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Homocoupling of arylboronic acids and potassium aryltrifluoroborates catalyzed by protein-stabilized palladium nanoparticles under air in water

Alessandro Prastaro [a], Pierpaolo Ceci [c], Emilia Chiancone [b,c], Alberto Boffi [b,c], Giancarlo Fabrizi [a], Sandro Cacchi [a,*]

[a] Dipartimento di Chimica e Tecnologie del Farmaco, Sapienza, Università di Roma, P.le A. Moro 5, 00185 Rome, Italy
[b] Dipartimento di Scienze Biochimiche, Sapienza, Università di Roma, P.le A. Moro 5, 00185 Rome, Italy
[c] Istituto di Biologia e Patologia Molecolari CNR, P.le A. Moro 5, 00185 Rome, Italy

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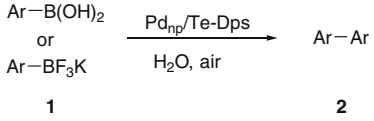
ABSTRACT

Palladium nanoparticles stabilized primarily within the protein cavity of a highly thermostable Dps protein (DNA binding protein from starved cells) from the thermophilic bacterium *Thermosynechoccus elongatus* provide an efficient catalyst for the homocoupling of boronic acids and potassium aryltrifluoroborates in water under aerobic phosphine-free conditions. Symmetrical biaryls have been isolated in good to excellent yields. Potassium aryltrifluoroborates give similar or better results than the corresponding arylboronic acids.

The symmetrical biaryl motif is diffused among a variety of products exhibiting interesting properties. For example, symmetrical biaryl systems are present in Crisamicin A, a natural product that is active against B16 murine melanoma cells, the herpes simplex, and vesicular stomatitis viruses,[1] in polymers showing conductive properties,[2] and in ligands used in catalysis.[3] Because of their non-toxic nature, stability, broad tolerance of functional groups, and ability to couple sterically demanding substrates, arylboronic acids represent one of the most reliable substrates for the synthesis of this class of compounds via palladium-catalyzed homocoupling reactions. Symmetrical biaryls have been prepared from arylboronic acids with homogeneous[4] and heterogeneous[4j,5] palladium catalysts under base-,[4j,l,5a] phosphine-free,[4i,l,5,6], and ultrasound[5b] conditions. Usually, the reactions have been carried out using Pd(II) salts in the presence of oxidants,[4d–g,i–m,6a,b,7,8] required to restore the active Pd(II) catalyst from the Pd(0) species generated from bis(aryl)palladium(II) intermediates. Examples of homocoupling reactions performed in the presence of Pd(0) species such as $Pd(PPh_3)_4$[4h] or Pd/C[5] and oxidants have also been described. Organic solvents have been typically employed, but the reactions have also been carried out in supercritical carbon dioxide[7] and using water as a cosolvent,[4k,5a,6b,8,9] including water/ionic liquid mixtures.[8a] To the best of our knowledge, there are only two reports of reactions carried out in water.[6a,9] One requires a phase transfer catalyst[6a] and the other uses a $Pd(OAc)_2$/*p*-benzoquinone system under anaerobic electro-oxidative conditions.[9] There are no reports of homocoupling of arylboronic acids in the presence of palladium nanoparticles in water.

Herein we show that the palladium nanoparticles (Pd_{np}) stabilized primarily within the protein cavity of a highly thermostable Dps protein (DNA binding protein from starved cells) from the thermophilic bacterium *Thermosynechoccus elongatus* (Te-Dps) provide an efficient catalyst for the synthesis of symmetrical biaryls from arylboronic acids in water under aerobic and phosphine-free conditions (Scheme 1). The procedure was also extended to the less explored[9] homocoupling of potassium aryltrifluoroborates.

Te-Dps-stabilized palladium nanoparticles (Pd_{np}/Te-Dps) were prepared as described previously[10] by the exposure of K_2PdCl_4 to Te-Dps at room temperature and reduction with $NaBH_4$.



Scheme 1. Homocoupling of boronic acids and potassium aryltrifluoroborates catalyzed by Te-Dps-stabilized palladium nanoparticles.

* Corresponding author. Tel.: +39 06 4991 2795; fax: +39 06 4991 2780.
E-mail address: sandro.cacchi@uniroma1.it (S. Cacchi).

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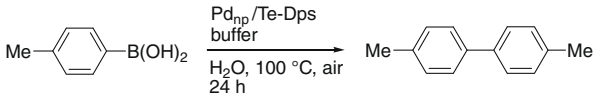
Table 1
The influence of Tris buffer concentration on the homocoupling of 4-tolylboronic acid catalyzed by protein-stabilized palladium nanoparticles (Pd_{np}/Te-Dps)[a]



1a **2a**

Entry	Tris buffer concentration (M)	Yield% of **2a**[b]
1	0.10	78
2	0.25	82
3	0.50	80
4	0.75	85
5	1.00	91
6	1.50	51
7	2.00	33

[a] Reactions were carried out at 100 °C, under air, using 0.25 mmol 4-tolylboronic acid, in 2 mL of Tris–HCl buffer at pH 8.9 for 24 h in the presence of 0.05 mol % of [Pd].
[b] Yields refer to single runs and are given for isolated products.

