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Palladium Catalyzed Coupling of Aryl Chlorides with Arylboronic Acids

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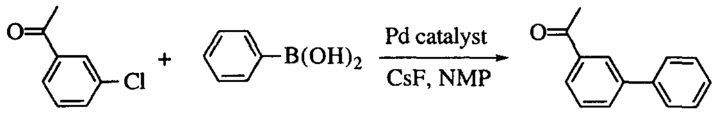
Abstract: Aryl chlorides bearing electron withdrawing groups were successfully coupled with arylboronic acids (Suzuki reaction). Two palladium catalyst ligands, tricyclohexylphosphine (PCy_3) and 1,3-bis(diphenylphosphino)propane (dppp), were found to be superior in catalyzing the reaction.

Palladium-mediated transformations of aryl halides and triflates have found extensive use in organic synthesis.[1] Because much higher energy is required for the oxidative insertion of palladium catalysts into the C—Cl bond of aryl chlorides,[2] transformations of these substrates remains a significant challenge in organic synthesis,[3] and aryl bromides and aryl iodides are therefore far more frequently used. On the other hand, aryl chlorides are inexpensive and readily available from small to bulk quantities, rendering them attractive candidates in small scale and industrial applications.

In this study, couplings of electron deficient aryl chlorides with arylboronic acids, an extension of the Suzuki reaction,[4] were investigated. Prior to this report only limited examples in the literature employed aryl chlorides in Suzuki couplings. Beller and co-workers described the use of a more thermally stable palladacycle catalyst to couple electron-deficient aryl chlorides with phenylboronic acid at a high temperature.[5] Mitchell and co-workers reported efficient coupling of electron-deficient heteroaryl chlorides with 1,4-bis-(diphenylphosphino)butane (dppb) as the ligand.[6]

Existence of electron-withdrawing groups in aryl chlorides is critical to the reaction. Substrates lacking electron-withdrawing substitients fail to react with phenylboronic acid under a variety of conditions. Aryl chlorides with one electron-withdrawing group at the *meta* position were less reactive than those with electron-withdrawing substitients at the *ortho* or *para* positions. A survey of reaction conditions is summarized in Table 1, employing 1-acetyl-3-chlorobenzene as the substrate (Scheme 1).

It is noteworthy that a slight excess of ligand is beneficial for the coupling reaction (entry 3 vs. entry 2, Table 1). When a large excess of ligand (entry 4, Table 1) is used, it is observed that the reaction mixture does not turn black at the end of heating as in all other entries in the same table, and no product is detected. Similar to the reports of palladium-catalyzed carbonylation reactions,[3,7] tricyclohexylphosphine (PCy_3) was found to be the most effective ligand for activation of the aryl chlorides in these Suzuki reactions. This might be explained by the more electron donating nature of PCy_3 compared with triphenylphosphine, which might enhance the oxidative insertion of palladium into the Ar–Cl bond. The increased steric demand of the ligand also might facilitate dissociation of the ligand from the palladium complex.[8]



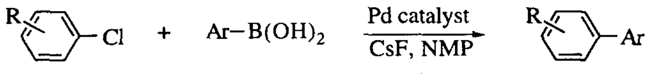
Scheme 1

Table 1. Ligand Effect on Aryl Chloride Couplings.

Entry	Catalyst[a]	Temp (°C)	Time (h)	Ratio (prod/sm[b])
1	5% $Pd(OAc)_2$, 5% dppp	100	10	24/76
2	5% $Pd(OAc)_2$, 5% dppp	120	10	68/32
3	5% $Pd(OAc)_2$, 10% dppp	120	10	94/6
4	5% $Pd(OAc)_2$, 50% dppp	120	10	0/100
5	5% $Pd(PCy_3)_2Cl_2$[c]	100	10	>98/<2
6	5% $Pd(dppf)Cl_2$[c]	100	10	77/33
7	5% $Pd(OAc)_2$, 5% dppb	100	10	10/90
8	5% $Pd(PPh_3)_2Cl_2$[c]	100	10	5/95
9	5% $Pd(OAc)_2$, 10% P(*o*-Tol)$_3$	100	10	48/52
10	5% $Pd(OAc)_2$, 10% $AsPh_3$	100	10	25/75
11	5% $Pd(OAc)_2$, 10% P(2-Furyl)$_3$	100	10	0/100

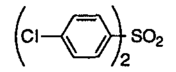
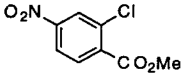
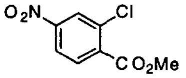
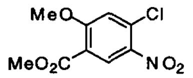
(a). Catalysts and ligands were in mole%; $Pd(OAc)_2$ and the ligand were mixed in the reaction. Abbreviations used: 1,3-bis(diphenylphosphino)propane (dppp), tricyclohexylphophine (PCy_3), 1,1'-bis(diphenylphoshphino)ferrocene (dppf), 1,4-bis(diphenylphosphino)butane (dppb), (b) Ratio was determined by ^1H NMR integration of the crude reaction mixture. (c) Commercially available catalyst.

