JOC The Journal of Organic Chemistry

Article

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Metal Cocatalyzed Tandem Alkynylative Cyclization Reaction of in Situ Formed *N*-Iminoisoquinolinium Ylides with Bromoalkynes via C−H Bond Activation

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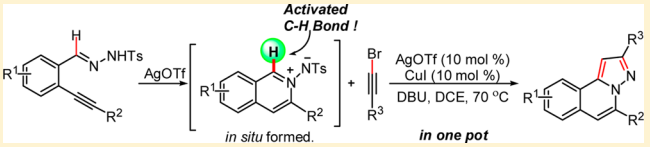
Supporting Information

ABSTRACT: Silver triflate and copper(I) iodide cocatalyzed direct alkynylation and cyclization reaction of in situ formed *N*-iminoisoquinolinium ylides with bromoalkynes is described. The reaction proceeds efficiently through a combination of C−H activation and subsequent tandem reaction in one pot, leading to diverse *H*-pyrazolo[5,1-*a*]isoquinolines in good yields under mild reaction conditions.



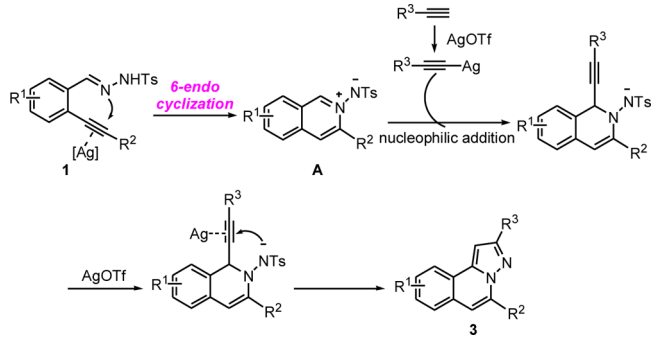
INTRODUCTION

Transition-metal-catalyzed C−H activation/functionalization reactions have emerged as an attractive strategy for the synthesis of interesting natural product like or pharmaceutical compounds.[1] The attraction to applying C−H direct functionalization in complex molecule synthesis originates from the notion that C−H bonds can be regarded as potential synthetic equivalents of various active functional groups. However, the principal challenge in the theme of C−H activation that limits its synthetic application is its chemo- and regioselectivity, especially for a C−H bond targeted over the others that ubiquitously exist in a complex organic molecule. In 1993, Murai reported in a pioneering work that a pendant heteroatom could function as a directing group to achieve selectivity.[2] Since then, many directing groups that contain heteroatoms, such as −OH,[3] −NH_2,[4] imine,[5] −COOR,[6] amide,[7] heterocyclics,[8] etc., have been well developed. Recently, Charette described palladium-catalyzed direct alkenylation reactions of *N*-iminopyridinium ylides to produce 2-substituted pyrazolo[1,5-*a*]pyridines, through a combination of C−H activation and a subsequent tandem reaction process in one reaction vessel.[9] Although N-activated pyridines have emerged as versatile scaffolds whereby complex pyridine derivatives can be prepared,[9a] the *N*-iminoisoquinolinium ylides, especially for those in situ generated ylides used as directing groups for further C−H activation transformations, still remain largely unexplored.

Recently, the construction of natural product like compounds used in different biological assays has attracted much attention. We noticed that the compounds with a *H*-pyrazolo[5,1-*a*]isoquinoline core, which incorporates both isoquinoline and pyrazolo[1,5-*a*]pyridine skeletons,[10] showed remarkable biological activity for the inhibition of CDC25B, TC-PTP, and PTP1B. Therefore, a large collection of diverse *H*-pyrazolo[5,1-*a*]isoquinolines is in great demand in the discovery of lead compounds.

The synthesis of *H*-pyrazolo[5,1-*a*]isoquinolines has been developed by Wu and co-workers.[10] They used silver triflate to catalyze a tandem reaction of *N*′-(2-alkynylbenzylidene)-hydrazide **1** with alkynes to produce *H*-pyrazolo[5,1-*a*]-isoquinolines.[10g] The reaction was believed to occur through the reactive intermediate *N*-iminoisoquinolinium ylide **A**, which was produced via 6-endo cyclization of *N*′-(2-alkynylbenzylidene)hydrazide **1** under the catalysis of silver salt, and following nucleophilic addition of alkynes to the isoquinolinium intermediate **A** afforded the corresponding *H*-pyrazolo[5,1-*a*]isoquinolines **3** (Scheme 1). More recently, we have described a silver triflate and palladium acetate cocatalyzed tandem reaction of *N*′-(2-alkynylbenzylidene)hydrazide **1** with

Scheme 1



Received: July 4, 2012
Published: September 4, 2012

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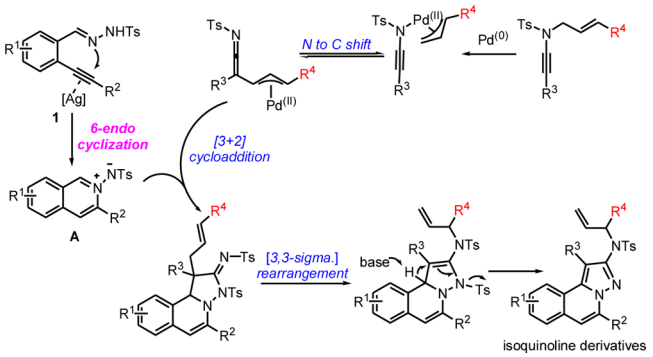
dx.doi.org/10.1021/jo3013429 | *J. Org. Chem.* 2012, 77, 8092−8098

N-allyl ynamide to produce 2-amino-*H*-pyrazolo[5,1-*a*]isoquinolines (Scheme 2).[11]

