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Cu-Catalyzed alkynylation–cyclization cascade for the construction of the pyrazolo[5,1-*a*]isoquinoline skeleton†

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A Cu-catalyzed Sonogashira-type coupling of 3-(2-bromophenyl)pyrazoles with terminal alkynes combined with a subsequent electrophilic cyclization in the same pot was developed to afford pyrazolo[5,1-*a*]isoquinolines. The transformation proceeds without the necessity of using Pd or ligands, while an Ag additive is beneficial.

Introduction

The Sonogashira coupling[1,2] has been recognized as one of the most effective methods to construct C(sp^2)–C(sp) bonds. Traditionally, the Sonogashira coupling was co-catalyzed both by Pd and Cu species, and was performed with excesses of amines typically used as co-solvents. Recently, both Pd[3] and Cu[4,5] have proved effective as the sole catalyst for this transformation. The Pd-independent Sonogashira coupling has certain advantages, including lowered cost, no Pd residue, and the avoidance of environmentally hazardous amines, which make it an attractive alternative to the conventional protocol.

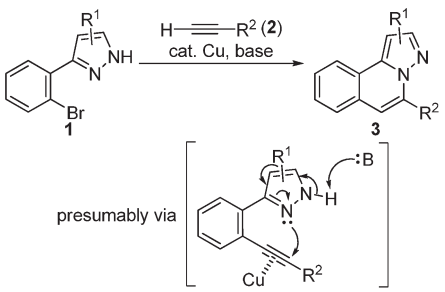
Since its discovery,[4a] several attempts have been made to strategically combine this Cu-catalyzed alkynylation with a subsequent cyclization to construct an additional ring in a single operation, providing that there is an internal nucleophile at a suitable position in the substrate. Such a method exploits the ability of the same Cu catalyst to act as a soft Lewis acid during the cyclization step.[6] In this regard, Venkatarman,[7] Ma,[8] Cacchi,[9] and their co-workers have developed Cu-catalyzed alkynylation–cyclization cascades to synthesize indoles and benzofurans. Ma[10] and co-workers have additionally developed tandem reactions to synthesize isocoumarins, furans, and 3-alkylideneisoindolinones. The Thibonnet–Abarbri group[11] has also been successful in the construction of several other heterocyclic scaffolds. To date, the scope of the internal nucleophiles that can be employed in this cascade covers alcohols, phenols, amides, and acids.

Despite the success above, this strategy has limitations. Most existing protocols have to work with aryl/vinyl iodides and perform unsatisfactorily for the corresponding bromides[4a,7a] which are cheaper, more accessible, and easier to store. In addition, the scope of the internal nucleophile is yet to be broadened. Herein, we wish to report a one-pot Cu-catalyzed alkynylation–cyclization reaction of 3-(2-bromophenyl)pyrazoles (**1**) with terminal alkynes to afford pyrazolo[5,1-*a*]isoquinolines (**3**)[12] under Pd- and ligand-free conditions (Scheme 1). We are using a heterocyclic nitrogen as the nucleophile for the subsequent cyclization, which not only broadens the scope of nucleophiles, but may also serve as a potential coordinator for activating the C–Br bond during the alkynylation stage, thus allowing for the chemistry to operate on bromides in addition to iodides.

Results and discussion

Development of reaction conditions

We commenced our work optimizing the model reaction of substrate **1a** with phenylacetylene **2a** (Table 1). Under the



Scheme 1 Cu-catalyzed alkynylation–cyclization cascade for the construction of pyrazolo[5,1-*a*]isoquinolines.

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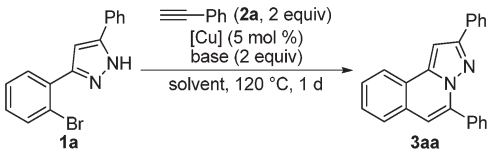
† Electronic supplementary information (ESI) available: additional experimental procedures and characterization data, as well as copies of NMR spectra for all products. See DOI: 10.1039/c3ra40270c

Table 1 Optimization of reaction conditions[a,b]



entry	cat.	base	solvent/mL	yield[c] (%)	entry	cat.	base	solvent/mL	yield[c] (%)
1	CuI	KOAc	DMF/2.0	trace	11	CuI	K_2CO_3	NMP/0.6	75
2	CuI	K_2CO_3	DMF/2.0	63	12	CuBr	K_2CO_3	NMP/0.6	78
3	CuI	Cs_2CO_3	DMF/2.0	25	13	$CuBr_2$	K_2CO_3	NMP/0.6	80
4	CuI	2,6-lutidine	DMF/2.0	trace	14	CuCl	K_2CO_3	NMP/0.6	84
5	CuI	K_3PO_4	DMF/2.0	21	15	$CuCl_2$	K_2CO_3	NMP/0.6	68
6	CuI	K_2CO_3	Tol/2.0	trace	16	CuOTf	K_2CO_3	NMP/0.6	61
7	CuI	K_2CO_3	Dioxane/2.0	trace	17	$Cu(OTf)_2$	K_2CO_3	NMP/0.6	61
8	CuI	K_2CO_3	DMSO/2.0	66	18	$Cu(OAc)_2$	K_2CO_3	NMP/0.6	73
9	CuI	K_2CO_3	DMSO/0.6	67	19	CuBr-phen	K_2CO_3	NMP/0.6	46
10	CuI	K_2CO_3	DMAc/0.6	74	20	CuBr-d^{t}bpy	K_2CO_3	NMP/0.6	56

[a] The reaction was carried out on a 0.3 mmol scale in a sealed vial under N_2. DMAc = *N*,*N*-dimethylacetamide; NMP = *N*-methylpyrrolidinone; phen = 1,10-phenanthroline; d^{t}bpy = 4,4′-di-*tert*-butyl-2,2′-bipyridyl. [b] Under all successful conditions a small quantity of another isomeric product was observed. [c] Isolated yield.

