Palladium-Catalyzed Peripheral Arylation of 5-Pyrazolones via Enolizable Bond Protection

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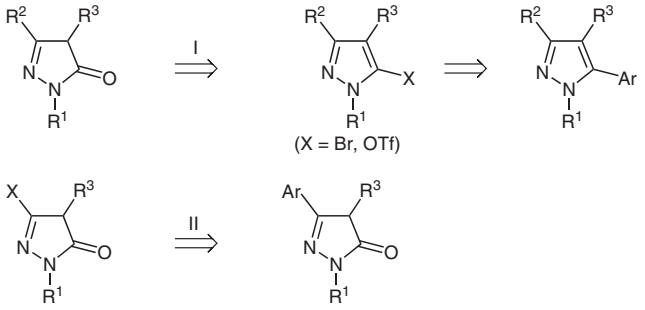
Abstract: Peripheral cross-coupling of the enol form of the 5-pyrazolone scaffold with arylboronic acids promoted by [$PdCl_2$(dppf)] afforded the arylated products in good yields. In this coupling, the protection of the enolizable hydroxyl group of pyrazolone is a prerequisite for ensuring the Suzuki–Miyaura cross-coupling. A particular feature of this process is that it enables the synthesis of 5-hydroxy-3-biphenyl and -terphenylpyrazole derivatives with structural diversity.

Key words: Suzuki–Miyaura, tautomers, pyrazolone, peripheral arylation, arylpyrazole

Pyrazoles are structural units that are frequently found in natural products and pharmaceuticals, and there has been a growing interest in new synthetic methods for their preparation. Such heterocyclic frameworks serve as important core structures that are required for a wide range of biological activities, such as antibacterial/antitumor, anti-inflammatory, analgesic, and anti-hyperglycemic activity,[1] and are interesting templates that can be used to access highly functionalized pyrazole derivatives. In particular, many arylated pyrazoles have been synthesized and have proven to be effective inhibitors of COX-2, p38 MAP kinase, and CDK2/Cyclin A.[2] As part of pyrazole diversity-oriented syntheses,[3] we were interested in an efficient method for incorporating an aryl group onto a peripheral site on enolizable pyrazolone derivatives.

Decades of progress in transition-metal-catalyzed arylation of pyrazoles has provided an indispensable method for the construction of a number of diversely arylated pyrazoles.[4] Substantial effort has focused on the use of pyrazole halides or triflates derived from pyrazolones through enolizable bond activation (Scheme 1, route I).[5] These approaches are rather limited to the use of tautomerizable heterocycles as synthetic precursors for halides or pseudohalides. However, palladium-catalyzed peripheral arylation of the pyrazolone fragment keeping the structure intact has not been widely explored to date (Scheme 1, route II).[6] Herein, we wish to report Suzuki–Miyaura cross-coupling of the peripheral haloaryl group of enolizable 1-(2-pyridinyl)pyrazolone derivatives with arylboronic acids promoted by [$PdCl_2$(dppf)] [dppf = 1,1'-bis(diphenylphosphino)ferrocene], resulting in good yields of arylated products.



Scheme 1 Strategies for the utilization of the tautomeric pyrazolone scaffold

To examine the feasibility of peripheral arylation of the tautomeric pyrazolone scaffold, we initiated Suzuki–Miyaura cross-coupling of 1-(2-pyridinyl)-5-hydroxypyrazole (**1a**) and 1-phenyl-5-pyrazolone (**1b**) as substrates. Based on NMR analysis ($CDCl_3$, r.t.), it was noted that **1a** exists exclusively in enol form, whereas **1b** remains as it stands.[7] Despite employing various conditions reported in literature, we failed to accomplish the Suzuki coupling of **1a** with phenylboronic acid (Table 1, entries 1–3). It is assumed that the palladium catalyst is stabilized and inactivated through chelation with the substrate bearing a bidentate ligand.[8] On the other hand, the Suzuki cross-coupling of **1b** furnished the corresponding 3-(3-biphenyl)pyrazolone **1c** in 71% yield within one hour (entry 4). The observed difference indicates that initial oxidative addition of palladium(0) to bromide **1a** may hamper or compete with substantial complexation, with the substrate leading to the formation of inactive species **1a′** (Figure 1).[8a–c] We rule out a plausible alternative Pd complex with the two nitrogen atoms of the pyridine–pyrazole ligand,[8d,e] because 1-(2-pyridinyl)pyrazole **1d** also exists in the enol form, and the X-ray crystal structure clearly shows that the carbonyl oxygen and pyridine nitrogen adopt an almost *syn*-periplanar arrangement that is capable of accommodating intramolecular hydrogen bonding (Figure 2).

These results led to further investigations into whether protection of the enolizable ketone could influence the outcome of the Suzuki reaction. Suzuki coupling with acetate **2a** was unsuccessful,[4b] and only led to liberation of

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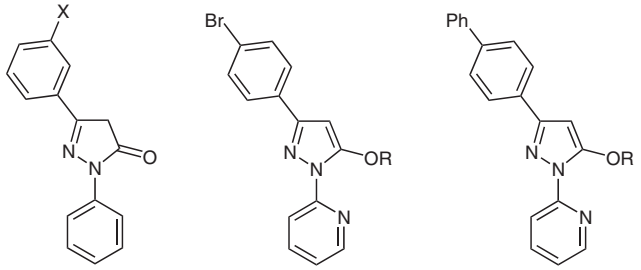
Table 1 Suzuki Cross-Coupling of 5-Pyrazolone/5-Hydroxypyrazole Derivatives with Phenylboronic Acid[a]



Entry	Bromide	Reagents	Solvent	Time (h)	Product [yield (%)[b]]
1	**1a**	$[Pd(PPh_3)_4]$, Na_2CO_3	DME	72	–[c]
2	**1a**	$[Pd(PPh_3)_4]$, $CsCO_3$	DME	72	–[c]
3	**1a**	$[PdCl_2(dppf)]$, dppf, K_3PO_4	1,4-dioxane	20	–[c,d]
4	**1b**	$[PdCl_2(dppf)]$, dppf, K_3PO_4	1,4-dioxane	0.5	**1c** (71)
5	**2a**	$[Pd(PPh_3)_4]$, Na_2CO_3	DME	30	**1a** (23)
6	**3a**	$[PdCl_2(dppf)]$, dppf, K_3PO_4	1,4-dioxane	1	**3b** (5), **6a** (24)
7	**4a**	$[PdCl_2(dppf)]$, dppf, K_3PO_4	1,4-dioxane	0.5	**5a** (90)

[a] Reaction conditions: phenylboronic acid (2–3 equiv), Pd (5–8 mol%), dppf (4 mol%), base (2–3 equiv), 85–100 °C.
[b] Isolated yield.
[c] No reaction observed; the starting material decomposed.
[d] Trace amounts of two unidentified byproducts were isolated.

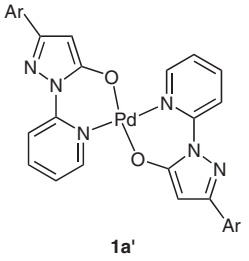


Figure 1 Proposed structure for inactive palladium complex **1a′** (Ar = 4-BrC_6H_4)

the parent molecule (entry 5). Protection of **1a** with TIPS-Cl and imidazole in *N*,*N*-dimethylformamide (DMF) smoothly afforded the corresponding silyl enol ether **3a**. However, even when the TIPS group was used, the Suzuki coupling gave the two arylated pyrazoles **3b** and **6a** in poor yields (entry 6). We reasoned that a pentacoordinated silicon species, which was brought about by coordination with the adjacent pyridine nitrogen, was presumably responsible for the unusual basic hydrolysis of the TIPS group.[9] The hydrolytic susceptibility of this moiety eventually forced us to find protecting groups that were more stable towards base-mediated hydrolysis. A survey of protecting groups revealed that the *tert*-butoxycarbonyl (Boc) group allows facile Suzuki coupling to take place within one hour in excellent yield (entry 7). Thus, this strategy was subsequently employed for all substrates.

