Article

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Regioselective Synthesis of Indolopyrazines through a Sequential Rhodium-Catalyzed Formal [3 + 3] Cycloaddition and Aromatization Reaction of Diazoindolinimines with Azirines

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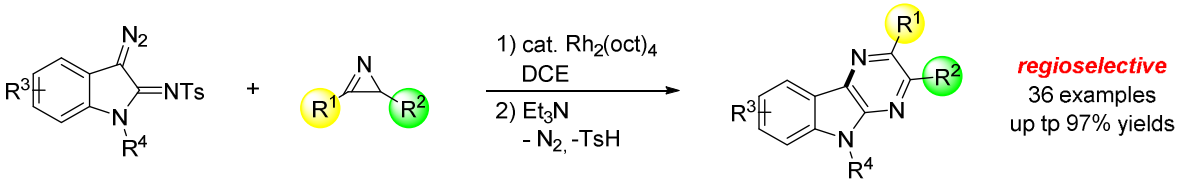


ABSTRACT: A regioselective synthetic method for the preparation of indolopyrazines was demonstrated through a sequential Rh-catalyzed formal [3 + 3] cycloaddition and aromatization reaction of a wide range of diazoindolinimines with azirines. Because the previously reported synthetic methods afforded mixtures of indolopyrazines, the present method using unsymmetrical azirines has a strong advantage from a regioselectivity viewpoint.

INTRODUCTION

Indolopyrazines possessing both indole and pyrazine moieties are significant structural motifs in a number of naturally occurring products, show a wide range of biological activities, including antitumor and antiviral activities and function as fluorescent and host materials (Figure 1).[1] In this

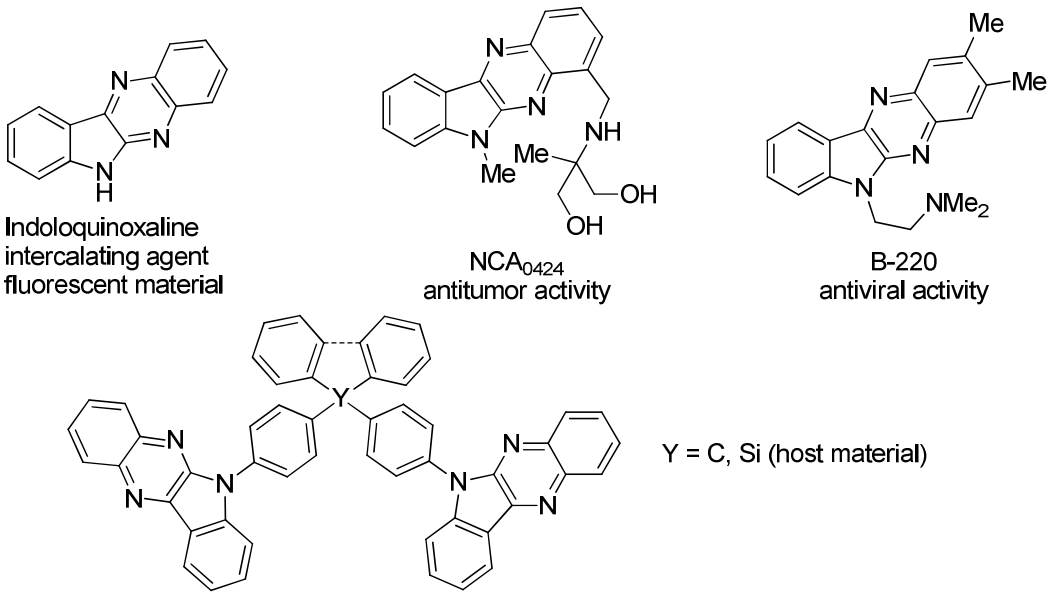
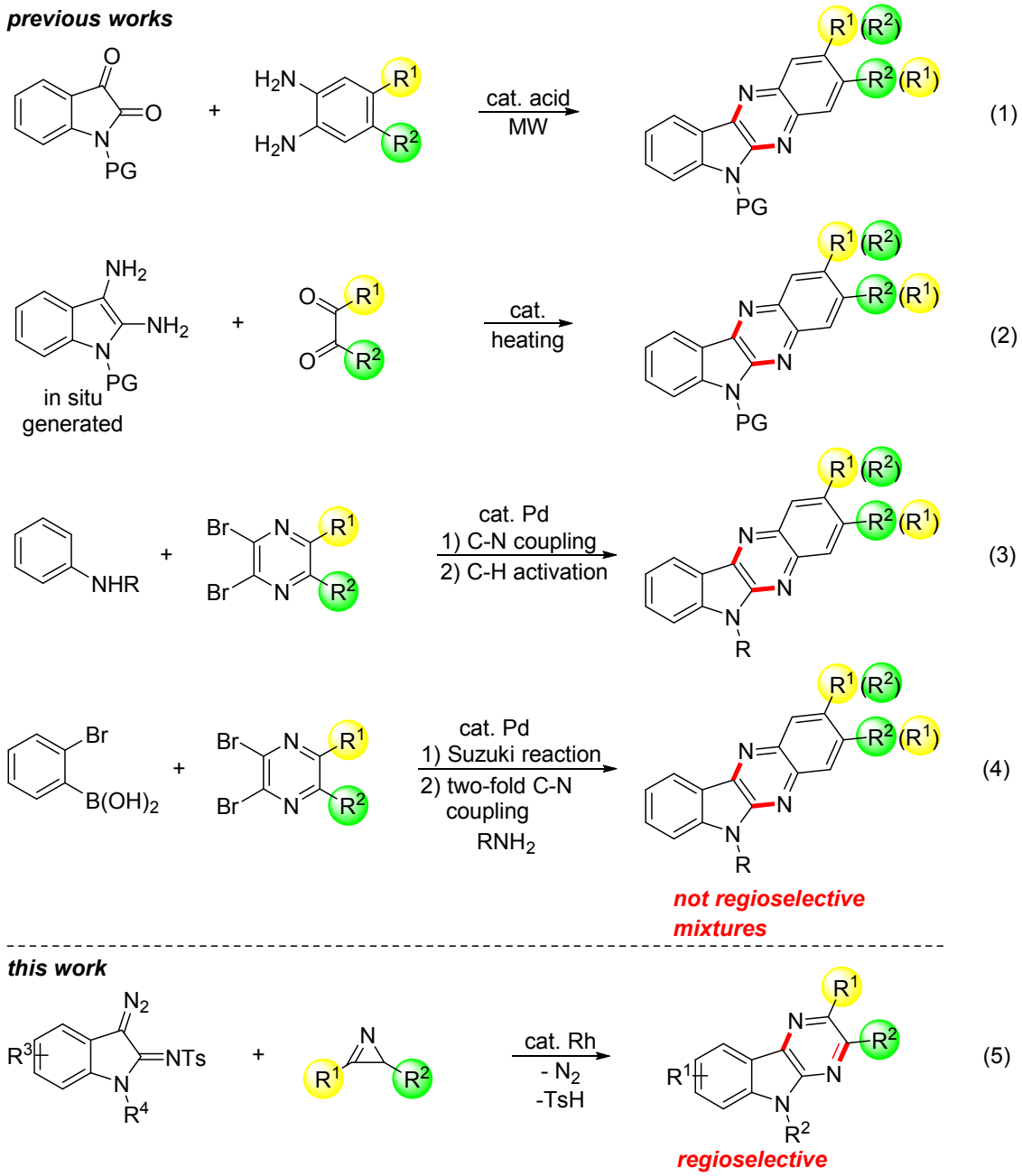


Figure 1. Representative Compounds Bearing Indolopyrazines

regard, the indolopyrazine motif has continuously received the attention of synthetic chemists. Thus, establishing synthetic approaches for preparing regioselective indolopyrazines from simply attainable starting materials is highly demanded. To date, a variety of indolopyrazine derivatives have been prepared by the condensation of isatin with *o*-phenylenediamine in glacial acetic acid under microwave irradiation (eq 1, Scheme 1),[2] condensation of *in situ* generated diamine with α-dicarbonyl compounds (eq 2),[3] Pd-catalyzed C–N coupling followed by C–H activation reactions from secondary aromatic amines and 2,3-dibromoquinoxaline in one pot (eq 3),[4] and a two-step approach using Pd-catalyzed Suzuki coupling reactions and subsequent annulation by Pd-catalyzed

two-fold C–N coupling reaction with aromatic and aliphatic amines (eq 4).[4,5] Although condensation reactions using *o*-phenylenediamines, α-dicarbonyl compounds, and 2,3-dibromoquinoxalines provide efficient synthetic approaches for indolopyrazines, these methods afford regioisomeric mixtures of indolopyrazines when unsymmetrical *o*-phenylenediamines, α-dicarbonyl compounds, or 2,3-dibromoquinoxalines are employed. Given the limitations of these methods, we were stimulated to develop a selective synthesis of indolopyrazines bearing unsymmetrical pyrazine skeletons. For this reason, we envisioned that, if azirines[6] were employed to react with diazoindolinimines,[7] indolopyrazines could be regioselectively produced. In our continuing investigations to establish scaffold-based chemical libraries,[6e,8] we were fascinated to invent an efficient and useful approach for preparing a multitude of heterocyclic-fused indols.[9] Herein, we demonstrate a regioselective method for the synthesis of the indolopyrazines through a sequential Rh-catalyzed formal [3 + 3] cycloaddition and aromatization reaction of a wide range of diazoindolinimines with azirines (eq 5).[10]

Scheme 1. Synthetic Methods for Indolopyrazines

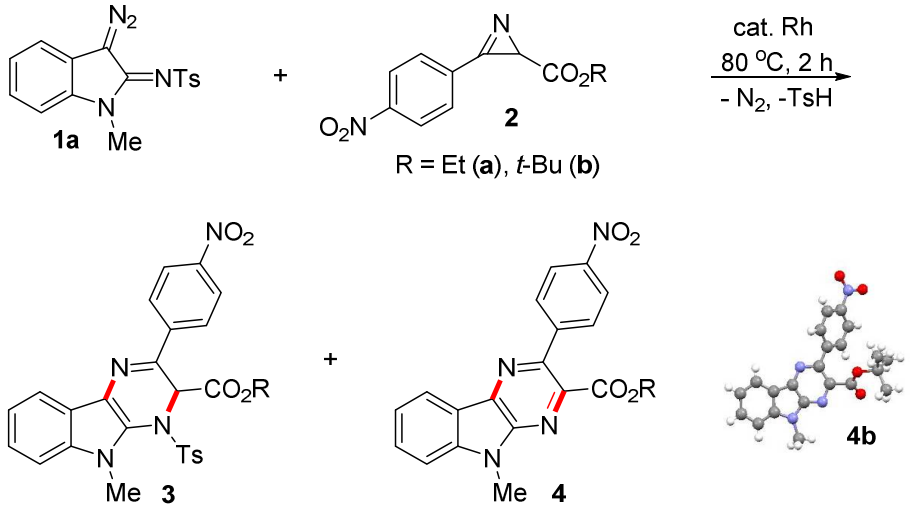


RESULTS AND DISCUSSION

First, we investigated the reaction of diazoindolinimine (**1a**) with ethyl 3-(4-nitrophenyl)-2*H*-azirine-2-carboxylate (**2a**) using a variety of Rh catalysts (Table 1). When $Rh_2(esp)_2$ was used in

dichloroethane (DCE) at 80 °C for 2 h, indolodihydropyrazine (**3a**) bearing the desired skeleton was gratifyingly obtained in 8% yield (entry 1). A variety of rhodium catalysts, such as $Rh_2(TFA)_4$, $Rh_2(OAc)_4$, and $Rh_2(oct)_4$, in DCE were screened to reveal that $Rh_2(oct)_4$ was the best performing catalyst, affording **3a** in 63% yield (entries 2, 3, and 4). Then, the desired product indolopyrazine (**4a**) was pleasingly accompanied in 16% yield by elimination of 4-methylbenzenesulfinic acid (TsH) from **3a**. The production of **4a** indicates that a Rh-catalyzed formal [3 + 3] cycloaddition followed by armatization reaction occurred in the present reaction. Thus, we tried to selectively prepare **4a** from the reaction of diazoindolinimine **1a** with azirine **2a**. Heating at 120 °C in DCE produced indolopyrazine **4a** selectively in 68% yield (entry 7). The addition of triethylamine (1.5 equiv) to *in situ* generated indolodihydropyrazine (**3a**) increased the yield of **4a** up to 79% (entry 8). When *tert*-butyl 3-(4-nitrophenyl)-2*H*-azirine-2-carboxylate (**2b**) was employed to the reaction with (**1a**) in the presence of $Rh_2(oct)_4$ in DCE at 80 °C for 2 h, indolodihydropyrazine (**3b**) was selectively produced in quantitative yield (entry 9). Moreover, when triethylamine was added to **3b**, the elimination reaction of TsH occurred, and the desired indolopyrazine (**4b**) was selectively obtained in 96% yield (entry 10). The sequential reaction could be scaled up without difficulty (entry 11). The structure of **4b** was confirmed by X-ray crystallography (see the Supporting Information).

Table 1. Reaction Optimization[a]

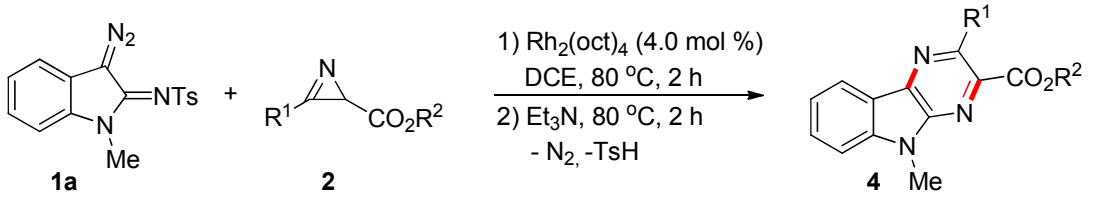


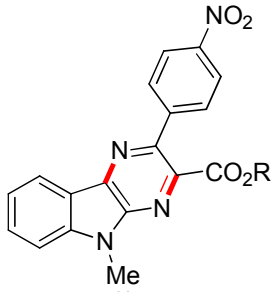
entry	R	cat.	solvent	temp (°C)	time (h)	yield (%)[b] 3	yield (%)[b] 4
1	Et	$Rh_2(esp)_2$	DCE	80	2	8	0
2	Et	$Rh_2(TFA)_4$	DCE	80	2	13	0
3	Et	$Rh_2(OAc)_4$	DCE	80	2	61	9
4	Et	$Rh_2(oct)_4$	DCE	80	2	63	16
5	Et	$Rh_2(oct)_4$	toluene	80	2	38	0
6	Et	$Rh_2(oct)_4$	EtOAc	80	2	17	0
7	Et	$Rh_2(oct)_4$	DCE	120	6	0	68
8[c]	Et	$Rh_2(oct)_4$	DCE	80	2	0	79[d]
9	*t*-Bu	$Rh_2(oct)_4$	DCE	80	2	99	0
10[c]	*t*-Bu	$Rh_2(oct)_4$	DCE	80	2	0	96[d]
11[c]	*t*-Bu	$Rh_2(oct)_4$	DCE	80	2	0	82[d,e]

[a]Reactions were carried out with **1a** (2.0 equiv), **2** (0.2 mmol, 1.0 equiv), and the Rh catalyst (4.0 mol %) in solvent (1.0 mL) at 80 °C for 2 h under a nitrogen atmosphere. [b]NMR yield using dibromomethane as an internal standard. [c]After 2 h, Et_3N (1.5 equiv) was added at 80 °C for 2 h. [d]Isolated yield of **4a** and **4b**. [e]This reaction was carried out 1.0 mmol scale of **2b**.