Scheme 2



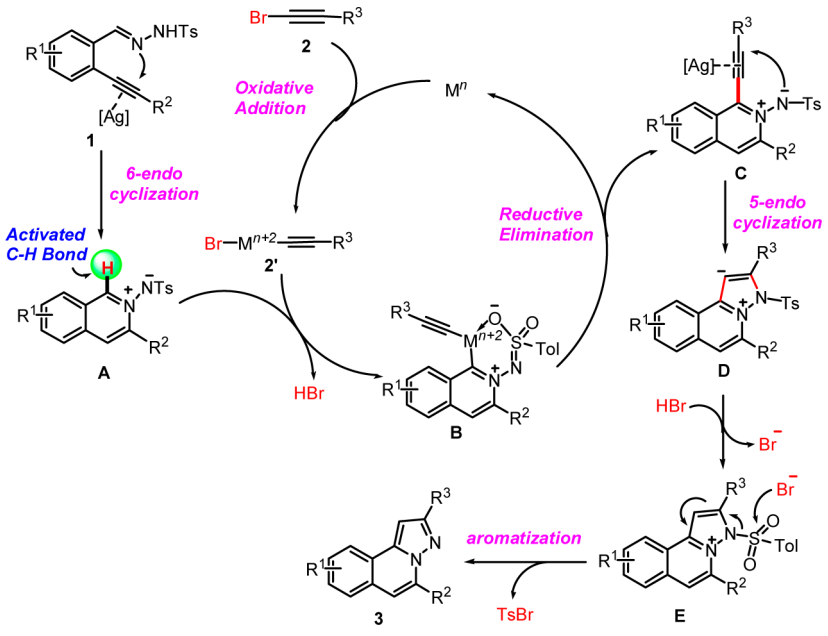
On the other hand, as a versatile and useful synthon, haloalkyne has been widely applied in synthetic organic chemistry.[12] The reactivity of 1-haloalkynes has been demonstrated recently. For example, Jiang and co-workers reported an expedient synthesis of functionalized conjugated enynes through a palladium-catalyzed bromoalkynylation of alkynes.[12f]

Encouraged by the results and inspired by the work of Charette,[9] we conceived that haloalkyne might be a good choice for the reaction development. We envisioned that in the presence of a suitable transition-metal catalyst, the α-C−H bond in the *N*-iminoisoquinolinium ylide intermediate **A** might be selectively activated under the direction of an *N*-imino ylide group (Scheme 3). Meanwhile, bromoalkyne would be activated via oxidative addition under the metal catalyst conditions, which resulted in attack of the in situ formed isoquinolinium-2-yl amide **A** and subsequently proceeded through a concerted metalation/deprotonation (CMD) process[9c,13] to form intermediate **B**. Also, the next reductive elimination reaction would occur to furnish the 1-alkylisoquinoline compound **C**. Finally, intramolecular 5-endo cyclization, protonation, and aromatization reactions would occur, leading to the functionalized *H*-pyrazolo[5,1-*a*]isoquinolines **3**. Theoretically, the proposed synthetic route is feasible. The efficiency of multicatalytic processes[14] has been demonstrated in tandem reactions. Usually, the combination of two or more catalysts in a reaction is powerful for distinct chemical transformations. Prompted by these results, we conceived that the combination of bimetal catalysts such as those shown in Scheme 3 would facilitate the reaction of *N*′-(2-alkynylbenzylidene)hydrazide **1** with haloalkyne **2** successfully.

RESULTS AND DISCUSSION

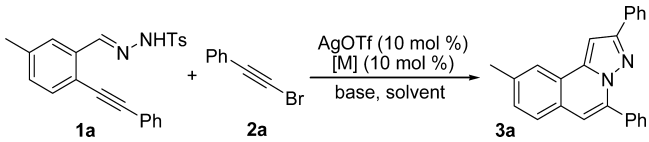
The initial attempt was performed between the reaction of *N*′-(2-alkynylbenzylidene)hydrazide **1a** and 1-(2-bromoethynyl)-benzene **2a**. Since silver triflate was demonstrated to be the most efficient catalyst for the 6-endo cyclization of *N*′-(2-alkynylbenzylidene)hydrazide,[10g] the combinations of silver triflate and other metal salts were investigated in the model reaction (Table 1). At the outset, the reaction occurred in the presence of DBU as the base in dichloroethane (DCE) at room temperature. Only a trace amount of product was observed when $Pd(PPh_3)_2Cl_2$ or $Au(PPh_3)_3Cl$ was employed as the cocatalyst in the above reaction (Table 1, entries 1 and 2). Gratifyingly, the desired product **3a** could be isolated in 54% yield when copper(I) iodide was used as catalyst in the transformation (Table 1, entry 3). The structure of **3a** was identified by NMR and HRMS (the analogous structure of **3k** was identified unambiguously by X-ray diffraction analysis; see the Supporting Information). Switching the copper catalyst to CuBr, CuCl, $Cu(OTf)_2$, or $Cu(OAc)_2$, however, led to production with lower yields (Table 1, entries 4−7). Next, we examined the base effect of the reaction (Table 1, entries 8−12). No better results were generated. Subsequently, different solvents were screened (Table 1, entries 13−17), and the final outcome could not be improved. Similar yields (53%) were

Scheme 3. Generation of *H*-Pyrazolo[5,1-*a*]isoquinolines via the Reaction of *N*′-(2-Alkynylbenzylidene)hydrazide 1 with Bromoalkyne 2



dx.doi.org/10.1021/jo3013429 | J. Org. Chem. 2012, 77, 8092−8098

Table 1. Initial Studies for the Bimetal-Catalyzed Reaction of *N*′-(2-Alkynylbenzylidene)hydrazide 1a with 1-(2-Bromoethynyl)benzene 2a



entry	[M]	base	solvent	*T* (°C)	yield (%)[a]
1	$Pd(PPh_3)_2Cl_2$	DBU	DCE	25	trace
2	$Au(PPh_3)_3Cl$	DBU	DCE	25	trace
3	CuI	DBU	DCE	25	54
4	CuBr	DBU	DCE	25	45
5	CuCl	DBU	DCE	25	31
6	$Cu(OTf)_2$	DBU	DCE	25	38
7	$Cu(OAc)_2$	DBU	DCE	25	42
8	CuI	K_3PO_4	DCE	25	5
9	CuI	Cs_2CO_3	DCE	25	12
10	CuI	DABCO	DCE	25	8
11	CuI	KOH	DCE	25	trace
12	CuI	K_2CO_3	DCE	25	9
13	CuI	DBU	THF	25	45
14	CuI	DBU	dioxane	25	30
15	CuI	DBU	MeCN	25	28
16	CuI	DBU	toluene	25	43
17	CuI	DBU	DMF	25	12
18	CuI	DBU	DCE	50	53
19	CuI	DBU	DCE	70	62
20	CuI	DBU	DCE	90	53

[a]Isolated yield based on *N*′-(2-alkynylbenzylidene) hydrazide **1a**.

obtained when the reaction was performed at 50 or 90 °C (Table 1, entries 18 and 20). Interestingly, the reaction afforded the corresponding *H*-pyrazolo[5,1-*a*]isoquinoline **3a** in 62% yield when it took place at 70 °C (Table 1, entry 19).