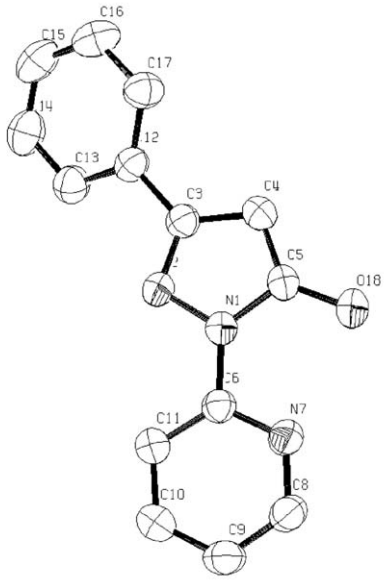
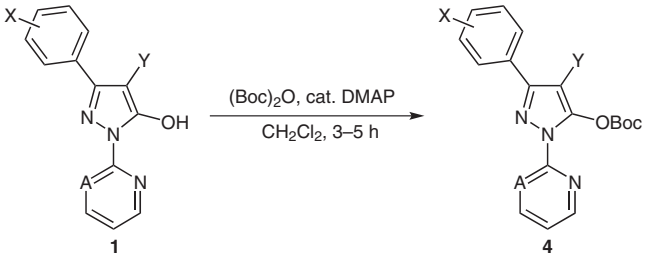


Figure 2 X-ray crystal structure of 1-(2-pyridinyl)-3-phenyl-5-hydroxypyrazole (**1d**)

The 5-hydroxypyrazole derivatives **1e–k** were conveniently prepared by treatment of the corresponding benzoylacetates with 2-hydrazinopyridines, respectively, in refluxing acetic acid.[7] Benzoylacetates were available from commercial sources and α-alkylated derivatives were prepared according to a previous procedure.[10] Con-

sequently, the 5-hydroxypyrazole derivatives were readily protected to provide their Boc-derivatives **4b–h** using di-*tert*-butyldicarbonate (Boc_2O) in the presence of catalytic amount of 4-(*N*,*N*-dimethylamino)pyridine (DMAP) in dichloromethane.[11] The Boc-protected pyrazoles were sufficiently stable to allow chromatographic separation and isolation in excellent yields, as shown in Table 2.

Table 2 Boc-Protection of 5-Hydroxypyrazole Derivatives



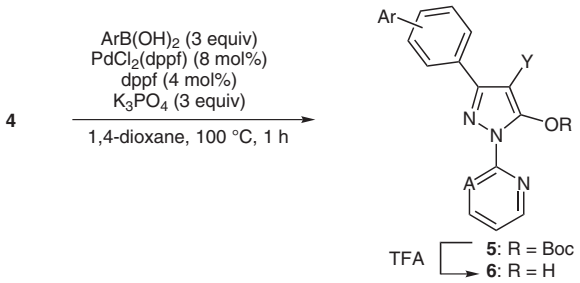
Entry	1	A	X	Y	4	Yield (%)
1	**1a**	CH	4-Br	H	**4a**	97
2	**1e**	CH	4-I	H	**4b**	99
3	**1f**	CH	3-I	H	**4c**	99
4	**1g**	CH	2-I	H	**4d**	98
5	**1h**	CH	4-Br	*n*-Pr	**4e**	89
6	**1i**	CH	4-Br	Bn	**4f**	94
7	**1j**	CCl	3-I	H	**4g**	95
8	**1k**	N	4-I	H	**4h**	97

With substrates in hand, we wished to demonstrate the scope of this protocol for the palladium-catalyzed peripheral arylation of 3-haloarylpyrazole derivatives with electronic and steric variations on both coupling partners, and to secure synthesis of biphenyl and terphenylpyrazole analogues with structural diversity. Coupling of the Boc-protected pyrazoles with arylboronic acids was accomplished with [$PdCl_2$(dppf)] in 1,4-dioxane, with K_3PO_4 as the base, to provide the coupling products within one hour. The reaction with electron-rich arylboronic acids generally tolerates differing substitution patterns on the peripheral aryl group, as shown in Table 3. In addition, reaction of sterically hindered 2-phenoxyphenylboronic acid with either *p*- or *m*-iodide-substituted starting materials **4b** and **4c**, respectively, provided the corresponding products in moderate yields (entries 6 and 8). However, the reaction failed with electron-poor arylboronic acids. Although the coupling of *o*-isomers showed a decreased reactivity compared to those of the corresponding *m*-congeners, the yields were still acceptable (Table 3, entries 9 and 10 vs. entries 13 and 14).

A higher degree of substitution, for example in **4e** and **4f**, ultimately led to a drop in yields although the reactions proceeded smoothly (Table 3, entries 15 and 16). Variation at the pyridine moiety did not affect the yield or reaction times (entries 17 and 18). Therefore, the Boc group protecting strategy was suitable for the Suzuki cross-coupling of 3-haloarylpyrazoles and prevented problems caused by the pyridine nitrogen.

The Boc group is widely used in organic synthesis as both an amine and a phenol protecting group, and cleavage is usually achieved by treatment with an acid such as trifluoroacetic acid (TFA) or HCl. In a typical procedure, Boc-protected 3-biphenylpyrazole **5a** was thus treated with TFA at ambient temperature in dichloromethane to release the desired product **6a** in 93% yield.[11] All the Boc-protected derivatives were deprotected within five hours, to produce 5-hydroxy-3-biphenyl and -terphenylpyrazole analogues **6b–s** in good yields (Table 3). Again, all the products existed exclusively in the enol form.

Table 3 Pd-Catalyzed Arylation of 5-(*tert*-Butoxycarbonyloxy)pyrazole Derivatives **4** and TFA-Mediated Boc-Deprotection



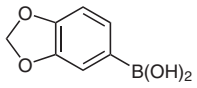
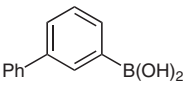
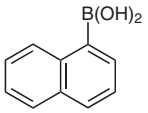
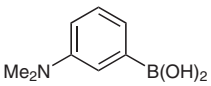
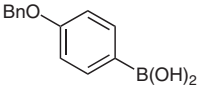
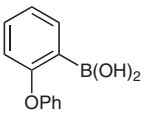
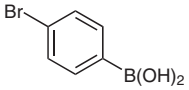
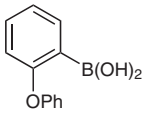
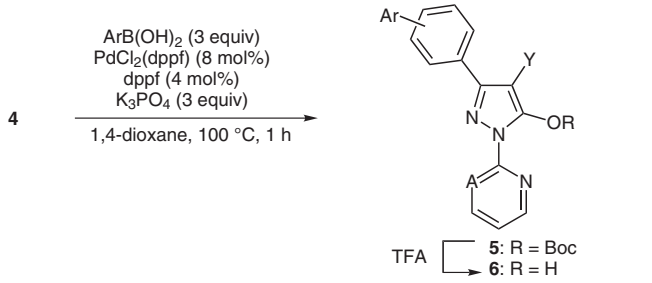
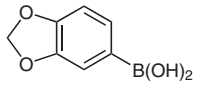
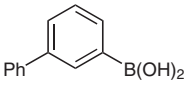
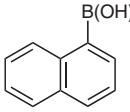
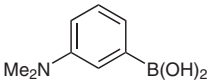
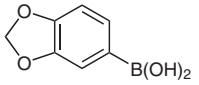
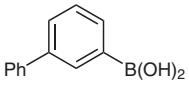
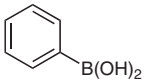
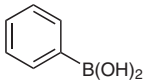
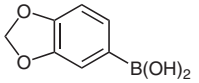
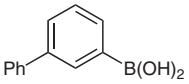
Entry	4	$ArB(OH)_2$	5 (% yield)	6 (% yield)
1	**4a**		**5b** (70)	**6b** (70)
2	**4a**		**5c** (95)	**6c** (58)
3	**4a**		**5d** (98)	**6d** (71)
4	**4a**		**5e** (81)	**6e** (99)
5	**4b**		**5f** (98)	**6f** (85)
6	**4b**		**5g** (63)	**6g** (86)
7	**4c**		**5h** (66)	**6h** (84)
8	**4c**		**5i** (56)	**6i** (80)

Table 3 Pd-Catalyzed Arylation of 5-(*tert*-Butoxycarbonyloxy)pyrazole Derivatives **4** and TFA-Mediated Boc-Deprotection (continued)



Entry	4	$ArB(OH)_2$	5 (% yield)	6 (% yield)
9	**4c**		**5j** (99)	**6j** (98)
10	**4c**		**5k** (90)	**6k** (85)
11	**4c**		**5l** (84)	**6l** (97)
12	**4c**		**5m** (90)	**6m** (99)
13	**4d**		**5n** (84)	**6n** (84)
14	**4d**		**6o** (82)[a]	
15	**4e**		**5p** (74)	**6p** (91)
16	**4f**		**5q** (87)	**6q** (96)
17	**4g**		**5r** (95)	**6r** (90)
18	**4h**		**5s** (90)	**6s** (93)

[a] The deprotected product **6o** was obtained in 82% yield.

