Sequential Functionalization of Pyrazole 1-Oxides via Regioselective Metalation: Synthesis of 3,4,5-Trisubstituted 1-Hydroxypyrazoles

Anna Sif Paulson, Jørgen Eskildsen, Per Vedsø,* and Mikael Begtrup

Department of Medicinal Chemistry, The Royal Danish School of Pharmacy, Universitetsparken 2, DK-2100 Copenhagen, Denmark

pv@dfh.dk

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Abstract: A range of 3,5-diarylated and 3,4,5-triarylated 2-(4-methoxybenzyl)pyrazole 1-oxides have been prepared by regioselective deprotonation at C-5 or bromine−magnesium exchange at C-3 or C-4 followed by transmetalation with $ZnCl_2$ and palladium(0)-catalyzed cross-coupling. Furthermore, the metalated pyrazole 1-oxides could be trapped with electrophiles. The sequential metalation/functionalization of the pyrazole 1-oxides may follow the order C-5, C-3, C-4, or alternatively the order C-3, C-5, C-4. The 4-methoxybenzyl group of the functionalized 2-(4-methoxybenzyl)-pyrazole 1-oxides could be removed by treatment with TFA and *i*-Pr_3SiH in CH_2Cl_2, providing the corresponding functionalized 1-hydroxypyrazoles.

Pyrazoles possessing aryl substituents appear frequently in molecules of pharmaceutical interest. A large number of drugs incorporating C-arylated pyrazole moieties have been reported to have a wide range of important biological activities, such as hypocholesterolemic activity,[1] selective inhibition of cyclooxygenase-2 (COX-2),[2,3] HIV-1 protease inhibition,[4] selective ligands for human dopamine D_4 receptor in treatment of schizophrenia,[5,6] anti-diabetic activity,[7] and high-affinity selectivity for the estrogen receptor.[8−10] Typically these C-arylated pyrazoles were prepared in condensation reactions between hydrazines and α,β-unsaturated carbonyl compounds or 1,3-dicarbonyl compounds. However, these reaction types almost inevitably produce mixtures of regioisomers.[11,12] Subtle variations and combinations of the arylation pattern on the pyrazole motif often have a profound effect on the biological activities.[2,3,9] Accordingly, efficient protocols for regioselective and sequential arylation of the pyrazole nucleus in a flexible manner and at a late stage of the reaction sequence would be desirable.

Previously we reported the preparation of C-4-[13] and C-5-substituted[14] 1-(benzyloxy)pyrazoles using metalated intermediates generated from 1-(benzyloxy)pyrazole by C-4 iodination and subsequent iodine−magnesium exchange or by direct C-5 lithiation. However, these methodologies were incapable of providing access to C-3-substituted derivatives, as metalation at the C-3 position of 1-substituted pyrazoles is hampered by the adjacent lone-pair effect[15] and, moreover, no direct approach to C-3 halogenated pyrazoles exists. Recently we reported a methodology for the introduction of aryl substituents at the C-3 position based on the transformation of **1** to the pyrazole 1-oxide **2**, which underwent selective monobromination at C-3 followed by smooth bromine−magnesium exchange, transmetalation with $ZnCl_2$, and Pd(0)-catalyzed cross-coupling.[16]

We now wish to report how 2-(4-methoxybenzyl)-pyrazole 1-oxides can undergo C-4 and C-5 arylation, which in combination with the protocol for C-3 arylation led to the synthesis of 3,5-diarylated and 3,4,5-triarylated 1-hydroxypyrazoles via sequential and regioselective metalation/arylation of the appropriate 2-(4-methoxybenzyl)pyrazole 1-oxides.

