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Palladium-Catalyzed Borylation of Phenyl Bromides and Application in One-Pot Suzuki–Miyaura Biphenyl Synthesis

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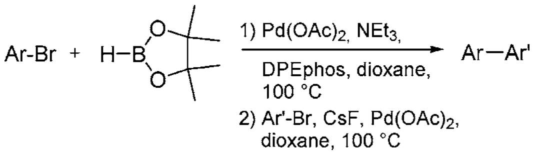
ABSTRACT

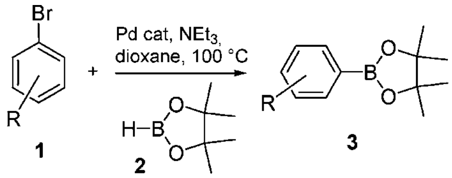


The coupling reaction of pinacolborane with various aryl bromides in the presence of a catalytic amount of $Pd(OAc)_2$ together with DPEphos as ligand and Et_3N as base provided arylboronates. High yields were obtained in the case of electron-donor substituted aryl bromides. The direct preparation of arylboronates allowed the one-pot, two-step synthesis of unsymmetrical biaryls in high yields.

Substituted biphenyls are central components of fine chemicals for a diverse range of applications. In particular, pharmaceuticals and herbicides with biaryl substructures are of general interest.[1] In addition, biaryls are applied as chiral ligands in catalysis, as liquid crystals, or organic conductors.[2] The most common method used for linking the central aryl-aryl bond is the palladium-catalyzed coupling of aryl halides or pseudo halides with arylboronic acids (Suzuki−Miyaura reaction).[3] This method has the advantage over other alternatives in that stoichiometric amounts of heavy metals are not required. Although this method is well-established, improvements are still necessary, especially when electronically deactivated coupling partners are involved.

The arylboronic acids or arylboronates needed for the Suzuki−Miyaura coupling can be synthesized by two principal methods: (1) the transmetalation between arylmagnesium or -lithium intermediates and boron compounds that have good leaving groups such as halogen or alkoxy groups,[4] (2) the more recently developed $PdCl_2(dppf)$-catalyzed borylation of aryl halides with tetra(alkoxy)-

Scheme 1. Arylboronate Synthesis Using Pinacolborane



R = H, *o*-MeO, *m*-MeO, *p*-MeO, *o*-NO_2, *m*-NO_2, *p*-NO_2, *o*-NH_2, *m*-NH_2, *p*-NH_2, *o*-NMe_2, *m*-NMe_2, *p*-NMe_2, *o*-Me, *m*-Me, *p*-Me, 2,4,6-Me, *o*-CN

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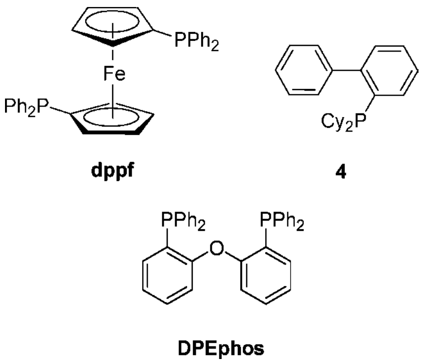


Figure 1. Ligands used for the palladium-catalyzed borylation of aryl halides.

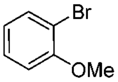
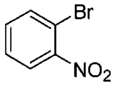
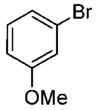
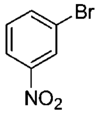
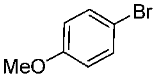
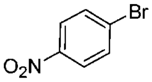
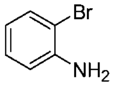
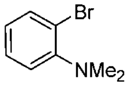
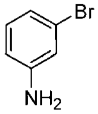
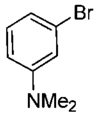
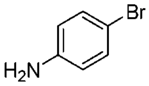
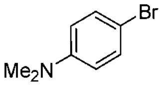
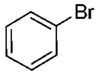
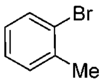
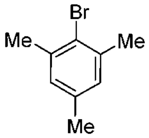
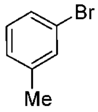
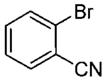
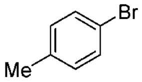
diboron[5] or with dialkoxyboranes such as pinacolborane (Scheme 1).[6] The latter method possesses several advantages. The borylation using pinacolborane is an atom economical manner, tolerating various functional groups, being insensitive to air, moisture, temperature and mostly chromatography stable.[7]