In summary, transition-metal-catalyzed arylation of pyrazoles provides a powerful method for the construction of a number of diversely arylated pyrazoles. However, approaches have mainly been based on the use of pyrazole halides and triflates derived from pyrazolones through enolizable bond activation. In this study, we revealed that the peripheral cross-coupling of the enol form of the 5-pyrazolone scaffold with arylboronic acids promoted by [$PdCl_2$(dppf)] afforded the arylated products in good yields. To ensure the Suzuki–Miyaura cross-coupling, protection of the enolizable hydroxyl group of pyrazolone is crucial. The advantage of this process is the ability to secure the synthesis of 5-hydroxy-3-biphenyl and -terphenylpyrazole derivatives with structural diversity.

The reactions were monitored by TLC with Merck silica gel 60 F_{254} TLC glass plates, and the products were purified by flash chromatography with Merck Kiesel 60 silica gel (particles size 0.040–0.063 mm) using a glass column. ^{1}H (300 MHz) and ^{13}C (75 MHz) NMR spectra were recorded with a Jeol Eclipse FT 300 MHz spectrometer. Mass spectra were recorded with an Agilent 1100 Series VLL or a JEOL the MStation JMS 700 mass Spectrometer.

Preparation of 5-Pyrazolone/5-Hydroxypyrazole; General Procedure

The starting 5-pyrazolone (keto form) and 5-hydroxypyrazole (enol form) were obtained in 65–88% yields after chromatographic separation, by the treatment of the appropriate hydrazines with β-keto esters in refluxing acetic acid according to the procedure described by Huang et al.[7]

1-(2-Pyridinyl)-3-(4-bromophenyl)-5-hydroxypyrazole (1a)

Yield: 81%.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 12.86–12.84 (br s, 1 H), 8.30–8.28 (m, 1 H), 8.03 (d, *J* = 8.4 Hz, 1 H), 7.94–7.88 (m, 1 H), 7.74 (d, *J* = 8.5 Hz, 2 H), 7.54 (d, *J* = 8.4 Hz, 2 H), 7.21–7.16 (m, 1 H), 5.91 (s, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 157.5, 154.6, 151.6, 145.3, 140.1, 132.1, 131.8, 127.5, 122.6, 120.2, 112.4, 85.7.

HRMS (EI): *m*/*z* calcd for $C_{14}H_{10}BrN_3O$: 315.0007; found: 314.9998.

1-Phenyl-3-(3-bromophenyl)-5-pyrazolone (1b)

Yield: 88%.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.97–7.93 (m, 3 H), 7.67–7.56 (m, 2 H), 7.46–7.40 (m, 2 H), 7.33 (t, *J* = 7.9 Hz, 1 H), 7.25–7.20 (m, 1 H), 3.81 (s, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 170.0, 153.2, 138.0, 133.6, 132.9, 130.5, 129.0, 128.9, 125.6, 124.7, 123.3, 119.2, 39.5.

HRMS (EI): *m*/*z* calcd for $C_{15}H_{11}BrN_2O$: 314.0055; found: 314.0056.

1-(2-Pyridinyl)-3-(phenyl)-5-hydroxypyrazole (1d)

Yield: 87%.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 12.83 (br s, 1 H), 8.28–8.27 (m, 1 H), 8.05 (d, *J* = 8.4 Hz, 1 H), 7.92–7.85 (m, 3 H), 7.48–7.32 (m, 3 H), 7.19–7.14 (m, 1 H), 5.94 (s, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 157.3, 154.7, 152.7, 145.2, 140.0, 133.2, 128.7, 128.6, 125.9, 120.0, 112.4, 85.8.

EIMS (70 eV): *m*/*z* (%) = 237 (100) $[M]^+$, 209 (28), 196 (77), 180 (17), 160 (28), 102 (31), 79 (65).

X-ray Crystallographic Data (1d)

Empirical formula: $C_{14}H_{11}N_3O$; Formula weight: 237.26; Crystal system: monoclinic; Space group: P2(1)/c; Unit cell dimensions: *a* = 9.8059(4) Å, *α* = 90°, *b* = 10.6374(5) Å, *β* = 104.000(2)°, *c* = 11.4730(5) Å, *γ* = 90°; Density (calculated): 1.357 Mg/m^3; Reflections collected: 11635; Final *R* indices [$I > 2\sigma(I)$], *R*1 = 0.0451, *wR*2 = 0.1206; *R* indices (all data), *R*1 = 0.0594, *wR*2 = 0.1316. Atomic coordinates and crystallographic parameters have been deposited at the Cambridge Crystallographic Data Centre (CCDC 805262). These data can be obtained free of charge from the

Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Pd-Catalyzed Direct Arylation of 5-Pyrazolone: Preparation of 1-Phenyl-3-(3-biphenyl)-5-pyrazolone (1c)

To a stirred solution of **1b** (120 mg, 0.38 mmol), phenylboronic acid (139 mg, 1.14 mmol), K_3PO_4 (242 mg, 1.14 mmol), [$PdCl_2$(dppf)] (25 mg, 0.03 mmol), and dppf (8.4 mg, 0.015 mmol) in 1,4-dioxane (6 mL) was heated at 100 °C for 1 h. The reaction mixture was cooled to r.t., filtered through Celite, and the filtrate was concentrated to dryness. The residue was taken up with EtOAc (20 mL), and the organic layer was washed with H_2O (3 × 10 mL), dried over anhydrous $MgSO_4$, and concentrated in vacuo. The crude product was purified by column chromatography on silica gel (hexane–EtOAc, 10:1) to afford **1c**.

Yield: 85 mg (72%).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.00–7.97 (m, 3 H), 7.73–7.62 (m, 4 H), 7.55–7.40 (m, 6 H), 7.25–7.20 (m, 1 H), 3.89 (s, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 170.3, 154.7, 142.2, 140.4, 138.2, 131.5, 129.6, 129.5, 129.1, 129.0, 127.3, 127.3, 125.5, 125.0, 124.7, 119.2, 39.8.

HRMS (EI): *m*/*z* calcd for $C_{21}H_{16}N_2O$: 312.1263; found: 312.1263.

Boc-Protection of 5-Hydroxypyrazoles: *tert*-Butyl 1-(2-Pyridinyl)-3-(4-bromophenyl)-5-pyrazolyl Carbonate (4a); Typical Procedure

To a solution of **1a** (272 mg, 0.86 mmol) and di-*tert*-butyldicarbonate (0.24 mL, 1.03 mmol) in CH_2Cl_2 (7 mL), DMAP (5 mg, 0.04 mmol) was added. When the reaction was complete (1 h as judged by TLC), the mixture was washed with H_2O (3 × 5 mL), dried over anhydrous $MgSO_4$, and concentrated to dryness. The crude material was purified by column chromatography on silica gel (hexane–EtOAc, 10:1) to afford **4a**.

Yield: 347 mg (97%).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.43–8.41 (m, 1 H), 7.99–7.96 (m, 1 H), 7.85–7.80 (m, 1 H), 7.75 (d, *J* = 8.5 Hz, 2 H), 7.55 (d, *J* = 8.5 Hz, 2 H), 7.22–7.18 (m, 1 H), 6.49 (s, 1 H), 1.57 (s, 9 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 152.2, 150.1, 149.6, 147.8, 146.6, 138.6, 131.9, 131.8, 127.3, 122.6, 121.7, 115.2, 96.0, 85.0, 27.7.

MS (CI$^+$): *m*/*z* (%) = 418 (3) [M]$^+$, 416 (2) [M]$^+$, 358 (26), 356 (17), 317 (100), 315 (87), 79 (16).

***tert*-Butyl 1-(2-Pyridinyl)-3-(4-iodophenyl)-5-pyrazolyl Carbonate (4b)**

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.42–8.40 (m, 1 H), 7.99–7.96 (m, 1 H), 7.85–7.80 (m, 1 H), 7.76 (d, *J* = 8.5 Hz, 2 H), 7.61 (d, *J* = 8.5 Hz, 2 H), 7.22–7.18 (m, 1 H), 6.50 (s, 1 H), 1.57 (s, 9 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 152.1, 150.2, 149.6, 147.8, 146.6, 138.6, 137.8, 132.4, 127.5, 121.7, 115.2, 96.0, 94.3, 85.0, 27.7.

MS (CI$^+$): *m*/*z* (%) = 465 (1) [M]$^+$, 464 (43) [M]$^+$, 420 (12), 406 (12), 365 (15), 364 (100), 363 (29), 238 (2), 237 (1).