Preparation of 5-Arylated Pyrazole 1-Oxides. To investigate the C-5 arylation of 2-(4-methoxybenzyl)-pyrazole 1-oxide (**2**), prepared from **1** as previously reported,[16] **2** was deprotonated with various bases followed by transmetalation with $ZnCl_2$ and finally cross coupling[17] with 4-iodoanisole in the presence of 3 mol % $Pd(PPh_3)_4$. When the initial deprotonation of **2** was performed with *i*-PrMgCl, **3** was obtained in 95% yield. In contrast, deprotonation performed with the lithium bases LDA or *n*-BuLi produced significantly lower isolated yields of **3**: 57% and 56%, respectively (Scheme 1). The ^1H NMR spectra of the crude products showed full conversion of **2**, suggesting that the putative 5-lithio intermediate is unstable even at −78 °C. In comparison, the corresponding 5-lithio-1-(benzyloxy)pyrazole[18] is stable at −78 °C. However, H-5 in 1-(benzyloxy)pyrazole is considerably less acidic than H-5 of **2**, as attempted C-5 magnesiation of 1-(benzyloxy)pyrazole using *i*-PrMgCl failed and consequently the *N*-oxide **2** undergoes C-5 arylation under milder conditions than 1-(benzyloxy)-pyrazole.

* To whom correspondence should be addressed. Tel: +45 35 30 60 00. Fax: +45 35 30 60 40.

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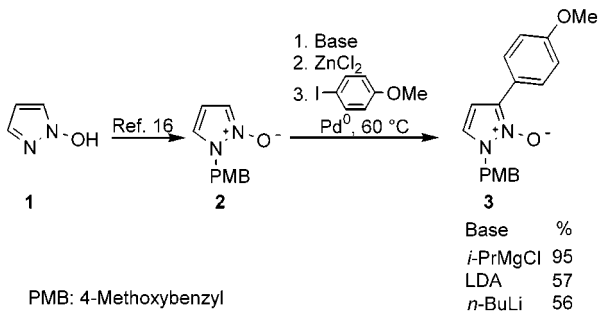
Scheme 1



Preparation of 3,5-Diarylated Pyrazole 1-Oxides via Stepwise Metalation/Arylation. To access 3,5-diarylated pyrazole 1-oxides such as **6a**−**e**, we investigated two strategies. First, C-3 arylation of 5-arylated pyrazole 1-oxides was investigated, and second, C-5 arylation of 3-arylated pyrazole 1-oxides such as **7a**,**b**[16] was examined**.** For the first approach a 5-arylated pyrazole 1-oxide metalated at C-3 was required. In a test experiment, **3** was treated with 2 equiv of *i*-PrMgCl at −78 °C for 15 min. Subsequent quench with MeOD resulted in complete recovery of **3**. Performing the reaction at 0 °C for 1 h gave 25% deuterium incorporation at C-3 along with extensive decomposition. Fortunately, 3-magnesiated pyrazole 1-oxides can be obtained via bromine−magnesium exchange from the corresponding 3-bromo derivatives.[16] In contrast to the bromination of **2**, which takes place exclusively at C-3,[19] attempted monobromination of **3** proceeded with poor regioselectivity. Thus, treatment of **3** with 1.1 equiv of NBS produced a 8:23:46:23 mixture of unchanged **3** along with the 3-bromo (**5a**), 4-bromo, and 3,4-dibromo (**8**) derivatives, as determined by ^{1}H NMR. Using Br_2 instead of NBS gave the four compounds in a 52:5:38:5 mixture. As monobromination of **3** proved unsuccessful, we could obtain the 5-arylated 3-bromopyrazoles **5a**,**b** from the 3-bromopyrazole **4** via C-5 lithiation/transmetalation and subsequent arylation. It was crucial to use the hard base LDA for C-5 metalation, as *i*-PrMgCl and *n*-BuLi resulted in bromine−metal exchange at C-3. Moreover, the C-5 lithiation/transmetalation was advantageously performed at −100 °C instead of −78 °C, as the isolated yields of **5a** and **5b** increased from 53% to 76% (Table 1, entries 1 and 2) and from 55% to 79% (Table 1, entries 3 and 4), respectively. This observation supports the fact that 5-lithiated pyrazole 1-oxides are unstable intermediates even at low temperature. Using our recently reported protocol for C-3 arylation[16] based on bromine−magnesium exchange, transmetalation with $ZnCl_2$, and Pd(0) catalyzed cross coupling, **5a**,**b** were cross-coupled with a range of aryl halides possessing either electron-donating (Table 1, entry 5), or -withdrawing groups (Table 1, entries 6−8), affording 3,5-diarylated pyrazoles **6a**−**d** in 70−77% yield.

Preparation of the 3,5-diarylated pyrazoles **6a**,**e** (Table 2, entries 1 and 2) via C-3 arylation and subsequent C-5 arylation was accomplished by using first the protocol for C-3 arylation[16] followed by C-5 arylation using the *i*-PrMgCl-based protocol developed above for conversion of **2** to **3**.