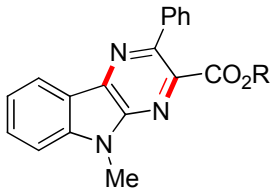
With these optimized reaction conditions, we examined the scope and limitation of the sequential reaction of diazoindolinimines **1a** with azirines **2** (Scheme 2). Likewise, ethyl 3-phenyl-2*H*-azirine-2-carboxylate was reacted with **1a** to produce indolopyrazine **4c** in 40% yield, while *tert*-butyl 3-phenyl-2*H*-azirine-2-carboxylate gave **4d** in 83% yield. Next, the substrate scope of a wide range of azirines **2** in the reaction with diazoindolinimine **1a** was investigated. Electronic modification of the substituents on the aryl group of *tert*-butyl 3-aryl-2*H*-azirine-2-carboxylate slightly influenced the reaction efficiency. An electron-donating 3-methyl group provided the desired indolopyrazine **4e** in 65% yield. The conditions of the sequential reaction were compatible with a variety of electron-withdrawing groups, including chloro, iodo, trifluoromethyl, and cyano groups, affording the corresponding indolopyrazines (**4f**, **4g**, **4h**, **4i**, and **4j**) in good yields varying from 71% to 89%. *tert*-Butyl azirine carboxylate bearing a 2-naphthyl group was also readily employed in the Rh-catalyzed formal [3 + 3] cycloaddition followed by the aromatization reaction, producing **4l** in 87% yield. A 2-furyl-substituted *tert*-butyl azirine carboxylate tolerated the optimized reaction conditions and provided the desired 2-furyl-substituted indolopyrazine **4m** in 64% yield. It was notable that a 2-thiophenyl-substituted azirine was also successfully applied to the sequential Rh-catalyzed cycloaddition and aromatization reaction, affording **4n** in 66% yield. The current approach worked equally well even with methyl-substituted *n*-butyl and *tert*-butyl azirine carboxylates, leading to the formation of indolopyrazines **4o** and **4p** in 76% and 71% yields, respectively.

Scheme 2. Scope of Azirines[a]

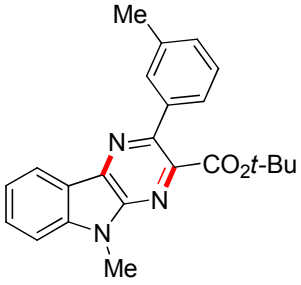




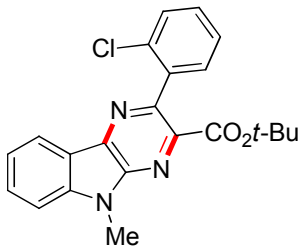
4a (79%, R = Et)
4b (96%, R = *t*-Bu)



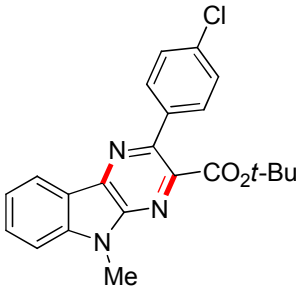
4c (40%, R = Et)
4d (83%, R = *t*-Bu)



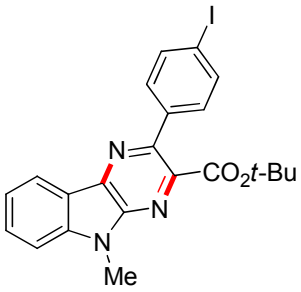
4e (65%)



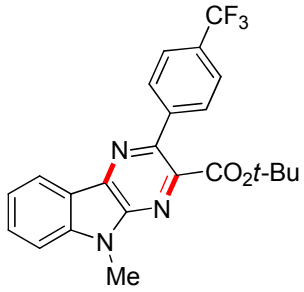
4f (71%)



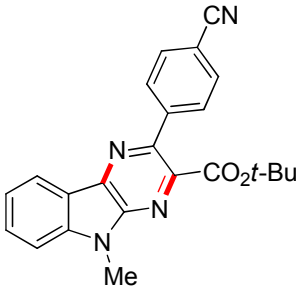
4g (80%)



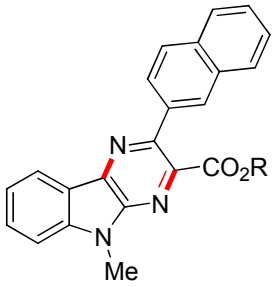
4h (83%)



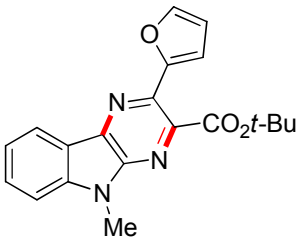
4i (75%)



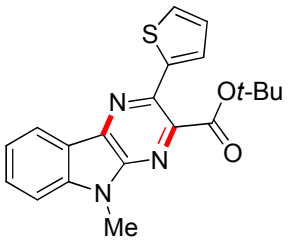
4j (89%)



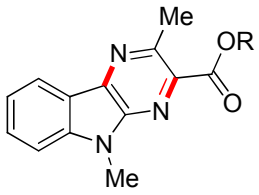
4k (42%, R = Et)
4l (87%, R = *t*-Bu)



4m (64%)



4n (66%)

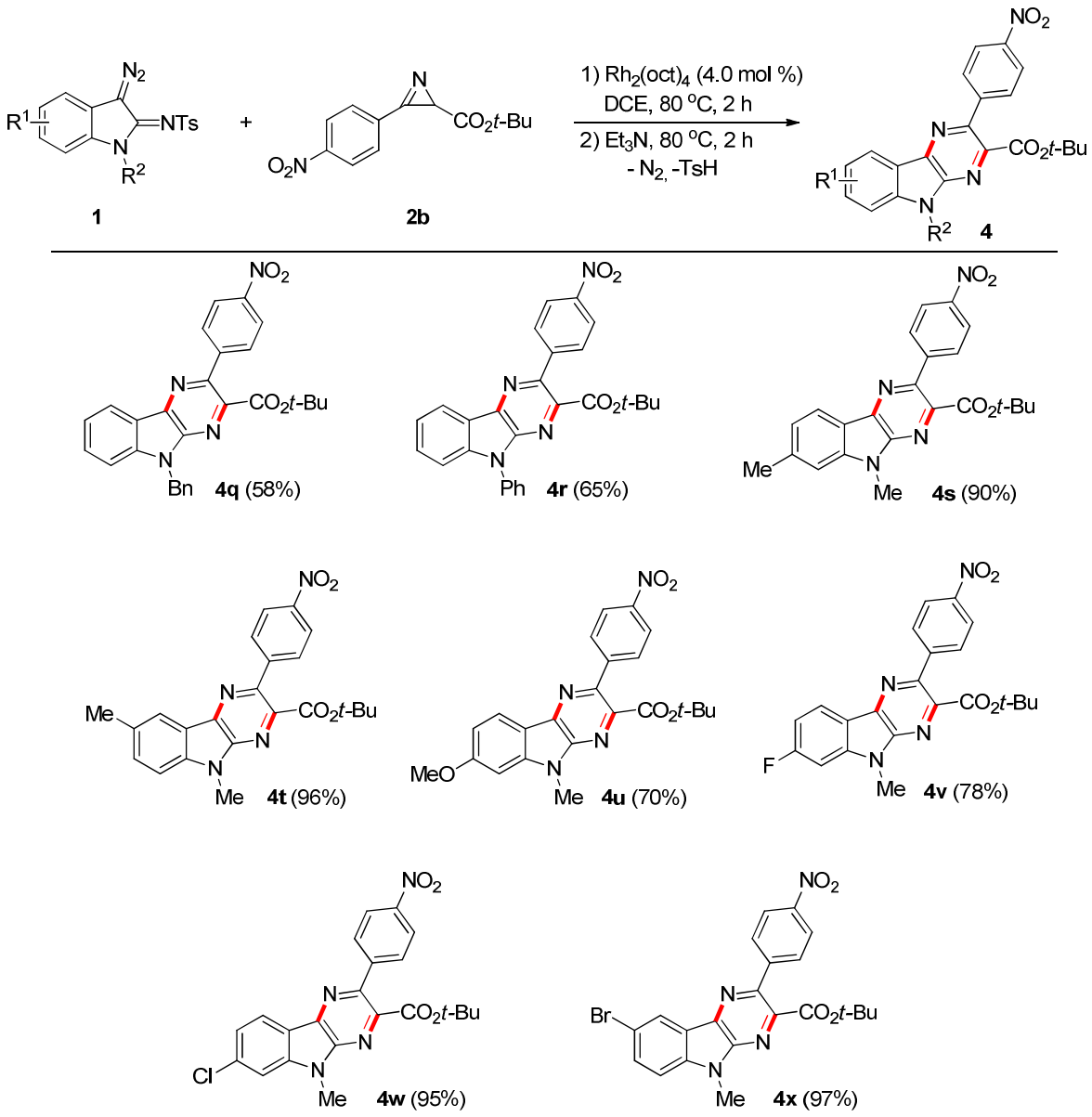


4o (76%, R = *n*-Bu)
4p (71%, R = *t*-Bu)

[a]After the reactions were carried out with **1a** (2.0 equiv), **2** (0.2 mmol, 1.0 equiv), and $Rh_2(oct)_4$ (4.0 mol %) in DCE (1.0 mL) at 80 ^oC for 2 h under a nitrogen atmosphere, Et_3N (1.5 equiv) was added, and then, the reaction mixture was stirred at 80 ^oC for 2 h.

Next, we examined the substrate scope as well as the functional group tolerance of diazoindolinimines in the reaction with azirine (**2b**) (Scheme 3). Modification of the substituents at the N1 position of diazoindolinimines **1** affected the efficiency of the reaction. *N*-Benzyl- and *N*-phenyl-substituted diazoindoloimines were less reactive than *N*-methyl-substituted one and afforded the indolopyrazines **4q** and **4r** in 58% and 65% yields, respectively. Thus, a variety of *N*-methyl-substituted diazoindolimines were employed to the sequential Rh-catalyzed formal [3 + 3] cycloaddition and aromatization reaction. Electronic modification of the substituents on the aryl ring of the *N*-methyl-substituted diazoindoloimines (**1**) did not largely influence the reaction efficiency. For instance, *N*-methyl-substituted diazoindoloimines bearing electron-donating 6-methyl, 5-methyl, and 6-methoxy groups on the phenyl ring were converted to the indolopyrazines (**4s**, **4t**, and **4u**) in good to excellent yields varying from 70% to 96%. Additionally, substrates with electron-withdrawing 6-fluoro, 6-chloro, and 5-bromo groups on the phenyl ring underwent the sequential reaction, providing the desired indolopyrazines (**4v**, **4w**, and **4x**). The tolerance of halides, including fluoro, chloro and bromo groups, was significant, as further transformations of these functional groups are possible.

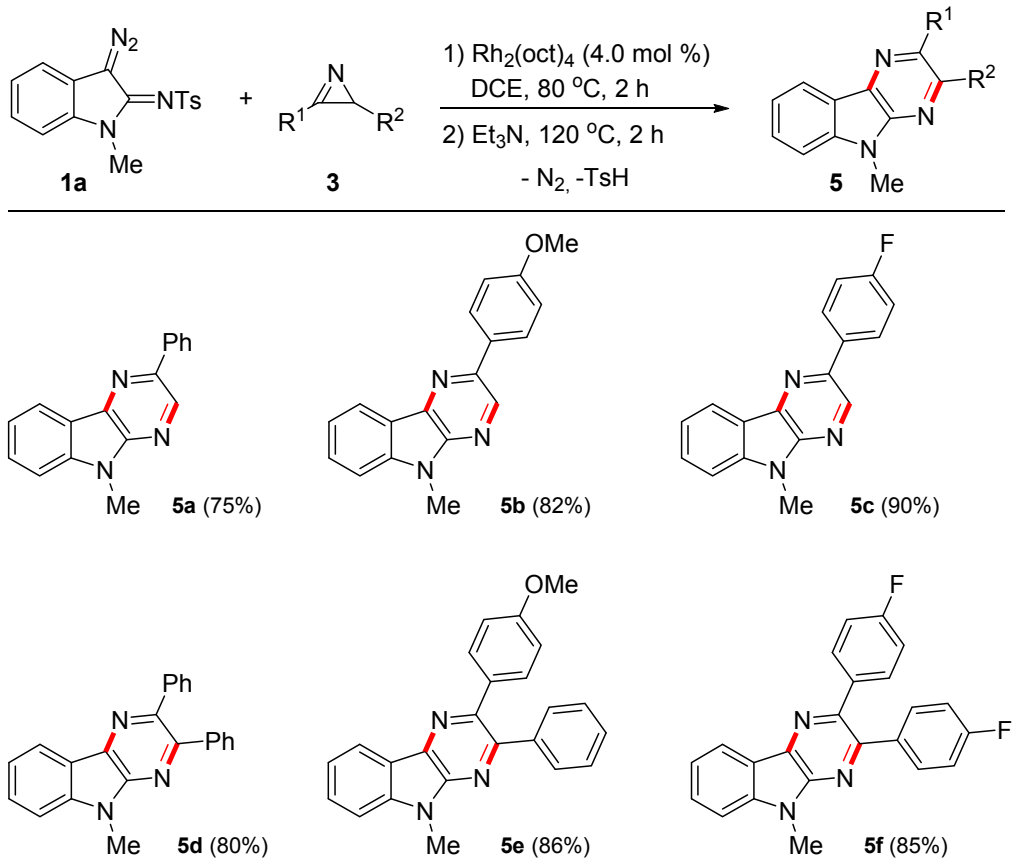
Scheme 3. Scope of 3-Diazoindoline-2-imines[a]



[a]After the reactions were carried out with **1** (2.0 equiv), **2b** (0.2 mmol, 1.0 equiv), and $Rh_2(oct)_4$ (4.0 mol %) in DCE (1.0 mL) at 80 °C for 2 h under a nitrogen atmosphere, Et_3N (1.5 equiv) was added, and then, the reaction mixture was stirred at 80 °C for 2 h.

Based on these results, we next explored the scope of this reaction with respect to a wide range of unactivated and unsymmetrical azirines (Scheme 4). When phenylazirine was treated with *N*-methyl diazoindolinimine **1a** under the optimized conditions, the sequential Rh-catalyzed formal [3 + 3] cycloaddition and aromatization reaction occurred and afforded the desired indolopyrazine **5a** in 75% yield. 4-Methoxyphenyl- and 4-fluorophenyl-substituted azirines were also smoothly converted to the corresponding indolopyrazines **5b** (82%) and **5c** (90%), respectively. Diphenylazirine worked equally well with *N*-methyl diazoindolinimine **1a** to give indolopyrazine **5d** in 80% yield. 3-(4-Methoxyphenyl)-2-phenyl-*2H*-azirine took part in the reaction with **1a** to afford indolopyrazine **5e** in 86% yield. 2,3-Bis(4-fluorophenyl)-2*H*-azirine was found to couple with **1a** to furnish the corresponding product **5f** in 85% yield.