With this promising result in hand, we started to explore the generality of this bimetal cocatalyzed reaction of *N*′-(2-alkynylbenzylidene)hydrazide **1** with bromoalkyne **2** under the conditions highlighted above (10 mol % of AgOTf, 10 mol % of CuI, 3.0 equiv of DBU, DCE, 70 °C). The results are summarized in Table 2. We found that all reactions proceeded smoothly for the evaluation of various substituted *N*′-(2-alkynylbenzylidene)hydrazides **1** and bromoalkynes **2**. Not only 2-aryl-substituted bromoalkynes but also 2-alkyl-substituted bromoalkynes were demonstrated to be good partners in the transformation. For instance, *N*′-(2-alkynylbenzylidene)-hydrazide **1a** reacted with 1-(2-bromoethynyl)-4-methoxybenzene **2b**, leading to the desired *H*-pyrazolo[5,1-*a*]isoquinoline **3b** in 80% yield (Table 2, entry 2). When 1-(2-bromoethynyl)-4-chlorobenzene **2c** was used as a replacement, the corresponding product **3c** was afforded in 62% yield (Table 2, entry 3). The product was obtained with a slightly higher yield when 1-bromohex-1-yne **2d** or (2-bromoethynyl)-cyclopropane **2e** was employed in the reaction (Table 2, entries 4 and 5). Reactions of *N*′-(2-alkynylbenzylidene)-hydrazide **1b** with various bromoalkynes were examined subsequently, which furnished the desired products in good yields (Table 2, entries 6–10). We further discovered that reactions of *N*′-(2-alkynylbenzylidene)hydrazides **1** bearing alkyl substituents at the R^2 position provided good yields of the targeted structures using the standard protocol (entries 11–16). It is well-known that the molecules bearing a fluorine moiety are of great importance in pharmaceuticals, since the fluorinated compounds can significantly improve their properties such as solubility, bioavailability, and metabolic stability.[15] Thus, reactions of fluoro-substituted *N*′-(2-alkynylbenzylidene)hydrazides **1f–i** were explored. As expected, all reactions involving **1f–i** gave acceptable yields of the tricyclic products under the standard conditions (entries 17–25).

Although a detailed mechanism has yet to be determined,[10] we propose the following mechanism for this one-pot C–H activation and subsequent tandem cyclization reaction, on the basis of the above observations (Scheme 4). We believe that the reaction first occurred through the reactive intermediate *N*-iminoisoquinolinium ylides **A**[10] and then proceeds by three possible routes as depicted in Scheme 4: (1) direct alkynylation,[10i] (2) dipolar cycloaddition,[10j] or (3) C–H activation alkynykation. First, for the possible route 1, the electron-deficient carbon, which was linked with a bromo atom in the bromoalkyne, could not attack the C-1 position of the *N*-iminoisoquinolinium ylide **A** to form **B1**, therefore ruling out the possibility of direct alkynylation (1). Second, dipolar cycloaddition of *N*-iminoisoquinolinium ylides **A** with bromoalkyne may lead to the 2-bromo-*H*-pyrazolo[5,1-*a*]-isoquinoline **Br-3** instead of **3**. Therefore, we think that the reaction may involve oxidative addition of the copper(I) catalyst to haloalkynes[16] and then C–H activation alkynylation of the *N*-iminoisoquinolinium ylide **A** to produce *H*-pyrazolo-[5,1-*a*]isoquinoline **3** (route 3). Further exploration of the mechanism is ongoing in our laboratory.

■ CONCLUSION

In summary, we have described a novel and efficient C–H activation direct alkynylation reaction of in situ formed *N*-iminoisoquinolinium ylide with bromoalkyne cocatalyzed by silver triflate and copper(I) iodide under mild conditions, which generates diverse *H*-pyrazolo[5,1-*a*]isoquinolines in good yields. A wide substrate scope with good functional group tolerance has been demonstrated. This method is an alternative route for the preparation of *H*-pyrazolo[5,1-*a*]isoquinolines via a C–H activation mechanism. Further library construction and subsequent biological evaluation are in progress in our laboratory.

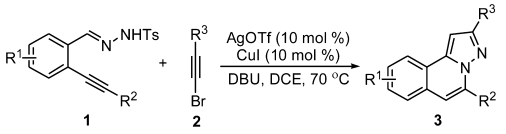
■ EXPERIMENTAL SECTION

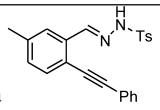
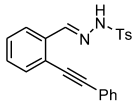
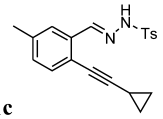
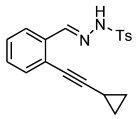
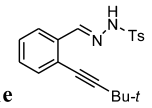
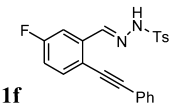
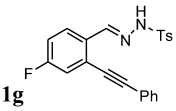
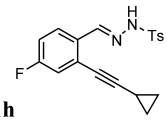
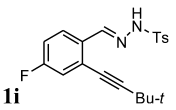
Typical Procedure for the Silver Triflate and Copper(I) Iodide Cocatalyzed Reaction of *N*′-(2-Alkynylbenzylidene)-hydrazide 1 with Bromoalkyne 2. A mixture of *N*′-(2-alkynylbenzylidene)hydrazide **1** (0.20 mmol) and silver triflate (10 mol %) in anhydrous DCE (0.5 mL) was heated at 70 °C for 1 h. The mixture was then cooled to room temperature. Copper(I) iodide (10 mol %) and a solution of DBU (0.6 mmol, 3.0 equiv) with bromoalkyne **2** (0.3 mmol, 1.5 equiv) in DCE (2.0 mL) were added subsequently. The mixture was stirred at 70 °C overnight. After completion of the reaction as indicated by TLC, the solvent was evaporated. The residue was diluted with EtOAc (10 mL), washed with H_2O (10 mL), and dried over anhydrous $MgSO_4$. Evaporation of the solvent followed by purification on silica gel provided the corresponding product **3**.