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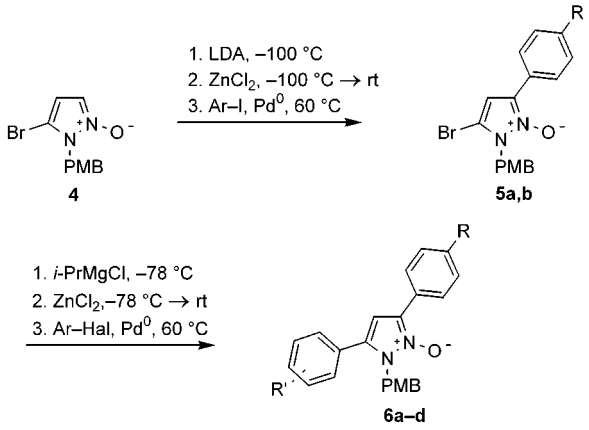
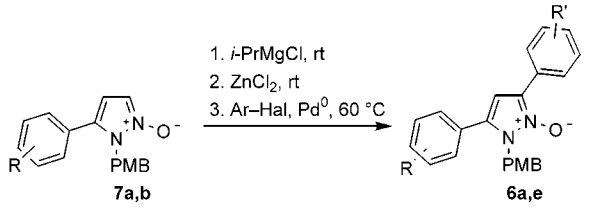
Table 1. Synthesis of 3,5-Disubstituted Pyrazole 1-Oxides: Arylation at C-5 Followed by Arylation at C-3



entry	arylation at C-5 R	arylation at C-3 R	arylation at C-3 R′	product	yield (%)
1[a]	OMe			**5a**	53
2	OMe			**5a**	76
3[a]	Me			**5b**	55
4	Me			**5b**	79
5		4-OMe	4-OMe	**6a**	76
6		4-OMe	2-NO_2	**6b**	74
7		4-Me	2-CHO	**6c**	70
8		4-Me	2-CN	**6d**	77

[a] C-5 lithiation was performed at −78 °C.

Table 2. Synthesis of 3,5-Disubstituted Pyrazole 1-Oxides: C-5 Arylation of 3-Arylated Pyrazole 1-Oxides



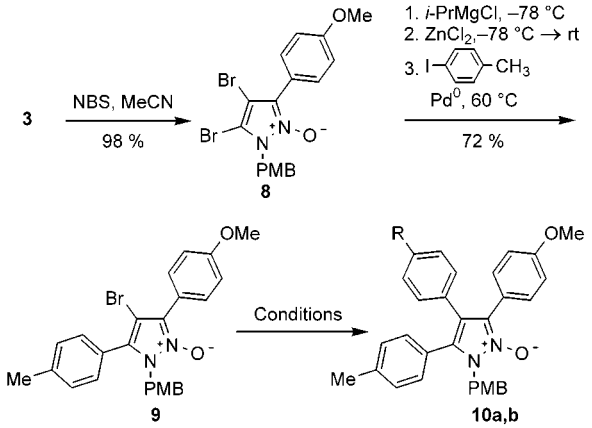
entry	R	R′	product	yield (%)
1	4-OMe	4-OMe	**6a**	82
2	2-F	2-CN	**6e**	69

Thus, 3,5-diarylated pyrazoles can be accessed via stepwise metalation/arylation at C-5 and C-3 or alternatively in the opposite order. This flexibility in the cross-coupling protocol allows the presence of base-sensitive groups in the aryl substituent to be introduced in the final cross-coupling step: e.g., nitro (compound **6b**), formyl (compound **6c**), and cyano groups (compounds **6d**,**e**).

Preparation of 3,4,5-Triarylated Pyrazole 1-Oxides. While monobromination of **3** was not possible, treatment of **3** with excess NBS in acetonitrile afforded the 3,4-dibrominated pyrazole **8** in 98% yield (Table 3). As expected, treatment of **8** with *i*-PrMgCl resulted in bromine−magnesium exchange exclusively at the C-3 position.[20] Transmetalation with $ZnCl_2$ and cross coupling with 4-iodotoluene produced **9** in 72% yield.

