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Efficient Routes to Pyrazolo[3,4-*b*]indoles and Pyrazolo[1,5-*a*]benzimidazoles via Palladium- and Copper-Catalyzed Intramolecular C−C and C−N Bond Formation[†]

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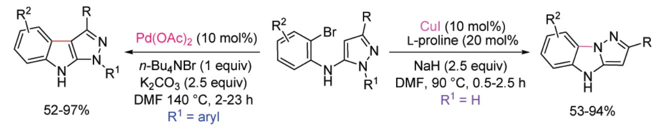

Efficient synthetic routes to pyrazolo[3,4-*b*]indoles and pyrazolo[1,5-*a*]benzimidazoles via intramolecular palladium- and copper-catalyzed cyclization of 1-aryl/1-unsubstituted 5-(2-bromoanilino)-pyrazole precursors via intramolecular C−C and C−N bond formation have been reported.

Introduction

Nitrogen-containing heterocycles are one of the most important class of medicinal compounds and are structural components of many bioactive natural products and organic materials.[1] Classical approaches for their syntheses involve inter- or intramolecular C−C or C−N bond formation usually requiring activated substrates and harsh reaction conditions. During the past several decades, palladium-catalyzed cross-coupling reactions have emerged as one of the most powerful and versatile tools in modern synthetic chemistry.[2] While most of the cross-coupling reactions are oriented toward formation of C−C bonds, during the past decades, the new methodologies developed for the construction of C−N bond through palladium catalysis have become extraordinarily popular.[3] Since the pioneering discovery in 1995 by Buchwald and Hartwig,[4] substrate scope of this method has been tremendously expanded mainly by the development of new ligands. In the past few years, the reaction has been successfully adopted for the construction and decoration of nitrogen-containing heterocyclic scaffolds, which represents a conceptually different approach for heterocycle synthesis.[5−7]

In comparison to palladium-catalyzed amination/amidation reactions, its Cu-mediated version, best known as the Ullmann reaction[8a−c] (*N*-arylation of amines) and Goldberg reaction[8d] (*N*-arylation of amides), has been known for more

[†] Dedicated to Prof. C. N. R. Rao on his 75th birthday.

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than 100 years, although the harsh reaction conditions and the necessity to use a stoichiometric amount of copper nevertheless limited the scope of these two otherwise powerful reactions. However, the recent resurgence of interest in performing Ullmann-type reactions under mild conditions with a catalytic amount of copper along with the introduction of an impressive array of bidentate ligands has led to the growing number of papers on copper-catalyzed C−N bond formation as a cheaper alternative to palladium-catalyzed C−N bond formation.[9] Besides intermolecular *N*-arylation under copper catalysis, these reactions have been further extended for the synthesis of an array of nitrogen heterocycles involving intramolecular *N*-arylation/alkenylation process.[10,11]

During the course of our continued interest in heterocycle synthesis,[12,13] we further became interested in developing new and efficient synthetic routes for biologically important heterocyclic frameworks via Pd- or Cu-catalyzed intramolecular heterocyclization[13f] of the appropriately designed precursors derived from polarized ketene *S*,*S*-, *N*,*S*-, and *N*,*N*-acetals or related compounds.[12]

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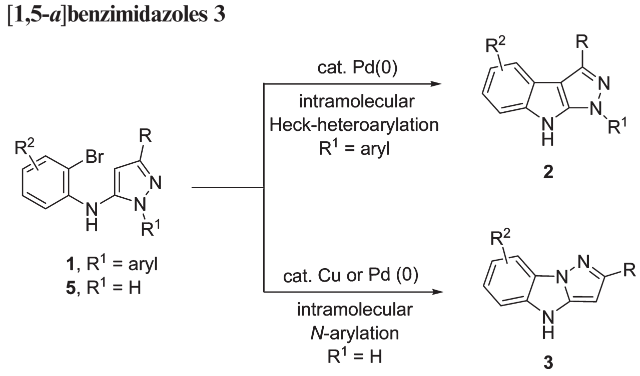
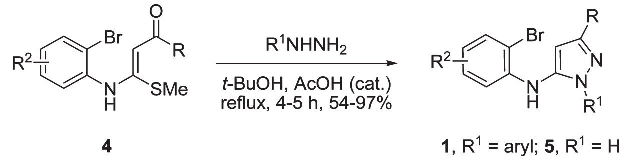
SCHEME 1. Synthesis of Pyrazolo[3,4-*b*]indoles 2 and Pyrazolo[1,5-*a*]benzimidazoles 3



SCHEME 2. Synthesis of 5-(2-Bromoanilino)pyrazoles 1 and 5



In the present work we envisaged to elaborate 3(5)-(*o*-bromoanilino)pyrazoles of the general structure **1** and **5** to novel fused heterocyclic scaffolds via intramolecular palladium (or copper)-catalyzed C−C or C−N bond formation. Thus, it was anticipated that palladium-catalyzed intramolecular Heck-type heteroarylation[14] of **1** (R^1 = aryl) should yield pyrazolo[3,4-*b*]indoles of type **2**, whereas an intramolecular palladium (or copper)-catalyzed *N*-arylation process of 5-(2-bromoarylamino)pyrazoles **5** involving participation of pyrazole nitrogen (NH) should provide a new route to pyrazolo[1,5-*a*]benzimidazoles **3** (Scheme 1). We have successfully realized these goals, and the results of these studies are presented herein.

