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## *Graphical Abstract*

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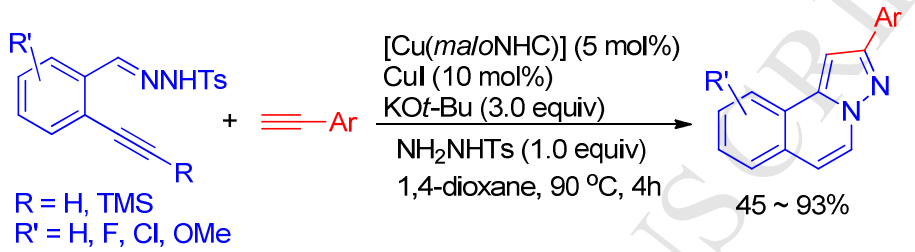

# [Cu(*malo*NHC)]-catalyzed synthesis of 2-aryl pyrazolo[5,1-*a*]isoquinolines by annulation of *N*′-(2-((trimethylsilyl)ethynyl)benzylidene)hydrazides with terminal aromatic alkynes

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**Abstract:** A [Cu(*malo*NHC)]-catalyzed synthesis of 2-aryl pyrazolo[5,1-*a*]isoquinolines *via* annulation of *N*′-(2-((trimethylsilyl)ethynyl)benzylidene)hydrazides with terminal aromatic alkynes was developed.

*Keywords*: annulation; alkynes; pyrazolo[5,1-*a*]isoquinolines; *N*-heterocyclic carbene.

## 1. Introduction

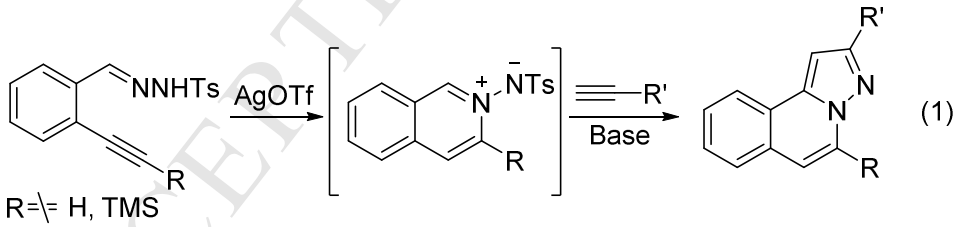
It is one of the interesting and important research topics to synthesize the fused *N*-heterocyclic compounds due to their potential physiological and biological activity.[1] Pyrazoles[2] and isoquinolines[3] are the important classes of *N*-heterocyclic compounds. Pyrazolo[5,1-*a*]isoquinolines, incorporated both isoquinoline and pyrazole skeletons, represent one of the interesting structures of the fused *N*-heterocyclic compounds, which may show the promising biological activity.[4]

Wu's group has well-studied and reported the construction of pyrazolo[5,1-*a*]isoquinoline skeleton bearing *multi*-substituents by AgOTf-catalyzed tandem reactions of *N*′-(2-alkynylbenzylidene)hydrazides (or generated *in situ*, R ≠ H, $SiMe_3$) (Scheme 1) with a variety of other reactants,[5] and the reactive intermediate is proposed to be the *N*-tosyl isoquinolinium-2-yl amide, generated *via* 6-*endo*-cyclization by intramolecular nucleophilic

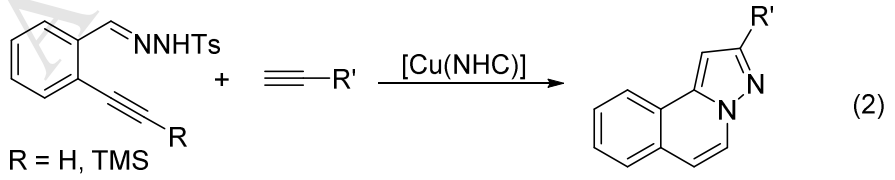
attack of hydrazide group to carbon-carbon triple bond. The reaction of *N*′-(2-alkynylbenzylidene)hydrazides with terminal alkynes provides an efficient method for the synthesis of 2,5-disubstituted pyrazolo[5,1-*a*]isoquinolines (Scheme 1, eq. 1).[5a] The similar intermediates of *N*-benzoylpyridinium imides have been also well used in the synthesis of pyrazolo[1,5-*a*]pyridines *via* a [3+2] cycloaddition with alkynes under different conditions.[6]

On the other hand, Cu/NHC (*N*-heterocyclic carbene)-catalyzed transformation has attracted widespread attention,[7] but the application of Cu/NHC as catalyst in the synthesis of *N*-heterocycles is limited to the [3+2] cycloaddition of azides with alkynes for the synthesis of 1,2,3-triazoles.[8] With several Cu/NHC complexes in hand, and in continuation of our previous work on the synthesis of *N*-heterocycles *via* annulation reactions using alkynes as one of the reactants,[9] we explored the possibility to extend the application of Cu/NHC complexes as catalysts to catalyze the annulation of *N*′-(2-alkynylbenzylidene)hydrazide (R = H) (Scheme 1, eq. 2) with terminal aromatic alkynes for the synthesis of 2-aryl pyrazolo[5,1-*a*]isoquinolines.

Wu's work: AgOTf-catalyzed synthesis of 2,5-disubstituted pyrazolo[5,1-*a*]isoquinolines




This work: [Cu(NHC)]-catalyzed synthesis of 2-substituted pyrazolo[5,1-*a*]isoquinolines

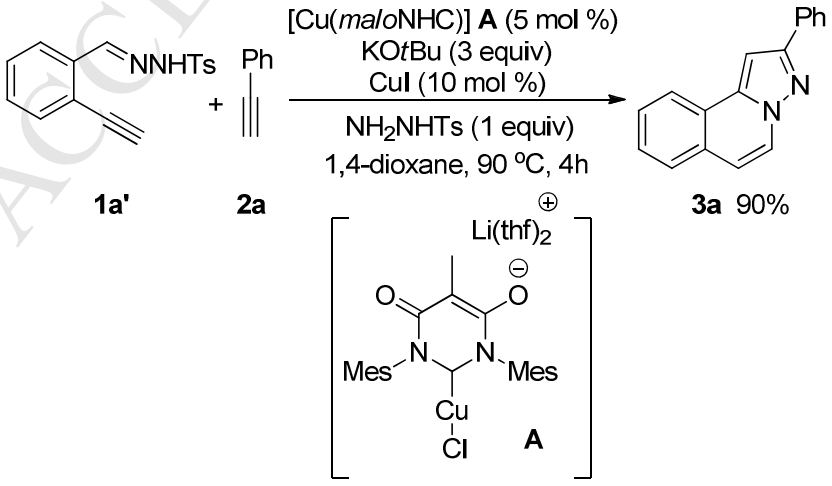



**Scheme 1.** Synthesis of pyrazolo[5,1-*a*]isoquinolines

## 2. Results and discussion

At first, we carried out the reaction of *N*'-(2-ethynylbenzylidene)hydrazide (**1a'**) (R = H, as shown in Scheme 1) with phenylacetylene (**2a**) in the presence of [Cu(*malo*NHC)] (**A**) ([(*malo*NHC)CuCl]·Li(THF)$_2$,[10] 5 mol%), CuI (10 mol%), 3.0 equivalent of KO*t*Bu and 1.0 equivalent of $NH_2NHTs$ in 1,4-dioxane at 90 °C under $N_2$ for 4 h, and the desired product of 2-phenyl pyrazolo[5,1-a]isoquinoline (**3a**) could be isolated from the reaction mixture in 90% yield (Scheme 2).[11] Because **1a** (R = $SiMe_3$, in Scheme 1) is the precursor of **1a'**, which can be converted into **1a'** under basic conditions, we therefore performed the reaction of **1a** with **2a** under the same reaction conditions, and fortunately **3a** could be obtained in 85% yield (Table 1, entry 1).