Preparation of the highly functionalized triarylated pyrazole **10a** was achieved either via a Suzuki−Miyaura type cross-coupling[21] between 4-fluorobenzeneboronic acid and **9** (Table 3, entries 1 and 2) or via bromine−magnesium exchange, using *i*-PrMgCl, followed by transmetalation with $ZnCl_2$ and Pd(0)-catalyzed cross-coupling with 4-fluoroiodobenzene (Table 3, entry 4). Attempts to

Table 3. Synthesis of 3,4,5-Trisubstituted Pyrazole 1-Oxides



Entry	Conditions	R	Product	Yield (%)
1	F–C$_6$H$_4$–B(OH)$_2$, Pd^0, Toluene/EtOH, K_2CO_3, 80 °C	F	**10a**	41
2	F–C$_6$H$_4$–B(OH)$_2$, Pd^0, Dioxane, K_3PO_4, 90 °C	F	**10a**	66
3	1. *n*-BuLi, –78 °C, $ZnCl_2$, → rt 2. F–C$_6$H$_4$–I, Pd^0, 60°C	F	**10a**	0
4	1. *i*-PrMgCl, 0 °C, $ZnCl_2$, → rt 2. F–C$_6$H$_4$–I, Pd^0, 60 °C	F	**10a**	64
5	1. *i*-PrMgCl, 0 °C, $ZnCl_2$, → rt 2. I–C$_6$H$_4$–NO_2, Pd^0, 60 °C	NO_2	**10b**	72

use *n*-BuLi instead of *i*-PrMgCl led to the total decomposition of **9** (Table 3, entry 3).

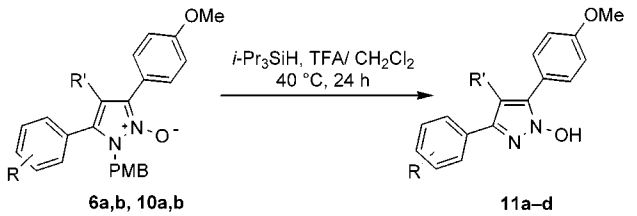
Suzuki−Miyaura type cross-coupling in EtOH/toluene with K_2CO_3 as base[21] (Table 3, entry 1) was hampered by considerable C-4 debromination. However, performing the coupling in dioxane with K_3PO_4 as base[21] led to a notable increase in the yield of **10a** (Table 3, entry 2).

By reversing the polarity of the cross-coupling, pyrazoles **10a**,**b** were prepared via bromine−magnesium exchange followed by transmetalation with $ZnCl_2$ and Pd(0)-catalyzed cross-coupling (Table 3, entries 4 and 5).

De-*p*-methoxybenzylation of Arylated Pyrazole 1-Oxides. The PMB group of **6a**,**b** and **10a**,**b** was readily removed by treatment with TFA in the presence of triisopropylsilane,[16] providing the corresponding 1-hydroxypyrazoles **11a**−**d** in 68−84% yield (Table 4, entries 1−4). Thus, the procedure described herein represents a convergent approach for the conversion of 1-hydroxypyrazole (**1**) to 3,5-diarylated or 3,4,5-triarylated 1-hydroxypyrazoles such as **11a**−**d** via pyrazole 1-oxides.

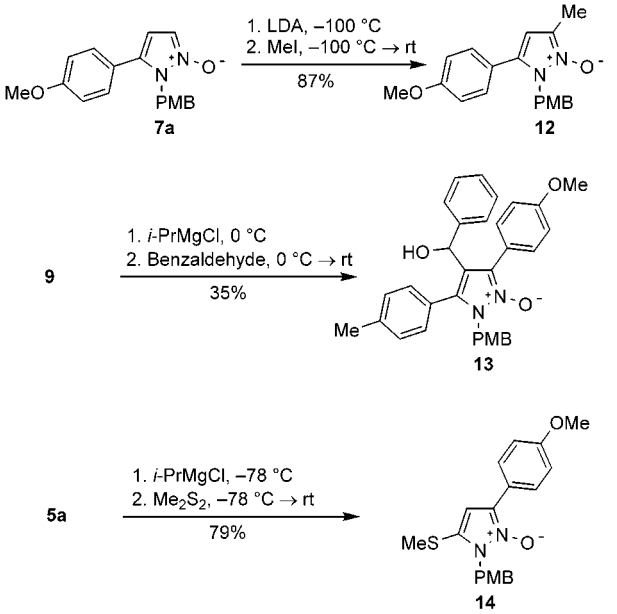
Introduction of Electrophiles. To demonstrate the general utility of the metalated pyrazole 1-oxides described herein, the metalation was succeeded by reaction with an electrophile. By way of example, introduction of electrophiles was carried out on selected arylated pyrazole 1-oxides. Thus, pyrazole **7a** was lithiated at C-5

