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Synthesis of Fused-Pyrazines via Palladium-Catalyzed Double Benzyl Isocyanide Insertion and Cross-Dehydrogenative Coupling

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Abstract. A palladium-catalyzed cascade reaction has been realized for the synthesis of 5*H*-pyrrolo[2,3-*b*]pyrazines and 5*H*-pyrazino[2,3-*b*]indoles with benzyl isocyanide by choosing *o*-pivaloyloximes or *o*-iodoanilines as a suitable substrate. The key steps involved are (i) oxidative addition of palladium through N-O or C-I cleavage; (ii) migratory double isocyanide insertion; and (iii) cross-dehydrogenative coupling. Notable features are good functional group tolerance, formation of three C-C and one C-N bonds.

Keywords: Palladium; Benzyl isocyanide; Fused-Pyrazines; CDC; Catalysis

Introduction

5*H*-pyrrolo [2,3-*b*]pyrazines also known as aloisines are important class of *N*-heterocycles with versatile biological properties. For examples, they are used as CDKs,[1a,b,d,e] GSK,[1a,c,d] JAK,[2a] Syk,[2b] Topo II[3a] inhibitors and also as multi-target antimalarial agents[3b] (Figure 1). Despite its potential bioactivity, only a few synthetic strategies have been identified in the literature so far probably due to the lack of suitable design in the starting materials and reaction conditions.[4]

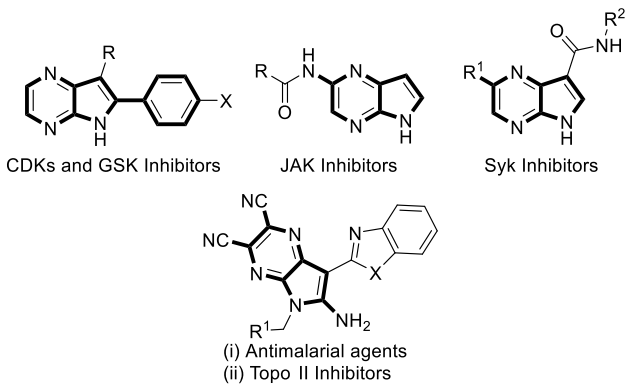

Figure 1. Representative examples of bioactive pyrrolopyrazines

In 1981, Vierfond et al developed the synthesis of 5*H*-pyrrolo[2,3-*b*]pyrazines from methylpyrazines with aromatic nitriles through a sequence of lithiation, condensation and intramolecular cyclization (Scheme 1a).[5] In 2004, Hopkins et al developed a palladium-catalyzed heteroannulation process from readily accessible *N*-(3-chloropyrazin-2-yl)-methane sulfonamide and commercially available terminal alkynes (Scheme 1b).[6] In 2006, Kasatkin et al developed a two-step process from 2,3-dichloropyrazine with lithiated ketones/esters and nitriles followed by cyclization with primary amines (Scheme 1c).[7] In 2012, Keivanloo et al improved the yield of aloisines by modifying the conditions of Hopkins using the combination of Pd-Cu in the presence of SDS surfactant in the water.[8] Recently, in 2016, Scheidt et al disclosed couple of examples through an interception of a reactive aza ortho-azaquinone methide intermediate by an acyl anion equivalent generated through carbene catalysis (Scheme 1d).[9]

In spite of these useful methods, some of them suffer from low yields, limited substrate scopes, difficult to synthesize starting material and hazardous reagents. Thus, the development of new synthetic routes for highly functionalized pyrrolopyrazines is highly desirable to explore its versatile properties.

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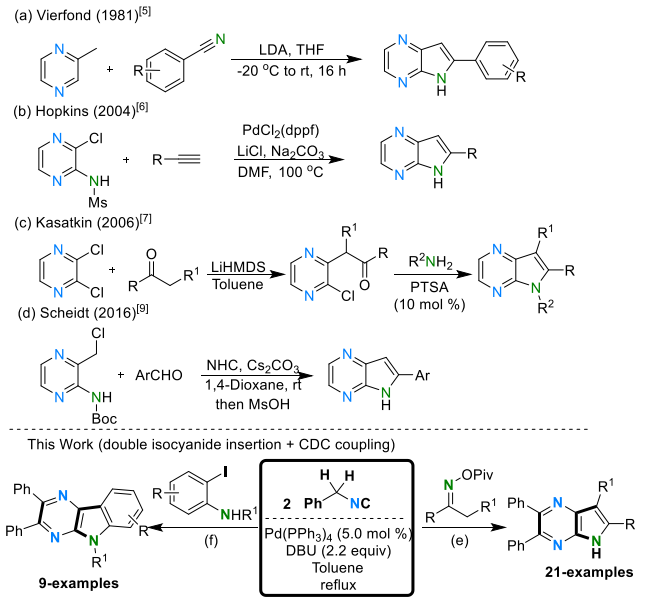


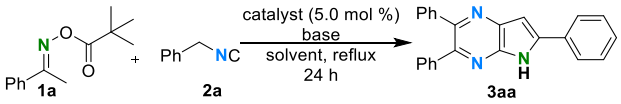
Scheme 1. Previous reports and this work fused-pyrazines

Isocyanides are important synthetic precursors in the synthesis of aza-heterocycles.[10] Among them, α-carbon of the benzyl isocyanides have been recently involved in synthesis of heterocycles such as oxazoles,[11a] imidazoles,[11b] pyrroles[11c] and imidazo[1,5-*a*]pyridines[11d] with the aid of intrinsic α-acidity under basic conditions. In this context and our experience on isocyanides chemistry,[12] herein, we disclosed the synthesis of pyrrolopyrazines through a sequence of N-O cleavage, double isocyanide insertion and cross-dehydrogenative coupling[13] with *o*-pivaloyl oximes and benzyl isocyanide under palladium-catalysis (Scheme 1e). On the other hand, replacing the *o*-pivaloyl oximes with o-iodoanilines under the identical conditions gave the 5*H*-pyrazino[2,3-*b*]indoles (Scheme 1f).

Results and Discussion

The systematic investigation of our methodology began with (*E*)-1-phenylethan-1-one *O*-acetyl oxime and benzyl isocyanide **2a** using our recently published catalytic condition for the synthesis of 2*H*-pyrrolo-2-imines using oximes acetates and isocyanide[12b] as shown in Table 1. To our surprise the desired compound **3aa** was obtained in 40% yield (Table 1, entry 1) with its structure confirmed by x-ray analysis (Figure 2).[14] Subsequent reaction by changing acetyl oxime to (*E*)-1-phenylethan-1-one *O*-pivaloyl oxime **1a** with benzyl isocyanide **2a** in the presence of 5 mol% of $Pd(PPh_3)_4$, 2.2 equiv of 1,8-diazabicyclo(5.4.0)undec-7-ene in toluene at reflux for 24 h gave 2,3,6-triphenyl-5*H*-pyrrolo[2,3-*b*]pyrazine **3aa** in 50% yield (Table 1, entry 2). Changing the base from DBU to other organic and inorganic bases failed to improve the reaction yields (Table 1, entries 3-9). On the other hand Pd(0) and Pd(II) with reducing agents also resulted in low yields (Table 1, entries 10-15) except $Pd(dba)_2$ which afforded 40% yield of **3aa** (Table 1, entry 11). The effect of solvent was investigated with CH_3CN, 1,4-dioxane, THF, MeOH, DMSO and PhCl (Table 1, entries 16-21). However, none of them gave better yield than toluene (Table 1, entry 2). Thus, of the reaction conditions screened in Table 1, entry 2 was chosen as the optimum conditions.

