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Catalyst- and Base-Controlled Site-Selective sp^2 and sp^3 Direct Arylation of 5,7-Dimethyl-2-phenylpyrazolo[1,5-*a*]pyrimidine Using Aryl Bromides

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The palladium-catalyzed direct C–H arylation of various heterocyclic is now recognized to be the most effective methodology for making aromatic compounds. In this paper, we present a new approach to control the site-selective direct C–H arylation of both sp^2 and sp^3 sites in 5,7-dimethyl-2-phenylpyrazolo[1,5-*a*]pyrimidine by using aryl bromides. The desired compounds were obtained in satisfactory yields. The effects of each reaction parameter including catalyst, base, and solvent were investigated.

Introduction

Aryl-substituted pyrazolo[1,5-*a*]pyrimidines are known for their potent utility as analgesics, selective peripheral benzodiazepine receptor ligands, angiogenesis inhibitors, anti-inflammatory agents, neuropeptide Y (NPY1) receptor antagonists, COX-2 selective inhibitors, and corticotropin-releasing hormone receptor type 1 ($CRHR^1$) antagonists.[1] Our research group has targeted the development of heterocycles with a bridgehead nitrogen atom and has studied their reactivity toward palladium-mediated cross-couplings.[2] In continuation of our research program, we report here a direct C–H arylation reaction that would enable the selective arylation of 5,7-dimethyl-2-phenylpyrazolo-[1,5-*a*]pyrimidine at both the sp^2 and sp^3 centers.

Cross-coupling reactions have been extensively used for the synthesis of heterocyclic compounds.[3] However, only a few of these publications are devoted to the Pd-catalyzed coupling of pyrazolo[1,5-*a*]pyrimidines. Shiota and Yamamori[4] have described the regioselective coupling of organozinc reagents with 5,7-dichloropyrazolo[1,5-*a*]pyrimidine. Kumar[5] has reported the synthesis of 3-aryl-7-(diethylamino)pyrazolo[1,5-*a*]pyrimidines by Suzuki coupling of 3-bromopyrazolo[1,5-*a*]pyrimidine. Fraley et al. have reported the Suzuki cross-coupling reactions of 6-aryl-3-bromopyrazolo[1,5-*a*]pyrimidines[6] and 3-aryl-6-bromopyrazolo[1,5-*a*]pyrimidines.[7] Liebscher et al. have recently reported two examples of Heck[8] and Sonogashira[9] coupling of 3-iodopyrazolo[1,5-*a*]pyrimidines. In the past few years, direct C–H arylation has been intensively studied as an attractive and simple alternative to traditional cross-coupling methods to generate heteroaryl–aryl bonds.[10] As far as we know, there are no examples of direct C–H arylations of pyrazolo[1,5-*a*]pyrimidines reported to date.

Results and Discussion

We started our optimization with the investigation of the direct arylation of 5,7-dimethyl-2-phenylpyrazolo[1,5-*a*]pyrimidine (**1**)[11] with 3-bromotoluene (**2**). We first applied the reaction conditions already used in our laboratory.[2g] Compound **1** (1 equiv.) was treated with **2** (1.5 equiv.) in the presence of palladium(II) acetate (10 mol-%), triphenylphosphane (20 mol-%), and K_2CO_3 (2 equiv.) in toluene at 110 °C for 48 h. Under these experimental conditions, the direct C–H arylation took place at the 3-position of **1** to give product **3** in 53% yield (Table 1, Entry 1). Encouraged by this initial result, we decided to evaluate the influence of each reaction parameter such as catalyst, ligands, bases, and solvents. Results are summarized in Table 1. For example, toluene was found to be a convenient solvent. On the contrary, DMF, dioxane, and DMA lowered the yield to 5, 23, and 4%, respectively (Table 1, Entries 2–4). Other catalyst systems as $Pd(PPh_3)Cl_2$ and $Pd(OH)_2/C$[12] (Table 1, Entries 11–13) were also tested. These experiments confirmed that $Pd(OAc)_2$ is the optimal palladium catalyst in toluene. To complete our investigation, we assessed the effect of changing the ligand and/or base on the cross-coupling Pd-catalyzed arylation reaction.

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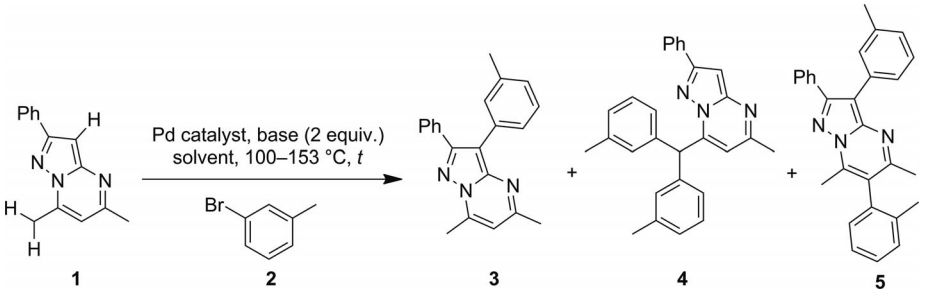
Table 1. Optimization of reaction conditions for the C–H arylation of **1** with 3-bromotoluene (**2**).