Table 4. De-*p*-methoxybenzylation of Arylated Pyrazole 1-Oxides



entry	R	R′	product	yield (%)
1	4-OMe	H	**11a**	84
2	2-NO_2	H	**11b**	82
3	4-Me	4-F-Ph	**11c**	68
4	4-Me	4-NO_2-Ph	**11d**	79

Scheme 2



using LDA at −100 °C, and subsequent reaction with methyl iodide afforded the 5-methylated pyrazole **12** in 87% yield. The sterically highly congested pyrazole **13** was prepared in 35% yield by bromine−magnesium exchange of pyrazole **9** using *i*-PrMgCl followed by reaction with benzaldehyde. Finally, the 3-thiomethyl-substituted pyrazole **14** was prepared in 79% yield by bromine−magnesium exchange of pyrazole **5a** followed by reaction with dimethyl disulfide (Scheme 2).

The procedures described herein represent convergent approaches for conversion of 1-hydroxypyrazole (**1**) to 3,5-diarylated or 3,4,5-triarylated pyrazole 1-oxides and the corresponding arylated 1-hydroxypyrazoles via selectively metalated pyrazole 1-oxides. The metalation/arylation can be effected in the order C-5, C-3, C-4 or in the orderC-3, C-5, C-4. The flexibility in the cross-coupling protocols allows the presence of base-sensitive groups in the aryl substituent being introduced in the final step. Furthermore, it was shown that the magnesiated and lithiated pyrazole 1-oxides could be trapped with electrophiles to give the corresponding functionalized pyrazole 1-oxides.

Experimental Section

General Methods and Materials. See the Supporting Information.

Representative Procedures for Arylation at the C-5 Position: 2-(4-Methoxybenzyl)-5-(4-methoxyphenyl)pyra-

(20) When the bromine−magnesium exchange was followed by quenching with MeOH, 4-bromo-2-(4-methoxybenzyl)-5-(4-methoxyphenyl) pyrazole 1-oxide with $\delta_H(CH_2)$ at 5.27 ppm and δ_H(H-3) at 6.87 ppm was isolated as the sole product. A NOE difference spectrum with irradiation at 5.27 ppm resulted in a 5% NOE on H-3.

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zole 1-Oxide (3). Pyrazole **2**[16] (409 mg, 2.0 mmol) was dissolved in THF (16 mL) at room temperature. *i*-PrMgCl (1.1 mL, 2.1 M, 2.4 mmol) was added dropwise over 3 min, and the mixture was stirred for 30 min. A solution of $ZnCl_2$ in THF (6.0 mL, 1.0 M, 6 mmol) was added dropwise over 5 min, followed by stirring for 30 min. 4-Iodoanisole (3.0 mmol) and $Pd(PPh_3)_4$ (69 mg, 3 mol %) were added, and the mixture was stirred at 60 °C for 3 h before standard workup. FC (CH_2Cl_2 → EtOAc) gave 590 mg (95%) of **3** as beige crystals: mp 136−137 °C (EtOAc). R_f (EtOAc): 0.51. δ_H ($CDCl_3$): 3.81 (s, 3H), 3.85 (s, 3H), 5.29 (s, 2H), 6.36 (d, $^3J_{H-4,H-3}$ = 4.0 Hz, 1H, H-4), 6.80 (d, $^3J_{H-3,H-4}$ = 4.0 Hz, 1H, H-3), 6.90 (d, J_{app} = 8.8 Hz, 2H), 6.98 (d, J_{app} = 9.1 Hz, 2H), 7.31 (d, J_{app} = 8.8 Hz, 2H), 8.15 (d, J_{app} = 9.1 Hz, 2H). δ_C ($CDCl_3$): 48.3, 55.22, 55.24, 99.1, 113.9, 114.5, 118.0, 121.2, 126.4, 127.7, 129.6, 130.2, 159.7, 159.8. Anal. Calcd for $C_{18}H_{18}N_2O_3$: C, 69.66; H, 5.85; N, 9.03. Found: C, 69.41; H, 5.82; N, 8.94.