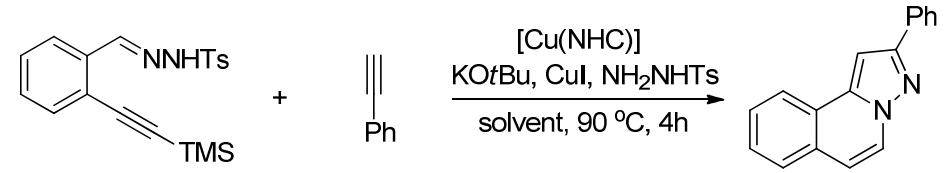
Screening of other [Cu(NHC)] complexes in the reaction of **1a** with **2a** under the similar conditions revealed that **B** showed the similar catalytic activity as **A** (Table 1, entry 2). The use of **C** and **D** complexes gave low yields of **3a** (Table 1, entries 3-4). In case of either without Cu(NHC) complex or without CuI, no product formed at all (Table 1, entries 5 and 6).[12] Other solvents such as toluene, DCE and MeCN are less effective and afforded **3a** in low yields (Table 1, entries 7-9). In addition, no desired product could be obtained without use of KO*t*Bu (Table 1, entry 10).



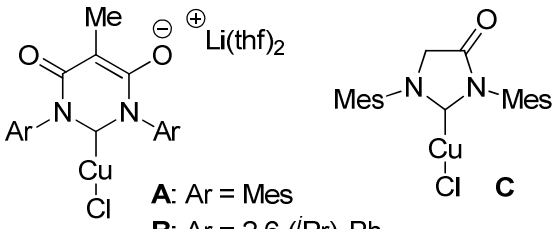

**Scheme 2.** Synthesis of 2-phenylpyrazolo[5,1-*a*]isoquinoline from **1a'**

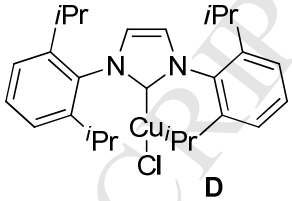
**Table 1**

Reaction optimization for the synthesis of **3a** [a]




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




| Entry | Cu(NHC) | Solvent | Yield (%)[b] |
|---|---|---|---|
| 1 | **A** | 1,4-dioxane | 85 |
| 2 | **B** | 1,4-dioxane | 88 |
| 3 | **C** | 1,4-dioxane | 20 |
| 4 | **D** | 1,4-dioxane | 35 |
| 5 | | 1,4-dioxane | 0 |
| 6[c] | **B** | 1,4-dioxane | 0 |
| 7 | **B** | toluene | 31 |
| 8 | **B** | DCE | 43 |
| 9 | **B** | MeCN | 18 |
| 10[d] | **B** | 1,4-dioxane | 0 |

[a] The reactions were carried out at 90 °C for 4 h by using **1a** (0.25 mmol), **2a** (0.2 mmol), Cu(NHC) (5 mol%), CuI (10 mol%), KO*t*Bu (3 equiv) and $NH_2NHTs$ (1 equiv) in solvent (5 mL) under $N_2$.

[b] Isolated yield.

[c] Without CuI.

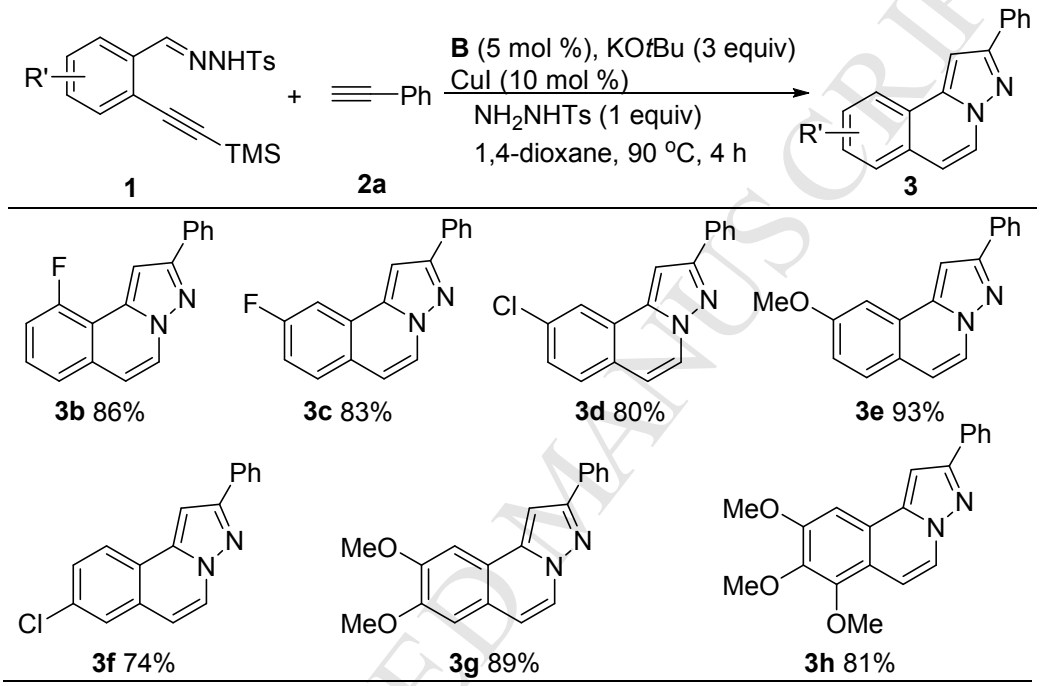
[d] Without base.

Under the optimized reaction conditions (indicated in entry 2 of Table 1), we then examined the scope of the reactants, and Table 2 shows the effect of substituents in starting material **1**, when it was allow to react with **2a**. Neither significant electron effect nor steric hindrance effect could be observed by using **1** bearing electron-withdrawing groups or

electron-donating groups at different position, and the corresponding products **3b-e** and **3g-h** were obtained good yields. Only in the case of **1** having chloro group at 4-position of phenyl ring used, the corresponding product **3f** was formed in a declined yield (77%).