***tert*-Butyl 1-(2-Pyridinyl)-3-(3-iodophenyl)-5-pyrazolyl Carbonate (4c)**

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.43–8.41 (m, 1 H), 8.26–8.25 (m, 1 H), 8.01–7.98 (m, 1 H), 7.86–7.78 (m, 2 H), 7.70–7.66 (m, 1 H), 7.23–7.18 (m, 1 H), 7.15–7.13 (m, 1 H), 6.50 (s, 1 H), 1.57 (s, 9 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 152.1, 149.6, 149.5, 147.8, 146.5, 138.6, 137.5, 134.9, 134.6, 130.4, 125.0, 121.7, 115.2, 96.1, 94.7, 85.0, 27.7.

MS (CI$^+$): *m*/*z* (%) = 465 (5) [M]$^+$, 464 (25) [M]$^+$, 420 (9), 406 (10), 365 (15), 364 (100), 363 (26), 238 (3), 237 (1).

***tert*-Butyl 1-(2-Pyridinyl)-3-(2-iodophenyl)-5-pyrazolyl Carbonate (4d)**

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.42–8.41 (m, 1 H), 7.97 (d, *J* = 8.1 Hz, 2 H), 7.83–7.78 (m, 1 H), 7.63–7.61 (m, 1 H), 7.41 (t, *J* = 7.6 Hz, 1 H), 7.21–7.17 (m, 1 H), 7.08–7.02 (m, 1 H), 6.58 (m, 1 H), 1.57 (s, 9 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 153.0, 152.2, 149.7, 147.8, 145.3, 140.3, 138.6, 138.0, 130.8, 130.0, 128.2, 121.7, 115.3, 99.6, 96.8, 84.9, 27.7.

MS (CI$^+$): *m*/*z* (%) = 465 (12) [M]$^+$, 464 (54) [M]$^+$, 420 (8), 419 (6), 406 (11), 404 (6), 365 (15), 364 (100), 363 (26), 238 (3), 237 (1).

***tert*-Butyl 1-(2-Pyridinyl)-3-(4-bromophenyl)-4-propyl-5-pyrazolyl Carbonate (4e)**

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.39–8.37 (m, 1 H), 7.96 (d, *J* = 8.3 Hz, 1 H), 7.81–7.15 (m, 1 H), 7.59 (dd, *J* = 14.8, 8.8 Hz, 4 H), 7.18–7.14 (m, 1 H), 2.56 (t, *J* = 7.7 Hz, 2 H), 1.59–1.54 (m, 2 H), 1.52 (s, 9 H), 0.92 (t, *J* = 7.4 Hz, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 152.3, 149.9, 149.4, 147.7, 143.6, 138.5, 132.8, 131.7, 129.3, 122.4, 121.3, 114.6, 110.6, 84.7, 27.7, 24.6, 22.8, 14.0.

MS (CI$^+$): *m*/*z* (%) = 460 (50) [M]$^+$, 458 (49) [M]$^+$, 402 (14), 400 (20), 398 (9), 361 (17), 360 (96), 359 (57), 358 (100), 357 (40), 328 (13).

***tert*-Butyl 1-(2-Pyridinyl)-3-(4-bromophenyl)-4-benzyl-5-pyrazolyl Carbonate (4f)**

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.40–8.38 (m, 1 H), 8.01–7.98 (m, 1 H), 7.83–7.77 (m, 1 H), 7.48 (s, 4 H), 7.24–7.15 (m, 6 H), 3.94 (s, 2 H), 1.48 (s, 9 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 152.3, 149.9, 149.6, 147.7, 144.5, 139.3, 138.6, 132.2, 131.7, 129.4, 128.6, 128.3, 126.3, 122.6, 121.4, 114.6, 108.8, 84.9, 28.5, 27.6.

MS (CI$^+$): *m*/*z* (%) = 508 (40) [M]$^+$, 506 (38) [M]$^+$, 450 (17), 448 (22), 446 (9), 409 (21), 408 (98), 407 (62), 406 (100), 405 (40), 328 (4), 318 (1).

***tert*-Butyl 1-[2-(3-Chloro)pyridinyl]-3-(3-iodophenyl)-5-pyrazolyl Carbonate (4g)**

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.57–8.55 (m, 1 H), 7.94 (d, *J* = 8.0 Hz, 1 H), 7.86 (d, *J* = 7.7 Hz, 1 H), 7.66–7.63 (m, 2 H), 7.58–7.56 (m, 1 H), 7.50–7.34 (m, 1 H), 6.71 (s, 1 H), 1.52 (s, 9 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 150.7, 148.3, 147.3, 147.0, 146.9, 139.8, 137.4, 134.9, 134.7, 130.3, 128.9, 125.4, 125.1, 94.6, 92.4, 85.6, 27.5.

MS (CI$^+$): *m*/*z* (%) = 500 (25) [M]$^+$, 499 (16) [M]$^+$, 498 (74) [M]$^+$, 454 (7), 440 (14), 400 (32), 399 (22), 398 (100), 397 (21), 364 (6), 363 (2), 362 (1), 306 (1), 272 (1).

***tert*-Butyl 1-(2-Pyrimidinyl)-3-(4-iodophenyl)-5-pyrazolyl Carbonate (4h)**

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.79 (d, *J* = 4.8 Hz, 2 H), 7.76 (d, *J* = 8.4 Hz, 2 H), 7.67 (d, *J* = 8.4 Hz, 2 H), 7.26–7.22 (m, 1 H), 6.55 (s, 1 H), 1.58 (s, 9 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 158.7, 156.2, 151.7, 149.5, 147.5, 137.7, 131.7, 127.9, 118.9, 97.2, 94.9, 85.2, 27.7.

MS (CI$^+$): *m*/*z* (%) = 465 (15) [M$^+$ + 1], 421 (6), 407 (7), 405 (5), 366 (15), 365 (100), 364 (25), 273 (5), 239 (2).

Pd-Catalyzed Arylation of Boc-Protected 5-Hydroxypyrazoles: *tert*-Butyl 1-(2-Pyridinyl)-3-[4-(3′,4′-methylenedioxy)biphenyl]-5-pyrazolyl Carbonate (5b); Typical Procedure

A stirred solution of **4a** (624 mg, 1.50 mmol), 3,4-(methylenedioxy)phenylboronic acid (747 mg, 4.50 mmol), K_3PO_4 (955 mg, 4.49 mmol), [$PdCl_2$(dppf)] (98 mg, 0.12 mmol), and dppf (33 mg, 0.06 mmol) in 1,4-dioxane (20 mL) was heated at 100 °C for 1 h. The reaction mixture was cooled to r.t., filtered through Celite, and the filtrate was concentrated to dryness. The residue was taken up with EtOAc (50 mL), and the organic layer was washed with H_2O (3 × 10 mL), dried over anhydrous $MgSO_4$, and concentrated in vacuo. The crude material was purified by column chromatography on silica gel (hexane–EtOAc, 8:1) to afford **5b**.

Yield: 481 mg (70%).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.43–8.40 (m, 1 H), 8.03–8.00 (m, 1 H), 7.92–7.89 (m, 2 H), 7.85–7.80 (m, 1 H), 7.59–7.56 (m, 2 H), 7.21–7.17 (m, 1 H), 7.13–7.10 (m, 2 H), 6.91–6.88 (m, 1 H), 6.54 (s, 1 H), 6.01 (s, 1 H), 1.57 (s, 9 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 152.3, 150.9, 149.7, 148.3, 147.8, 147.3, 146.5, 141.1, 138.5, 135.2, 131.4, 127.1, 126.2, 121.1, 120.7, 115.2, 108.7, 108.2, 106.7, 101.3, 98.4, 96.1, 84.9, 27.7.

MS (CI^+): *m*/*z* (%) = 458 (4) $[M]^+$, 415 (2), 414 (12), 400 (12), 364 (4), 358 (100), 69 (1).

***tert*-Butyl 1-(2-Pyridinyl)-3-(4-biphenyl)-5-pyrazolyl Carbonate (5a)**

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.44–8.41 (m, 1 H), 8.05–8.02 (m, 1 H), 7.97–7.93 (m, 2 H), 7.87–7.81 (m, 1 H), 7.69–7.64 (m, 4 H), 7.49–7.44 (m, 2 H), 7.39–7.34 (m, 1 H), 7.22–7.18 (m, 1 H), 6.56 (s, 1 H), 1.58 (s, 9 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 152.3, 150.9, 149.7, 147.8, 146.5, 141.3, 140.8, 138.5, 131.8, 128.9, 127.5, 127.4, 127.1, 126.2, 121.5, 115.1, 96.1, 84.9, 27.7.

