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Ligand promoted palladium-catalyzed homo-coupling of arylboronic acids

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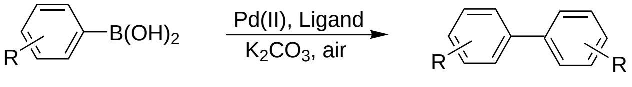
Abstract—Palladium-catalysed homo-coupling of arylboronic acids can be promoted by phosphine or phosphite ligands thereby offering a simple and efficient protocol for the synthesis of symmetrical bi-aryl molecules and their higher homologues. © 2001 Elsevier Science Ltd. All rights reserved.

The palladium-catalyzed Suzuki cross-coupling of aryl halides with organoboronic acids or esters has become one of the most widely investigated and used synthetic methods for C(sp^2)–C(sp^2) bond formation.[1,2] Bi-aryl units and their higher homologues constitute important building blocks in natural products and advanced materials. Most cross-coupling protocols including phosphine ligand promoted and ligandless reaction conditions utilize a large excess of the organoboronic reagents in order to drive the reaction with aryl halides to completion. This is mainly due to undesirable side-reactions of the arylboronic acids which include homo-coupling of the arylboronic acid, cross-coupling of the arylboronic acid with a phenyl group of a triphenylphosphine ligand[3] and decomposition of the arylboronic acids into phenolic compounds under the reaction conditions. As arylboronic acids are easily accessible and stable in air, it is of particular interest to explore the synthetic utility of the homo-coupling of arylboronic acids which may provide a simple and general alternative to the nickel catalyzed homo-coupling reaction,[4] in the preparation of symmetrical bi-aryl molecules and their higher homologues. However, there have only been a few studies in this area so far. Recently, mechanistic aspects of the palladium-catalyzed homo-coupling of arylboronic acids have been proposed.[5] Jackson et al. found that the ligandless palladium acetate (Pd(OAc)$_2$) can catalyze the homo-coupling of arylboronic acids at ambient temperature, but the reaction proceeds rather slowly, and affords only moderate isolated yields.[6]

In the course of synthesizing aryl-substituted calixarene assemblies using a Suzuki cross-coupling protocol, we have observed that the palladium-catalyzed homo-coupling of arylboronic acids can be enhanced by ligands at elevated temperatures. We report herein an investigation of phosphine or phosphite ligand promoted palladium-catalyzed homo-coupling of arylboronic acids (Scheme 1).

The investigation was initially carried out with 4-fluoroboronic acid using ligandless Pd(OAc)$_2$ as the catalyst in the presence of K$_2$CO$_3$ at 60°C, in DMF for 2 h under an air atmosphere to afford 4,4′-difluorobiphenyl in a moderate yield (Table 1, entry 1). In contrast, with tri-*o*-tolylphosphine (P(*o*-tol)$_3$) as the ligand in which Pd(0) species are known to be generated in situ,[7] the homo-coupling reaction proceeded at a faster rate. The homo-coupling can be further and efficiently enhanced if the triphenylphosphine (PPh$_3$) ligand is employed. It is worth mentioning that triethyl phosphite (P(OEt)$_3$) was also found to be a useful ligand in promoting the homo-coupling reaction (entries 2–4). However, it is interesting to find that the catalytic activity of Pd[PPh$_3$]$_4$ was inferior to that of the ligandless Pd(OAc)$_2$ (entry 5). To evaluate further the scope of the phosphine ligand promoted protocol, several reaction parameters based on the PPh$_3$ ligand were investigated. It was found that proper control of the



Scheme 1.

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Table 1. Palladium-catalyzed homo-coupling reaction of arylboronic acids

