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Pd(DIPHOS)$_2$-Catalyzed Cross-Coupling Reactions of Organoborons with Free or Polymer-Bound Aryl Halides[†]

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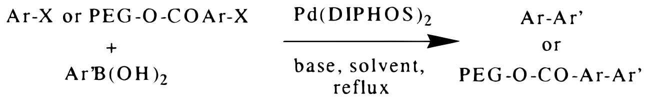
ABSTRACT



Bis[1,2-bis(diphenylphosphino)ethane]palladium(0) [Pd(DIPHOS)$_2$] catalyzes cross-coupling reactions of free or polymer-bound aryl halides with organoboron compounds to produce biaryls in overall yields of 60–96%.

Palladium-catalyzed Suzuki cross-couplings are important strategies for organic synthesis.[1,2] These coupling reactions offer a powerful tool for the formation of C−C bonds. In the past few years a number of methods have been developed which permit the use of organoboron compounds that are thermally stable and inert to water and oxygen.[2b] Further, these coupling reactions have been used successfully for the synthesis of natural products,[3a,b] pharmaceutical intermediates,[3c] and combinatorial libraries of organic compounds.[4] Suzuki couplings likely follow a catalytic cycle, which is initiated by the oxidative addition of organic halides to the Pd species and followed by transmetalation of the Ar group from boron to Pd.[2d,e] After transmetalation, the reaction proceeds smoothly when it has been activated by a suitable base.

Despite the broad synthetic utility of Pd(PPh$_3$)$_4$ in cross-coupling reactions, it is air and light sensitive and often forms a number of byproducts in these reactions.[5] Thus, a wide range of Pd catalysts has been employed for the synthesis of biaryls including Pd(OAc)$_2$ plus PPh$_3$ which is reported to be rapidly reduced to Pd(0) complexes with phosphines in situ.[2d,6]

As part of our research we were interested in a simple, straightforward, and reliable method for cross-coupling reactions. Herein we report the Pd(DIPHOS)$_2$-catalyzed coupling of aryl halides with organoboron compounds.

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(8) Abbreviations: Pd(PPh$_3$)$_4$ {(tetrakistriphenylphosphine)palladium}; Pd(DIPHOS)$_2$ {bis[1,2-bis(diphenylphosphino)ethane]palladium}; Pd$_2$(dba)$_3$ {(dibenzylideneacetone)dipalladium}; PdCl$_2$(dppf) {[1,1′-bis(diphenylphosphino)ferrocene]palladium dichloride}; PdCl$_2$(PPh$_3$)$_2$ {bis(triphenyl-phosphine)palladium dichloride}.

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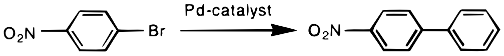
Pd(DIPHOS)$_2$ has been known in the literature and is available commercially. However, the use of this catalyst for organic synthesis has been limited,[7,8] and to our knowledge little is known about its use for the coupling of organoborons with aryl halides (Scheme 1). We began these studies by examining the effects of various Pd catalysts on the coupling of 1-bromo-4-nitrobenzene with phenylboronic acid (Table 1). Pd(DIPHOS)$_2$ catalyzed the coupling reaction and produced 4-nitrobiphenyl in 90% yield (Table 1). In contrast, in our laboratory, traditional Pd catalysts such as Pd(PPh$_3$)$_4$,[9] Pd$_2$(dba)$_3$,[10] Pd(OAc)$_2$ plus PPh$_3$,[2b] PdCl$_2$(dppf),[11] and PdCl$_2$(PPh$_3$)$_2$[2b] produced the desired products in only 45−70% yield. The reduced yield of products from reactions in which Pd complexes were used with PPh$_3$ ligands was likely due to undesired side reactions between phenylboronic acid and PPh$_3$.[5,11b] Furthermore, the presence or absence of an inert atmosphere (N$_2$) had little effect on the catalytic activity of Pd(DIPHOS)$_2$ (entries 3 and 4, Table 1). This is an advantage for the industrial use of this coupling reaction with organoborons and aryl halides. Although coupling

