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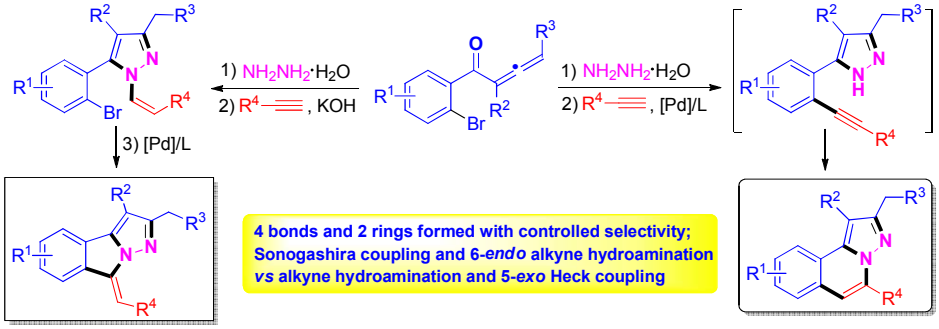
Synthesis of pyrazolo[5,1-*a*]isoquinolines and 8-methylenepyrazolo[5,1-*a*]isoindoles *via* regio-selective C-C coupling and alkyne hydroamination

Xuesen Fan*, Meng Yan, Yuanyuan Wang, and Xinying Zhang*

School of Chemistry and Chemical Engineering, Collaborative Innovation Center of Henan Province for Green Manufacturing of Fine Chemicals, Henan Key Laboratory of Green Chemical Media and Reactions, Key Laboratory of Green Chemical Media and Reactions, Ministry of Education, Henan Normal University, Xinxiang, Henan 453007, China

E-mail: xuesen.fan@htu.cn; xinyingzhang@htu.cn



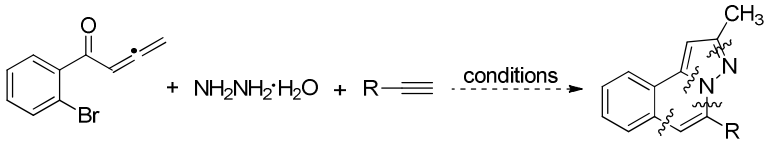
Abstract: An efficient and convenient synthesis of pyrazolo[5,1-*a*]isoquinolines has been achieved *via* palladium-catalyzed Sonogashira coupling of terminal alkynes with 5-(2-bromophenyl)-1*H*-pyrazoles, *in situ* formed from the condensation of 1-(2-bromophenyl) buta-2,3-dien-1-ones with hydrazine hydrate, followed by 6-*endo* intramolecular alkyne hydroamination. More interestingly, 8-methylenepyrazolo[5,1-*a*]isoindoles, the regio-isomer of pyrazolo[5,1-*a*]isoquinolines, could also be selectively synthesized from the same starting materials through an initial intermolecular hydroamination of terminal alkynes with 5-(2-bromophenyl)-1*H*-pyrazoles followed by palladium-catalyzed 5-*exo* intramolecular Heck coupling reaction.

INTRODUCTION

Fused nitrogen-containing heterocycles constitute one of the most prominent entities as candidates for new drugs and functional materials.[1] Among them, isoquinoline[2] and pyrazolo[1,5-*a*]pyridine[3] are well recognized privileged structures embedded in a significant number of pharmaceutically relevant compounds. Consequently, it is not surprising that pyrazolo[5,1-*a*]isoquinoline (PIQ), as the hybrid structure of isoquinoline and pyrazolo[1,5-*a*] pyridine, is found to be the origin of remarkable biological activities.[4] Due to its importance, numerous synthetic strategies have been developed for the construction of the PIQ scaffold, and one of the most frequently used protocols involves the tandem reaction of *N*′-2-alkynylbenzylidenehydrazide with various nucleophiles such as alkynes, proparygyl amines and alcohols under the catalysis of Lewis acids.[5] Another elegant approach toward PIQs is based on a copper-catalyzed three-component reaction of 1-(2-bromophenyl)-3-phenylprop-2-yn-1-one with hydrazine and active methylene compounds.[6] More recently, Wu et al described a tandem reaction of 2-alkynylbromobenzene with pyrazole to provide a facile route toward PIQs *via* copper(I)-catalyzed hydroamination and C–H activation.[4] Alternatively, Ackermann et al discovered an efficient new pathway toward PIQs through Ru-catalyzed alkyne annulations with substituted 1*H*-pyrazoles.[7] While these literature procedures are generally efficient and reliable, the development of simple methods in which both the required pyrazole and the alkyne units are introduced *in situ* along with the construction of the isoquinoline and the pyrazolo[1,5-*a*]pyridine framework *via* a one-pot procedure featured with facile operation and easily accessible starting materials remains an attractive but still challenging task.

Meanwhile, allene derivatives as valuable synthetic building blocks have attracted

tremendous attention due to their diverse reactivity.[8] Among various kinds of functionalized allenes, the electron-deficient allenic ketones are good receptors for nucleophilic conjugate addition. More interestingly, this Michael type addition is often followed by simultaneous intramolecular cyclizations to afford various carbo- or heterocyclic compounds. In this regard, our own effort has resulted in an efficient synthesis of substituted pyrazoles by reacting allenic ketones with hydrazine hydrate under extremely mild conditions.[9] As a continuation of our study in developing novel synthetic strategies by using allene derivatives as substrates,[10] we envisioned a novel synthesis of PIQs *via* the one-pot multi-component reaction of the easily obtainable 1-(2-bromophenyl)buta-2,3-dien-1-one with the commercially available hydrazine hydrate and terminal alkyne (shown in Scheme 1).

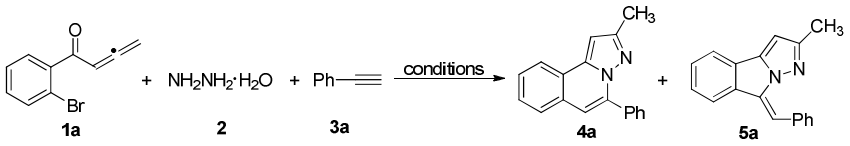


Scheme 1. Proposed synthetic pathway toward pyrazolo[5,1-*a*]isoquinoline

RESULTS AND DISCUSSION

Initially, 1-(2-bromophenyl)buta-2,3-dien-1-one (**1a**) was treated with hydrazine hydrate (**2**) in DMF at room temperature for 10 min. Then, ethynylbenzene (**3a**), $Pd(OAc)_2$, PPh_3 and K_2CO_3 were added. The resulting mixture was allowed to react at 100 ^oC under nitrogen for 12 h. From this reaction, the expected 2-methyl-5-phenylpyrazolo[5,1-*a*]isoquinoline (**4a**) was obtained in a yield of 52% along with its regio-isomer 8-benzylidene-2-methyl-8*H*-pyrazolo [5,1-*a*]isoindole (**5a**) in 7% yield (Table 1, entry 1). To improve the efficiency, other catalysts such as $Pd(PPh_3)_2Cl_2$, $PdCl_2$, and tris(dibenzylideneacetone)dipalladium ($Pd_2(dba)_3$) were then tried. However, they were found to be less effective than $Pd(OAc)_2$ in catalyzing this reaction

Table 1. Optimization studies on the synthesis of **4a** [a]



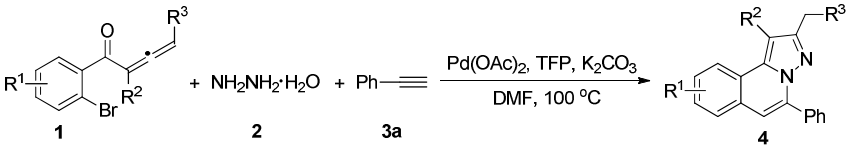
Entry	Catalyst	Co-catalyst	Ligand	Base	Solvent	T (°C)	Yield (%) [b]	
							4a	**5a**
1	$Pd(OAc)_2$	-	PPh_3	K_2CO_3	DMF	100	52	7
2	$Pd(PPh_3)_2Cl_2$	-	PPh_3	K_2CO_3	DMF	100	50	6
3	$PdCl_2$	-	PPh_3	K_2CO_3	DMF	100	35	trace
4	$Pd_2(dba)_3$	-	PPh_3	K_2CO_3	DMF	100	48	5
5	$Pd(OAc)_2$	-	phen	K_2CO_3	DMF	100	30	trace
6	$Pd(OAc)_2$	-	SPhos	K_2CO_3	DMF	100	55	5
7	$Pd(OAc)_2$	-	XPhos	K_2CO_3	DMF	100	58	6
8	$Pd(OAc)_2$	-	TFP	K_2CO_3	DMF	100	68	trace
9	$Pd(OAc)_2$	-	TCHP	K_2CO_3	DMF	100	50	trace
10	$Pd(OAc)_2$	-	-	K_2CO_3	DMF	100	16	trace
11	$Pd(OAc)_2$	-	TFP	Cs_2CO_3	DMF	100	30	trace
12	$Pd(OAc)_2$	-	TFP	NaOH	DMF	100	35	trace
13	$Pd(OAc)_2$	-	TFP	NaOAc	DMF	100	66	trace
14	$Pd(OAc)_2$	-	TFP	DBU	DMF	100	40	trace
15	$Pd(OAc)_2$	-	TFP	DABCO	DMF	100	45	trace
16	$Pd(OAc)_2$	-	TFP	Et_3N	DMF	100	30	trace
17	$Pd(OAc)_2$	-	TFP	K_2CO_3	DCE	85	29	trace
18	$Pd(OAc)_2$	-	TFP	K_2CO_3	dioxane	100	36	trace
19	$Pd(OAc)_2$	-	TFP	K_2CO_3	DMSO	100	59	trace
20	$Pd(OAc)_2$	-	TFP	K_2CO_3	DMF	120	65	trace
21	$Pd(OAc)_2$	CuBr	TFP	K_2CO_3	DMF	100	52	6
22	$Pd(OAc)_2$	CuI	TFP	K_2CO_3	DMF	100	57	8

[a] Reaction conditions: **1a** (0.5 mmol), **2** (0.6 mmol), **3a** (0.75 mmol), catalyst (0.025 mmol), ligand (0.05 mmol), base (1.5 mmol), solvent (4 mL), N_2, 12 h; [b] Isolated yield.

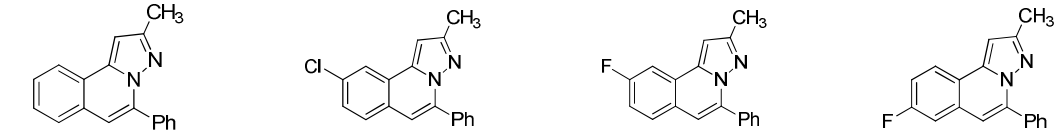
(entries 2-4). Next, the effect of different ligands including 1,10-phenanthroline (phen), 2-dicyclohexylphosphino-2',6'-dimethoxybiphenyl (SPhos), 2-dicyclohexylphosphino-2′,4′,6′-triisopropylbiphenyl (XPhos), tris(2-furanyl)phosphine (TFP), and tricyclohexylphosphine (TCHP) was tested (entries 5-9). We were pleased to find that with TFP as the ligand, the yield of **4a** could be improved to 68% while **5a** was formed only in a trace amount (entry 8). It was also found that in the absence of any ligand the yield of **4a** was very low (entry 10). Next, the suitability of several inorganic and organic bases was studied (entries 11-16). Among them, NaOAc could give similar result as that of K_2CO_3 (entry 13 *vs* 8). When other solvents such as DCE, dioxane, or DMSO were used to replace DMF as the reaction medium, the yield of **4a** decreased (entries 17-19 *vs* 8). Increasing the reaction temperature from 100 to 120 ^{o}C did not give higher yield of **4a** (entry 20 *vs* 8). Finally, addition of CuI or CuBr as co-catalyst resulted in decreased yield of **4a** but increased yield of **5a** (entries 21-22 *vs* 8).

With the optimized conditions in hand (Table 1, entry 8), we then studied the scope and generality of this one-pot three-component cascade reaction leading to PIQ (**4**). Firstly, with **3a** as a model substrate, the reactions of different 2-bromophenyl allenic ketones (**1**) were studied. The results listed in Table 2 showed that substrates **1** with various substituents on the phenyl ring underwent this cascade reaction smoothly to afford **4a**-**4h** in moderate to good yields. Various functional groups, from the electron-donating methoxy to the electron-withdrawing trifluoromethyl, were well compatible with the reaction conditions, and the electronic nature of the substrates did not show obvious effect on the yield of the corresponding products. Interestingly, using allenic ketones with a methyl or ethyl group on the internal or terminal position of the allenic moiety, the reactions still proceeded smoothly and gave the corresponding products (**4i**-**4l**) with reasonably good yields.