However, there are few examples of the Pd-catalyzed borylation of *ortho*-substituted aryl bromides. Baudoin et al. reported on the improved borylation of sterically hindered aryl halides using the biphenyl ligand **4** (Figure 1) in the presence of $Pd(OAc)_2$ instead of $PdCl_2(dppf)$.[8]

In the course of our investigations on the Suzuki–Miyaura coupling reaction leading potentially to the biphenyl part of Vancomycin as well as Steganacin, we turned our attention toward the use of DPEphos[9] (Figure 1) as ligand in the borylation of phenyl bromides. The advantage of DPEphos toward dppf is its cheaper availability (DPEphos: 7 kEuros/mol vs dppf: 15 kEuros/mol) and its higher air stability compared to ligand **4**.

To investigate the scope and limitations of this ligand, we subjected various phenyl bromides bearing different electron-donating and electron-withdrawing substituents in the *ortho*-,

Table 1. Synthesis of Arylboronates **3** from Phenyl Bromides **1**[a]

entry	bromide **1**	catalyst[b]	time (h)	**3** (%)	entry	bromide **1**	catalyst	time (h)	**3** (%)
1		A	4	78[c]	10		A	20	<3[c]
		B	1	59[8]			B	3	20[8]
2		A	20	27[c]	11		A	20	<1[c]
3		A	4	99[c]	12		A	20	<1[c]
		C	3	77[6]					
4		A	20	39[c]	13		A	20	0
		B		49[8]					
		C		48[6]					
5		A	20	29[c]	14		A	4	63[c]
6		A	20	52[c]	15		A	3	96[c]
							C	2	79[6]
7		A	4	33[c]	16		A	4	84[c]
		C	6	67[6]					
8		A	20	25[c]	17		A	4	70[c]
9		A	20	–	18		A	4	36[c]

[a] Conditions: Et_3N (4.0 equiv), **2** (3.0 equiv), dioxane, 100 °C. [b] A = 5 mol % $Pd(OAc)_2$/10 mol % DPEphos (this work), B = 5mol % $Pd(OAc)_2$/20 mol % **4**, C = 5 mol % $PdCl_2(dppf)$. [c] Isolated yields after flash chromatography.

meta-, and *para*-position of the phenyl ring to the same reaction conditions (Table 1).

We observed a high difference in the yields among phenyl bromides having electron-donating or -withdrawing groups. In previous studies such a strong reactivity difference was never observed.[6b] Although it is known that the presence of powerful electron-withdrawing substituents such as NO_2 induces the reductive dehalogenation of the aryl halide,[10] the yields among aryl halides having electron-donating or -withdrawing groups were not substantially affected by their substituents. In contrast, in our studies we observed very low yields for aryl halides having electron-withdrawing substituents and high yields in the case of electron-donor-substituted ones.

Thus, 2-bromoanisol, 3-bromoanisol, and 4-bromoanisol gave the corresponding boronates in yields of 78%, 27%, and 99%, respectively (Table 1, entries 1−3). The same holds for the NMe_2-substituted phenyl bromides. *N*,*N*-(Dimethylamino)-3-bromoaniline and *N*,*N*-(dimethylamino)-4-bromoaniline afforded the *m*- and *p*-phenyl boronates in 63% and 96% yield, respectively (Table 1, entries 14 and 15). In both cases the strong electron-donor capacity (+M-effect) of the substituent (OMe and NMe_2), being only effective in the *ortho*- and *para*-position, leads to the high yields with these derivatives. In contrast, only low yields were obtained for the unactivated *meta*-substituted phenyl bromides. As a result of the strong steric hindrance in the case of *N*,*N*-(dimethylamino)-2-bromoaniline, no borylation can be observed in this case (Table 1, entry 13).