**Table 2**

Substrate scope of **1**[a]



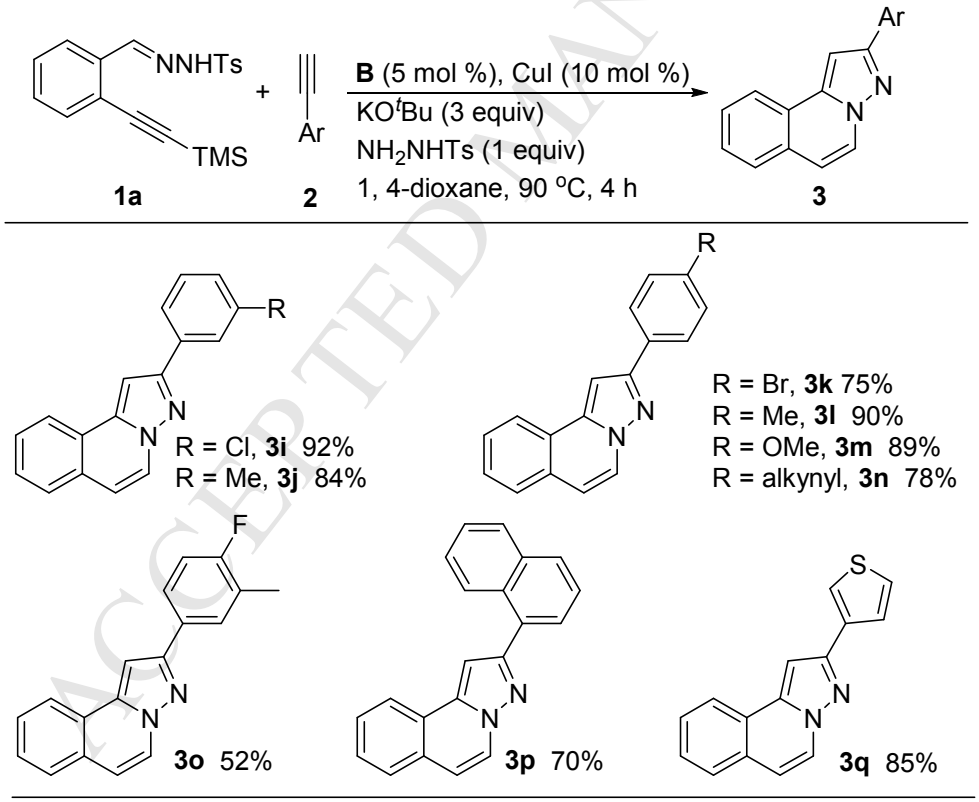

[a] Reactions were carried out with **1** (0.25 mmol), **2a** (0.2 mmol), B (5 mol%), CuI (10 mol%), KO*t*Bu (3 equiv) and $NH_2NHTs$ (1 equiv) in 1,4-dioxane (5 mL) at 90 °C for 4 h.

Table 3 summaries the results from the reaction of **1a** with various terminal aromatic alkynes (**2**), and various 2-arylpyrazolo[5,1-*a*]isoquinoline (**3i-q**) were obtained in good to excellent yields. The effects of substituent(s) in aryl group of alkynes are apparently observed. Terminal aromatic alkynes bearing electron-withdrawing group (Cl group) at *meta*-position showed higher reactivity than that having electron-donating group (Me) at the same position, and the corresponding products **3i** and **3j** formed in 92% and 84%, respectively. However, in the cases of *para*-substituted aromatic alkynes employed, alkynes having electron-donating group showed higher reactivity (products **3l** and **3m**) than those bearing electron-withdrawing

groups (products **3k** and **3n**). Noted that 1,4-diethynylbenzene also showed good reactivity to give **3n** with one alkynyl group untouched, which is expected to be the interesting intermediate for further transformation. In addition, the use of 4-fluoro-3-methylphenylacetylene and 1-ethynylnaphthalene led to relative low yields of the expected products **3o** and **3p**. The reaction of 3-ethynylthiophene afforded **3q** in 85% yield. Moreover, the structures of **3k** and **3q** were further confirmed by x-ray diffraction (see SI for details). However, all attempts to realize the annulation of terminal aliphatic alkynes under similar conditions have been unsuccessful to date.

**Table 3**

Substrate scope of alkynes[a]



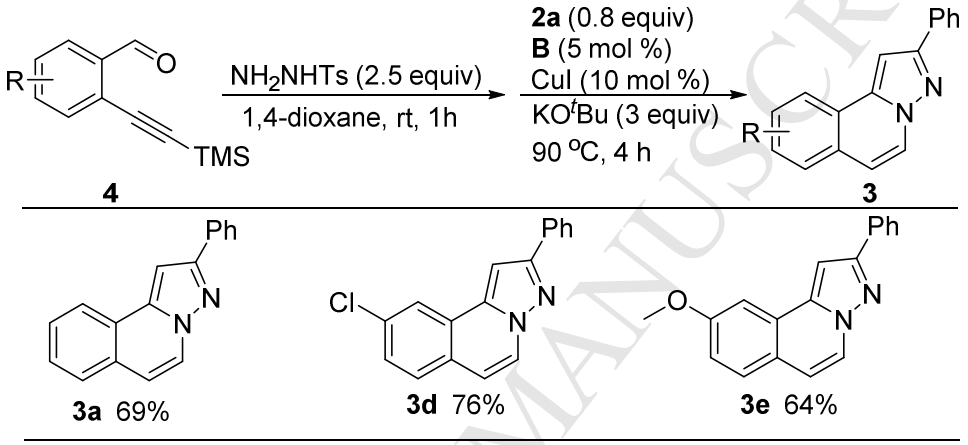

[a] Reactions were carried out with **1a** (0.25 mmol), **2** (0.2 mmol), B (5 mol%), CuI (10 mol%), KO*t*Bu (3 equiv) and $NH_2NHTs$ (1 equiv) in 1,4-dioxane (5 mL) at 90 °C for 4 h.

Since the transformation of aldehydes to the corresponding tosylhydrazones is highly

efficient, and then a one-pot/two steps process for the synthesis of **3** using 2-((trimethylsilyl)ethynyl)benzaldehyde as one of the starting materials was also studied. As shown in Table 4, the reaction occurred smoothly to afford the corresponding products in acceptable yields.

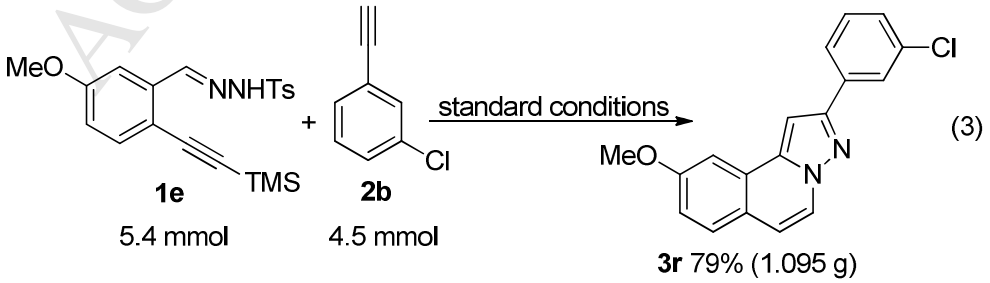
**Table 4**

One-pot synthesis of pyrazolo[5,1-*a*]isoquinoline [a]




[a] Reactions were carried out with **4** (0.25 mmol), $NH_2NHTs$ (2.5 equiv), **2a** (0.2 mmol), **B** (5 mol%), CuI (10 mol%) and KO*t*Bu (3 equiv) in 1,4-dioxane (5 mL).