catalysis of 5 mol% of CuI, K_2CO_3 appeared to be the optimal base for the transformation in DMF (entries 1–5). Among different solvents, non-coordinating ones such as toluene and dioxane did not effect the reaction (entries 6 and 7). DMSO proved comparable to DMF (entries 8 and 9), and the best yields were obtained in DMAc or NMP (entries 10 and 11). Besides CuI, many other Cu salts were also catalytically active (entries 12–18). CuCl, CuBr, and $CuBr_2$ were the best among them (entries 12–14),[13] but CuO and Cu_2O were inactive (not shown). A control experiment using a Pd catalyst without Cu under otherwise identical conditions afforded no more than trace amounts of product, and standard Sonogashira conditions (cat. $Pd(PPh_3)_2$–CuI, Et_3N–DMF at 100 °C) resulted in a suppressed cyclization (*ca.* 10% yield of **3aa**) despite a successful cross-coupling (*ca.* 40% yield of the simple alkynylated intermediate). Although we may not completely rule out the possible synergistic effects of trace quantities of Pd,[14] side-by-side reactions suggest that the yield of **3aa** does not change upon artificial addition of ppm levels of Pd.

Under all conditions, no ligand or amine was needed for the transformation, and somewhat surprisingly, the addition of 1,10-phenanthroline or bipyridyl ligand decreased the yield (entries 19 and 20). Last but not least, the 6-*endo-dig* cyclization was the preferred mode of cyclization under all conditions described above, and only small quantities (<10%) of what appeared to be the 5-*exo-dig* cyclization product were obtained.

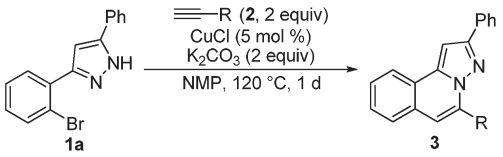
Scope and limitation

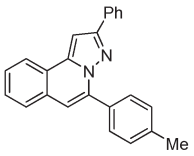
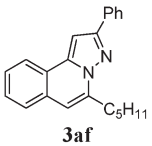
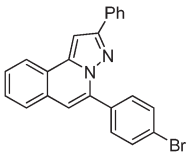
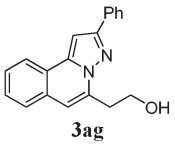
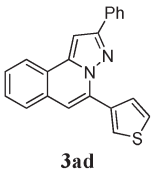
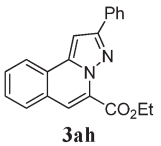
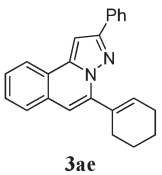
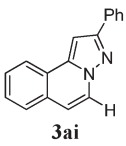
The scope of the reaction was first tested against a range of alkynes (Table 2). As expected, the reaction worked well with aryl- and heteroarylacetylenes (entries 1–3). Pleasingly, a vinyl acetylene (**2e**, entry 4) and two alkylacetylenes (**2f** and **2g**, entries 5 and 6) could also be employed. Even the presence of a free hydroxyl group (entry 6) did not lower the yield. Propiolate could not be utilized in this reaction (entry 7), but use of a silylacetylene delivered a high yield with *in situ* desilylation (entry 8). The preparation of this type of product may not be straightforward using existing methods,[12] which makes our chemistry complementary in this respect.

The scope of 3-(2-bromoaryl)pyrazoles (**1**) was studied next (Table 3). A variety of substitutions on the benzene ring (R^1) could be tolerated (entries 1–4). While the yields remained high for most substitutions, a methoxy group in the *para* position to the bromide (substrate **1c**, entry 2) lowered the yield, indicative of a modest detrimental effect of electron-donating groups. For this type of substrate, CuBr proved to be a better catalyst. A pyridine-based substrate **1f** was also transformed smoothly (entry 5). The 5-position of the pyrazole (R^3) could accommodate a variety of substitutions, including aryl (entries 6 and 7), heteroaryl (entry 8), alkyl (entry 9), and ester (entry 10) groups. Specifically, a remote bromide in substrate **1h** remained intact (entry 7), highlighting a potential chemoselectivity.

Unfortunately, substitution at the 4-position of the pyrazole (R^2) caused a lower yield together with another isomeric fraction, presumably a 5-*exo* cyclization product (entry 11).[15] This problem was not as significant when the R^2 and R^3 groups were tethered into a ring (entry 12). Further optimization of these reactions revealed that these low yields could be improved by the addition of an Ag salt. Thus, the yield of **3la** was improved from 24% to 46% (entry 11) by adding 1 equiv. of AgOTf, and the yield of **1m** was increased from 43% to 56% (entry 12). This Ag effect was more pronounced in the reaction of the indazole derivative **1n** (Scheme 2). Thus, compared to the failure using a Cu catalyst alone (<5% yield for CuBr, <10% yield for CuCl), addition of AgOTf, preferably in substoichiometric or stoichiometric quantities, significantly increased the yield. Although AgOTf has been known to catalyze Sonogashira-type coupling reactions,[16] it was inactive

Table 2 Scope of alkynes[a]



Entry	R^4	3	yield[b] (%)	entry	R^4	3	yield[b] (%)
1	4-MeC_6H_4 (**2b**)	 **3ab**	81	5	*n*-pentyl (**2f**)	 **3af**	59
2	4-BrC_6H_4 (**2c**)	 **3ac**	61	6	CH_2CH_2OH (**2g**)	 **3ag**	73
3	3-thiophenyl (**2d**)	 **3ad**	80	7	CO_2Et (**2h**)	 **3ah**	not observed
4	cyclohexenyl (**2e**)	 **3ae**	46[c]	8	TIPS (**2i**)	 **3ai**	92[d]

[a] The reaction was carried out on a 0.3–0.5 mmol scale in 0.6–1.2 mL of NMP in a sealed vial under N_2. [b] Isolated yield. [c] Reaction for 2 d. [d] Reaction was performed with CuBr instead of CuCl for 30 h.

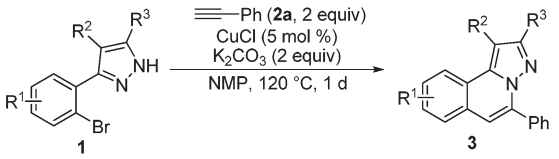
in our transformation in the absence of Cu. For this reason, Ag appears to have an enhancing role in the catalytic effect of Cu. The mechanistic rationale, particularly the reason for the need for stoichiometric quantities, remains unclear.