*9-Methyl-2,5-diphenylpyrazolo[5,1-a]isoquinoline (**3a**).* Compound **3a** was obtained as a white solid: mp 126–127 °C; yield 62%; ^1H NMR (400 MHz, $CDCl_3$) δ 2.53 (s, 3H), 6.99 (s, 1H), 7.31–7.58 (m, 9H), 7.90 (s, 1H), 7.98–8.02 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.8, 94.5, 112.4, 123.2, 123.9, 126.3, 127.0, 128.0, 128.5, 129.0, 129.5, 129.6, 133.5, 133.8, 137.3, 137.5, 140.6, 152.0; HRMS calcd for $C_{24}H_{18}N_2^+$ $[M + H]^+$ 335.1548, found 335.1532.

dx.doi.org/10.1021/jo3013429 | J. Org. Chem. 2012, 77, 8092–8098

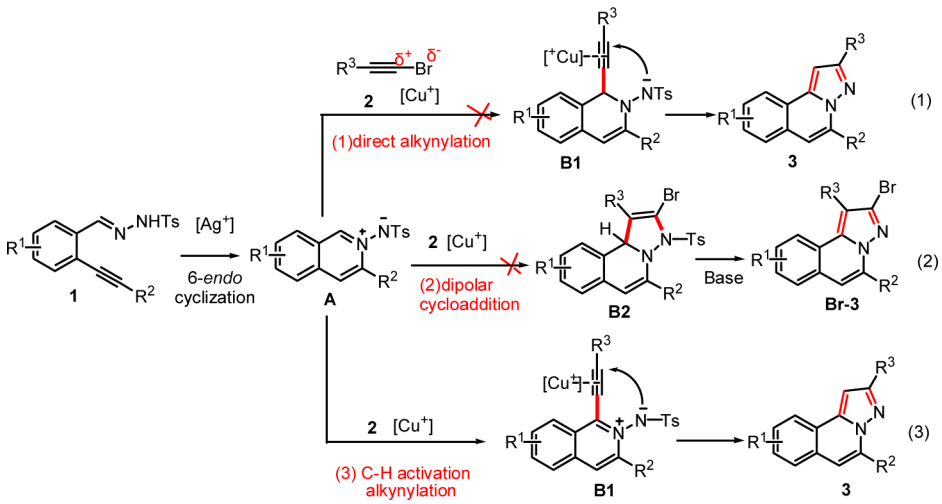
Table 2. Silver Triflate and Copper(I) Iodide Cocatalyzed Reaction of *N*′-(2-Alkynylbenzylidene)hydrazide 1 with Bromoalkyne 2



Entry	Substrate **1**	R^3	Yield (%)[a]
1	 **1a**	C_6H_5 (**2a**)	62 (**3a**)
2	**1a**	*p*-$MeOC_6H_5$ (**2b**)	80 (**3b**)
3	**1a**	*p*-ClC_6H_5 (**2c**)	62 (**3c**)
4	**1a**	*n*-C_4H_9 (**2d**)	73 (**3d**)
5	**1a**	Cyclopropyl (**2e**)	65 (**3e**)
6	 **1b**	C_6H_5 (**2a**)	67 (**3f**)
7	**1b**	*p*-$MeOC_6H_5$ (**2b**)	65 (**3g**)
8	**1b**	*p*-ClC_6H_5 (**2c**)	60 (**3h**)
9	**1b**	*n*-C_4H_9 (**2d**)	70 (**3i**)
10	**1b**	Cyclopropyl (**2e**)	55 (**3j**)
11	 **1c**	*p*-$MeOC_6H_5$ (**2b**)	58 (**3k**)
12	**1c**	*p*-ClC_6H_5 (**2c**)	58 (**3l**)
13	 **1d**	*p*-$MeOC_6H_5$ (**2b**)	57 (**3m**)
14	**1d**	*p*-ClC_6H_5 (**2c**)	55 (**3n**)
15	 **1e**	*p*-$MeOC_6H_5$ (**2b**)	68 (**3o**)
16	**1e**	*p*-ClC_6H_5 (**2c**)	63 (**3p**)
17	 **1f**	C_6H_5 (**2a**)	61 (**3q**)
18	**1f**	*p*-ClC_6H_5 (**2c**)	65 (**3r**)
19	**1f**	*n*-C_4H_9 (**2d**)	55 (**3s**)
20	 **1g**	C_6H_5 (**2a**)	54 (**3t**)
21	 **1h**	C_6H_5 (**2a**)	63 (**3u**)
22	**1h**	*p*-$MeOC_6H_5$ (**2b**)	56 (**3v**)
23	**1h**	*p*-ClC_6H_5 (**2c**)	63 (**3w**)
24	**1h**	Cyclopropyl (**2e**)	46 (**3x**)
25	 **1i**	*p*-$MeOC_6H_5$ (**2b**)	63 (**3y**)

[a]Isolated yield based on *N*′-(2-alkynylbenzylidene)hydrazide **1**.

Scheme 4. Plausible Mechanism for the Formation of *H*-Pyrazolo[5,1-*a*]isoquinolines via the Reaction of *N*′-(2-Alkynylbenzylidene)hydrazide (1) with Bromoalkyne (2)



dx.doi.org/10.1021/jo3013429 | *J. Org. Chem.* 2012, 77, 8092−8098

*2-(4-Methoxyphenyl)-9-methyl-5-phenylpyrazolo[5,1-a]isoquinoline (**3b**).* Compound **3b** was obtained as a white solid: mp 178−179 °C; yield 80%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.56 (s, 3H), 3.85 (s, 3H), 6.96−7.00 (m, 3H), 7.34 (d, J = 8.0 Hz, 1H), 7.48−7.56 (m, 4H), 7.61 (d, J = 8.0 Hz, 1H), 7.92−7.95 (m, 3H), 8.04 (d, J = 7.5 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.7, 55.2, 94.0, 112.0, 114.0, 123.2, 123.8, 126.2, 127.0, 127.6, 128.0, 129.0, 129.4, 129.6, 133.9, 137.2, 137.5, 140.5, 151.9, 159.7; HRMS calcd for $C_{25}H_{20}N_2O^+$ $[M + H]^+$ 365.1654, found 365.1638.