Table 1. Screening of the reactions conditions[a)]



Entry	Catalyst (mol %)	Base	Solvent	Yield (%)[b)]
1[c)]	$Pd(PPh_3)_4$	DBU	Toluene	40
2	$Pd(PPh_3)_4$	DBU	Toluene	50
3	$Pd(PPh_3)_4$	DABCO	Toluene	<10
4	$Pd(PPh_3)_4$	pyridine	Toluene	<10
5	$Pd(PPh_3)_4$	Cs_2CO_3	Toluene	<10
6	$Pd(PPh_3)_4$	Na_2CO_3	Toluene	trace
7	$Pd(PPh_3)_4$	NaOAc	Toluene	trace
8	$Pd(PPh_3)_4$	K_2CO_3	Toluene	trace
9	$Pd(PPh_3)_4$	CsF	Toluene	trace
10	$Pd_2(dba)_3$	DBU	Toluene	24
11	$Pd(dba)_2$	DBU	Toluene	40
12[d)]	$Pd(OAc)_2$/ PPh_3	DBU	Toluene	20
13[d)]	$PdCl_2(PPh_3)_2$/PPh_3	DBU	Toluene	30
14[d)]	$PdCl_2/PPh_3$	DBU	Toluene	31
15[d)]	PdI_2/PPh_3	DBU	Toluene	35
16	$Pd(PPh_3)_4$	DBU	CH_3CN	20
17	$Pd(PPh_3)_4$	DBU	Dioxane	22
18	$Pd(PPh_3)_4$	DBU	THF	<10
19	$Pd(PPh_3)_4$	DBU	MeOH	0
20[e)]	$Pd(PPh_3)_4$	DBU	DMSO	20
21[e)]	$Pd(PPh_3)_4$	DBU	PhCl	22

[a)] Reaction conditions: **1a** (0.5 mmol), **2a** (1.05 mmol), catalyst (5.0 mol %), base (1.1 mmol) and solvent (0.5 M) was stirred at reflux for 24 h unless otherwise noted. [b)] Yield of isolated product. [c)] Reaction was performed with (*E*)-1-phenylethan-1-one *O*-acetyl oxime. [d)] 20 mol % of triphenylphosphine was used. [e)] Reaction was carried out at 120 °C.

With the optimized conditions in hand, the scope and limitations of oximes **1a-t** with benzyl isocyanide **2a** has been investigated as shown in Scheme 2. The scope of R- functionalities with aryl group containing various electron-donating and electron-withdrawing groups at *o*-/*m*-/*p*- positions like *m*-Me-Ph (**1b**), *p*-Me-Ph (**1c**), 4-MeO-Ph (**1d**), 3,4-di-MeO-Ph (**1e**), 3,5-di-MeO-Ph (**1f**), *o*-F-Ph (**1g**), *m*-F-Ph (**1h**), *p*-F-Ph (**1i**), *o*-Cl-Ph (**1j**), *p*-Cl-Ph (**1k**), 2,4-di-Cl-Ph (**1l**), *p*-Br-Ph (**1m**), and *p*-CN-Ph (**1o**) worked well to afford the desired alosines **3aa-ma**, **oa** in 29%-69% yields respectively. However, the reaction gave traces of **3na** along with some other unidentified spots when

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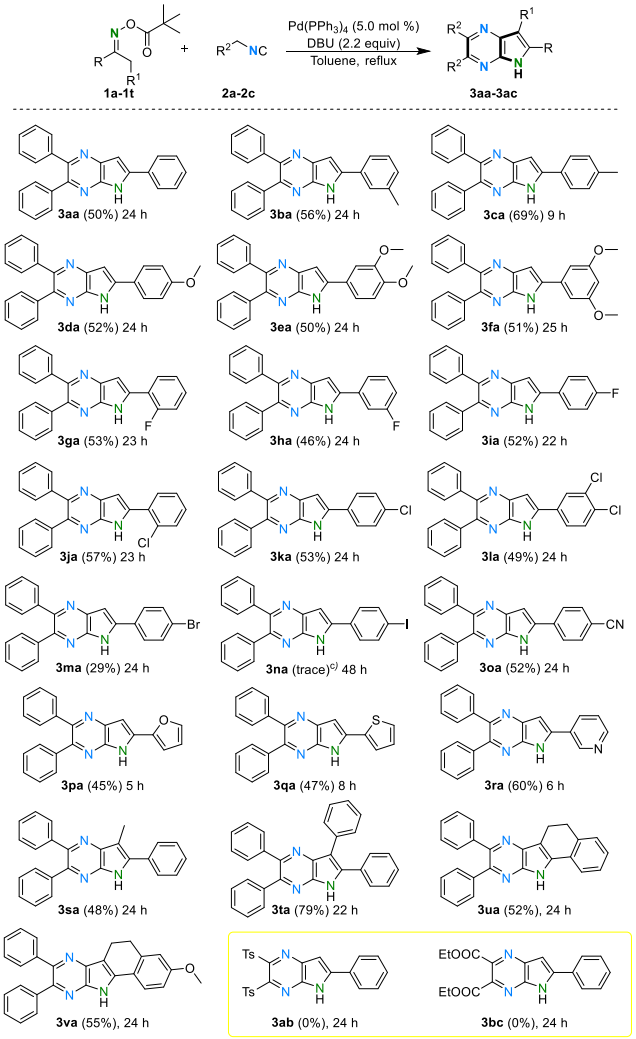
performed with *p*-I-Ph (**1n**). The probable reason could be the competitive oxidation addition of iodo functionality with $Pd(PPh_3)_4$ and leading to complex mixture. Subsequently, the scope was evaluated by replacing aryl functionalilty with heteroaryl groups such as 2-furyl (**1p**), 2-thiophenyl (**1q**) and 3-pyridyl (**1r**). Interestingly, the reaction worked well to afford the desired heteroaryl derivatives **3pa-ra** in 45%-60% yields. The reaction also underwent smooth conversion by changing the R^1- functionalities with methyl (**1s**) and phenyl (**1t**) to afford compounds **3sa-ta** in 48%-79% yields. In general, reactions underwent smooth conversion irrespective of electronic and steric factors to afford the desired alosines **3aa-ta** in moderate yields. We next evaluated the feasibility of the reaction with tetralone (**1u**) and 6-methoxy-

Scheme 2. Scope and limitations of oximes with isocyanides[a),b)]

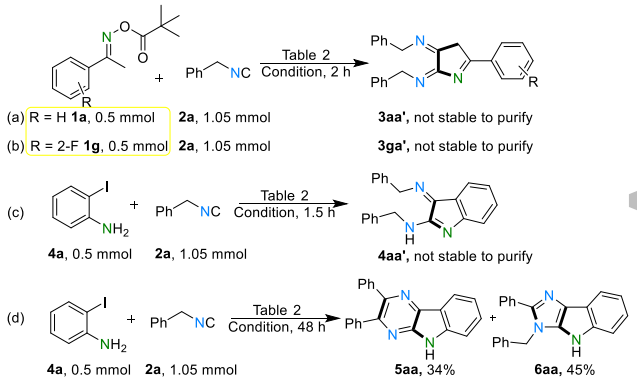


[a)] Reaction conditions: **1a-t** (0.5 mmol), **2a-c** (1.05 mmol), $Pd(PPh_3)_4$ (5.0 mol %), DBU (1.1 mmol) and Toluene (0.5 M) was stirred at reflux for indicated time unless otherwise noted. [b)] Yield of isolated product. [c)] Trace refers to no product isolation.

tetralone (**1v**) under the standard condition of Table 2. The reaction proceeded smoothly to produce the desired compounds **3ua-va** in 52%-55% yields. The reaction failed to afford the desired compounds **3ab** and **3ac** when benzyl isocyanide **2a** was replaced by TOSMIC **2b** as well as ethyl isocyanoacetate **2c**. The reason may be high acidity of the α-proton leading to some other transformation under basic conditions.

