Palladium-Catalyzed Cross-Coupling Reactions of 2-Pyridylborates with Air-Stable HASPO Preligands

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Abstract: A novel, air-stable TADDOLP(O)H derivative bearing electron-withdrawing substituents allows for efficient Suzuki–Miyaura cross-couplings with challenging electron-deficient 2-pyridylborates as nucleophiles.

Key words: borates, cross-coupling, heteroarenes, palladium, pyridines

Heterobiaryls are ubiquitous in natural products, bioactive compounds and functional materials, and are predominantly prepared by transition-metal catalyzed cross-coupling reactions.[1–3] Particularly, Suzuki–Miyaura reactions have matured into being indispensable tools because of their remarkable tolerance of functional groups, as well as the relatively low toxicity and ready availability of organoboron compounds.[4,5] As a result, various efficient palladium catalysts, which largely rely on the use of electron-rich tertiary phosphines or phosphine mimetics[6,7] as stabilizing ligands, have been developed for this transformation.[5] While these efforts significantly expanded the generality of Suzuki–Miyaura couplings,[8,9] a broadly applicable protocol for high-yielding cross-coupling reactions of electron-deficient 2-substituted, nitrogen-containing[10,11] organoboron compounds has proven, until very recently, elusive. Thus, palladium complexes derived from secondary aryl- or alkyl-substituted phosphine oxides[12–15] and chlorides were elegantly shown to allow for cross-coupling reactions of 2-pyridylborates[16] or 2-pyridyl boronic esters.[17] We previously reported on the application of air-stable, heteroatom-substituted secondary phosphine oxides (HASPO)[18,19] and chlorides as preligands to efficient metal-catalyzed C–C and C–N bond formation reactions.[20] Considering the remarkable pharmacological activities of 2-pyridyl-substituted arenes, we, thus, became interested in exploring the use of our HASPO preligands for palladium-catalyzed cross-couplings of 2-pyridylborates. We report our findings on this subject herein.

At the outset of our studies, we tested various (pre)ligands in the challenging palladium-catalyzed cross-coupling reaction of borate **1a** with electron-rich bromide **2a**. The use of biaryl monophosphines, such as X-Phos (**4**),[21] did not significantly affect the outcome of the reaction (Table 1, entries 1 and 2). However, more promising results were achieved with sterically hindered diamino phosphine oxide **5**[20f] as preligand (entry 3). A comparable efficacy was observed for palladium complexes derived from either unsubstituted TADDOLP(O)H [**6a**; entry 4; TADDOL = 4,5-bis(diphenylhydroxymethyl)-2,2-dimethyl-1,3-dioxolane][20c,22] or analogs **6b**[23] and **6c** bearing electron-releasing groups on their arene rings (entries 5 and 6). Interestingly, the use of HASPO preligand **6d**,[24] which contains electron-deficient aryl-substituents, considerably enhanced the catalytic activity (entry 7). Furthermore, a preligand/palladium ratio of 2:1 (entry 8) combined with the inorganic base K_3PO_4 provided optimal results (entries 7–12). Importantly, the use of simple trisubstituted phosphites, such as **7**, as additives had no beneficial effect on catalytic performance (entry 13), highlighting the unique reactivity profile of HASPO preligands.

With an optimized catalytic system in hand, we explored its scope in Suzuki–Miyaura cross-coupling reactions between 2-pyridylborate **1a** and various aryl bromides **2** (Table 2).[25] Electrophiles **2b–e** with a range of functional groups were converted chemoselectively into the desired products **3b–e** (entries 1–4), as were electron-rich bromides **2f** and **2g** (entries 5 and 6). Furthermore, heteroaromatic electrophiles, such as pyrimidyl bromide **2h**, were well tolerated by the catalytic system (entry 7). However, the sterically more demanding coupling partner **2i** led to a lower yield (entry 8).

Since the catalytic system derived from preligand **6d** proved valuable for cross-coupling reactions of pyridylborate **1a**, we probed its application to the conversion of substituted nucleophiles **1b–d** (Table 3). Notably, various functionalized aryl bromides could be employed as electrophiles for the cross-coupling reactions with borates **1b–d** (entries 1–7). Likewise, heteroaryl bromide **2h** was also found to be a suitable starting material (entries 8, and 9). The protocol was not restricted to the use of electron-deficient electrophiles **2**, but also enabled the conversion of the electron-rich aryl bromide **2a** (entries 10 and 11).

In summary, we have reported on the use of a novel, air-stable HASPO preligand for effective Suzuki–Miyaura cross-coupling reactions of 2-pyridylborates. Thus, an electron-deficient TADDOLP(O)H derivative was found to be broadly applicable to coupling reactions of these challenging nucleophiles.