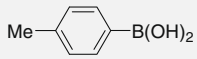
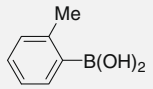
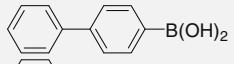
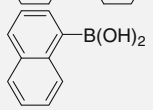
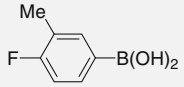
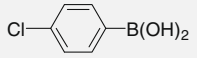
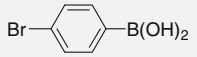
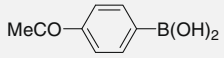
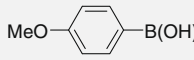
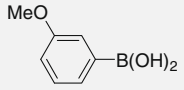
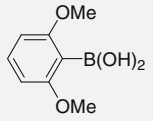
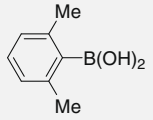
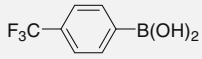
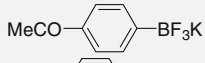
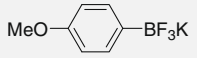
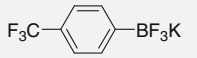
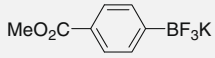
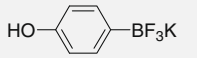
The catalytic properties of water-soluble Pd_{np}/Te-Dps were evaluated initially in the homocoupling of 4-tolylboronic acid at 100 °C for 24 h using a palladium loading down to 0.05 mol % in the presence of a 0.1 M Tris [tris(hydroxymethyl)aminomethane]–HCl buffer at pH 8.9 in water under air. Under these conditions, the product **2a** was isolated in 78% yield. No evidence of homocoupling product formation was obtained when the reaction was carried out under an argon atmosphere. Thereafter the influence of buffer concentration on the reaction outcome under air was explored. As shown in Table 1, the yield of the homocoupling product increases with increasing concentration of Tris, reaching the best result by using a 1 M Tris–HCl buffer (Table 1, entry 5). A further increase of the buffer concentration produced lower yields.

Using oxygen gas can accelerate the rate of the homocoupling reaction. Compound **2a** was isolated in 89% yield after 10 h under a balloon of oxygen. However, for practical reasons, the optimized conditions under air were used[11] when we next explored the scope and generality of the process. As shown by the results listed in Table 2, homocoupling products were isolated in good to excellent yields with a variety of arylboronic acids. Potassium aryltrifluoroborates were also investigated. At least with the examples that we have examined, they have been found to give similar or better results than the corresponding arylboronic acids in a shorter reaction time (Table 2, compare entries 9, 10, and 14 with entries 15, 16, and 17, respectively). The methodology tolerates several useful functional groups such as phenol, ether, keto, chloro, and bromo substituents as well as a single or two ortho substituents (Table 2, entries 2, 5, 12, 13). The ester **1r**, however, undergoes a hydrolytic process and the corresponding homocoupling product was isolated as a dicarboxylic acid derivative.

As to the mechanism, the fact that no homocouplìng product was observed in the absence of air supports the notion that the reaction proceeds through the intermediacy of peroxo complexes generated in the reaction of dioxygen with Pd(0) species.[4j,12]

In conclusion, we have shown that the palladium nanoparticles stabilized primarily within the cage of a Dps protein from a thermophilic protein (Pd_{np}/Te-Dps) can be used successfully in the homocoupling of arylboronic acids and potassium aryltrifluoroborates under aerobic phosphine-free conditions in water. Homocoupling products were isolated in good to excellent yields in the presence of electron-donating and electron-withdrawing groups. Single and two ortho substituents are also tolerated. Potassium aryltrifluoroborates gave similar or better results than the corresponding arylboronic acids.

Table 2
Homocoupling of arylboronic acids and potassium aryltrifluoroborates catalyzed by protein-stabilized palladium nanoparticles (Pd_{np}/Te-Dps)[a]

Entry	Arylboronic acid **1**		Time (h)	Yield% of **2**[b]
1		**1a**	24	91
2		**1b**	24	85
3		**1c**	24	92
4		**1d**	48	67
5		**1e**	48	65
6		**1f**	48	73
7		**1g**	24	82
8		**1h**	24	78
9		**1i**	24	63
10		**1j**	48	81
11		**1k**	48	87
12		**1l**	48	73
13		**1m**	17	80
14		**1n**	10	85
15		**1p**	10	82
16		**1q**	24	87
17		**1o**	7	80
18		**1r**	24	60[c]
19		**1s**	24	70

[a] Reactions were carried out at 100 °C, under air, using 0.25 mmol arylboronic acid or potassium aryltrifluoroborate in 2 mL of 1 M Tris–HCl buffer at pH 8.9 in the presence of 0.05 mol % of [Pd] and monitored by HPLC.
[b] Yields refer to single runs and are given for isolated products.
[c] Isolated as dicarboxylic acid derivative.

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11. *Typical procedure for the homocoupling of arylboronic acids or potassium aryltrifluoroborates catalyzed by Pd_{np}/Te-Dps*: 4-tolylboronic acid (34 mg, 0.25 mmol) and 0.05 mol % of Pd_{np}/Te-Dps in 2 mL of 1 M Tris–HCl buffer at pH = 8.9 were orbitally stirred for 24 h at 100 °C with a Heidolph Synthesis System. After cooling, the liquid phase was extracted with CH_2Cl_2, the organic layer was washed with deionized water ,and dried over Na_2SO_4. The solvent was removed under vacuum and the residue was purified by chromatography (SiO_2, 35 g, *n*-hexane/AcOEt, 95:5 v/v) to give 41.4 mg (91% yield) of **2a** as a white solid; mp 122 °C (lit. mp 119 °C; Li, G. Y. *J. Org. Chem.* **2002**, *67*, 3643–3650); ^{1}H NMR ($CDCl_3$) δ: 2.35 (s, 6H), 7.21 (d, J = 7.8 Hz, 4H), 7.40 (d, J = 8.0 Hz, 4H); ^{13}C NMR ($CDCl_3$) δ: 21.0, 126.5, 129.2, 136.5, 138.0; EI-MS m/z (rel intensity): 182 (M+, 100).
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