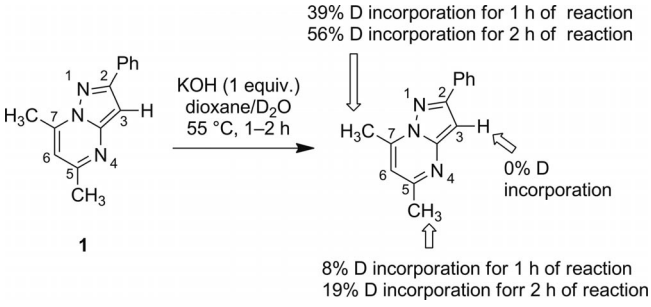


Entry	Pd catalyst (mol-%)	Solvent	Base	ArBr [equiv.]	*t* [h]	Yield [%][a]		
						3	**4**	**5**
1	$Pd(OAc)_2$ (10)/PPh_3 (20)	toluene	K_2CO_3	1.5	48	53	–	2
2	$Pd(OAc)_2$ (10)/PPh_3 (20)	dioxane	K_2CO_3	1.5	48	23	–	–
3	$Pd(OAc)_2$ (10)/PPh_3 (20)	DMF	K_2CO_3	1.5	48	5	–	–
4	$Pd(OAc)_2$ (10)/PPh_3 (20)	DMA	K_2CO_3	1.5	48	4	–	–
5	$Pd(OAc)_2$ (10)/PPh_3 (20)	toluene	KOAc	1.5	48	40	–	–
6	$Pd(OAc)_2$ (10)/PPh_3 (20)	toluene	Na_2CO_3	1.5	48	8	–	–
7	$Pd(OAc)_2$ (10)/PPh_3 (20)	toluene	Cs_2CO_3	1.5	48	5	27	–
8	$Pd(OAc)_2$ (10)/PPh_3 (20)	toluene	Cs_2CO_3	2	48	6	46	–
9	$Pd(OAc)_2$ (10)/PPh_3 (20)	toluene	Cs_2CO_3	2.5	24	trace	50	–
10	$Pd(OAc)_2$ (10)/PPh_3 (20)	toluene	NaH	1.5	48	–	–	–
11	$PdCl_2(PPh_3)$ (10)	toluene	K_2CO_3	1.5	48	–	–	–
12	$Pd(OH)_2$/C (10)	toluene	K_2CO_3	1.5	48	–	–	–
13	$Pd(OH)_2$/C (10)	DMA	KOAc	3	24	14	–	–
14	$Pd(OAc)_2$ (10)/$AsPPh_3$ (20)	toluene	K_2CO_3	1.5	48	22	–	–
15	$Pd(OAc)_2$ (10)/P*t*Bu_3HBF_4 (20)	toluene	K_2CO_3	1.5	48	60	–	–
16	$Pd(OAc)_2$ (10)/P*t*Bu_3HBF_4 (20)	toluene	K_2CO_3	2	48	62	–	–
17	$Pd(OAc)_2$ (10)/P*t*Bu_3HBF_4 (20)	toluene	K_2CO_3	2	48	51[b]	–	–

[a] Isolated yield. [b] Using 0.5 equiv. of Ag_2CO_3.

It was found that the use of P*t*Bu_3HBF_4[13] instead of PPh_3 in the presence of 10 mol-% of $Pd(OAc)_2$, 3-bromotoluene (**2**, 2 equiv.), and K_2CO_3 (2 equiv.) in toluene at 110 °C for 48 h provided **3** in 62% isolated yield with no change in selectivity (Table 1, Entry 16). The use of Cs_2CO_3 in place of K_2CO_3 gave **3** and product **4** in 5 and 27% yield, respectively (Table 1, Entry 7). Increasing the quantity of **2** from 1.5 to 2.5 equiv., under same reaction conditions, improved the selectivity and led predominantly to compound **4** in 50% yield (Table 1, Entry 9). It was noticed that, under these conditions reaction, only a trace amount of desired product **3** was detected by ^{1}NMR spectroscopic analysis of the crude reaction mixture (Table 1, Entry 9) showing that the base is of importance in determining the sp²/sp³ site selectivity. It is also possible that the C–H bond acidity plays a role in the selectivity of these reactions explaining the selective sp³ arylation at the 7-methyl position.

Deuterium incorporation experiments were carried out to study the role that the acidity of the C–H functionality plays in the site selectivity of these reactions (Scheme 1). Deuterium exchange of **1** by treatment with KOH (1 equiv.) in a mixture of D_2O/dioxane at 55 °C shows that the 7-methyl position exchanges at a significantly faster rate than the 5-methyl position. It is to note that under these conditions, no exchange at the sp² position was detected (see the Supporting Information). These results indicate that the C–H bond of the methyl group in the 7-position is the most acidic and may be deprotonated in the presence of a strong base such as Cs_2CO_3. Further to these results, we wanted to investigate the scope of both sp²/sp³ C–H arylation of **1**.

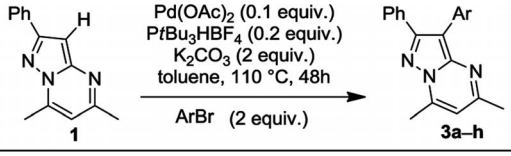


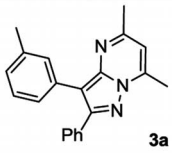
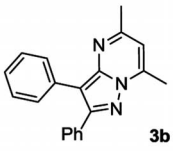
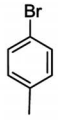
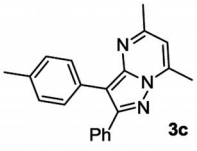
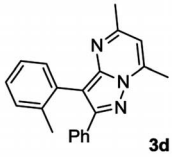
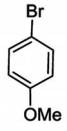
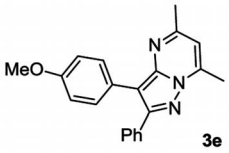
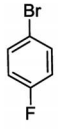
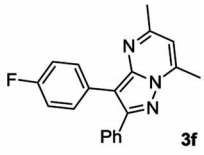
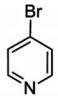
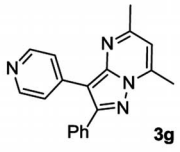
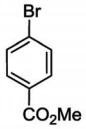
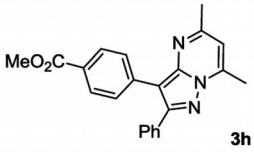
Scheme 1. Deuterium incorporation of **1**.

The results summarized in Table 2 reveal that the optimized conditions described above can be applied to a wide variety of aryl bromides. A variety of substitution patterns including *ortho*, *meta*, and *para* are tolerated on the aryl bromides. Both electron-rich (R = Me, OMe) and electron-poor (R = F, CO_2Me) groups reacted to give desired products **3a**–**h** in good yields of 55–78%.