*2-(4-Chlorophenyl)-9-methyl-5-phenylpyrazolo[5,1-a]isoquinoline (**3c**).* Compound **3c** was obtained as a light yellow solid: mp 164−165 °C; yield 62%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.52 (s, 3H), 6.98 (s, 1H), 7.25 (s, 1H), 7.30−7.40 (m, 3H), 7.50−7.57 (m, 4H), 7.86−7.88 (m, 3H), 7.97 (d, J = 8.0 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.8, 94.5, 112.6, 123.2, 123.8, 127.0, 127.1, 127.5, 128.1, 128.7, 129.1, 129.5, 129.6, 132.0, 133.7, 133.8, 137.4, 140.7, 150.8; HRMS calcd for $C_{24}H_{17}ClN_2^+$ $[M + H]^+$ 369.1159, found 369.1169.

*2-Butyl-9-methyl-5-phenylpyrazolo[5,1-a]isoquinoline (**3d**).* Compound **3d** was obtained as a light yellow solid: mp 112−113 °C; yield 73%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.96 (t, J = 7.3 Hz, 3H), 1.40−1.47 (m, 2H), 1.72−1.78 (m, 2H), 2.50 (s, 3H), 2.84 (t, J = 7.8 Hz, 2H), 6.84 (s, 1H), 6.89 (s, 1H), 7.28 (d, J = 7.8 Hz, 1H), 7.43−7.48 (m, 3H), 7.54 (d, J = 8.2 Hz, 1H), 7.82 (s, 1H), 7.92 (d, J = 7.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.9, 21.7, 22.6, 28.4, 31.9, 96.0, 111.5, 123.1, 123.7, 126.8, 126.9, 128.2, 128.9, 129.2, 129.4, 134.1, 136.9, 137.3, 139.8, 155.0; HRMS calcd for $C_{22}H_{22}N_2^+$ $[M + H]^+$ 315.1861, found 315.1834.

*2-Cyclopropyl-9-methyl-5-phenylpyrazolo[5,1-a]isoquinoline (**3e**).* Compound **3e** was obtained as a white solid: mp 188−189 °C; yield 65%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.85−0.86 (m, 2H), 0.99−1.02 (m, 2H), 2.14−2.17 (m, 1H), 2.50 (s, 3H), 6.63 (s, 1H), 6.89 (s, 1H), 7.29 (d, J = 8.2 Hz, 1H), 7.42−7.50 (m, 3H), 7.56 (d, J = 7.8 Hz, 1H), 7.80 (s, 1H), 7.93 (d, J = 6.9 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 9.0, 9.8, 21.7, 92.9, 111.4, 123.1, 123.6, 126.9, 127.0, 128.1, 128.9, 129.3, 129.4, 134.0, 137.0, 137.3, 140.0, 157.0; HRMS calcd for $C_{21}H_{18}N_2^+$ $[M + H]^+$ 299.1548, found 299.1530.

*2,5-Diphenylpyrazolo[5,1-a]isoquinoline (**3f**).* Compound **3f** was obtained as a white solid: mp 142−143 °C; yield 67%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.04 (s, 1H), 7.31−7.54 (m, 9H), 7.68−7.72 (m, 1H), 7.98−8.03 (m, 4H), 8.12 (d, J = 7.3 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 94.8, 112.4, 123.5, 123.9, 126.4, 127.2, 127.3, 127.9, 128.1, 128.6, 129.2, 129.6, 132.2, 133.4, 133.7, 138.4, 140.7, 152.2; HRMS calcd for $C_{23}H_{16}N_2^+$ $[M + Na]^+$ 343.1211, found 343.1211.

*2-(4-Methoxyphenyl)-5-phenylpyrazolo[5,1-a]isoquinoline (**3g**).* Compound **3g** was obtained as a white solid: mp 130−131 °C; yield 65%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.85 (s, 3H), 6.97 (d, J = 8.7 Hz, 2H), 7.04 (s, 1H), 7.31 (s, 1H), 7.51−7.55 (m, 5H), 7.72 (d, J = 7.6 Hz, 1H), 7.94 (d, J = 8.3 Hz, 2H), 8.04 (d, J = 7.8 Hz, 2H), 8.12 (d, J = 7.3 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 55.4, 94.4, 112.3, 114.1, 123.6, 124.0, 126.3, 127.1, 127.3, 127.8, 128.0, 128.3, 129.3, 129.4, 129.8, 133.9, 138.5, 140.8, 152.2, 159.9; HRMS calcd for $C_{24}H_{18}N_2O^+$ $[M + H]^+$ 351.1497, found 351.1489.

*2-(4-Chlorophenyl)-5-phenylpyrazolo[5,1-a]isoquinoline (**3h**).* Compound **3h** was obtained as a white solid: mp 149−150 °C. yield 60%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.03 (s, 1H), 7.29 (s, 1H), 7.36 (d, J = 8.2 Hz, 2H), 7.50−7.53 (m, 4H), 7.63−7.70 (m, 2H), 7.88 (d, J = 8.2 Hz, 2H), 7.98 (d, J = 6.9 Hz, 2H), 8.07 (d, J = 6.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 94.7, 112.7, 116.9, 123.4, 127.1, 127.2, 127.3, 127.6, 128.0, 128.1, 128.7, 129.2, 129.6, 133.4, 133.9, 138.2, 140.8, 151.0; HRMS calcd for $C_{23}H_{15}ClN_2^+$ $[M + Na]^+$ 377.0821, found 377.0830.

