Palladium-Catalyzed Homocoupling of Arylboronic Acids and Esters Using Fluoride in Aqueous Solvents

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Abstract: Homocoupling of both arylboronic acids and esters has been found to proceed using catalytic amounts of Pd^{II} and stoichiometric amounts of TBAF under air atmosphere at room temperature, offering a mild and efficient protocol for the synthesis of symmetrical biaryls via $C(sp^2)$ – $C(sp^2)$ bond formation. Aryl boronic acids bearing bromide substitution form polyphenylenes.

Key words: boronic acids, palladium, fluoride, biaryls, water

Palladium-catalyzed carbon-carbon bond forming reactions such as the Suzuki-Miyaura cross-coupling of organic halides with organoboron compounds¹ have been widely used in the synthesis of building blocks for active pharmaceutical components and natural products,² polymers and electronic materials,³ liquid crystals⁴ and catalysts.⁵ Several other methods used for the homocoupling of organoboron compounds predate the palladium processes, including nickel-mediated reactions.⁶ The application of Pd catalysis to the production of symmetrical products from aryl or vinylboronic compounds has recently been advanced by reports of: (a) new phosphorus ligands to promote homocoupling;⁷ (b) dimerization of arylboronic acids using catalytic Pd^{II} under an oxygen atmosphere with water as solvent;⁸ (c) similar dimerization initiated by transmetallation of palladium enolates;⁹ (d) the unexpected dimerization of an aryl bromide during Pd-catalyzed borylation under base-free conditions, presumably via Suzuki coupling of the desired boronic ester with the bromide;¹⁰ (e) base-free oxidative homocoupling of arylboronic esters with catalytic amounts of Pd-dppp [dppp = 1,3-*bis*(diphenylphophino)propane] complexes under O₂ in DMSO at 80 °C;¹¹ and (f) radical coupling mediated by manganese(III) acetate.¹²

Most of these transformations require long reaction times (>20 h), polar solvents (DMSO, DMF, NMP), base (Na₂CO₃, K₂CO₃, NaOH), or elevated temperatures. Here we report the discovery of mild and convenient conditions for the homocoupling of arylboronic acids or esters with simple Pd(II) catalysts, featuring the use of $(n-Bu)_4$ NF (TBAF) in 4:1 THF–H₂O as solvent at room temperature in air (Scheme 1). To the best of our knowledge, fluoride

SYNLETT 2004, No. 13, pp 2351–2354 Advanced online publication: 24.09.2004 DOI: 10.1055/s-2004-832845; Art ID: S03504ST © Georg Thieme Verlag Stuttgart · New York salts have only been used thus far in the cross-coupling of arylboronic acids and aryl halides.¹³

Omission of either Pd or TBAF prevents any conversion of starting material, and a stoichiometric amount of TBAF was found to be essential for complete conversion. Very little conversion (a few percent yield) was observed after several days when the reaction was performed in dry THF or under a nitrogen atmosphere, in the presence of either catalytic or stoichiometric amounts of Pd(PPh₃)₂Cl₂, but introduction of a stoichiometric amount of Cu^{II} as an oxidant under inert atmosphere restored full catalytic activity. An extensive survey established the optimal pH of the aqueous component of the solvent mixture to be 7.0–9.5, with the reaction being completely suppressed at pH < 5.0. Other tetrabutylammonium halides (chloride, bromide, and iodide) were ineffective, and only CsF was found to work as well as TBAF from a collection of fluoride salts (ammonium, barium, calcium, lead, magnesium, sodium and thulium). As source of palladium, $Pd(PPh_3)_2Cl_2$ showed the best results. Table 1 outlines the results obtained with a variety of both arylboronic acids and arylboronic esters under a standard set of conditions. Alkylboronic derivatives were found to be unreactive, showing decomposition rather than coupling after extended periods.

 $Ar-[B] \xrightarrow{Pd(PPh_3)_2Cl_2 (10 \text{ mol}\%)}_{Har} Ar-Ar$ $Bl_4NF H_2O (1.0 \text{ equiv})_{Har} Ar-Ar$ $FHF/H_2O (4:1), \text{ air, r.t.}$ [B] = boronic acid, boronic ester

Scheme 1

As shown in Table 1, both arylboronic acids and arylboronic esters gave the corresponding biaryls in good yields, along with small amounts (5-10%) of the corresponding phenols. The base-free nature of the process allowed the sensitive methyl ester to be used without difficulty (entry 9). Bromoarylboronic acids formed oligo- or polyphenylenes (entries 10-12),¹⁴ which could offer a very easy route to interesting polymeric materials.

Equimolar mixtures of phenylboronic acid and *n*-butylacrylate or allylbenzene provided both biphenyl and cinnamate compounds (plus small amounts of unidentified by-products), reflecting the presence of a competing Heck-type coupling pathway (Scheme 2).¹⁵ Similarly, Suzuki-type reactivity was observed from mixtures of arylboronic acids and aryl iodides, providing nearly equimolar amounts of homocoupled and cross-coupled products (Scheme 2). The use of arylboronic acids bearing silyl, carboxylic acid, aldehyde or hydroxyl substituents gave mixtures of products that were troublesome to isolate and identify. In the case of hydroxyl groups, the formation of some polymeric material was also observed.