Table 2. Substrate scope for the preparation of **4** (I) [a, b]



1 2 3a 4



4a, 68% **4b**, 66% **4c**, 75% **4d**, 79%

4e, 70% **4f**, 65% **4g**, 70% **4h**, 66%

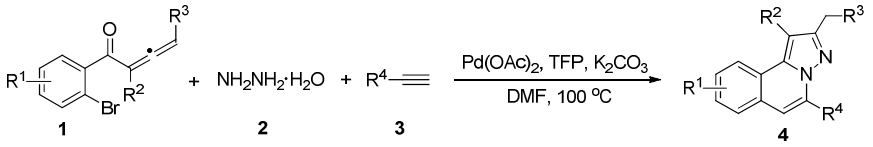
4i, 58% **4j**, 56% **4k**, 55% **4l**, 50%

[a] Reaction conditions: **1** (0.5 mmol), **2** (0.6 mmol), **3a** (0.75 mmol), $Pd(OAc)_2$ (0.025 mmol), TFP (0.05 mmol), K_2CO_3 (1.5 mmol), DMF (4 mL), 100 °C, N_2, 12 h; [b] Isolated yield.

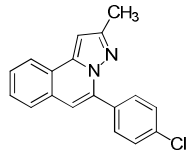
Next, the scope of the alkyne substrate (**3**) was screened. Thus, 1-chloro-4-ethynylbenzene (**3b**), 1-ethynyl-4-fluorobenzene (**3c**), 1-ethynyl-4-methoxybenzene (**3d**), and 1-ethynyl-3-methylbenzene (**3e**) were chosen to react with different allenic ketones (**1**) and hydrazine hydrate (**2**). The results listed in Table 3 indicated that ethynylbenzenes (**3**) bearing different substituents on the phenyl ring could take part in this tandem reaction smoothly to give PIQ derivatives **4m-4p** in moderate yields. Functional groups such as chloro, fluoro, methoxy and methyl were well tolerable, and the electronic and steric nature of the substituents did not show obvious effect on the yield of **4**. When **3b-3d** were reacted with allenic ketones bearing a methyl or ethyl group on the internal or terminal positions of the allenic moiety, the corresponding products (**4q-4w**) were obtained in an equally efficient manner. Interestingly,

in addition to aryl substituted alkynes, prop-2-ynylbenzene was also found to be a suitable substrate for this cascade reaction to give **4x**.

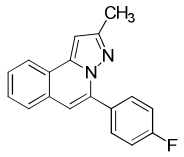
Table 3. Substrate scope for the preparation of **4** (II) [a, b]



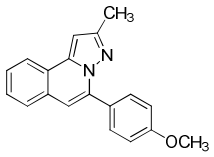
1 2 3 4



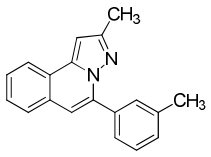
4m, 50%



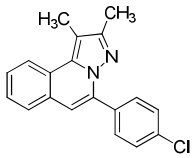
4n, 60%



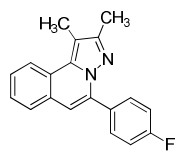
4o, 56%



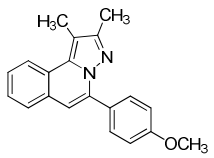
4p, 54%



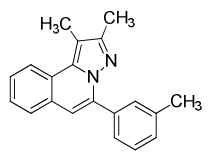
4q, 48%



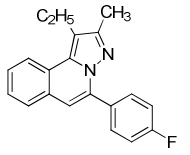
4r, 58%



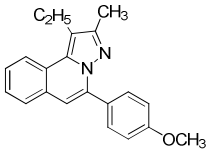
4s, 55%



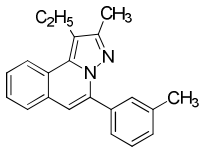
4t, 52%



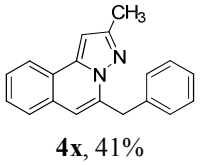
4u, 51%



4v, 49%



4w, 47%

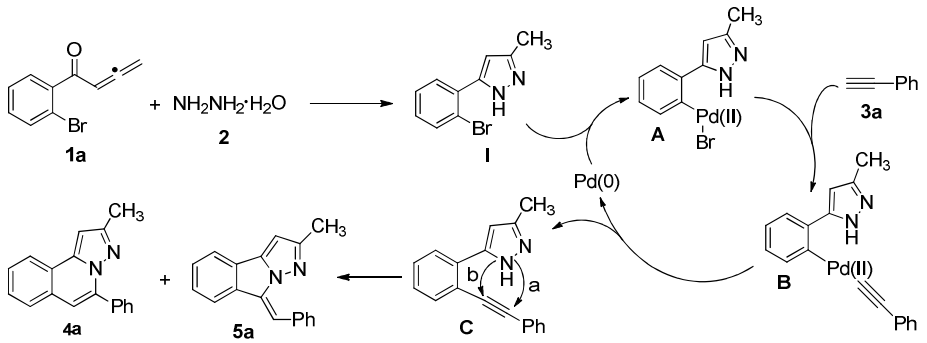


4x, 41%

[a] Reaction conditions: **1** (0.5 mmol), **2** (0.6 mmol), **3** (0.75 mmol), $Pd(OAc)_2$ (0.025 mmol), TFP (0.05 mmol), K_2CO_3 (1.5 mmol), DMF (4 mL), 100 °C, N_2, 12 h; [b] Isolated yield.

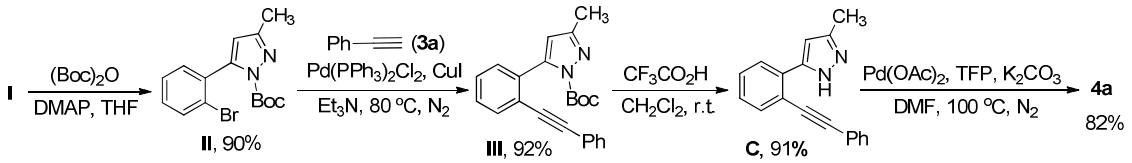
Based on the above results and previous reports,[11] a plausible pathway to account for the formation of **4a** and **5a** from the reaction of **1a**, **2** and **3a** is proposed in Scheme 2. Initially, condensation of 1-(2-bromophenyl)buta-2,3-dien-1-one (**1a**) with hydrazine hydrate (**2**) affords 5-(2-bromophenyl)-1*H*-pyrazole (**I**). Then, oxidative insertion of Pd(0) into the C–Br bond of **I** gives a Pd(II) intermediate (**A**). The following coordination of the triple bond of ethynylbenzene (**3a**) with Pd(II) gives a new palladium complex (**B**). In the next stage, reductive elimination occurs with **B** to regenerate the Pd(0) catalyst and afford the key intermediate **C**, which then undergoes an intramolecular 6-*endo* hydroamination to give **4a**

(path a). Alternatively, an intramolecular 5-*exo* hydroamination of **C** would afford **5a** (path b). Under the reaction conditions as shown in Table 1, path a is preferred. Therefore, **4a** is eventually obtained as the dominating product.



Scheme 2. Plausible pathways for the formation of **4a** and **5a**

The proposed reaction mechanism as shown in Scheme 2 is partly confirmed by the following control experiments (Scheme 3). Firstly, 5-(2-bromophenyl)-1*H*-pyrazole (**I**) was treated with $(Boc)_2O$ in the presence of DMAP to give pyrazole derivative **II**. **II** was then treated with **3a** under the standard Sonogashira coupling conditions to give **III**. By treating **III** with CF_3CO_2H, the protecting group in **III** was removed to give 3-methyl-5-(2-(phenylethynyl) phenyl)-1*H*-pyrazole (**C**). Upon subjected to the standard reaction conditions as listed in Table 1, entry 8, **C** was transformed into **4a** in 82% yield. This result should be considered as positive evidence in supporting the proposed reaction pathway, in which **C** acts as a key intermediate for the formation of **4a**.

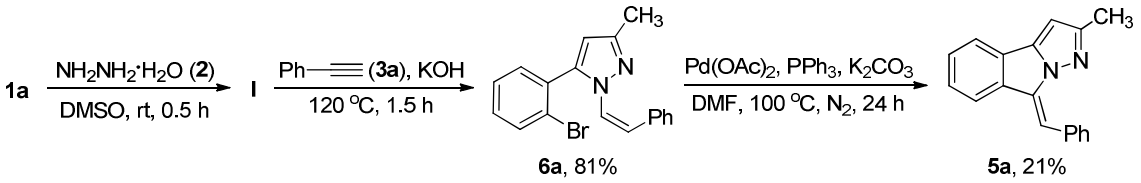


Scheme 3. Control experiment in supporting the proposed mechanism for the formation of **4a**

Having established an efficient synthesis of PIQs (**4**) *via* the condensation, Sonogashira coupling and intramolecular hydroamination cascade from 1-(2-bromophenyl)buta-2,3-dien-1

-ones (**1**), hydrazine hydrate (**2**) and alkynes (**3**), we moved our attention to study the possibility of developing a selective synthesis of 8-methylenepyrazolo[5,1-*a*]isoindole (**5**), the regio-isomer of **4**, by using the same starting materials. This challenging task turns out to be quite attractive as pyrazolo[5,1-*a*]isoindoles are endowed with a plethora of biological activities and thus have played an active role in pharmaceutical chemistry.[12-15] Despite of their importance, efficient and reliable methods for the preparation of pyrazolo[5,1-*a*]isoindole derivatives have only been sporadically reported.[16-22]

Meanwhile, we noticed that the Heck type coupling between enamines and aryl halides usually occurs regio-selectively on the inner carbon atom of the enamine unit.[23-24] Inspired by these observations, we designed a new synthetic approach toward **5** as shown in Scheme 4. Thus, 5-(2-bromophenyl)-1*H*-pyrazole (**I**), *in situ* formed through the condensation of **1a** with **2**, was reacted with **3a** in the presence of KOH to afford (*Z*)-5-(2-bromophenyl)-3-methyl-1-styryl-1*H*-pyrazole (**6a**).[25] Next, **6a** was treated with $Pd(OAc)_2/PPh_3/K_2CO_3$ in DMF at 100 ^oC for 24 h. To our delight, the expected 5-*exo* intramolecular Heck reaction (IHR) took place to afford **5a** in a yield of 21%. It was also noted that under these conditions the formation of the 6-*endo* product **4a** was not observed.

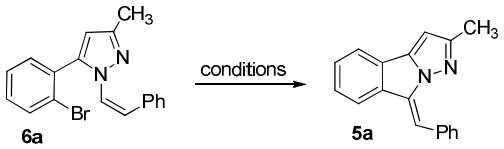


Scheme 4. Preparation of **5a** from **1a** through a hydroamination and Heck coupling sequence

To improve the yield of **5a**, various ligands such as tri-(*tert*-butyl)phosphoniumtetrafluoro-borate (TBPF), P(*o*-tol)$_3$, SPhos, TCHP, and TFP were screened (Table 4, entries 2-6). Among them, TFP turned out to be the most efficient. Then, $Pd(PPh_3)_2Cl_2$, $PdCl_2$, and $Pd_2(dba)_3$ were used to replace $Pd(OAc)_2$ as the catalyst, and $Pd_2(dba)_3$ was found to be the

best (entries 6-9). Next, Et_3N, Cs_2CO_3, and DBU were tried as the base to promote this cross coupling reaction, but they were found less effective than K_2CO_3 (entries 10-12). In addition to DMF, CH_3CN and DMSO were also tested as possible media. To our delight, the yield of **5a** increased to 41% when the reaction was carried out in DMSO (entry 14). Finally, it was also found that elevating the reaction temperature to 120 ^oC (entry 15) or using CuI as a co-catalyst (entry 16) did not improve the efficiency. As a summary of the optimization study, treatment of **6a** with 0.1 equiv of $Pd_2(dba)_3$, 0.2 equiv of TFP and 2 equiv of K_2CO_3 in DMSO under nitrogen at 100 ºC for 24 h gave **5a** in a yield of 41%.