In a vain attempt to incorporate an iodine atom at the 6-position of the pyrazolo[5,1-*a*]isoquinolines,[17] we performed the reaction in the presence of stoichiometric amounts of NIS (Scheme 3) or I_2. The failure of these reactions under various conditions lead us to the hypothesis that the cyclization step after the alkynylation might be so facile that the assumed "I^+" could not get involved. To probe this possibility, we prepared the presumed intermediate **5a** and observed that the cyclization of **5a** to **3aa** was very facile. Even at 80 °C, conversion of **5a** to **3aa** was complete within 20 min without Cu. In sharp contrast, only a trace amount of **3aa** was observed in the absence of K_2CO_3, whether or not a Cu catalyst was present. Similarly, despite a lower yield, the cyclization of **5b** to **3na** could be effected without Cu as well, but not without K_2CO_3 (Scheme 4). These data indicate that the cyclization described in our chemistry is rather a base-promoted process. The involvement of Cu as a soft Lewis acid was not required (let alone Ag). The presumed carbanion resulting from the cyclization might be much more easily protonated than iodinated. Thus, going back to Ag as an additive, it appears clear that its beneficial role lies at the cross-coupling stage, not the cyclization stage. Surely, studying this Ag effect in a broader picture of Cu-catalyzed alkynylation should be encouraged, which may help to widen the scope of the current protocols.

Conclusions

In summary, we presented a Cu-catalyzed alkynylation–cyclization approach that transforms 3-(2-bromophenyl)pyrazoles to pyrazolo[5,1-*a*]isoquinolines. The reaction expands the

Table 3 Scope of 3-(2-bromoaryl)pyrazoles[a]



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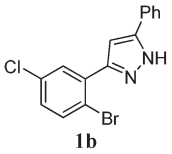
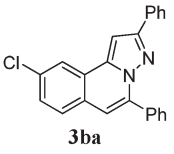
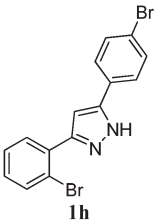
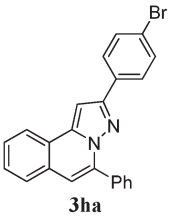
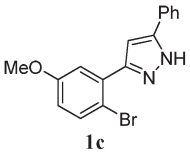
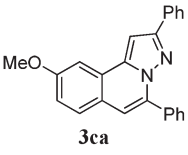
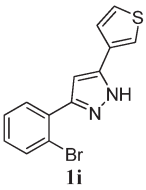
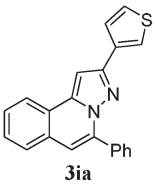
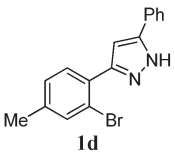
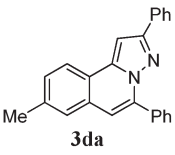
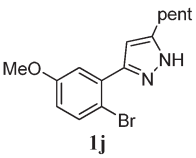
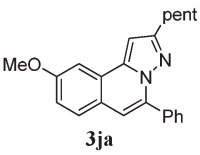
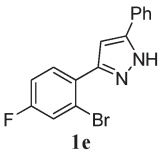
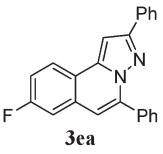
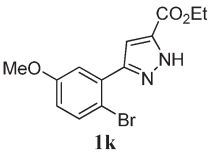
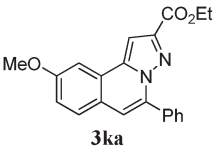
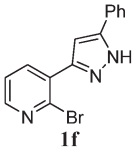
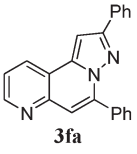
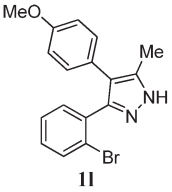
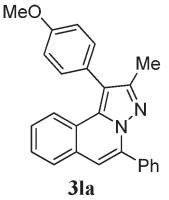
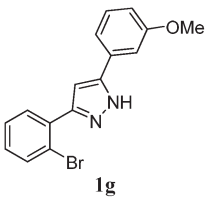
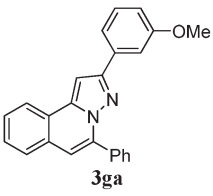
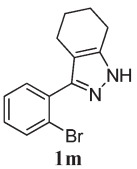
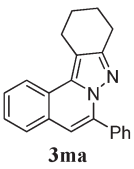
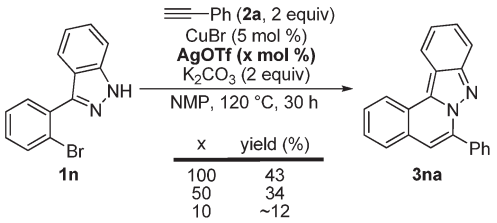
1	 1b	 3ba	86	7	 1h	 3ha	78
2	 1c	 3ca	66[c]	8	 1i	 3ia	72
3	 1d	 3da	77	9	 1j	 3ja	45[c]
4	 1e	 3ea	88	10	 1k	 3ka	63[cd]
5	 1f	 3fa	59	11	 1l	 3la	24[ce] (46[c])
6	 1g	 3ga	75	12	 1m	 3ma	43[c] (56[c])

[a] The reaction was carried out on a 0.2–0.5 mmol scale in 0.5–1.2 mL of NMP in a sealed vial under N_2. [b] Isolated yield. Yields in parentheses were obtained with 1 equiv. of AgOTf. [c] The reaction was performed with CuBr instead of CuCl. [d] The reaction was carried out for 30 h. [e] Another 15% of what appeared to be the 5-*exo* cyclization product (32% with the addition of 1 equiv. of AgOTf) was also isolated. For its characterization, see ESI†.



Scheme 2 Reaction with an indazole-derived substrate.

scope of the current Cu-catalyzed alkynylation reactions. In addition, an Ag effect was observed that appears to facilitate the Cu-catalyzed alkynylation protocol.

