when the optimized reaction was performed with $ArB(OH)_2$ in the absence of heterocycle, GC-MS studies shown the formation of phenol and biphenyl also suggested that Fe^{2+}/SO_4^{2-} system activate the aryl boronic acid. Based on a literature precedent[10, 11] and present experimental findings, the plausible mechanism seemed to be similar as reported by Baran *et al.*[10]

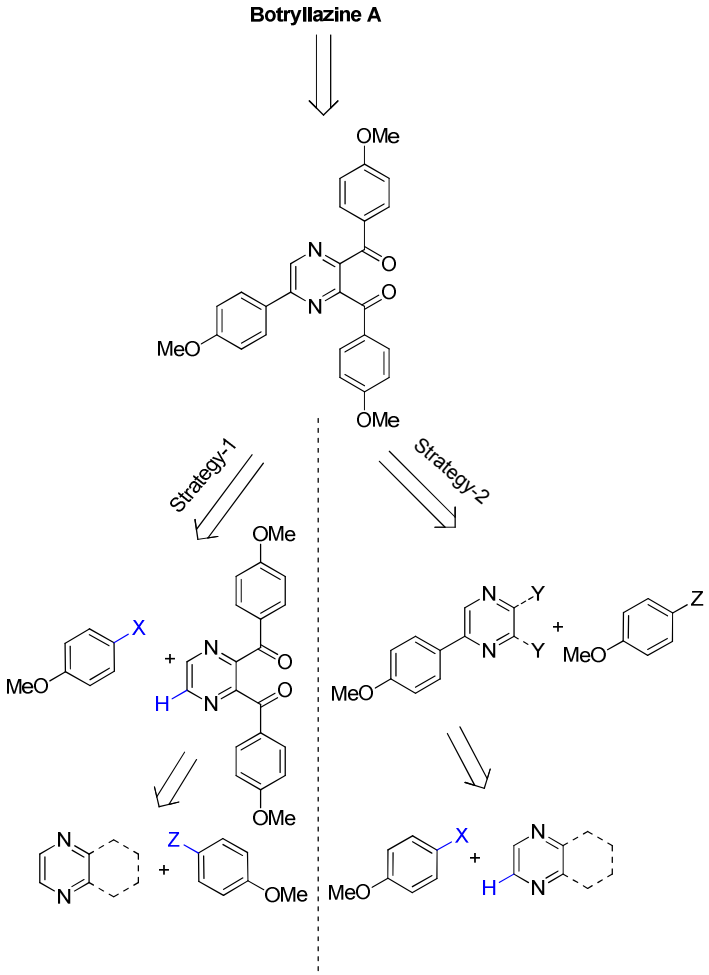
Fig 2: Exploration of present method towards free-radical mechanism



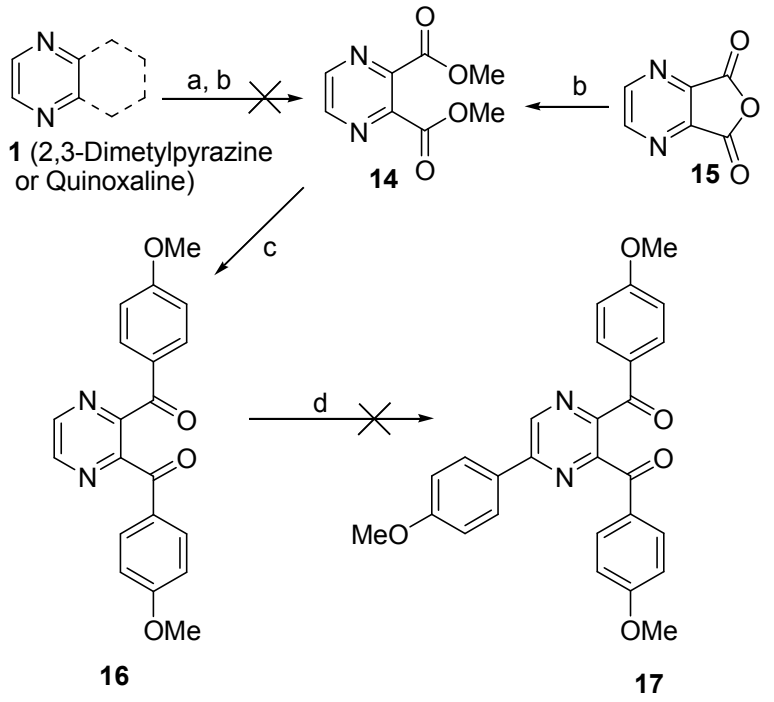
After exploring the versatility and diversity of present iron catalyzed cross-coupling reaction of N-heterocycles with hetero(aryl)boron reagent, its application towards the synthesis of bio-active natural product was explored. In this direction, we successfully developed a new and more