MS (CI^+): *m*/*z* (%) = 414 (19) $[M]^+$, 371 (2), 370 (8), 356 (13), 354 (5), 315 (21), 314 (100), 313 (38).

***tert*-Butyl 1-(2-Pyridinyl)-3-[4-(3′-phenyl)biphenyl]-5-pyrazolyl Carbonate (5c)**

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.44–8.41 (m, 1 H), 8.04–7.95 (m, 3 H), 7.86–7.80 (m, 2 H), 7.73–7.27 (m, 11 H), 7.22–7.17 (m, 1 H), 6.57 (s, 1 H), 1.58 (s, 9 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 156.1, 152.3, 150.9, 149.7, 147.8, 146.5, 142.0, 141.4, 140.9, 138.6, 131.9, 130.0, 129.3, 128.9, 128.8, 127.5, 127.4, 127.2, 126.4, 126.3, 126.1, 121.5, 119.8, 115.2, 114.3, 114.2, 96.2, 85.0, 27.7.

MS (CI^+): *m*/*z* (%) = 446 (8), 432 (12), 392 (4), 390 (100), 358 (8).

***tert*-Butyl 1-(2-Pyridinyl)-3-[4-(1-naphthyl)phenyl]-5-pyrazolyl Carbonate (5d)**

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.44–8.42 (m, 1 H), 8.06–7.81 (m, 7 H), 7.58–7.42 (m, 6 H), 7.22–7.18 (m, 1 H), 6.59 (s, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 152.3, 151.0, 149.7, 147.8, 146.5, 141.1, 140.0, 138.6, 133.9, 131.8, 131.7, 130.5, 128.4, 127.9, 127.0, 126.2, 126.1, 125.9, 125.7, 125.5, 121.5, 115.1, 96.2, 84.9, 27.8.

MS (CI^+): *m*/*z* (%) = 464 (4) $[M]^+$, 420 (10), 406 (13), 390 (6), 364 (100), 363 (29), 283 (13), 69 (7).

***tert*-Butyl 1-(2-Pyridinyl)-3-[4-(3′-dimethylamino)biphenyl]-5-pyrazolyl Carbonate (5e)**

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.43–8.41 (m, 1 H), 8.04–8.01 (m, 1 H), 7.93 (d, *J* = 8.2 Hz, 2 H), 7.86–7.80 (m, 1 H), 7.66 (d, *J* = 8.2 Hz, 2 H), 7.35–7.30 (m, 1 H), 7.21–7.17 (m, 1 H), 7.00–6.98 (m, 2 H), 6.78–6.75 (m, 1 H), 6.55 (s, 1 H), 3.02 (s, 6 H), 1.57 (s, 9 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 152.3, 151.1, 151.0, 149.7, 147.8, 146.5, 142.4, 141.8, 138.5, 131.6, 129.6, 127.6, 126.1, 121.5, 116.0, 115.1, 112.0, 111.5, 96.1, 84.9, 40.9, 27.7.

MS (CI^+): *m*/*z* (%) = 457 (5) $[M]^+$, 456 (2), 413 (10), 399 (9), 364 (8), 357 (100), 356 (36), 283 (11), 69 (7).

***tert*-Butyl 1-(2-Pyridinyl)-3-[4-(4′-benzyloxy)biphenyl]-5-pyrazolyl Carbonate (5f)**

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.43–8.41 (m, 1 H), 8.03–8.01 (m, 1 H), 7.92 (d, *J* = 8.3 Hz, 2 H), 7.86–7.80 (m, 1 H), 7.63–7.56 (m, 4 H), 7.48–7.33 (m, 5 H), 7.21–7.17 (m, 1 H), 7.09–7.05 (m, 2 H), 6.54 (s, 1 H), 1.57 (s, 9 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 158.6, 152.3, 150.9, 149.7, 147.8, 146.5, 140.9, 138.5, 137.1, 133.6, 131.2, 128.7, 128.2, 127.6, 126.9, 126.2, 121.5, 116.1, 115.3, 115.1, 96.1, 84.9, 70.2, 27.7.

MS (EI, 70 eV): *m*/*z* (%) = 519 (1) $[M]^+$, 460 (2), 329 (24), 328 (100), 300 (5), 91 (48).

***tert*-Butyl 1-(2-Pyridinyl)-3-[4-(2′-phenoxy)biphenyl]-5-pyrazolyl Carbonate (5g)**

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.41–8.39 (m, 1 H), 8.00 (d, *J* = 8.28 Hz, 1 H), 7.87–7.78 (m, 3 H), 7.62 (d, *J* = 8.1 Hz, 2 H), 7.52–7.49 (m, 1 H), 7.34–7.15 (m, 5 H), 7.04–6.91 (m, 4 H), 6.51 (s, 1 H), 1.56 (s, 9 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 158.1, 156.2, 151.0, 149.8, 147.7, 138.5, 138.0, 131.8, 131.3, 129.7, 129.6, 129.0, 128.5, 126.1, 125.6, 125.0, 124.3, 122.7, 121.5, 120.5, 118.1, 115.1, 84.9, 27.7.

MS (CI^+): *m*/*z* (%) = 462 (5), 448 (13), 446 (3), 407 (27), 406 (100), 405 (30).

***tert*-Butyl 1-(2-Pyridinyl)-3-[3-(4′-bromo)biphenyl]-5-pyrazolyl Carbonate (5h)**

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.43–8.42 (m, 1 H), 8.06–8.00 (m, 2 H), 7.86–7.81 (m, 2 H), 7.60–7.49 (m, 6 H), 7.22–7.18 (m, 1 H), 6.57 (s, 1 H), 1.57 (s, 9 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 152.2, 150.9, 149.7, 147.8, 146.5, 140.6, 140.1, 138.6, 133.5, 132.0, 129.3, 129.0, 127.2, 125.2, 124.4, 121.8, 121.6, 115.2, 96.2, 85.0, 27.7.

MS (CI^+): *m*/*z* (%) = 494 (5) $[M]^+$, 492 (6) $[M]^+$, 450 (10), 448 (11), 434 (16), 432 (7), 394 (100), 392 (98), 314 (6).

***tert*-Butyl 1-(2-Pyridinyl)-3-[3-(2′-phenoxy)biphenyl]-5-pyrazolyl Carbonate (5i)**

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.40–8.39 (m, 1 H), 8.03 (s, 1 H), 7.95–7.92 (m, 2 H), 7.82–7.77 (m, 2 H), 7.56–7.52 (m, 2 H), 7.42–7.15 (m, 6 H), 7.05–6.93 (m, 3 H), 6.44 (s, 1 H), 1.56 (s, 9 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 158.1, 153.6, 152.3, 151.1, 149.7, 147.7, 146.4, 138.5, 138.2, 133.7, 132.7, 131.4, 129.7, 129.5, 128.9, 128.5, 126.7, 124.7, 124.3, 122.6, 121.4, 120.6, 118.1, 115.1, 96.1, 84.8, 27.7.

MS (CI^+): *m*/*z* (%) = 506 (3) $[M]^+$, 462 (12), 448 (14), 407 (28), 406 (100), 405 (32), 69 (1).

***tert*-Butyl 1-(2-Pyridinyl)-3-[3-(3′,4′-methylenedioxy)biphenyl]-5-pyrazolyl Carbonate (5j)**

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.43–8.41 (m, 1 H), 8.04–8.01 (m, 2 H), 7.86–7.78 (m, 2 H), 7.52–7.43 (m, 2 H), 7.21–7.11 (m, 3 H), 6.91–6.89 (m, 1 H), 6.56 (s, 1 H), 6.01 (s, 2 H), 1.57 (s, 9 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 152.3, 151.1, 149.7, 148.2, 147.8, 147.3, 146.5, 141.4, 138.5, 135.5, 133.3, 129.1, 127.2, 124.5, 124.3, 121.5, 120.9, 115.2, 108.7, 107.9, 101.3, 96.2, 84.9, 27.7.

MS (CI$^+$): *m*/*z* (%) = 456 (1) [M]$^+$, 415 (3), 414 (11), 400 (13), 359 (23), 358 (100), 357 (35), 299 (6), 145 (2), 69 (2).