Experimental section

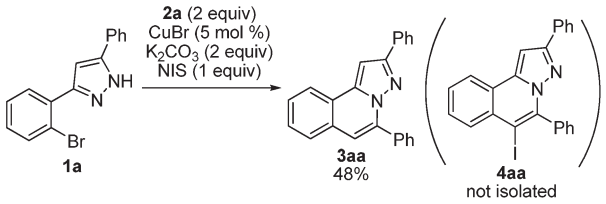
Materials and methods

All materials supplied from commercial sources were used as received unless otherwise noted. DMF, DMAc, and NMP were dried first over K_2CO_3 followed by 4 Å molecular sieves. Silica gel for column chromatography was supplied as 300–400 mesh from Haiyang Chemicals (Qingdao, China, which gives a different retardation compared with silica gel typically used in western countries). All melting points were uncorrected. The ^1H and ^{13}C NMR spectra were referenced to the residual solvent signals (7.26 ppm for ^1H and 77.0 ppm for ^{13}C in $CDCl_3$). HRMS (ESI) spectra were recorded using a Fourier transformed ion cyclotron resonance analyzer, and HRMS (EI) spectra were recorded using a double focusing magnetic sector analyzer.

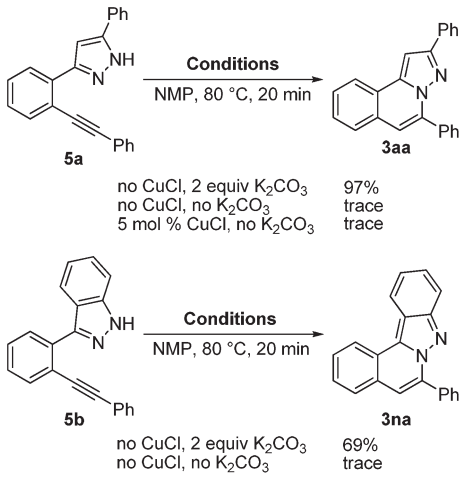
Substrates **1a** through **1k** and **1m** were prepared according to literature procedures.[18] Substrate **1n** was prepared according to our own protocol.[19] Procedures for the synthesis of **1l** are listed in the ESI†.

Representative procedure and characterization of the products

2,5-Diphenylpyrazolo[5,1-*a*]isoquinoline (3aa). To an oven-dried 1-dram vial equipped with a stirrer were added CuCl (1.5 mg, 0.015 mmol, 5 mol%), **1a** (90 mg, 0.3 mmol), and K_2CO_3 (83 mg, 0.6 mmol, 2 equiv.). NMP (0.6 mL) was added *via* syringe, followed by the addition of alkyne **2a** (61 mg, 0.6 mmol, 2 equiv.). The vial was flushed with nitrogen and sealed. The mixture was heated in an oil bath at 120 °C for 24 h. After being cooled to room temperature, the reaction mixture was filtered, and the filtrate was diluted with brine.



Scheme 3 An unsuccessful iodination attempt.



Scheme 4 Testing the involvement of Cu in the cyclization step.

The aqueous phase was extracted with EtOAc, and the combined extracts were dried over $MgSO_4$, filtered, and evaporated. The residue was purified by column chromatography (PE/DCM = 3/1) to afford 81 mg (84%) of the desired product **3aa** as a slightly yellow solid; mp 95–96 °C (lit[20,21] 142–143 °C). ^1H NMR ($CDCl_3$, 400 MHz) δ 8.19–8.14 (m, 1 H), 8.08–7.99 (m, 4 H), 7.78–7.73 (m, 1 H), 7.62–7.49 (m, 5 H), 7.44 (t, J = 7.7 Hz, 2 H), 7.41 (s, 1 H), 7.38–7.32 (m, 1 H), 7.08 (s, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.2, 140.7, 138.4, 133.7, 133.4, 129.6, 129.24, 129.18, 128.6, 128.2, 128.1, 127.9, 127.3, 127.2, 126.4, 123.9, 123.5, 112.5, 94.8; HRMS (ESI) calcd for $C_{23}H_{17}N_2$ [M + H] 321.1392, found 321.1384.

2-Phenyl-5-*p*-tolylpyrazolo[5,1-*a*]isoquinoline (3ab). The general procedure was applied to 90 mg of **1a**, 1.5 mg of CuCl, 83 mg of K_2CO_3, and 70 mg of alkyne **2b** to afford 81 mg (81%) of the desired product **3ab** as a white solid; mp 109–110 °C. ^1H NMR ($CDCl_3$, 400 MHz) δ 8.18–8.14 (m, 1 H), 8.02 (d, J = 7.7 Hz, 2 H), 7.96 (d, J = 8.0 Hz, 2 H), 7.77–7.71 (m, 1 H), 7.60–7.51 (m, 2 H), 7.44 (t, J = 7.7 Hz, 2 H), 7.40 (s, 1 H), 7.39–7.32 (m, 3 H), 7.06 (s, 1 H), 2.48 (s, 3 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 152.1, 140.7, 139.2, 138.4, 133.4, 130.8, 129.5, 129.3, 128.8, 128.6, 128.1, 127.8, 127.1 (overlapped signal), 126.4, 123.8, 123.4, 112.0, 94.7, 21.4; IR (KBr): 1632, 1549, 1458, 816, 741, 681 cm^{-1}; HRMS (ESI) calcd for $C_{24}H_{19}N_2$ [M + H] 335.1548, found 335.1537.