Results and Discussion

The requisite cyclization precursors, i.e., 1-*N*-aryl-3-substituted-5-(2-bromoanilino)pyrazoles **1** or the corresponding *N*-unsubstituted analogues **5** were readily obtained by modification of our earlier reported procedure[15] by refluxing the appropriate *N*,*S*-acetals[15a] **4** with aryl hydrazine or hydrazine hydrate in *t*-BuOH in the presence of a catalytic amount of acetic acid (Scheme 2).

The palladium-catalyzed intramolecular Heck heteroarylation of 1,3-diphenyl-5-(2-bromoanilino)pyrazole **1a** was investigated as a model reaction in the presence of various palladium catalyst and base combinations generally employed for such cyclizations, and the results are summarized in Table 1. DMF was found to be the solvent of choice in these cyclization reactions. Our initial attempt to effect cyclization of **1a** in the presence of $Pd(PPh_3)_4$ and Na_2CO_3 (2.5 equiv) as base gave the cyclized product **2a** in 52% yield along with considerable amount (25%) of the debrominated side product **6a** (entry 1, Table 1). The reactions using other catalyst systems such as $PdCl_2(PPh_3)_2$, which is generally

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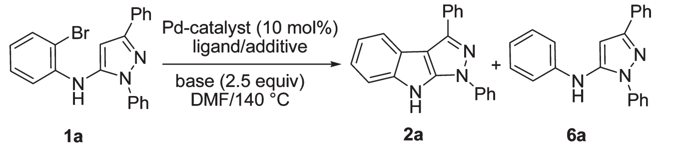
TABLE 1. Optimization of Reaction Conditions for Pd-Catalyzed Synthesis of Pyrazolo[3,4-*b*]indole 2a



entry	Pd source/ligand[a]/additive	base	time (h)	% yield[b] **2a** (**6a**)[c]
1	$Pd(PPh_3)_4$	Na_2CO_3	12	52 (25)
2	$PdCl_2(PPh_3)_2$	$NaOAc \cdot 3H_2O$	12	65 (13)
3	$Pd_2(dba)_3$/dppp	$NaOAc \cdot 3H_2O$	8	53 (19)
4	$Pd(OAc)_2$/(±)-BINAP	$NaOAc \cdot 3H_2O$	18	53 (17)
5	$Pd(OAc)_2$/ P(*o*-tol)$_3$	K_2CO_3	18	61 (18)
6	$Pd(OAc)_2$	Na_2CO_3	10	66 (9)
7	$Pd(OAc)_2$/TBAB[d]	K_2CO_3	13	74 (0)
8	$Pd(OAc)_2$/TBAB[d]	Na_2CO_3	16	61 (8)
9	$Pd(OAc)_2$/TBAB[d]	Cs_2CO_3	12	64 (7)
10	$Pd(OAc)_2$/TBAB[d]	K_3PO_4	13	68 (11)
11[e]	$Pd(OAc)_2$/TBAB[d]	K_2CO_3	26	42 (11)[f]

[a]Ligand (20 mol %). [b]Isolated yields . [c]Yield in parentheses of **6a**. [d]TBAB = *n*-Bu_4NBr (1.0 equiv). [e]MeCN as solvent. [f]24% unreacted **1a**.

employed in such cyclizations, or $Pd_2(dba)_3$ (in the presence of dppp) provided **2a** in 65% and 53% yields, respectively, along with the formation of reduced product (entries 2 and 3, Table 1). Similarly, the use of ligands such as (±)-BINAP or tri(*o*-tolyl)phosphine also proved to be effective, in this case furnishing **2a** in 53% and 61% yields accompanied with debrominated product **6a** (entries 4 and 5, Table 1). When the reaction was effected under Sakamoto's cyclization conditions,[14g] the pyrazoloindole **2a** was obtained in 66% yield (entry 6, Table 1). Finally, Jeffery's condition[16] with tetrabutylammonium bromide additive proved to be most effective, allowing the cyclization of **1a** to **2a** in 74% yield, and formation of debrominated product **4a** was not observed (entry 7, Table 1). Use of other bases such as Na_2CO_3, Cs_2CO_3, or K_3PO_4 (entries 8−10) or use of solvent such as CH_3CN (entry 11, Table 1) gave only decreased yield of **2a**.