Scheme 1. Pd(DIPHOS)$_2$-Catalyzed Couplings of Organoborons with Aryl Halides

$$\text{Ar-X} + \text{Ar'B(OH)}_2 \xrightarrow[\text{base, solvent, reflux}]{\text{Pd(DIPHOS)}_2} \text{Ar-Ar'}$$

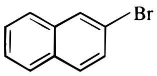
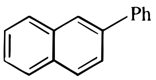
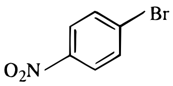
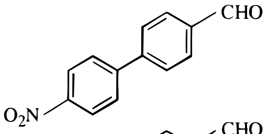
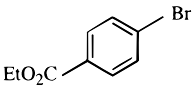
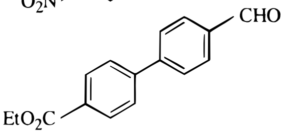
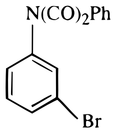
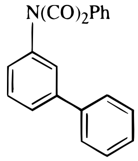
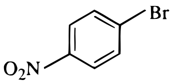
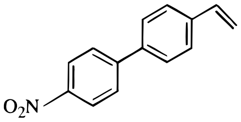
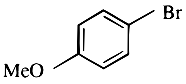
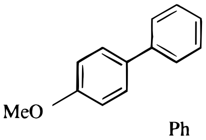
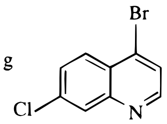
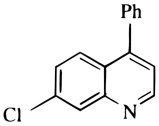
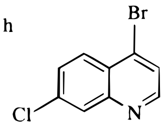
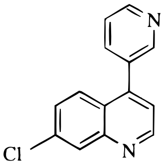
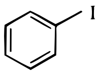
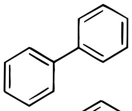
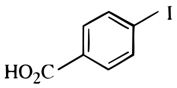
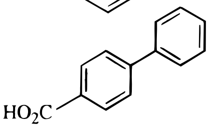
Table 1. Efficiency of Various Pd Catalysts on the Formation of 4-Nitrobiphenyl in THF−MeOH[a]



entry	catalyst	mol %[b]	time (h)	yield (%)
1	Pd(PPh$_3$)$_4$	1.03	12	65
2	Pd(OAc)$_2$ + PPh$_3$	2.20	6	47
3	Pd(DIPHOS)$_2$	1.32	2	90
4	Pd(DIPHOS)$_2$[c]	1.32	3	92
5	PdCl$_2$(dppf)	1.70	5	45
6	Pd$_2$(dba)$_3$	1.31	2	70
7	PdCl$_2$(PPh$_3$)$_2$	1.42	6	66

[a] Reactions were carried out in 10 mL of THF−MeOH under reflux for specified hours with palladium catalyst, 2 M aqueous K$_2$CO$_3$, 1-bromo-4-nitrobenzene (1 mmol), and phenylboronic acid (1 mmol). [b] mol % of palladium catalyst. [c] Reaction was carried out in air; all other reactions were carried out in an N$_2$ atmosphere.

Table 2. Pd(DIPHOS)$_2$-Catalyzed Coupling Reactions of Organoborons with Aryl Halides

entry (1)	aryl halides	boron reagents[a]	product (2)	yield (%)[b]
a		A		95
b		B		65
c		B		60
d		A		90
e		C		85
f		A		60
g		A		80
h		D		70
i		A		96
j		A		93

[a] A = PhB(OH)$_2$; B = (4-CHO)-PhB(OH)$_2$; C = (4-CH$_2$CH)-PhB(OH)$_2$; D = 3-Et$_2$B−pyridine. [b] Isolated yield.