5-(4-Bromophenyl)-2-phenylpyrazolo[5,1-*a*]isoquinoline (3ac). The general procedure was applied to 90 mg of **1a**, 1.5 mg of CuCl, 83 mg of K_2CO_3, and 109 mg of alkyne **2c** to afford 73 mg (61%) of the desired product **3ac** as a bright yellow solid; mp 162–163 °C. ^1H NMR ($CDCl_3$, 400 MHz) δ 8.18–8.14 (m, 1 H), 8.02–7.97 (m, 2 H), 7.96–7.91 (m, 2 H), 7.77–7.73 (m, 1 H), 7.71–7.65 (m, 2 H), 7.62–7.53 (m, 2 H), 7.45 (t, J = 7.5 Hz, 2 H), 7.40 (s, 1 H), 7.38–7.33 (m, 1 H), 7.06 (s, 1 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 152.3, 140.7, 137.2, 133.2, 132.6, 131.3, 131.2, 129.0, 128.6, 128.3, 128.0, 127.5, 127.2, 126.3, 123.9, 123.5, 123.4, 112.5, 94.9; IR (KBr): 1634, 1549, 1489, 1458, 1437, 814, 739, 681 cm^{-1}; HRMS (EI) calcd for $C_{23}H_{15}{}^{81}BrN_2$ [M] 400.0398, found 400.0393.

2-Phenyl-5-(thiophen-3-yl)pyrazolo[5,1-*a*]isoquinoline (3ad). The general procedure was applied to 90 mg of **1a**, 1.5 mg of CuCl, 83 mg of K_2CO_3, and 65 mg of alkyne **2d** to afford 78 mg (80%) of the desired product **3ad** as a slightly yellow solid; mp 111–112 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.72 (d, J = 3.0 Hz, 1 H), 8.17–8.11 (m, 1 H), 8.08 (d, J = 8.1 Hz, 2 H), 7.85 (d, J = 5.1 Hz, 1 H), 7.77–7.71 (m, 1 H), 7.59–7.45 (m, 5 H), 7.43–7.37 (m, 1 H), 7.40 (s, 1 H), 7.30 (s, 1 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 152.1, 140.9, 133.44, 133.36, 133.3, 129.1, 128.7, 128.3, 127.92, 127.89, 127.23, 127.18, 127.1, 126.4, 124.9, 123.5, 123.4, 111.1, 94.7; IR (KBr): 1626, 1547, 1458, 1356, 837, 795, 750, 683 cm^{-1}; HRMS (ESI) calcd. for $C_{21}H_{15}N_2S$ [M + H] 327.0956, found 327.0950.

5-Cyclohexenyl-2-phenylpyrazolo[5,1-*a*]isoquinoline (3ae). The general procedure was applied to 90 mg of **1a**, 1.5 mg of CuCl, 83 mg of K_2CO_3, and 64 mg of alkyne **2e** for 2 days to afford 46 mg (contaminated by a petroleum ether residue at 1.25 and 0.87 ppm respectively, ^{1}H NMR ratio 100 : 4 (product/PE as dodecane), corresponding to 45 mg of pure product, 46%) of the desired product **3ae** as a yellow glass. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.14–8.09 (m, 1 H), 8.07–8.02 (m, 2 H), 7.72–7.67 (m, 1 H), 7.56–7.43 (m, 4 H), 7.39–7.33 (m, 1 H), 7.33 (s, 1 H), 6.89 (s, 1 H), 6.44–6.40 (m, 1 H), 2.81–2.74 (m, 2 H), 2.37–2.30 (m, 2 H), 1.93–1.79 (m, 4 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.0, 141.3, 140.4, 133.8, 133.5, 130.6, 129.5, 128.6, 128.1, 127.7, 126.9, 126.8, 126.3, 123.7, 123.4, 110.2, 94.2, 27.4, 25.7, 22.6, 22.1; IR (film): 1632, 1545, 1458, 835, 752, 692 cm^{-1}; HRMS (ESI) calcd for $C_{23}H_{21}N_2$ [M + H] 325.1705, found 325.1700.

5-Pentyl-2-phenylpyrazolo[5,1-*a*]isoquinoline (3af). The general procedure was applied to 90 mg of **1a**, 1.5 mg of CuCl, 83 mg of K_2CO_3, and 58 mg of alkyne **2f** to afford 56 mg (59%) of the desired product **3af** as a slightly yellow solid; mp 57–58 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.15–8.09 (m, 1 H), 8.06 (d, J = 7.9 Hz, 2 H), 7.71–7.65 (m, 1 H), 7.55–7.44 (m, 4 H), 7.40–7.35 (m, 1 H), 7.34 (s, 1 H), 6.83 (s, 1 H), 3.24 (t, J = 7.7 Hz, 2 H), 2.02–1.90 (m, 2 H), 1.55–1.40 (m, 4 H), 0.96 (t, J = 7.0 Hz, 3 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 152.0, 140.1, 139.8, 133.7, 129.3, 128.7, 128.1, 127.6, 126.5, 126.41, 126.35, 123.4 (overlapped signal), 109.3, 94.6, 31.6, 30.8, 26.5, 22.5, 14.1; IR (KBr): 1645, 1547, 1460, 1437, 818, 745, 681 cm^{-1}; HRMS (ESI) calcd for $C_{22}H_{23}N_2$ [M + H] 315.1861, found 315.1850.

2-(2-Phenylpyrazolo[5,1-*a*]isoquinolin-5-yl)ethanol (3ag). The general procedure was applied to 90 mg of **1a**, 1.5 mg of CuCl, 83 mg of K_2CO_3, and 42 mg of alkyne **2g** to afford 63 mg (73%) of the desired product **3ag** as a white solid; mp 87–88 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.14–8.09 (m, 1 H), 8.01–7.96 (m, 2 H), 7.70–7.64 (m, 1 H), 7.59–7.51 (m, 2 H), 7.47 (t, J = 7.5 Hz, 2 H), 7.41–7.36 (m, 1 H), 7.34 (s, 1 H), 6.88 (s, 1 H), 4.58 (brs, 1 H), 4.14 (t, J = 5.4 Hz, 2 H), 3.50 (t, J = 5.3 Hz, 2 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 152.3, 140.5, 137.6, 132.8, 129.3, 128.8, 128.5, 128.2, 127.1, 126.7, 126.4, 123.6 (overlapped signal), 111.8, 95.1, 61.9, 35.7; IR (KBr): 3100–3500(br), 1643, 1547, 1460, 1327, 1051, 829, 754, 687 cm^{-1}; HRMS (ESI) calcd for $C_{19}H_{17}N_2O$ [M + H] 289.1341, found 289.1335.