With the optimized reaction conditions in hand, we next studied intramolecular Heck arylation of other 1,3-substituted 5-(2-bromoarylamino)pyrazoles **1b−m** with a view to examine the generality and scope of this cyclization reaction (Table 2). Thus, the cyclization is compatible with substrates bearing both electron-donating and -withdrawing substituents on various 1-, 3-, and 5-anilino aryl groups and also with 3-(2-furyl) and 3-(2-thienyl) groups on the pyrazole ring, affording the product pyrazolo[3,4-*b*]indoles **2b−k** in 54−87% yield (entries 1−10, Table 2). Interestingly, the trifluoroaryl-substituted pyrazole **1i** afforded the trifluoro-substituted pyrazoloindole **2i** in highest yield of 87% (entry 8, Table 2). Similarly, an aliphatic 3-methyl or 3-isopropyl group in the pyrazoles **1l,m** along with an electron-rich anilino group (**1m**) are also tolerated furnishing the products **2l,m** in reasonable yields (entries 11 and 12, Table 2).

In contrast, our attempts to cyclize the 3-(2-pyridyl)- or 3-(4-pyridyl)-substituted pyrazoles **1n** or **1o** to the corresponding 3-(2-/4-pyridyl)indolo[3,4-*b*]pyrazoles **2n,o** under the above-described conditions did not meet with any success, affording only unreacted starting materials **1n,o** (Scheme 3).

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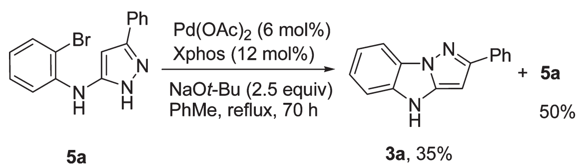
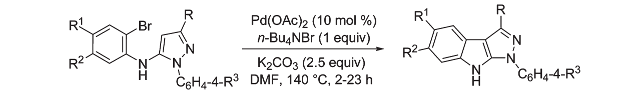
After successfully accomplishing the intramolecular Heck heteroarylation of 1,3-substituted 5-(2-bromoarylamino)-pyrazoles **1** to pyrazolo[3,4-*b*]indoles **2** (Table 2), we next focused our attention to achieve palladium (or copper)-catalyzed intramolecular arylamination of the corresponding 1-*N*-unsubstitued pyrazoles **5** to novel tetracyclic pyrazolo[1,5-*a*]benzimidazoles **3** via C−N bond formation (Scheme 1). The pyrazole **5a** was chosen as test substrate and subjected to optimization studies for its effective conversion to pyrazolo[1,5-*a*]benzimidazole **3a** under palladium catalysis. However, despite screening of a range of palladium catalysts comprising different palladium sources [$Pd(OAc)_2$, $Pd_2(dba)_3$] and mono-/bidentate ligands such as dppp, (±)-BINAP, Xantphos, DPPF, P(*o*-tol)$_3$, and Xphos, typically employed in inter- and intramolecular palladium-catalyzed *N*-arylations, our attempts to obtain pyrazolo[1,5-*a*]benzimidazole **3a** in synthetically useful yields from **5a** were not successful, and **3a** could be obtained in maximum yield of only 35% when **5a** was reacted with palladium acetate (6 mol %) using Xphos as ligand (12 mol %) in the presence of sodium *tert*-butoxide (2.5 equiv) as base in toluene under prolonged (70 h) refluxing along with the unreacted starting material **5a** (50%) (eq 1). Screening of a range of bases (NaO*t*-Bu, K_2CO_3, Cs_2CO_3) and solvents (toluene, 1,4-dioxane, DMF) also did not lead to any improvement of the yield of **3a** (see Supporting Information).



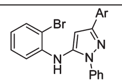
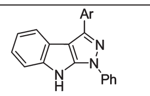
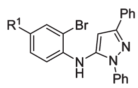
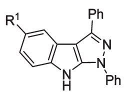
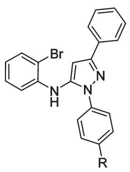
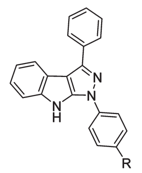
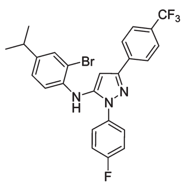
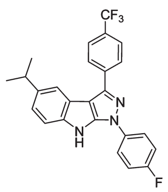
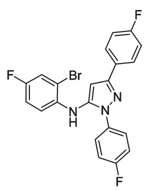
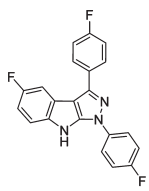
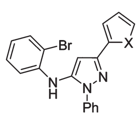
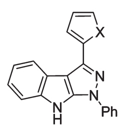
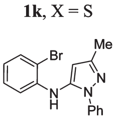
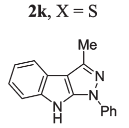
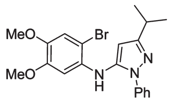
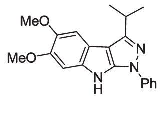
(1)

Having failed to optimize reaction conditions for Pd-catalyzed intramolecular arylamination of **5a** to **3a** in acceptable yields, we diverted our attention toward copper-catalyzed intramolecular *N*-arylation of **5a** to **3a** under varying conditions, and the results are summarized in Table 3. Thus, CuI was found to be most effective among various copper sources such as copper powder (bronze), $Cu(OAc)_2$, $Cu(acac)_2$, $Cu(OTf)_2$, Cu_2O, and although bases such as K_2CO_3, K_3PO_4 (entries 1 and 2, Table 3) were able to