*2-Butyl-5-phenylpyrazolo[5,1-a]isoquinoline (**3i**).* Compound **3i** was obtained as a light yellow solid: mp 115−116 °C; yield 70%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.96 (t, J = 7.3 Hz, 3H), 1.40−1.50 (m, 2H), 1.72−1.80 (m, 2H), 2.85 (t, J = 7.8 Hz, 2H), 6.87 (s, 1H), 6.93 (s, 1H), 7.44−7.49 (m, 5H), 7.66 (d, J = 7.3 Hz 1H), 7.93 (d, J = 6.4 Hz, 2H), 8.03 (d, J = 7.3 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.9, 22.6, 28.4, 32.0, 96.3, 111.6, 123.3, 123.7, 127.0, 127.6, 128.2, 129.1, 129.2, 129.4, 134.0, 138.2, 140.0, 155.2; HRMS calcd for $C_{21}H_{20}N_2^+$ $[M + H]^+$ 301.1705, found 301.1701.

*2-Cyclopropyl-5-phenylpyrazolo[5,1-a]isoquinoline (**3j**).* Compound **3j** was obtained as a white solid: mp 106−107 °C; yield 55%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.86−0.87 (m, 2H), 1.01−1.03 (m, 2H), 2.15−2.18 (m, 1H), 6.67 (s, 1H), 6.95 (s, 1H), 7.46−7.51 (m, 5H), 7.69 (d, J = 7.8 Hz 1H), 7.94 (d, J = 7.8 Hz, 2H), 8.01 (d, J = 6.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 9.0, 9.8, 93.2, 111.4, 123.3, 123.6, 127.0, 127.7, 128.2, 129.1, 129.3, 129.5, 133.9, 138.2, 140.1, 157.2; HRMS calcd for $C_{20}H_{16}N_2^+$ $[M + H]^+$ 285.1392, found 285.1367.

*5-Cyclopropyl-2-(4-methoxyphenyl)-9-methylpyrazolo[5,1-a]isoquinoline (**3k**).* Compound **3k** was obtained as a white solid: mp 161−162 °C; yield 58%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.94−0.95 (m, 2H), 1.17−1.19 (m, 2H), 2.51 (s, 3H), 2.82−2.83 (m, 1H), 3.85 (s, 3H), 6.52 (s, 1H), 6.99 (d, J = 8.2 Hz, 2H), 7.22 (s, 1H), 7.28 (d, J = 7.8 Hz, 1H), 7.49 (d, J = 7.8 Hz, 1H), 7.86 (s, 1H), 7.98 (d, J = 8.2 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 7.6, 11.2, 21.8, 55.4, 94.2, 105.7, 114.2, 123.3, 126.4, 126.7, 127.1, 127.8, 129.4, 134.1, 136.3, 140.1, 140.4, 152.0, 159.8; HRMS calcd for $C_{22}H_{20}N_2O^+$ $[M + H]^+$ 329.1654, found 329.1639.

*2-(4-Chlorophenyl)-5-cyclopropyl-9-methylpyrazolo[5,1-a]isoquinoline (**3l**).* Compound **3l** was obtained as a white solid: mp 129−130 °C; yield 58%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.93−0.94 (m, 2H), 1.17−1.19 (m, 2H), 2.51 (s, 3H), 2.79−2.80 (m, 1H), 6.55 (s, 1H), 7.29 (d, J = 7.8 Hz, 1H), 7.41 (d, J = 8.2 Hz, 2H), 0.48−7.49 (m, 2H), 7.85 (s, 1H), 7.97 (d, J = 8.2 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 7.4, 11.0, 21.7, 94.5, 106.2, 123.1, 126.4, 127.0, 127.6, 128.8, 129.4, 132.3, 133.7, 136.4, 140.1, 140.2, 150.8; HRMS calcd for $C_{21}H_{17}ClN_2^+$ $[M + H]^+$ 333.1159, found 333.1148.

*5-Cyclopropyl-2-(4-methoxyphenyl)pyrazolo[5,1-a]isoquinoline (**3m**).* Compound **3m** was obtained as a white solid: mp 108−109 °C; yield 57%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.95−0.96 (m, 2H), 1.18−1.24 (m, 2H), 2.82−2.87 (m, 1H), 3.84 (s, 3H), 6.54 (s, 1H), 6.99 (d, J = 8.2 Hz, 2H), 7.24 (s, 1H), 7.44−7.46 (m, 2H), 7.57 (d, J = 6.0 Hz, 1H), 7.98 (d, J = 8.7 Hz, 2H), 8.05 (d, J = 6.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 7.6, 11.1, 55.3, 94.2, 105.5, 114.1, 123.0, 123.4, 126.3, 126.4, 127.6, 127.7, 129.2, 140.1, 141.2, 152.0, 159.7; HRMS calcd for $C_{21}H_{18}N_2O^+$ $[M + H]^+$ 315.1497, found 315.1488.

*2-(4-Chlorophenyl)-5-cyclopropylpyrazolo[5,1-a]isoquinoline (**3n**).* Compound **3n** was obtained as a white solid: mp 111−112 °C; yield 55%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.95−0.97 (m, 2H), 1.20−1.22 (m, 2H), 2.80−2.83 (m, 1H), 6.58 (s, 1H), 7.27 (s, 1H), 7.41−7.49 (m, 4H), 7.59−7.60 (m, 1H), 7.98 (d, J = 8.2 Hz, 2H), 8.05−8.06 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 7.6, 11.1, 29.7, 94.7, 106.2, 123.0, 123.4, 126.5, 127.6, 127.8, 128.8, 129.2, 132.2, 133.8, 140.2, 141.2, 160.0; HRMS calcd for $C_{20}H_{15}ClN_2^+$ $[M + H]^+$ 319.1002, found 319.0995.

*5-Butyl-2-(4-methoxyphenyl)pyrazolo[5,1-a]isoquinoline (**3o**).* Compound **3o** was obtained as a white solid: mp 105−106 °C; yield 68%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.01 (t, J = 7.3 Hz, 3H), 1.49−1.55 (m, 2H), 1.86−1.92 (m, 2H), 3.20 (t, J = 7.8 Hz, 2H), 3.84 (s, 3H), 6.76 (s, 1H), 6.99 (d, J = 8.0 Hz, 2H), 7.21 (s, 1H), 7.45−7.48 (m, 2H), 7.61 (d, J = 6.8 Hz, 1H), 7.97 (d, J = 8.2 Hz, 2H), 8.04−8.05 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.0, 22.5, 28.9, 30.5, 55.3, 94.0, 109.0, 114.1, 123.3, 123.4, 126.3, 126.4, 127.6, 129.3, 139.7, 140.0, 151.8, 160.0; HRMS calcd for $C_{22}H_{22}ON_2^+$ $[M + H]^+$ 331.1810, found 331.1815.