The scope of the sp³ arylation of compound **1** is outlined in Table 3. The results showed that the variety of substitution patterns including *ortho*, *meta*, and *para* are tolerated on the aryl bromides. Both electron-rich (R = Me, OMe)

Table 2. Scope of the sp^2 C–H arylation of **1**.

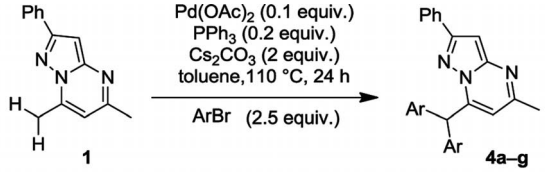


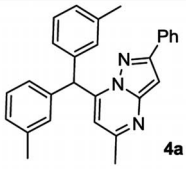
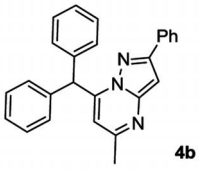
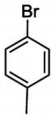
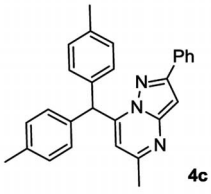
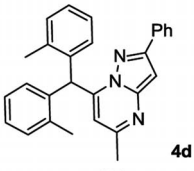
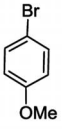
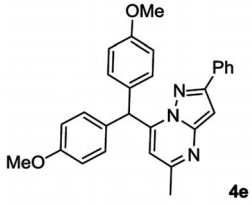
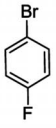
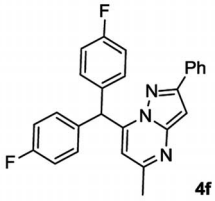
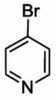
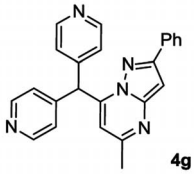
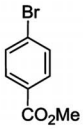
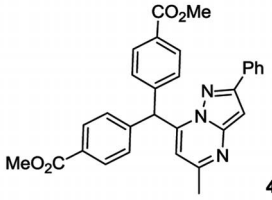
Entry	ArBr	Product	Yield [%][a]
1		 **3a**	62
2		 **3b**	65
3		 **3c**	61
4		 **3d**	58
5		 **3e**	78
6		 **3f**	64
7		 **3g**	43/55[b]
8		 **3h**	59

[a] Isolated yield. [b] Using 3 equiv. of ArBr.

and electron-poor (R = F, CO_2Me) groups reacted to give expected products **4a**–**h** in good yields of 50–63%. However, when compound **1** was treated with 4-bromopyridine under sp^3 C–H arylation conditions, no reaction occurred and only the starting material was recovered (Table 3, Entry 6).

Table 3. Scope of the sp^3 C–H arylation of **1**.



Entry	ArBr	Product	Yield [%][a]
1		 **4a**	50
2		 **4b**	57
3		 **4c**	55
4		 **4d**	51
5		 **4e**	53
6		 **4f**	63
7		 **4g**	0
8		 **4h**	50

[a] Isolated yield.

This result can be explained by the formation of a stable palladacycle similar to that reported by Fagnou et al.[15a] which is unable to participate in the reaction.

Structures of products **3a**, **4b**, and **4c** were established by single-crystal X-ray diffraction analysis. ORTEP diagrams of these compounds are shown in Figure 1.

A plausible mechanism is proposed in Scheme 2. The active Pd^0 catalyst oxidatively inserts into the aryl halide bond to generate intermediate [**A**]. The next step, palladation of **1**, determines site selectivity and is base dependant. When using K_2CO_3 as base, the reaction takes place at the C3 position of the 5,7-dimethyl-2-phenylpyrazolo[1,5-*a*]pyr-