***tert*-Butyl 1-(2-Pyridinyl)-3-[3-(3′-phenyl)biphenyl]-5-pyrazolyl Carbonate (5k)**

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.43–8.41 (m, 1 H), 8.15 (s, 1 H), 8.04 (d, *J* = 8.3 Hz, 1 H), 7.88–7.80 (m, 3 H), 7.69–7.45 (m, 9 H), 7.40–7.35 (m, 1 H), 7.22–7.17 (m, 1 H), 6.59 (s, 1 H), 1.58 (s, 9 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 152.3, 151.1, 149.7, 147.8, 146.5, 141.9, 141.8, 141.3, 138.5, 133.4, 129.3, 129.2, 128.9, 127.6, 127.5, 127.4, 126.4, 124.9, 124.7, 121.5, 115.2, 96.3, 84.9, 27.7.

MS (CI$^+$): *m*/*z* (%) = 446 (5), 433 (4), 432 (12), 430 (4), 392 (4), 391 (28), 390 (100), 389 (33), 215 (7).

***tert*-Butyl 1-(2-Pyridinyl)-3-[3-(1-naphthyl)phenyl]-5-pyrazolyl Carbonate (5l)**

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.41–8.39 (m, 1 H), 8.01–7.87 (m, 6 H), 7.82–7.76 (m, 1 H), 7.57–7.41 (m, 6 H), 7.19–7.15 (m, 1 H), 6.55 (s, 1 H), 1.56 (s, 9 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 152.3, 151.0, 149.7, 147.7, 146.5, 141.3, 140.1, 138.5, 133.9, 132.9, 131.8, 130.3, 128.7, 128.3, 127.9, 127.5, 127.0, 126.2, 126.2, 125.9, 125.5, 124.7, 121.5, 115.1, 96.3, 84.9, 27.7.

MS (CI$^+$): *m*/*z* (%) = 464 (2) [M]$^+$, 420 (9), 406 (12), 390 (10), 364 (100), 363 (33), 272 (3), 144 (1), 69 (6).

***tert*-Butyl 1-(2-Pyridinyl)-3-[3-(3′-dimethylamino)biphenyl]-5-pyrazolyl carbonate (5m)**

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.42–8.40 (m, 1 H), 8.07–8.01 (m, 2 H), 7.86–7.79 (m, 2 H), 7.59–7.56 (m, 1 H), 7.50–7.45 (m, 1 H), 7.36–7.30 (m, 1 H), 7.20–7.16 (m, 1 H), 7.01–6.97 (m, 2 H), 6.78–6.75 (m, 1 H), 6.56 (s, 1 H), 3.02 (s, 6 H), 1.57 (s, 9 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 152.3, 151.2, 151.0, 149.7, 147.7, 146.5, 142.8, 142.3, 138.5, 133.1, 129.5, 129.5, 127.7, 124.9, 124.6, 121.5, 116.2, 115.1, 112.0, 111.9, 96.3, 84.9, 40.9, 27.7.

MS (CI$^+$): *m*/*z* (%) = 457 (4) [M]$^+$, 456 (2) [M]$^+$, 413 (9), 399 (10), 397 (3), 364 (5), 358 (23), 357 (100), 356 (43), 138 (4), 69 (2).

***tert*-Butyl 1-(2-Pyridinyl)-3-[2-(3′,4′-methylenedioxy)biphenyl]-5-pyrazolyl Carbonate (5n)**

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.38–8.36 (m, 1 H), 7.94–7.88 (m, 2 H), 7.82–7.76 (m, 1 H), 7.41–7.31 (m, 3 H), 7.17–7.13 (m, 1 H), 6.78 (m, 3 H), 5.96 (s, 2 H), 5.55 (s, 1 H), 1.51 (s, 9 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 152.3, 151.4, 149.5, 147.6, 147.4, 146.9, 145.1, 140.8, 138.5, 135.4, 131.8, 130.5, 129.2, 128.5, 127.5, 123.1, 121.3, 114.9, 110.3, 108.2, 101.1, 99.8, 84.7, 27.6.

MS (CI$^+$): *m*/*z* (%) = 459 (18), 458 (62) [M]$^+$, 457 (6), 419 (3), 415 (5), 414 (20), 400 (13), 359 (22), 358 (100), 357 (32), 183 (4), 138 (3), 123 (1).

1-(2-Pyridinyl)-3-[2-(3′-phenyl)biphenyl]-5-hydroxypyrazole (6o)

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.10–8.06 (m, 2 H), 7.67 (s, 1 H), 7.56–7.47 (m, 5 H), 7.40–7.26 (m, 9 H), 6.04 (s, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 159.4, 155.7, 147.1, 143.3, 142.3, 142.2, 140.4, 140.4, 138.0, 132.4, 131.9, 130.6, 128.8, 128.1, 127.4, 126.9, 126.3, 119.8, 113.7, 96.6, 90.5.

HRMS (EI): *m*/*z* calcd for $C_{26}H_{19}N_3O$: 389.1528; found: 389.1523.

***tert*-Butyl 1-(2-Pyridinyl)-3-(4-biphenyl)-4-propyl-5-pyrazolyl Carbonate (5p)**

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.40–8.37 (m, 1 H), 8.00 (d, *J* = 8.3 Hz, 1 H), 7.84–7.75 (m, 3 H), 7.70–7.63 (m, 4 H), 7.48–7.43 (m, 2 H), 7.38–7.33 (m, 1 H), 7.17–7.12 (m, 1 H), 2.63 (t, *J* = 7.7 Hz, 2 H), 1.65–1.60 (m, 2 H), 1.57 (s, 9 H), 0.95 (t, *J* = 7.4 Hz, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 152.4, 150.2, 150.0, 147.6, 146.8, 143.6, 140.9, 140.8, 138.4, 132.8, 131.7, 129.3, 128.9, 128.1, 127.4, 127.3, 127.1, 121.1, 114.5, 110.7, 85.2, 27.7.

MS (CI$^+$): *m*/*z* (%) = 457 (10), 456 (33) [M]$^+$, 412 (9), 398 (13), 396 (3), 357 (24), 356 (100), 355 (40), 326 (16).

***tert*-Butyl 1-(2-Pyridinyl)-3-(4-biphenyl)-4-benzyl-5-pyrazolyl Carbonate (5q)**

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.40–8.38 (m, 1 H), 8.05 (d, *J* = 8.3 Hz, 1 H), 7.84–7.78 (m, 1 H), 7.71 (d, *J* = 8.3 Hz, 2 H), 7.62–7.58 (m, 4 H), 7.46–7.41 (m, 2 H), 7.36–7.31 (m, 1 H), 7.27–7.25 (m, 4 H), 7.20–7.15 (m, 2 H), 4.01 (s, 2 H), 1.48 (s, 9 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 152.3, 150.5, 149.5, 147.6, 146.6, 144.3, 141.0, 140.7, 139.5, 138.4, 132.1, 128.8, 128.5, 128.3, 128.1, 127.4, 127.2, 127.0, 126.2, 121.2, 114.5, 108.8, 85.2, 27.4.

MS (CI$^+$): *m*/*z* (%) = 504 (5) [M]$^+$, 447 (5), 446 (16), 405 (28), 404 (100), 403 (38), 356 (9), 326 (4).

***tert*-Butyl 1-[2-(3-Chloro)pyridinyl]-3-[3-(3′,4′-methylenedioxy)biphenyl]-5-pyrazolyl Carbonate (5r)**

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.55–8.53 (m, 1 H), 8.02 (s, 1 H), 7.94 (d, *J* = 8.0 Hz, 1 H), 7.82 (d, *J* = 7.2 Hz, 1 H), 7.48–7.37 (m, 3 H), 7.13–7.10 (m, 2 H), 6.88 (d, *J* = 7.8 Hz, 1 H), 6.70 (s, 1 H), 5.99 (s, 2 H), 1.52 (s, 9 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 152.2, 148.4, 148.1, 147.3, 137.2, 146.8, 141.3, 139.8, 135.5, 133.4, 129.0, 128.9, 127.0, 125.3, 124.6, 124.5, 120.9, 108.6, 107.9, 101.2, 92.5, 85.5, 27.6.

MS (CI$^+$): *m*/*z* (%) = 492 (1) [M]$^+$, 463 (1), 447 (4), 419 (27), 392 (26), 391 (100), 279 (36), 205 (69), 111 (24), 69 (13).

***tert*-Butyl 1-(2-Pyrimidinyl)-3-[4-(3′-phenyl)biphenyl]-5-pyrazolyl Carbonate (5s)**

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.80 (d, *J* = 4.8 Hz, 2 H), 8.03 (d, *J* = 8.5 Hz, 2 H), 7.85–7.84 (m, 1 H), 7.73–7.44 (m, 9 H), 7.40–7.35 (m, 1 H), 7.25–7.21 (m, 1 H), 6.62 (s, 1 H), 1.59 (s, 9 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 158.7, 156.3, 152.5, 149.6, 147.5, 142.0, 141.8, 141.3, 131.4, 129.3, 128.9, 127.5, 127.4, 126.8, 126.5, 126.1, 118.8, 97.4, 85.2, 27.8.