2-Phenylpyrazolo[5,1-*a*]isoquinoline (3ai). The general procedure was applied to 150 mg of **1a** (0.5 mmol scale), 3.6 mg of CuBr, 140 mg of K_2CO_3, and 182 mg of alkyne **2i** in 1.2 mL of NMP for 30 h to afford 117 mg (contaminated by a petroleum ether residue at 1.25 and 0.87 ppm respectively, ^{1}H NMR ratio 100 : 2.5 (product/PE as dodecane), corresponding to 112 mg of pure product, 92%) of the desired product **3ai** as a white solid; mp 115–116 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.27 (d, J = 7.4 Hz, 1 H), 8.13 (d, J = 7.6 Hz, 1 H), 8.01 (d, J = 7.6 Hz, 2 H), 7.72 (d, J = 7.3 Hz, 1 H), 7.62–7.52 (m, 2 H), 7.48 (t, J = 7.5 Hz, 2 H), 7.40–7.36 (m, 1 H), 7.29 (s, 1 H), 6.99 (d, J = 7.4 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 153.0, 139.8, 133.2, 128.81, 128.76, 128.3, 127.9, 127.6, 127.2, 126.33, 126.31, 124.5, 123.7, 112.0, 94.6; IR (KBr): 1634, 1537, 1462, 1362, 793, 758, 696 cm^{-1}; HRMS (ESI) calcd for $C_{17}H_{13}N_2$ [M + H] 245.1079, found 245.1079.

9-Chloro-2,5-diphenylpyrazolo[5,1-*a*]isoquinoline (3ba). The general procedure was applied to 100 mg of **1b**, 1.5 mg of CuCl, 83 mg of K_2CO_3, and 61 mg of alkyne **2a** to afford 92 mg (86%) of the desired product **3ba** as a white solid; mp 158–159 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.13 (d, J = 2.1 Hz, 1 H), 8.05–7.97 (m, 4 H), 7.67 (d, J = 8.5 Hz, 1 H), 7.58–7.51 (m, 3 H), 7.49 (dd, J = 8.5, 2.1 Hz, 1 H), 7.47–7.42 (m, 2 H), 7.39–7.33 (m, 1 H), 7.38 (s, 1 H), 7.03 (s, 1 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 152.4, 139.6, 138.6, 133.3, 133.0, 132.9, 129.6, 129.3, 128.62, 128.57, 128.31, 128.30, 128.2, 127.5, 126.4, 124.8, 122.9, 111.6, 95.2; IR (KBr): 1636, 1597, 1549, 1450, 1398, 858, 764, 691 cm^{-1}; HRMS (ESI) calcd for $C_{23}H_{16}{}^{35}ClN_2$ [M + H] 355.1002, found 355.0994.

9-Methoxy-2,5-diphenylpyrazolo[5,1-*a*]isoquinoline (3ca). The general procedure was applied to 165 mg of **1c** (0.5 mmol scale), 3.6 mg of CuBr, 140 mg of K_2CO_3, and 102 mg of alkyne **2a** in 1.2 mL of NMP to afford 115 mg (66%) of the desired product **3ca** as a slightly yellow solid; mp 97–98 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.08–8.00 (m, 4 H), 7.65 (d, J = 8.7 Hz, 1 H), 7.58–7.43 (m, 6 H), 7.39–7.34 (m, 1 H), 7.36 (s, 1 H), 7.17 (dd, J = 8.7, 2.5 Hz, 1 H), 7.03 (s, 1 H), 3.99 (s, 3 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 158.9, 151.9, 140.4, 136.3, 133.9, 133.4, 129.5, 128.9, 128.8, 128.6, 128.1 (overlapped signal), 126.3, 125.0, 123.4, 117.8, 112.3, 104.6, 94.6, 55.6; IR (KBr): 1612, 1547, 1499, 1450, 1259, 1209, 1022, 860, 764, 735, 692 cm^1; HRMS (ESI) calcd for $C_{24}H_{19}N_2O$ [M + H] 351.1497, found 351.1489.

8-Methyl-2,5-diphenylpyrazolo[5,1-*a*]isoquinoline (3da). The general procedure was applied to 94 mg of **1d**, 1.5 mg of CuCl, 83 mg of K_2CO_3, and 61 mg of alkyne **2a** to afford 77 mg (77%) of the desired product **3da** as a white solid; mp 114–115 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.07–7.98 (m, 5 H), 7.58–7.49 (m, 4 H), 7.46–7.38 (m, 3 H), 7.37–7.32 (m, 1 H), 7.35 (s, 1 H), 7.01 (s, 1 H), 2.53 (s, 3 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 152.1, 140.8, 138.3, 137.9, 133.8, 133.5, 129.6, 129.4, 129.1, 128.9, 128.6, 128.09, 128.07, 126.9, 126.4, 123.3, 121.7, 112.3, 94.2, 21.6; IR (KBr): 1634, 1549, 1481, 1460, 762, 739, 692 cm^{-1}; HRMS (ESI) calcd for $C_{24}H_{19}N_2$ [M + H] 335.1548, found 335.1540.

8-Fluoro-2,5-diphenylpyrazolo[5,1-*a*]isoquinoline (3ea). The general procedure was applied to 95 mg of **1e**, 1.5 mg of CuCl, 83 mg of K_2CO_3, and 61 mg of alkyne **2a** to afford 89 mg (88%) of the desired product **3ea** as a slightly yellow solid; mp 106–107 °C (lit[20] 121–122 °C). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.13 (dd, J = 8.8, 5.3 Hz, 1 H), 8.05–7.97 (m, 4 H), 7.59–7.50 (m, 3 H), 7.44 (t, J = 7.5 Hz, 2 H), 7.41–7.28 (m, 3 H), 7.34 (s, 1 H), 7.01 (s, 1 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 162.0 (d, $^1J_{CF}$ = 247.6 Hz), 152.5, 140.4, 139.4, 133.4, 133.2, 130.9 (d, $^3J_{CF}$ = 9.3 Hz), 129.6,

129.4, 128.6, 128.3, 128.2, 126.4, 125.7 (d, $^3J_{CF}$ = 9.0 Hz), 120.5 (d, $^4J_{CF}$ = 1.7 Hz), 115.9 (d, $^2J_{CF}$ = 24.0 Hz), 111.9 (d, $^2J_{CF}$ = 21.8 Hz), 111.6 (d, $^4J_{CF}$ = 3.4 Hz), 94.5; HRMS (ESI) calcd for $C_{23}H_{16}FN_2$ [M + H] 339.1298, found 339.1291.