Scheme 4. Scope of Unactivated and Unsymmetrical Azirines[a]



[a]After reactions were carried out with **1a** (2.0 equiv), **3** (0.2 mmol, 1.0 equiv), and $Rh_2(oct)_4$ (4.0 mol %) in DCE (1.0 mL) at 80 °C for 2 h under a nitrogen atmosphere, Et_3N (1.5 equiv) was added, and then, the reaction mixture was stirred at 120 °C for 2 h.

Because indolopyrazines (**5**) are fluorescent, their optical properties in CH_2Cl_2 solution were studied (Figure 2). The indolopyrazine fluorophores displayed Stokes shifts ranging from 41 to 146 units. The extinction coefficients were variable from 107,298 to 585,478 $M^{-1}cm^{-1}$ (Table 2). The indolopyrazine (**5e**) affords high quantum yields and extinction coefficients, which are an attractive property for biological probes.

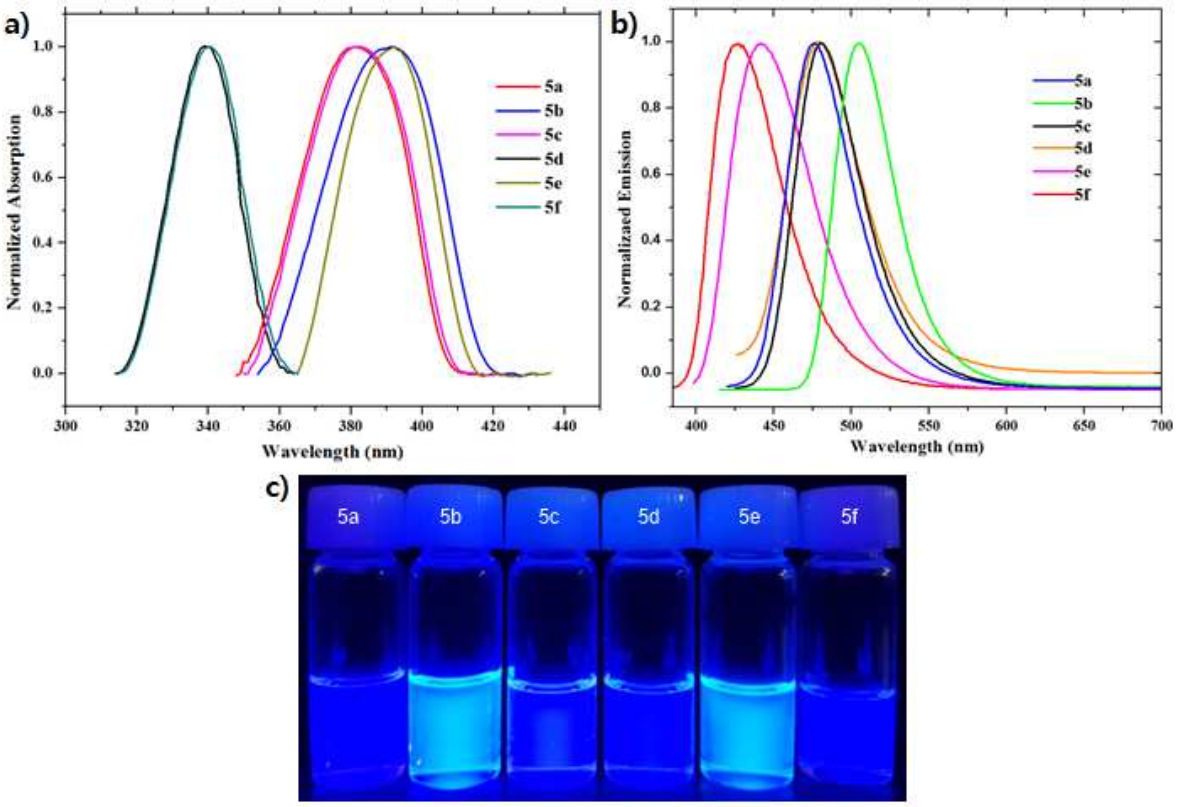


Figure 2. Normalized Absorption (a) and Fluorescence Emission (b) Spectra for Selected Fluorophores (5a-5f). Observed Fluorescence under UV Excitation (365 nm) (c).

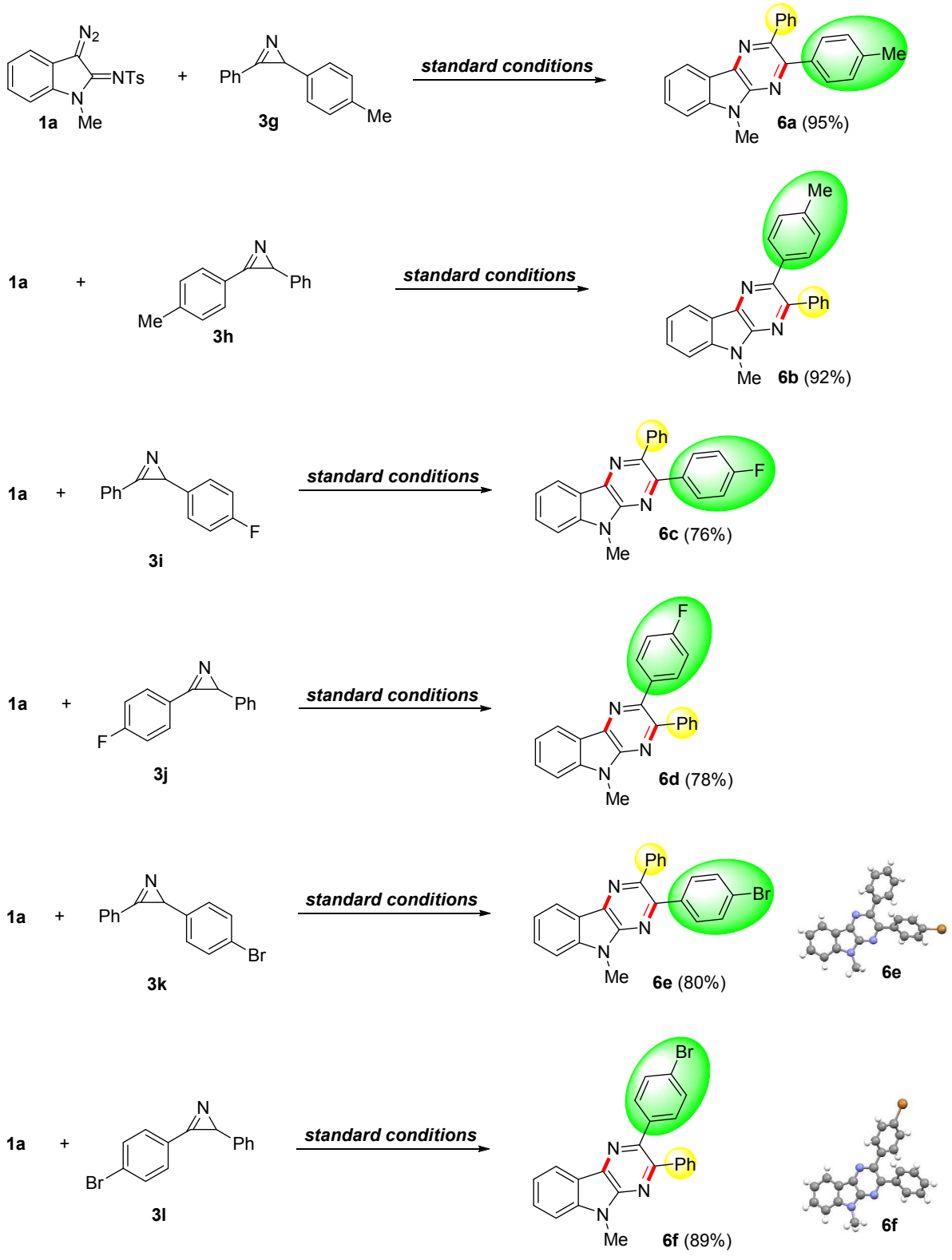
Table 2. Photophysical Properties of Indolopyrazines[a]

Compound	$\lambda_{max,abs}$ (nm)	$\lambda_{max,em}$ (nm)	ε ($M^{-1}.cm^{-1}$)	ϕ
5a	330	476	253,856	0.22
5b	387	505	343,107	0.27
5c	378	419	174,025	0.13
5d	339	425	143,133	0.11
5e	383	443	585,478	0.45
5f	340	426	107,298	0.08

[a]Absorption peaks ($\lambda_{max,abs}$) and molar extinction coefficients (ε) were measured in CH_2Cl_2 (10^{-5} M).

To demonstrate the synthetic utility of this cyclization, we next attempted the regioselective synthesis of indolopyrazines using azirines bearing two unsymmetrical aryl groups (Scheme 5). Isomeric 3-phenyl-2-(*p*-tolyl)-2*H*-azirine and 2-phenyl-3-(*p*-tolyl)-2*H*-azirine are applicable to the present transformation, leading to the regioselective formation of the corresponding indolopyrazines **6a** and **6b** in 95% and 92% yields, respectively. Likewise, 2-(4-fluorophenyl)-3-phenyl-2*H*-azirine and 3-(4-fluorophenyl)-2-phenyl-2*H*-azirine were compatible with the reaction conditions, affording selectively the desired indolopyrazines **6c** (76%) and **6d** (78%). In the case of 2-(4-bromophenyl)-3-phenyl-2*H*-azirine and 3-(4-bromophenyl)-2-phenyl-2*H*-azirine, the corresponding indolopyrazines **6e** and **6f** were selectively produced in good yield. The structure of **6e** and **6f** was confirmed by X-ray crystallography (see the Supporting Information). Because the previously reported synthetic methods afforded mixtures of indolopyrazines, the present approach using unsymmetrical azirines has a strong advantage from a regioselectivity viewpoint.

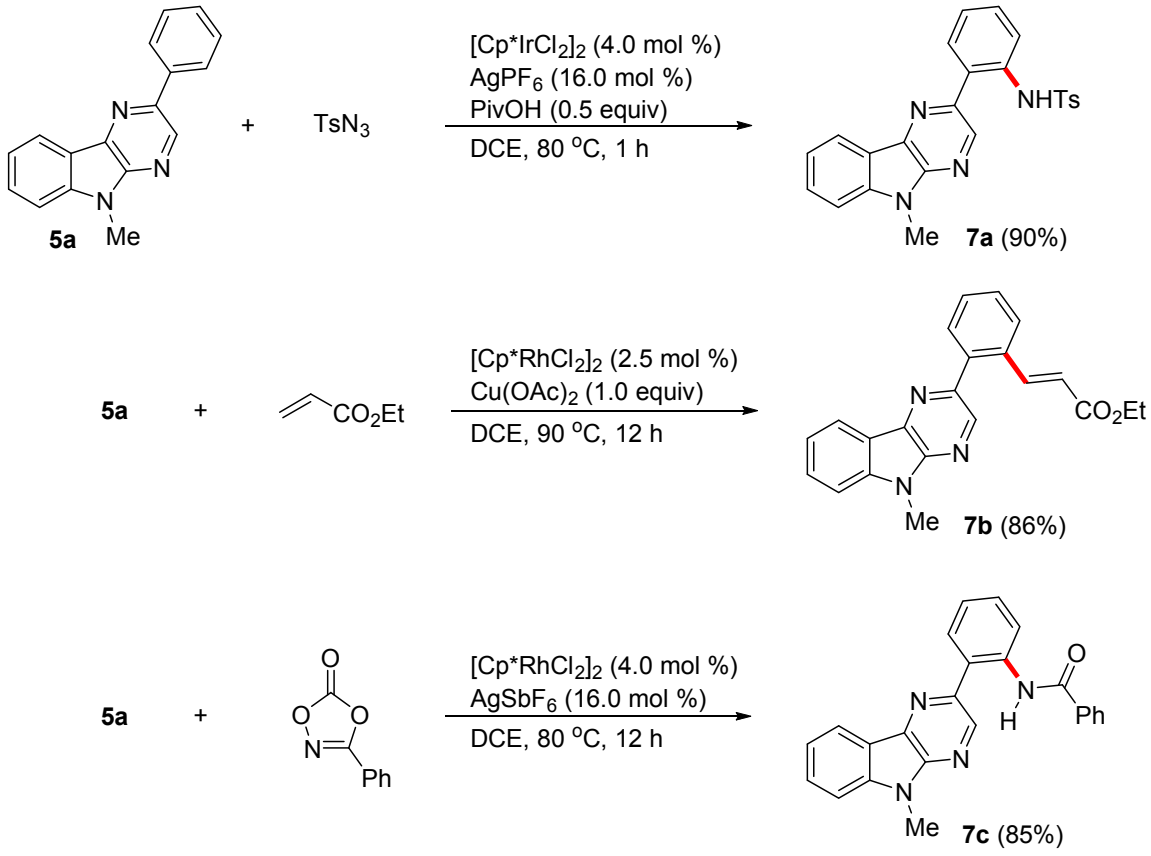
Scheme 5. Regioselective Synthesis of Indolopyrazines Using Unsymmetrical Azirines



standard conditions: 1) $Rh_2(oct)_4$ (4.0 mol %), DCE, 80 °C, 2 h. 2) Et_3N, 120 °C, 2 h. - N_2, -TsH

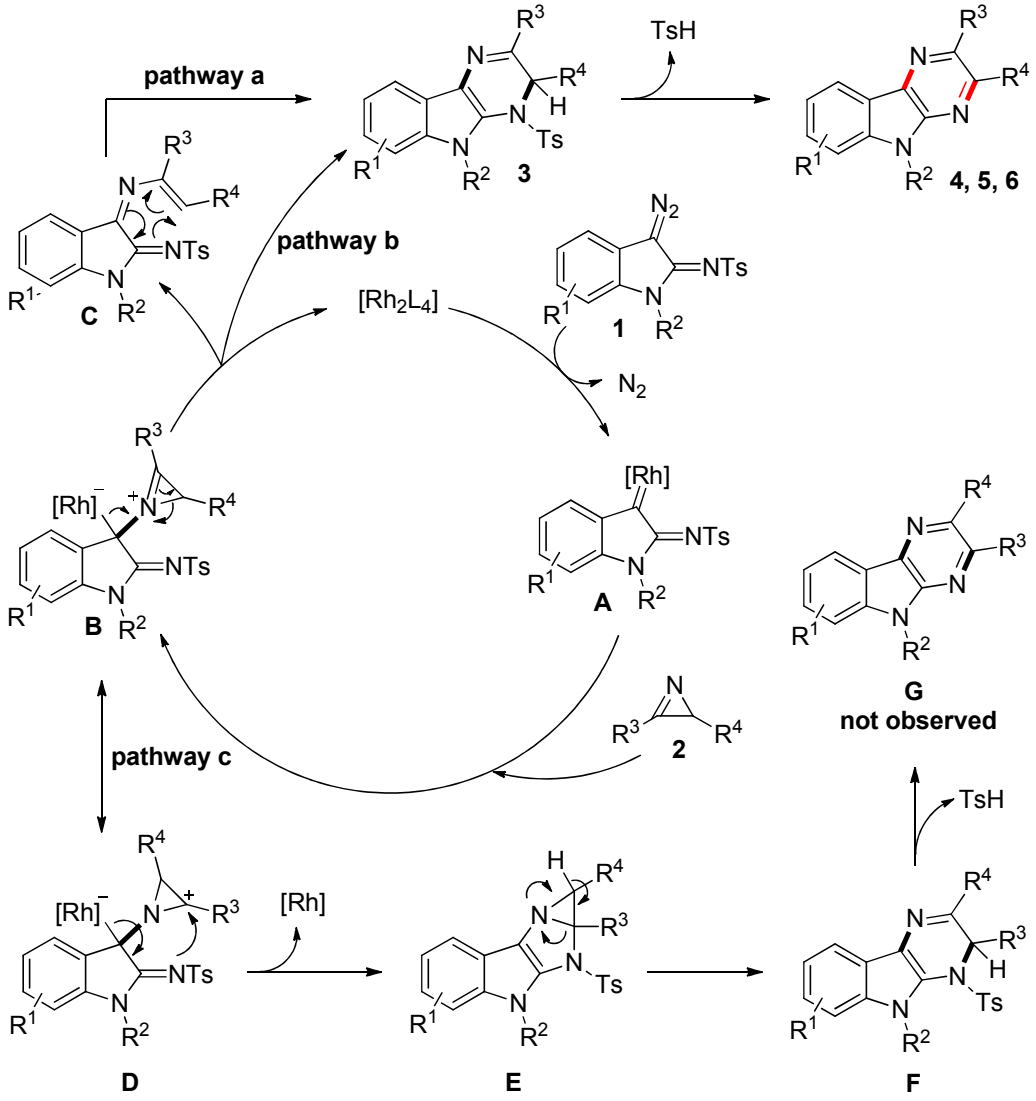
Next, we investigated the synthetic application of 5-methyl-2-phenyl-5*H*-pyrazino[2,3-b]indole (**5a**) in C–H activation (Scheme 6). When **5a** was reacted with TsN_3 in the presence of $[Cp^*IrCl_2]_2$, $AgPF_6$, and pivalic acid, the sulfonyl-aminated indolopyrazine **7a** was produced in 90% yield.[11] The Rh-catalyzed olefination of **5a** with ethyl acrylate was efficient and provided **7b** in 86% yield.[12] In addition, the Rh-catalyzed C–H activation of **5a** and dioxazolone occurred, and the benzoyl-aminated product **7c** was obtained in 86% yield.[13]