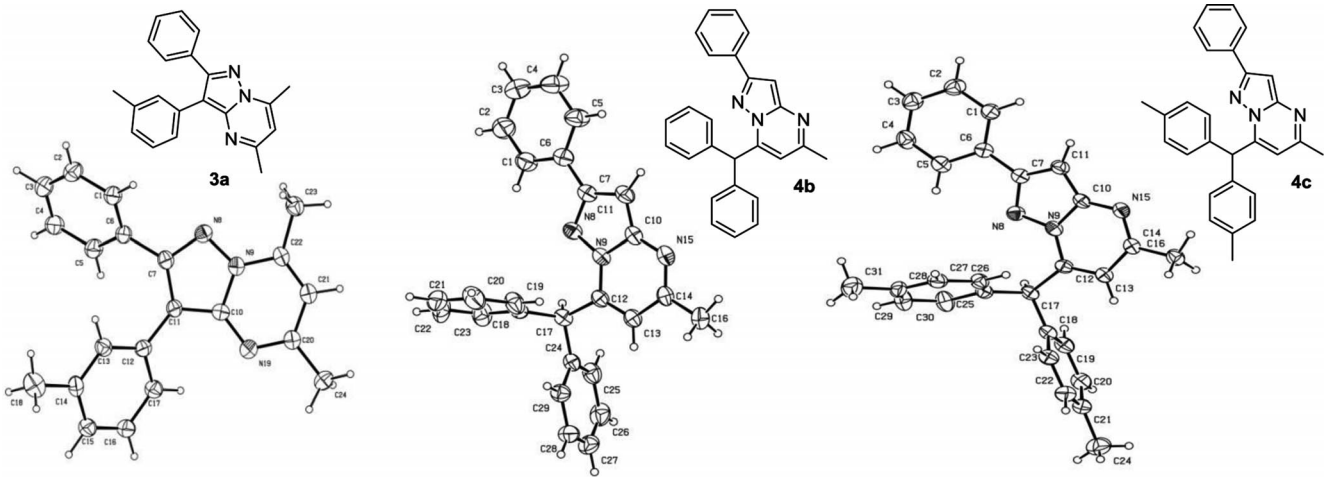
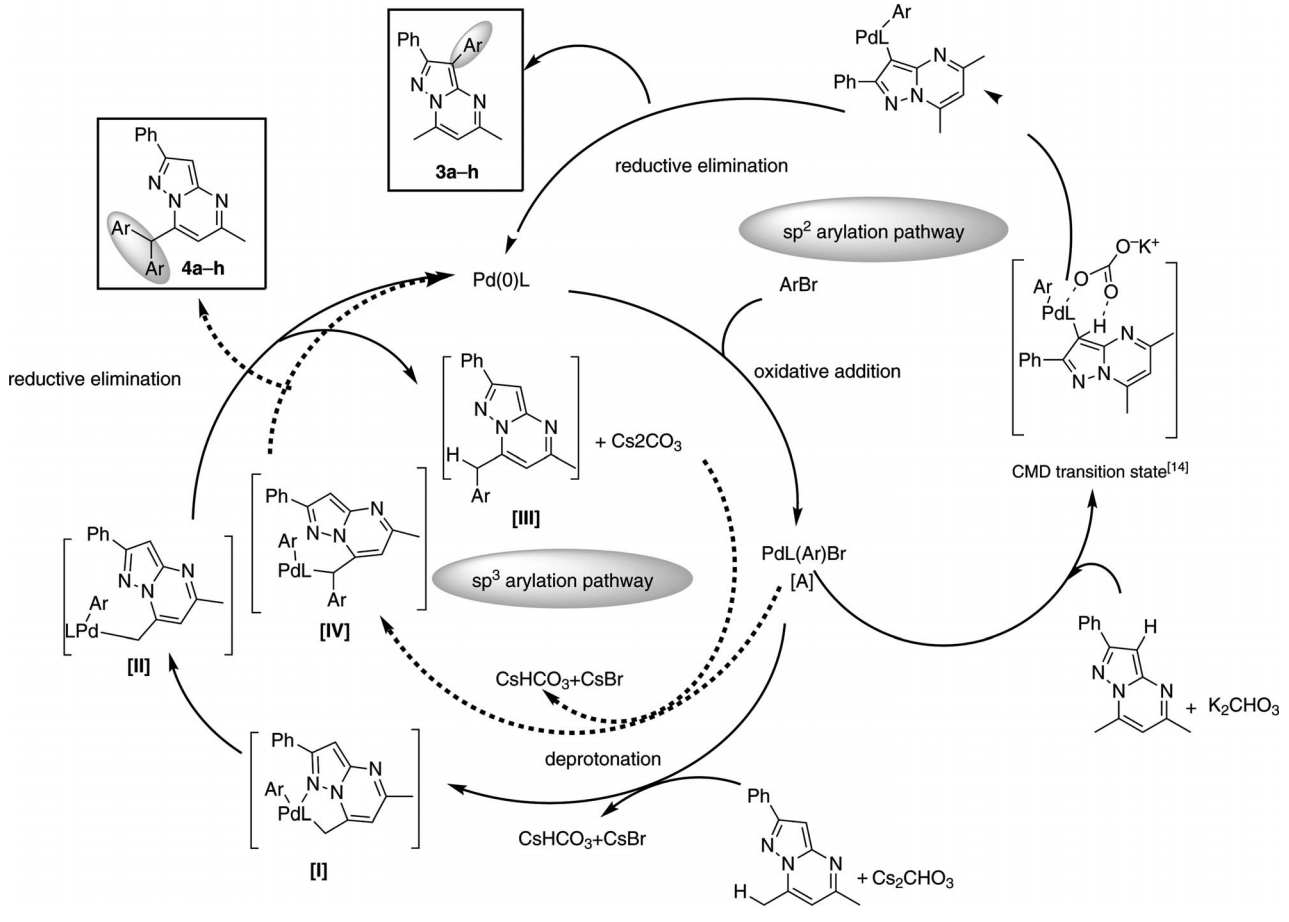


Figure 1. ORTEP drawings of crystal structures of **3a**, **4b**, and **4c**.



Scheme 2. Proposed mechanism.

imidine. The six-membered transition state of a concerted metalation–deprotonation (CMD) pathway[14] activates the sp^2 position giving, after reductive elimination, compounds **3a**–**h**. The formation of **4a**–**h** can be explained by a deprotonation–palladation pathway. With a strong and soluble base such as Cs_2CO_3, the most acidic sp^3 7-methyl position may be deprotonated and proceeds through a pathway similar to that reported[15] to generate [**II**] and giving, after reductive elimination, intermediate [**III**]. Afterwards, [**III**] reacts rapidly in the catalytic cycle due to the high acidity of the 7-methyl position monoarylated to generate, after reductive elimination, desired products **4a**–**h**.

Conclusions

In summary, we have described new methodology allowing the control of the direct arylation site of 5,7-dimethyl-2-phenylpyrazolo[1,5-*a*]pyrimidine; the reaction may be induced to occur at either an sp^3 or an sp^2 carbon atom. The scope of this procedure was established by the synthesis of a library of various mono-/diarylated 5,7-dimethyl-2-phenylpyrazolo[1,5-*a*]pyrimidines, which should make this approach useful for the rapid derivatization of heterocyclic compounds such as bioactive derivatives containing the pyrazolo[1,5-*a*]pyrimidine core structure.

Experimental Section

General: Melting points were determined with a Büchi apparatus. ^1H NMR and ^{13}C NMR were recorded with a Bruker DPX 250 or AV 400 spectrometer (250.19 MHz for ^1H, 62.89 MHz for ^{13}C) by using tetramethylsilane as the internal standard, multiplicities were determined by using a DEPT 135 sequence. Splitting patterns are designated as s, singlet; d, doublet, dd, doublet of doublets; ddd, doublet of doublets of doublets; t, triplet, dt, doublet of triplets; m, multiplet. High-resolution mass spectra (HRMS) were recorded with a MAXIS Q-TOF Bruker TOF spectrometer in the electrospray ionization (ESI) mode or in chemical ionization (CI) mode. All commercial solvents were used without further purification. Column chromatography was carried out by using silica gel 60N (spherical, neutral, 40–63 μm). Thin-layer chromatography (TLC) was carried out on silica gel $60F_{254}$ precoated plates. Visualization was achieved with ultraviolet light. Compounds **1**, **3b**, and **3e** are known compounds, which were identified by comparison of their spectral data with that reported.[11,16]