*5-Butyl-2-(4-chlorophenyl)pyrazolo[5,1-a]isoquinoline (**3p**).* Compound **3p** was obtained as a white solid: mp 97−98 °C; yield 63%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.03 (t, J = 7.2 Hz, 3H), 1.51−1.58 (m, 2H), 1.88−1.95 (m, 2H), 3.21 (t, J = 7.5 Hz, 2H), 6.81 (s, 1H), 7.25 (s, 1H), 7.42 (d, J = 7.9 Hz, 2H), 7.49−7.51 (m, 2H), 7.63−7.66 (m, 1H), 7.97 (d, J = 7.9 Hz, 2H), 8.05−8.07 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.0, 22.6, 28.9, 29.7, 30.5, 94.5, 109.6, 123.3, 123.4, 126.5, 127.5, 127.8, 128.8, 129.2, 132.2, 133.8, 139.6, 140.1, 150.8, HRMS calcd for $C_{21}H_{19}ClN_2^+$ $[M + H]^+$ 335.1315, found 335.1340.

*9-Fluoro-2,5-diphenylpyrazolo[5,1-a]isoquinoline (**3q**).* Compound **3q** was obtained as a white solid: mp 113−114 °C; yield 61%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.93 (s, 1H), 7.22−7.27 (m, 2H), 7.30−7.42 (m, 4H), 7.51 (d, J = 6.4 Hz, 3H), 7.95−8.09 (m,

5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 94.5, 111.5, 111.8 (d, $^2J_{CF}$ = 21.8 Hz), 115.8 (d, $^2J_{CF}$ = 23.8 Hz), 120.5, 125.6 (d, $^3J_{CF}$ = 8.6 Hz), 126.4, 128.3, 128.6, 129.4, 129.6, 130.8 (d, $^3J_{CF}$ = 8.6 Hz), 132.2, 133.1, 133.3, 139.4, 140.3, 152.5, 160.8 (d, $^1J_{CF}$ = 246.0 Hz); HRMS calcd for $C_{23}H_{15}FN_2^+$ $[M + H]^+$ 339.1298, found 339.1290.

*2-(4-Chlorophenyl)-9-fluoro-5-phenylpyrazolo[5,1-a]isoquinoline (**3r**).* Compound **3r** was obtained as a light yellow solid: mp 188−189 °C; yield 65%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.95 (s, 1H), 7.21−7.26 (m, 2H), 7.31−7.38 (m, 3H), 7.51−7.52 (m, 3H), 7.86 (d, J = 8.2 Hz, 2H), 7.96 (d, J = 6.4 Hz, 2H), 8.03−8.08 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 94.4, 111.8, 112.0 (d, $^2J_{CF}$ = 23.8 Hz), 115.9 (d, $^2J_{CF}$ = 23.8 Hz), 120.4, 125.6 (d, $^3J_{CF}$ = 8.6 Hz), 127.2, 127.6, 128.2, 128.7, 129.5, 129.6, 131.7, 133.2 (d, $^3J_{CF}$ = 8.6 Hz), 134.0, 139.3, 140.4, 151.3, 160.8 (d, $^1J_{CF}$ = 246.0 Hz); HRMS calcd for $C_{23}H_{14}ClFN_2^+$ $[M + H]^+$ 373.0908, found 373.0916.

*2-Butyl-9-fluoro-5-phenylpyrazolo[5,1-a]isoquinoline (**3s**).* Compound **3s** was obtained as a white solid: mp 96−97 °C; yield 55%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.96 (t, J = 7.3 Hz, 3H), 1.40−1.47 (m, 2H), 1.71−1.77 (m, 2H), 2.83 (t, J = 7.3 Hz, 2H), 6.82 (s, 1H), 6.86 (s, 1H), 7.23 (t, J = 6.4 Hz, 1H), 7.31 (d, J = 8.2 Hz, 1H), 7.48−7.51 (m, 3H), 7.92 (d, J = 7.3 Hz, 2H), 8.00−8.05 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.9, 22.6, 28.4, 31.9, 96.1, 110.7, 111.6 (d, $^2J_{CF}$ =21.0 Hz), 115.5 (d, $^2J_{CF}$ = 23.8 Hz), 120.4, 125.6 (d, $^3J_{CF}$ = 9.5 Hz), 128.3, 129.4, 130.8 (d, $^3J_{CF}$ = 8.6 Hz), 133.6, 139.3, 139.7, 155.6, 160.6 (d, $^1J_{CF}$ = 246.0 Hz); HRMS calcd for $C_{21}H_{19}FN_2^+$ $[M + H]^+$ 319.1611, found 319.1584.

*8-Fluoro-2,5-diphenylpyrazolo[5,1-a]isoquinoline (**3t**).* Compound **3t** was obtained as a white solid: mp 121−122 °C; yield 54%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.94 (s, 1H), 7.22−7.52 (m, 9H), 7.95−8.00 (m, 4H), 8.04−8.08 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 94.5, 111.5, 111.8 (d, $^2J_{CF}$ = 21.9 Hz), 115.8 (d, $^2J_{CF}$ = 23.8 Hz), 120.5, 125.7 (d, $^3J_{CF}$ = 8.6 Hz), 126.4, 127.2, 128.2, 128.3, 129.4, 129.6, 130.8 (d, $^3J_{CF}$ = 9.5 Hz), 133.2, 133.3, 139.4, 140.3, 152.5, 160.8 (d, $^1J_{CF}$ = 246.9 Hz); HRMS calcd for $C_{23}H_{15}FN_2^+$ $[M + Na]^+$ 361.1117, found 361.1113.