Scheme 6. Applications of Indolopyrazine to C–H Activation



A feasible reaction mechanism for the production of indolopyrazine (**4**, **5**, and **6**) from diazoindolinimine **1** and azirine **2** is depicted in the Scheme 7. First, diazoindolinimines by reaction of a rhodium catalyst affords rhodium carbenoid **A** together with release of nitrogen molecule. Addition of azirine **2** to the carbene center of **A** provides the rhodium-bond zwitterionic intermediate **B**. Next, a ring-opening reaction via the release of an electron pair from anionic rhodium of **B** furnishes dihydroindolopyrazine **3** (**pathway b**). Finally, elimination of 4-methylphenylsulfinic acid (TsH) from **3** affords indolopyrazine (**4**, **5**, and **6**). 6-Electrocyclization (**pathway a**) of 1,4-diazatriene **C** might be involved to the production of dihydroindolopyrazine **3.** Because regioisomeric indolopyrazine **G** are not detected from the present reaction, an intramolecular hydrogen transfer (**pathway c**) can be ruled out. In fact, this postulation is provided by X-ray structure of indolopyrazine **6e** and **6f**.

Scheme 7. A Plausible Mechanism



CONCLUSION

In summary, we developed a regioselective synthetic method to prepare indolopyrazines through a sequential Rh-catalyzed formal [3 + 3] cycloaddition and aromatization reaction of a wide range of diazoindolinimines with azirines. Because the previously reported synthetic methods afforded mixtures of indolopyrazines, the present method using unsymmetrical azirines has the an excellent merit from a regioselectivity standpoint.

Experimental Section

General: Commercial available reagents were used without purification. All reaction mixtures were stirred magnetically and were monitored by thin-layer chromatography using silica gel pre-coated glass plates, which were visualized with UV light and then, developed using either iodine or a solution of anisaldehyde. Flash column chromatography was carried out using silica gel (230-400 mesh). ^{1}H NMR (400 MHz), ^{13}C{^{1}H} NMR (100 MHz), and ^{19}F NMR (377 MHz) spectra were recorded on NMR spectrometer. Deuterated chloroform was used as the solvent and chemical shift values (δ) are reported in parts per million relative to the residual signals of this solvent [δ 7.26 for ^{1}H (chloroform-*d*), δ 2.05 for ^{1}H (acetone-d_6), δ 77.2 for ^{13}C{^{1}H} (chloroform-*d*) and δ 29.84, 206.26 for ^{13}C{^{1}H} (acetone-d_6)]. Infrared spectra were recorded on FT-IR spectrometer as either a thin film pressed between two sodium chloride plates or as a solid suspended in a potassium bromide disk. High resolution mass spectra (HRMS) were obtained by fast atom bombardment (FAB) using a double focusing magnetic sector mass spectrometer and electron impact (EI) ionization technique (magnetic sector - electric sector double focusing mass analyzer) from the KBSI (Korea Basic Science Institute Daegu Center). Melting points were determined in open capillary tube.

Synthetic procedure of azirines

Preparation of substrates

Azirines were prepared by reported method.[14,15,16,17]

General procedure for azirines ester[14]

To a mixture of β-ketoester (2.2 mmol, 1.0 equiv), $NH_2OH{\cdot}HCl$ (160 mg, 2.2 mmol, 1.0 equiv) and sodium acetate (210 mg, 2.2 mmol, 1.0 equiv) was added methanol (15 mL) and water (0.7 mL). After being stirred at room temperature for 4 h, the solvent was removed in vacuo. The reaction

mixture was partitioned between Et_2O and water. After saperation, the organic extract was washed with saturated aqueous $NaHCO_3$, brine, and dried over anhydrous $MgSO_4$. The solvents were removed in vacuo, and the resulting crude was used directly in the next reaction. To an ice cold solution of crude oxime and Et_3N (0.9 mL, 6.6 mmol, 3.0 equiv) in DCM (20 mL) was slowly added TsCl (500 mg, 2.6 mmol, 1.2 equiv), and the mixture was stirred at the same temperature for 2.5 h. The reaction was quenched with water, and the organic material was extracted three times with ethyl acetate. The combined extracts were washed with water, brine, and dried over anhydrous $MgSO_4$. The solvents were removed in vacuo, and the resulting crude materials were used immediately for the next step without further purification. To an ice cold solution of crude ketoxime tosylate in DCM (8 mL) was slowly added DBU (0.4 mL, 2.6 mmol, 1.2 equiv), and the mixture was stirred at the same temperature for 1 h. The reaction was quenched with water, and the organic materials were extracted with DCM. The combined extracts were washed with brine, and dried over anhydrous $MgSO_4$. After the solvents were removed in vacuo, the residue was purified by column chromatography to give the corresponding azirines ester.

***tert*-Butyl 3-(*m*-tolyl)-2*H*-azirine-2-carboxylate (2e):** Yield: 104 mg (20%); R_f = 0.5 (EtOAc:Hexane = 1:10); Red oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68 (d, J = 8.1 Hz, 2H), 7.45 (d, J = 6.3 Hz, 2H), 2.45 (s, 3H), 1.47 (s, 9H) ; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 171.1, 159.0, 139.4, 134.7, 130.9, 129.3, 127.7, 122.6, 81.7, 30.7, 28.2, 21.4; IR (film) 2976, 2928, 1729, 1584, 1367, 1152, 787, 689 cm^{-1}; HRMS (FAB) *m/z*: $[M + H]^+$ Calcd for $C_{14}H_{18}NO_2$ 232.1338; Found 232.1335.

***tert*-Butyl 3-(4-chlorophenyl)-2*H*-azirine-2-carboxylate (2g):** Yield: 208.3 mg (55%); R_f = 0.3 (EtOAc:Hexane = 1:5); Yellow solid; Melting point: 55-57 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82 (d, J = 8.6 Hz, 2H), 7.56 (d, J = 8.6 Hz, 2H), 2.77 (s, 1H), 1.47 (s, 9H) ; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 170.7, 158.5, 140.3, 131.6, 130.0, 121.3, 82.0, 30.9, 28.2; IR (film) 2979, 2933, 1991, 1725, 1594, 1485, 1157, 835, 556 cm^{-1}; HRMS (FAB) *m/z*: $[M + H]^+$ Calcd for $C_{13}H_{15}ClNO_2$

252.0791; Found 252.0794.

***tert*-Butyl 3-(4-iodophenyl)-2*H*-azirine-2-carboxylate (2h):** Yield: 256 mg (30%); R_f = 0.3 (EtOAc:Hexane = 1:5); Yellow solid; Melting point: 74-76 ^oC; ^1H NMR (400 MHz, $CDCl_3$) δ 7.95 (d, J = 8.4 Hz, 2H), 7.59 (d, J = 8.4 Hz, 2H), 2.76 (s, 1H), 1.46 (s, 9H) ; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 170.6, 152.4, 135.2, 135.2, 128.6, 125.2, 81.9, 31.5, 28.2; IR (film) 2977, 1942, 1723, 1651, 1342, 1156, 824, 554 cm^{-1}; HRMS (FAB) *m/z*: $[M + H]^+$ Calcd for $C_{13}H_{15}INO_2$ 344.0147; Found 344.0145.

***tert*-Butyl 3-(4-(trifluoromethyl)phenyl)-2*H*-azirine-2-carboxylate (2i):** Yield: 85.5 mg (25%); R_f = 0.6 (EtOAc:Hexane = 1:5); Ivory oil; ^1H NMR (400 MHz, $CDCl_3$) δ 8.02 (d, J = 8.0 Hz, 2H), 7.85 (d, J = 8.1 Hz, 2H), 2.84 (s, 1H), 1.47 (s, 9H) ; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 170.4, 159.1, 135.3(q, J = 33.1 Hz), 130.6, 126.5(q, J = 3.7 Hz), 126.2, 122.1(t, J = 272.9 Hz), 82.2, 31.2, 28.2; IR (film) 2982, 2936, 1867, 1725, 1636, 1328, 1132, 1064, 847 cm^{-1}; HRMS (FAB) *m/z*: $[M + H]^+$ Calcd for $C_{14}H_{15}F_3NO_2$ 286.1055; Found 286.1053.

***tert*-Butyl 3-(4-cyanophenyl)-2*H*-azirine-2-carboxylate (2j):** Yield: 502 mg (34%); R_f = 0.4 (EtOAc:Hexane = 1:10); White solid; Melting point: 94-96 ^oC; ^1H NMR (400 MHz, $CDCl_3$) δ 8.01 (d, J = 8.4 Hz, 2H), 7.88 (d, J = 8.5 Hz, 2H), 2.86 (s, 1H), 1.48 (s, 1H) ; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 170.1, 159.1, 133.1, 130.6, 126.8, 117.7, 117.1, 82.3, 31.4, 28.1; IR (film) 2979, 2232, 1722, 1347, 1157, 845, 566 cm^{-1}; HRMS (FAB) *m/z*: [M + H]+ Calcd for $C_{14}H_{15}N_2O_2$ 243.1134; Found 243.1136.

General procedure for azirines ester[15]

To a solution of $NH_2OH{\cdot}HCl$ (2.0 equiv) in pyridine (12.0 equiv) was added β-ketoester (1.0 equiv) dropwise. The solution was stirred for 1-20 h and the solvent was removed under reduced pressure.

The residue was extracted twice with ethyl acetate. The combined organic layers were dried over $MgSO_4$ and concentrated in vacuo to give ketoxime, which was used for the next step without purification. To the ketoxime was added TsCl (1.2 equiv) and pyridine (12.0 equiv). The solution was stirred for 20 h and quenched with saturated aqueous NH_4Cl. The mixture was extracted three times with DCM. The combined organic layers were dried over $MgSO_4$ and concentrated in vacuo. The crude material was purified by column chromatography using ethyl acetate : hexane (1:4). To a solution of ketoxime tosylate in DCM was added Et_3N dropwise, and the mixture was stirred at room temperature for 3 h. Upon completion of the reaction as indicated by TLC, the reaction mixture was quenched with H_2O and the layers were separated. The aqueous layer was extracted with DCM and the combined layers were washed with water and brine, and dried over anhydrous $MgSO_4$. The crude material was purified by column chromatography using ethyl acetate : hexane (1:6).

Butyl 3-methyl-2*H*-azirine-2-carboxylate (2o): Yield: 1050 mg (83%); R_f = 0.5 (EtOAc:Hexane = 1:5); White Yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.18-4.07 (m, 2H), 2.53 (s, 3H), 2.43 (s, 1H), 1.66-1.59 (m, 2H), 1.43-1.34 (m, 2H), 0.94 (t, J = 7.4 Hz, 3H) ; ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 172.2, 159.2, 65.0, 30.7, 28.9, 19.1, 13.7, 12.6; IR (film) 2961, 2874, 1909, 1728, 1637, 1337, 1192, 961, 638 cm^{-1}; HRMS (FAB) *m/z*: $[M + H]^+$ Calcd for $C_8H_{14}NO_2$ 156.1025; found 156.1026.

General procedure for synthesis of unsubstituted 2*H*-azirine[16]

To a stirred solution of ICl (2.2 mmol) in MeCN (4 mL) was added NaN_3 (4 mmol) at rt, 1.5 h later, the reaction mixture was cooled to 0℃, a solution of alkene (2 mmol) in MeCN (4 mL) was added. After 5 h later, the mixture was partitioned between Ether and H_2O, the organic phase was separated, then dried ($MgSO_4$) and concentrated. The crude was dissolved in Et_2O (6 mL), KO^{t}Bu (3.1 mmol) was added. The reaction was stirred for 5 h at rt, then partitioned between ethyl acetate and H_2O, the organic phase was separated, then dried ($MgSO_4$) and concentrated. The solvent was removed in

vacuo, and the resulting crude materials were purified by silicagel flash column chromatography (eluant : hexane) to give the corresponding vinyl azide. To a solution of vinyl azide (3 mmol) in toluene was heated in reflux and until completion was showed by TLC. The reaction was allowed to cool to room temperature and toluene was evaporated. The crude residue was purified by flash column chromatography (in pentane) to give 2*H*-azirine.

General procedure for unsymmetrical azirines[17]

The mixture of ketone (1.0 equiv), $NH_2OH{\cdot}HCl$ (1.5 equiv) and sodium acetate were dissolved in $MeOH/H_2O$ (20:1) at room temperature and monitored by TLC. After the reaction completed, the solution was sequentially washed with sat. $NaHCO_3$ and brine. The organic layer was dried over $MgSO_4$. Concentration led to the oxime which was used directly for the next step. Triethylamine (1.5 equiv) and methanesulfonyl chloride (1.5 equiv) was added sequentially to the solution of oxime (1 equiv) in dry THF at rt or 0 ^oC. The solution got cloudy after the addition of methanesulfonyl chloride. Then, the resulting mixture was stirred for 30 min and DBU (1.5 equiv) was added over 10 min. After stirring for additional 30 min, the reaction mixture was passed through a pad of silica gel and washed with ethyl acetate. The mixture was concentrated in vacuo and the resulting residue was purified by column chromatography on silica gel to give the unsymmetrical azirines.