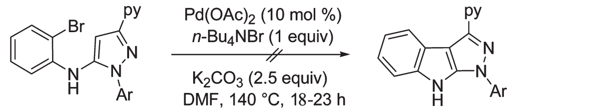
TABLE 2. Substrate Scope for the Palladium-Catalyzed Synthesis of Pyrazolo[3,4-*b*]indoles 2



1 → 2

entry	1	2	time (h)	yield 2 (%)
				
1	**1b**, Ar = 4-OMeC_6H_4	**2b**, Ar = 4-OMeC_6H_4	9	76
2	**1c**, Ar = 4-ClC_6H_4	**2c**, Ar = 4-ClC_6H_4	8	63
				
3	**1d**, R^1 = Me	**2d**, R^1 = Me	13	68
4	**1e**, R^1 = OMe	**2e**, R^1 = OMe	19	58
				
5	**1f**, R = OMe	**2f**, R = OMe	13	67
6	**1g**, R = Cl	**2g**, R = Cl	18	54
				
7	**1h**	**2h**	23	62
				
8	**1i**	**2i**	10	87
				
9	**1j**, X = O	**2j**, X = O	2	68
10	**1k**, X = S	**2k**, X = S	5	65
				
11	**1l**	**2l**	11	76
				
12	**1m**	**2m**	18	52

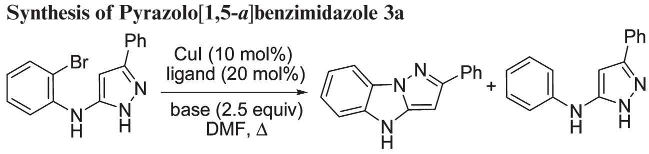
SCHEME 3. Attempted Palladium-Catalyzed Heck Heteroarylation of 1-Aryl-5-(2-bromoanilino)-3-(2/4-pyridyl)pyrazoles 1n,o



1n, py = 2-pyridyl; Ar = 4-MeOC_6H_4
1o, py = 4-pyridyl; Ar = 4-FC_6H_4

2n, py = 2-pyridyl; Ar = 4-MeOC_6H_4
2o, py = 4-pyridyl; Ar = 4-FC_6H_4

TABLE 3. Optimization of Reaction Conditions for the Cu-Catalyzed Synthesis of Pyrazolo[1,5-*a*]benzimidazole 3a



5a → **3a** + **7a**

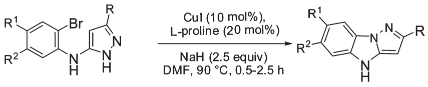
entry	ligand	base	time (h)	temp (°C)	yield[a] 3a (%)	yield[a] 7a (%)
1		K_2CO_3	3	140	69	
2		K_3PO_4	3	140	51	
3		NaH	0.5	140	84	
4	EDA	NaH	1	90	23 (47)[b]	
5	glycine	NaH	1	90	71	
6	1,10-phen	NaH	1	90	79	
7	L-proline	NaH	1	90	90	
8	L-proline	K_2CO_3	6	90	19 (24)[b]	27
9	L-proline	K_3PO_4	7	90	17 (21)[b]	20
10[c]	L-proline	NaH	3	90	19 (27)[b]	30
11[d]	L-proline	NaH	1.5	90	65	

[a] Isolated yields. EDA = ethylene diamine; 1,10-phen = 1,10-phenanthroline. [b] Yield in parentheses is of recovered **5a**. [c] DMSO as solvent. [d] DMA as solvent.

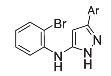
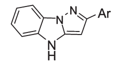
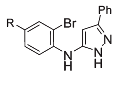
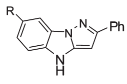
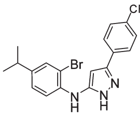
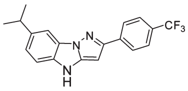
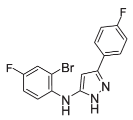
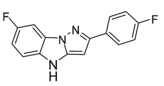
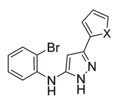
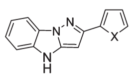
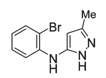
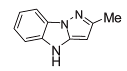
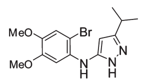
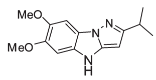
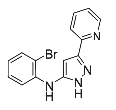
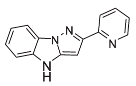
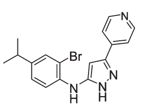
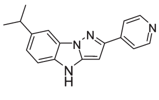
promote the reaction, the best yield of **3a** (84%) was obtained when the reaction was performed with 10 mol % of CuI in the presence of NaH as a base in DMF at 140 °C for 0.5 h (entry 3, Table 3). Screening of various bidentate ligands such as ethylenediamine, glycine, 1,10-phenanthroline, and L-proline showed L-proline to be more effective affording **3a** in 90% yield at 90 °C in 1 h (entry 7, Table 3). Use of other bases such as K_2CO_3 or K_3PO_4 (entries 8 and 9, Table 3) or solvents (entries 10 and 11, Table 3) resulted in the decreased yield of **3a** along with recovery of the starting material and formation of the debrominated product **8a**.