Table 4. Optimization studies on the synthesis of **5a** [a]



6a 5a

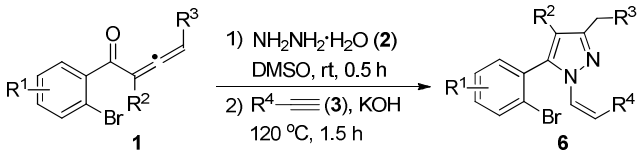
Entry	Catalyst	Co-catalyst	Ligand	Base	Solvent	T(°C)	Yield (%) [b]
1	$Pd(OAc)_2$	-	PPh_3	K_2CO_3	DMF	100	21
2	$Pd(OAc)_2$	-	TBPF	K_2CO_3	DMF	100	18
3	$Pd(OAc)_2$	-	P(*o*-tol)$_3$	K_2CO_3	DMF	100	15
4	$Pd(OAc)_2$	-	SPhos	K_2CO_3	DMF	100	19
5	$Pd(OAc)_2$	-	TCHP	K_2CO_3	DMF	100	12
6	$Pd(OAc)_2$	-	TFP	K_2CO_3	DMF	100	24
7	$Pd(PPh)_3Cl_2$	-	TFP	K_2CO_3	DMF	100	16
8	$PdCl_2$	-	TFP	K_2CO_3	DMF	100	33
9	$Pd_2(dba)_3$	-	TFP	K_2CO_3	DMF	100	36
10	$Pd_2(dba)_3$	-	TFP	Et_3N	Et_3N	90	12
11	$Pd_2(dba)_3$	-	TFP	Cs_2CO_3	DMF	100	35
12	$Pd_2(dba)_3$	-	TFP	DBU	DMF	100	15
13	$Pd_2(dba)_3$	-	TFP	K_2CO_3	CH_3CN	80	trace
14	$Pd_2(dba)_3$	-	TFP	K_2CO_3	DMSO	100	41

15	$Pd_2(dba)_3$	-	TFP	K_2CO_3	DMSO	120	40
16	$Pd_2(dba)_3$	CuI	TFP	K_2CO_3	DMSO	100	38

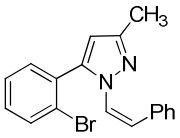
[a] Reaction conditions: **6a** (0.5 mmol), catalyst (0.05 mmol), ligand (0.1 mmol), base (1 mmol), solvent (4 mL), N_2, 24 h; [b] Isolated yield.

Following the optimization study, the scope and generality of this novel protocol for the preparation of **5** was studied. For this purpose, a series of (*Z*)-5-(2-bromophenyl)-1-styryl-1*H*-pyrazoles (**6**) were prepared *via* a one-pot cascade reaction of 1-(2-bromophenyl)buta-2,3-dien-1-one (**1**) with hydrazine hydrate (**2**) and terminal alkynes (**3**) by firstly reacting **1** with **2** in DMSO at room temperature for 0.5 h followed by treatment of the resulting mixture with **3** under the promotion of KOH at 120 °C for 1.5 h. The results were listed in Table 5.

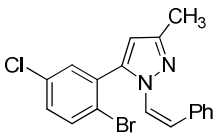
Table 5. Substrate scope for the preparation of **6** [a, b]



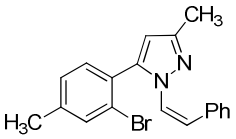
1 **6**



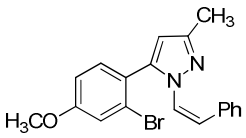
6a, 81%



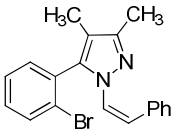
6b, 79%



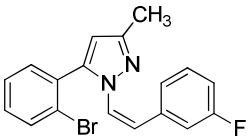
6c, 82%



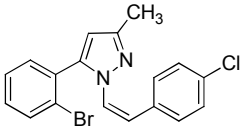
6d, 82%



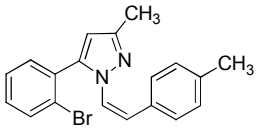
6e, 81%



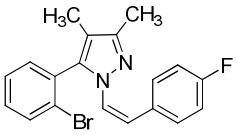
6f, 80%



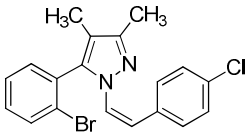
6g, 79%



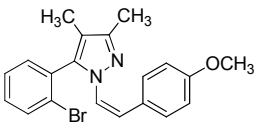
6h, 75%



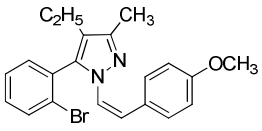
6i, 82%



6j, 77%



6k, 78%

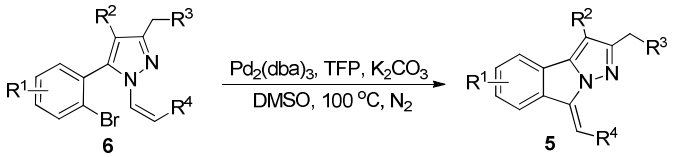


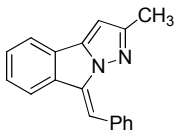
6l, 80%

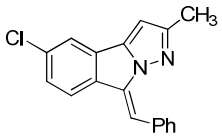
[a] Reaction conditions: **1** (1 mmol), **2** (1.2 mmol), **3** (1.2 mmol), KOH (1.25 mmol), DMSO (2 mL), N_2; [b] Isolated yield.

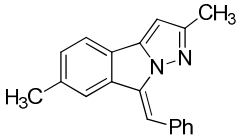
Next, the (*Z*)-5-(2-bromophenyl)-1-styryl-1*H*-pyrazole substrates (**6**) were subjected to the optimized reaction conditions as described above. The results included in Table 6 firstly indicated that substrates **6** with hydrogen, chloro, methyl or methoxy group on the 2-bromophenyl moiety underwent this coupling reaction smoothly to afford the desired products (**5a**-**5e**) in moderate yields, and the electronic nature of the substrates did not show obvious effect on the efficiency. Secondly, substrates **6** bearing chloro, fluoro, methyl or methoxy group on the R^4 unit could also take part in this reaction smoothly to give the corresponding products **5f**-**5l**.

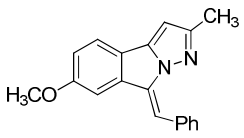
Table 6. Substrate scope for the preparation of **5** [a, b]

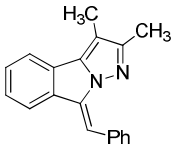


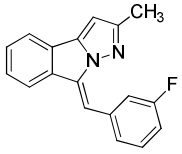

5a, 41%

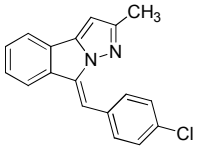

5b, 46%

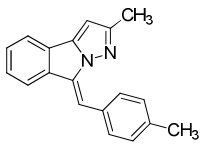

5c, 38%

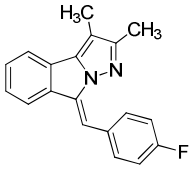

5d, 42%

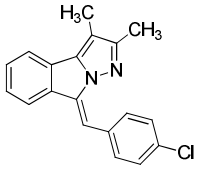

5e, 40%

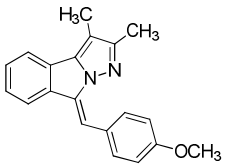

5f, 40%

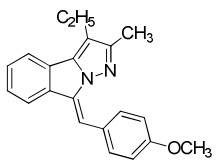

5g, 36%


5h, 34%


5i, 42%


5j, 39%

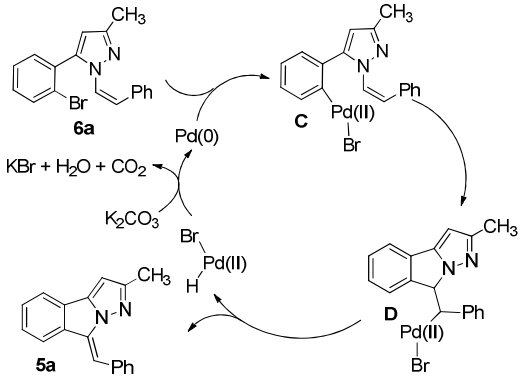

5k, 44%


5l, 37%

[a] Reaction conditions: **6** (0.5 mmol), $Pd_2(dba)_3$ (0.05 mmol), TFP (0.1 mmol), K_2CO_3 (1 mmol), DMSO (4 mL), 100 °C, N_2; [b] Isolated yield.

Based on previous reports,[23-24] a plausible pathway for the formation of **5a** was described in Scheme 5. Initially, the active Pd(0) inserts into the C–Br bond of **6a**, generating the

arylpalladium complex **C**, which then undergoes an intramolecular carbopalladation in a 5-*exo* manner to afford intermediate **D**. In the next stage, **D** undergoes a β-hydride elimination to generate **5a** and the palladium(II) bromide, which, after reductive elimination of HBr under the promotion of potassium carbonate, regenerates the active Pd(0) species for the next catalytic cycle.



Scheme 5. Plausible pathway for the formation of **5a**

CONCLUSION

In summary, we have developed a novel and convenient synthesis of pyrazolo[5,1-*a*] isoquinolines *via* palladium-catalyzed Sonogashira coupling of 5-(2-bromophenyl)-1*H*-pyrazoles with terminal alkynes, followed by 6-*endo* intramolecular alkyne hydroamination. More interestingly, a selective synthesis of 8-methylenepyrazolo[5,1-*a*]isoindoles, the regio-isomer of pyrazolo[5,1-*a*]isoquinolines, from the same starting materials has also been established through an initial intermolecular terminal alkyne hydroamination with 5-(2-bromophenyl)-1*H*-pyrazoles followed by palladium-catalyzed 5-*exo* intramolecular Heck coupling reaction. Compared with literature procedures for the preparation of pyrazolo[5,1-*a*] isoquinoline and pyrazolo[5,1-*a*]isoindole derivatives, the synthetic strategies developed herein exhibit advantages such as easily obtainable or commercially available starting

materials, broad substrate scope, simple procedure, and divergent reaction patterns toward different products with tunable selectivity.

EXPERIMENTAL SECTION

General Methods

Commercial reagents were used without further purification and solvents were dried prior to use. 1-(2-Bromophenyl)buta-2,3-dien-1-ones (**1**) were synthesized through oxidation of the corresponding homopropargyl alcohols,[26] which were prepared through zinc promoted propargylation of aldehydes.[27] ^{1}H and ^{13}C NMR spectra were recorded at 400 and 100 MHz, respectively. Chemical shifts were reported in ppm from tetramethylsilane (TMS) as internal standard in $CDCl_3$ solutions. Multiplicity was indicated as follows: s (singlet), d (doublet), t (triplet), m (multiplet), q (quadruplet), dd (doublet of doublets). Coupling constants were given in Hz. High-resolution mass spectra (HRMS) were obtained by using a MicrOTOF mass spectrometer. All the reactions were monitored by thin-layer chromatography (TLC) using silica gel plates (silica gel 60 F_{254} 0.25 mm).

Typical procedure for the synthesis of 4a and spectroscopic data of 4a-4w

A solution of 1-(2-bromophenyl)buta-2,3-dien-1-one (**1a**, 111 mg, 0.5 mmol) and hydrazine hydrate (**2**, 80%, 37 μL, 0.6 mmol) in DMF (4 mL) was stirred at room temperature for 10 min. It was then added with ethynylbenzene (**3a**, 77 mg, 0.75 mmol), $Pd(OAc)_2$ (6 mg, 0.025 mmol), TFP (12 mg, 0.05 mmol), and K_2CO_3 (207 mg, 1.5 mmol). The resulting mixture was stirred at 100 ºC under N_2 atmosphere. Upon completion as indicated by TLC analysis, the reaction was quenched with aqueous ammonium chloride and extracted with ethyl acetate (10 mL×3). The combined organic layers were washed with brine, and then dried over anhydrous

Na_2SO_4. The solvent was evaporated under vacuum and the crude product was purified by column chromatography on silica-gel eluting with petroleum ether-ethyl acetate (30:1) to afford **4a** in 68% yield. **4b**-**4w** were obtained in a similar manner.