2-(4-bromophenyl)-3-phenyl-2H-azirine (3k): Yield: 1401 mg (58%); R_f = 0.4 (EA:Hexane = 1:10); White solid; Melting point: 43-45 ^oC; ^1H NMR (400 MHz, $CDCl_3$) δ 7.89-7.87 (m, 2H), 7.63-7.53 (m, 3H), 7.41-7.38 (m, 2H), 7.03-7.00 (m, 2H), 3.28 (s, 1H) ; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 163.4, 140.1, 133.5, 131.5, 130.0, 129.5, 127.8, 123.8, 121.0, 34.0; IR (film) 2987, 1896, 1743, 1487, 1069, 759, 519 cm^{-1}; HRMS (EI) *m/z*: $[M]^+$ Calcd for $C_{14}H_{10}{}^{79}BrN$ 270.9997, $C_{14}H_{10}{}^{81}BrN$ 272.9977; Found 270.9999, 272.9993.

Synthetic procedure of diazoindoloimines[18]

To an oven-dried 10 mL Schlenk tube equipped with a magnetic stirring bar were added sequentially indole (0.25 mmol), sulfonyl azide (0.5 mmol), and DMSO (0.5 mL). The reaction mixture was stirred at 50 ^{o}C for 12 h. Then, the reaction was quenched by H_2O (10 mL) and extracted with CH_2Cl_2 (15 mL × 3). The combined organic layers were dried over anhydrous $MgSO_4$ and concentrate+d in vacuo. The crude product was purified by column chromatography on silica gel (petroleum ether : EtOAc = 3:1).

Synthetic procedure of indolopyrazines

To a test tube were added 3-diazoindolin-2-imines (**1**) (2.0 equiv, 0.4 mmol), azirines (**2**) (1.0 equiv, 0.2 mmol), and $[Rh_2(oct)_4]_2$ (4.0 mol %) in DCE (1.0 mL). The resulting mixture was stirred at 80 oC for 2 h under nitrogen after 2 h, Et_3N (1.5 equiv) was added in one-pot, and the solution was stirred at 80 °C for 2 h. The mixture was cooled to room temperature, filtered through a pad of Celite, and concentrated under reduced pressure. The residue was then purified by flash column chromatography to give indolopyrazines **4**.

Ethyl 5-methyl-2-(4-nitrophenyl)-4-tosyl-4,5-dihydro-3*H*-pyrazino[2,3-*b*]indole-3-carboxylate

(3a): Yield: 67 mg (63%); R_f = 0.3 (DCM:Hexane = 2:1); Red solid; Melting point: 134-136 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.22 (d, J = 9.0 Hz, 2H), 7.86 (d, J = 9.0 Hz, 2H), 7.79 (d, J = 7.8 Hz, 1H), 7.45 (d, J = 8.3 Hz, 1H), 7.39-7.35 (m, 1H), 7.28-7.25 (m, 1H), 7.08 (d, J = 8.4 Hz, 2H), 6.79 (d, J = 8.0 Hz, 2H), 5.98 (s, 1H), 4.12-4.08 (m, 1H), 4.02 (s, 3H), 4.00-3.95 (m, 1H), 2.20(s, 3H), 1.06 (t, J = 7.1 Hz, 3H) ; ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 165.9, 148.0, 145.6, 144.9, 142.2, 136.0, 133.1, 129.4, 127.6, 126.8, 125.5, 123.7, 123.5, 122.2, 121.7, 120.4, 118.5, 110.4, 62.9, 58.2, 31.4, 21.6, 14.0; IR (film) 2985, 2941, 1843, 1750, 1645, 1342, 1170, 747 cm^{-1}; HRMS (EI) *m/z*: $[M]^+$ Calcd for $C_{27}H_{24}N_4O_6S$ 532.1417; Found 532.1414.

***tert*-Butyl 5-methyl-2-(4-nitrophenyl)-4-tosyl-4,5-dihydro-3*H*-pyrazino[2,3-*b*]Indole-3-carboxylate (3b):** Yield: 78 mg (99%); R_f = 0.3 (DCM:Hexane = 2:1); Red solid; Melting point: 265-267 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.21 (d, J = 8.7 Hz, 2H), 7.87 (d, J = 8.8 Hz, 2H), 7.80 (d, J = 7.8 Hz, 1H), 7.45 (d, J = 8.2 Hz, 1H), 7.37 (t, J = 7.6 Hz, 1H), 7.28-7.24 (m, 1H), 7.08 (d, J = 8.1 Hz, 2H), 6.78 (d, J = 8.2 Hz, 2H), 5.88 (s, 1H), 4.03 (s, 3H), 2.20(s, 3H), 1.20 (s, 9H) ; ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 164.4, 147.8, 145.5, 145.4,142.3, 135.9, 133.2, 129.3, 127.7, 126.8, 125.6, 123.5, 123.3, 122.1, 121.6, 120.2, 118.4, 110.3, 84.4, 58.6, 31.4, 27.8, 21.6; IR (film) 2924, 1852, 1626, 1598, 1169, 1143, 1010, 812 cm^{-1}; HRMS (EI) *m/z*: $[M]^+$ Calcd for $C_{29}H_{28}N_4O_6S$ 560.1730; Found 560.1726.

Ethyl 5-methyl-2-(4-nitrophenyl)-5*H*-pyrazino[2,3-*b*]indole-3-carboxylate (4a): Yield: 59.5 mg (79%); R_f = 0.2 (DCM:Hexane = 2:1); White Yellow solid; Melting point: 190-192 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.43 (d, J = 7.8 Hz, 1H), 8.37-8.34 (m, 2H), 7.89-7.85 (m, 2H), 7.77-7.73 (m, 1H), 7.57 (d, J = 8.3 Hz, 1H), 7.46-7.42 (m, 1H), 4.32 (q, J = 7.1 Hz, 2H), 4.05 (s, 3H), 1.19 (t, J = 7.1 Hz, 3H) ; ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 167.1, 147.8, 145.8, 143.8, 143.6, 143.6, 139.6, 137.1, 130.9, 130.1, 123.6, 122.7, 121.8, 119.1, 110.0, 62.4, 28.1, 13.9; IR (film) 2978, 2936, 1730, 1517, 1345, 1330, 1190, 749 cm^{-1}; HRMS (EI) *m/z*: $[M]^+$ Calcd for $C_{20}H_{16}N_4O_4$ 376.1172; Found 376.1174.

***tert*-Butyl 5-methyl-2-(4-nitrophenyl)-5*H*-pyrazino[2,3-*b*]indole-3-carboxylate (4b):** Yield: 78 mg (96%); R_f = 0.2 (DCM:Hexane = 2:1); Yellow solid; Melting point: 188-190 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.41 (d, J = 7.9 Hz, 1H), 8.37 (d, J = 8.8 Hz, 1H), 7.88 (d, J = 8.8 Hz, 1H), 7.73 (d, J = 7.8 Hz, 1H), 7.57 (d, J = 8.2 Hz, 1H), 7.43 (t, J = 7.5 Hz, 1H), 4.05 (s, 3H), 1.40 (s, 9H) ; ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 166.1, 147.8, 146.3, 143.8, 143.6, 143.3, 141.0, 136.7, 130.6, 130.3, 123.6, 122.6, 121.7, 119.2, 110.0, 83.6, 28.1, 27.8; IR (film) 2977, 2933, 1730, 1519, 1144, 846, 749 cm^{-1}; HRMS (EI) *m/z*: $[M]^+$ Calcd for $C_{22}H_{20}N_4O_4$ 404.1485; Found 404.1484.

Ethyl 5-methyl-2-phenyl-5*H*-pyrazino[2,3-*b*]indole-3-carboxylate (4c): Yield: 26.5 mg (40%); R_f = 0.2 (DCM:Hexane = 2:1); Brown solid; Melting point: 134-136 ^oC; ^1H NMR (400 MHz, $CDCl_3$) δ 8.43 (d, J = 7.8 Hz, 1H), 7.71-7.67 (m, 3H), 7.54-7.44 (m, 4H), 7.41-7.37 (m, 1H), 4.26 (q, J = 7.1 Hz, 2H), 4.01 (s, 3H), 1.09 (s, 3H) ; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 167.9, 146.0, 143.5, 143.3, 139.9, 139.3, 136.8, 130.3, 129.1, 128.5, 122.6, 121.3, 119.4, 109.8, 62.1, 28.0, 13.8; IR (film) 2938, 2792, 1853, 1728, 1631, 1187, 778 cm^{-1}; HRMS (EI) *m/z*: $[M]^+$ Calcd for $C_{20}H_{17}N_3O_2$ 331.1321; Found 331.1319.

***tert*-Butyl 5-methyl-2-phenyl-5*H*-pyrazino[2,3-*b*]indole-3-carboxylate (4d):** Yield: 59.6 mg (83%); R_f = 0.3 (DCM:Hexane = 2:1); Yellow solid; Melting point: 165-167 ^oC; ^1H NMR (400 MHz, $CDCl_3$) δ 8.41 (d, J = 7.8 Hz, 1H), 7.69-7.65 (m, 3H), 7.52-7.45 (m, 4H), 7.39-7.35 (m, 1H), 4.01 (s, 3H), 1.35 (s, 9H) ; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 166.8, 145.9, 143.4, 143.3, 141.0, 139.7, 136.3, 130.0, 129.3, 128.4, 128.3, 122.5, 121.2, 119.4, 109.7, 83.0, 28.0, 27.7; IR (film) 2672, 2641, 1861, 1723, 1641, 1144, 832 cm^{-1}; HRMS (EI) *m/z*: $[M]^+$ Calcd for $C_{22}H_{21}N_3O_2$ 359.1634; Found 359.1636.

***tert*-Butyl 5-methyl-2-(*m*-tolyl)-5*H*-pyrazino[2,3-b]indole-3-carboxylate (4e):** Yield: 48.5 mg (65%); R_f = 0.2 (DCM:Hexane = 2:1); White Yellow solid; Melting point: 148-150 ^oC; ^1H NMR (400 MHz, $CDCl_3$) δ 8.42 (d, J = 7.8 Hz, 1H), 7.67 (t, J = 8.2 Hz, 1H), 7.52-7.46 (m, 3H), 7.37 (t, J = 7.56 Hz, 2H), 7.27-7.25 (m, 1H), 4.01 (s, 3H), 2.44 (s, 3H), 1.36 (s, 9H) ; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 166.9, 146.1, 143.4, 143.3, 141.1, 139.6, 137.9, 136.3, 130.0, 129.1, 128.4, 126.5, 122.5, 121.2, 119.5, 109.7, 82.9, 28.0, 27.7, 21.6; IR (film) 2670, 2629, 1889, 1637, 1141, 780, 687 cm^{-1}; HRMS (EI) *m/z*: $[M]^+$ Calcd for $C_{23}H_{23}N_3O_2$ 373.1790; Found 373.1792.

***tert*-Butyl 2-(2-chlorophenyl)-5-methyl-5*H*-pyrazino[2,3-*b*]indole-3-carboxylate (4f):** Yield: 55.8 mg (71%); R_f = 0.3 (DCM:Hexane = 2:1); Red solid; Melting point: 177-179 ^oC; ^1H NMR

(400 MHz, $CDCl_3$) δ 8.41 (d, J = 7.8 Hz, 1H), 7.70-7.66 (m, 1H), 7.53-7.48 (m, 3H), 7.43-7.35 (m, 3H), 4.04 (s, 3H), 1.29 (s, 9H) ; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 165.2, 144.6, 143.9, 143.5, 140.4, 139.7, 136.6, 133.8, 131.3, 130.4, 129.5, 129.3, 126.9, 122.6, 121.3, 119.1, 109.8, 82.6, 28.0, 27.6; IR (film) 3068, 2977, 1828, 1725, 1445, 1147, 740 cm^{-1}; HRMS (EI) *m/z*: $[M]^+$ Calcd for $C_{22}H_{20}ClN_3O_2$ 393.1244; Found 393.1241.

***tert*-Butyl 2-(4-chlorophenyl)-5-methyl-5*H*-pyrazino[2,3-*b*]indole-3-carboxylate (4g):** Yield: 62.9 mg (80%); R_f = 0.3 (DCM:Hexane = 2:1); Yellow solid; Melting point: 149-151 ^oC; ^1H NMR (400 MHz, $CDCl_3$) δ 8.37 (d, J = 7.8 Hz, 1H), 7.67-7.61 (m, 3H), 7.49-7.45 (m, 3H), 7.38-7.34 (m, 1H), 3.98 (s, 3H), 1.40 (s, 1H) ; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 166.5, 144.4, 143.4, 143.3, 140.8, 138.2, 136.3, 134.5, 130.6, 130.1, 128.5, 122.4, 121.3, 119.2, 109.7, 83.2, 28.0, 27.8; IR (film) 3059, 2977, 1845, 1725, 1450, 1144, 850, 740 cm^{-1}; HRMS (EI) *m/z*: $[M]^+$ Calcd for $C_{22}H_{20}ClN_3O_2$ 393.1244; Found 393.1244.

***tert*-Butyl 2-(4-iodophenyl)-5-methyl-5*H*-pyrazino[2,3-*b*]indole-3-carboxylate (4h):** Yield: 80.5 mg (83%); R_f = 0.3 (DCM:Hexane = 2:1); Pink solid; Melting point: 175-177 ^oC; ^1H NMR (400 MHz, $CDCl_3$) δ 8.35 (d, J = 7.8 Hz, 1H), 7.84-7.81 (m, 2H), 7.65-7.61 (m, 1H), 7.46-7.42 (m, 3H), 7.35 (t, J = 7.5 Hz, 1H), 3.96 (s, 3H), 1.40 (s, 9H) ; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 166.4, 144.5, 143.3, 143.2, 140.7, 139.2, 137.4, 136.3, 131.1, 130.1, 122.3, 121.2, 119.1, 109.6, 94.3, 83.1, 27.9, 27.7; IR (film) 2977, 1844, 1717, 1636, 1143, 785, 603 cm^{-1}; HRMS (EI) *m/z*: $[M]^+$ Calcd for $C_{22}H_{20}IN_3O_2$ 485.0600; Found 485.0603.

***tert*-Butyl 5-methyl-2-(4-(trifluoromethyl)phenyl)-5*H*-pyrazino[2,3-*b*]indole-3-carboxylate (4i):** Yield: 64.1 mg (75%); R_f = 0.2 (DCM:Hexane = 2:1); White Yellow solid; Melting point: 194-196 ^oC; ^1H NMR (400 MHz, $CDCl_3$) δ 8.40 (d, J = 7.7 Hz, 1H), 7.78 (t, J = 8.9 Hz, 4H), 7.72-7.68 (m, 1H), 7.53 (d, J = 8.3 Hz, 1H), 7.40 (t, J = 7.5 Hz, 1H), 4.02 (s, 3H), 1.36 (s, 9H) ; $^{13}C\{^1H\}$

NMR (100 MHz, $CDCl_3$) δ 166.3, 144.4, 143.7, 143.5, 143.5, 140.9, 136.5, 130.4 (q, J = 32.5 Hz), 130.4, 129.7, 124.4 (q, J = 272.2 Hz), 125.3 (q, J = 3.7 Hz), 122.5, 121.5, 119.3, 109.8, 83.3, 28.0, 27.7; IR (film) 1853, 1833, 1640, 1475, 1145, 772, 631 cm^{-1}; HRMS (EI) *m/z*: $[M]^+$ Calcd for $C_{23}H_{20}F_3N_3O_2$ 427.1508; Found 427.1511.