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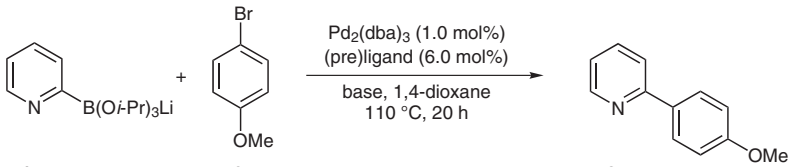
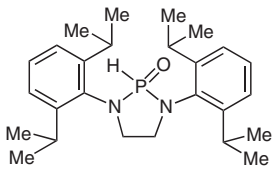
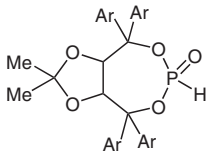
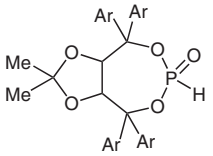
Table 1 Optimization of Palladium-Catalyzed Suzuki–Miyaura Coupling of Borate **1a**[a]

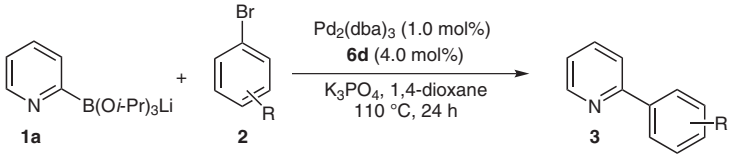


1a **2a** **3a**

Entry	(Pre)Ligand		Base	Yield (%)[b]
1	–	–	K_3PO_4	24
2	X-Phos[c]	**4**	K_3PO_4	24
3		**5**	K_3PO_4	30
4		Ar = Ph: **6a**	K_3PO_4	31
5		Ar = 2-MeC_6H_4: **6b**	K_3PO_4	37
6		Ar = 4-MeC_6H_4: **6c**	K_3PO_4	35
7		Ar = 4-FC_6H_4: **6d**	K_3PO_4	52
8		Ar = 4-FC_6H_4: **6d**	K_3PO_4	64[d]
9		Ar = 4-FC_6H_4: **6d**	Et_3N	<5
10		Ar = 4-FC_6H_4: **6d**	Na_3PO_4	<5
11		Ar = 4-FC_6H_4: **6d**	KOH	19
12		Ar = 4-FC_6H_4: **6d**	Cs_2CO_3	49
13	$P(OPh)_3$	**7**	K_3PO_4	14

[a] Reaction conditions: **1a** (0.75 mmol), **2a** (0.50 mmol), $Pd_2(dba)_3$ (1.0 mol%), (pre)ligand (6.0 mol%), base (1.5 mmol), 1,4-dioxane (2 mL), 110 °C, 20 h.
[b] Yield of isolated product.
[c] X-Phos = 2-dicyclohexyl phosphino-2′,4′,6′-triisopropylbiphenyl.
[d] Preligand **6d** (4.0 mol%).

Table 2 Scope of Suzuki–Miyaura Cross-Coupling Reactions of Borate **1a** with Air-Stable Preligand **6d**[a]



1a **2** **3**

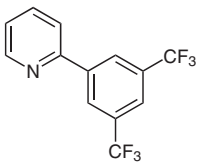
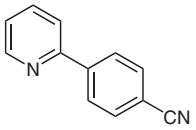
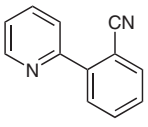
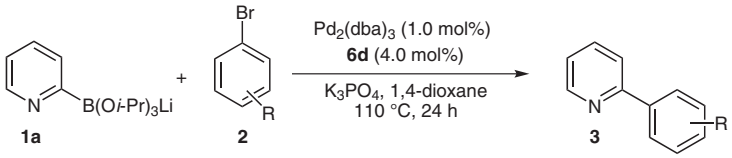
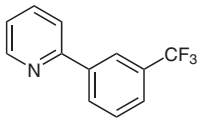
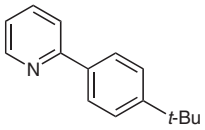
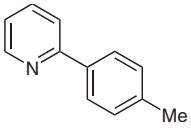
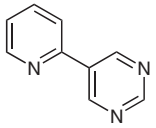
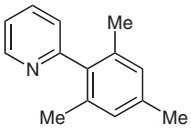
Entry	**2**	**3**	Yield (%)[b]
1	3,5-$(CF_3)_2C_6H_3$ **2b**	 **3b**	78
2	4-NCC_6H_4 **2c**	 **3c**	87
3	2-NCC_6H_4 **2d**	 **3d**	80