To investigate the potential applications of this transformation, a gram-scale reaction of **1e** (5.4 mmol) with **2b** (4.5 mmol) under standard conditions was conducted, and the desired **3r** was obtained in 79% yield (1.095 g) (eq 3).




The mechanism of the present annulation in the presence of [Cu(*malo*NHC)] is considered to be essentially similar to AgOTf-catalyzed reaction of *N*′-(2-alkynylbenzylidene)hydrazides

with terminal alkynes.[5a]

## 3. Conclusion

In conclusion, we have developed an efficient [Cu(*malo*NHC)]-catalyzed synthesis of 2-arylpyrazolo[5,1-*a*]isoquinolines by the annulation of *N*′-(2-((trimethylsilyl)ethynyl)-benzylidene)hydrazides with terminal aromatic alkynes. The present work not only extends the application of Cu/NHC as catalyst in the synthesis of *N*-heterocyclic compounds with the use of alkyne as one of the reactants, but also broadens the molecular library of 2-substituted pyrazolo[1,5-*a*]isoquinolines.[13] Further investigations on the application of the products as the ligands of organic phosphorescent materials are in progress.

## 4. Experimental section

### 4.1 General methods

All organic compounds and inorganic salts were analytically pure and used directly after purchased. Nuclear magnetic resonance (NMR) spectra were recorded at 298 K. $^{1}$H NMR (400 MHz) chemical shifts (δ) were referenced to internal standard TMS (δ = 0.00 ppm). $^{13}$C NMR (100 MHz) chemical shifts were referenced to internal solvent $CDCl_3$ (δ = 77.16 ppm). HRMS spectra were obtained on a microTOF-Q 10142 spectrometer with electron spray ionization (ESI) source. The melting points were uncorrected. Single crystal X-ray diffraction data were collected on a diffraction meter.

### 4.2 A typical experiment procedure for synthesis of 3a

A mixture of *N*'-(2-((trimethylsilyl)ethynyl)-benzylidene)-4-methylbenzenesulfono-hydrazide (**1a**, 92.5 mg, 0.25 mmol), phenylacetylene (**2a**, 20.2 mg, 0.2 mmol), [Cu(*malo*NHC)] **B** (6.9 mg, 0.01 mmol, 5 mol %), CuI (3.8 mg, 0.02 mmol, 10 mol %), KO*t*Bu (67.2 mg, 0.6 mmol, 3 equiv) and $NH_2NHTs$ (37.2 mg, 0.2 mmol, 1 equiv) and 1,4-dioxane (5.0 mL) was heated at 90 °C (oil bath temperature) with stirring in a 25 mL screw-capped thick-walled Pyrex tube under nitrogen atmosphere. When TLC control showed

the completion of the reaction (after 4 h), the mixture was extracted with dichloromethane (DCM) three times, and dried over $Na_2SO_4$. The solvent was evaporated and the crude residue was purified by column chromatography on silica gel to afford **3a** as a white solid in 88% yield (42.9 mg).

### 4.3 Characterization data of new starting materials and products

The new starting materials and all the products were characterized by $^1$H-NMR, $^{13}$C-NMR and HRMS (for new compounds). The copies of NMR charts were reported in supplementary data.

*N'-(2-Fluoro-2-((trimethylsilyl)ethynyl)benzylidene)-4-methylbenzenesulfonohydrazide* ***(1b)***. White solid; mp 152-154 $^o$C; $^1$H-NMR (400 MHz, $CDCl_3$): δ 8.70 (s, 1H), 8.22 (s, 1H), 7.92 (dd, *J* = 8.0, 1.6 Hz, 2H), 7.31 (d, *J* = 8.0 Hz, 2H), 7.26-7.21 (m, 2H), 7.04-6.99 (m, 1H), 2.40 (s, 3H), 0.23 (s, 9H); $^{13}$C-NMR (100 MHz, $CDCl_3$): δ 160.3 (d, *J* = 258 Hz), 144.3, 143.0 (d, *J* = 4 Hz), 135.2, 130.5 (d, *J* = 9 Hz), 129.6, 129.1 (d, *J* = 3 Hz), 128.1, 125.2 (d, *J* = 4 Hz), 122.5 (d, *J* = 10 Hz), 117.1 (d, *J* = 21 Hz), 102.3, 100.8 (d, *J* = 4 Hz), 21.7, -0.2; HRMS (ESI) calcd for $C_{19}H_{22}FN_2O_2SSi$ m/z $[M+H]^+$: 389.1155; found: 389.1149.

*N'-(5-Fluoro-2-((trimethylsilyl)ethynyl)benzylidene)-4-methylbenzenesulfonohydrazide* ***(1c)***. White solid; mp 171-173 $^o$C; $^1$H-NMR (400 MHz, $CDCl_3$): δ 8.63 (s, 1H), 8.23 (s, 1H), 7.89 (d, *J* = 8.0 Hz, 2H), 7.55 (dd, *J* = 9.6, 2.6 Hz, 1H), 7.42-7.38 (m, 1H), 7.34 (d, *J* = 8.0 Hz, 2H), 2.42 (s, 3H), 0.22 (s, 9H); $^{13}$C-NMR (100 MHz, $CDCl_3$): δ 162.5 (d, *J* = 248 Hz), 144.6, 144.5 (d, *J* = 3 Hz), 136.9 (d, *J* = 8 Hz), 135.3, 134.8 (d, *J* = 8 Hz), 129.9, 128.1, 119.4 (d, *J* = 3 Hz), 117.5 (d, *J* = 23 Hz), 111.9 (d, *J* = 24 Hz), 100.7, 100.5, 21.7, -0.06; HRMS (ESI) calcd for $C_{19}H_{22}FN_2O_2SSi$ *m/z* $[M+H]^+$: 389.1155; found: 389.1159.

*N'-(5-Chloro-2-((trimethylsilyl)ethynyl)benzylidene)-4-methylbenzenesulfonohydrazide* ***(1d)***. White solid; mp 141-144 $^o$C; $^1$H-NMR (400 MHz, $CDCl_3$): δ 8.52 (s, 1H), 8.20 (s, 1H), 7.88 (d, *J* = 8.0, 2H), 7.85 (d, *J* = 2.4 Hz, 1H), 7.35 (s, 1H), 7.34 (d, *J* = 8.0, 2H), 7.26-7.22 (m, 1H), 2.43 (s, 3H), 0.23 (s, 9H); $^{13}$C-NMR (100 MHz, $CDCl_3$): δ 144.6, 144.3, 135.9, 135.3,

135.0, 134.0, 130.0, 129.9, 128.1, 125.2, 121.6, 102.1, 100.4, 21.7, -0.08; HRMS (ESI) calcd for $C_{19}H_{22}ClN_2O_2SSi$ *m/z* $[M+H]^+$: 405.0860; found: 405.0853.