2-Methyl-5-phenylpyrazolo[5,1-*a*]isoquinoline (4a)

Eluent: petroleum ether-ethyl acetate (30:1); Yellow solid (88 mg, 68%), mp: 78-79 ^{o}C. IR (KBr) 3055, 2928, 2848, 1472, 1459, 1450, 1396, 1329, 828, 746, 701 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.57 (s, 3H), 6.89 (s, 1H), 6.98 (s, 1H), 7.50-7.58 (m, 5H), 7.71 (d, J = 7.6 Hz ,1H), 7.98 (d, J = 7.2 Hz, 2H), 8.06 (d, J = 7.6 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 14.4, 97. 7, 111.7, 123.5, 123.7, 127.09, 127.13, 127.8, 128.4, 129.3, 129.5, 134.1, 138.3, 140.3, 150.6. HRMS (ESI-TOF) calcd for $C_{18}H_{15}N_2$: 259.1230 $[M+H]^+$, found: 259.1238.

9-Chloro-2-methyl-5-phenylpyrazolo[5,1-*a*]isoquinoline (4b)

Eluent: petroleum ether-ethyl acetate (30:1); White solid (96 mg, 66%), mp: 157-158 ^{o}C; IR (KBr) 3065, 2960, 2924, 2852, 1552, 1482, 1465, 1446, 1396, 1305, 1078, 1020, 850, 759, 730, 689 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.52 (s, 3H), 6.85 (s, 1H), 6.91 (s, 1H), 7.44-7.54 (m, 4H), 7.63 (d, J = 8.4 Hz ,1H), 7.91 (d, J = 6.8 Hz, 2H), 8.01 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 14.3, 98.1, 110.9, 122.9, 124.6, 127.6, 128.2, 128.4, 128.5, 129.4, 129.5, 132.8, 133.6, 138.5, 139.2, 150.9. HRMS (ESI-TOF) calcd for $C_{18}H_{14}ClN_2$: 293.0840 $[M+H]^+$, found: 293.0845.

9-Fluoro-2-methyl-5-phenylpyrazolo[5,1-*a*]isoquinoline (4c)

Eluent: petroleum ether-ethyl acetate (30:1); Yellow solid (104 mg, 75%), mp: 84-85 ^{o}C; IR (KBr) 3052, 2931, 1610, 1554, 1492, 1472, 1445, 1401,1322, 1251, 1164, 852, 805, 739, 733, 686 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ : 2.54 (s, 3H), 6.80 (s, 1H), 6.90 (s, 1H), 7.22-7.24

(m, 1H), 7.50-7.56 (m, 3H), 7.61-7.66 (m, 2H), 7.92-7.94 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 14.3, 98.2, 108.6 (d, $^2J_{C\text{-}F}$ = 22.1 Hz), 110.9, 116.4 (d, $^2J_{C\text{-}F}$ = 23.6 Hz), 124.9 (d, $^3J_{C\text{-}F}$ = 9.1 Hz), 125.8 (d, $^4J_{C\text{-}F}$ = 2.2 Hz), 128.4, 129.3 (d, $^3J_{C\text{-}F}$ = 9.1 Hz), 129.5, 133.8, 137.6 (d, $^4J_{C\text{-}F}$ = 2.3 Hz), 139.47, 139.52, 150.6, 161.5 (d, $^1J_{C\text{-}F}$ = 245.4 Hz). HRMS (ESI-TOF) calcd for $C_{18}H_{14}FN_2$: 277.1136 $[M+H]^+$, found: 277.1141.

8-Fluoro-2-methyl-5-phenylpyrazolo[5,1-*a*]isoquinoline (4d)

Eluent: petroleum ether-ethyl acetate (30:1); Yellow solid (109 mg, 79%), mp: 133-134 ^oC; IR (KBr) 3061, 2928, 1634, 1622, 1555, 1488, 1456, 1402, 1323, 1226, 1142, 867, 732, 687 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.52 (s, 3H), 6.81 (s, 1H), 6.87 (s, 1H), 7.22-7.27 (m, 1H), 7.32-7.35 (m, 1H), 7.50-7.55 (m, 3H), 7.92 (d, *J* = 7.2 Hz, 2H), 8.00-8.22 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 14.3, 97.4, 110.8 (d, $^4J_{C\text{-}F}$ = 3.8 Hz), 111.7 (d, $^2J_{C\text{-}F}$ = 21.3 Hz), 115.8 (d, $^2J_{C\text{-}F}$ = 24.4 Hz), 120.3 (d, $^4J_{C\text{-}F}$ = 1.5 Hz), 125.7 (d, $^3J_{C\text{-}F}$ = 9.2 Hz), 128.4, 129.5, 130.9 (d, $^3J_{C\text{-}F}$ = 9.1 Hz), 133.7, 139.3, 139.9, 150.9, 162.0 (d, $^1J_{C\text{-}F}$ = 245.4 Hz). HRMS (ESI-TOF) calcd for $C_{18}H_{14}FN_2$: 277.1136 $[M+H]^+$, found: 277.1139.

9-Methoxy-2-methyl-5-phenylpyrazolo[5,1-*a*]isoquinoline (4e)

Eluent: petroleum ether-ethyl acetate (30:1); Red solid (101 mg, 70%), mp: 121-122 ^oC; IR (KBr) 3058, 2925, 2834, 1616, 1546, 1497, 1476, 1465, 1447, 1349, 1257, 1234, 1197, 1179, 1032, 846, 740, 689 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.55 (s, 3 H), 3.98 (s, 3H), 6.86 (s, 1H), 6.94 (s, 1H), 7.15-7.18 (m, 1H), 7.44 (d, *J* = 2.0 Hz, 1H), 7.48-7.55 (m, 3H), 7.65 (d, *J* = 8.8 Hz, 1H), 7.94 (d, *J* = 7.2 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 14.3, 55.6, 97.5, 104.7, 111.6, 117.7, 123.5, 124.8, 128.3, 128.7, 129.0, 129.4, 134.1, 136.2, 139.9, 150.2, 158.8. HRMS (ESI-TOF) calcd for $C_{19}H_{17}N_2O$: 289.1335 $[M+H]^+$, found: 289.1343.

2,8-Dimethyl-5-phenylpyrazolo[5,1-*a*]isoquinoline (4f)

Eluent: petroleum ether-ethyl acetate (30:1); Yellow solid (89 mg, 65%), mp: 97-98 ^{o}C; IR (KBr) 3052, 2918, 1634, 1553,1488, 1457, 1446, 1323, 1307, 840, 769, 746, 736, 693 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.51 (s, 3H), 2.58 (s, 3H), 6.83 (s, 1H), 6.91 (s, 1H), 7.35 (d, *J* = 8.4 Hz, 1H), 7.48 (s, 1H), 7.52-7.59 (m, 3H), 7.94-8.00 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 14.4, 21.7, 97.2, 111.6, 121.5, 123.4, 126.8, 128.4, 128.7, 129.2, 129.5, 129.6, 134.2, 137.7, 138.3, 140.4, 150.5. HRMS (ESI-TOF) calcd for $C_{19}H_{17}N_2$: 273.1386 $[M+H]^+$, found: 273.1387.

2-Methyl-5-phenyl-9-(trifluoromethyl)pyrazolo[5,1-*a*]isoquinoline (4g)

Eluent: petroleum ether-ethyl acetate (30:1); Yellow solid (114 mg, 70%), mp: 148-149 ^{o}C; IR (KBr) 2924, 1552, 1472, 1448, 1394, 1319,1253, 1144, 1106, 1069, 900, 855, 748, 694, 684 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.55 (s, 3H), 6.93 (d, *J* = 6.4 Hz, 2H), 7.52-7.55 (m, 3H), 7.69 (d, *J* = 1.6 Hz, 1H), 7.74 (d, *J* = 8.4 Hz, 1H), 7.93-7.95 (m, 2H), 8.28 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 14.3, 98.5, 110.6, 120.8 (q, $^{3}J_{C\text{-}F}$ = 4.6 Hz), 123.1, 123.7 (q, $^{3}J_{C\text{-}F}$ = 3.1 Hz), 124.2 (q, $^{1}J_{C\text{-}F}$ = 270.5 Hz), 127.7, 128.4, 128.6 (q, $^{2}J_{C\text{-}F}$ = 32.8 Hz), 129.5, 129.7, 131.4, 133.4, 139.7, 140.2, 151.2. HRMS (ESI-TOF) calcd for $C_{19}H_{14}F_3N_2$: 327.1104 $[M+H]^+$, found: 327.1106.

2-Methyl-5-phenyl-[1,3]dioxolo[4,5-*g*]pyrazolo[5,1-*a*]isoquinoline (4h)

Eluent: petroleum ether-ethyl acetate (20:1); Yellow solid (99 mg, 66%), mp: 150-151 ^{o}C; IR (KBr) 3052, 2988, 2908, 1546, 1484, 1472, 1454, 1413, 1273, 1244, 1212, 1032, 942, 913, 865, 827, 746, 730, 690 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.53 (s, 3H), 6.07 (s, 2H), 6.69 (s, 1H), 6.84 (s, 1H), 7.05 (s, 1H), 7.38 (s, 1H), 7.48-7.55 (m, 3H), 7.94 (d, *J* = 7.2 Hz, 2H).

^{13}C NMR (100 MHz, $CDCl_3$) δ: 14.3, 96.3, 101.5, 101.9, 105.0, 111.5, 119.2, 125.3, 128.4, 129.1, 129.4, 134.0, 136.7, 140.3, 147.9, 148.4, 150.4. HRMS (ESI-TOF) calcd for $C_{19}H_{15}N_2O_2$: 303.1128 $[M+H]^+$, found: 303.1132.

2-Ethyl-5-phenylpyrazolo[5,1-*a*]isoquinoline (4i)

Eluent: petroleum ether-ethyl acetate (30:1); Yellow oil (78 mg, 58%). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.40 (t, *J* = 7.6 Hz, 3H), 2.92 (q, *J* = 7.6 Hz, 2H), 6.94 (s, 1H), 7.00 (s, 1H), 7.49-7.55 (m, 5H), 7.73 (d, *J* = 7.2, Hz, 1H), 7.97 (d, *J* = 8.0 Hz, 2H), 8.10 (d, *J* = 7.6 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 14.1, 22.0, 95.9, 111.7, 123.5, 123.8, 127.07, 127.09, 127.7, 128.3, 129.2, 129.3, 129.5, 134.0, 138.3, 140.1, 156.6. HRMS (ESI-TOF) calcd for $C_{19}H_{17}N_2$: 273.1386 $[M+H]^+$, found: 273.1377.

5-Phenyl-2-propylpyrazolo[5,1-*a*]isoquinoline (4j)

Eluent: petroleum ether-ethyl acetate (30:1); Yellow oil (80 mg, 56%). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.11 (t, *J* = 7.6 Hz, 3H), 1.85-1.91 (m, 2H), 2.91 (t, *J* = 7.6 Hz, 2H), 6.95 (s, 1H), 7.00 (s, 1H), 7.52-7.58 (m, 5H), 7.72-7.74 (m, 1H), 8.01 (d, *J* = 6.4 Hz, 2H), 8.09-8.11 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 14.2, 23.2, 30.9, 96.5, 111.7, 123.5, 123.8, 127.1, 127.7, 128.3, 129.26, 129.29, 129.5, 134.1, 138.3, 140.1, 155.2. HRMS (ESI-TOF) calcd for $C_{20}H_{19}N_2$: 287.1543 $[M+H]^+$, found: 287.1551.

1,2-Dimethyl-5-phenylpyrazolo[5,1-*a*]isoquinoline (4k)

Eluent: petroleum ether-ethyl acetate (30:1); Yellow solid (75 mg, 55%), mp: 145-146 ^{o}C; IR (KBr) 3053, 2922, 2852, 1477, 1486, 1458, 1449, 1399, 1320, 838, 767, 744, 697 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.57 (s, 3H), 2.62 (s, 3H), 6.94 (s, 1H), 7.50-7.62 (m, 5H), 7.71 (d, *J* = 7.6 Hz, 1H), 8.05 (d, *J* = 6.4 Hz, 2H), 8.32 (d, *J* = 8.0 Hz, 1H). ^{13}C NMR (100 MHz,

$CDCl_3$) δ: 10.8, 12.3, 107.9, 111.4, 123.0, 125.3, 126.8, 126.9, 127.0, 128.3, 129.2, 129.5, 129.7, 134.2, 135.7, 138.3, 149.5. HRMS (ESI-TOF) calcd for $C_{19}H_{17}N_2$: 273.1386 $[M+H]^+$, found: 273.1385.