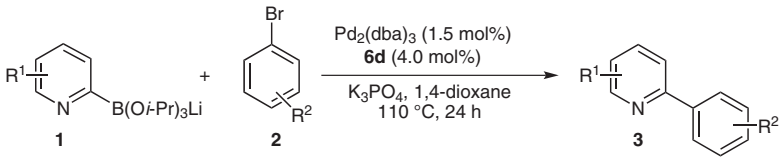
Table 2 Scope of Suzuki–Miyaura Cross-Coupling Reactions of Borate **1a** with Air-Stable Preligand **6d**[a] (continued)



Entry	2	3		Yield (%)[b]
4	3-$(CF_3)C_6H_4$ **2e**		**3e**	69
5	4-*t*-BuC_6H_4 **2f**		**3f**	61
6	4-MeC_6H_4 **2g**		**3g**	65
7	5-$C_4N_2H_3$ **2h**		**3h**	81
8	2,4,6-$Me_3C_6H_2$ **2i**		**3i**	30

[a] Reaction conditions: **1a** (0.75 mmol), **2** (0.50 mmol), $Pd_2(dba)_3$ (1.0 mol%), **6d** (4.0 mol%), K_3PO_4 (1.5 mmol), 1,4-dioxane (2 mL), 110 °C, 24 h.
[b] Yield of isolated product.

Table 3 Preligand **6d** for Palladium-Catalyzed Couplings with Substituted Nucleophiles **1**[a]



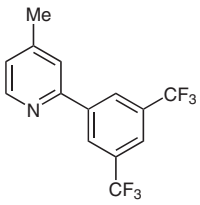
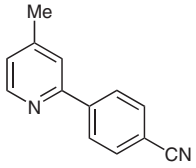
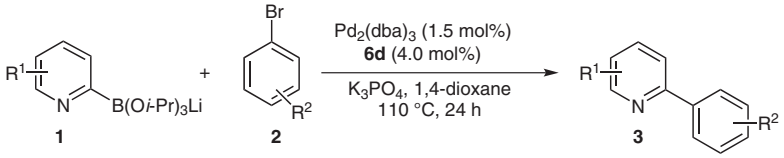
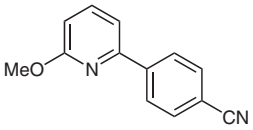
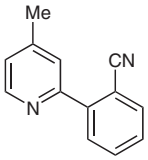
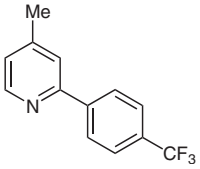
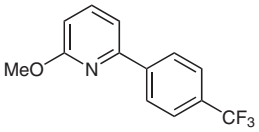
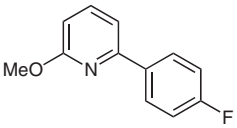
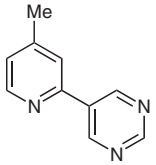
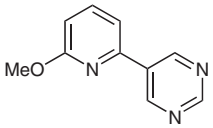
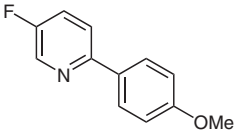
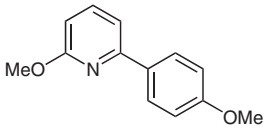
Entry	1	2	3		Yield (%)[b]
1	4-Me **1b**	3,5-$(CF_3)_2C_6H_3$ **2b**		**3j**	67
2	4-Me **1b**	4-NCC_6H_4 **2c**		**3k**	57

Table 3 Preligand **6d** for Palladium-Catalyzed Couplings with Substituted Nucleophiles **1**[a] (continued)



Entry	1	2	3		Yield (%)[b]
3	6-MeO **1c**	4-NCC_6H_4 **2c**		**3l**	64
4	4-Me **1b**	2-NCC_6H_4 **2d**		**3m**	54
5	4-Me **1b**	4-$(CF_3)C_6H_4$ **2j**		**3n**	71
6	6-MeO **1c**	4-$(CF_3)C_6H_4$ **2j**		**3o**	68
7	6-MeO **1c**	4-FC_6H_4 **2k**		**3p**	66
8	4-Me **1b**	5-$C_4N_2H_3$ **2h**		**3q**	63
9	6-MeO **1c**	5-$C_4N_2H_3$ **2h**		**3r**	82
10	5-F **1d**	4-$MeOC_6H_4$ **2a**		**3s**	41
11	6-MeO **1c**	4-$MeOC_6H_4$ **2a**		**3t**	62

[a] Reaction conditions: **1a** (0.75 mmol), **2** (0.50 mmol), $Pd_2(dba)_3$ (1.5 mol%), **6d** (4.0 mol%), K_3PO_4 (1.5 mmol), 1,4-dioxane (2 mL), 110 °C, 24 h.
[b] Yield of isolated product.