3-Bromo-2-(4-methoxybenzyl)-5-(4-methoxyphenyl)pyrazole 1-Oxide (5a). Pyrazole **4**[16] (283 mg, 1.0 mmol) was dissolved in THF (8 mL) at room temperature and cooled to −100 °C (Et_2O/N_2(l)). A freshly prepared solution of LDA in THF (4.26 mL, 0.31 M, 1.3 mmol) was added over 3 min, and immediately after a solution of $ZnCl_2$ in THF (3.0 mL, 1.0 M, 3 mmol) was added. The mixture was warmed to room temperature, and then 4-iodoanisole (1.5 mmol) and $Pd(PPh_3)_4$ (35 mg, 3 mol %) were added and the mixture was stirred at 60 °C for 3 h before standard workup. FC (CH_2Cl_2 → CH_2Cl_2/EtOAc, 4:1) provided 296 mg (76%) of **5a** as beige crystals. Recrystallization gave off-white crystals, mp 118−119 °C (EtOAc). R_f (EtOAc): 0.80. δ_H ($CDCl_3$): 3.78 (s, 3H), 3.84 (s, 3H), 5.42 (s, 2H), 6.47 (s, 1H, H-4), 6.86 (d, J_{app} = 8.8 Hz, 2H), 6.96 (d, J_{app} = 9.1 Hz, 2H), 7.42 (d, J_{app} = 8.8 Hz, 2H), 8.07 (d, J_{app} = 9.1 Hz, 2H). δ_C ($CDCl_3$): 46.7, 55.17, 55.20, 100.2, 102.2, 114.0, 114.1, 120.3, 126.9, 127.9, 129.8, 130.6, 159.6, 160.0. Anal. Calcd for $C_{18}H_{17}BrN_2O_3$: C, 55.54; H, 4.40; N, 7.20. Found: C, 55.45; H, 4.36; N, 7.12.

Representative Procedure for Arylation at the C-3 Position: 3-(2-Cyanophenyl)-2-(4-methoxybenzyl)-5-(4-methylphenyl)pyrazole 1-Oxide (6d) (Table 1, Entry 8). 3-Bromo-2-(4-methoxybenzyl)-5-(4-methylphenyl)pyrazole 1-oxide (**5b**; 0.51 mmol) was dissolved in THF (10 mL) and cooled to −78 °C. *i*-PrMgCl (0.52 mL, 1.99 M, 1.03 mmol) was added dropwise over 2 min, and the solution was stirred for 15 min at −78 °C. Then $ZnCl_2$ (1.54 mL, 1.0 M, 1.54 mmol) was added dropwise over 3 min. The mixture was warmed to room temperature over 45 min. 2-Bromobenzonitrile (1.03 mmol) and $Pd(PPh_3)_4$ (18 mg, 3 mol %) were added, and the mixture was heated to 60 °C for 10 h. Standard workup followed by FC (CH_2Cl_2 → CH_2Cl_2/EtOAc, 17:3) gave 154 mg (77%) of **6d** as slightly brownish crystals. Recrystallization gave off-white crystals, mp 162−163 °C (EtOAc). R_f (CH_2Cl_2/EtOAc, 8:2): 0.68. δ_H ($CDCl_3$): 2.38 (s, 3H), 3.73 (s, 3H), 5.37 (s, 2H), 6.72 (s, 1H, H-4), 6.74 (d, J_{app} = 8.9 Hz, 2H), 6.96 (d, J_{app} = 8.6 Hz, 2H), 7.27 (d, J_{app} = 8.1 Hz, 2H), 7.33 (d (br), J = 7.7 Hz, 1H), 7.51 (dt, J = 7.7, 1.2 Hz, 1H), 7.60 (dt, J = 7.7, 1.3 Hz, 1H), 7.76 (dd, J = 7.7, 1.1 Hz, 1H), 8.12 (d, J_{app} = 8.3 Hz, 2H). δ_C ($CDCl_3$): 22.4 (q), 47.8 (t), 56.3 (q), 103.3 (d), 113.9 (s), 115.3 (d), 118.4 (s), 126.3 (s), 127.6 (d), 128.6 (s), 129.6 (s), 129.9 (d), 130.5 (d), 130.7 (d), 131.1 (s), 131.8 (d), 133.7 (s), 134.1 (d), 135.2 (d), 140.0 (s), 160.5 (s). Anal. Calcd for $C_{25}H_{21}N_3O_2$: C, 75.93; H, 5.35; N, 10.63. Found: C, 75.97; H, 5.46; N, 10.65.