***tert*-Butyl 2-(4-cyanophenyl)-5-methyl-5*H*-pyrazino[2,3-b]indole-3-carboxylate (4j):** Yield: 68.43 mg (89%); R_f = 0.2 (DCM:Hexane = 2:1); Yellow solid; Melting point: 221-223 ^oC; ^1H NMR (400 MHz, $CDCl_3$) δ 8.40 (d, J = 7.8 Hz, 1H), 7.81 (d, J = 1.8 Hz, 4H), 7.74-7.70 (m, 1H), 7.55 (d, J = 8.3 Hz, 1H), 7.42 (t, J = 7.5 Hz, 1H), 4.03 (s, 3H), 1.39 (s, 9H) ; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 166.1, 144.4, 143.7, 143.6, 140.8, 136.6, 132.1, 130.6, 130.1, 122.6, 121.6, 119.2, 119.0, 112.0, 109.9, 83.5, 28.1, 27.8; IR (film) 2933, 2227, 1725, 1397, 1144, 749, 557 cm^{-1}; HRMS (EI) *m/z*: [M]+ Calcd for $C_{23}H_{20}N_4O_2$ 384.1586; Found 384.1589.

Ethyl 5-methyl-2-(naphthalen-2-yl)-5*H*-pyrazino[2,3-*b*]indole-3-carboxylate (4k): Yield: 32 mg (42%); R_f = 0.3 (DCM:Hexane = 2:1); Green solid; Melting point: 109-111 ^oC; ^1H NMR (400 MHz, $CDCl_3$) δ 8.46 (d, J = 7.8 Hz, 1H), 8.17 (s, 1H), 7.97-7.89 (m, 3H), 7.85-7.83 (m, 1H), 7.72-7.68 (m, 1H), 7.54-7.50 (m, 3H), 7.41 (t, J = 7.5 Hz, 1H), 4.25 (q, J = 7.1 Hz, 2H), 4.03 (s, 3H), 1.01 (t, J = 7.1 Hz, 3H) ; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 167.9, 145.7, 143.4, 143.2, 140.0, 136.8, 136.5, 133.3, 133.2, 130.2, 128.4, 128.3, 128.1, 127.7, 126.7, 126.4, 126.3, 122.6, 121.3, 119.3, 109.7, 62.0, 27.9, 13.7; IR (film) 2981, 2936, 1728, 1624, 1473, 1398, 1187, 1143, 746 cm^{-1}; HRMS (EI) *m/z*: $[M]^+$ Calcd for $C_{24}H_{19}N_3O_2$ 381.1477; Found 381.1479.

***tert*-Butyl 5-methyl-2-(naphthalen-2-yl)-5*H*-pyrazino[2,3-*b*]indole-3-carboxylate (4l):** Yield: 71.2 mg (87%); R_f = 0.3 (DCM:Hexane = 2:1); White Yellow solid; Melting point: 191-193 ^oC; ^1H NMR (400 MHz, $CDCl_3$) δ 8.42 (d, J = 7.8 Hz, 1H), 8.13 (s, 1H), 7.97 (d, J = 8.4 Hz, 1H), 7.91-7.87 (m, 3H), 7.66-7.62 (m, 1H), 7.51 (q, J = 3.2 Hz, 2H), 7.47 (d, J = 8.3 Hz, 1H), 7.38-7.34 (m,

1H), 3.99 (s, 3H), 1.27 (s, 9H) ; $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 166.9, 145.7, 143.4, 143.2, 140.0, 136.8, 136.5, 133.3, 133.2, 130.2, 128.4, 128.3, 128.1, 127.7, 126.7, 126.4, 126.3, 122.6, 121.3, 119.3, 109.7, 62.0, 27.9, 13.7; IR (film) 2263, 2629, 1883, 1834, 1642, 1141, 772 cm^{-1}; HRMS (EI) *m/z*: $[M]^+$ Calcd for $C_{26}H_{23}N_3O_2$ 409.1790; Found 409.1787.

***tert*-Butyl 2-(furan-2-yl)-5-methyl-5*H*-pyrazino[2,3-*b*]indole-3-carboxylate (4m):** Yield: 44.7 mg (64%); R_f = 0.2 (DCM:Hexane = 2:1); Brown solid; Melting point: 155-157 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.42 (d, *J* = 7.8 Hz, 1H), 7.69-7.65 (m, 1H), 7.57-7.57 (m, 1H), 7.50 (d, *J* = 8.2 Hz, 1H), 7.41-7.37 (m, 1H), 7.06 (dd, *J* = 1.4 Hz, 1H), 6.59 (q, *J* = 1.7 Hz, 1H), 3.98 (s, 3H), 1.62 (s, 9H) ; $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 166.6, 152.2, 143.2, 143.1, 140.2, 136.0, 134.7, 130.0, 122.5, 121.3, 119.3, 112.1, 109.7, 109.7, 109.7, 83.3, 28.1, 28.0; IR (film) 2978, 2936, 1861, 1725, 1625, 1157, 738 cm^{-1}; HRMS (EI) *m/z*: $[M]^+$ Calcd for $C_{20}H_{19}N_3O_3$ 349.1426; Found 349.1428.

***tert*-Butyl 5-methyl-2-(thiophen-2-yl)-5*H*-pyrazino[2,3-*b*]indole-3-carboxylate (4n):** Yield: 48.2 mg (66%); R_f = 0.3 (DCM:Hexane = 2:1); White Yellow solid; Melting point: 144-146 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.37 (d, *J* = 7.8 Hz, 1H), 7.65-7.61 (m, 1H), 7.48-7.44 (m, 2H), 7.39-7.33 (m, 2H), 7.12 (q, *J* = 2.9 Hz, 1H), 3.95 (s, 3H), 1.52 (s, 9H) ; $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 166.9, 143.2, 143.1, 141.6, 140.9, 138.2, 136.0, 130.0, 127.6, 127.4, 127.4, 122.5, 121.3, 119.2, 109.7, 83.4, 28.0, 27.9; IR (film) 2979, 2936, 1771, 1720, 1645, 1263, 1128, 953 cm^{-1}; HRMS (EI) *m/z*: $[M]^+$ Calcd for $C_{20}H_{19}N_3O_2S$ 365.1198; Found 365.1201.

Butyl 2,5-dimethyl-5*H*-pyrazino[2,3-*b*]indole-3-carboxylate (4o): Yield: 42.2 mg (71%); R_f = 0.3 (DCM:Hexane = 2:1); White Yellow solid; Melting point: 117-119 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.39 (d, *J* = 7.8 Hz, 1H), 7.70-7.66 (m, 1H), 7.50 (d, *J* = 8.3 Hz, 1H), 7.38 (t, *J* = 7.5 Hz, 1H), 4.47 (t, *J* = 6.8 Hz, 1H), 3.97 (s, 1H), 2.97 (s, 1H), 1.89-1.82 (m, 2H), 1.58-1.49 (m, 2H), 1.02 (t, *J* = 7.4 Hz, 3H) ; $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 167.1, 145.9, 143.6, 143.3, 138.2, 137.1,

130.2, 122.4, 121.1, 119.1, 109.7, 65.9, 30.9, 27.9, 23.2, 19.5, 13.9; IR (film) 2960, 2872, 2651, 1646, 1540, 1239, 1020, 749 cm^{-1}; HRMS (EI) *m/z*: $[M]^+$ Calcd for $C_{17}H_{19}N_3O_2$ 297.1477; Found 297.1479.

***tert*-Butyl 2,5-dimethyl-5*H*-pyrazino[2,3-*b*]indole-3-carboxylate (4p):** Yield: 45.2 mg (76%); R_f = 0.3 (DCM:Hexane = 2:1); White Yellow solid; Melting point: 99-101 ^oC; ^1H NMR (400 MHz, $CDCl_3$) δ 8.36 (d, J = 7.8 Hz, 1H),), 7.67-7.63 (m, 1H), 7.47 (d, J = 8.3 Hz, 1H), 7.36 (t, J = 8.0 Hz, 1H), 3.96 (s, 3H), 2.93(s, 3H), 1.70 (s, 9H) ; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 166.3, 144.8, 143.3, 143.2, 139.7, 136.5, 129.9, 122.2, 120.9, 119.0, 109.6, 82.9, 28.4, 27.8, 23.3; IR (film) 2614, 1645, 1636, 1540, 1257, 1105, 686 cm^{-1}; HRMS (EI) *m/z*: $[M]^+$ Calcd for $C_{17}H_{19}N_3O_2$ 297.1477; Found 297.1476.

***tert*-Butyl 5-benzyl-2-(4-nitrophenyl)-5*H*-pyrazino[2,3-*b*]indole-3-carboxylate (4q):** Yield: 55.7 mg (58%); R_f = 0.2 (DCM:Hexane = 2:1); White Yellow solid; Melting point: 193-195 ^oC; ^1H NMR (400 MHz, $CDCl_3$) δ 8.42-8.35 (m, 3H), 7.92-7.89 (m, 2H), 7.62-7.58 (m, 1H), 7.45-7.37 (m, 2H), 7.31-7.25 (m, 5H), 5.75 (s, 2H), 1.42 (s, 9H) ; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 166.0, 147.8, 146.1, 143.7, 143.6, 142.8, 141.1, 136.6, 136.2, 130.6, 130.3, 128.9, 128.0, 127.5, 123.6, 122.6, 121.8, 119.5, 111.0, 83.6, 45.6, 27.8; IR (film) 2930, 2853, 1721, 1640, 1344, 1141, 829 cm^{-1}; HRMS (EI) *m/z*: $[M]^+$ Calcd for $C_{28}H_{24}N_4O_4$ 480.1798; Found 480.1801.

***tert*-Butyl 2-(4-nitrophenyl)-5-phenyl-5*H*-pyrazino[2,3-*b*]indole-3-carboxylate (4r):** Yield: 60.6 mg (65%); R_f = 0.2 (DCM:Hexane = 2:1); White Yellow solid; Melting point: 224-226 ^oC; ^1H NMR (400 MHz, $CDCl_3$) δ 8.46 (d, J = 7.8 Hz, 1H),), 8.38-8.36 (m, 2H), 7.92-7.89 (m, 2H), 7.71-7.62 (m, 6H), 7.53-7.44 (m, 2H), 1.36 (s, 9H) ; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 165.7, 147.9, 146.0, 144.3, 143.7, 143.4, 141.4, 137.0, 135.1, 130.7, 130.3, 129.9, 128.3, 127.1, 123.6, 122.5, 122.5, 119.6, 111.4, 83.6, 27.8; IR (film) 1860, 1775, 1640, 1518, 1344, 1139, 668 cm^{-1}; HRMS (EI) *m/z*:

$[M]^+$ Calcd for $C_{27}H_{22}N_4O_4$ 466.1641; Found 466.1644.

***tert*-Butyl 5,7-dimethyl-2-(4-nitrophenyl)-5*H*-pyrazino[2,3-*b*]indole-3-carboxylate (4s):** Yield: 75.3 mg (90%); R_f = 0.3 DCM:Hexane = 2:1); Yellow solid; Melting point: 189-191 ^oC; ^1H NMR (400 MHz, $CDCl_3$) δ 8.35 (d, J = 8.7 Hz, 2H),), 8.26 (d, J = 8.0 Hz, 1H), 7.87 (d, J = 8.7 Hz, 2H), 7.33 (s, 1H), 7.23 (d, J = 8.0 Hz, 1H), 3.99 (s, 3H), 2.62 (s, 3H), 1.40 (s, 9H) ; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 166.2, 147.7, 146.5, 144.2, 143.8, 143.2, 141.8, 140.2, 136.9, 130.3, 123.5, 123.3, 122.3, 116.8, 110.1, 83.5, 28.0, 27.8, 22.8; IR (film) 2982, 1720, 1632, 1517, 1343, 1152, 806 cm^{-1}; HRMS (EI) *m/z*: $[M]^+$ M^+ Calcd for $C_{23}H_{22}N_4O_4$ 418.1641; Found 418.1638.

***tert*-Butyl 5,8-dimethyl-2-(4-nitrophenyl)-5*H*-pyrazino[2,3-*b*]indole-3-carboxylate (4t):** Yield: 80.3 mg (96%); R_f = 0.3 (DCM:Hexane = 2:1); Yellow solid; Melting point: 224-226 ^oC; ^1H NMR (400 MHz, $CDCl_3$) δ 8.37-8.34 (m, 2H), 8.18 (s, 1H), 7.89-7.85 (m, 2H), 7.52 (dd, J = 3.3 Hz, 1H), 7.42 (d, J = 8.4 Hz, 1H), 3.99 (s, 3H), 2.55 (s, 3H),), 1.41 (s, 9H) ; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 166.1, 147.7, 146.4, 143.8, 143.0, 141.9, 140.6, 136.5, 132.0, 131.3, 130.3, 123.5, 122.2, 119.2, 109.6, 83.5, 28.0, 27.8, 21.4; IR (film) 2979, 2940, 1909, 1725, 1636, 1347, 1138, 776 cm^{-1}; HRMS (EI) *m/z*: $[M]^+$ Calcd for $C_{23}H_{22}N_4O_4$ 418.1641; Found 418.1643.

***tert*-Butyl 7-methoxy-5-methyl-2-(4-nitrophenyl)-5*H*-pyrazino[2,3-*b*]indole-3-carboxylate (4u):**

Yield: 60.8 mg (70%); R_f = 0.2 (DCM:Hexane = 2:1); Orange solid; Melting point: 269-271 ^oC; ^1H NMR (400 MHz, $CDCl_3$) δ 8.37-8.25 (m, 2H), 8.26 (d, J = 8.7 Hz, 1H), 7.86-7.83 (m, 2H), 7.00 (dd, J = 3.6 Hz, 1H), 6.94 (d, J = 2.1 Hz, 1H), 3.99 (d, J = 3.8 Hz, 6H), 1.39 (s, 9H) ; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 166.2, 162.8, 147.7, 146.7, 145.8, 144.0, 143.5, 139.0, 137.1, 130.3, 123.9, 123.5, 112.7, 110.6, 93.9, 83.4, 55.9, 28.1, 27.8; IR (film) 2616, 1889, 1636, 1343, 1217, 1149, 780 cm^{-1}; HRMS (EI) *m/z*: $[M]^+$ Calcd for $C_{23}H_{22}N_4O_5$ 434.1590; Found 434.1593.

***tert*-Butyl 7-fluoro-5-methyl-2-(4-nitrophenyl)-5*H*-pyrazino[2,3-*b*]indole-3-carboxylate (4v):**

Yield: 65.9 mg (78%); R_f = 0.4 (DCM:Hexane = 2:1); White Brown solid; Melting point: 194-196 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.37-8.33 (m, 3H), 7.87 (d, J = 8.6 Hz, 2H), 7.21 (d, J = 9.1 Hz, 1H), 7.14 (t, J = 8.9 Hz, 1H), 4.00 (s, 3H), 1.40 (s, 9H) ; ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 165.9, 163.5, 147.8, 146.1, 144.8(d, J = 12.5 Hz), 144.2, 143.8, 140.5, 136.3, 130.3, 124.3(d, J = 10.9 Hz), 123.6, 115.6, 110.3(d, J = 24.6 Hz), 97.3(d, J = 27.1 Hz), 83.7, 28.3, 27.8; IR (film) 2979, 2938, 1868, 1634, 1343, 1145, 832, 609 cm^{-1}; HRMS (EI) *m/z*: $[M]^+$ Calcd for $C_{22}H_{19}FN_4O_4$ 422.1390; Found 422.1389.