Procedure for the Synthesis of 5,7-Dimethyl-2-phenylpyrazolo[1,5-*a*]pyrimidines 1: Prepared according to a literature procedure.[11] A round-bottomed flask was charged with 3-amino-5-phenylpyrazole (1 g, 6.282 mmol), acetyl acetone (7.02 mmol), and 37% hydrochloric acid (7 mL). The mixture was heated at reflux for 10 h. After the reaction was complete, the mixture was cooled, neutralized with aq. Na_2CO_3, and extracted with $CHCl_3$ (3×40 mL). The combined organic layers were dried with anhydrous $MgSO_4$. The solvent was evaporated, and the crude product was purified by recrystallization (ethanol/hexane, 4:1) and gave a beige solid (72%). M.p. 154–155 °C. ^1H NMR (400 MHz, $CDCl_3$): δ = 8.01 (d, J = 8.0 Hz, 2 H, H_{Ar}), 7.46 (t, J = 7.5 Hz, 2 H, H_{Ar}), 7.38 (t, J = 7.3 Hz, 1 H, H_{Ar}), 6.85 (s, H^3), 6.54 (s, H^6), 2.79 (s, 3 H, CH_3-C^7), 2.56 (s, 3 H, CH_3-C^5) ppm. ^{13}C NMR (100.62 MHz, $CDCl_3$): δ = 158.3, 155.6, 149.7, 145.2, 133.2, 128.7, 128.7, 126.5, 108.3, 92.6, 24.6, 17.1 ppm. MS (ESI): m/z = 224 $[M + H]^+$.

Preparation of P*t*Bu$_3$HBF$_4$: This procedure has been described.[13] HBF_4 (48 wt.-% aqueous solution; 0.72 mL, 11.5 mmol) was added to a solution of P(tBu$_3$) (0.4 mL, 1.65 mmol) in CH_2Cl_2 (15 mL), and the resulting mixture was stirred vigorously for 5–10 min. The organic layer was then separated from the aqueous layer, dried with $MgSO_4$, and filtered. The residue was purified by recrystallization (ethanol) and gave the desired compound in 84% yield as a white powder. ^1H NMR (400 MHz, $CDCl_3$): δ = 6.18 (d, $^1J_{PH}$ = 468 Hz, 1 H), 1.66 (d, $^3J_{PH}$ = 15.3 Hz, 27 H) ppm. ^{13}C NMR (100.62 MHz, $CDCl_3$): δ = 37.2 (d, $^1J_{PC}$ = 29 Hz, C), 30.1 ppm.

General Procedure for the sp^2 Direct Arylation: Under an atmosphere of argon, a mixture of 5,7-dimethyl-2-phenylpyrazolo[1,5-*a*]-pyrimidine **1** (0.1 g, 0.45 mmol), aryl or heteroaryl bromide **2** (0.9 mmol, 2 equiv.), K_2CO_3 (0.9 mmol, 2 equiv.), PtBu$_3$HBF$_4$ (0.09 mmol, 0.2 equiv.), and $Pd(OAc)_2$ (0.045 mmol, 0.1 equiv.) in toluene (2 mL), in air, was heated to 110 °C. The reaction mixture was stirred for 48 h, and the mixture was then allowed to cool to room temperature. After evaporation of the solvent under reduced pressure and the addition of water (15 mL), the residue was extracted with CH_2Cl_2 (3×15 mL). The combined organic layers were dried with $MgSO_4$ and concentrated under vacuum. The residue was purified by column chromatography on silica gel (EtOAc/petroleum ether).

5,7-Dimethyl-2-phenyl-3-*m*-tolylpyrazolo[1,5-*a*]pyrimidine (3a): Column chromatography: EtOAc/petroleum ether, 1:9. Brown solid (87 mg), m.p. 134–135 °C. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.66–7.64 (m, 2 H, H_{Ar}), 7.39 (s, 1 H, H_{Ar}), 7.35–7.34 (m, 3 H, H_{Ar}), 7.29 (d, J = 7.6 Hz, 1 H, H_{Ar}), 7.23 (t, J = 7.6 Hz, 1 H, H_{Ar}), 7.08 (d, J = 7.6 Hz, 1 H, H_{Ar}), 6.58 (s, H^6), 2.80 (s, 3 H, CH_3-C^7), 2.57 (s, 3 H, CH_3-C^5), 2.34 (CH_3, s) ppm. ^{13}C NMR (100.62 MHz, $CDCl_3$): δ = 158.7, 153.6, 146.9, 145.0, 137.9, 133.8, 132.3, 130.8, 129.2, 128.5, 128.4, 128.3, 127.4, 127.4, 109.0, 108.3, 25.0, 21.7, 17.2 ppm. HRMS: calcd. for $C_{21}H_{19}N_3$ $[M + H]^+$ 314.1657; found 314.1645.

5,7-Dimethyl-2,3-diphenylpyrazolo[1,5-*a*]pyrimidine (3b): Column chromatography: EtOAc/petroleum ether, 1:9. White solid (86.8 mg, 65% yield), m.p. 161–162 °C.[16] ^1H NMR (400 MHz, $CDCl_3$): δ = 7.66–7.63 (m, 2 H, H_{Ar}), 7.55 (d, J = 7.2 Hz, 2 H, H_{Ar}), 7.37–7.34 (m, 5 H, H_{Ar}), 7.28–7.24 (m, 1 H, H_{Ar}), 6.58 (d, J = 0.8 Hz, H^6), 2.80 (d, J = 0.4 Hz, 3 H, CH_3-C_7), 2.58 (s, 3 H, CH_3-C_5) ppm. ^{13}C NMR (100.62 MHz, $CDCl_3$): δ = 158.9, 153.7, 146, 145.04, 133.8, 132.5, 130.1, 129.3, 128.5, 128.4, 126.5, 109.0, 108.2, 25.1, 17.2 ppm. MS (ESI): m/z = 300 $[M + H]^+$.