*5-Cyclopropyl-8-fluoro-2-phenylpyrazolo[5,1-a]isoquinoline (**3u**).* Compound **3u** was obtained as a white solid: mp 118−119 °C; yield 63%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.96−0.97 (m, 2H), 1.21−1.28 (m, 2H), 2.85−2.87 (m, 1H), 6.47 (s, 1H), 7.17−7.24 (m, 3H), 7.36 (t, J = 6.8 Hz, 1H), 7.44−7.48 (m, 2H), 8.01−8.05 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 7.9, 11.1, 94.5, 105.0, 111.1 (d, $^2J_{CF}$ = 21.0 Hz), 114.9 (d, $^2J_{CF}$ = 23.8 Hz), 119.7, 125.5 (d, $^3J_{CF}$ = 8.6 Hz), 126.4, 128.2, 128.7, 130.9 (d, $^3J_{CF}$ = 9.5 Hz), 133.5, 139.7, 142.5, 152.4, 160.7 (d, $^1J_{CF}$ = 246.0 Hz); HRMS calcd for $C_{20}H_{15}FN_2^+$ $[M + H]^+$ 303.1298, found 303.1312.

*5-Cyclopropyl-8-fluoro-2-(4-methoxyphenyl)pyrazolo[5,1-a]-isoquinoline (**3v**).* Compound **3v** was obtained as a white solid: mp 110−111 °C; yield 56%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.95−0.96 (m, 2H), 1.19−1.21 (m, 2H), 2.84−2.86 (m, 1H), 3.85 (s, 3H), 6.43 (s, 1H), 6.98 (d, J = 7.4 Hz, 2H), 7.15−7.24 (m, 3H), 7.96 (d, J = 8.7 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 7.9, 11.1, 55.3, 94.0, 104.6, 111.0 (d, $^2J_{CF}$ = 21.9 Hz), 114.1, 114.8 (d, $^2J_{CF}$ = 23.8 Hz), 119.6, 125.5 (d, $^3J_{CF}$ = 9.5 Hz), 127.7, 130.9 (d, $^3J_{CF}$ = 9.5 Hz), 139.7, 142.5, 152.3, 159.8, 160.7, 163.1 (d, $^1J_{CF}$ = 246.0 Hz); HRMS calcd for $C_{21}H_{17}FN_2O^+$ $[M + H]^+$ 333.1403, found 333.1388.

*2-(4-Chlorophenyl)-5-cyclopropyl-8-fluoropyrazolo[5,1-a]iso-quinoline (**3w**).* Compound **3w** was obtained as a white solid: mp 172−173 °C; yield 63%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.95−0.96 (m, 2H), 1.20−1.22 (m, 2H), 2.81−2.82 (m, 1H), 6.47 (s, 1H), 7.17−7.23 (m, 3H), 7.41 (d, J = 8.2 Hz, 2H), 7.93−8.00 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 7.8, 11.0, 94.4, 105.3, 111.1 (d, $^2J_{CF}$ = 21.9 Hz), 115.0 (d, $^2J_{CF}$ = 23.8 Hz), 119.6, 125.5 (d, $^3J_{CF}$ = 9.5 Hz), 127.6, 128.8, 130.9 (d, $^3J_{CF}$ = 9.5 Hz), 132.0, 134.0, 139.8, 142.4, 151.2, 160.8 (d, $^1J_{CF}$ = 246.0 Hz); HRMS calcd for $C_{20}H_{14}ClFN_2^+$ $[M + H]^+$ 337.0908, found 337.0922.

*2,5-Dicyclopropyl-8-fluoropyrazolo[5,1-a]isoquinoline (**3x**).* Compound **3x** was obtained as a light yellow solid: mp 101−102 °C; yield 46%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.89−0.92 (m, 4H), 1.06−1.08 (m, 2H), 1.18−1.20 (m, 2H), 2.20−2.23 (m, 1H), 2.72−2.76 (m, 1H), 6.41 (s, 1H), 6.57 (s, 1H), 7.14−7.22 (m, 2H), 7.92−7.95 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 7.7, 8.9, 9.8, 11.1, 92.9, 104.1, 110.9 (d, $^2J_{CF}$ = 21.9 Hz), 114.7 (d, $^2J_{CF}$ = 23.8 Hz), 119.4, 125.4 (d, $^3J_{CF}$ = 9.5 Hz), 130.9, 139.2, 142.1, 157.4, 160.6 (d, $^1J_{CF}$ = 246.0 Hz); HRMS calcd for $C_{17}H_{15}FN_2^+$ $[M + H]^+$ 267.1298, found 267.1273.

*5-Butyl-8-fluoro-2-(4-methoxyphenyl)pyrazolo[5,1-a]iso-quinoline (**3y**).* Compound **3y** was obtained as a white solid: mp 150−151 °C; yield 63%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.01 (t, J = 7.3 Hz, 3H), 1.48−1.54 (m, 2H), 1.84−1.89 (m, 2H), 3.17 (t, J = 7.8 Hz, 2H), 3.84 (s, 3H), 6.66 (s, 1H), 6.98 (d, J = 8.2 Hz, 2H), 7.11 (s, 1H), 7.15−7.19 (m, 1H), 7.24 (d, J = 8.6 Hz, 1H), 7.93−7.96 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.9, 22.5, 28.9, 30.5, 55.3, 93.7, 108.2, 111.0 (d, $^2J_{CF}$ = 21.0 Hz), 114.1, 114.8 (d, $^2J_{CF}$ = 23.8 Hz), 119.9, 125.5 (d, $^3J_{CF}$ = 8.6 Hz), 126.2, 127.6, 130.9 (d, $^3J_{CF}$ = 9.5 Hz), 139.6, 140.8, 152.1, 159.8, 160.6 (d, $^1J_{CF}$ = 246.0 Hz), HRMS calcd for $C_{22}H_{21}FN_2O^+$ $[M + H]^+$ 349.1716, found 349.1691.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Figures giving ^{1}H and ^{13}C NMR spectra of all products and CIF files giving crystallographic data for **3k**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We thank the National Natural Science Foundation of China (Nos. 20962010 and 21162012) and the Jiangxi Provincial Department of Science and Technoloy (for Jiangxis Key Laboratory of Green Chemistry) for their financial support.

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