To understand the preliminary reaction mechanism few control experiments were carried out as presented in Scheme 3. Recently, we disclosed that oximes can react with isocyanides under palladium catalysis to form 2*H*-pyrrolo-2-imines.[12b] From this stand point, we carried out reaction with (*E*)-1-phenylethan-1-one *O*-pivaloyl oxime **1a** and benzyl isocyanide under the standard condition of Table 2 for 2 h and examined the formation of 2*H*-pyrrolo-2,3-diimine **3aa'** (Scheme 3a). Unfortunately, the desired **3aa'** could not be isolated due to the purification and stability difficulties, when the reaction was continued for longer time the ratio of **3aa** was predominant with traces of **3aa'**. By changing the substrate from **1a** to **1g** also ended in the same problem (Scheme 3b).

In recent past, we also developed the synthesis of isatins from *o*-iodo anilines through double isocyanide insertion via the formation of 3*H*-indolo-3-imines.[12d,15] Herein, we used this strategy to synthesize (*E*)-*N*-benzyl-3-(benzylimino)-3*H*-indol-2-amine **4aa'** with *o*-iodo anilines **4a** and benzyl isocyanide **2a** under the standard condition of Table 2 for 2 h. The desired intermediate **4aa'** was formed as a major yellow spot by TLC (Scheme 3c). When this intermediate was subjected to column purification, we couldn't able to isolate **4aa'** rather the conversion of **4aa'** to **6aa** was noticed in the aerobic atmosphere. At the same time, when the reaction was continued for longer time (~24 h), the intermediate was completely disappeared to afford 2,3-diphenyl-5*H*-pyrazino[2,3-*b*]indole **5aa** as minor product along with 3-benzyl-2-phenyl-3,4-dihydroimidazo[4,5-*b*]indole (**6aa**) as major product (Scheme 3d). The structure of compounds **5aa** and **6aa** were confirmed by X-ray analysis (Figure 2).[14]

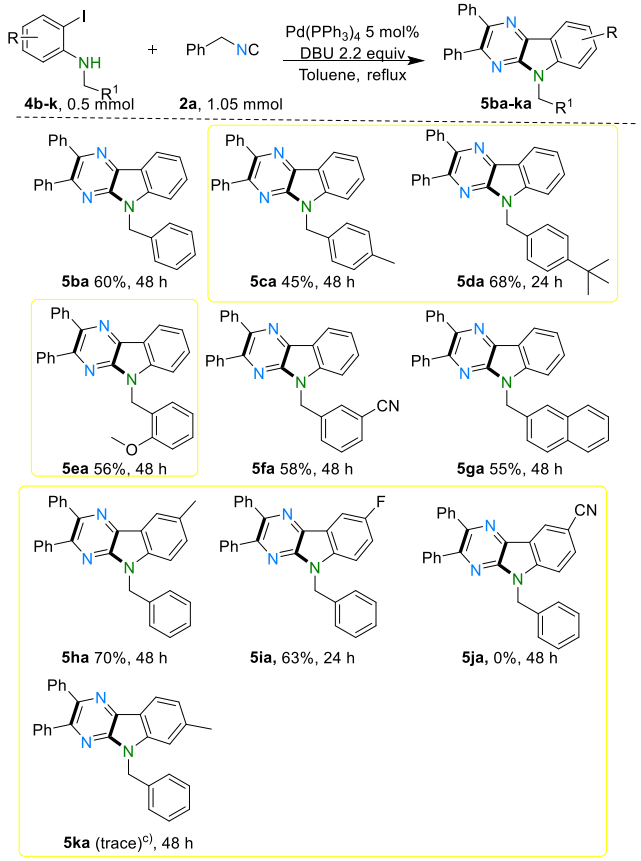


Scheme 3. Preliminary mechanistic studies

From these control experiments, we could rationalize that the regioselective formation of **3** could

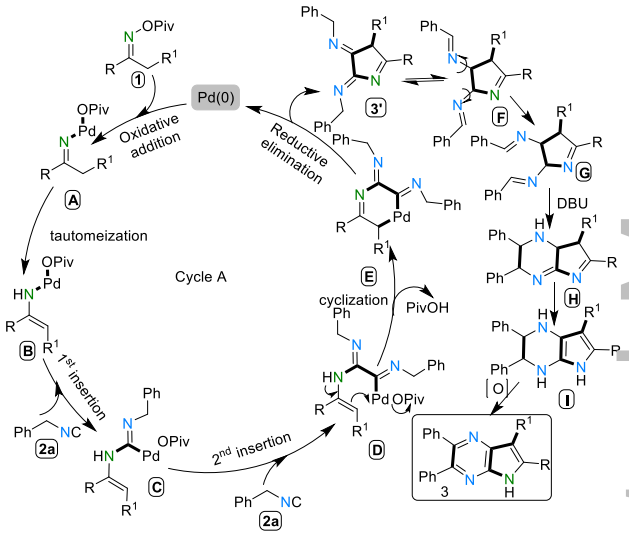
be due to selective *exo* (benzylic) isomerization. Whereas in the case of *o*-iodoaniline as a substrate, we observed a moderate regioselectivity, this may be attributed to *endo* as well as *exo* isomerization. The major *endo* isomerization product observed was due to [1,3-*H*] proton shift from more acidic nitrogen atom. To elucidate our hypothesis, we next focused on the reaction of *N*-substituted-*o*-iodoanilines as presented in Scheme 4 under the standard condition of Table 2. Interestingly, we observed the regioselective formation of 5*H*-pyrazino[2,3-*b*]indole[16a] derivatives through *exo* (benzylic) isomerization. This high selective could be attributed to the absence of acidic nitrogen atom. The reaction worked well with various R^2-functionalities having electron-donating as well as withdrawing groups such as *p*-Me-Ph (**5ca**), *p*-*tert*-butyl-Ph (**5da**), *o*-MeO-Ph (**5ea**) and *m*-CN-Ph (**5ea**) derivatives in 45%-68% yields. In addition, the reaction also underwent smooth conversion with naphthyl functionality (**5ga**). On the other hand, the reaction proceeded well with *o*-iodoaniline derivatives such as *p*-Me-Ph (**5ha**) and *p*-F-Ph (**5ia**) in moderate to good yields. Unfortunately, the reaction failed to provide the desired compound with *p*-CN-Ph (**5ja**) and traces of product with *m*-Me-Ph (**5ka**).

Scheme 4. Scope and limitations of 5*H*-pyrazino[2,3-*b*]indole derivatives [a),b)]



[a)] Reaction conditions: **4b-k** (0.5 mmol), **2a** (1.05 mmol), $Pd(PPh_3)_4$ (5.0 mol %), DBU (1.1 mmol) and Toluene (0.5 M) was stirred at reflux for indicated time unless otherwise noted. [b)] Yield of isolated product. [c)] Trace refers to no product isolation.

A plausible reaction mechanism is proposed on Schemes 5 and 6 based on the preliminary mechanistic studies/previous literature reports.[12,13,15,17] Oxidative addition of *O*-pivaloyl oximes **1** to Pd(0) would afford the *N*-O cleaved intermediate **A**.[12b] Tautomerization of intermediate **A** will result in the formation of enamine-derived palladium (II) species **B**.[12b] Migratory double isocyanide insertion of **B** will produce the imidoyl intermediate **D**.[12b] Base mediated cyclization of intermediate **D** will generate the 6-membered palladacycle **E**.[12b] Reductive elimination of **E** would afford the key intermediate **3'**. Furthermore, intermediate **3**' can undergo carbon-carbon rotation followed by *exo*-isomerization rather than *endo* isomerization to get intermediate **G**. Base promoted cyclization of compound **G** results in intermediate **H**. Isomerization of **H** would generate the more stable pyrrole ring intermediate **I**. Finally, oxidation of intermediate **I** would produce the alosine derivatives **3** *via* the formation of pyrazine ring (Scheme 5).