MS (CI$^+$): *m*/*z* (%) = 447 (1), 419 (2), 391 (6), 373 (20), 329 (4), 275 (32), 274 (19), 273 (100), 272 (13), 239 (16), 111 (2), 69 (7).

Boc-Deprotection: 1-(2-Pyridinyl)-3-[4-(3′,4′-methylenedioxy)biphenyl]-5-hydroxypyrazole (6b); Typical Procedure

To a solution of **5b** (286 mg, 0.62 mmol) in CH_2Cl_2 (10 mL), TFA (707 mg, 6.2 mmol) was added. When the reaction was complete (3 h as judged by TLC), the mixture was washed with H_2O (3 × 5 mL), dried over anhydrous $MgSO_4$, and concentrated to dryness. The crude material was purified by column chromatography on silica gel (hexane–EtOAc, 10:1) to afford **6b**.

Yield: 155 mg (70%).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.29–8.27 (m, 1 H), 8.08–8.05 (m, 1 H), 7.93–7.87 (m, 3 H), 7.59–7.55 (m, 2 H), 7.19–7.14 (m, 1 H), 7.12–7.09 (m, 2 H), 6.90–6.88 (m, 1 H), 6.00 (s, 2 H), 5.96 (s, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 157.5, 152.4, 148.3, 147.3, 145.2, 141.1, 140.0, 135.2, 131.7, 127.1, 126.3, 120.7, 120.0, 112.4, 108.7, 108.2, 107.6, 106.7, 101.3, 101.2, 85.9.

HRMS (EI): *m*/*z* calcd for $C_{21}H_{15}N_3O_3$: 357.1113; found: 357.1121.

1-(2-Pyridinyl)-3-(4-biphenyl)-5-hydroxypyrazole (6a)
^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.31–8.28 (m, 1 H), 8.10–8.07 (m, 1 H), 7.96–7.89 (m, 3 H), 7.69–7.63 (m, 4 H), 7.49–7.44 (m, 2 H), 7.39–7.33 (m, 1 H), 7.20–7.16 (m, 1 H), 5.99 (s, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 157.5, 154.6, 152.4, 145.2, 141.4, 140.8, 140.0, 132.1, 129.7, 128.9, 127.5, 127.4, 127.1, 126.3, 120.0, 112.4, 86.07.

HRMS (EI): *m*/*z* calcd for $C_{20}H_{15}N_3O$: 313.1215; found: 313.1218.

1-(2-Pyridinyl)-3-[4-(3′-phenyl)biphenyl]-5-hydroxypyrazole (6c)
^{1}H NMR (300 MHz, $CDCl_3$): δ = 12.84–12.83 (br s, 1 H), 8.30–8.28 (m, 1 H), 8.09–8.06 (m, 1 H), 7.97–7.85 (m, 4 H), 7.73–7.45 (m, 9 H), 7.40–7.36 (m, 1 H), 7.20–7.16 (m, 1 H), 6.00 (s, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 157.4, 154.7, 152.4, 145.2, 142.0, 141.4, 141.3, 140.1, 132.3, 129.3, 128.9, 127.5, 127.5, 127.4, 126.4, 126.1, 120.1, 112.4, 85.9.

HRMS (EI): *m*/*z* calcd for $C_{26}H_{19}N_3O$: 389.1528; found: 389.1533.

1-(2-Pyridinyl)-3-[4-(1-naphthyl)phenyl]-5-hydroxypyrazole (6d)
^{1}H NMR (300 MHz, $CDCl_3$): δ = 12.89 (br s, 1 H), 8.31–8.29 (m, 1 H), 8.10–8.08 (m, 1 H), 8.00–7.86 (m, 6 H), 7.58–7.41 (m, 6 H), 7.21–7.17 (m, 1 H), 6.03 (s, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 157.5, 154.7, 152.6, 145.2, 141.1, 140.1, 140.0, 133.9, 132.2, 131.7, 130.4, 128.4, 127.8, 127.7, 127.0, 126.5, 126.2, 126.1, 125.9, 125.5, 125.2, 120.0, 112.4, 108.7, 85.9.

HRMS (EI): *m*/*z* calcd for $C_{24}H_{17}N_3O$: 363.1372; found: 363.1372.

1-(2-Pyridinyl)-3-[4-(3′-dimethylamino)biphenyl]-5-hydroxypyrazole (6e)
^{1}H NMR (300 MHz, $CDCl_3$): δ = 10.26 (br s, 1 H), 8.31–8.30 (m, 1 H), 8.10–8.07 (m, 1 H), 7.98–7.90 (m, 3 H), 7.75–7.50 (m, 5 H), 7.50–7.49 (m, 1 H), 7.22–7.18 (m, 1 H), 5.99 (s, 1 H), 3.27 (s, 6 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 157.6, 154.4, 151.9, 145.3, 144.4, 143.6, 140.2, 139.1, 133.2, 131.0, 127.8, 127.4, 126.7, 120.2, 118.7, 118.5, 112.5, 86.1, 46.2.

HRMS (EI): *m*/*z* calcd for $C_{22}H_{20}N_4O$: 356.1637; found: 356.1644.

1-(2-Pyridinyl)-3-[4-(4′-benzyloxy)biphenyl]-5-hydroxypyrazole (6f)
^{1}H NMR (300 MHz, $CDCl_3$): δ = 12.85–12.83 (br s, 1 H), 8.30–8.28 (m, 1 H), 8.08–8.05 (m, 1 H), 7.93–7.89 (m, 3 H), 7.63–7.56 (m, 4 H), 7.50–7.29 (m, 5 H), 7.19–7.15 (m, 1 H), 7.08–7.05 (m, 2 H), 5.97 (s, 1 H), 5.12 (s, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 158.6, 157.5, 155.8, 152.5, 145.2, 140.0, 137.1, 133.7, 131.9, 128.7, 128.2, 128.1, 127.6, 126.9, 126.3, 120.0, 116.2, 115.3, 112.4, 84.2, 70.2.

HRMS (EI): *m*/*z* calcd for $C_{27}H_{21}N_3O_2$: 419.1634; found: 419.1635.

1-(2-Pyridinyl)-3-[4-(2′-phenoxy)biphenyl]-5-hydroxypyrazole (6g)
^{1}H NMR (300 MHz, $CDCl_3$): δ = 12.78 (br s, 1 H), 8.26–8.25 (m, 1 H), 8.04–7.83 (m, 4 H), 7.62–7.48 (m, 3 H), 7.33–6.92 (m, 9 H), 5.93 (m, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 157.9, 157.4, 154.9, 153.7, 152.5, 145.2, 140.0, 138.0, 133.6, 132.0, 131.2, 129.7, 129.5, 128.9, 125.7, 124.2, 122.7, 120.4, 120.0, 118.1, 112.4, 85.8.

HRMS (EI): *m*/*z* calcd for $C_{26}H_{19}N_3O_2$: 405.1477; found: 405.1476.

1-(2-Pyridinyl)-3-[3-(4′-bromo)biphenyl]-5-hydroxypyrazole (6h)
^{1}H NMR (300 MHz, $CDCl_3$): δ = 12.85–12.83 (br s, 1 H), 8.30–8.28 (m, 1 H), 8.08–8.06 (m, 2 H), 7.94–7.88 (m, 1 H), 7.84–7.81 (m, 1 H), 7.60–7.46 (m, 6 H), 7.20–7.16 (m, 1 H), 5.99 (s, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 157.5, 154.7, 152.4, 145.3, 140.5, 140.2, 140.1, 133.9, 132.0, 129.2, 129.0, 127.2, 125.3, 124.5, 121.8, 120.1, 112.5, 85.9.

HRMS (EI): *m*/*z* calcd for $C_{20}H_{14}BrN_3O$: 391.0320; found: 391.0294.

1-(2-Pyridinyl)-3-[3-(2′-phenoxy)biphenyl]-5-hydroxypyrazole (6i)
^{1}H NMR (300 MHz, $CDCl_3$): δ = 12.76 (br s, 1 H), 8.27–8.25 (m, 1 H), 8.03–7.77 (m, 4 H), 7.55–6.93 (m, 12 H), 5.86 (s, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 158.1, 157.3, 154.7, 153.6, 152.6, 145.2, 140.0, 138.1, 133.8, 133.0, 131.4, 129.7, 129.5, 128.9, 128.4, 126.9, 124.8, 124.3, 122.6, 120.5, 119.9, 118.1, 112.4, 85.8.