Entry	Arylboronic acid	Catalyst	Solvent	Temp (°C)	Time (h)	Yield[a] (%)
1	4-F-Ph-B(OH)$_2$	Pd(OAc)$_2$	DMF	60	2	48
2	4-F-Ph-B(OH)$_2$	Pd(OAc)$_2$:2P(*o*-tol)$_3$	DMF	60	2	67
3	4-F-Ph-B(OH)$_2$	Pd(OAc)$_2$:2PPh$_3$	DMF	60	2	79
4	4-F-Ph-B(OH)$_2$	Pd(OAc)$_2$:2P(OEt)$_3$	DMF	60	2	73
5	4-F-Ph-B(OH)$_2$	Pd[PPh$_3$]$_4$	DMF	60	2	27
6	4-F-Ph-B(OH)$_2$	Pd(OAc)$_2$:2PPh$_3$	DMF	25	2	21
7	4-F-Ph-B(OH)$_2$	Pd(OAc)$_2$:2PPh$_3$	DMF	90	1.7	79
8	4-F-Ph-B(OH)$_2$	Pd(OAc)$_2$:2PPh$_3$	DMF	100	2	71
9	4-F-Ph-B(OH)$_2$	Pd(OAc)$_2$:2PPh$_3$	DMF	120	2	55
10	4-F-Ph-B(OH)$_2$	PdCl$_2$:2PPh$_3$	DMF	60	2	65
11	4-F-Ph-B(OH)$_2$	Pd$_2$(dba)$_3$:2PPh$_3$	DMF	60	2	57
12	4-F-Ph-B(OH)$_2$	Pd(OAc)$_2$:2PPh$_3$	DMF	60	2	44[b]
13	4-F-Ph-B(OH)$_2$	Pd(OAc)$_2$:2PPh$_3$	Toluene	60	2	81
14	4-PrS-Ph-B(OH)$_2$	Pd(OAc)$_2$:2PPh$_3$	DMF	60	2	72
15	4-PrS-Ph-B(OH)$_2$	Pd(OAc)$_2$:2PPh$_3$	DMF	90	2	72
16	4-PrS-Ph-B(OH)$_2$	Pd(OAc)$_2$:2PPh$_3$	DMF	120	2	60
17	4-PrS-Ph-B(OH)$_2$	Pd(OAc)$_2$:2PPh$_3$	Toluene	90	2	81
18	Ph-B(OH)$_2$	Pd(OAc)$_2$:2PPh$_3$	DMF	90	2	83
19	3,5-Me$_2$-4-PrO-Ph-B(OH)$_2$	Pd(OAc)$_2$:2PPh$_3$	Toluene	90	2	78
20	3,4-MeO$_2$-Ph-B(OH)$_2$	Pd(OAc)$_2$:2PPh$_3$	DMF	90	2	85
21[c]	3,5-Me$_2$-4-DeO-Ph-Ph-B(OH)$_2$	Pd(OAc)$_2$:2PPh$_3$	Toluene	90	2	66
22	4-Br-Ph-B(OH)$_2$	Pd(OAc)$_2$:2PPh$_3$	DMF	90	4	12

[a] Isolated yield.

[b] Under nitrogen.

[c] De = decyl.

reaction temperature is critical to ensure that the ligand promoted palladium-catalyzed homo-coupling proceeds efficiently. The best temperature range was found to be between 60 and 90°C (entries 3, 6–9). Amongst various commonly employed palladium compounds, Pd(OAc)$_2$ was found to be the most effective catalyst used in this improved protocol (entries 3, 5, 10–11). As was the case with previous findings, oxygen can accelerate the rate of the homo-coupling reaction (entry 12). In addition to the electron withdrawing group substituted arylboronic acids, this improved protocol also works well with phenylboronic and electron rich arylboronic acids which, however, appear to require slightly more vigorous reaction conditions (entries 17–20). On the other hand, the use of the non-polar solvent toluene afforded a slightly better yield than the polar solvent, DMF. In addition to the synthesis of bi-aryl molecules, this protocol can also be applied to the preparation of their higher homologues[8] (entry 21). In the case of the bromide-substituted arylboronic acid (entry 22), the low yield of the homo-product is attributed to the slightly favorable cross-coupling reaction under the reaction conditions employed. This has been verified by an independent competition experiment.

In summary, we have developed a general and efficient phosphine or phosphite ligand promoted palladium-catalyzed homo-coupling of arylboronic acids for the synthesis of symmetrical bi-aryl molecules and their homologues.

Acknowledgements

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8. All products were fully characterized by ^{1}H NMR and MS. General procedure for the homo-coupling reaction of arylboronic acids. To a stirred solution of arylboronic acid (~0.45 mmol), 5 mol% of Pd(OAc)$_2$ and ligand PPh$_3$ (1:2) in 5 mL of DMF (or toluene), was added 2.5 equiv. of K$_2$CO$_3$. After being heated at 60–90°C for 2 h under an air atmosphere, the reaction mixture was cooled to room temperature, quenched with water and then extracted with CH$_2$Cl$_2$ (3×50 mL). The combined organic layers were dried over anhydrous MgSO$_4$ and evaporated to dryness. The crude product was purified

by silica gel column chromography using petroleum ether and CH_2Cl_2 as eluent.

Selected spectroscopic data: product of entry 21: ^1H NMR (400 MHz, $CDCl_3$) δ 7.67 (d, $J = 8.4$ Hz, 4H), 7.62 (d, $J = 8.4$ Hz, 4H), 7.28 (s, 4H), 3.79 (t, $J = 6.4$ Hz, 4H), 2.34 (s, 12H), 1.83–1.79 (m, 4H), 1.56–1.51 (m, 4H), 1.35–1.24 (m, 24H), 0.88 (t, $J = 6.8$ Hz, 6H). MS (FAB) m/z 674.6 (M^+). Mp = 102–103°C.