5,7-Dimethyl-2-phenyl-3-*p*-tolylpyrazolo[1,5-*a*]pyrimidine (3c): Column chromatography: EtOAc/petroleum ether, 1:9. Yellow solid (85 mg, 61% yield), m.p. 167–168 °C. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.67–7.65 (m, 2 H, H_{Ar}), 7.43 (d, J = 8 Hz, 2 H, H_{Ar}), 7.36 (dd, J = 5.2, 2 Hz, 3 H, H_{Ar}), 7.17 (d, J = 8 Hz, 2 H, H_{Ar}), 6.58 (s, H^6), 2.79 (s, 3 H, CH_3-C_7), 2.57 (s, 3 H, CH_3-C_5), 2.37 (s, 3 H, CH_3) ppm. ^{13}C NMR (100.62 MHz, $CDCl_3$): δ = 158.7, 153.5, 146.9, 144.9, 136.1, 133.9, 130.0, 129.4, 129.2, 128.5, 128.4, 108.9, 108.2, 25.0, 21.4, 17.2 ppm. HRMS: calcd. for $C_{21}H_{20}N_3$ $[M + H]^+$ 314.1657; found 314.1637.

5,7-Dimethyl-2-phenyl-3-*o*-tolylpyrazolo[1,5-*a*]pyrimidine (3d): Column chromatography: EtOAc/petroleum ether, 1:9. Yellow solid (81 mg, 58% yield), m.p. 109–110 °C. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.53–7.51 (m, 2 H, H_{Ar}), 7.21–7.16 (m, 7 H, H_{Ar}), 6.49 (d, J = 0.8 Hz, 1 H, H^6), 2.74 (d, J = 0.4 Hz, 3 H, CH_3-C_7), 2.45 (s, 3 H, CH_3-C_5), 2.00 (s, 3 H, CH_3) ppm. ^{13}C NMR (100.62 MHz,

$CDCl_3$): δ = 158.5, 153.3, 147.1, 144.9, 138.2, 133.9, 132.1, 132.0, 130.4, 128.5, 128.3, 128.1, 127.7, 125.9, 108.8, 108.1, 24.9, 20.5, 17.1 ppm. HRMS: calcd. for $C_{21}H_{20}N_3$ $[M + H]^+$ 314.165544; found 314.165174.

3-(4-Methoxyphenyl)-5,7-dimethyl-2-phenylpyrazolo[1,5-*a*]-pyrimidine (3e): Column chromatography: EtOAc/petroleum ether, 1:9. White solid (115 mg, 78% yield), m.p. 173–174 °C.[16] ^1H NMR (400 MHz, CDCl3): δ = 7.67–7.64 (m, 2 H, H_{Ar}), 7.46 (d, *J* = 8.8 Hz, 2 H, H_{Ar}), 7.35 (dd, *J* = 5.2, 1.6 Hz, 3 H, H_{Ar}), 6.92 (d, *J* = 8.8 Hz, 2 H, H_{Ar}), 6.57 (s, H^6), 3.83 (s, 3 H, CH_3-O), 2.79 (s, 3 H, CH_3-C_7), 2.57 (s, 3 H, CH_3-C_5) ppm. ^{13}C NMR (100.62 MHz, $CDCl_3$): δ = 158.6, 158.4, 153.4, 146.8, 145.0, 133.9, 131.2, 129.2, 128.5, 128.4, 124.8, 114.1, 108.9, 107.9, 55.4, 25.0, 17.2 ppm. MS (ESI): *m*/*z* = 330 $[M + H]^+$.

3-(4-Fluorophenyl)-5,7-dimethyl-2-phenylpyrazolo[1,5-*a*]pyrimidine (3f): Column chromatography: EtOAc/petroleum ether, 1:9. Yellow solid (91.5 mg, 64% yield), m.p. 152–153 °C. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.63–7.60 (m, 2 H, H_{Ar}), 7.50 (dd, $J_{H,H}$ = 8.8, 4 Hz, $J_{H,F}$ = 5.6 Hz, 2 H, H_{Ar}), 7.37–7.35 (m, 3 H, H_{Ar}), 7.04 (t, $J_{H,H}$ = 3 Hz, $J_{H,F}$ = 8.8 Hz, 2 H, H_{Ar}), 6.59 (s, H^6), 2.79 (s, 3 H, CH_3-C_7), 2.57 (s, 3 H, CH_3-C_5) ppm. ^{13}C NMR (100.62 MHz, $CDCl_3$): δ = 161.8 (d, $^1J_{CF}$ = 245.1 Hz), 159.0, 153.6, 146.8, 145.1, 133.6, 131.6 (d, $^3J_{CF}$ = 7.8 Hz), 129.2, 128.6, 128.5, 128.4 (d, $^4J_{CF}$ = 3.3 Hz), 115.4 (d, $^2J_{CF}$ = 21.3 Hz), 109.1, 107.1, 25.0, 17.2 ppm. HRMS: calcd. for $C_{20}H_{16}FN_3$ $[M + H]^+$ 318.1407; found 318.1422.

5,7-Dimethyl-2-phenyl-3-(pyridine-4-yl)pyrazolo[1,5-*a*]pyrimidine (3g): Column chromatography: acetone/petroleum ether, 2:8. Yellow solid (57.8 mg, 43% yield for 2 equiv. of 4-bromopyridine; 73.5 mg, 55% yield for 3 equiv. of 4-bromopyridine), m.p. 141–142 °C. ^1H NMR (400 MHz, $CDCl_3$): δ = 8.53 (d, *J* = 5.6 Hz, 2 H, H_{Ar}), 7.63–7.60 (m, 2 H, H_{Ar}), 7.56 (d, *J* = 6.0 Hz, 2 H, H_{Ar}), 7.43–7.41 (m, 3 H, H_{Ar}), 6.68 (s, H^6), 2.81 (s, 3 H, CH_3-C_7), 2.63 (s, 3 H, CH_3-C_5) ppm. ^{13}C NMR (100.62 MHz, $CDCl_3$): δ = 160.0, 154.6, 149.7, 147.1, 145.6, 140.8, 133.3, 129.4, 129.0, 128.8, 123.9, 109.7, 105.0, 25.1, 17.2 ppm. HRMS: calcd. for $C_{19}H_{16}N_4$ $[M + H]^+$ 301.1453; found 301.1461.