Scheme 5. Plausible reaction mechanism for 5*H*-pyrrolo[2,3-*b*]pyrazines

A similar mechanism was proposed for the formation of 5*H*-pyrrolo[2,3-*b*]indoles and 3-benzyl-2-phenyl-3,4-dihydroimidazo[4,5-*b*]indole as shown in Scheme 6. Oxidative addition of *o*-iodo aniline derivatives **4** to palladium (0) would afford the palladium (II) intermediate **J**.[12d] Migratory double isocyanide insertion of intermediate **J** will produce the imidoyl intermediate **L**. Base mediated cyclization of intermediate **L** will generate the 6-membered palladacycle **M**. Reductive elimination of **M** would afford the key intermediate **N**. Furthermore, intermediate **N** can be transformed into two pathways depending on the nature of *o*-iodoanilines **4**. In case of secondary amines, the reaction proceeds via *exo* isomerization intermediate **O** followed by annulation intermediate **P**, isomerization intermediate **Q** and oxidation sequence to afford compounds **5aa-ka**.

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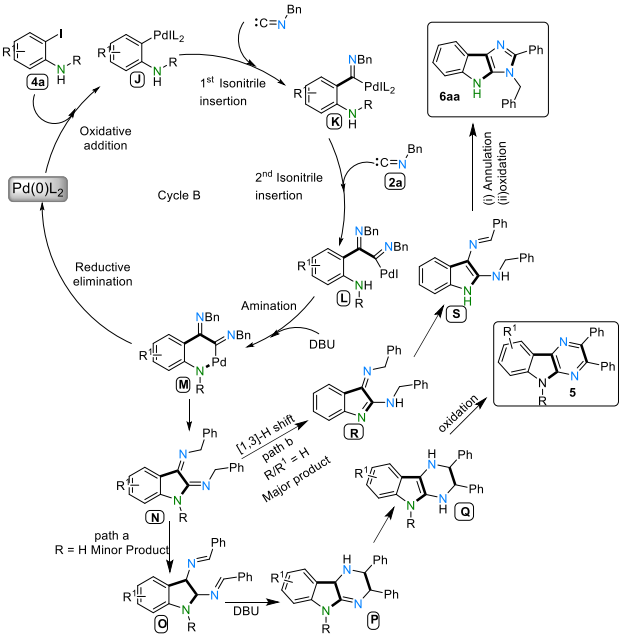
Whereas with primary amine the reaction proceeds via *endo* isomerization [1,3-*H*] proton shift from more acidic nitrogen atom to give intermediate **R**. Intermediate **R** underwent subsequent transformations such as isomerization/annulation and oxidation to afford compound **6aa** as major product.



Scheme 6. Plausible reaction mechanism for 5*H*-pyrrolo[2,3-*b*]indoles and 3-benzyl-2-phenyl-3,4-dihydroimidazo[4,5-*b*]indole.

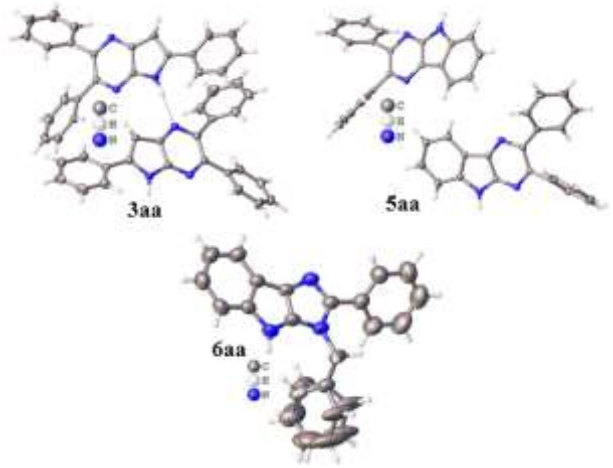


Figure 2. X-Ray structure of 3aa, 5aa and 6aa

Conclusion

In conclusions, we have developed an elegant method for the synthesis of 5*H*-pyrrolo[2,3-*b*]pyrazines through a reaction sequence of N-O cleavage/double benzyl isocyanide insertion followed by cross-dehydrogenative coupling. A plausible reaction mechanism is proposed based on the control studies and previous literature studies. At this stage, only benzyl isocyanide has been used as a proof of concept. The reaction also produced 2,3-diphenyl-5*H*-pyrazino[2,3-*b*]indoles when 2-iodo aniline derivatives was used. The key advantages are broad functional group tolerance of oximes derivatives and construction of two heterocyclic rings from acyclic precursors in a cascade way.

Experimental Section

General Procedure (A) for the Preparation of Compound 3aa: To an oven dried sealed tube was added (*E*)-1-phenylethan-1-one *O*-pivaloyl oxime 1a (110 mg, 0.5 mmol) in toluene (0.5 M) followed by the sequential addition of benzyl isocyanide 2a (129 µL, 1.05 mmol), DBU (166 µL, 1.1 mmol), and $Pd(PPh_3)_4$ (29 mg, 5 mol %). The reaction mixture was allowed to stir at reflux for indicated time. After the completion, the reaction mixture was cooled to room temperature and diluted with 5.0 mL of water. The water layer was extracted with (3X10 mL) of ethyl acetate and the combined ethyl acetate layer was given brine wash (1X10 mL). The final ethyl acetate layer was dried over sodium sulfate and concentrated under reduced pressure to get the crude compound. The obtained crude was purified using column chromatography by eluting from hexane to 18% ethyl acetate/hexane to afford pure 2,3,6-triphenyl-5*H*-pyrrolo[2,3-*b*]pyrazine (**3aa**) as a yellow solid (87 mg, 50%); mp 245-247 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.71 (s, 1H), 7.65 – 7.61 (m, 2H), 7.48 – 7.36 (m, 7H), 7.31-7.29 (m, 3H), 7.25-7.21 (m, 3H), 7.05 (d, J = 2.1 Hz, 1H); ^{13}C NMR (100 MHz,$CDCl_3$) δ 148.29, 145.95, 143.53, 141.66, 140.30, 139.71, 139.39, 130.93, 130.03, 129.99, 129.24, 128.09, 127.87, 127.67, 125.52, 98.96; HRMS (ESI) calcd for $C_{24}H_{18}N_3$ $[M+H]^+$: 348.1495 found 348.1487.

2,3-diphenyl-6-(*m*-tolyl)-5*H*-pyrrolo[2,3-*b*]pyrazine (3ba). Following the general procedure (A) on a 0.5 mmol scale giving the desired compound as a light yellow solid (101 mg, 56%); mp 183-185 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.65 (s, 1H), 7.48 – 7.44 (m, 3H), 7.43 – 7.40 (m, 3H), 7.32 – 7.27 (m, 4H), 7.22-7.18 (m, 4H), 7.03 (d, J = 2.0 Hz, 1H), 2.40 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.18, 145.85, 143.75, 141.62, 140.34, 139.72, 139.39, 138.94, 130.90, 130.11,130.06, 129.80, 129.13, 128.05, 127.71, 126.24, 122.65, 98.83, 21.52; HRMS (ESI) calcd for $C_{25}H_{20}N_3$ $[M+H]^+$: 362.1652 found 362.1643.