Having thoroughly optimized the reaction condition (Table 3, entry 7), we applied it to various 3(5)-substituted 5(3)-(2-bromoarylamino)pyrazoles **5b−m** with a view to study the scope of this novel intramolecular arylamination (Table 4). Thus, the pyrazoles **5b−d** and **5f,g** bearing electron-donating and -withdrawing substituents on 3-aryl group underwent smooth intramolecular *N*-arylation under these conditions, furnishing the product pyrazolo[1,5-*a*]benzimidazoles **3b−d** and **3f,g** in high yields (except **3g**, entries 1−3, 5, and 6, Table 4), whereas the pyrazole **5e** bearing a methoxy group on anilino aryl ring failed to cyclize to **3e**, yielding only an intractable reaction mixture under these conditions (entry 4, Table 4). The pyrazoles **5h,i** and **5j,k** bearing 3-(2-furyl), 3-(2-thienyl), 3-methyl, and 3-isopropyl groups along with a (dimethoxyanilino) moiety (in **5k**) also yielded the cyclized products **3h,i** and **3j,k** in 67−94% yields

TABLE 4. Substrate Scope for the Cu-Catalyzed Synthesis of Pyrazolo[1,5-*a*]benzimidazoles 3



5 → 3

entry	5	3	time (h)	yield 3 (%)
				
1	**5b**, Ar = 4-OMeC$_6$H$_4$	**3b**, Ar = 4-OMeC$_6$H$_4$	1	84
2	**5c**, Ar = 4-ClC$_6$H$_4$	**3c**, Ar = 4-ClC$_6$H$_4$	1.5	72
				
3	**5d**, R = Me	**3d**, R = Me	1.25	83
4	**5e**, R = OMe	**3e**, R = OMe	1.5	0
				
5	**5f**	**3f**	1.5	76
				
6	**5g**	**3g**	1	53
				
7	**5h**, X = O	**3h**, X = O	1.5	94
8	**5i**, X = S	**3i**, X = S	2.5	80
				
9	**5j**	**3j**	1	67
				
10	**5k**	**3k**	0.75	81
				
11	**5l**	**3l**	0.5	78
				
12	**5m**	**3m**	0.75	72

(entries 7−10, Table 4). Gratifyingly, in contrast to failure of palladium-catalyzed intramolecular Heck arylation of 1-aryl-3-(2-pyridyl) or 3-(4-pyridyl)-5-(2-bromoanilino)pyrazoles **1n,o** to the desired pyrazoloindoles **2n,o** (Scheme 3), the copper-catalyzed intramolecular *N*-arylation of the corresponding 1-*N*-unsubstituted pyrazoles **5l,m** proceeded efficiently, providing the corresponding 2-(2-pyridyl)- and 2-(4-pyridyl)-substituted pyrazolo[1,5-*a*]benzimidazoles **3l,m** in good yields (entries 11 and 12, Table 4).

Conclusion

In conclusion, we have developed two efficient synthetic protocols for the construction of two classes of heterocyclic frameworks from a common heterocyclic precursor of the type **1** or **5** employing Pd- and Cu-catalyzed intramolecular C−C and C−N bond formations as key steps. A survey of the literature revealed that only a few pyrazolo[3,4-*b*]indole skeletons have been reported,[17] and some of the nucleosides of this basic skeleton have been found to display antiviral activity against HCMV (human cytomegalovirus).[17c] Similarly, the pyrazolo[1,5-*a*]benzimidazole ring system has been scarcely studied,[18] and the parent pyrazolo[1,5-*a*]benzimidazole has been reported to be formed during photochemical cyclization of 1-(2-azidoaryl)pyrazole.[18f] The published methods for the synthesis of these heterocycles are poorly elaborated without further details regarding generality and scope.[17,18] The present methods therefore provide general synthetic approaches for these two heterocylic frameworks and are compatible with a range of electron-donating and -withdrawing substituents on the three aryl groups. The intramolecular heteroaryl Heck cyclization of this type involving pyrazole ring as a nucleophilic partner in palladium-catalyzed coupling leading to pyrazolo-fused heterocycles is unprecedented in the literature. Similarly, although palladium- and copper-catalyzed intermolecular *N*-arylation of pyrazole *NH* is reported,[19] to the best of our knowledge this is the first report of intramolecular *N*-arylation of *N*-unsubstituted pyrazoles.

Experimental Section

General Procedure for the Preparation of 1-Aryl-5-(2-bromoanilino)pyrazoles (1) and 5-(2-Bromoanilino)-1*H*-pyrazoles (5). A mixture of *N*,*S*-acetal **4** (5.00 mmol) and aryl hydrazine (7.50 mmol) or hydrazine hydrate (0.30 mL, 80%, 7.5 mmol) in *t*-BuOH (30 mL) containing a catalytic amount of AcOH (0.3 mL) was refluxed (4−5 h) (monitored by TLC). Reaction mixture was cooled to room temperature and poured into water (100 mL). Extraction was done with ethyl acetate (3 × 50 mL). The combined organic extracts were washed with water (2 × 50 mL) and brine (1 × 100 mL) and dried over anhydrous Na_2SO_4. Solvent was evaporated under reduced pressure, and the crude product was purified by column chromatography over silica gel using hexane/ethyl acetate as eluent.