Methyl-4-(5,7-dimethyl-2-phenylpyrazolo[1,5-*a*]pyrimidin-3-yl)-benzoate (3h): Column chromatography: EtOAc/petroleum ether, 2:8. Yellow solid (93.9 mg, 59% yield), m.p. 205–206 °C. ^1H NMR (400 MHz, $CDCl_3$): δ = 8.01 (d, *J* = 8.4 Hz, 2 H, H_{Ar}), 7.66 (d, *J* = 8.4 Hz, 2 H, H_{Ar}), 7.62–7.60 (m, 2 H, H_{Ar}), 7.39–7.37 (m, 3 H, H_{Ar}), 6.64 (s, H^6), 3.91 (s, 3 H, CH_3-O), 2.81 (s, 3 H, CH_3-C_7), 2.60 (s, 3 H, CH_3-C_5) ppm. ^{13}C NMR (100.62 MHz, $CDCl_3$): δ = 167.4,159.5, 154.1, 146.9, 145.3, 137.6, 133.5, 129.7, 129.6, 129.3, 128.7, 128.7, 127.7, 109.4, 107.1, 52.1, 25.1, 17.2 ppm. HRMS: calcd. for $C_{22}H_{19}N_3O_2$ $[M + H]^+$ 358.1556; found 358.1571.

General Procedure for the sp³ Direct Arylation: Under an atmosphere of argon, a mixture of 5,7-dimethyl-2-phenylpyrazolo[1,5-*a*]-pyrimidine **1** (0.1 g, 0.45 mmol), aryl or heteroaryl bromide **2** (1.12 mmol, 2.5 equiv.), Cs_2CO_3 (0.9 mmol, 2 equiv.), PPh_3 (0.09 mmol, 0.2 equiv.), and $Pd(OAc)_2$ (0.045 mmol, 0.1 equiv.) in toluene (2 mL) was heated to 110 °C. The reaction mixture was stirred for 24 h, and the mixture was then allowed to cool to room temperature. After evaporation of the solvent under reduced pressure and the addition of water (15 mL), the residue was extracted with CH_2Cl_2 (3 × 15 mL). The combined organic layers were dried with $MgSO_4$ and concentrated under vacuum and the residue was purified by column chromatography on silica gel (EtOAc/petroleum Ether).

7-(Di-*m*-tolylmethyl)-5-methyl-2-phenylpyrazolo[1,5-*a*]pyrimidine (4a): Column chromatography: EtOAc/petroleum ether, 2:8. Brown solid (90 mg, 50%), m.p. 144–145 °C. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.89 (d, *J* = 7.2 Hz, 2 H, H_{Ar}), 7.41 (t, *J* = 7.4 Hz, 2 H, H_{Ar}), 7.34 (t, *J* = 7.2 Hz, 1 H, H_{Ar}), 7.22 (t, *J* = 7.4 Hz, 2 H, H_{Ar}), 7.10–7.01 (m, 6 H, H_{Ar}), 6.83 (s, H^3), 6.44 (s, H^6), 6.26 (s, 1 H, CH-C_7), 2.54 (s, 3 H, CH_3-C_5), 2.32 (s, 6 H, 2×CH_3) ppm. ^{13}C NMR (100.62 MHz, $CDCl_3$): δ = 158.4, 155.3, 150.4, 149.9, 139.3, 138.4, 133.4, 130.2, 128.8, 128.7, 128.6, 128.2, 126.7, 126.5, 108.9, 92.6, 51.0, 25.1, 21.6 ppm. HRMS: calcd. for $C_{28}H_{25}N_3$ $[M + H]^+$ 404.2127; found 404.2138.

7-(Diphenylmethyl)-5-methyl-2-phenylpyrazolo[1,5-*a*]pyrimidine (4b): Column chromatography: EtOAc/petroleum ether, 1:9. Beige solid (96 mg, 57% yield), m.p. 209–210 °C. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.87 (d, *J* = 7.2 Hz, 2 H, H_{Ar}), 7.39 (d, *J* = 7.2 Hz, 2 H, H_{Ar}), 7.30 (dd, *J* = 7.2, 16 Hz, 7 H, H_{Ar}), 7.25–7.23 (m, 4 H, H_{Ar}), 6.84 (s, H^3), 6.51 (s, H^6), 6.24 (s, 1 H, CH-C_7), 2.52 (s, 3 H, CH_3-C_5) ppm. ^{13}C NMR (100.62 MHz, $CDCl_3$): δ = 158.3, 155.3, 150.2, 149.9, 139.2, 133.3, 130.2, 129.4, 128.8, 128.7, 127.4, 126.6, 108.8, 92.7, 51.1, 25.1 ppm. HRMS: calcd. for $C_{26}H_{21}N_3$ $[M + H]^+$ 376.1814; found 376.1819.

7-(Di-*p*-tolylmethyl)-5-methyl-2-phenylpyrazolo[1,5-*a*]pyrimidine (4c): Column chromatography: EtOAc/petroleum ether, 1:9. White solid (99 mg, 55% yield), m.p. 150–151 °C. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.89 (d, *J* = 7.2 Hz, 2 H, H_{Ar}), 7.40 (t, *J* = 7.6 Hz, 2 H, H_{Ar}), 7.33 (t, *J* = 7.2 Hz, 2 H, H_{Ar}), 7.12 (s, 8 H, H_{Ar}), 6.82 (s, H^3), 6.43 (s, H^6), 6.26 (s, 1 H, CH-C_7), 2.53 (s, 3 H, CH_3-C_5), 2.33 (s, 6 H, 2×CH_3) ppm. ^{13}C NMR (100.62 MHz, $CDCl_3$): δ = 158.3, 155.2, 150.6, 149.8, 136.9, 136.4, 133.3, 129.4, 129.2, 128.7, 128.7, 126.6, 108.6, 92.5, 50.2, 25.1, 21.2 ppm. HRMS: calcd. for $C_{28}H_{26}N_3$ $[M + H]^+$ 404.2127; found 404.2146.