*N'-(5-Methoxy-2-((trimethylsilyl)ethynyl)benzylidene)-4-methylbenzenesulfonohydrazide* ***(1e)***. White solid; mp 148-150 $^oC$; $^1H$-NMR (400 MHz, $CDCl_3$): δ 8.67 (s, 1H), 8.26 (s, 1H), 7.89 (d, *J* = 8.0 Hz, 2H), 7.37-7.30 (m, 4H), 6.83 (dd, *J* = 7.4, 1.8 Hz, 1H), 3.82 (s, 3H), 2.40 (s, 3H), 0.21 (s, 9H); $^{13}C$-NMR (100 MHz, $CDCl_3$): δ 159.7, 145.8, 144.4, 136.0, 135.4, 134.2, 129.8, 128.0, 117.2, 115.9, 108.9, 101.6, 99.1, 55.5, 21.6, 0.03; HRMS (ESI) calcd for $C_{20}H_{25}N_2O_3SSi$ *m/z* $[M+H]^+$: 401.1355; found: 401.1362.

*N'-(4-Chloro-2-((trimethylsilyl)ethynyl)benzylidene)-4-methylbenzenesulfonohydrazide* ***(1f)***. White solid; mp 137-139 $^oC$; $^1H$-NMR (400 MHz, $CDCl_3$): δ 8.84 (s, 1H), 8.23 (s, 1H), 7.89 (d, *J* = 8.0 Hz, 2H), 7.79 (d, *J* = 8.0 Hz, 1H), 7.38 (d, *J* = 2.0 Hz, 1H), 7.32 (d, *J* = 8.2 Hz, 2H), 7.21 (dd, *J* = 8.6, 1.9 Hz, 1H), 2.40 (s, 3H), 0.22 (s, 9H); $^{13}C$-NMR (100 MHz, $CDCl_3$): δ 144.7, 144.5, 135.6, 135.3, 133.0, 132.3, 129.8, 129.2, 128.0, 126.6, 124.5, 102.4, 99.9, 21.7, -0.18; HRMS (ESI) calcd for $C_{19}H_{22}ClN_2O_2SSi$ *m/z* $[M+H]^+$: 405.0860; found: 405.0860.

*N'-(4,5-Dimethoxy-2-((trimethylsilyl)ethynyl)benzylidene)-4-methylbenzenesulfonohydrazide* ***(1g)***. White solid; mp 161-163 $^oC$; $^1H$-NMR (400 MHz, $CDCl_3$): δ 8.32 (s, 1H), 8.22 (s, 1H), 7.88 (d, *J* = 8.1 Hz, 2H), 7.34 (s, 1H), 7.30 (d, *J* = 8.1 Hz, 2H), 6.84 (s, 1H), 3.90 (s, 3H), 3.86 (s, 3H), 2.41 (s, 3H), 0.22 (s, 9H); $^{13}C$-NMR (100 MHz, $CDCl_3$): δ 150.6, 149.8, 146.2, 144.3, 135.5, 129.7, 128.4, 128.1, 116.6, 114.1, 106.9, 101.5, 99.4, 56.1, 56.0, 21.7, 0.02; HRMS (ESI) calcd for $C_{21}H_{27}N_2O_4SSi$ *m/z* $[M+H]^+$: 431.1461; found: 431.1455.

*4-Fluoro-5-methoxy-2-((trimethylsilyl)ethynyl)benzaldehyde* ***(1h')***. white solid; mp 90-93 $^oC$; $^1H$-NMR (400 MHz, $CDCl_3$): δ 10.3 (s, 1H), 7.36 (d, *J* = 8.0 Hz, 2H), 7.15 (d, *J* = 8.6 Hz, 1H), 3.86 (s, 3H), 0.20 (s, 9H); $^{13}C$-NMR (100 MHz, $CDCl_3$): δ 190.0, 152.2 (d, *J* = 256 Hz), 148.8 (d, *J* = 11 Hz), 133.5 (d, *J* = 3 Hz), 120.5, 120.4 (d, *J* = 20 Hz), 110.4 (d, *J* = 4 Hz), 101.8, 98.7 (d, *J* = 2 Hz), 56.2, -0.3; HRMS (ESI) calcd for $C_{13}H_{16}FO_2Si$ *m/z* $[M+H]^+$: 251.0904; found: 251.0910.

*N'-(4-Fluoro-5-methoxy-2-((trimethylsilyl)ethynyl)benzylidene)-4-methylbenzenesulfonohydrazide (**1h**).* White solid; mp 131-134 $^{o}$C; $^{1}$H-NMR (400 MHz, $CDCl_3$): δ 8.40 (s, 1H), 8.20 (s, 1H), 7.88 (d, *J* = 8.0 Hz, 2H), 7.41 (d, *J* = 8.3 Hz, 1H), 7.32 (d, *J* = 8.0 Hz, 2H), 7.10 (d, *J* = 8.0 Hz, 1H), 3.91 (s, 3H), 2.41 (s, 3H), 0.22 (s, 9H); $^{13}$C-NMR (100 MHz, $CDCl_3$): δ 153.1 (d, *J* = 251 Hz), 148.7, (d, *J* = 12 Hz), 145.2, 144.6, 135.4, 131.7, 129.9, 128.1, 119.8 (d, *J* = 20 Hz), 116.4 (d, *J* = 8 Hz), 109.2, 100.4, 100.3, 56.4, 21.7, -0.04; HRMS (ESI) calcd for $C_{20}H_{24}FN_2O_3SSi$ *m/z* $[M+H]^+$: 419.1261; found: 419.1263.

*N'-(4,5,6-Trimethoxy-2-((trimethylsilyl)ethynyl)benzylidene)-4-methylbenzenesulfonohydrazide (**1i**).* Yellow solid; mp 129-131 $^{o}$C; $^{1}$H-NMR (400 MHz, $CDCl_3$): δ 8.42 (s, 1H), 8.21 (s, 1H), 7.87 (d, *J* = 8.2 Hz, 2H), 7.29 (d, *J* = 8.2 Hz, 2H), 7.18 (s, 1H), 3.90 (s, 3H), 3.88 (s, 3H), 3.86 (s, 3H), 2.40 (s, 3H), 0.22 (s, 9H); $^{13}$C-NMR (100 MHz, $CDCl_3$): δ 155.0, 154.1, 145.7, 144.4, 144.1, 135.5, 130.8, 129.7, 128.0, 111.9, 104.0, 103.6, 97.3, 61.2, 56.2, 21.7, -0.00; HRMS (ESI) calcd for $C_{22}H_{29}N_2O_5SSi$ *m/z* $[M+H]^+$: 461.1566; found: 461.1554.

*2-Phenylpyrazolo[5,1-a]isoquinoline (**3a**).*[12] White solid (42.9 mg, 88% yield); mp 109-111 $^{o}$C ; $^{1}$H-NMR (400 MHz, $CDCl_3$): δ 8.30 (d, *J* = 8.1 Hz, 1H), 8.13 (d, *J* = 8.0 Hz, 1H), 8.03-8.01 (m, 2H), 7.72 (d, *J* = 8.0 Hz, 1H), 7.61-7.53 (m, 2H), 7.51-7.47 (m, 2H), 7.39 (dd, *J* = 7.2, 1.6 Hz, 1H), 7.29 (s, 1H), 7.00 (d, *J* = 8.0 Hz, 1H); $^{13}$C-NMR (100 MHz, $CDCl_3$): δ 152.9, 139.8, 133.0, 128.9, 128.5, 128.1, 127.7, 127.3, 126.4, 126.3, 124.4, 123.8, 112.2, 94.7; HRMS (ESI) calcd for $C_{17}H_{13}N_2$ *m/z* $[M+H]^+$: 245.1079; found: 245.1091.