For aryl chlorides having two strongly electron-withdrawing groups $Pd(PPh_3)_2Cl_2$ is sufficient to catalyze the coupling (entries 19, 20, 21, Table 2). However, for aryl chlorides bearing only one electron-withdrawing group on the aromatic ring the same reaction conditions failed to provide coupled products. Contrary to literature reports in the Heck reaction of aryl chlorides,[3,9] while using $Pd(PPh_3)_2Cl_2$ as the catalyst, either addition of sodium iodide and a nickel co-catalyst[9a] or addition of sodium iodide alone[9b] failed to promote the Suzuki coupling in this study. Finally, it was found that coupling of phenylboronic acid and aryl chlorides with *ortho* or *para* electron-withdrawing substitients was efficiently catalyzed by $Pd(OAc)_2$ and dppp, or by $Pd(PCy_3)_2Cl_2$. Substrates bearing aldehyde groups were an exception (entries 4, 11, Table 2). These results are summarized in Scheme 2 and Table 2.



Scheme 2

Table 2. Suzuki Coupling of Aryl Chlorides and Arylboronic acids.

Entry	R	$ArB(OH)_2$	Catalyst[a]	Temperature (°C)	Time (h)	Yield (%)
1	4–CN	$PhB(OH)_2$	$Pd(OAc)_2$/dppp	100	10	61
2	4–COMe	$PhB(OH)_2$	$Pd(OAc)_2$/dppp	100	10	82
3	4–CO_2Me	$PhB(OH)_2$	$Pd(OAc)_2$/dppp	100	10	82
4	4–CHO	$PhB(OH)_2$	$Pd(OAc)_2$/dppp $Pd(PCy_3)_2Cl_2$	100 100	10 10	48 91
5	4–NO_2	$PhB(OH)_2$	$Pd(OAc)_2$/dppp	100	10	92
6	4–CF_3	$PhB(OH)_2$	$Pd(OAc)_2$/dppp	100	10	96
7		$PhB(OH)_2$	$Pd(OAc)_2$/dppp	100	10	95[d]
8	2–CN	$PhB(OH)_2$	$Pd(OAc)_2$/dppp	100	10	59
9	2–COMe	$PhB(OH)_2$	$Pd(OAc)_2$/dppp	100	10	75
10	2–CO_2Me	$PhB(OH)_2$	$Pd(OAc)_2$/dppp[b]	100	20	58
11	2–CHO	$PhB(OH)_2$	$Pd(OAc)_2$/dppp[b] $Pd(PCy_3)_2Cl_2$	100 100	20 10	42[e] 89
12	2–NO_2	$PhB(OH)_2$	$Pd(OAc)_2$/dppp	100	10	85
13	3–CN	$PhB(OH)_2$	$Pd(OAc)_2$/dppp	100	10	75
14	3–COMe	$PhB(OH)_2$	$Pd(OAc)_2$/dppp[c] $Pd(PCy_3)_2Cl_2$	120 100	10 10	68 91
15	3–CO_2Me	$PhB(OH)_2$	$Pd(OAc)_2$/dppp	100	10	56
16	3–CHO	$PhB(OH)_2$	$Pd(PCy_3)_2Cl_2$	100	10	83
17	3–NO_2	$PhB(OH)_2$	$Pd(OAc)_2$/dppp[c] $Pd(PCy_3)_2Cl_2$	120 100	10 10	46 97
18	*Trans*-3-CH:$CHCO_2Me$	$PhB(OH)_2$	$Pd(PCy_3)_2Cl_2$	100	10	98
19		$PhB(OH)_2$	$Pd(PPh_3)_2Cl_2$[f]	100	6	96[g]
20		*o*–$TolylB(OH)_2$	$Pd(PPh_3)_2Cl_2$[f]	100	12	81[g]
21		3,5–$Cl_2PhB(OH)_2$	$Pd(PPh_3)_2Cl_2$[f]	100	10	77[g]

(a) 5 mol% catalyst was used, except where otherwise noted; $Pd(OAc)_2$ and dppp were combined in the reaction mixture; other catalysts used were commercially available. (b) Additional 5 mol% catalyst was added after 10 h. (c) 10 mol% catalyst was used. (d) 2.4 equivalents of $PhB(OH)_2$ were used, and both chlorides were replaced by phenyl groups. (e) The yield was 62% after recovery of starting material. (f) Tetrakis(triphenylphosphine) also efficiently catalyze these reactions. (g) Reactions were run on multi-gram scale.

The following is a typical experimental procedure. A mixture of methyl *trans*-3-chlorocinnamate (entry 18, Table 2) (393.2 mg, 2 mmol), dichlorobis(tricyclohexylphosphine)palladium(II) (73.8 mg, 0.10 mmol), phenylboronic acid (292.6 mg, 2.4 mmol), and cesium fluoride (607 mg, 4.0 mmol) in 1-methyl-2-pyrrolidinone (NMP, 5 mL) was degassed by purging with nitrogen. The mixture was then heated at 100 °C for 10 hours. The mixture was then partitioned between ethyl acetate (90 mL) and water (20 mL). The organic layer was separated, washed with water, dried, and concentrated. The residue was then purified by column chromatography eluting with 50/50/5 toluene/hexane/ether to give the coupled product (466 mg, 98%).

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