7-(Di-*o*-tolylmethyl)-5-methyl-2-phenylpyrazolo[1,5-*a*]pyrimidine (4d): Column chromatography: EtOAc/petroleum ether, 1:9. Brown solid (92.6 mg, 51% yield), m.p. 205–206 °C. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.89 (d, *J* = 6.8 Hz, 2 H, H_{Ar}), 7.37 (dt, *J* = 7.4 Hz, 3 H, H_{Ar}), 7.24–7.19 (m, 4 H, H_{Ar}), 7.11 (t, *J* = 7.4 Hz, 2 H, H_{Ar}), 6.91 (d, *J* = 7.6 Hz, 2 H, H_{Ar}), 6.85 (s, 1 H, H^3), 6.69 (s, 1 H, H^6), 6.15 (s, 1 H, CH-C_7), 2.53 (s, 3 H, CH_3-C_5), 2.32 (s, 6 H, 2 CH_3) ppm. ^{13}C NMR (100.62 MHz, $CDCl_3$): δ = 158.3,155.3, 149.8, 137.4, 137.1, 133.3, 130.9, 128.8, 128.7, 128.3, 127.5, 126.6, 126.2, 108.8, 92.6, 44.6, 25.1, 19.7 ppm. HRMS: calcd. for $C_{28}H_{25}N_3Na$ $[M + Na]^+$ 426.194119; found 426.194069.

7-[Bis(4-methoxyphenyl)methyl]-5-methyl-2-phenylpyrazolo[1,5-*a*]-pyrimidine (4e): Column chromatography: acetone/petroleum ether, 1:9. Yellow solid (104 mg, 53% yield), m.p. 131–132 °C. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.89 (d, *J* = 7.2 Hz, 2 H, H_{Ar}), 7.37 (ddd, *J* = 6.8, 7.6, 27.6 Hz, 3 H, H_{Ar}), 7.14 (d, *J* = 8.8 Hz, 4 H, H_{Ar}), 6.86 (d, *J* = 8.8 Hz, 4 H, H_{Ar}), 6.83 (s, H^3), 6.40 (s, H^6), 6.24 (s, 1 H, CH-C_7), 3.79 (s, 6 H, 2 OCH_3), 2.53 (s, 3 H, CH_3-C_5) ppm. ^{13}C NMR (100.62 MHz, $CDCl_3$): δ = 158.8,158.4, 155.3, 150.9, 149.9, 133.4, 131.6, 130.4, 128.8, 128.7, 126.6, 114.1, 108.6, 92.6, 55.4, 49.5, 25.1 ppm. HRMS: calcd. for $C_{28}H_{25}N_3O_2$ $[M + H]^+$ 436.2025; found 436.2026.

7-[Bis(4-fluorophenyl)methyl]-5-methyl-2-phenylpyrazolo[1,5-*a*]-pyrimidine (4f): Column chromatography: dichloromethane. Brown solid (115.4 mg, 63% yield), m.p. 170–171 °C. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.86 (d, *J* = 6.8 Hz, 2 H, H_{Ar}), 7.41 (t, *J* = 7.2 Hz, 2 H, H_{Ar}), 7.35 (t, *J* = 7.2 Hz, 1 H, H_{Ar}), 7.18 (dd, $J_{H,H}$ = 8.4 Hz, $^4J_{H,F}$ = 5.2 Hz, 4 H, H_{Ar}), 7.04 (t, $J_{H,H}$ = $^3J_{H,F}$ = 8.4 Hz, 4 H, H_{Ar}), 6.85 (s, H^3), 6.44 (s, H^6), 6.18 (s, 1 H, CH-C_7), 2.54 (s, 3 H, CH_3-C_5) ppm. ^{13}C NMR (100.62 MHz, $CDCl_3$): δ = 162.2 (d, $^1J_{CF}$ = 246.6 Hz), 158.4, 155.6, 149.9, 149.7, 134.8 (d, $^4J_{CF}$ = 3.3 Hz), 133.1, 130.9 (d, $^3J_{CF}$ = 8 Hz), 129.0, 128.8, 126.6, 115.9 (d, $^2J_{CF}$ =

21.5 Hz), 108.6, 92.9, 49.6, 25.14 ppm. HRMS: calcd. for $C_{26}H_{19}F_2N_3$ $[M + H]^+$ 412.1625; found 412.1640.

Dimethyl 4,4′-{(5-Methyl-2-phenylpyrazolo[1,5-*a*]pyrimidin-7-yl)-methylene}dibenzoate (4h): Column chromatography: acetone/petroleum ether, 1.5:8.5. Yellow solid (111 mg, 50% yield), m.p. 224–225 °C. ^1H NMR (400 MHz, $CDCl_3$): δ = 8.03 (d, J = 8 Hz, 4 H, H_{Ar}), 7.83 (d, J = 7.2 Hz, 2 H, H_{Ar}), 7.41–7.34 (m, 3 H, H_{Ar}), 7.30 (d, J = 8 Hz, 4 H, H_{Ar}), 6.86 (s, H^3), 6.56 (s, H^6), 6.17 (s, 1 H, C_7-CH), 3.91 (s, 6 H, 2 CH_3O), 2.53 (s, 3 H, CH_3-C_5) ppm. ^{13}C NMR (100.62 MHz, $CDCl_3$): δ = 166.8, 158.4, 155.7, 149.8, 148.5, 143.6, 133.0, 130.3, 129.7, 129.4, 129.0, 128.8, 126.6, 108.9, 93.0, 52.3, 51.1, 25.1 ppm. HRMS: calcd. for $C_{30}H_{25}N_3O_4$ $[M + H]^+$ 492.1923; found 492.1901.

CCDC-793971 (for **3a**), -793972 (for **4b**), and -793973 (for **4a**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Supporting Information (see footnote on the first page of this article): Copies of all NMR spectra (^1H and ^{13}C) and additional X-ray crystallography data for **3a**, **4b**, and **4c**.

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