2,3-diphenyl-6-(*p*-tolyl)-5*H*-pyrrolo[2,3-*b*]pyrazine (3ca) Following the general procedure (A) on a 0.5 mmol scale giving the desired compound as a light yellow solid (125 mg, 69%); mp 241-243 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.59 (s, 1H), 7.47-7.45 (m, 2H), 7.42 (dd, J = 8.0, 1.6 Hz, 2H), 7.37 (d, J = 8.0 Hz, 2H), 7.30-7.27 (m, 3H), 7.12 (d, J = 7.2 Hz, 3H), 7.06 (d, J = 8.0 Hz, 2H), 6.99 (d, J = 1.7 Hz, 1H), 2.33 (s, 3H); ^{13}C NMR (100 MHz,$CDCl_3$) δ 147.99, 145.27, 144.39, 141.91, 140.41, 139.74, 139.51, 139.08, 130.05, 129.72, 128.05, 127.91, 127.81, 127.56,125.39, 98.10, 21.27; HRMS (ESI) calcd for $C_{25}H_{20}N_3$ $[M+H]^+$: 362.1652 found 362.1644.

6-(4-methoxyphenyl)-2,3-diphenyl-5*H*-pyrrolo[2,3-*b*]pyrazine (3da). Following the general procedure (A) on a 0.5 mmol scale giving the desired compound as a yellow solid (98 mg, 52%); mp ; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.71 (s, 1H), 7.58 (d, J = 8.8 Hz, 2H), 7.47 – 7.40 (m, 4H), 7.29-7.27 (m, 3H), 7.22 (dd, J = 5.0, 1.9 Hz, 3H), 6.96 – 6.91 (m, 3H), 3.85 (d, J = 4.3 Hz, 3H).; ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.52, 147.97, 145.25, 143.83, 141.67, 140.41, 139.80, 139.76, 130.07, 130.01, 128.05, 127.66, 126.96, 114.70, 97.62, 55.42; HRMS (ESI) calcd for $C_{25}H_{20}N_3O$ $[M+H]^+$: 378.1601 found 378.1595.

6-(3,4-dimethoxyphenyl)-2,3-diphenyl-5*H*-pyrrolo[2,3-*b*]pyrazine (3ea). Following the general procedure (A) on a 0.5 mmol scale giving the desired compound as a dark yellow solid (102 mg, 50%); mp 106-108 °C; ^{1}H NMR

(400 MHz, $CDCl_3$) δ 9.43 (s, 1H), 7.47 – 7.40 (m, 4H), 7.32 – 7.28 (m, 3H), 7.26 – 7.21 (m, 4H), 7.20 (d, J = 2.1 Hz, 1H), 6.94 (dd, J = 5.2, 4.2 Hz, 2H), 3.96 (s, 3H), 3.94 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.33, 149.61, 148.10, 145.50, 143.73, 141.57, 140.35, 139.71, 130.02, 128.06, 127.70, 123.96, 118.38, 111.69, 108.90, 97.97, 56.07; HRMS (ESI) calcd for $C_{26}H_{22}N_3O_2$ $[M+H]^+$: 408.1707 found 408.1697.

6-(3,5-dimethoxyphenyl)-2,3-diphenyl-5*H*-pyrrolo[2,3-*b*]pyrazine (3fa). Following the general procedure (A) on a 0.5 mmol scale giving the desired compound as a dark yellow solid (104 mg, 51%); mp 203-205 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.52 (s, 1H), 7.47 – 7.42 (m, 2H), 7.40 (dd, J = 6.6, 3.0 Hz, 2H), 7.31 – 7.27 (m, 3H), 7.25 – 7.20 (m, 3H), 7.02 (d, J = 2.0 Hz, 1H), 6.82 (d, J = 2.4 Hz, 2H), 6.50 (t, J= 2.0 Hz, 1H), 3.85 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.38, 148.31, 146.17, 143.35, 141.43, 140.26, 139.67, 139.14, 132.91, 130.05, 129.99, 128.08, 128.03, 127.81, 127.66, 104.03, 101.03, 99.34, 55.50; HRMS (ESI) calcd for $C_{26}H_{22}N_3O_2$ $[M+H]^+$: 408.1707 found 408.1701.

6-(3,5-dimethoxyphenyl)-2,3-diphenyl-5*H*-pyrrolo[2,3-*b*]pyrazine (3ga). Following the general procedure (A) on a 0.5 mmol scale giving the desired compound as a light yellow solid (97 mg, 53%); mp 221-223 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.73 (s, 1H), 7.80 (td, J = 7.8, 1.7 Hz, 1H), 7.48 – 7.41 (m, 4H), 7.40 – 7.33 (m, 1H), 7.30-7.29 (m, 3H), 7.28 – 7.24 (m, 4H), 7.22 (ddd, J = 12.1, 3.7, 1.1 Hz, 1H), 7.18 – 7.15 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.63 (d, $J_{C\text{-}F}$ = 247.0 Hz), 148.51, 146.69, 140.24, 139.78, 138.11, 130.58 (d, $J_{C\text{-}F}$ = 9.0 Hz), 129.99, 128.27 (d, $J_{C\text{-}F}$ = 3.2 Hz), 127.78 (d, $J_{C\text{-}F}$ = 18.7 Hz), 125.09 (d, $J_{C\text{-}F}$ = 3.1 Hz), 118.67 (d, $J_{C\text{-}F}$ = 10.7 Hz), 116.78 (d, $J_{C\text{-}F}$ = 22.6 Hz), 100.53 (d, $J_{C\text{-}F}$ = 3.1 Hz); HRMS (ESI) calcd for $C_{24}H_{17}FN_3$ $[M+H]^+$: 366.1401 found 366.1395.

6-(3-fluorophenyl)-2,3-diphenyl-5*H*-pyrrolo[2,3-*b*]pyrazine (3ha). Following the general procedure (A) on a 0.5 mmol scale giving the desired compound as a yellowish- green solid (84 mg, 46%); mp 253-255 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.70 (s, 1H), 7.49 – 7.43 (m, 2H), 7.43 – 7.37 (m, 2H), 7.31-7.25 (m, 3H), 7.26 (dd, J = 7.4, 5.5 Hz, 2H), 7.21 – 7.14 (m, 1H), 7.14 – 7.07 (m, 3H), 7.06 (d, J = 0.8 Hz, 1H), 6.98 (m, J = 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.99 (d, $J_{C\text{-}F}$ = 245.0 Hz), 147.56, 146.21, 142.54, 141.91, 140.15, 139.31 (d, $J_{C\text{-}F}$ = 6.5 Hz), 133.08 (d, $J_{C\text{-}F}$ = 8.2 Hz), 130.68 (d, $J_{C\text{-}F}$ = 8.4 Hz), 130.03, 129.96, 128.13, 128.05, 127.96, 127.76, 121.095 (d, $J_{C\text{-}F}$ = 2.1 Hz), 115.88 (d, $J_{C\text{-}F}$ = 21.2 Hz), 112.46 (d, $J_{C\text{-}F}$ = 22.8 Hz), 99.66; HRMS (ESI) calcd for $C_{24}H_{17}FN_3$ $[M+H]^+$: 366.1401 found 366.1391.

6-(4-fluorophenyl)-2,3-diphenyl-5*H*-pyrrolo[2,3-*b*]pyrazine (3ia). Following the general procedure (A) on a 0.5 mmol scale giving the desired compound as a dark yellow solid (95 mg, 52%); mp 249-251 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.06 (s, 1H), 7.59 – 7.53 (m, 2H), 7.47 – 7.44 (m, 2H), 7.43 – 7.40 (m, 2H), 7.33 – 7.28 (m, 3H), 7.20 (dd, J = 5.1, 1.9 Hz, 3H), 7.06 (t, J = 8.6 Hz, 2H), 6.99 (d, J = 2.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.18 (d, $J_{C\text{-}F}$ = 248.40 Hz), 147.38, 145.85, 142.83, 141.77, 140.23, 139.52 (d, $J_{C\text{-}F}$ = 4.2 Hz) , 130.02 (d, $J_{C\text{-}F}$ = 4.1 Hz), 128.11 (d, $J_{C\text{-}F}$ = 4.8 Hz) 127.83 (d, $J_{C\text{-}F}$ = 20.60 Hz), 116.34 (d, $J_{C\text{-}F}$ = 21.90 Hz), 98.81; HRMS (ESI) calcd for $C_{24}H_{17}FN_3$ $[M+H]^+$: 366.1401 found 366.1392.