HRMS (EI): *m*/*z* calcd for $C_{26}H_{19}N_3O_2$: 405.1477; found: 405.1475.

1-(2-Pyridinyl)-3-[3-(3′,4′-methylenedioxy)biphenyl]-5-hydroxypyrazole (6j)
^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.30–8.28 (m, 1 H), 8.09 (d, *J* = 8.4 Hz, 1 H), 8.03–8.02 (m, 1 H), 7.94–7.88 (m, 1 H), 7.80–7.76 (m, 1 H), 7.52–7.46 (m, 2 H), 7.20–7.12 (m, 3 H), 6.92–6.89 (m, 1 H), 6.02 (s, 2 H), 5.99 (s, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 157.5, 154.6, 152.6, 148.2, 147.3, 145.2, 141.4, 140.1, 135.6, 133.6, 129.1, 127.2, 124.7, 124.5, 120.9, 120.1, 112.5, 108.7, 107.9, 101.3, 86.0.

HRMS (EI): *m*/*z* calcd for $C_{21}H_{15}N_3O_3$: 357.1113; found: 357.1107.

1-(2-Pyridinyl)-3-[3-(3′-phenyl)biphenyl]-5-hydroxypyrazole (6k)
^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.31–8.28 (m, 1 H), 8.6–8.15 (m, 1 H), 8.10 (d, *J* = 8.4 Hz, 1 H), 7.94–7.84 (m, 3 H), 7.70–7.45 (m, 9 H), 7.41–7.36 (m, 1 H), 7.20–7.16 (m, 1 H), 6.02 (s, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 157.5, 154.6, 152.6, 145.2, 141.9, 141.8, 141.7, 141.3, 140.1, 133.7, 129.3, 129.1, 128.9, 127.6, 127.5, 127.4, 127.2, 126.4, 125.1, 124.8, 120.1, 112.5, 86.0, 29.8.

HRMS (EI): *m*/*z* calcd for $C_{26}H_{19}N_3O$: 389.1528; found: 389.1525.

1-(2-Pyridinyl)-3-[3-(1-naphthyl)phenyl]-5-hydroxypyrazole (6l)
^{1}H NMR (300 MHz, $CDCl_3$): δ = 12.81 (s, 1 H), 8.27–8.25 (m, 1 H), 8.03–8.00 (m, 2 H), 7.95–7.83 (m, 5 H), 7.57–7.40 (m, 6 H), 7.17–7.12 (m, 1 H), 5.97 (s, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 157.4, 154.7, 152.6, 145.2, 141.2, 140.2, 140.0, 133.9, 133.3, 131.8, 130.3, 128.6, 128.3, 127.8, 127.6, 127.0, 126.2, 125.9, 125.5, 124.9, 120.0, 112.4, 85.9.

HRMS (EI): *m*/*z* calcd for $C_{24}H_{17}N_3O$: 363.1372; found: 363.1367.

1-(2-Pyridinyl)-3-[3-(3′-dimethylamino)biphenyl]-5-hydroxypyrazole (6m)
^{1}H NMR (300 MHz, $CDCl_3$): δ = 13.09 (s, 1 H), 8.31–8.29 (m, 1 H), 8.10–8.07 (m, 2 H), 7.95–7.84 (m, 2 H), 7.69–7.44 (m, 6 H), 7.22–7.17 (m, 1 H), 6.00 (s, 1 H), 3.23 (s, 6 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 157.6, 154.5, 152.2, 145.4, 145.3, 143.7, 140.2, 140.1, 133.9, 130.8, 129.4, 127.5, 126.5, 126.0, 124.6, 120.2, 118.1, 117.9, 112.5, 45.4, 86.1.

HRMS (EI): *m*/*z* calcd for $C_{22}H_{20}N_4O$: 356.1637; found: 356.1629.

1-(2-Pyridinyl)-3-[2-(3′,4′-methylenedioxy)biphenyl]-5-hydroxypyrazole (6n)

^{1}H NMR (300 MHz, $CDCl_3$): δ = 12.58 (s, 1 H), 8.26–8.24 (m, 1 H), 7.98–7.95 (m, 1 H), 7.90–7.84 (m, 2 H), 7.42–7.30 (m, 3 H), 7.16–7.12 (m, 1 H), 6.78 (s, 3 H), 5.97 (s, 2 H), 5.05 (s, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 156.0, 154.7, 153.2, 147.3, 146.8, 145.2, 140.9, 140.0, 135.7, 132.3, 130.7, 129.3, 128.4, 127.4, 123.0, 119.9, 112.4, 110.3, 108.1, 101.1, 89.6.

HRMS (EI): *m*/*z* calcd for $C_{21}H_{15}N_3O_3$: 357.1113; found: 357.1105.

1-(2-Pyridinyl)-3-(4-biphenyl)-4-propyl-5-hydroxypyrazole (6p)

^{1}H NMR (300 MHz, $CDCl_3$): δ = 12.55 (s, 1 H), 8.28–8.27 (m, 1 H), 8.03 (d, *J* = 8.3 Hz, 1 H), 7.89–7.79 (m, 3 H), 7.69–7.64 (m, 4 H), 7.46 (m, 2 H), 7.38–7.36 (m, 1 H), 7.16–7.12 (m, 1 H), 2.61–2.55 (m, 2 H), 1.68–1.60 (m, 2 H), 0.97 (t, *J* = 7.1 Hz, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 154.6, 154.2, 152.1, 145.3, 140.9, 139.9, 133.2, 128.9, 128.2, 127.4, 127.3, 127.2, 119.8, 112.3, 100.4, 24.4, 23.1, 14.1.

HRMS (EI): *m*/*z* calcd for $C_{23}H_{21}N_3O$: 355.1685; found: 355.1686.

1-(2-Pyridinyl)-3-(4-biphenyl)-4-benzyl-5-hydroxypyrazole (6q)

^{1}H NMR (300 MHz, $CDCl_3$): δ = 12.61 (br s, 1 H), 8.29–8.27 (m, 1 H), 8.06 (d, *J* = 8.4 Hz, 1 H), 7.92–7.86 (m, 1 H), 7.72 (d, *J* = 8.4 Hz, 2 H), 7.62–7.60 (m, 4 H), 7.46–7.41 (m, 2 H), 7.36–7.25 (m, 5 H), 7.20–7.14 (m, 2 H), 3.97 (s, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 154.7, 154.6, 152.4, 145.3, 141.0, 141.0, 140.8, 140.0, 132.6, 128.9, 128.5, 128.3, 127.5, 127.2, 127.1, 126.0, 120.0, 112.3, 98.6, 29.8, 22.83.

HRMS (EI): *m*/*z* calcd for $C_{27}H_{21}N_3O$: 403.1685; found: 403.1676.

1-[2-(3-Chloro)pyridinyl]-3-[3-(3′,4′-methylenedioxy)biphenyl]-5-hydroxypyrazole (6r)

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.57–8.54 (m, 1 H), 7.93–7.90 (m, 2 H), 7.67–7.57 (m, 2 H), 7.49–7.44 (m, 1 H), 7.38–7.34 (m, 1 H), 7.09–7.05 (m, 2 H), 6.89 (d, *J* = 8.5 Hz, 1 H), 6.00 (s, 2 H), 3.90 (s, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 170.4, 156.0, 148.3, 147.5, 147.0, 141.8, 139.7, 134.6, 131.2, 131.0, 129.4, 128.9, 128.8, 124.9, 124.8, 124.5, 120.9, 108.7, 107.8, 101.4, 38.4.

HRMS (EI): *m*/*z* calcd for $C_{21}H_{14}ClN_3O_3$: 391.0724; found: 391.0720.

1-(2-Pyrimidinyl)-3-[4-(3′-phenyl)biphenyl]-5-hydroxypyrazole (6s)

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.78 (d, *J* = 4.9 Hz, 2 H), 8.01 (d, *J* = 8.3 Hz, 2 H), 7.85–7.83 (m, 1 H), 7.73–7.44 (m, 9 H), 7.39–7.34 (m, 1 H), 7.23–7.22 (m, 1 H), 6.06 (s, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 158.3, 157.4, 157.4, 154.2, 141.9, 141.7, 141.2, 131.5, 129.3, 128.9, 127.5, 127.3, 126.9, 126.4, 126.1, 117.6, 86.7.

HRMS (EI): *m*/*z* calcd for $C_{25}H_{18}N_4O$: 390.1481; found: 390.1488.

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