1-Ethyl-2-methyl-5-phenylpyrazolo[5,1-*a*]isoquinoline (4l)

Eluent: petroleum ether-ethyl acetate (30:1); Yellow solid (72 mg, 50%), mp: 101-102 °C; IR (KBr) 3058, 2965, 2921, 2851, 1563, 1481, 1465, 1448, 1399, 1332, 1307, 838, 771, 762, 745, 695 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 1.36 (t, *J* = 7.6 Hz, 3H), 2.47 (s, 3H), 3.06 (q, *J* = 7.6 Hz, 2H), 6.91 (s, 1H), 7.49-7.60 (m, 5H), 7.72 (d, *J* = 7.6 Hz, 1H), 7.92 (d, *J* = 7.6 Hz, 2H), 8.27 (d, *J* = 8.0 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 12.1, 14.3, 18.1, 111.4, 114.8, 122.8, 125.0, 127.0, 127.2, 128.2, 128.3, 128.5, 129.1, 129.5, 129.8, 134.3, 138.4, 149.1. HRMS (ESI-TOF) calcd for $C_{20}H_{19}N_2$: 287.1543 $[M+H]^+$, found: 287.1550.

5-(4-Chlorophenyl)-2-methylpyrazolo[5,1-*a*]isoquinoline (4m)

Eluent: petroleum ether-ethyl acetate (30:1); Yellow solid (73 mg, 50%), mp: 124-125 °C; IR (KBr) 3055, 2918, 1550, 1486, 1466, 1415, 1324, 1091, 1014, 934, 864, 817, 763, 733, 722, 660 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 2.55 (s, 3H), 6.88 (s, 1H), 6.94 (s, 1H), 7.50-7.56 (m, 4H), 7.69-7.72 (m, 1H), 7.90 (d, *J* = 8.4 Hz, 2H), 8.05-8.07 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 14.3, 97.8, 111.7, 123.5, 123.8, 127.1, 127.3, 127.9, 128.6, 129.1, 130.8, 134.4, 135.2, 137.1, 140.2, 150.7. HRMS (ESI-TOF) calcd for $C_{18}H_{14}ClN_2$: 293.0840 $[M+H]^+$, found: 293.0849.

5-(4-Fluorophenyl)-2-methylpyrazolo[5,1-*a*]isoquinoline (4n)

Eluent: petroleum ether-ethyl acetate (30:1); Yellow solid (83 mg, 60%), mp: 112-113 °C; IR (KBr) 3054, 2922, 2853, 1634, 1604, 1552, 1511, 1468, 1096, 1016, 937, 822, 734 cm^{-1}; ^1H

NMR (400 MHz, $CDCl_3$) δ: 2.54 (s, 3H), 6.90 (s, 1H), 6.95 (s, 1H), 7.23 (t, J = 8.4 Hz, 2H), 7.54-7.56 (m, 2H), 7.72 (d, J = 8.4 Hz, 1H), 7.93-7.96 (m, 2H), 8.06-8.08 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 14.3, 97.7, 111.6, 115.4 (d, $^2J_{C\text{-}F}$ = 21.3 Hz), 123.5, 123.7, 127.0, 127.2, 127.8, 129.2, 130.0 (d, $^4J_{C\text{-}F}$ = 3.0 Hz), 131.4 (d, $^3J_{C\text{-}F}$ = 7.7 Hz), 137.2, 140.3, 150.7, 163.3 (d, $^1J_{CF}$ = 247.6 Hz). HRMS (ESI-TOF) calcd for $C_{18}H_{14}FN_2$: 277.1136 $[M+H]^+$, found: 277.1135.

5-(4-Methoxyphenyl)-2-methylpyrazolo[5,1-*a*]isoquinoline (4o)

Eluent: petroleum ether-ethyl acetate (20:1); White solid (81 mg, 56%), mp: 120-121 ^{o}C; IR (KBr) 3052, 3017, 2971, 2921, 1631, 1605, 1572, 1510, 1465, 1182, 1024, 937, 827, 740 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.55 (s, 3H), 3.91 (s, 3H), 6.89 (s, 1H), 6.95 (s, 1H), 7.07 (d, J = 8.8 Hz, 2H), 7.52-7.54 (m, 2H), 7.70-7.72 (m, 1H), 7.92 (d, J = 8.8 Hz, 2H), 8.05-8.08 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 14.4, 55.4, 97.5, 110.9, 113.8, 123.45, 123.48, 126.4, 126.8, 126.9, 127.7, 129.4, 130.9, 138.1, 140.3, 150.5, 160.4. HRMS (ESI-TOF) calcd for $C_{19}H_{17}N_2O$: 289.1335 $[M+H]^+$, found: 289.1343.

2-Methyl-5-*m*-tolylpyrazolo[5,1-*a*]isoquinoline (4p)

Eluent: petroleum ether-ethyl acetate (30:1); Yellow oil (74 mg, 54%). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.51 (s, 3H), 2.58 (s, 3H), 6.90 (s, 1H), 6.98 (s, 1H), 7.34 (d, J = 7.6 Hz, 1H), 7.46 (t, J = 7.6 Hz, 1H), 7.53-7.55 (m, 2H), 7.71-7.78 (m, 3H), 8.07-8.09 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 14.4, 21.6, 97.6, 111.6, 123.5, 123.7, 126.7, 127.0, 127.7, 128.3, 129.3, 130.08, 130.11, 134.0, 138.0, 138.5, 140.2, 150.6. HRMS (ESI-TOF) calcd for $C_{19}H_{17}N_2$: 273.1386 $[M+H]^+$, found: 273.1385.

5-(4-Chlorophenyl)-1,2-dimethylpyrazolo[5,1-*a*]isoquinoline (4q)

Eluent: petroleum ether-ethyl acetate (30:1); Yellow solid (73 mg, 48%), mp: 161-162 ^{o}C; IR (KBr) 3052, 2920, 2852, 1629, 1594, 1566, 1490, 1462, 1253, 1017, 926, 818, 742 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.46 (s, 3H) , 2.60 (s, 3H), 6.89 (s, 1H), 7.48-7.60 (m, 4H), 7.72 (d, *J* = 8.0 Hz, 1H), 7.88 (d, *J* = 8.4 Hz, 2H), 8.32 (d, *J* = 8.0 Hz, 1H).^{13}C NMR (100 MHz, $CDCl_3$) δ: 10.8, 12.3, 108.0, 111.4, 123.0, 125.4, 127.05, 127.11, 128.5, 129.5, 130.8, 132.6, 135.0, 135.7, 137.1, 149.6. HRMS (ESI-TOF) calcd for $C_{19}H_{16}ClN_2$: 307.0997 $[M+H]^+$, found: 307.0995.

5-(4-Fluorophenyl)-1,2-dimethylpyrazolo[5,1-*a*]isoquinoline (4r)

Eluent: petroleum ether-ethyl acetate (30:1); Yellow solid (84 mg, 58%), mp: 141-142 ^{o}C; IR (KBr) 3054, 2922, 2853, 1636, 1603, 1569, 1509, 1450, 1095, 1018, 924, 824, 747 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.47 (s, 3H), 2.60 (s, 3H), 6.88 (s, 1H), 7.21 (t, *J* = 8.8 Hz, 2H), 7.50-7.60 (m, 2H), 7.72 (d, *J* = 7.6 Hz, 1H), 7.92 (dd, *J* = 8.4, 5.6 Hz, 2H), 8.32 (d, *J* = 8.0 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 10.5, 12.2, 108.0, 111.3, 115.3 (d, $^{2}J_{C\text{-}F}$ = 22.2 Hz), 123.0, 125.3, 126.9, 127.0, 129.6, 130.2 (d, $^{4}J_{C\text{-}F}$ = 3.1 Hz), 131.4 (d, $^{3}J_{C\text{-}F}$ = 7.9 Hz), 135.7, 137.3, 149.6, 163.2 (d, $^{1}J_{C\text{-}F}$ = 246.9 Hz). HRMS (ESI-TOF) calcd for $C_{19}H_{16}FN_2$: 291.1292 $[M+H]^+$, found: 291.1295.

5-(4-Methoxyphenyl)-1,2-dimethylpyrazolo[5,1-*a*]isoquinoline (4s)

Eluent: petroleum ether-ethyl acetate (30:1); White solid (83 mg, 55%), mp: 155-156 ^{o}C; IR (KBr) 3054, 3008, 2963, 2929, 2838, 1637, 1608, 1571, 1513, 1460, 819, 753 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.47 (s, 3H), 2.60 (s, 3H), 3.90 (s, 3H), 6.88 (s, 1H), 7.05 (d, *J* = 8.4 Hz, 2H), 7.51-7.57 (m, 2H), 7.71 (d, *J* = 7.6 Hz, 1H), 7.88 (d, *J* = 8.8 Hz, 2H), 8.31 (d, *J* = 7.6 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 10.8, 12.3, 55.4, 107.8, 110.7, 113.7, 123.0, 125.1, 126.6,

126.9, 129.9, 130.8, 135.7, 138.0, 149.3, 160.3. HRMS (ESI-TOF) calcd for $C_{20}H_{19}N_2O$: 303.1492 $[M+H]^+$, found: 303.1495.

1,2-Dimethyl-5-*m*-tolylpyrazolo[5,1-*a*]isoquinoline (4t)

Eluent: petroleum ether-ethyl acetate (30:1); Yellow solid (74 mg, 52%), mp: 101-102 ^oC. ^1H NMR (400 MHz, $CDCl_3$) δ: 2.47 (s, 6H), 2.61 (s, 3H), 6.89 (s, 1H), 7.30 (d, J = 7.6 Hz, 1H), 7.42 (t, J = 7.6 Hz, 1H), 7.50-7.58 (m, 2H), 7.70-7.73 (m, 3H), 8.32 (d, J = 8.0 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 10.8, 12.3, 21.6, 107.8, 111.3, 123.0, 125.3, 126.66, 126.73, 126.9, 127.0, 128.2, 129.8, 129.97, 130.04, 134.1, 135.7, 137.9, 138.5, 149.4. HRMS (ESI-TOF) calcd for $C_{20}H_{19}N_2$: 287.1543 $[M+H]^+$, found: 287.1545.

1-Ethyl-5-(4-fluorophenyl)-2-methylpyrazolo[5,1-*a*]isoquinoline (4u)

Eluent: petroleum ether-ethyl acetate (30:1); Yellow solid (78 mg, 51%), mp: 115-116 ^oC; IR (KBr) 3053, 2962, 2920, 2851, 1637, 1599, 1567, 1508, 1480, 1095, 1015, 934, 823, 742 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 1.36 (t, J = 7.6 Hz, 3H), 2.47 (s, 3H), 3.06 (q, J = 7.2 Hz, 2H), 6.88 (s, 1H), 7.21 (t, J = 8.4 Hz, 2H), 7.52-7.58 (m, 2H), 7.72 (d, J = 7.6 Hz, 1H), 7.89-7.93 (m, 2H), 8.27 (d, J = 7.6 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 12.0, 14.3, 18.1, 111.3, 114.9, 115.3 (d, $^2J_{C\text{-}F}$ = 21.4 Hz), 122.8, 124.9, 127.1 (d, $^4J_{C\text{-}F}$ = 3.2 Hz), 127.2, 129.7, 130.2, 130.3, 131.4 (d, $^3J_{C\text{-}F}$ = 8.7 Hz), 135.2, 137.3, 149.2, 163.2 (d, $^1J_{C\text{-}F}$ = 246.9 Hz). HRMS (ESI-TOF) calcd for $C_{20}H_{18}FN_2$: 305.1449 $[M+H]^+$, found: 305.1450.

1-Ethyl-5-(4-methoxyphenyl)-2-methylpyrazolo[5,1-*a*]isoquinoline (4v)

Eluent: petroleum ether-ethyl acetate (30:1); Yellow solid (77 mg, 49%), mp: 120-121 ^oC; IR (KBr) 3050, 2960, 2923, 2868, 2852, 1633, 1604, 1563, 1513, 1464, 1249, 1027, 941, 824, 738 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 1.36 (t, J = 7.6 Hz, 3H), 2.47 (s, 3H), 3.06 (q, J =

7.6 Hz, 2H), 3.91 (s, 3H), 6.88 (s, 1H), 7.05 (d, *J* = 8.0 Hz, 2H), 7.49-7.58 (m, 2H), 7.71 (d, *J* = 7.6 Hz, 1H), 7.88 (d, *J* = 8.0 Hz, 2H), 8.26 (d, *J* = 7.6 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 12.1, 14.4, 18.1, 55.4, 110.8, 113.7, 114.8, 122.8, 124.7, 126.6, 126.7, 126.9, 127.0, 129.9, 130.9, 135.2, 138.1, 149.0, 160.2. HRMS (ESI-TOF) calcd for $C_{21}H_{21}N_2O$: 317.1648 $[M+H]^+$, found: 317.1656.