3,4-Dibromo-2-(4-methoxybenzyl)-5-(4-methoxyphenyl)-pyrazole 1-Oxide (8). Pyrazole **3** (3.14 g, 10.7 mmol) was dissolved in CH_3CN (200 mL) and cooled to 0 °C. NBS (3.96 g, 22.2 mmol) was added in small portions. The mixture was stirred for 2 h at 0 °C and 2 h at room temperature. Addition of water (900 mL) caused precipitation. The precipitate was isolated by filtration, washed with water (30 mL) and cold Et_2O (30 mL), and dried at 0.1 mmHg to give 4.71 g (98%) of **8** as colorless crystals, mp 115−117 °C (EtOAc). R_f (EtOAc/PE, 2:1): 0.62. δ_H ($CDCl_3$): 3.78 (s, 3H), 3.84 (s, 3H), 5.46 (s, 2H), 6.86 (d, J_{app} = 8.8 Hz, 2H), 6.99 (d, J_{app} = 9.1 Hz, 2H), 7.47 (d, J_{app} = 8.8 Hz, 2H), 7.87 (d, J_{app} = 9.1 Hz, 2H). δ_C ($CDCl_3$): 48.0, 55.2, 55.3, 92.8, 102.4, 113.8, 114.2, 118.6, 126.4, 129.4, 130.3, 130.6, 159.8, 160.3. Anal. Calcd for $C_{18}H_{16}Br_2N_2O_3$: C, 46.18; H, 3.44; N, 5.98. Found: C, 46.47; H, 3.32; N, 5.92.

4-Bromo-2-(4-methoxybenzyl)-5-(4-methoxyphenyl)-3-(4-methylphenyl)pyrazole 1-Oxide (9). Following the procedure for preparation of **6d** in a 1.02 mmol scale using **8** and 4-iodotoluene gave after FC (CH_2Cl_2 → CH_2Cl_2/EtOAc, 4:1) 347 mg (72%) of **9** as beige crystals. Recrystallization gave off-white crystals, mp 149−150 °C (EtOAc). R_f (CH_2Cl_2/EtOAc, 4:1): 0.41. δ_H ($CDCl_3$): 2.45 (s, 3H), 3.77 (s, 3H), 3.86 (s, 3H), 5.34 (s, 2H), 6.77 (d, J_{app} = 8.8 Hz, 2H), 7.02 (d, J_{app} = 9.0 Hz, 2H), 7.08 (d, J_{app} = 8.8 Hz, 2H), 7.26 (d, J_{app} = 8.4 Hz, 2H), 7.31 (d, J_{app} = 8.1 Hz, 2H), 7.95 (d, J_{app} = 9.0 Hz, 2H). δ_C ($CDCl_3$): 21.6, 47.3, 55.3, 55.4, 89.5, 113.9, 114.1, 119.4, 124.8, 127.8, 129.8, 129.9, 130.3, 130.9, 131.88, 131.90, 140.2, 159.6, 160.3. Anal. Calcd for $C_{25}H_{23}BrN_2O_3$: C, 62.64; H, 4.84; N, 5.84. Found: C, 62.70; H, 4.74; N, 5.73.