5-(2-Bromoanilino)-3-(4-methoxyphenyl)-1-phenyl-1*H*-pyrazole (1b). White solid (1.68 g, 80%); mp 103−104 °C; R_f 0.2 (1:9

(17) (a) Lande, B.; Soufiaoui, M.; Arriau, J. J. *Heteroat. Chem.* **1977**, *14*, 1183. (b) Daou, B.; Soufiaoui, M. J. *Heteroat. Chem.* **1989**, *26*, 1485. (c) Williams, J. D.; Drach, J. C.; Townsend, L. B. *Nucleosides, Nucleotides Nucleic Acids* **2004**, *23*, 805.

(18) (a) Khan, M. A.; Ribeiro, V. L. T. *Heterocycles* **1977**, *6*, 979. (b) Kuz'menko, T. A.; Kuz'menko, V. V.; Anisimova, V. A. *Russ. J. Org. Chem.* **2004**, *40*, 221. (c) Romano, C.; Cuesta, E.; Avendaño, C. *J. Org. Chem.* **1991**, *56*, 74. (d) Lazaro, R.; Elgnero, J. J. *Heteroat. Chem.* **1978**, *15*, 715. (e) Elguero, J.; Claramunt, R. M.; Summers, A. J. H. *Adv. Heteroat. Chem.* **1978**, *22*, 183. (f) Carra, C.; Bally, T.; Albini, A. *J. Am. Chem. Soc.* **2005**, *127*, 5552.

(19) (a) Zhang, H.; Cai, Q.; Ma, D. *J. Org. Chem.* **2005**, *70*, 5164. (b) Antilla, J. C.; Baskin, J. M.; Border, T. E.; Buchwald, S. L. *J. Org. Chem.* **2004**, *69*, 5578.

EtOAc/hexane). IR (cm^{-1}) KBr: 3354, 1591, 1526, 1170, 752. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.85 (d, J = 7.3 Hz, 2H), 7.66 (dd, J = 7.4, 1.2 Hz, 2H), 7.53−7.47 (m, 3H), 7.38 (td, J = 7.1, 1.0 Hz, 1H), 7.24 (d, J = 7.7 Hz, 1H), 7.18 (dd, J = 8.3, 1.4 Hz, 1H), 6.99 (d, J = 7.1 Hz, 2H), 6.80 (td, J = 7.6, 1.7 Hz, 1H), 6.54 (s, 1H), 6.21 (br s, 1H), 3.87 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 159.1, 151.2, 140.7, 140.3, 137.9, 132.7, 129.4, 128.6, 127.9, 127.0, 125.3, 124.2, 121.6, 115.3, 114.0, 111.0, 94.9, 55.3. HRMS (ESI) calcd for $C_{22}H_{19}N_3OBr$ [M + H$^+$] 420.0711, found 420.0711.

5(3)-(2-Bromoanilino)-3(5)-(4-methoxyphenyl)-1*H*-pyrazole (5b). White solid (1.44 g, 84%); mp 123−124 °C; R_f 0.3 (1:4 EtOAc/hexane). IR (cm^{-1}) KBr: 3392, 2931, 1595, 1525, 1450, 1251, 1021, 745. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.72 (br s, 1H), 7.51 (d, J = 6.9 Hz, 2H), 7.48 (dd, J = 8.3, 1.4 Hz, 1H), 7.45 (dd, J = 8.6, 1.1 Hz, 1H), 7.15 (td, J = 7.9, 1.3 Hz, 1H), 6.84 (d, J = 6.9 Hz, 2H), 6.70 (td, J = 7.7, 1.5 Hz, 1H), 6.53 (brs, 1H), 6.22 (s, 1H), 3.77 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 160.0, 150.4, 145.0, 140.6, 132.6, 128.3, 126.9, 121.7, 120.9, 115.7, 114.3, 111.1, 92.6, 55.3. HRMS (ESI) calcd for $C_{16}H_{15}N_3OBr$ [M + H$^+$] 344.0398, found 344.0398.

General Procedure for Palladium-Catalyzed Synthesis of 1-Arylpyrazolo[3,4-*b*]indoles (2). A mixture of 1-aryl pyrazole **1** (1.00 mmol), $Pd(OAc)_2$ (22.4 mg, 0.10 mmol), *n*-Bu_4NBr (0.32 g, 1.00 mmol), and K_2CO_3 (0.29 g, 2.50 mmol) in dry DMF (10 mL) was heated at 140 °C for 2−30 h under nitrogen atmosphere (monitored by TLC). Reaction mixture was cooled to room temperature and poured into water (50 mL). Extraction was done with ethyl acetate (3×20 mL). The combined organic extracts were washed with water (3 × 20 mL) and brine (1 × 30 mL) and dried over anhydrous Na_2SO_4. Solvent was evaporated under reduced pressure, and the crude product was purified by column chromatography over silica gel (100−200 mesh) using hexane/ethyl acetate as eluent.