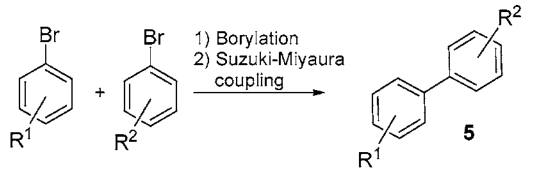
Next we studied the borylation of Me-substituted phenyl bromides. As expected, the Me-group as an inductive electron-donor substituent (+I-effect) activates strongly the *ortho*- and to a small extent the *meta*-substituted phenyl bromide. Both 2- and 3-bromotoluene afforded the corresponding boronates in 84% and 70% yield, respectively (Table 1, entries 16 and 17). The *para*-substituted derivative, 4-bromotoluene, being not activated, is formed in a poor yield of 36% (Table 1, entry 18). This result can be compared to the borylation of the unsubstituted bromobenzene (Table 1, entry 7, 33%).

With phenyl bromides bearing electron-withdrawing substituents such as bromonitrobenzene or bromobenzonitrile (Table 1, entries 9−12), little or no pinacolboronate was obtained, in accordance with literature observations.[6]

It should be noted that the yields using DPEphos are significantly higher in the case of phenyl bromides with electron-donating substituents compared to previous results using the more expensive dppf ligand or the biphenyl ligand **4** (see Table 1, entries 1, 3, and 15). Contrarily, dppf gave higher yields in the case of the unsubstituted bromobenzene (Table 1, entry 7). The borylation of a sterically hindered phenyl bromide, mesityl bromide, afforded with DPEphos the corresponding mesityl pinacolboronate in a yield of 25% (Table 1, entry 8). In contrast, Baudoin showed that the analogous 2,6-dimethylbromobenzene could be converted into the corresponding boronate using the ligand **4** in a yield of 51%.[8] The same borylation using dppf as ligand gave only very poor yields (<5%) of boronate.[8] Thus, the borylation of sterically hindered bromides works particularly well with higher yields and under milder conditions with the ligand **4**, as shown by Baudoin.

With these results in hand, we thought that this methodology could be extended to the synthesis of unsymmetrically substituted biphenyls via a one-pot, two-step Suzuki−Miyaura cross-coupling reaction. This was indeed achieved by adding after completion of the borylation step the needed ingredients in the same reaction flask (Table 2).

Table 2. One-Pot, Two-Step Synthesis of Biphenyls **5**[a]



5a : R^1 = *p*-NMe_2, R^2 = *o*-Me
5b : R^1 = *p*-NMe_2, R^2 = *p*-Me
5c : R^1 = *p*-NMe_2, R^2 = *o*-CN
5d : R^1 = *p*-NMe_2, R^2 = *p*-CN
5e : R^1 = *p*-NMe_2, R^2 = *o*-NO_2
5f : R^1 = *p*-NMe_2, R^2 = *p*-NO_2
5g : R^1 = *p*-OMe, R^2 = *p*-CN

entry	product	yield (%)
1	**5a**	62
2	**5b**	72
3	**5c**	51
4	**5d**	73
5	**5e**	58
6	**5f**	90
7	**5g**	80

[a] Conditions: (1) Et_3N (3.0 equiv), **2** (2.0 equiv), $Pd(OAc)_2$ (5 mol %), dioxane, 100 °C, 3 h; (2) bromide (1.0 equiv), $Pd(OAc)_2$ (5 mol %), CsF (8 equiv), dioxane, 100 °C, 20 h.

Thus, the borylation of 4-bromo-*N*,*N*-dimethylaniline in the above conditions (100 °C, 3 h) was followed by addition of excess CsF (8 equiv), $Pd(OAc)_2$ (5 mol %), and the second aryl bromide (2-bromotoluene, 4-bromotoluene, 2-bromobenzonitrile, 4-bromobenzonitrile, 2-bromonitrobenzene, and 4-bromonitrobenzene, respectively). The corresponding biphenyls were obtained in high yields (Table 2). Similarly, 4-bromoanisole was cross-coupled with 4-bromobenzonitrile.

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In conclusion, we reported the borylation of various unactivated and sterically hindered phenyl bromides, using the cheap and oxidatively stable phosphine ligand DPEphos. These findings were extended to the one-pot, two-step Suzuki−Miyaura reaction with different phenyl bromides, yielding dissymmetrically substituted biphenyls in a simple, rapid, and efficient manner.

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Supporting Information Available: Experimental procedures and details of compound characterization. This material is available free of charge via the Internet at http://pubs.acs.org.

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