concise (5 steps as compared to 7 steps literature reported method[15b]) and effective route for the synthesis of a pyrazine alkaloid Botryllazine A, isolated from marine red ascidian *Botryllus leachi*.[15a-b] As per strategy 1, we first tried the synthesis of 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 in all 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-dibenzoyl pyrazine **16** but the subsequent arylation with 4-anisyl boronic acid under optimized condition did not give the expected methylated Botryllazine A **17** (Scheme 1). Then as per strategy 2, quinoxaline **1** under optimized condition was converted into 2-(*p*-methoxyphenyl)quinoxaline **6c** which on oxidation with aq. $KMNO_4$ or HNO_3 condition underwent decomposition of pyrazine ring and gave *p*-methoxybenzoic acid **18** as a sole product (Scheme 2). Next, 2,3-dimethyl pyrazine under optimized condition 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 ^oC gave Botryllazine skelton **21** which on oxidation with PCC gave methylated Botryllazine A **17**. The methylated Botryllazine A **17** on demethylated with pyridinehydrochloride[15b] gave final Botryllazine A **22** (Scheme 3). This reaction has opened new opportunities to iron catalysed functionalization of electron-deficient heterocycles as well as towards the synthesis of these heterocycles containing natural products.

Fig 4: Retro-synthetic strategies for the synthesis of pyrazine alkaloid-Botryllazine A

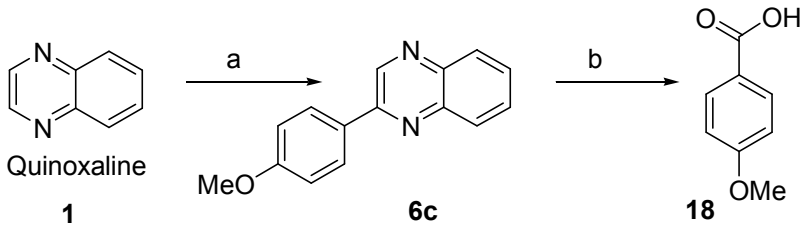


Scheme 1: Studies towards the synthesis of pyrazine alkaloid-Botryllazine A



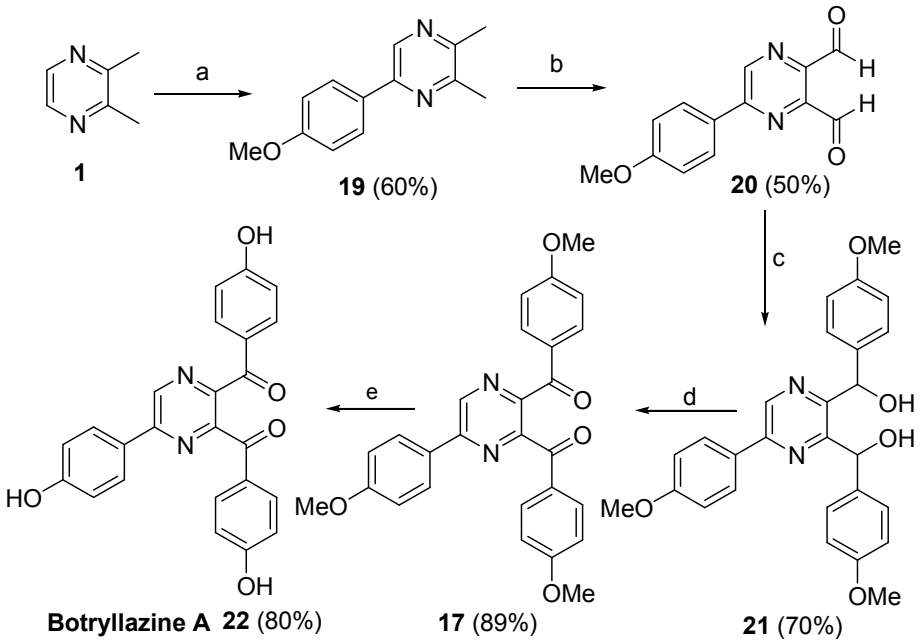
Reagents and conditions: **a**) Aq.$KMnO_4$ or 60%HNO_3 reflux, 18h; **b**) PTSA, MeOH rt, 12h; **c**) 4-anisyl-MgBr, Dry THF, -70^{0}C; **d**) 4-anisyl-$B(OH)_2$, TFA, $Fe(acac)_2$, $K_2S_2O_8$, TBAB, CH_2Cl_2:H_2O, 12h.