3-(4-Methoxyphenyl)-1-phenylpyrazolo[3,4-*b*]indole (2b). White solid (0.26 g, 76%); mp 213-214 °C; R_f 0.4 (1:4 EtOAc/hexane). IR (cm^{-1}) KBr: 3324, 2919, 1592, 1493, 1230, 836, 756. ^{1}H NMR (400 MHz, $CDCl_3$ + a little DMSO-d_6): δ 11.21 (br s, 1H), 7.81 (dd, J = 7.8, 2.0 Hz, 2H), 7.66 (d, J = 8.5 Hz, 2H), 7.63 (d, J = 7.8 Hz, 1H), 7.28−7.22 (m, 3H), 6.97 (t, J = 7.8 Hz, 2H), 6.91 (t, J = 7.4 Hz, 1H), 6.79 (dd, J = 8.8, 1.7 Hz, 2H), 3.60 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$+little DMSO-d_6): δ 158.9, 144.7, 143.3, 142.0, 138.4, 128.7, 127.5, 125.4, 124.4, 121.8, 119.4, 118.5, 117.7, 113.4, 111.8, 107.8, 54.5. HRMS (ESI) calcd for $C_{22}H_{18}N_3O$ [M + H$^+$] 340.1450, found 340.1450.

1-(4-Fluorophenyl)-5-isopropyl-3-(4-trifluoromethylphenyl) pyrazolo[3,4-*b*]indole (2h). White solid (0.27 g, 62%); mp 160−161 °C; R_f 0.5 (1:4 EtOAc/hexane). IR (cm^{-1}) KBr: 3453, 2959, 2924, 1568, 1511, 1324, 1105, 1065, 802. ^{1}H NMR (400 MHz): δ 8.28 (d, J = 8.0 Hz, 2H), 8.14 (s, 1H), 7.84 (d, J = 8.1 Hz, 2H), 7.79−7.75 (m, 3H), 7.37 (d, J = 8.3 Hz, 1H), 7.29−7.22 (m, 3H), 3.12 (sept, J = 6.8 Hz, 1H), 1.39 (d, J = 6.8 Hz, 6H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 160.8 (d, J = 247.1 Hz), 145.7, 143.5, 142.4, 140.6, 137.1, 135.3, 130.0 (q, j = 32.4 Hz), 127.3, 125.8 (d, J = 3.6 Hz), 124.4 (q, J = 272.3 Hz), 122.1, 120.9 (d, J = 8.4 Hz), 120.0, 117.6, 116.7 (d, J = 24.0 Hz), 112.2, 109.8, 34.5, 24.8. HRMS (ESI) calcd for $C_{25}H_{20}N_3F_4$ [M + H$^+$] 438.1593, found 438.1593.

3-(Furan-2-yl)-1-phenylpyrazolo[3,4-*b*]indole (2j). Pale yellow solid (0.20 g, 68%); mp 221−222 °C; R_f 0.4 (1:4 EtOAc/hexane). IR (cm^{-1}) KBr: 3069, 2955, 1561, 1514, 1414, 1230, 742. ^{1}H NMR (400 MHz, $CDCl_3$+little DMSO-d_6): δ 11.07 (br s, 1H), 7.90 (t, J = 6.5 Hz, 1H), 7.78−7.76 (m, 2H), 7.52−7.50 (m, 1H), 7.37−7.30 (m, 3H), 7.12−7.05 (m, 3H), 6.92 (dd, J = 6.6, 3.4 Hz, 1H), 6.47−6.44 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$+little DMSO-d_6): δ 148.2, 144.7, 142.4, 142.1, 138.6, 135.4, 129.0, 125.1, 122.5, 120.0. HRMS (ESI) calcd for $C_{19}H_{14}N_3O$ [M + H$^+$] 300.1137, found 300.1143.

5,6-Dimethoxy-3-isopropyl-1-phenylpyrazolo[3,4-*b*]indole (2m). White solid (0.17 g, 52%); mp 203−204 °C; R_f 0.2 (1:3 EtOAc/hexane). IR (cm^{-1}) KBr: 3197, 2959, 2930, 1596, 1499, 1196, 1141, 814. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.13 (br s, 1H), 7.68 (d, J = 7.8 Hz, 2H), 7.45 (t, J = 7.9 Hz, 2H), 7.23 (s, 1H), 7.21 (t, J = 7.4 Hz, 1H), 6.94 (s, 1H), 3.98 (s, 3H), 3.91 (s, 3H), 3.33 (sept, J = 6.9 Hz, 1H), 1.52 (d, J = 7.1 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 151.9, 146.4, 145.0, 144.7, 139.3, 135.8, 129.5, 124.9, 118.2, 112.9, 109.2, 103.9, 96.8, 56.7, 56.2, 28.8, 22.2. HRMS (ESI) calcd for $C_{20}H_{22}N_3O_2$ [M + H$^+$] 336.1712, found 336.1714.