6-(2-chlorophenyl)-2,3-diphenyl-5*H*-pyrrolo[2,3-*b*]pyrazine (3ja). Following the general procedure (A) on a 0.5 mmol scale giving the desired compound as a beige solid (109 mg, 57%); mp 223-225 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.92 (s, 1H), 7.67 – 7.62 (m, 1H), 7.50 – 7.47 (m, 1H), 7.45 (ddd, J = 4.5, 2.4, 1.5 Hz, 2H), 7.42 (ddd, J = 6.0, 3.5, 1.8 Hz, 2H), 7.35 – 7.32 (m, 2H), 7.30 (dd, J = 6.0, 2.5 Hz, 3H), 7.23 (dd, J = 6.5, 2.8 Hz, 3H), 7.10 (d, J = 2.1 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.44, 146.69, 140.91, 140.66, 140.22, 139.67, 138.10, 131.70, 131.06, 130.82, 129.99, 128.23 – 127.82, 127.58, 102.63; HRMS (ESI) calcd for $C_{24}H_{17}ClN_3$ $[M+H]^+$: 382.1106 found 382.1100.

6-(4-chlorophenyl)-2,3-diphenyl-5*H*-pyrrolo[2,3-*b*]pyrazine (3ka). Following the general procedure (A) on a 0.5 mmol scale giving the desired compound as a light yellow solid (101 mg, 53%); mp 260-262 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.09 (s, 1H), 7.51 (d, J = 8.6 Hz, 2H), 7.47 – 7.43 (m, 2H), 7.43 – 7.39 (m, 2H), 7.35 – 7.28 (m, 5H), 7.19 (dd, J = 5.1, 2.0 Hz, 3H), 7.03 (d, J = 2.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.56, 146.14, 142.48, 141.81, 140.19, 139.47, 139.37, 135.10, 130.04, 129.99, 129.44, 128.15, 128.08, 128.01, 127.77, 126.69, 99.31; HRMS (ESI) calcd for $C_{24}H_{17}ClN_3$ $[M+H]^+$: 382.1106 found 382.1100.

6-(3,4-dichlorophenyl)-2,3-diphenyl-5*H*-pyrrolo[2,3-*b*]pyrazine (3la). Following the general procedure (A) on a 0.5 mmol scale giving the desired compound as a light yellow solid (102 mg, 49%); mp 220-222 °C; ^{1}H NMR (400 MHz,$CDCl_3$) δ 10.37 (s, 1H), 7.65 (d, J = 1.1 Hz, 1H), 7.47 – 7.42 (m, 2H), 7.41 – 7.36 (m, 4H), 7.33 – 7.29 (m, 3H), 7.16 (dd, J = 5.0, 2.2 Hz, 3H), 7.04 (d, J = 2.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.86, 146.58, 141.88, 141.14, 140.05, 139.23, 133.51, 133.16, 131.11, 129.98, 128.02, 127.31, 124.56, 100.12; HRMS (ESI) calcd for $C_{24}H_{16}Cl_2N_3$ $[M+H]^+$: 416.0716 found 416.0708.

6-(4-bromophenyl)-2,3-diphenyl-5*H*-pyrrolo[2,3-*b*]pyrazine (3ma). Following the general procedure (A) on a 0.5 mmol scale giving the desired compound as a light yellow solid (62 mg, 29%); mp 258-260 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.59 (s, 1H), 7.47 – 7.43 (m, 2H), 7.42 – 7.38 (m, 4H), 7.36 (d, J = 8.8 Hz, 2H), 7.33 – 7.29 (m, 3H), 7.15 (dd, J = 4.8, 2.5 Hz, 3H), 7.03 (d, J = 2.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.58, 146.02, 142.80, 141.96, 140.20, 139.41, 132.28, 129.96, 128.11, 127.78, 126.89, 123.21, 99.28; HRMS (ESI) calcd for $C_{24}H_{17}BrN_3$ $[M+H]^+$: 426.0600 found 426.0592.

4-(2,3-diphenyl-5*H*-pyrrolo[2,3-*b*]pyrazin-6-yl)benzonitrile (3oa). Following the general procedure (A) on a 0.5 mmol scale giving the desired compound as a brown solid (97 mg, 52%); mp 192-194 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.24 (s, 1H), 7.66-7.62 (m, 3H), 7.46 – 7.40 (m, 3H), 7.36 – 7.25 (m, 6H), 7.21 (dd, J = 5.0, 1.9 Hz, 3H), 7.17 (d, J = 1.9 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.23, 147.17, 141.95, 140.87, 139.90, 139.24, 138.90, 135.05, 132.91, 129.98, 128.83, 128.26, 128.22, 128.17, 127.99, 127.89, 127.84, 127.50, 125.79, 118.36, 112.23, 101.30, 43.80; HRMS (ESI) calcd for $C_{25}H_{17}N_4$ $[M+H]$+: 373.1448 found 373.1440.

6-(furan-2-yl)-2,3-diphenyl-5*H*-pyrrolo[2,3-*b*]pyrazine (3pa). Following the general procedure (A) on a 0.5 mmol scale giving the desired compound as a dark brown solid (76 mg, 45%); mp 242-244 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.50 (s, 1H), 7.50 (d, J = 1.4 Hz, 1H), 7.44-7.41 (m, 4H), 7.28-7.23 (m, 7H), 6.93 (d, J = 1.8 Hz, 1H), 6.75 (d, J = 3.4 Hz, 1H), 6.52 (dd, J = 3.4, 1.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.34, 146.25, 145.97, 143.39, 140.99, 140.26, 139.74, 138.93, 134.22, 130.03, 127.92, 112.29, 108.59, 97.40; HRMS (ESI) calcd for $C_{22}H_{16}N_3O$ $[M+H]^+$: 338.1288 found 338.1279.

2,3-diphenyl-6-(thiophen-2-yl)-5*H*-pyrrolo[2,3-*b*]pyrazine (3qa). Following the general procedure (A) on a 0.5 mmol scale giving the desired compound as a dark brown solid (83 mg, 47%); mp 226-228 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.49 (s, 1H), 7.46 – 7.41 (m, 4H), 7.37 (dd, J = 5.0, 1.1 Hz, 1H), 7.32 – 7.28 (m, 3H), 7.26 – 7.22 (m, 4H), 7.05 (dd, J = 5.0, 3.7 Hz, 1H), 6.92 (d, J = 2.0 Hz, 1H); ^{13}C NMR (100 MHz,$CDCl_3$) δ 148.38, 145.97, 141.43, 140.23, 139.70, 139.26, 137.94, 134.12, 130.03, 128.33, 128.30 – 127.77, 127.70, 126.75, 124.86, 98.95; HRMS (ESI) calcd for $C_{22}H_{16}N_3S$ $[M+H]^+$: 354.1059 found 354.1051.