***tert*-Butyl 7-chloro-5-methyl-2-(4-nitrophenyl)-5*H*-pyrazino[2,3-*b*]indole-3-carboxylate (4w):** Yield: 83.2 mg (95%); R_f = 0.3 (DCM:Hexane = 2:1); Green solid; Melting point: 194-196 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.38-8.34 (m, 2H), 8.27 (d, J = 8.4 Hz, 1H), 7.89-7.86 (m, 2H), 7.52 (d, J = 1.4 Hz, 1H), 7.36 (dd, J = 3.3 Hz, 1H), 3.99 (s, 3H), 1.41 (s, 9H) ; ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 165.8, 147.8, 145.9, 143.9, 143.9, 143.8, 141.1, 136.6, 135.9, 130.2, 123.6, 123.4, 122.4, 117.6, 110.3, 83.8, 28.2, 27.8; IR (film) 2685, 2590, 1637, 1345, 1153, 778, 673 cm^{-1}; HRMS (EI) *m/z*: $[M]^+$ Calcd for $C_{22}H_{19}ClN_4O_4$ 438.1095; Found 438.1093.

***tert*-Butyl 8-bromo-5-methyl-2-(4-nitrophenyl)-5*H*-pyrazino[2,3-*b*]indole-3-carboxylate (4x):** Yield: 93.5 mg (97%); R_f = 0.3 (DCM:Hexane = 2:1); White Green solid; Melting point: 269-271 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.52 (d, J = 1.6 Hz, 1H), 8.37-8.35 (m, 2H), 7.88-7.86 (m, 2H), 7.79 (dd, J = 3.6 Hz, 1H), 7.44 (d, J = 8.7 Hz, 1H), 4.01 (s, 3H), 1.41 (s, 9H) ; ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 165.9, 147.9, 145.8, 143.7, 143.7, 142.0, 141.8, 135.3, 133.2, 130.2, 125.2, 123.6, 120.7, 114.7, 111.5, 83.9, 28.2, 27.8; IR (film) 2980, 1967, 1718, 1646, 1345, 1150, 783, 578 cm^{-1}; HRMS (EI) *m/z*: $[M]^+$ Calcd for $C_{22}H_{19}BrN_4O_4$ 482.0590; Found 482.0591.

5-Methyl-2-phenyl-5*H*-pyrazino[2,3-*b*]indole (5a): Yield: 39.2 mg (75%); R_f = 0.3 (DCM:Hexane = 2:1); Yellow solid; Melting point: 152-154 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.84 (s, 1H), 8.43

(d, J = 7.8 Hz, 1H), 8.13-8.10 (m, 2H), 7.65-7.61 (m, 1H), 7.55-7.36 (m, 5H), 3.96 (s, 3H) ; $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 145.4, 144.8, 142.2, 138.3, 137.5, 135.7, 129.2, 129.1, 128.5, 127.0, 122.1, 120.9, 120.0, 109.5, 27.7; IR (film) 3058, 2932, 2884, 1805, 1623, 1186, 1143, 739 cm^{-1}; HRMS (EI) *m/z*: $[M]^+$ Calcd for $C_{17}H_{13}N_3$ 259.1109; Found 259.1107.

2-(4-Methoxyphenyl)-5-methyl-5*H*-pyrazino[2,3-*b*]indole (5b): Yield: 47.4 mg (82%); R_f = 0.2 (DCM:Hexane = 2:1); Brown solid; Melting point: 111-113 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.75 (s, 1H), 8.38 (d, J = 7.8 Hz, 1H), 8.03 (d, J = 8.6 Hz, 2H), 7.58 (t, J = 7.7 Hz, 1H), 7.41 (d, J = 8.2 Hz, 1H), 7.33 (t, J = 7.5 Hz, 1H), 7.03 (d, J = 8.6 Hz, 2H), 3.86 (d, J = 14.9 Hz, 6H) ; $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 160.1, 145.2, 144.3, 142.0, 137.0, 135.4, 130.9, 128.9, 128.1, 121.9, 120.7, 119.9, 114.4, 109.4, 55.5, 27.6; IR (film) 2965, 2834, 1909, 1646, 1248, 1185, 788 cm^{-1}; HRMS (EI) *m/z*: $[M]^+$ Calcd for $C_{18}H_{15}N_3O$ 289.1215; Found 289.1214.

2-(4-Fluorophenyl)-5-methyl-5*H*-pyrazino[2,3-*b*]indole (5c): Yield: 49.9 mg (90%); R_f = 0.2 (DCM:Hexane = 2:1); Gray solid; Melting point: 147-149 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.73 (s, 1H), 8.37 (d, J = 7.8 Hz, 1H), 8.06-8.02 (m, 2H), 7.62-7.58 (m, 1H), 7.41 (d, J = 8.2 Hz, 1H), 7.34 (t, J = 7.9 Hz, 1H), 7.20-7.15 (m, 2H), 3.89 (s, 3H) ; $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 164.5, 162.1, 144.5(d, J = 28.0 Hz), 142.1, 137.1, 135.5, 134.4(d, J = 3.0 Hz), 129.2, 128.6(d, J = 8.1 Hz), 122.0, 120.9, 119.8, 115.9(d, J = 21.7 Hz), 109.5, 27.6; IR (film) 1869, 1845, 1642, 1509, 1220, 1142, 830 cm^{-1}; HRMS (EI) *m/z*: $[M]^+$ Calcd for $C_{17}H_{12}FN_3$ 277.1015; Found 277.1017.

5-Methyl-2,3-diphenyl-5*H*-pyrazino[2,3-*b*]indole (5d): Yield: 53.7 mg (80%); R_f = 0.5 (DCM:Hexane = 2:1); White solid; Melting point: 190-192 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.43 (d, J = 7.8 Hz, 1H), 7.66-7.62 (m, 1H), 7.54-7.49 (m, 5H), 7.37 (t, J = 7.5 Hz, 1H), 7.32-7.30 (m, 6H), 4.01 (s, 3H) ; $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 148.5, 145.6, 144.5, 142.5, 140.5, 140.2, 134.3, 130.4, 130.4, 129.0, 128.3, 128.2, 127.7, 122.1, 120.9, 119.9, 109.5, 27.7; IR (film) 2718,

2673, 2359, 2341, 1643, 1329, 668 cm^{-1}; HRMS (EI) *m/z*: $[M]^+$ Calcd for $C_{23}H_{17}N_3$ 335.1422; Found 335.1419.

2-(4-Methoxyphenyl)-5-methyl-3-phenyl-5*H*-pyrazino[2,3-*b*]indole (5e): Yield: 53.7 mg (80%); R_f = 0.5 (DCM:Hexane = 2:1); White Yellow solid; Melting point: 192-194 ^oC; ^1H NMR (400 MHz, $CDCl_3$) δ 8.42 (d, *J* = 7.7 Hz, 1H), 7.62 (t, *J* = 7.62 Hz, 1H), 7.56-7.53 (m, 2H), 7.48 (d, *J* = 8.2 Hz, 1H), 7.43 (d, *J* = 8.8 Hz, 2H), 7.37-7.31(m, 4H), 6.85(d, *J* = 8.9 Hz, 2H), 3.98 (s, 3H) ; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 159.4, 148.2, 145.4, 144.3, 142.5, 140.4, 134.2, 133.0, 131.6, 130.4, 128.9, 128.2, 128.1, 122.0, 120.8, 119.9, 113.8, 109.5, 55.4, 27.7; IR (film) 3058, 2933, 2835, 1844, 1609, 1248, 836, 746 cm^{-1}; HRMS (EI) *m/z*: $[M]^+$ Calcd for $C_{24}H_{19}N_3O$ 365.1528; Found 365.1525.

2,3-Bis(4-fluorophenyl)-5-methyl-5*H*-pyrazino[2,3-*b*]indole (5f): Yield: 63.1 mg (85%); R_f = 0.5 (DCM:Hexane = 2:1); White Yellow solid; Melting point: 194-196 ^oC; ^1H NMR (400 MHz, $CDCl_3$) δ 8.4 (d, *J* = 7.8 Hz, 1H), 7.66-7.62 (m, 1H), 7.51-7.44 (m, 5H), 7.37 (t, *J* = 7.9 Hz, 1H), 7.05-7.00 (m, 4H), 3.98 (s, 3H) ; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 164.0(d, *J* = 25.9 Hz), 161.5(d, *J* = 24.9 Hz), 147.2, 144.4(d, *J* = 11.2 Hz), 142.6, 136.4(d, *J* = 3.2 Hz), 136.1(d, *J* = 3.3 Hz), 134.4, 132.2, 132.1(d, *J* = 2.6 Hz), 132.0, 129.2, 122.1, 121.1, 119.7, 115.5(d, *J* = 3.4 Hz), 115.3(d, *J* = 3.4 Hz), 109.6, 27.7; IR (film) 2685, 1868, 1637, 1328, 1223, 1139, 838, 607 cm^{-1}; HRMS (EI) *m/z*: $[M]^+$ Calcd for $C_{23}H_{15}F_2N_3$ 371.1234; Found 371.1232.

5-Methyl-2-phenyl-3-(*p*-tolyl)-5*H*-pyrazino[2,3-*b*]indole (6a): Yield: 53.7 mg (80%); R_f = 0.6 (DCM:Hexane = 2:1); White Yellow solid; Melting point: 164-166 ^oC; ^1H NMR (400 MHz, $CDCl_3$) δ 8.42 (d, *J* = 7.7 Hz, 1H), 7.62 (t, *J* = 7.7 Hz, 1H), 7.53-7.47 (m, 3H), 7.42 (d, *J* = 8.1 Hz, 2H), 7.38-7.29 (m, 4H), 7.12 (d, *J* = 7.9 Hz, 2H), 3.99 (s, 3H), 2.35 (s, 3H) ; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 148.5, 145.5, 144.5, 142.4, 140.7, 138.1, 137.3, 134.0, 130.4, 130.3, 129.0, 128.8, 128.3, 127.6, 122.0, 120.8, 119.9, 109.5, 27.7, 21.4; IR (film) 3082, 2921, 1879, 1393, 1330, 1140, 699cm^-

^{1}; HRMS (EI) *m/z*: $[M]^+$ Calcd for $C_{24}H_{19}N_3$ 349.1579; Found 349.1576.

5-Methyl-3-phenyl-2-(*p*-tolyl)-5*H*-pyrazino[2,3-*b*]indole (6b): Yield: 53.7 mg (80%); R_f = 0.7 (DCM:Hexane = 2:1); White Yellow solid; Melting point: 225-227 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.41 (d, *J* = 7.6 Hz, 1H), 7.61 (t, *J* = 7.7 Hz, 1H), 7.55-7.53 (m, 2H), 7.47 (d, *J* = 8.2 Hz, 1H), 7.40-7.30 (m, 6H), 7.11 (d, *J* = 7.8 Hz, 2H), 3.97 (s, 3H), 2.35 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 148.4, 145.7, 144.4, 142.5, 140.4, 137.6, 137.4, 134.2, 130.4, 130.2, 129.0, 128.9, 128.2, 128.1, 122.1, 120.8, 119.9, 109.4, 27.7, 21.4; IR (film) 1909, 1637, 1473, 1330, 1178, 926, 747 cm^{-1}; HRMS (EI) *m/z*: $[M]^+$ Calcd for $C_{24}H_{19}N_3$ 349.1579; Found 349.1577.

3-(4-Fluorophenyl)-5-methyl-2-phenyl-5*H*-pyrazino[2,3-*b*]indole (6c): Yield: 53.7 mg (80%); R_f = 0.5 (DCM:Hexane = 2:1); White solid; Melting point: 174-176 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.42 (d, *J* = 7.7 Hz, 1H), 7.65-7.61 (m, 1H), 7.52-7.47 (m, 5H), 7.39-7.31 (m, 4H), 7.02-6.98 (m, 2H), 3.99 (s, 3H) ; ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 162.9 (d, *J* = 248.2 Hz), 147.3, 145.5, 144.4, 142.6, 140.4, 136.2 (d, *J* = 3.2 Hz), 134.4, 132.2 (d, *J* = 8.2 Hz), 130.4, 129.1, 128.4, 127.8, 122.1, 121.0, 115.2 (d, *J* = 21.7 Hz), 109.5, 27.7; IR (film) 2931, 1941, 1828, 1623, 1509, 1393, 1139, 747 cm^{-1}; HRMS (EI) *m/z*: $[M]^+$ Calcd for $C_{23}H_{16}F_1N_3$ 353.1328; Found 353.1330.

2-(4-Fluorophenyl)-5-methyl-3-phenyl-5*H*-pyrazino[2,3-*b*]indole (6d): Yield: 53.7 mg (80%); R_f = 0.5 (DCM:Hexane = 2:1); White solid; Melting point: 192-194 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.42 (d, *J* = 7.8 Hz, 1H), 7.66-7.62 (m, 1H), 7.52-7.45 (m, 5H), 7.40-7.36 (m, 1H), 7.35-7.32 (m, 3H), 7.03-6.98 (m, 2H), 4.00 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 162.6 (d, *J* = 246.9 Hz), 148.4, 144.5, 142.6, 140.1, 136.6 (d, *J* = 3.4 Hz), 134.3, 132.2, 132.1, 130.4, 129.1, 128.3, 128.3, 122.1, 121.0, 119.8, 115.3 (d, *J* = 21.4 Hz), 109.6, 27.8; IR (film) 1848, 1640, 1509, 1329, 1221, 1139, 647 cm^{-1}; HRMS (EI) *m/z*: $[M]^+$ Calcd for $C_{23}H_{16}F_1N_3$ 353.1328; Found 353.1326.

3-(4-bromophenyl)-5-methyl-2-phenyl-5*H*-pyrazino[2,3-b]indole (6e): Yield: 66.3 mg (80%); R_f

= 0.5 (DCM:Hexane = 2:1); White Yellow solid; Melting point: 194-196 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.42 (d, J = 7.8 Hz, 1H), 7.67-7.63 (m, 1H), 7.52-7.32 (m, 12H), 4.00 (s, 3H) ; $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 147.0, 145.4, 144.4, 142.6, 140.2, 139.1, 134.5, 132.0, 131.4, 130.3, 129.2, 128.5, 127.9, 122.7, 122.1, 121.0, 119.8, 109.5, 27.7; IR (film) 2932, 1774, 1472, 1328, 1140, 1009, 544 cm^{-1}; HRMS (EI) *m/z*: $[M]^+$ Calcd for $C_{23}H_{16}{}^{79}BrN_3$ 413.0528, $C_{23}H_{16}{}^{81}BrN_3$ 415.0508; Found 413.0526, 415.0531.

2-(4-bromophenyl)-5-methyl-3-phenyl-5*H*-pyrazino[2,3-b]indole (6f): Yield: 74 mg (89%); R_f = 0.5 (DCM:Hexane = 2:1); White Yellow solid; Melting point: 237-239 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.40 (d, J = 7.8 Hz, 1H), 7.65-7.61 (m, 1H), 7.52-7.48 (m, 3H), 7.44-7.36 (m, 5H), 7.34-7.33 (m, 3H), 3.98 (s, 3H) ; $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 148.4, 144.5, 144.2, 142.6, 139.9, 139.5, 134.4, 132.0, 131.4, 130.4, 129.2, 128.4, 122.1, 122.1, 121.0, 119.8, 109.6, 27.8; IR (film) 2932, 1694, 1472, 1397, 1139, 705, 549 cm^{-1}; HRMS (EI) *m/z*: $[M]^+$ Calcd for $C_{23}H_{16}{}^{79}BrN_3$ 413.0528, $C_{23}H_{16}{}^{81}BrN_3$ 415.0508; Found 413.0529, 415.0528.