*10-Fluoro-2-phenylpyrazolo[5,1-a]isoquinoline (**3b**).* White solid (45.1 mg, 86% yield); mp 129-130 $^{o}$C ; $^{1}$H-NMR (400 MHz, $CDCl_3$): δ 8.21 (d, *J* = 8.0 Hz, 1H), 7.95-7.92 (m, 2H), 7.41-7.35 (m, 5H), 7.32-7.30 (m, 1H), 7.22-7.17 (m, 1H), 6.88 (dd, *J* = 7.8, 1.7 Hz, 1H); $^{13}$C-NMR (100 MHz, $CDCl_3$): δ 158.7 (d, *J* = 251 Hz), 153.5, 134.9, 133.0, 131.3 (d, *J* = 4 Hz), 128.9, 128.6, 128.5 (d, *J* = 9 Hz), 127.4, 126.6, 122.8 (d, *J* = 4 Hz), 114.3 (d, *J* = 15 Hz), 113.4 (d, *J* = 20 Hz), 111.4 (d, *J* = 3 Hz), 99.4 (d, *J* = 10 Hz); HRMS (ESI) calcd for $C_{17}H_{12}N_2F$ *m/z* $[M+H]^+$: 263.0985; found: 263.0989.

*9-Fluoro-2-phenylpyrazolo[5,1-a]isoquinoline (**3c**).* Yellow solid (43.5 mg, 83% yield); mp 130-132 $^{o}$C ; $^{1}$H-NMR (400 MHz, $CDCl_3$): δ 8.26 (d, *J* = 8.0 Hz, 1H), 8.01 (dd, *J* = 8.2, 2.6 Hz, 2H), 7.75 (dd, *J* = 9.2, 2.6 Hz, 1H), 7.70 (dd, *J* = 8.8, 5.4 Hz, 1H), 7.49-7.47 (m, 2H), 7.42-7.40 (m, 1H), 7.29-7.27 (m, 2H), 6.98 (d, *J* = 8.0 Hz, 1H); $^{13}$C-NMR (100 MHz, $CDCl_3$): δ 162.0 (d, *J* = 247 Hz), 153.1, 139.2, 132.9, 129.7 (d, *J* = 9 Hz), 129.0, 128.7, 126.5, 125.9 (d, *J* = 10 Hz), 125.7 (d, *J* = 3 Hz), 125.5 (d, *J* = 2 Hz), 116.8 (d, *J* = 24 Hz), 111.7, 109.2 (d, *J* = 23 Hz), 95.3; HRMS (ESI) calcd for $C_{17}H_{12}N_2F$ *m/z* $[M+H]^+$: 263.0985; found: 263.0986.

*9-Chloro-2-phenylpyrazolo[5,1-a]isoquinoline (**3d**).* White solid (44.5 mg, 80% yield); mp 158-160 $^{o}$C ; $^{1}$H-NMR (400 MHz, $CDCl_3$): δ 8.20 (d, *J* = 7.4 Hz, 1H), 8.01 (d, *J* = 1.9 Hz, 1H), 7.93-7.91 (m, 2H), 7.56 (d, *J* = 8.5 Hz, 1H), 7.42-7.39 (m, 3H), 7.34-7.30 (m, 1H), 7.18 (s, 1H), 6.87 (d, *J* = 7.4 Hz, 1H); $^{13}$C-NMR (100 MHz, $CDCl_3$): δ 153.4, 138.8, 133.6, 132.8, 128.9, 128.8, 128.7, 128.6, 127.3, 126.6, 126.5, 125.6, 123.4, 111.6, 95.3; HRMS (ESI) calcd for $C_{17}H_{12}N_2Cl$ *m/z* $[M+H]^+$: 279.0689; found: 279.0685.

*9-Methoxy-2-phenylpyrazolo[5,1-a]isoquinoline (**3e**).* Yellow liquid (51.0 mg, 93% yield); $^{1}$H-NMR (400 MHz, $CDCl_3$): δ 8.18 (d, *J* = 7.3 Hz, 1H), 8.03-8.00 (m, 2H), 7.61 (d, *J* = 8.7 Hz, 1H), 7.49-7.46 (m, 3H), 7.40-7.36 (m, 1H), 7.20 (s, 1H), 7.15 (dd, *J* = 8.7, 2.5 Hz, 1H), 6.92 (d, *J* = 7.3 Hz, 1H), 3.96 (s, 3H); $^{13}$C-NMR (100 MHz, $CDCl_3$): δ 159.2, 152.6, 139.5, 133.2, 128.9, 128.4, 126.4, 125.7, 124.2, 123.0, 117.8, 112.0, 105.1, 94.5, 55.6; HRMS (ESI) calcd for $C_{18}H_{15}N_2O$ *m/z* $[M+H]^+$: 275.1184; found: 275.1190.

*8-Chloro-2-phenylpyrazolo[5,1-a]isoquinoline (**3f**).* White solid (41.1 mg, 74% yield); mp 161-163 $^{o}$C ; $^{1}$H-NMR (400 MHz, $CDCl_3$): δ 8.39 (d, *J* = 7.4 Hz, 1H), 8.04-87.98 (m, 3H), 7.69 (d, *J* = 1.5 Hz, 1H), 7.53-7.46 (m, 3H), 7.41-7.31 (m, 1H), 7.24 (s, 1H), 6.90 (d, *J* = 7.4 Hz, 1H); $^{13}$C-NMR (100 MHz, $CDCl_3$): δ 153.4, 139.3, 134.0, 132.9, 130.2, 128.9, 128.7, 128.2, 127.4, 126.6, 126.5, 125.3, 122.9, 111.2, 95.0; HRMS (ESI) calcd for $C_{17}H_{12}N_2Cl$ *m/z* $[M+H]^+$: 279.0689; found: 279.0689.

*8,9-Dimethoxy-2-phenylpyrazolo[5,1-a]isoquinoline (**3g**).* Yellow solid (54.1 mg, 89% yield);

mp 171-174 $^{o}$C ; $^{1}$H-NMR (400 MHz, $CDCl_3$): δ 8.14 (d, *J* = 7.3 Hz, 1H), 7.92 (dd, *J* = 8.3, 1.2 Hz, 2H), 7.40-7.36 (m, 2H), 7.31-7.29 (m, 2H), 7.11 (s, 1H), 7.05 (s, 1H), 5.88 (d, *J* = 7.3 Hz, 1H), 4.13 (s, 3H), 4.07 (s, 3H); $^{13}$C-NMR (100 MHz, $CDCl_3$): δ 152.6, 150.2, 150.0, 139.6, 133.1, 128.8, 128.5, 126.4, 124.7, 123.7, 118.7, 111.7, 107.7, 104.4, 93.2, 56.2, 56.1; HRMS (ESI) calcd for $C_{19}H_{17}N_2O_2$ *m/z* $[M+H]^+$: 305.1290; found: 305.1293.