1-Ethyl-2-methyl-5-*m*-tolylpyrazolo[5,1-*a*]isoquinoline (4w)

Eluent: petroleum ether-ethyl acetate (30:1); Yellow oil (71 mg, 47%). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.37 (t, *J* = 7.6 Hz, 3H), 2.48 (s, 6H), 3.07 (q, *J* = 7.6 Hz, 2H), 6.89 (s, 1H), 7.31 (d, *J* = 7.6 Hz, 1H), 7.42 (t, *J* = 8.0 Hz, 1H), 7.51-7.58 (m, 2H), 7.71-7.73 (m, 3H), 8.27 (d, *J* = 8.0 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 12.1, 14.3, 18.1, 21.6, 111.3, 114.8, 122.8, 124.9, 126.7, 126.9, 127.0, 127.1, 128.2, 129.8, 129.9, 130.1, 132.3, 134.2, 137.9, 138.6, 149.1. HRMS (ESI-TOF) calcd for $C_{21}H_{21}N_2$: 301.1699 $[M+H]^+$, found: 301.1695.

5-Benzyl-2-methylpyrazolo[5,1-*a*]isoquinoline (4x)

Eluent: petroleum ether-ethyl acetate (30:1); Yellow oil (56 mg, 41%); IR (neat) 3027, 2924, 1638, 1548, 1485, 1470, 1452, 1409,1327, 1031, 841, 753, 706, 692, 678 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ: 2.59 (s, 3H), 4.52 (s, 2H), 6.44 (s, 1H), 6.87 (s, 1H), 7.33-7.35 (m, 1H), 7.39-7.42 (m, 4H), 7.45-7.51 (m, 2H), 7.54 (d, *J* = 7.8 Hz, 1H), 8.04 (d, *J* = 7.8 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 14.2, 36.9, 97.6, 109.7, 123.2, 123.4, 126.6, 126.7, 126.9, 127.5, 128.6, 129.1, 130.0, 137.0, 138.7, 139.6, 150.3. HRMS (ESI-TOF) calcd for $C_{19}H_{17}N_2$: 273.1386 $[M+H]^+$, found: 273.1390.

Typical procedure for the synthesis of 6a and spectroscopic data of 6a-6l

A solution of 1-(2-bromophenyl)buta-2,3-dien-1-one (**1a**, 222 mg, 1 mmol) and hydrazine

hydrate (**2**, 80%, 73 μL, 1.2 mmol) in DMSO (2 mL) was stirred at room temperature for 30 min. Then, to the mixture were added ethynylbenzene (**3a**, 122 mg, 1.2 mmol) and KOH (70 mg, 1.25 mmol). The resulting mixture was then stirred at 120 ºC under N_2 atmosphere. Upon completion as indicated by TLC analysis, the reaction was quenched with water and the mixture was extracted with ethyl acetate (10 mL×3). The combined organic layers were washed with water and brine, and then dried over anhydrous Na_2SO_4. The solvent was evaporated under vacuum, and the crude product was purified by column chromatography on silica-gel eluting with petroleum ether-ethyl acetate (20:1) to afford **6a** in 81% yield.

(*Z*)-5-(2-Bromophenyl)-3-methyl-1-styryl-1*H*-pyrazole (6a)

Eluent: petroleum ether-ethyl acetate (20:1); 274 mg, 81%. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.08 (s, 3H), 6.58 (d, *J* = 8.8 Hz, 2H), 6.86 (d, *J* = 8.8 Hz, 1H), 7.05-7.07 (m, 2H), 7.17-7.21 (m, 1H), 7.25-7.27 (m, 3H), 7.34 (t, *J* = 7.6 Hz, 1H), 7.65-7.69 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 11.4, 107.5, 122.2, 124.3, 127.4, 128.4, 128.48, 128.53, 129.0, 129.2, 131.2, 133.5, 134.0, 134.6, 139.6, 151.2. HRMS (ESI-TOF) calcd for $C_{18}H_{16}BrN_2$: 339.0491 $[M+H]^+$, found: 339.0495.

(*Z*)-5-(2-Bromo-5-chlorophenyl)-3-methyl-1-styryl-1*H*-pyrazole (6b)

Eluent: petroleum ether-ethyl acetate (20:1); 294 mg, 79%. IR (neat) 3056, 2919, 2862, 1646, 1448, 1433, 1355, 1384, 1025, 1008, 910, 785, 757, 727, 692, 677 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.06 (s, 3H), 6.54 (d, *J* = 9.2 Hz, 1H), 6.68 (s, 1H), 6.81 (d, *J* = 8.8 Hz, 1H), 7.08-7.12 (m, 3H), 7.25-7.29 (m, 3H), 7.52 (d, *J* = 8.4 Hz, 1H), 7.80 (d, *J* = 2.4 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 11.4, 107.3, 119.8, 124.0, 128.4, 128.47, 128.53, 128.9, 129.0, 130.9, 133.4, 133.9, 134.5, 136.0, 139.8, 149.9. HRMS (ESI-TOF) calcd for $C_{18}H_{15}BrClN_2$:

373.0102 $[M+H]^+$, found: 373.0105.

(*Z*)-5-(2-Bromo-4-methylphenyl)-3-methyl-1-styryl-1*H*-pyrazole (6c)

Eluent: petroleum ether-ethyl acetate (20:1); 289 mg, 82%. IR (neat) 3067, 2915, 2853, 1499, 1448, 1421, 1345, 1275, 1138, 956, 874, 1036, 844, 832, 797, 762, 689 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 2.04 (s, 3H), 2.33 (s, 3H), 6.54 (d, *J* = 7.2 Hz, 2H), 6.81 (d, *J* = 6.0 Hz, 1H), 7.03-7.05 (m, 2H), 7.10 (d, *J* = 5.2 Hz, 1H), 7.22-7.25 (m, 3H), 7.46 (s, 1H), 7.54 (d, *J* = 5.2 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 11.3, 20.9, 107.4, 121.8, 124.3, 128.27, 128.30, 128.4, 128.5, 129.0, 130.9, 131.7, 133.9, 134.0, 139.4, 139.5, 151.2. HRMS (ESI-TOF) calcd for $C_{19}H_{18}BrN_2$: 353.0648 $[M+H]^+$, found: 353.0649.

(*Z*)-5-(2-Bromo-4-methoxyphenyl)-3-methyl-1-styryl-1*H*-pyrazole (6d)

Eluent: petroleum ether-ethyl acetate (20:1); 302 mg, 82%. ^1H NMR (400 MHz, $CDCl_3$) δ: 2.11 (s, 3H), 3.78 (s, 3H), 6.57 (d, *J* = 8.8 Hz, 1H), 6.63 (s, 1H), 6.75-6.78 (m, 1H), 6.85 (dd, *J* = 8.8, 1.2 Hz, 1H), 7.06-7.08 (m, 2H), 7.20-7.28 (m, 4H), 7.51 (dd, *J* = 8.8, 1.2 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 11.4, 55.6, 107.4, 112.5, 115.3, 116.3, 124.1, 128.0, 128.2, 128.4, 129.0, 134.1, 135.2, 139.5, 151.1, 158.8. HRMS (ESI-TOF) calcd for $C_{19}H_{18}BrN_2O$: 369.0597 $[M+H]^+$, found: 369.0598.

(*Z*)-5-(2-Bromophenyl)-3,4-dimethyl-1-styryl-1*H*-pyrazole (6e)

Eluent: petroleum ether-ethyl acetate (20:1); 287 mg, 81%. ^1H NMR (400 MHz, $CDCl_3$) δ: 1.95 (s, 3H), 1.98 (s, 3H), 6.52 (d, *J* = 8.8 Hz, 1H), 6.83 (d, *J* = 9.2 Hz, 1H), 7.08-7.10 (m, 2H), 7.19-7.26 (m, 4H), 7.32-7.36 (m, 1H), 7.43-7.45 (m, 1H), 7.66 (d, *J* = 8.0 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 9.1, 9.9, 113.8, 124.2, 124.6, 127.2, 128.3, 128.4, 129.1, 129.6, 132.2, 132.7, 134.0, 135.5, 136.7, 151.6. HRMS (ESI-TOF) calcd for $C_{19}H_{18}BrN_2$: 353.0648

$[M+H]^+$, found: 353.0650.

(*Z*)-5-(2-Bromophenyl)-1-(3-fluorostyryl)-3-methyl-1*H*-pyrazole (6f)

Eluent: petroleum ether-ethyl acetate (20:1); 285 mg, 80%. IR (neat) 3071, 2922, 1650, 1610, 1581, 1484, 1441, 1352, 1250, 1239, 1024, 954, 877, 788, 757, 726, 686, 675 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 2.12 (s, 3H), 6.46 (d, J = 8.8 Hz, 1H), 6.63 (s, 1H), 6.84 (d, J = 9.2 Hz, 1H), 6.88-6.95 (m, 3H), 7.15-7.23 (m, 2H), 7.31-7.35 (m, 1H), 7.64-7.71 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 11.4, 107.7, 115.2 (d, $^2J_{C-F}$ = 21.4 Hz), 115.8 (d, $^2J_{C-F}$ = 22.2 Hz), 122.2, 124.9, 125.1 (d, $^4J_{C-F}$ = 3.1 Hz), 126.0 (d, $^4J_{C-F}$ = 1.6 Hz), 127.4, 129.3, 129.8 (d, $^3J_{C-F}$ = 7.9 Hz), 131.2, 133.5, 134.5, 136.1 (d, $^3J_{C-F}$ = 7.9 Hz), 139.6, 151.4, 162.6 (d, $^1J_{C-F}$ = 243.8 Hz). HRMS (ESI-TOF) calcd for $C_{18}H_{15}BrFN_2$: 357.0397 $[M+H]^+$, found: 357.0401.

(*Z*)-5-(2-Bromophenyl)-1-(4-chlorostyryl)-3-methyl-1*H*-pyrazole (6g)

Eluent: petroleum ether-ethyl acetate (20:1); 294 mg, 79%. ^1H NMR (400 MHz, $CDCl_3$) δ: 2.10 (s, 3H), 6.45 (d, J = 9.2 Hz, 1H), 6.63 (s, 1H), 6.82 (d, J = 8.8 Hz, 1H), 7.04 (d, J = 8.4 Hz, 2H), 7.15-7.19 (m, 1H), 7.23 (d, J = 8.4 Hz, 2H), 7.31-7.35 (m, 1H), 7.64-7.69 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 11.4, 107.7, 122.2, 124.5, 126.3, 127.5, 128.6, 129.3, 130.4, 131.2, 132.5, 133.5, 134.0, 134.5, 139.5, 151.3. HRMS (ESI-TOF) calcd for $C_{18}H_{15}BrClN_2$: 373.0102 $[M+H]^+$, found: 373.0106.

(*Z*)-5-(2-Bromophenyl)-3-methyl-1-(4-methylstyryl)-1*H*-pyrazole (6h)

Eluent: petroleum ether-ethyl acetate (20:1); 264 mg, 75%. IR (neat) 2958, 2920, 2853, 1644, 1546, 1511, 1431, 1364, 1185, 1164, 1022, 956, 949, 820, 794, 759, 745, 725, 675 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 1.98 (s, 3H), 2.23 (s, 1H), 6.47-6.50 (m, 2H), 6.71 (d, J = 5.6 Hz, 1H), 6.83 (d, J = 5.2 Hz, 2H), 6.97 (d, J = 5.2 Hz, 2H), 7.09-7.12 (m, 1H), 7.25 (t, J = 5.2 Hz,

1H), 7.57 (d, J = 5.2 Hz, 1H), 7.62 (d, J = 5.2 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 11.4, 21.3, 107.3, 123.5, 127.2, 127.3, 128.8, 129.1, 129.2, 131.0, 131.1, 131.2, 133.4, 134.7, 138.4, 139.5, 151.1. HRMS (ESI-TOF) calcd for $C_{19}H_{18}BrN_2$: 353.0648 $[M+H]^+$, found: 353.0651.