Applications of indolopyrazine to C–H activation

Synthetic procedure of 4-methyl-*N*-(2-(5-methyl-5*H*-pyrazino[2,3-b]indol-2-yl)phenyl)benzenesulfonamide

To a test tube were added 5-methyl-2-phenyl-5*H*-pyrazino[2,3-b]indole **5a** (77.8 mg, 0.3 mmol), tosyl azide (39.5 mg, 0.2 mmol), $[Cp^*IrCl_2]_2$ (9.6 mg, 0.012 mmol), and $AgPF_6$ (12.14 mg, 0.048 mmol) in DCE (1.0 mL). The resulting mixture was stirred at 80 ^{o}C for 1 h under N_2. After Celite filtration and evaporation of the solvent in vacuo, the crude product was purified by column chromatography on silica gel using DCM:Hexane = 2:1

4-Methyl-*N*-(2-(5-methyl-5*H*-pyrazino[2,3-*b*]indol-2-yl)phenyl)benzenesulfonamide (7a): Yield: 39.2 mg (75%); R_f = 0.2 (DCM:Hexane = 2:1); Yellow solid; Melting point: 198-200 ^{o}C; ^{1}H

NMR (400 MHz, $CDCl_3$) δ 11.58 (s, 2H), 8.43 (d, J = 7.6 Hz, 1H), 7.78(d, J = 8.1 Hz, 1H), 7.71(t, J = 7.7 Hz, 1H), 7.64(d, J = 7.8 Hz, 1H), 7.55(d, J = 8.3 Hz, 1H), 7.45(t, J = 7.5 Hz, 1H), 7.39(t, J = 7.7 Hz, 1H), 7.26-7.21 (m, 2H), 6.78(d, J = 8.1 Hz, 2H), 3.98 (s, 3H), 2.23 (s, 3H) ; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 144.0, 143.3, 142.2, 139.1, 136.5, 136.3, 132.8, 129.9, 129.8, 129.0, 128.3, 127.0, 126.8, 126.6, 125.4, 124.5, 122.1, 121.7, 118.9, 109.8, 27.7, 21.5; IR (film) 3063, 2930, 1861, 1624, 1475, 1338, 1159, 738 cm^{-1}; HRMS (EI) *m/z*: $[M]^+$ Calcd for $C_{24}H_{20}N_4O_2S$ 428.1307; Found 428.1308.

Synthetic procedure of (*E*)-ethyl 3-(2-(5-methyl-5*H*-pyrazino[2,3-*b*]indol-2-yl)phenyl) acrylate

To a test tube were added 5-methyl-2-phenyl-5*H*-pyrazino[2,3-b]indole **5a** (77.8 mg, 0.3 mmol), ethyl acrylate (20.0 mg, 0.2 mmol), $[Cp^*RhCl_2]_2$ (3.1 mg, 0.005 mmol), and $Cu(OAc)_2$ (36.33 mg, 02 mmol) in DCE (2.0 mL). The resulting mixture was stirred at 90 ^oC for 12 h under N_2. After Celite filtration and evaporation of the solvent in vacuo, the crude product was purified by column chromatography on silica gel using DCM:Hexane = 2:1

(*E*)-Ethyl 3-(2-(5-methyl-5*H*-pyrazino[2,3-*b*]indol-2-yl)phenyl)acrylate (7b): Yield: 39.2 mg (75%); R_f = 0.4 (DCM:Hexane = 2:1); Orange solid; Melting point: 139-141 ^oC; ^1H NMR (400 MHz, $CDCl_3$) δ 8.52 (s, 1H), 8.40 (d, J = 7.8 Hz, 1H), 7.97 (d, J = 15.9 Hz, 1H), 7.76 (d, J = 7.8 Hz, 1H), 7.72 (d, J = 7.6 Hz, 1H), 7.64 (t, J = 7.7 Hz, 1H), 7.55-7.44 (m, 3H), 7.37 (t, J = 7.53 Hz, 1H), 6.47 (d, J = 15.9 Hz, 1H), 4.19 (q, J = 7.1 Hz, 2H), 3.98 (s, 3H), 1.24 (t, J = 7.1 Hz, 3H) ; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 166.8, 145.3, 144.5, 143.7, 142.3, 140.5, 139.1, 135.6, 133.7, 131.0, 130.1, 129.4, 128.8, 127.4, 122.1, 121.1, 120.0, 119.8, 109.6, 27.7, 14.4; IR (film) 2981, 2933, 2850, 1861, 1708, 1630, 1179, 742 cm^{-1}; HRMS (EI) *m/z*: $[M]^+$ Calcd for $C_{22}H_{19}N_3O_2$ 357.1477; Found 357.1479.

Synthetic procedure of *N*-(2-(5-methyl-5*H*-pyrazino[2,3-*b*]indol-2-yl)phenyl) benzamide

To a test tube were added 5-methyl-2-phenyl-5*H*-pyrazino[2,3-*b*]indole **5a** (51.8 mg, 0.2 mmol), dioxazolone (49.0 mg, 0.3 mmol), $[Cp^*RhCl_2]_2$ (4.9 mg, 0.008 mmol), and $AgSbF_6$ (11 mg, 0.032 mmol), in DCE (1.0 mL). The resulting mixture was stirred at 80 ^oC for 12 h under N_2. After Celite filtration and evaporation of the solvent in vacuo, the crude product was purified by column chromatography on silica gel using DCM:Hexane = 2:1.

***N*-(2-(5-methyl-5*H*-pyrazino[2,3-*b*]indol-2-yl)phenyl)benzamide (7c):** Yield: 39.2 mg (75%); R_f = 0.3 (DCM:Hexane = 2:1); White Green solid; Melting point: 234-236 ^oC; ^1H NMR (400 MHz, $CDCl_3$) δ 12.56 (s, 1H), 8.86 (s, 1H), 8.79 (d, J = 8.3 Hz, 1H), 8.33 (d, J = 7.8 Hz, 2H), 8.10 (d, J = 7.4 Hz, 1H), 7.77 (d, J = 7.8 Hz, 1H), 7.72 (t, J = 7.8 Hz, 1H), 7.58-7.26 (m, 5H), 7.29 (d, J = 7.7 Hz, 1H), 4.00 (s, 3H) ; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 165.5, 145.4, 144.1, 142.4, 140.3, 137.4, 135.6, 132.9, 131.7, 129.8, 129.8, 129.1, 128.8, 127.5, 125.4, 124.2, 122.4, 121.9, 121.2, 118.9, 110.1, 27.8; IR (film) 2850, 1867, 1771, 1646, 1473, 1191, 697 cm^{-1}; HRMS (EI) *m/z*: $[M]^+$ Calcd for $C_{24}H_{18}N_4O$ 378.1481; Found 378.1478.

ASSOCIATED CONTENT

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Notes

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Supporting Information

X-ray crystallography data (**4b**, **6e**, and **6f**), and copies of NMR spectra for all products (PDF). This material is available free of charge *via* the Internet at http://pubs.acs.org.

REFERENCES

1. (a) Hirata, K.; Araya, J.; Nakaike, S.; Kitamura, K.; Ishida, T. *Chem. Pharm. Bull.* **2001**, *49*, 44. (b) Deady, L. W.; Kaye, a J.; Finlay, G. J.; Baguley, B. C.; a Denny, W. *J. Med. Chem.* **1997**, *40*, 2040.

2. (a) Manna, K.; Agrawal, Y. K. *Bioorg. Med. Chem. Lett*. **2009**, *19*, 2688. (b) Pai, N. R.; Pusalkar, D. A.; *J. Chem. Pharm. Res.* **2010**, *2*, 485. (c) Avula, S.; Komsani, J. R.; Koppireddi S.; Yadla, R.; Kanugula, A. k.; Kotamraju, S. *Med. Chem. Res.* **2013**, *22*, 3712. (d) Dandia, A.; Parewa, V.; Maheshwari, S.; Rathore, K. S. *J. Mol. Catal. A: Chem.* **2014**, *394*, 244. (e) Edayadulla, N.; Lee. Y. R. *RSC Adv*. **2014**, *4*, 11459

3. Mannes, P. Z.; Onyango, E. O.; Gribble, G. W. *J. Org. Chem.* **2016**, *81*, 12478.

4. (a) Ackermann, L.; Althammer, A.; Mayer, P. *Synthesis* **2009**, 3493. (b) Ackermann, L.; Althammer, A. *Angew. Chem., Int. Ed.* **2007**, *46*, 1627. (c) Hung, T. Q. Hoang, D. H.; Thang, N. N. Dang, T. T.; Ayub, K.; Villinger, A.; Friedrich, A.; Lochbrunner, S. Flechsig, G-U.; Langer, P. *Org. Biomol. Chem.* **2014**, *12*, 6151.

5. Hung, T. Q.; Dang, T. T.; Villinger, A.; Van Sung, T.; Langer, P. *Org. Biomol. Chem.* **2012**, ***10***, 9041.

6. (a) Palacios, F.; Retana, A. M. O. D.; Marigorta, E. M. D.; Santos, J. M. D. L. *Eur. J. Org. Chem.* **2001**, 2401. (b) Loy, N. S. Y.; Singh, A.; Xu, X.; Park, C.-M. *Angew. Chem. Int. Ed.* **2013**, *52*, 2212. (c) Jiang, Y.; Chen, W. C.; Park, C.-M. *J. Am. Chem. Soc.* **2012**, *134*, 4104. (d) Jiang, Y.; Park, C.-M.; Loh, T. -P. *Org. Lett.* **2014**, *16*, 3432. (e) Ryu, T.; Baek, Y.; Lee, P. H. *J. Org. Chem*. **2015**, *80*, 2376. (f) Loy, N. S. Y.; Kim, S.; Park, C.-M. *Org. Lett*. **2015**, *17*, 395.

7. For selected examples using 3-diazoindolin-2-imines, see: (a) Xing, Y.; Sheng, G.; Wang, J.; Lu, P.; Wang, Y. *Org. Lett.* **2014**, *16*, 1244. (b) Du, Z.; Xing, Y.; Lu, P.; Wang, Y. *Org. Lett.* **2015**, *17*, 1192. (c) Lang, B.; Zhu, H.; Wang, C.; Lu, P.; Wang, Y. *Org. Lett.* **2017**, *19*, 1630. (d) Wang, L.; Wu, Y.; Liu, Y.; Yang, H.; Liu, X.; Wang, J.; Li, X.; Jiang, J. *Org. Lett.* **2017**, *19*, 782. (e) Sheng, G.; Huang, K.; Chi, Z.; Ding, H.; Xing, Y.; Lu, P.; Wang, Y. *Org. Lett.* **2014**, *16*, 5096. (f) Wang, C.; Zhang, H.; Lang, B.; Ren, A.; Lu, P.; Wang, Y. *Org. Lett.* **2015**, *17*, 4412. (g) Ding, H.; Peng, Z.; Wang, J. Lu, P.; Wang, Y. *Org. Biomol. Chem.* **2016,** *14*, 7114. (h) Ko, G. H.; Son, J.-Y.; Kim, H.; Maeng, C.; Baek, Y.; Seo, B.; Um, K.; Lee, P. H. *Adv. Synth. Catal.* **2017**, *359*, 3362. (i) Kim, S.; Kim, H.; Um, K.; Lee, P. H. *J. Org. Chem.* **2017**, *82*, 9808.

8. (a) Lee, E.; Ryu, T.; Shin, E.; Son, J.-Y.; Choi, W.; Lee, P. H. *Org. Lett.* **2015**, *17*, 2470. (b) Seo, B.; Kim, Y. G.; Lee, P. H. *Org. Lett.* **2016**, *18*, 5050. (c) Son, J.-Y.; Kim, J.; Han, S. H.; Kim, S. H.; Lee, P. H. *Org. Lett.* **2016**, *18*, 5408. (d) Kim, J. E.; Lee, J.; Yun, H.; Baek, Y.; Lee, P. H. *J. Org. Chem.* **2017**, *82*, 1437. (e) Seo, B.; Kim, H.; Kim, Y. G.; Baek, Y.; Um, K.; Lee, P. H. *J. Org. Chem.* **2017**, *82*, 10574. (f) Jeon, W. H.; Son, J.-Y.; Kim, J. E.; Lee, P. H. *Org. Lett.* **2016**, *18*, 3498. (g) Kim, H.; Kim, S.; Kim, J.; Son, J.-Y.; Baek, Y.; Um, K.; Lee, P. H. *Org. Lett.* **2017**, *19*, 5677. (h) Son, J.-Y.; Kim, S.; Jeon, W. H.; Lee, P. H. *Org. Lett.* **2015**, *17*, 2518. (i) Park, S.; Kim, H.; Son, J.-Y.; Um, K.; Lee, S.; Baek, Y.; Seo, B.; Lee, P. H. *J. Org. Chem.* **2017**, *82*, 10209.

9. (a) Majumdar, K. C., Chattopadhyay, S. K., Eds. *Heterocycles in Natural Product Synthesis*; Wiley-VCH: Weinheim, 2011. (b) Katritzky, A. R., Ed. *Comprehensive Heterocyclic Chemistry III*; Elsevier: Amsterdam, NY, 2008.

10. During the preparation of this manuscript, the synthetic methods of indolopyrazine were reported independently by two groups: (a) Ding, H.; Wang, Z.; Bai, S.; Lu, P.; Wang, Y. *Org. Lett.* **2017**, *19*, 6514. (b) Ruvinskaya, J. O.; Rostovskii, N. V.; Filippov, I. P.; Khlebnikov, A. F.; Novikov, M. S. *Org. Biomol. Chem.* **2018**, *16*, 38.

11. (a) Kim, J. Y.; Park, S. H.; Ryu, J.; Cho, S. H.; Kim, S. H.; Chang, S. *J. Am. Chem. Soc.* **2012**,

134, 9110. (b) Park, Y.; Jee, S.; Kim, J. G.; Chang, S. *Org*. *Process Res*. *Dev*. **2015**, *19*, 1024.

12. Shi, J.; Yan, Y.; Li, Q.; Xu, H. E.; Yi, W. *Chem*. *Commun*. **2014**, *50*, 6483.

13. Park, Y.; Park, K. T.; Kim, J. G.; Chang, S. *J*. *Am*. *Chem*. *Soc*. **2015**, *137*, 453.

14. (a) Taber , D. F.; Tian, W. *J*. *Am*. *Chem*. *Soc*. **2006**, *128*, 1058; (b) Chiba, S.; Hattori,G.; Narasaka, K. *Chem*. *Lett*. **2007**, *36*, 52.

15. Loy, N. S. Y.; Singh, A.; Xu, X.; Park, C.-M. *Angew*. *Chem*., *Int*. *Ed*. **2013**, *52*, 2212.

16. (a) Gu, P.; Su, Y.; Wu, X.-P.; Sun, J.; Liu, W.; Xue, P.; Li, R. *Org*. *Lett*. **2012**, *14*, 2246; (b) Hortmann, A. G.; Robertson, D. A.; Gillard, B. K. *J*. *Org*. *Chem*. **1972**, *37*, 322.

17. Zhu, L.; Yu, Y.; Mao, Z.; Huang, X. *Org*. *Lett*. **2015**, *17*, 30.

18. Sheng, G.; Huang, K.; Chi, Z.; Ding, H.; Xing, Y.; Lu, P.; Wang, Y. *Org*. *Lett*. **2014**, *16*, 5096. (b) Du, Z.; Xing, Y.; Lu, P.; Wang, Y. *Org*. *Lett*. **2015**, *17*, 1192.