General Procedure for Copper- catalyzed Synthesis of 4*H*-pyrazolo[1,5-*a*]benzimidazoles (3). A mixture of pyrazole **5** (1.00 mmol), CuI (19 mg, 0.10 mmol), L-proline (23 mg, 0.20 mmol), and NaH (0.10 g, 60%, 2.5 mmol) in dry DMF (10 mL) was heated at 90 °C for 0.5−2.5 h under nitrogen atmosphere (monitored by TLC). The reaction mixture was cooled to room temperature and poured into water (50 mL). Extraction was done with ethyl acetate (3 × 20 mL). The combined organic extracts were washed with water (3×20 mL) and brine (1×30 mL) and dried over anhydrous Na_2SO_4. Solvent was evaporated under reduced pressure, and the crude product was purified by column chromatography over silica gel (100−200 mesh) using hexane/ethyl acetate as eluent.

2-(4-Methoxyphenyl)-4*H*-pyrazolo[1,5-*a*]benzimidazole (3b). White solid (0.22 g, 84%); mp 204−205 °C; R_f 0.3 (1:3 EtOAc/hexane). IR (cm^{-1}) KBr: 3072, 2922, 1566, 1248, 1029, 835. ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.52 (s, 1H), 7.80−7.77 (m, 3H), 7.25 (d, J = 7.8 Hz, 1H), 7.16−7.08 (m, 2H), 6.87 (d, J = 7.8 Hz, 2H), 5.93 (s, 1H), 3.76 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$ + a little DMSO-d_6): δ 159.5, 155.8, 145.0, 135.3, 127.2, 126.9, 126.2, 122.9, 120.3, 113.9, 111.6, 110.1, 77.2, 55.2. HRMS (ESI) calcd for $C_{16}H_{14}N_3O$ [M + H$^+$] 264.1137, found 264.1137.

2-(4-Trifluorophenyl)-7-isopropyl-4*H*-pyrazolo[1,5-*a*]benzimidazoles (3f). White solid (0.26 g, 76%); mp 241−242 °C; R_f 0.3 (1:4 EtOAc/hexane). IR (cm^{-1}) KBr: 3215, 3143, 2964, 602, 1385, 1323, 1160, 1124, 846. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.44 (br s, 1H), 8.06 (d, J = 8.0 Hz, 2H), 7.81 (s, 1H), 7.70 (d, J = 8.0 Hz, 2H), 7.25 (d, J = 8.3 Hz, 1H), 7.18 (d, J = 8.3 Hz, 1H), 6.13 (s, 1H), 3.07 (sept, J = 6.8 Hz, 1H), 1.33 (d, J = 6.8 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 154.5, 144.8, 142.9, 137.7, 133.1, 129.7 (d, j = 33 Hz), 126.5, 126.0, 125.6, 122.6, 111.3, 108.2, 78.6, 34.2, 24.3. HRMS (ESI) calcd for $C_{19}H_{17}N_3F_3$ [M + H$^+$] 344.1375, found 344.1375.

2-(Furan-2-yl)-4*H*-pyrazolo[1,5-*a*]benzimidazole (3h). White solid (0.21 g, 94%); mp 234−235 °C; R_f 0.3 (1:3 EtOAc/hexane). IR (cm^{-1}) KBr: 3424, 2924, 1598, 1482, 1309, 1010, 740. ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.56 (s, 1H), 7.77 (d, J = 7.8 Hz, 1H), 7.72 (d, J = 1.7 Hz, 1H), 7.44 (d, J = 8.0 Hz, 1H), 7.28 (t, J = 7.7 Hz, 1H), 7.19 (t, J = 7.5 Hz, 1H), 6.83 (d, J = 3.2 Hz, 1H), 6.58 (dd, J = 3.3 Hz, 1.7 Hz, 1H), 6.13 (s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 149.3, 147.3, 144.5, 142.4, 135.4, 125.3, 123.4, 120.3, 111.9, 111.6, 109.7, 106.1, 77.1. HRMS (ESI) calcd for $C_{13}H_{10}N_3O$ [M + H$^+$] 224.0824, found 224.0825.

2-Isopropyl-6,7-dimethoxy-4*H*-pyrazolo[1,5-*a*]benzimidazoles (3k). Red solid (0.21 g, 81%); mp 63−64 °C; R_f 0.3 (1:1 EtOAc/hexane). IR (cm^{-1}) KBr: 3330, 2927, 1590, 1500, 1273, 1152, 794. ^{1}H NMR (400 MHz, $CDCl_3$): 9.45 (s, 1H), 7.24 (s, 1H), 6.78 (s, 1H), 5.56 (s, 1H), 3.74 (s, 3H), 3.69 (s, 3H), 3.07 (sept, J = 6.9 Hz, 1H), 1.29 (d, J = 7.1 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.0, 146.4, 144.9, 144.2, 128.1, 119.8, 96.6, 94.8, 78.0, 56.5, 56.4, 29.0, 23.1. HRMS (ESI) calcd for $C_{14}H_{18}N_3O_2$ [M + H$^+$] 260.1399, found 260.1397.

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Supporting Information Available: Experimental details and spectroscopic data for all new compounds. ORTEP diagram of **2b**. This material is available free of charge via the Internet at http://pubs.acs.org.