*7,8,9-Trimethoxy-2-phenylpyrazolo[5,1-a]isoquinoline (**3h**).* White solid (54.1 mg, 81% yield); mp 178-181 $^{o}$C ; $^{1}$H-NMR (400 MHz, $CDCl_3$): δ 8.18 (d, *J* = 7.6 Hz, 1H), 8.01 (d, *J* = 8.1 Hz, 2H), 7.48-7.45 (m, 2H), 7.39-7.35 (m, 1H), 7.25 (s, 2H), 7.17 (s, 1H), 4.05 (s, 3H), 4.03 (s, 3H), 3.98 (s, 3H); $^{13}$C-NMR (100 MHz, $CDCl_3$): δ 154.1, 152.8, 149.0, 142.2, 139.3, 133.3, 128.8, 128.4, 126.3, 124.5, 121.1, 118.4, 106.4, 100.5, 94.0, 61.7, 61.3, 56.3; HRMS (ESI) calcd for $C_{20}H_{19}N_2O_3$ *m/z* $[M+H]^+$: 335.1396; found: 335.1392.

*2-(3-Chlorophenyl)pyrazolo[5,1-a]isoquinoline (**3i**).* White solid (51.2 mg, 92% yield); mp 162-165 $^{o}$C ; $^{1}$H-NMR (400 MHz, $CDCl_3$): δ 8.24 (d, *J* = 7.4 Hz, 1H), 8.10-8.08 (m, 1H), 8.00 (t, *J* = 1.7 Hz, 1H), 7.88-7.86 (m, 1H), 7.71-7.69 (m, 1H), 7.60-7.52 (m, 2H), 7.41-7.32 (m, 1H), 7.23 (s, 1H), 7.69 (d, *J* = 7.4 Hz, 1H); $^{13}$C-NMR (100 MHz, $CDCl_3$): δ 151.6, 139.9, 135.1, 134.9, 130.1, 128.9, 128.4, 128.2, 127.9, 127.4, 126.5, 126.3, 124.5, 123.8, 112.6, 94.9; HRMS (ESI) calcd for $C_{17}H_{12}N_2Cl$ *m/z* $[M+H]^+$: 279.0689; found: 279.0691.

*2-(3-Methylphenyl)pyrazolo[5,1-a]isoquinoline (**3j**).* White solid (43.4 mg, 84% yield); mp 112-115 $^{o}$C ; $^{1}$H-NMR (400 MHz, $CDCl_3$): δ 8.35 (d, *J* = 7.4 Hz, 1H), 8.12 (d, *J* = 7.4 Hz, 1H), 7.87 (s, 1H), 7.81 (d, *J* = 7.7 Hz, 1H), 7.73-7.70 (m, 1H), 7.61-7.53 (m, 2H), 7.39-7.35 (m, 1H), 7.28 (s, 1H), 7.21 (d, *J* = 7.5 Hz, 1H), 7.00 (d, *J* = 7.4 Hz, 1H), 2.46 (s, 3H); $^{13}$C-NMR (100 MHz, $CDCl_3$): δ 152.8, 139.8, 138.6, 132.5, 129.5, 129.0, 128.8, 128.3, 127.9, 127.4, 127.1, 126.1, 124.4, 123.9, 123.7, 112.4, 94.8, 21.6; HRMS (ESI) calcd for $C_{18}H_{15}N_2$ *m/z* $[M+H]^+$: 259.1235; found: 259.1236.

*2-(4-Bromophenyl)pyrazolo[5,1-a]isoquinoline (**3k**).* Yellow solid (48.3 mg, 75% yield); mp 176-179 $^{o}$C ; $^{1}$H-NMR (400 MHz, $CDCl_3$): δ 8.28 (d, *J* = 7.4 Hz, 1H), 8.12 (d, *J* = 7.8 Hz, 1H),

7.88 (d, *J* = 8.5 Hz, 2H), 7.73 (d, *J* = 7.2 Hz, 1H), 7.62-7.56 (m, 4H), 7.26-7.25 (m, 1H), 7.02 (d, *J* = 7.4 Hz, 1H); $^{13}$C-NMR (100 MHz, $CDCl_3$): δ 151.7, 140.0, 132.1, 131.9, 129.9, 129.0, 128.3, 128.0, 127.5, 126.2, 124.4, 123.9, 122.6, 112.7, 94.7; HRMS (ESI) calcd for $C_{17}H_{12}N_2$ Br *m/z* $[M+H]^+$: 323.0184; found: 323.0179.

*2-(4-Methylphenyl)pyrazolo[5,1-a]isoquinoline (**3l**).* White solid (46.4 mg, 90% yield); mp 144-146 $^o$C ; $^1$H-NMR (400 MHz, $CDCl_3$): δ 8.22 (d, *J* = 7.4 Hz, 1H), 8.04 (d, *J* = 7.2 Hz, 1H), 7.84-7.82 (m, 2H), 7.65-7.62 (m, 1H), 7.52-7.44 (m, 2H), 7.22-7.17 (m, 3H), 6.91 (d, *J* = 7.4 Hz, 1H), 2.33 (s, 3H); $^{13}$C-NMR (100 MHz, $CDCl_3$): δ 153.0, 139.9, 138.5, 130.2, 129.6, 129.0, 128.1, 127.8, 127.4, 126.4, 126.3, 124.5, 123.9, 112.2, 94.6, 21.5; HRMS (ESI) calcd for $C_{18}H_{15}N_2$ *m/z* $[M+H]^+$: 259.1235; found: 259.1236.

*2-(4-Methoxyphenyl)pyrazolo[5,1-a]isoquinoline (**3m**).* White solid (48.8 mg, 89% yield); mp 124-127 $^o$C ; $^1$H-NMR (400 MHz, $CDCl_3$): δ 8.30 (d, *J* = 6.9 Hz, 1H), 8.11 (d, *J* = 7.5 Hz, 1H), 7.95 (d, *J* = 8.6 Hz, 2H), 7.72-7.70 (m, 1H), 7.59-7.54 (m, 2H), 7.21 (s, 1H), 7.02-6.97 (m, 3H), 3.87 (s, 3H); $^{13}$C-NMR (100 MHz, $CDCl_3$): δ 160.1, 139.9, 133.5, 129.0, 128.1, 127.8, 127.4, 126.2, 125.7, 124.5, 123.9, 114.4, 113.4, 112.0, 94.3, 55.5; HRMS (ESI) calcd for $C_{18}H_{15}N_2O$ *m/z* $[M+H]^+$: 275.1184; found: 275.1190.