Acknowledgment

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(24) Analytical Data for HASPO **6d**: Mp 202.9–203.4 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.67–7.45 (m, 6 H), 7.19–7.15 (m, 2 H), 6.94–6.78 (m, 8 H), 6.89 (d, J_{H-P} = 744 Hz, 1 H), 5.67 (d, J = 8.3 Hz, 1 H), 5.18 (d, J = 8.3 Hz, 1 H), 0.71 (s, 3 H), 0.68 (s, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 162.5 (C_q, $^1J_{F-C}$ = 248 Hz), 162.5 (C_q, $^1J_{F-C}$ = 248 Hz), 162.3 (C_q, $^1J_{F-C}$ = 248 Hz), 162.3 (C_q, $^1J_{F-C}$ = 248 Hz), 139.3 (C_q, $^4J_{F-C}$ = 3 Hz), 139.3 (C_q, $^4J_{F-C}$ = 3 Hz), 138.7 (C_q, $^4J_{F-C}$ = 3 Hz), 134.5 (C_q, $^4J_{F-C}$ = 3 Hz), 130.7 (CH, $^3J_{F-C}$ = 8 Hz), 130.0 (CH, $^3J_{F-C}$ = 8 Hz), 128.6 (CH, $^3J_{F-C}$ = 8 Hz), 128.6 (CH, $^3J_{F-C}$ = 8 Hz), 115.6 (CH, $^2J_{F-C}$ = 21 Hz), 115.4 (CH, $^2J_{F-C}$ = 22 Hz), 114.6 (C_q), 114.5 (CH, $^2J_{F-C}$ = 22 Hz), 114.3 (CH, $^2J_{F-C}$ = 22 Hz), 88.7 (C_q), 87.6 (C_q), 80.0 (CH), 79.5 (CH), 26.8 (CH_3), 26.6 (CH_3). ^{31}P NMR (121 MHz, $CDCl_3$): δ = –2.5. ^{19}F NMR (282 MHz, $CDCl_3$): δ = –112.4 (m), –112.9 (m), –113.9 (m), –114.1 (m). IR (KBr): 3424, 2993, 2903, 2354, 2344, 1601, 1506, 1268, 1161, 1082, 937, 847, 762 cm^{-1}. HR-MS (ESI): *m/z* calcd for $C_{31}H_{24}F_4O_5P$: 583.1303; found: 583.1306.
(25) Synthesis of **3b** (Table 2, entry 1); Typical procedure: A suspension of Pd_2dba_3 (4.6 mg, 0.005 mmol, 1.0 mol%), **6d** (11.7 mg, 0.020 mmol, 4.0 mol%), K_3PO_4 (318 mg, 1.50 mmol), **1a** (205 mg, 0.75 mmol), **2b** (147 mg, 0.50 mmol) in 1,4-dioxane (2.0 mL) was stirred under N_2 for 20 h at 110 °C. After the reaction mixture was cooled to ambient temperature, MTBE (50 mL) and H_2O (50 mL) were added. The separated aqueous phase was extracted with MTBE (3 × 50 mL). The combined organic layers were washed with brine (50 mL), dried over Na_2SO_4 and concentrated in vacuo. The remaining residue was purified by column chromatography on silica gel (*n*-hexane–EtOAc, 9:1) to yield **3b** (114 mg, 78%) as a white solid (mp 45.0 °C). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.75 (dt, J = 4.8, 1.4 Hz, 1 H), 8.48 (s, 2 H), 7.91 (s, 1 H), 7.88–7.77 (m, 2 H), 7.40–7.29 (m, 1 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 154.1 (C_q), 150.1 (CH), 141.3 (C_q), 137.2 (CH), 132.1 (C_q, $^2J_{F-C}$ = 33 Hz), 126.9 (CH, $^3J_{F-C}$ = 4 Hz), 123.6 (CH), 123.4 (C_q, $^1J_{F-C}$ = 273 Hz), 122.3 (CH, $^3J_{F-C}$ = 4 Hz), 120.6 (CH). ^{19}F NMR (282 MHz, $CDCl_3$): δ = –62.9. IR (KBr): 3897, 2927, 1591, 1455, 1382, 1279, 1136, 897, 785, 683 cm^{-1}. MS (EI): *m/z* (%) = 291 (100) [M$^+$], 272 (22), 252 (10), 222 (38), 202 (12), 83 (28), 71 (34), 57 (66), 43 (64). HR-MS (EI): *m/z* calcd for $C_{13}H_7F_6N$: 292.0555; found: 292.0557. The spectral data were in accordance with those reported in the literature.[16]