(*Z*)-5-(2-Bromophenyl)-1-(4-fluorostyryl)-3,4-dimethyl-1*H*-pyrazole (6i)

Eluent: petroleum ether-ethyl acetate (20:1); 304 mg, 82%. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.93 (s, 3H), 2.03 (s, 3H), 6.48 (d, J = 8.8 Hz, 1H), 6.81 (d, J = 8.8 Hz, 1H), 6.91-6.95 (m, 2H), 7.04-7.07 (m, 2H), 7.22-7.26 (m, 1H), 7.33-7.39 (m, 1H), 7.65-7.67 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 8.9, 9.8, 113.9, 115.3 (d, $^2J_{C\text{-}F}$ = 21.4 Hz), 124.1, 124.2 (d, $^4J_{C\text{-}F}$ = 2.4 Hz), 127.1 (d, $^4J_{C\text{-}F}$ = 2.4 Hz), 129.6, 130.0, 130.1, 131.0 (d, $^3J_{C\text{-}F}$ = 7.9 Hz), 132.1, 132.6, 135.3, 136.6, 151.7, 162.4 (d, $^1J_{C\text{-}F}$ = 247.7 Hz). HRMS (ESI-TOF) calcd for $C_{19}H_{17}BrFN_2$: 371.0554 $[M+H]^+$, found: 371.0556.

(*Z*)-5-(2-Bromophenyl)-1-(4-chlorostyryl)-3,4-dimethyl-1*H*-pyrazole (6j)

Eluent: petroleum ether-ethyl acetate (20:1); 297 mg, 77%. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.93 (s, 3H), 2.03 (s, 3H), 6.45 (d, J = 8.8 Hz, 1H), 6.83 (d, J = 8.8 Hz, 1H), 7.02-7.04 (m, 2H), 7.20-7.26 (m, 3H), 7.35-7.37 (m, 2H), 7.66-7.68 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 8.9, 9.9, 114.1, 124.1, 124.9, 126.6, 127.1, 128.5, 129.7, 130.5, 132.1, 132.4, 132.7, 133.9, 135.2, 136.6, 151.8. HRMS (ESI-TOF) calcd for $C_{19}H_{17}BrClN_2$: 387.0258 $[M+H]^+$, found: 387.0261.

(*Z*)-5-(2-Bromophenyl)-1-(4-methoxystyryl)-3,4-dimethyl-1*H*-pyrazole (6k)

Eluent: petroleum ether-ethyl acetate (20:1); 299 mg, 78%. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.94 (s, 3H), 2.02 (s, 3H), 3.78 (s, 3H), 6.49 (d, J = 8.8 Hz, 1H), 6.72-6.78 (m, 3H), 6.97 (dd, J = 6.8, 2.0 Hz, 2H), 7.21-7.25 (m, 1H), 7.35 (td, J = 7.6, 1.2 Hz, 1H), 7.41 (dd, J = 7.6, 1.6

Hz, 1H), 7.66 (dd, *J* = 8.0, 1.2 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 9.0, 9.9, 55.2, 113.6, 113.7, 122.8, 124.1, 126.5, 127.1, 128.7, 129.5, 130.5, 132.2, 132.6, 135.5, 136.6, 151.5, 159.5. HRMS (ESI-TOF) calcd for $C_{20}H_{20}BrN_2O$: 383.0754 $[M+H]^+$, found: 383.0752.

(*Z*)-5-(2-Bromophenyl)-4-ethyl-1-(4-methoxystyryl)-3-methyl-1*H*-pyrazole (6l)

Eluent: petroleum ether-ethyl acetate (20:1); 317 mg, 80%. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.95 (t, *J* = 7.6 Hz, 3H), 2.01 (s, 3H), 2.36 (q, *J* = 7.6 Hz, 2H), 3.78 (s, 3H), 6.50 (d, *J* = 8.8 Hz, 1H), 6.72-6.77 (m, 3H), 6.96 (d, *J* = 8.8 Hz, 2H), 7.22-7.28 (m, 1H), 7.33-7.41 (m, 2H), 7.66 (d, *J* = 8.0 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 9.9, 15.2, 17.1, 55.2, 113.7, 120.2, 122.8, 124.3, 126.5, 127.0, 128.9, 129.5, 130.5, 132.2, 132.6, 135.7, 136.3, 150.9, 159.5. HRMS (ESI-TOF) calcd for $C_{21}H_{22}BrN_2O$: 397.0910 $[M+H]^+$, found: 397.0907.

Typical procedure for the synthesis of 5a from 6a and spectroscopic data of 5a-5l

To a flask containing (*Z*)-(2-bromophenyl)-3-methyl-1-styryl-1*H*-pyrazole (**6a**, 169 mg, 0.5 mmol) in DMSO (4 mL) were added $Pd(dba)_2$ (46 mg, 0.05 mmol), TFP (24 mg, 0.1 mmol) and K_2CO_3 (138 mg, 1 mmol). Then, the mixture was stirred at 100 ºC under N_2 atmosphere. Upon completion as indicated by TLC analysis, the reaction was quenched with water and extracted with ethyl acetate (10 mL×3). The combined organic layers were washed with water and brine, and then dried over anhydrous Na_2SO_4. The solvent was evaporated under vacuum, and the crude product was purified by column chromatography on silica-gel eluting with petroleum ether-ethyl acetate (20:1) to afford **5a** in 41% yield.

(*Z*)-8-Benzylidene-2-methyl-8*H*-pyrazolo[5,1-*a*]isoindole (5a)

Eluent: petroleum ether-ethyl acetate (20:1); Yellow oil (53 mg, 41%). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.44 (s, 3H), 6.23 (s, 1H), 6.82 (s, 1H), 7.35-7.39 (m, 3H), 7.46-7.54 (m, 3H), 7.73

(d, J = 7.2 Hz, 1H), 8.37 (d, J = 8.0 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 14.8, 97.6, 111.0, 120.2, 120.4, 127.2, 128.1, 128.2, 128.6, 128.7, 130.8, 131.0, 133.5, 137.9, 146.5, 154.4. HRMS (ESI-TOF) calcd for $C_{18}H_{15}N_2$: 259.1230 $[M+H]^+$, found: 259.1232.

(*Z*)-8-Benzylidene-5-chloro-2-methyl-8*H*-pyrazolo[5,1-*a*]isoindole (5b)

Eluent: petroleum ether-ethyl acetate (20:1); Yellow oil (67 mg, 46%); IR (neat) 3059, 2920, 2850, 1651, 1600, 1584, 1494, 1448, 1028, 941, 887, 799, 750, 692 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.09 (s, 3H), 6.59-6.63 (m, 2H), 6.85 (d, J = 8.8 Hz, 1H), 7.04-7.07 (m, 2H), 7.14-7.17 (m, 1H), 7.26-7.29 (m, 2H), 7.56 (d, J = 8.8 Hz, 1H), 7.70 (d, J = 2.8 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 11.3, 107.3, 119.8, 124.0, 128.4, 128.48, 128.53, 128.9, 129.0, 130.9, 133.4, 133.9, 134.5, 136.0, 139.8, 149.9. HRMS (ESI-TOF) calcd for $C_{18}H_{14}ClN_2$: 293.0840 $[M+H]^+$, found: 293.0842.

(*Z*)-8-Benzylidene-2,6-dimethyl-8*H*-pyrazolo[5,1-*a*]isoindole (5c)

Eluent: petroleum ether-ethyl acetate (20:1); Yellow solid (52 mg, 38%), mp 83-84 ^{o}C; IR (KBr) 3061, 2922, 2852, 1645, 1590, 1568, 1496, 1452, 1034, 918, 885, 825, 759, 689 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.42 (s, 3H), 2.47 (s, 3H), 6.17 (s, 1H), 6.78 (s, 1H), 7.19 (d, J = 7.6 Hz, 1H), 7.36-7.42 (m, 2H), 7.45-7.49 (m, 2H), 7.54 (s, 1H)，8.36 (d, J = 7.6 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 13.7, 20.8, 96.1, 109.5, 118.9, 110.0, 124.6, 127.2, 127.4, 128.5, 129.7, 130.1, 132.6, 136.2, 137.2, 145.6, 153.2. HRMS (ESI-TOF) calcd for $C_{19}H_{17}N_2$: 273.1386 $[M+H]^+$, found: 273.1388.

(*Z*)-8-Benzylidene-6-methoxy-2-methyl-8*H*-pyrazolo[5,1-*a*]isoindole (5d)

Eluent: petroleum ether-ethyl acetate (20:1); Yellow solid (60 mg, 42%), mp 109-110 ^{o}C; IR (KBr) 3064, 2922, 2851, 1617, 1585, 1486, 1455, 1223, 1024, 930, 865, 826, 742, 691 cm^{-1};

^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.43 (s, 3H), 3.91 (s, 3H), 6.21 (s, 1H), 6.68 (s, 1H), 6.88 (dd, *J* = 8.0, 2.4 Hz, 1H), 7.04 (d, *J* = 2.4 Hz, 1H), 7.35 (d, *J* = 7.6 Hz, 1H), 7.45 (t, *J* = 8.0 Hz, 2H), 7.62 (d, *J* = 8.4 Hz, 1H), 8.32 (d, *J* = 7.6 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 14.7, 55.7, 97.6, 105.3, 109.6, 113.6, 121.6, 128.17, 128.21, 128.6, 129.4, 130.6, 130.9, 133.7, 146.2, 154.2, 160.7. HRMS (ESI-TOF) calcd for $C_{19}H_{16}N_2ONa$: 311.1155 $[M+Na]^+$, found: 311.1154.

(*Z*)-8-Benzylidene-2,3-dimethyl-8*H*-pyrazolo[5,1-*a*]isoindole (5e)

Eluent: petroleum ether-ethyl acetate (20:1); Yellow solid (54 mg, 40%), mp 106-107 ^{o}C; IR (KBr) 3064, 2912, 2855, 1640, 1604, 1590, 1492, 1448, 1033, 910, 758, 746, 712, 685 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.27 (s, 3H), 2.36 (s, 3H), 6.72 (s, 1H), 7.31-7.40 (m, 3H), 7.48 (t, *J* = 7.6 Hz, 2H), 7.54 (d, *J* = 7.2 Hz, 1H), 7.70 (d, *J* = 8.0 Hz, 1H), 8.38 (d, *J* = 8.0 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 8.3, 12.7, 107.9, 109.8, 119.4, 120.4, 126.6, 128.2, 128.3, 128.6, 128.8, 130.6, 130.9, 133.8, 138.0, 143.2, 153.8. HRMS (ESI-TOF) calcd for $C_{19}H_{16}N_2Na$: 295.1206 $[M+Na]^+$, found: 295.1207.

(*Z*)-8-(3-Fluorobenzylidene)-2-methyl-8*H*-pyrazolo[5,1-*a*]isoindole (5f)

Eluent: petroleum ether-ethyl acetate (20:1); Yellow solid (55 mg, 40%), mp 107-108 ^{o}C; IR (KBr) 3090, 2923, 2851, 1649, 1607, 1575, 1491, 1463, 1123, 1089, 941, 760, 758, 681, 662 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.44 (s, 3H), 6.23 (s, 1H), 6.74 (s, 1H), 7.06 (t, *J* = 7.2 Hz,1H), 7.35-7.43 (m, 3H), 7.52 (d, *J* = 6.8 Hz, 1H), 7.71 (d, *J* = 7.2 Hz, 1H), 7.91 (d, *J* = 8.0 Hz, 1H), 8.47-8.51 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 14.7, 97.9, 109.5 (d, $^4J_{C\text{-}F}$ = 2.4 Hz), 115.3 (d, $^2J_{C\text{-}F}$ = 21.4 Hz), 117.2 (d, $^2J_{C\text{-}F}$ = 23.8 Hz), 120.3, 120.5, 126.7 (d, $^4J_{C\text{-}F}$ = 3.2 Hz), 127.4, 128.3, 129.0, 129.4 (d, $^3J_{C\text{-}F}$ = 7.9 Hz), 131.7, 135.7 (d, $^3J_{C\text{-}F}$ = 8.7 Hz), 137.8,

146.6, 154.8, 162.8 (d, $^{1}J_{C\text{-}F}$ = 243.0 Hz). HRMS (ESI-TOF) calcd for $C_{18}H_{14}FN_2$: 277.1136 $[M+H]^+$, found: 277.1138

(*Z*)-8-(4-Chlorobenzylidene)-2-methyl-8*H*-pyrazolo[5,1-*a*]isoindole (5g)

Eluent: petroleum ether-ethyl acetate (20:1); Yellow solid (53 mg, 36%), mp 84-85 ^{o}C; IR (KBr) 3068, 2963, 1646, 1586, 1489, 1473, 1257, 1087, 1012, 798, 757, 695, 685 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.42 (s, 3H), 6.22 (s, 1H), 6.73 (s, 1H), 7.35-7.43 (m, 4H), 7.51-7.53 (m, 1H), 7.70-7.72 (m, 1H), 8.31-8.33 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 13.7, 96.8, 108.5, 119.2, 119.4, 126.3, 127.1, 127.4, 127.9, 130.3, 130.98, 131.02, 133.1, 136.7, 145.5, 153.6. HRMS (ESI-TOF) calcd for $C_{18}H_{14}ClN_2$: 293.0840 $[M+H]^+$, found: 293.0843.