2,5-Diphenylpyrazolo[5,1-*f*][1,6]naphthyridine (3fa). The general procedure was applied to 90 mg of **1f**, 1.5 mg of CuCl, 83 mg of K_2CO_3, and 61 mg of alkyne **2a** to afford 57 mg (59%) of the desired product **3fa** as a yellow solid; mp 126–127 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.87 (dd, J = 4.5, 1.6 Hz, 1 H), 8.42 (dd, J = 8.1, 1.0 Hz, 1 H), 8.12–8.05 (m, 2 H), 8.02–7.96 (m, 2 H), 7.62–7.53 (m, 3 H), 7.50–7.40 (m, 4 H), 7.40–7.33 (m, 2 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 153.0, 150.7, 146.4, 142.1, 139.9, 133.0, 132.9, 131.1, 129.70, 129.66, 128.6, 128.5, 128.2, 126.4, 121.7, 119.4, 113.6, 96.0; IR (KBr): 1630, 1558, 1456, 1433, 1383, 845, 758, 745, 683 cm^{-1}; HRMS (ESI) calcd for $C_{22}H_{16}N_3$ [M + H] 322.1344, found 322.1337.

2-(3-Methoxyphenyl)-5-phenylpyrazolo[5,1-*a*]isoquinoline (3ga). The general procedure was applied to 99 mg of **1g**, 1.5 mg of CuCl, 83 mg of K_2CO_3, and 61 mg of alkyne **2a** to afford 79 mg (75%) of the desired product **3ga** as a white solid; mp 123–124 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.17–8.15 (m, 1 H), 8.07–8.02 (m, 2 H), 7.77–7.73 (m, 1 H), 7.62–7.48 (m, 7 H), 7.39 (s, 1 H), 7.36 (t, J = 7.9 Hz, 1 H), 7.08 (s, 1 H), 6.91 (ddd, J = 8.2, 2.6, 0.8 Hz, 1 H), 3.89 (s, 3 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 159.8, 152.0, 140.7, 138.4, 134.8, 133.7, 129.61, 129.60, 129.23, 129.16, 128.1, 127.9, 127.3, 127.2, 123.9, 123.4, 119.0, 113.7, 112.5, 111.9, 94.9, 55.3; IR (KBr): 1610, 1549, 1474, 1283, 1045, 768, 748, 692 cm^{-1}; HRMS (ESI) calcd for $C_{24}H_{19}N_2O$ [M + H] 351.1497, found 351.1491.

2-(4-Bromophenyl)-5-phenylpyrazolo[5,1-*a*]isoquinoline (3ha). The general procedure was applied to 113 mg of **1h**, 1.5 mg of CuCl, 83 mg of K_2CO_3, and 61 mg of alkyne **2a** to afford 93 mg (78%) of the desired product **3ha** as a white solid; mp 160–161 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.16–8.09 (m, 1 H), 8.05–7.98 (m, 2 H), 7.86 (d, J = 8.5 Hz, 2 H), 7.77–7.70 (m, 1 H), 7.62–7.49 (m, 7 H), 7.34 (s, 1 H), 7.08 (s, 1 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 151.0, 140.8, 138.3, 133.6, 132.3, 131.7, 129.6, 129.3, 129.2, 128.2, 128.0, 127.9, 127.4, 127.2, 123.8, 123.4, 122.1, 112.7, 94.7; IR (KBr): 1634, 1547, 1460, 1437, 1395, 831, 752, 689 cm^{-1}; HRMS (ESI) calcd for $C_{23}H_{16}N_2{}^{79}Br$ [M + H] 399.0497, found 399.0489.

5-Phenyl-2-(thiophen-3-yl)pyrazolo[5,1-*a*]isoquinoline (3ia). The general procedure was applied to 153 mg of **1i** (0.5 mmol scale), 2.5 mg of CuCl, 140 mg of K_2CO_3, and 102 mg of alkyne **2a** in 1.2 mL of NMP to afford 117 mg (72%) of the desired product **3ia** as a slightly yellow solid; mp 137–138 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.17–8.11 (m, 1 H), 8.05–8.00 (m, 2 H), 7.77 (dd, J = 2.9, 1.1 Hz, 1 H), 7.76–7.72 (m, 1 H), 7.64 (dd, J = 5.0, 1.0 Hz, 1 H), 7.60–7.48 (m, 5 H), 7.38 (dd, J = 5.0, 3.0 Hz, 1 H), 7.28 (s, 1 H), 7.07 (s, 1 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 148.6, 140.5, 138.4, 135.3, 133.7, 129.6, 129.3, 129.2, 128.1, 128.0, 127.3, 127.2, 126.6, 125.8, 123.8, 123.5, 121.8, 112.4, 95.1; IR (KBr): 1634, 1568, 1539, 1470, 1369, 854, 783, 760, 694 cm^{-1}; HRMS (ESI) calcd for $C_{21}H_{15}N_2S$ [M + H] 327.0956, found 327.0947.