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(12) **Typical procedure:** A mixture of aryl bromides (1 mmol) and Pd(DIPHOS)$_2$ (12 mg, 0.01 mmol) in THF was stirred at rt for 20 min before the addition of a solution of the appropriate arylboron compound in THF−MeOH or DMF. After 10 min of stirring, an appropriate base [2 M aqueous K$_2$CO$_3$ (2.4 mmol), or Et$_3$N (3 mmol), or K$_2$CO$_3$ (2 mmol)] was added with stirring. The reaction mixture was then heated to reflux for 2−12 h. Thereafter, the reaction was cooled before the addition of EtOAc (10 mL). The reaction mixture was then passed through a pad of Hyflo Super Cel and washed with EtOAc, and the combined filtrate was evaporated to dryness. After the residue was dissolved in water and extracted with EtOAc, the organic layer was dried over anhydrous Na$_2$SO$_4$, concentrated, and purified by recrystallization (Et$_2$O or Et$_2$O−CH$_2$Cl$_2$) or by being passed through a short column of silica gel (5−10% EtOAc−petroleum ether) to obtain the desired product in 60−96% yield.

proceeded slowly at ambient temperature, the reaction proceeded relatively rapidly under reflux.

A variety of aryl halides (**1a**−**j**) and organoboron compounds (A−D) were studied (Table 2).[12] In the presence of Pd(DIPHOS)$_2$ (1.0 mol %) and aqueous K_2CO_3 (2.0 M), 2-bromonaphthalene (**1a**) was reacted with phenylboronic acid (A) in THF−MeOH (4:1) under reflux for 4 h. Following the reaction, product **2a** was isolated in 95% yield after recrystallization from ether. Polar solvents such as DMF and THF−MeOH and bases such as K_2CO_3 and Et_3N were suitable for Pd(DIPHOS)$_2$ cross-coupling reactions (Table 3). In addition, Pd(DIPHOS)$_2$ was sufficiently stable that short exposures to air during handling had no detectable effects on its activity as a catalyst. The structural assignments of **2a**−**j** were based on ^{1}H and ^{13}C NMR and MS.[13−15] 2D NMR experiments further confirmed the structure of **2e**. The results in Table 2 suggest that biaryls with a variety of functional groups can be synthesized readily using this strategy. In contrast, our attempts to cross-couple aryl bromides with aliphatic boron derivatives such as *n*-butylboronic acid were unsuccessful. Although the mechanism responsible for these reactions is not yet understood, the bidentate phosphine ligand likely facilitates coordination with aromatic groups.

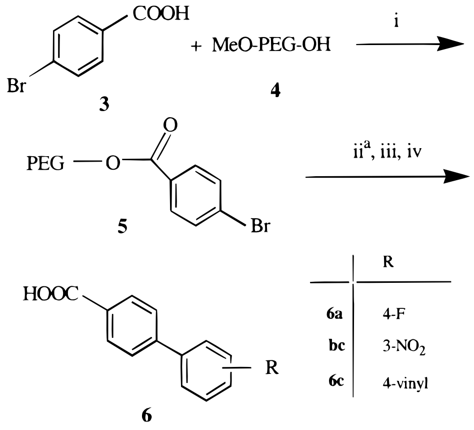
Table 3. Reaction Conditions of Pd(DIPHOS)$_2$-Catalyzed Coupling Reactions[a]

product[b]	solvent	base	hours
2a	THF−MeOH[c]	aqueous K_2CO_3[d]	4
2b	THF−MeOH	aqueous K_2CO_3	5
2c	THF−MeOH	Et_3N	10
2d	DMF[e]	K_2CO_3[f]	2
2e	THF−MeOH	aqueous K_2CO_3	5
2f	THF−MeOH	aqueous K_2CO_3	10
2g	THF−MeOH	aqueous K_2CO_3	4
2h	THF−MeOH	aqueous K_2CO_3	12
2i	THF−MeOH	aqueous K_2CO_3	4
2j	THF−MeOH	aqueous K_2CO_3	3

[a] Reactions were carried out on a 1−2 mmol scale of aryl halides. [b] 1−2 mol % of Pd(DIPHOS)$_2$ was used as catalyst. [c] THF−MeOH (4:1). [d] 2 M aqueous K_2CO_3. [e] DMF (75 °C). [f] K_2CO_3 powder.