Scheme 2 (a) $Pd(PPh_3)_2Cl_2$ (10 mol%), $Bu_4NF \cdot H_2O$ (1.0 equiv), THF-H₂O (4:1) air, r.t., 8 h. Ar = (*p*-OMe)C_6H_4.

Entry	Boronic acid/ester	Time (h)	Product ^a	Yield (%) ^b
1	PhB(OH) ₂	9	Ph-Ph	77
2		9	Ph-Ph	74
3	CH ₃ OH B OH	10	H ₃ C CH ₃	72
4	H ₃ C-C-BC	9	H ₃ C-CH ₃	81
5	H ₃ C-	9	H ₃ C-CH ₃	85
6	O ₂ N OH OH	12	O ₂ N NO ₂	59
7	СН ОН ОН	10		76
8		12		73
9	MeO ₂ C-C-BOH	8	MeO ₂ C	67
10 ^c	Br-C-B,OH OH	12	HO B HO' B-Br	-
11°		12	HQ HO HO Br	_
12 ^d	Br-OCH ₃ B-OH HO	12	OH HO ^{-B} MeO OMe n	-

 Table 1
 Results of the Palladium-Catalyzed Homocoupling of Arylboronic Acids and Esters

^a In most cases, a small amount (ca. 8%) of the corresponding phenol was also obtained.

^b Isolated yields of pure compounds after column chromatography.

^d The oligomer obtained was soluble in THF. MALDI analysis showed the maximum value of n as 12.

^c The polymer obtained was insoluble in all solvents tested, making unambiguous characterization difficult. Approximately 70 mg polymer was isolated from 200 mg of starting material.

It is unusual for Pd-catalyzed coupling reactions to occur without the oxidative addition of an organic electrophile. A simple mechanism is proposed (Scheme 3), requiring two aryl-for-halide ligand exchange steps followed by reductive elimination and regeneration of Pd^{II} by oxygen. Both fluoride and water¹⁶ are necessary for reactivity to occur under the mild conditions described here, and the optimal pH range for the reaction spans the pK_a values of arylboronic acids and esters.¹⁷ We therefore suspect that both fluoride and hydroxide¹⁸ boronate complexes are active nucleophiles in charging the Pd^{II} center; their order of addition, if it is ordered, is not known. The observation of mixed coupling products from a sequential reaction of arylboronic esters with stoichiometric amounts of Pd precursor (Scheme 4) shows that charging of the metal center with the first aryl fragment is either incomplete or reversible under these conditions (otherwise, the mixed biaryl product would have been formed selectively). The use of ArBF₂ or ArBF₃⁻K⁺ under the above conditions gave no reaction,¹⁹ suggesting that boron does not play a Lewis acidic role and that the ate complex intermediates must possess a minimum level of nucleophilicity.



Phenolic or polyether byproducts are proposed to arise by air oxidation of Pd^0 in the presence of water, giving hydroperoxide complexes and free hydrogen peroxide, which can oxidize arylboronic acids to phenols. In support of this hypothesis are the observations that hydrogen peroxide was detected by a standard Amplex Red-horseradish peroxidase assay (Molecular Probes. Inc.) at roughly the same concentration as that of Pd catalyst at the completion of boronic acid coupling reactions in air, and that the use of Cu^{II} as oxidant under a nitrogen atmosphere completely suppressed the formation of oxygenated byproducts. Olefinic or halide components can become incorporated through well-established mechanisms at the Pd⁰ stage, suggesting that such alternative pathways can be suppressed if oxidation of Pd⁰ to Pd^{II} is made more rapid.

In conclusion, the efficient homocoupling of arylboronic acids and arylboronic esters to give biaryls occurs with Pd^{II} catalysis under mild conditions, using fluoride ion in the presence of water and air, and is crucially dependent on each of these factors. Further refinement of this process and its application to the synthesis of polymers are underway in our laboratory.

Typical Procedure:

Phenylboronic acid (122 mg, 1.0 mmol, 1.0 equiv) was dissolved in THF–H₂O (4:1, 3 mL) in a scintillation vial, and Pd(PPh₃)₂Cl₂ (70 mg, 0.1 mmol, 0.1 equiv) and tetrabutylammonium fluoride hydrate (261 mg, 1.0 mmol, 1.0 equiv) were added sequentially. TBAF in THF solution can be also used. The reaction mixture was vigorously stirred for 10 h at r.t., and was then diluted with EtOAc (5 mL), extracted with EtOAc (3 × 5 mL), and washed with H₂O (5 mL). The combined organic layers were dried with MgSO₄, concentrated under vacuum, and subjected to flash chromatography (hexanes) to afford biphenyl (102 mg, 77%).

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