(*Z*)-2-Methyl-8-(4-methylbenzylidene)-8*H*-pyrazolo[5,1-*a*]isoindole (5h)

Eluent: petroleum ether-ethyl acetate (20:1); Yellow oil (46 mg, 34%); IR (neat) 3066, 2922, 2853, 1646, 1607, 1585, 1513, 1464, 1012, 916, 810, 755, 686 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.42 (s, 3H), 2.44 (s, 3H), 6.22 (s, 1H), 6.80 (s, 1H), 7.27-7.29 (m, 2H), 7.34-7.38 (m, 2H), 7.51-7.54 (m, 1H), 7.72 (t, *J* = 6.8 Hz, 1H), 8.27 (d, *J* = 8.0 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 14.8, 21.5, 97.4, 111.2, 120.1, 120.3, 127.1, 128.0, 128.5, 129.0, 130.4, 130.7, 130.8, 138.0, 138.7, 146.3, 154.2. HRMS (ESI-TOF) calcd for $C_{19}H_{16}N_2Na$: 295.1206 $[M+Na]^+$, found: 295.1205.

(*Z*)-8-(4-Fluorobenzylidene)-2,3-dimethyl-8*H*-pyrazolo[5,1-*a*]isoindole (5i)

Eluent: petroleum ether-ethyl acetate (20:1); Yellow solid (61 mg, 42%), mp 103-104 ^{o}C; IR (KBr) 3071, 2918, 2850, 1647, 1599, 1589, 1507, 1450, 1097, 1000, 912, 809, 760, 687 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.26 (s, 3H), 2.34 (s, 3H), 6.66 (s, 1H), 7.14 (t, *J* = 8.0 Hz,

2H), 7.29 (q, *J* = 7.2 Hz, 1H), 7.38 (t, *J* = 7.6 Hz, 1H), 7.54 (d, *J* = 7.6 Hz, 1H), 7.67 (d, *J* = 7.2 Hz, 1H), 8.36-8.39 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 8.3, 12.6, 107.9, 108.5, 115.1 (d, $^{2}J_{C\text{-}F}$ = 21.5 Hz), 119.5, 120.3, 126.7, 128.6, 128.8, 130.0 (d, $^{4}J_{C\text{-}F}$ = 3.2 Hz), 130.6, 132.6 (d, $^{3}J_{C\text{-}F}$ = 7.9 Hz), 137.8, 143.2, 153.7, 162.5 (d, $^{1}J_{C\text{-}F}$ = 247.7 Hz). HRMS (ESI-TOF) calcd for $C_{19}H_{16}FN_2$: 291.1292 $[M+H]^+$, found: 291.1295.

(*Z*)-8-(4-Chlorobenzylidene)-2,3-dimethyl-8*H*-pyrazolo[5,1-*a*]isoindole (5j)

Eluent: petroleum ether-ethyl acetate (20:1); Yellow solid (60 mg, 39%), mp 145-146 ^{o}C; IR (KBr) 3060, 2918, 2860, 1644, 1622, 1563, 1492, 1447, 1234, 1013, 911, 813, 749, 688 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.25 (s, 3H), 2.33 (s, 3H), 6.60 (s, 1H), 7.30 (t, *J* = 7.6 Hz, 1H), 7.35-7.41 (m, 3H), 7.52 (d, *J* = 7.6 Hz, 1H), 7.64 (d, *J* = 7.6 Hz, 1H), 8.30 (d, *J* = 8.8 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 8.3, 12.6, 108.1, 108.3, 119.5, 120.5, 126.7, 128.3, 128.7, 128.8, 131.2, 131.9, 132.3, 133.8, 137.7, 143.2, 154.0. HRMS (ESI-TOF) calcd for $C_{19}H_{16}ClN_2$: 307.0997 $[M+H]^+$, found: 307.0999.

(*Z*)-8-(4-Methoxybenzylidene)-2,3-dimethyl-8*H*-pyrazolo[5,1-*a*]isoindole (5k)

Eluent: petroleum ether-ethyl acetate (20:1); Yellow solid (66 mg, 44%), mp 155-156 ^{o}C; IR (KBr) 3081, 2921, 2839, 1640, 1600, 1572, 1514, 1449, 1184, 1029, 937, 813, 755, 688 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.28 (s, 3H), 2.36 (s, 3H), 3.89 (s, 3H), 6.70 (s, 1H), 7.00 (d, *J* = 8.8 Hz, 2H), 7.30-7.38 (m, 2H), 7.55 (d, *J* = 7.2 Hz, 1H), 7.68 (d, *J* = 7.6 Hz, 1H), 8.38 (d, *J* = 8.4 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 8.3, 12.6, 55.3, 107.5, 109.9, 113.7, 119.4, 120.1, 126.5, 126.6, 128.1, 128.5, 129.4, 132.4, 138.0, 142.9, 153.3, 159.7. HRMS (ESI-TOF) calcd for $C_{20}H_{19}N_2O$: 303.1492 $[M+H]^+$, found: 303.1488.

(*Z*)-3-Ethyl-8-(4-methoxybenzylidene)-2-methyl-8*H*-pyrazolo[5,1-*a*]isoindole (5l)

Eluent: petroleum ether-ethyl acetate (20:1); Yellow solid (58 mg, 37%), mp 112-113 ^{o}C; IR (KBr) 3078, 2956, 2926, 2835, 1641, 1597, 1572, 1510, 1447, 1170, 1033, 918, 805, 752, 700 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.28 (t, *J* = 7.6 Hz, 3H), 2.39 (s, 3H), 2.72 (q, *J* = 7.6 Hz, 2H), 3.89 (s, 3H), 6.72 (s, 1H), 7.00 (d, *J* = 8.8 Hz, 2H), 7.28-7.39 (m, 2H), 7.55 (d, *J* = 7.2 Hz, 1H), 7.70 (d, *J* = 7.2 Hz, 1H), 8.40 (d, *J* = 8.8 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 12.7, 15.3, 16.9, 55.3, 110.0, 113.7, 114.6, 119.6, 120.1, 126.52, 126.55, 128.2, 128.4, 129.4, 132.4, 138.0, 142.6, 152.7, 159.7. HRMS (ESI-TOF) calcd for $C_{21}H_{21}N_2O$: 317.1648 $[M+H]^+$, found: 317.1649.

Preparation of *tert*-butyl 5-(2-bromophenyl)-3-methyl-1*H*-pyrazole-1-carboxylate (II)

To a flask containing a solution of 5-(2-bromophenyl)-3-methyl-1*H*-pyrazole (**I**, 236 mg, 1 mmol) in THF (4 mL) were added di-*tert*-butyl dicarbonate (240 mg, 1.1 mmol) and DMAP (12 mg, 0.1 mmol). The mixture was stirred at room temperature for 2 h. Upon completion, the mixture was concentrated. To the residue were added with H_2O and ethyl acetate. The organic layer was separated and washed with brine, and then dried over anhydrous Na_2SO_4. The solvent was evaporated under vacuum, and the crude product was purified by column chromatography on silica gel using petroleum ether-ethyl acetate (4:1) as eluent to give **II** in 90% yield.

***tert*-Butyl 5-(2-bromophenyl)-3-methyl-1*H*-pyrazole-1-carboxylate (II)**

Eluent: petroleum ether-ethyl acetate (4:1); 303 mg, 90%; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.61 (s, 9H), 2.52 (s, 3H), 6.59 (s, 1H), 7.12-7.16 (m, 1H), 7.28 (t, *J* = 7.6 Hz, 1H), 7.55 (d, *J* = 7.6 Hz, 1H), 7.71 (dd, *J* = 7.6, 1.6 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 14.8, 28.0, 85.0, 111.1, 122.2, 127.4, 129.9, 131.5, 133.3, 133.6, 143.2, 148.7, 153.0. HRMS (ESI-TOF) calcd

for $C_{15}H_{18}BrN_2O_2$: 337.0546 $[M+H]^+$, found: 337.0542.

Preparation of *tert*-butyl 3-methyl-5-(2-(phenylethynyl)phenyl)-1*H*-pyrazole-1-carboxylate (III)

To a flask containing *tert*-butyl 5-(2-bromophenyl)-3-methyl-1*H*-pyrazole-1-carboxylate (**II**, 336 mg, 1 mmol) in Et_3N (5 mL) were added $Pd(PPh_3)_2Cl_2$ (14 mg, 0.02 mmol), CuI (2 mg, 0.01 mmol) and ethynylbenzene (**3a**, 122 mg, 1.2 mmol). Then, the mixture was stirred at 80 ºC under N_2 atmosphere. Upon completion as indicated by TLC analysis, the reaction was quenched with water and extracted with ethyl acetate (10 mL×3). The combined organic layers were washed with water and brine, and then dried over anhydrous Na_2SO_4. The solvent was evaporated under vacuum, and the crude product was purified by column chromatography on silica-gel eluting with petroleum ether-ethyl acetate (30:1) to afford **III** in 92% yield.

***tert*-Butyl 3-methyl-5-(2-(phenylethynyl)phenyl)-1*H*-pyrazole-1-carboxylate (III)**

Eluent: petroleum ether-ethyl acetate (30:1); 330 mg, 92%; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.68 (s, 9H), 2.61 (s, 3H), 6.97 (s, 1H), 7.36-7.41 (m, 5H), 7.50-7.53 (m, 2H), 7.62 (d, J = 6.8 Hz, 1H), 7.99 (d, J = 8.0 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 14.9, 28.0, 84.8, 89.5, 93.3, 110.7, 121.4, 123.4, 128.3, 128.4, 128.5, 128.6, 128.8, 131.4, 133.3, 134.1, 143.5, 148.9, 152.8. HRMS (ESI-TOF) calcd for $C_{23}H_{23}N_2O_2$: 359.1754 $[M+H]^+$, found: 359.1755.

Preparation of 3-methyl-5-(2-(phenylethynyl)phenyl)-1*H*-pyrazole (C)

To a flask containing a solution of *tert*-butyl 3-methyl-5-(2-(phenylethynyl)phenyl)-1*H*-pyrazole-1-carboxylate (**III**, 358 mg, 1 mmol) in CH_2Cl_2 (12 mL) was added TFA (1.5 mL). The resulting mixture was stirred at room temperature for 3.5 h, and quenched with saturated

solution of $NaHCO_3$. It was then extracted with diethyl ether (30 mL×3). The combined organic layers were washed with water and brine, and then dried over $MgSO_4$. The solvent was evaporated under vacuum, and the crude product was purified by column chromatography on silica-gel eluting with petroleum ether-ethyl acetate (3:1) to give **C** in 91% yield.

3-Methyl-5-(2-(phenylethynyl)phenyl)-1*H*-pyrazole (C)

Eluent: petroleum ether-ethyl acetate (3:1); 235 mg, 91%; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.30 (s, 3H), 6.85 (s, 1H), 7.34-7.41 (m, 5H), 7.61-7.63 (m, 2H), 7.71-7.73 (m, 1H), 7.86 (s, 1H), 13.35 (br s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 11.9, 89.7, 93.2, 105.3, 120.7, 122.4, 123.5, 127.5, 127.6, 128.5, 128.6, 128.7, 129.3, 131.4, 131.6, 133.5, 133.6. HRMS (ESI-TOF) calcd for $C_{18}H_{15}N_2$: 259.1230 $[M+H]^+$, found: 259.1233.

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Supporting Information. Copies of ^{1}H and ^{13}C NMR spectra. This material is available free of charge *via* the Internet at http://pubs.acs.org.

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