2,3-diphenyl-6-(pyridin-3-yl)-5*H*-pyrrolo[2,3-*b*]pyrazine (3ra). Following the general procedure (A) on a 0.5 mmol scale giving the desired compound as a beige solid (105 mg, 60%); mp 243-245 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.09 (s, 1H), 8.95 (d, J = 1.8 Hz, 1H), 8.58 – 8.53 (m, 1H), 7.78 (d, J = 8.1 Hz, 1H), 7.48 – 7.37 (m, 5H), 7.33 – 7.27 (m, 3H), 7.17 – 7.09 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.57, 148.65, 146.78, 146.37, 142.05, 140.53, 140.08, 139.24, 132.61, 132.11, 130.01, 128.48, 128.33, 128.01, 127.81, 127.25, 123.84, 99.93; HRMS (ESI) calcd for $C_{23}H_{16}N_4$ $[M]^+$: 348.1369 found 348.1489.

7-methyl-2,3,6-triphenyl-5*H*-pyrrolo[2,3-*b*]pyrazine (3sa). Following the general procedure (A) on a 0.5 mmol scale giving the desired compound as a light yellow solid (87 mg, 48%); mp 211-213 °C;^{1}H NMR (400 MHz, $CDCl_3$) δ 8.72 (s, 1H), 7.68 – 7.64 (m, 2H), 7.53 (t, J = 7.6 Hz, 2H), 7.47 (dd, J = 6.4, 3.3 Hz, 2H), 7.45 – 7.40 (m, 3H), 7.32 – 7.28 (m, 4H), 7.27 (d, J = 3.0 Hz, 2H), 2.62 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.50, 140.61, 140.13, 139.09, 132.12, 130.25, 129.98, 129.14, 128.60, 128.04, 127.63, 108.75, 8.71; HRMS (ESI) calcd for $C_{25}H_{20}N_3$ $[M+H]^+$: 362.1652 found 362.1640.

2,3,6,7-tetraphenyl-5*H*-pyrrolo[2,3-*b*]pyrazine (3ta). Following the general procedure (A) on a 0.5 mmol scale giving the desired compound as a light yellow solid (167 mg, 79%); mp 203-205 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.16 (s, 1H), 7.68 (dd, J = 8.3, 1.3 Hz, 2H), 7.50 – 7.42 (m, 6H), 7.38 – 7.32 (m, 5H), 7.29 – 7.24 (m, 8H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.25, 146.41, 140.58, 140.30, 140.00, 139.22, 137.83, 132.41, 131.85, 130.37, 130.02, 128.99, 128.40, 128.11, 127.88, 127.58, 126.65, 113.56; HRMS (ESI) calcd for $C_{30}H_{22}N_3$ $[M+H]^+$: 424.1808 found 424.1795.

8,9-diphenyl-6,11-dihydro-5*H*-benzo[*g*]pyrazino[2,3-*b*]indole (3ua). Following the general procedure (A) on a 0.5 mmol scale giving the desired compound as a yellow solid (97 mg, 52%); mp 234-236 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.51 (s, 1H), 7.46-7.41 (m, 4H), 7.31-7.18 (m, 10H), 3.20 – 3.06 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.74, 145.40, 142.01, 140.47, 139.98, 138.79, 137.64, 137.12, 130.10, 128.74, 128.49, 128.07, 127.85 – 127.06, 126.90, 120.76, 110.94, 29.08, 18.46; HRMS (ESI) calcd for $C_{26}H_{20}N_3$ $[M+H]^+$: 374.1652 found 374.1641.

3-methoxy-8,9-diphenyl-6,11-dihydro-5*H*-benzo[*g*]pyrazino[2,3-*b*]indole (3va). Following the general procedure (A) on a 0.5 mmol scale giving the desired compound as a yellowish-green solid (111 mg, 55%); mp 233-235 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.74 (s, 1H), 7.50 – 7.43 (m, 4H), 7.33 – 7.26 (m, 3H), 7.25 – 7.17 (m, 3H), 7.05 (d, J = 8.4 Hz, 1H), 6.84 (d, J = 2.5 Hz, 1H), 6.64 (dd, J = 8.4, 2.6 Hz, 1H), 3.82 (s, 3H), 3.16 – 3.10 (m, 2H), 3.06 (d, J = 7.5 Hz, 2H); ^{13}C NMR (100 MHz,$CDCl_3$) δ 159.94, 147.45, 144.46, 142.08, 140.64, 140.06, 139.73, 139.39, 137.50, 130.14, 128.05, 127.57, 122.22, 120.54, 114.87, 111.85, 108.94, 55.35, 29.56, 18.47; HRMS (ESI) calcd for $C_{27}H_{22}N_3O$ $[M+H]^+$: 404.1757 found 404.1748.

General experimental Procedure (B) for the Synthesis of 2,3-diphenyl-5*H*-pyrazino[2,3-*b*]indole (5aa) and 3-benzyl-2-phenyl-3,4-dihydroimidazo[4,5-*b*]indole (6aa). To an oven dried sealed tube was added 2-iodoaniline **4a** (110 mg, 0.5 mmol) in toluene (0.5 M) followed by the sequential addition of benzyl isocyanide **2a** (129 µL, 1.05 mmol), DBU (166 µL, 1.1 mmol), and $Pd(PPh_3)_4$ (29 mg, 5 mol %). The reaction mixture was allowed to stir at reflux for indicated time. After the completion, the reaction mixture was cooled to room temperature and diluted with 5.0 mL of water. The water layer was extracted with (3X10 mL) of ethyl acetate and the combined ethyl acetate layer was given brine wash (1X10 mL). The final ethyl acetate layer was dried over sodium sulfate and concentrated under reduced pressure to get the crude compound. The obtained crude was purified using column chromatography by eluting from hexane to ethyl acetate/hexane to afford pure compounds **5aa** as minor and **6aa** as major.

2,3-diphenyl-5*H*-pyrazino[2,3-*b*]indole (5aa). Following the general procedure (B) on a 0.5 mmol scale giving the desired compound as a brown solid (55 mg, 34%); mp 278-280 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.69 (s, 1H), 8.38 (d, J = 7.9 Hz, 1H), 7.59 (dd, J = 7.7, 1.6 Hz, 2H), 7.52 (dd, J = 6.5, 3.1 Hz, 2H), 7.45 – 7.25 (m, 9H), 6.63 (d, J = 8.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.87, 146.02, 144.36, 140.77, 139.85, 135.17, 130.27, 128.96, 128.49, 128.22, 127.71, 121.79, 120.99, 120.16, 111.80; HRMS (ESI) calcd for $C_{22}H_{16}N_3$ $[M+H]^+$: 322.1339 found 322.1337.

3-benzyl-2-phenyl-3,4-dihydroimidazo[4,5-*b*]indole (6aa). Following the general procedure (B) on a 0.5 mmol scale giving the desired compound as a brown solid (73 mg 45%); mp 208-210 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.34 (s, 1H), 7.85 (d, J = 7.8 Hz, 1H), 7.60 (dd, J = 7.5, 1.9 Hz, 2H), 7.42 – 7.35 (m, 3H), 7.32 – 7.23 (m, 4H), 7.19 – 7.09 (m, 4H), 5.30 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.10, 139.43, 135.24, 129.26, 128.80, 128.44, 126.92, 121.47, 120.57, 119.70, 118.00, 112.20, 49.56; HRMS (ESI) calcd for $C_{22}H_{18}N_3$ $[M+H]^+$: 324.1495 found 324.1489.

5-benzyl-2,3-diphenyl-5*H*-pyrazino[2,3-*b*]indole (5ba). Following the general procedure (B) on a 0.5 mmol scale giving the desired compound as a light yellow solid (123 mg, 60%); mp 203-205 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.44 (d, J = 7.8 Hz, 1H), 7.52 (m, 5H), 7.41 (d, J = 8.2 Hz, 1H), 7.30 (m, 13H), 5.73 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.41, 145.91, 144.26, 141.61, 140.32, 139.89, 136.82, 134.01, 130.29, 128.79, 128.31, 127.88, 127.61, 127.28, 121.99, 120.95, 120.04, 110.29, 45.09; HRMS (ESI) calcd for $C_{29}H_{22}N_3$ $[M+H]^+$: 412.1808 found 412.1814.