Representative Procedure for Arylation at the C-4 Position: 4-(4-Fluorophenyl)-2-(4-methoxybenzyl)-5-(4-methoxyphenyl)-3-(4-methylphenyl)pyrazole 1-Oxide (10a) (Table 3, Entry 2). Pyrazole **9** (300 mg, 0.63 mmol), 4-fluorobenzeneboronic acid (132 mg, 0.95 mmol), aqueous K_3PO_4 (3.0 mL, 2.0 M, 6.0 mmol), and dioxane were mixed, and N_2 was bubbled through for 15 min. $Pd(PPh_3)_4$ (36 mg, 5 mol %) was added, and the mixture was heated to 90 °C for 5 h and then poured into CH_2Cl_2 (60 mL) and washed with saturated aqueous $NaHCO_3$ (15 mL) and brine (15 mL). The organic layer was dried over anhydrous Na_2SO_4 and evaporated to dryness. FC (CH_2Cl_2 → CH_2Cl_2/EtOAc, 4:1) gave 207 mg (66%) of **10a** as beige crystals. Recrystallization gave off-white crystals, mp 137−138 °C (EtOAc). R_f (CH_2Cl_2/EtOAc, 4:1): 0.23. δ_H ($CDCl_3$): 2.38 (s, 3H), 3.79 (s, 3H), 3.81 (s, 3H), 5.34 (s, 2H), 6.81 (d, J_{app} = 8.7 Hz, 2H), 6.86 (d, J_{app} = 8.5 Hz, 4H), 6.95 (d, J_{app} = 8.7 Hz, 2H), 7.00 (d, J_{app} = 8.1 Hz, 2H), 7.14 (d, J_{app} = 7.9 Hz, 2H), 7.18 (d, J_{app} = 8.7 Hz, 2H), 7.55 (d, J_{app} = 9.0, 2H). δ_C ($CDCl_3$): 21.3 (q), 46.6 (t), 55.1 (q), 55.2 (q), 113.6 (d), 113.7 (s), 113.9 (d), 115.3 (d ($d_{C,F}$, $J_{C,F}$ = 21.5 Hz)), 121.1 (s), 125.3 (s), 127.5 (s ($d_{C,F}$, $J_{C,F}$, = 3.5 Hz)), 128.0 (s), 128,3 (s), 129.5 (d), 129.6 (d), 130.1 (s), 130.8 (d ($d_{C,F}$, J = 35.6 Hz)), 132.0 (d), 132.1 (d), 139.3 (s), 159.3 (s), 159.6 (s), 161.9 (s ($d_{C,F}$, ^1J = 248.4 Hz)). Anal. Calcd for $C_{31}H_{27}FN_2O_3$: C, 75.29; H, 5.50; N, 5.66. Found: C, 75.00; H, 5.61; N, 5.64.

Representative Procedure for De-*p*-methoxybenzylation of the Arylated 2-(4-methoxybenzyl)pyrazole 1-Oxides: 3,5-Bis(4-methoxyphenyl)-1-hydroxypyrazole (11a) (Table 4, Entry 1). To a solution of pyrazole **6a** (0.24 mmol) in CH_2Cl_2 (5 mL) was added triisopropylsilane (0.10 mL, 0.48 mmol). After slow addition of trifluoroacetic acid (TFA; 5 mL) the mixture was gently heated to reflux for 24 h. The mixture was evaporated to dryness. Addition of water (5 mL) was followed by extraction with EtOAc (3 × 10 mL), drying over anhydrous $MgSO_4$, and evaporation. The crude product was purified by FC (CH_2Cl_2 → CH_2Cl_2/EtOAc, 5:1) to give 60 mg (84%) of **11a** as slightly brownish crystals. Recrystallization gave off-white crystals, mp 184−186 °C (EtOAc). R_f (CH_2Cl_2:EtOAc, 4:1): 0.42. δ_H (DMSO-d_6): 3.75 (s, 3H), 3.78 (s, 3H), 6.84 (s, 1H, H-4), 6.96 (d, J_{app} = 8.9 Hz, 2H), 7.03 (d, J_{app} = 9.0 Hz, 2H), 7.70 (d, J_{app} = 8.9 Hz, 2H), 7.74 (d, J_{app} = 9.0 Hz, 2H). δ_C (DMSO-d_6): 55.5, 55.6, 98.4, 114.5, 114.6, 121.5, 126.29, 126.32, 129.1, 136.1, 142.6, 159.2, 159.6. Anal. Calcd for $C_{17}H_{16}N_2O_3$: C, 68.91; H, 5.44; N, 9.45. Found: C, 68.77; H, 5.49; N, 9.18.

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Supporting Information Available: Experimental details and spectral data for the compounds mentioned above. This material is available free of charge via the Internet at http://pubs.acs.org.

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