9-Methoxy-2-pentyl-5-phenylpyrazolo[5,1-*a*]isoquinoline (3ja). The general procedure was applied to 65 mg of **1j** (0.2 mmol scale), *ca.* 1.5 mg of CuBr, 56 mg of K_2CO_3, and 41 mg of alkyne **2a** in 0.5 mL of NMP to afford 32.2 mg (contaminated by petroleum ether residue at 1.25 and 0.87 ppm respectively, ^{1}H NMR ratio 100 : 8.5 (product/PE as dodecane), corresponding to 30.9 mg of pure product, 45%) of the desired product **3ja** as a light yellow glass. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97–7.93 (m, 2 H), 7.63 (d, J = 8.7 Hz, 1 H), 7.54–7.42 (m, 4 H), 7.14 (dd, J = 8.7, 2.5 Hz, 1 H), 6.93 (s, 1 H), 6.86 (s, 1 H), 3.97 (s, 3 H), 2.86 (t, J = 7.8 Hz, 2 H), 1.84–1.75 (m, 2 H), 1.47–1.36 (m, 4 H), 0.93 (t, J = 7.0 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.7, 155.0, 139.7, 136.2, 134.1, 129.3, 128.9, 128.6, 128.2, 124.9, 123.4, 117.5, 111.4, 104.5, 96.1, 55.5, 31.7, 29.6, 28.7, 22.5, 14.1; IR (film): 1616, 1547, 1501, 1466, 1261, 1234, 1034, 854, 741, 694 cm^{-1}; HRMS (ESI) calcd for $C_{23}H_{25}N_2O$ [M + H] 345.1967, found 345.1958.

Ethyl 9-methoxy-5-phenylpyrazolo[5,1-*a*]isoquinoline-2-carboxylate (3ka). The general procedure was applied to 98 mg of **1k**, 2.2 mg of CuBr, 83 mg of K_2CO_3, and 61 mg of alkyne **2a** for 30 h to afford 66 mg (63%) of the desired product **3ka** as a white solid; mp 137–138 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.97–7.92 (m, 2 H), 7.69 (d, J = 8.7 Hz, 1 H), 7.60 (s, 1 H), 7.54–7.44 (m, 4 H), 7.20 (dd, J = 8.7, 2.5 Hz, 1 H), 7.16 (s, 1 H), 4.45 (q, J = 7.1 Hz, 2 H), 3.99 (s, 3 H), 1.44 (t, J = 7.1 Hz, 3 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 162.8, 159.3, 143.8, 139.9, 136.3, 133.1, 129.4, 129.2, 128.9, 128.3, 125.2, 123.1, 118.4, 114.7, 104.6, 100.7, 61.2, 55.6, 14.3; IR (KBr): 1740, 1616, 1501, 1350, 1258, 1205, 1184, 1036, 1016, 854, 764, 692 cm^{-1}; HRMS (ESI) calcd for $C_{21}H_{19}N_2O_3$ [M + H] 347.1396, found 347.1384.

1-(4-Methoxyphenyl)-2-methyl-5-phenylpyrazolo[5,1-*a*]isoquinoline (3la). The general procedure was applied to 117 mg of **1l** (0.34 mmol scale), 2.5 mg of CuBr, 95 mg of K_2CO_3, and 70 mg of alkyne **2a** in 0.7 mL of NMP to afford 30 mg (24%) of the desired product **3la** (the low running spot on TLC) as a yellow solid; mp 153–154 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.98–7.92 (m, 2 H), 7.77 (d, J = 8.2 Hz, 1 H), 7.68 (d, J = 7.8 Hz, 1 H), 7.57–7.36 (m, 6 H), 7.29–7.23 (m, 1 H), 7.10–7.05 (m, 2 H), 6.96 (s, 1 H), 3.93 (s, 3 H), 2.33 (s, 3 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 158.9, 149.5, 138.1, 135.6, 134.1, 131.8, 129.8, 129.5, 129.2, 128.3, 127.4, 127.0, 126.6, 126.5, 124.4, 123.0, 114.8, 114.3, 111.8, 55.3, 12.6; IR (KBr): 1566, 1472, 1244, 1171, 1024, 835, 768, 698 cm^{-1}; HRMS (ESI) calcd for $C_{25}H_{21}N_2O$ [M + H] 365.1654 found 365.1643. For the other product (the high running spot on TLC) see the ESI†.

6-Phenyl-9,10,11,12-tetrahydroindazolo[3,2-*a*]isoquinoline (3ma). The general procedure was applied to 55 mg of **1m** (0.2 mmol scale), *ca.* 1.5 mg of CuBr, 56 mg of K_2CO_3, and 41 mg of alkyne **2a** in 0.5 mL of NMP to afford 26 mg (43%) of the desired product **3ma** as a yellow solid; mp 117–118 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.18 (d, J = 7.7 Hz, 1 H), 7.92–7.88 (m, 2 H), 7.73–7.69 (m, 1 H), 7.57–7.44 (m, 5 H), 6.91 (s, 1 H), 3.15 (t, J = 6.1 Hz, 2 H), 2.92 (t, J = 6.0 Hz, 2 H), 2.02–1.89 (m, 4 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 151.0, 138.4, 134.8, 134.3, 129.5, 129.4, 129.1, 128.3, 126.89, 126.87, 126.8, 125.3, 123.2, 111.4, 109.8, 24.2, 23.6, 23.0, 22.9; IR (KBr): 1568, 1485, 1398, 1352, 764, 692 cm^{-1}; HRMS (ESI) calcd for $C_{21}H_{19}N_2$ [M + H] 299.1548, found 299.1547.

6-Phenylindazolo[3,2-*a*]isoquinoline (3na). The general procedure was applied to 82 mg of **1n**, 2.2 mg of CuBr, 83 mg of K_2CO_3, and 61 mg of alkyne **2a** in the presence of 77 mg of

AgOTf for 30 h to afford 38 mg (43%) of the desired product **3na** as a yellow solid; mp 129–130 °C (lit[22] 134–135 °C). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.76 (d, J = 8.1 Hz, 1 H), 8.53 (d, J = 8.5 Hz, 1 H), 8.05–7.99 (m, 2 H), 7.97 (d, J = 8.7 Hz, 1 H), 7.92 (d, J = 7.9 Hz, 1 H), 7.80–7.75 (m, 1 H), 7.67–7.51 (m, 5 H), 7.46 (s, 1 H), 7.39–7.33 (m, 1 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 148.8, 138.4, 133.9, 131.4, 129.7, 129.5, 128.6, 128.5, 128.2, 127.6, 127.2, 127.1, 125.7, 122.7, 121.4, 121.1, 117.7, 116.9, 116.7; HRMS (ESI) calcd for $C_{21}H_{15}N_2$ [M + H] 295.1235, found 295.1233.

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