5-(4-methylbenzyl)-2,3-diphenyl-5*H*-pyrazino[2,3-*b*]indole (5ca). Following the general procedure (B) on a 0.5 mmol scale giving the desired compound as a pale yellow solid (96 mg, 45%); mp 181.6-183.3 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.43 (ddd, J = 7.8, 1.2, 0.7 Hz, 1H), 7.56 – 7.48 (m, 5H), 7.42 (dt, J = 8.3, 0.8 Hz, 1H), 7.36 – 7.27 (m, 7H), 7.23 (d, J = 8.0 Hz, 2H), 7.10 (d, J = 8.0 Hz, 2H), 5.69 (s, 2H), 2.30 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.35, 145.81, 144.23, 141.61, 140.34, 139.92, 137.29, 133.99, 133.79, 130.33, 130.23, 129.38, 128.80, 128.15, 128.02, 127.97, 127.56, 127.29, 121.94, 120.86, 120.00, 110.30, 44.84, 21.08 ; HRMS (ESI) calcd for $C_{30}H_{24}N_3$ $[M+H]^+$: 426.1964 found 426.1962.

5-(4-(*tert*-butyl)benzyl)-2,3-diphenyl-5*H*-pyrazino[2,3-*b*]indole (5da). Following the general procedure (B) on a 0.5 mmol scale giving the desired compound as a pale yellow solid (159 mg, 68%); mp 207-209 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.43 (ddd, J = 8.0, 1.2, 0.8 Hz, 1H), 7.57 – 7.49 (m, 5H), 7.46 (dt, J = 8.2, 0.8 Hz, 1H), 7.37 – 7.25 (m, 11H), 5.70 (s, 2H), 1.27 (s, 9H).; ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.53, 148.35, 145.80, 144.22, 141.65, 140.36, 139.91, 133.97, 133.82, 130.35, 130.23, 128.78, 128.15, 128.02, 127.96, 127.56, 127.07, 125.61, 121.95, 120.84, 119.98, 110.32, 109.96, 44.71, 34.48, 31.28; HRMS (ESI) calcd for $C_{33}H_{30}N_3$ $[M+H]^+$: 468.2434 found 468.2433.

5-(2-methoxybenzyl)-2,3-diphenyl-5*H*-pyrazino[2,3-*b*]indole (5ea). Following the general procedure (B) on a 0.5 mmol scale giving the desired compound as a pale yellow solid (122 mg, 56%); mp 176-178 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.44 (ddd, J = 8.0, 1.2, 0.8 Hz, 1H), 7.57 – 7.46 (m, 6H), 7.37 – 7.20 (m, 8H), 6.98 (dd, J = 7.6, 1.6 Hz, 1H), 6.92 (dd, J = 8.2, 0.8 Hz, 1H), 6.79 (td, J = 7.5, 1.0 Hz, 1H), 5.75 (s, 2H), 3.92 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.91, 148.30, 145.66, 144.47, 141.93, 140.40, 139.99, 134.06, 130.35, 130.24, 128.74, 128.58,

128.29, 128.13, 127.95, 127.93, 127.52, 124.87, 121.78, 120.74, 120.52, 119.86, 110.59, 110.22, 55.35, 39.91; HRMS (ESI) calcd for $C_{30}H_{24}ON_3$ $[M+H]^+$: 442.1913 found 442.1912.

3-((2,3-diphenyl-5*H*-pyrazino[2,3-*b*]indol-5-yl)methyl)benzonitrile (5fa). Following the general procedure (B) on a 0.5 mmol scale giving the desired compound as a light yellow solid (127 mg, 58%); mp 206-208 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.44 (ddd, J = 8.0, 1.2, 0.8 HZ, 1H), 7.63 – 7.48 (m, 8H), 7.44 – 7.29 (m, 9H), 5.73 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.61, 146.48, 144.03, 141.11, 140.07, 139.66, 138.41, 134.07, 131.64, 131.43, 130.79, 130.23 (d, J = 3.3 Hz), 129.66, 129.10, 128.12 (d, J = 13.0 Hz), 127.73, 122.26, 121.41, 120.21, 118.46, 112.95, 109.73, 44.33; HRMS (ESI) calcd for $C_{30}H_{21}N_4$ $[M+H]^+$: 437.1760 found 437.1761.

5-(naphthalen-2-ylmethyl)-2,3-diphenyl-5*H*-pyrazino[2,3-*b*]indole (5ga). Following the general procedure (B) on a 0.5 mmol scale giving the desired compound as a yellow solid (127 mg, 55%); mp 211-213 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.45 (td, J = 7.2, 1.2 Hz, 1H), 7.80 – 7.72 (m, 4H), 7.55 – 7.51 (m, 4H), 7.49 (dd, J = 7.1, 1.2 Hz, 1H), 7.43 (m, 4H), 7.36 – 7.27 (m, 7H), 5.88 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.45, 145.98, 144.33, 141.68, 140.31, 139.90, 134.17 (d, J = 17.9 Hz), 133.28, 132.82, 130.29 (d, J = 9.1 Hz), 128.89, 128.66, 128.26 – 127.92, 127.92 – 127.46, 126.29, 125.98 (d, J = 2.4 Hz), 125.25, 121.98, 121.00, 120.09, 110.36, 45.34; HRMS (ESI) calcd for $C_{33}H_{24}N_3$ $[M+H]^+$: 462.1965 found 462.1960.

5-benzyl-8-methyl-2,3-diphenyl-5*H*-pyrazino[2,3-*b*]indole (5ha). Following the general procedure (B) on a 0.5 mmol scale giving the desired compound as a pale yellow solid (149 mg, 70%); mp 172-174 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.25 – 8.23 (m, 1H), 7.54 – 7.49 (m, 4H), 7.37 – 7.23 (m, 13H), 5.70 (s, 2H), 2.52 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.17, 145.63, 144.39, 140.41, 139.96, 139.87, 136.93, 133.89, 130.45, 130.32, 130.22, 130.20, 128.69, 128.12, 127.98, 127.95, 127.53, 127.50, 127.23, 121.78, 120.07, 109.99, 109.96, 45.05, 21.31; HRMS (ESI) calcd for $C_{30}H_{24}N_3$ $[M+H]^+$: 426.1964 found 426.1963.

5-benzyl-8-fluoro-2,3-diphenyl-5*H*-pyrazino[2,3-*b*]indole (5ia). Following the general procedure (B) on a 0.5 mmol scale giving the desired compound as a pale yellow solid (136 mg, 63%); mp 205-207 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.09 (dd, J = 8.4, 2.3 Hz, 1H), 7.51 (m, 4H), 7.38 – 7.21 (m, 13H), 5.72 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.33, 156.96, 149.14, 146.13, 144.84, 139.89 (d, $J_{C\text{-}F}$ = 38.5 Hz), 137.75, 136.56, 133.45 (d, $J_{C\text{-}F}$ = 4.2 Hz), 130.30, 130.17, 128.79, 128.21, 128.19, 128.01, 127.72, 127.22, 127.18, 120.62 (d, $J_{C\text{-}F}$ = 9.2 Hz), 116.72 ($J_{C\text{-}F}$ = 25.5 Hz), 111.19 ($J_{C\text{-}F}$ = 8.8 Hz), 107.64 ($J_{C\text{-}F}$ = 24.1 Hz), 45.19; HRMS (ESI) calcd for $C_{29}H_{21}FN_3$ $[M+H]^+$: 430.1714 found 430.1711.

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