Scheme 2: Studies towards the synthesis of pyrazine alkaloid-Botryllazine A



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

Scheme 3: Studies towards the synthesis of pyrazine alkaloid-Botryllazine A



Reagents and conditions: **a**) 4-anisyl-$B(OH)_2$, TFA, $Fe(acac)_2$, $K_2S_2O_8$, TBAB, CH_2Cl_2:H_2O, 12h; **b**) SeO_2, dioxane, reflux, 24h; **c**) 4-anisyl-MgBr, Dry THF, -70^{0}C; **d**) PCC, DCM, rt; **e**) pyridinehydrochloride, 220 ^{o} C, 1h.

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 condition efficiently catalyzed the cross-coupling reaction of pyrazine with aryl boronic acids and gave monoarylated products in good to excellent yields. This 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 condition but gave less yield of coupled product. Further extension of present method to other (hetero)arenes and studies towards

yield improvement/regio-selectivity wherever noted are underway and will be reported in due course.

Experimental Section:

General:

All reactions were performed under air atmosphere. Analytical thin layer chromatography was performed using TLC pre-coated silica gel 60 F_{254} (20 x 20 cm). TLC plates were visualized by exposing UV light or by iodine vapours or immersion in an acidic staining solution of *p*-anisaldehyde followed by heating on hot plate. Organic solvent 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 LCMS-QTOF instrument. HPLC were performed on instrument equipped with DAD VL detector using 5µm, 4.6 x 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% *w.r.t.* (hetero)arenes} and the solution was stirred vigorously at room temperature till 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 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 (400MHz, $CDCl_3$) 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) cald. 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 (400MHz, $CDCl_3$) 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) cald. 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) cald. 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) cald. 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 ^{o}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) cald. 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) cald. 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) cald. 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) cald. for $C_{12}H_{12}N_2$ $[M + H]^+$ 185.1073; found 185.1067.

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) cald. 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) cald. 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) cald. 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; ^1H 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) cald. 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; ^1H 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) cald. 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; ^1H 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) cald. for $C_{16}H_{12}N_2$ $[M + H]^+$ 233.1073; found 233.1064.

2-(Naphthalene-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) cald. 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) cald. 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 ^{o}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) cald. 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 ^{o}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) cald. 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) cald. 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) cald. 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) cald. 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) cald. 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) cald. 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) cald. 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), 7.25 – 7.21 (m, 1H); HRMS (ESI-TOF) cald. 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 semi-solid; ^{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) cald. 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 semi-solid; ^1H 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) cald. 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 semi-solid; ^1H 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) cald. 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; ^1H 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) cald. 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) cald. 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) cald. 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) cald. 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) cald. 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; ^1H 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) cald. 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; ^1H 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) cald. 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; ^1H 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) cald. 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; ^1H 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) cald. 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) cald. 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) cald. 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 ^{o}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) cald. 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-dimethyl Pyrazine (324 mg, 3 mmol) in dichloromethane (20 mL) was added trifluoroacetic acid (250 μL, 3 mmol) followed by 4-methoxy phenyl boronic 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 the 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 colorless solid.

R_f = 0.5 (hexane/EtOAc, 7:3); mp 76-78 ^oC; ^1H 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) cald. 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*. Crude was purified by flash chromatography eluting with hexane/ethyl acetate to give 140 mg (50%) of **20** as light yellow solid.

R_f = 0.45 ($MeOH/CH_2Cl_2$, 1: 19); mp 142-143 ^oC; ^1H 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) cald. 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 ^oC and the reaction mixture was stirred at the same temperature for 1 h under Ar atmosphere. After that reaction was quenched with a saturated solution of NH_4Cl and reaction mixture was extracted with diethyl ether twice. 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 yellow solid. R_f = 0.55 (hexane/EtOAc, 5:5); mp 126-127 ^oC; ^1H 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) cald. 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 crude was purified by flash chromatography eluting with MeOH/CH_2Cl_2 to give 80 mg (75%) of **17** as 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) cald. 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 ^oC for 1 h and then poured on to ice. The solution was extracted with ether (3x10 mL), 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 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 (d, *J* = 8.7, 6.9 Hz, 4H); HRMS (ESI-TOF) cald. for $C_{24}H_{16}N_2O_5$ $[M + H]^+$ 413.1137; found 413.1115.

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Supporting Information

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

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