*2-(4-Ethynylphenyl)pyrazolo[5,1-a]isoquinoline (**3n**).* White solid (41.8 mg, 78% yield); mp 160-163 $^o$C ; $^1$H-NMR (400 MHz, $CDCl_3$): δ 8.27 (d, *J* = 7.4 Hz, 1H), 8.11 (d, *J* = 7.4 Hz, 1H), 7.97 (d, *J* = 8.3 Hz, 2H), 7.72 (d, *J* = 7.2 Hz, 1H), 7.61-7.53 (m, 4H), 7.27 (s, 1H), 7.01 (d, *J* = 7.4 Hz, 1H), 3.16 (s, 1H); $^{13}$C-NMR (100 MHz, $CDCl_3$): δ 152.0, 139.9, 133.5, 132.7, 128.9, 128.2, 127.9, 127.4, 126.3, 126.3, 124.5, 123.8, 122.1, 112.6, 95.0, 83.8, 78.1; HRMS (ESI) calcd for $C_{19}H_{13}N_2$ *m/z* $[M+H]^+$: 269.1079; found: 269.1087.

*2-(4-Fluoro-3-methylphenyl)pyrazolo[5,1-a]isoquinoline (**3o**).* White solid (28.7 mg, 52% yield); mp 164-166 $^o$C ; $^1$H-NMR (400 MHz, $CDCl_3$): δ 8.29 (d, *J* = 8.0 Hz, 1H), 8.11 (d, *J* = 8.0 Hz, 1H), 7.86 (d, *J* = 8.0 Hz, 1H), 7.79-7.75 (m, 1H), 7.73-7.71 (m, 1H), 7.63-7.53 (m, 2H), 7.22 (s, 1H), 7.12-7.07 (m, 1H), 7.00 (d, *J* = 7.2 Hz, 1H), 2.40 (s, 3H); $^{13}$C-NMR (100

MHz, $CDCl_3$): δ 161.8 (d, *J* = 245 Hz), 140.0, 129.6 (d, *J* = 5 Hz), 129.0, 128.9, 128.2, 127.9, 127.4, 126.2, 125.6, 125.5, 125.3, 124.4, 123.8, 115.5 (d, *J* = 23 Hz), 112.3, 94.7, 14.8 (d, *J* = 4 Hz); HRMS (ESI) calcd for $C_{18}H_{14}N_2F$ *m/z* $[M+H]^+$: 277.1141; found: 277.1146.

*2-(Naphthalen-1-yl)pyrazolo[5,1-a]isoquinoline (**3p**).* Yellow liquid (41.2 mg, 70% yield); $^1$H-NMR (400 MHz, $CDCl_3$): δ 8.54 (d, *J* = 8.0 Hz, 1H), 8.38 (d, *J* = 7.4 Hz, 1H), 8.15 (d, *J* = 7.3 Hz, 1H), 7.96-7.92 (m, 2H), 7.87 (d, *J* = 7.1 Hz, 1H), 7.75-7.74 (m, 1H), 7.61-7.55 (m, 5H), 7.29 (s, 1H), 7.04 (d, *J* = 7.4 Hz, 1H); $^{13}$C-NMR (100 MHz, $CDCl_3$): δ 152.9, 139.1, 134.1, 131.6, 131.2, 129.0, 128.9, 128.5, 128.1, 128.0, 127.8, 127.4, 126.6, 126.4, 126.2, 126.0, 125.5, 124.5, 123.9, 112.3, 98.8; HRMS (ESI) calcd for $C_{21}H_{15}N_2$ *m/z* $[M+H]^+$: 292.1235; found: 292.1235.

*2-(Thiophen-3-yl)pyrazolo[5,1-a]isoquinoline (**3q**).* Yellow solid (42.5 mg, 85% yield); mp 119-122 $^o$C ; $^1$H-NMR (400 MHz, $CDCl_3$): δ 8.23 (d, *J* = 7.4 Hz, 1H), 8.07-8.05 (m,1H), 7.81-7.80 (m, 1H), 7.69-7.64 (m, 2H), 7.55-7.51 (m, 2H), 7.43-7.41 (m, 1H), 7.12 (s, 1H), 6.94 (d, *J* = 7.4 Hz, 1H); $^{13}$C-NMR (100 MHz, $CDCl_3$): δ 149.2, 139.6, 134.9, 128.9, 128.0, 127.7, 127.3, 126.4, 126.2, 126.2, 124.4, 123.8, 121.9, 112.1, 95.0; HRMS (ESI) calcd for $C_{15}H_{11}N_2S$ *m/z* $[M+H]^+$: 251.0648; found: 251.0643.

*2-(3-Chlorophenyl)-9-methoxypyrazolo[5,1-a]isoquinoline (**3r**).* White solid (1.10 g, 79% yield); mp 145-147 $^o$C ; $^1$H-NMR (400 MHz, $CDCl_3$): δ 8.12 (d, *J* = 7.6 Hz, 1H), 7.99 (s, 1H), 7.86 (d, *J* = 8.0 Hz, 1H), 7.60 (d, *J* = 8.7 Hz, 1H), 7.42 (s, 1H), 7.39-7.32 (m, 2H), 7.18 (s, 1H), 7.4 (dd, *J* = 8.7, 2.4 Hz, 1H), 6.92 (d, *J* = 7.3 Hz, 1H), 3.95 (s, 3H); $^{13}$C-NMR (100 MHz, $CDCl_3$): δ 159.3, 151.3, 139.6, 135.2, 134.8, 130.1, 128.9, 128.3, 126.4, 124.4, 124.3, 117.8, 112.3, 105.0, 94.6, 55.6; HRMS (ESI) calcd for $C_{18}H_{13}ClN_2O$ *m/z* $[M+H]^+$: 309.0795; found: 309.0793.

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**Supplementary data**

Copies of $^{1}$H-NMR, $^{13}$C-NMR charts of new starting materials and all the products, as well as the x-ray structural details for **3k** and **3q** associated with this article can be found in the online version, at http://dx.doi.org/10.1016/j.tet.xxxx.

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11. The structures of all the products were identified by their $^{1}$H-NMR, $^{13}$C-NMR and HRMS (ESI). **3k** and **3q** were further confirmed by x-ray crystallography (see supplementary data). The supplementary crystallographic data of **3k**, CCDC 1566482 and **3q**, CCDC 1566483, can be obtained free of charge via www.ccdc.cam.ac.uk

12. Although it is not clear to know the role of CuI in the present annulations, we have noted that the presence of iodide anion is crucial to promote the catalytic activation of Cu(NHC) **B** in another reaction, due possible to the halogen exchange. The results will be concluded and published in the near future.

13. The reported most of pyrazolo[5,1-*a*]isoquinoline derivatives bear substituent at the position 5, and only 2-phenyl pyrazolo[5,1-*a*]isoquinoline was reported in two literatures *via* different processes. (a) AgOTf-catalyzed cascade bicyclization of propargylic

alcohols with *p*-tolylsulfonohydrazide: Xu, S.; Hao, L.; Wang, T.; Ding, Z.; Zhan, Z. *Org. Biomol. Chem.* **2013**, *11*, 294–298. (b) CuCl-catalyzed reaction of 3-(2-bromophenyl)pyrazoles with terminal alkynes: Yang, Y.; Ren, H.; Wang, D.; Shi, F.; Wu, C. *RSC Adv.* **2013**, *3*, 10434–10441.