The potential scope of Pd(DIPHOS)$_2$-promoted cross-coupling is not limited to the above reactions. We also synthesized several biaryl carboxylic acids using polymer-bound aryl bromides with aryl boronic acids (Scheme 2).

Scheme 2. Poly(ethylene glycol)-Supported Liquid-Phase Synthesis of Biaryl Carboxylic Acids



i) $EtN{=}C{=}N(CH_2)_3NMe_2$, HOBt, Et_3N, CH_2Cl_2, rt, 20h; ii) $RC_6H_4B(OH)_2$, K_2CO_3, DMF, 70-80 °C, 3-4h; iii) 1N NaOH, 90 °C, 1h; iv) 12N HCl. [a]Reaction conditions were not optimized.

The starting material MeO-PEG-OH is commercially available and soluble in CH_2Cl_2, $CHCl_3$, or DMF but is insoluble in ether, 2-propanol, or absolute ethanol.[16,17]

4-Bromobenzoic acid (**3**) was reacted with MeO-PEG-OH (M_n ∼5000) (**4**) in the presence of *N*-ethyl-*N*′-dimethylaminopropylcarbodiimide hydrochloride (EDAC), DMAP, HOBT, and Et_3N in CH_2Cl_2 at rt for 20 h. The product was isolated by precipitation using Et_2O−2-propanol (5:1) at 0−5 °C in ∼95% yield.[18] The structure of the polymer-bound product (**5**) was confirmed by ^{1}H NMR, and no detectable starting material was found in the product. In general, coupling reactions were performed in DMF with K_2CO_3 and heating at 70−80 °C for 3−4 h. In the preliminary studies, we used three aryl boronic acids [**6a**−**c**, Scheme 2]. After isolation of the intermediates, the desired products were obtained by saponification with 1 N NaOH, followed by neutralization with 12 N HCl (yield 55−60%).

In conclusion, Pd(DIPHOS)$_2$ promotes the coupling of either free or polymer-bound aryl halides with organoboron compounds in good to excellent yield. Additional studies to delineate the mechanism and further use of this catalyst in carbon−carbon bond formation are in progress.

Acknowledgment. The National Institute of Allergy and Infectious Diseases (AI 25136, D.J.K.) and the Burroughs-

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(18) **Typical procedure:** A mixture of MeO-PEG-OH (6.0 g, 1.2 mmol), 4-bromobenzoic acid (0.36 g, 1.8 mmol), *N*-ethyl-*N*′-dimethylaminopropylcarbodiimide hydrochloride (300 mg), HOBt (100 mg), and Et_3N (0.2 mL) in CH_2Cl_2 (20 mL) was stirred at rt for 20 h. The reaction was quenched by the addition of 2-propanol (50 mL), followed by Et_2O (100 mL). After the reaction mixture was cooled at 0 °C for 2 h, the precipitated **5** was filtered, washed with Et_2O, and dried under vacuum overnight. Compound **5** (1.5 g) was then dissolved in DMF and degassed by passing N_2 through the reaction mixture before Pd(DIPHOS)$_2$ (20 mg, 0.019 mmol) was added with stirring for 20 min. Thereafter, aryl boronic acid (0.60 mmol) and K_2CO_3 (100 mg, 0.7 mmol) were added sequentially. The reaction mixture was then heated at 70−80 °C for 3−4 h. After cooling, Et_2O was added and the precipitated solid was filtered, washed with Et_2O, and dried under vacuum. The solid was then dissolved in 1 N NaOH and heated at 90 °C for 1 h. After cooling, the reaction mixture was neutralized with concentrated HCl and extracted with EtOAc. The organic layer was washed with water and dried over anhydrous Na_2SO_4, and solvent was evaporated. The desired product was recrystallized from Et_2O.

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Supporting Information Available: Characterization data for compounds are listed in Tables 1 and 2. This material is available free of charge via the Internet at http://pubs.acs.org.

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