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Suzuki cross-coupling of arylboronic acids mediated by a hydrosoluble Pd(0)/TPPTS catalyst

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Abstract—Suzuki cross-coupling reactions between a range of aryl bromides and boronic acids using a water-soluble Pd(0)/TPPTS catalyst occur under mild conditions with high efficiency. The process tolerates electron-rich and electron-poor substituents and provides an efficient access to sterically hindered biaryls. Good turnovers are observed and the catalyst can be recycled three times without loss of activity. © 2001 Elsevier Science Ltd. All rights reserved.

Compounds which contain a biaryl linkage have found applications in areas ranging from pharmaceutical intermediates to materials science.¹ Their preparation, when effected through the palladium-catalyzed Suzuki cross-coupling of aryl halides with arylboronic acids, is both extremely versatile and very convenient: boronic acids, being generally non-toxic, thermally stable and insensitive to air and moisture, are much easier to handle than other commonly used cross-coupling reagents.² As well as aryl chlorides,³ arenediazonium salts can also act as electrophiles and our group has recently described an efficient palladium-catalyzed cross-coupling between arylboronic acids or aromatic potassium tetrafluoroborates which produces biaryls under mild conditions.⁴

We have been engaged in a program of organometallic catalysis in organoaqueous media which uses the watersoluble ligand, sodium triphenylphosphinometatrisulfonate (TPPTS) in combination with palladium for deprotective group chemistry and cross-coupling reactions.⁵ These hydrosoluble systems show the dual advantages of operating under mild conditions and allowing an easy separation of the products from the catalyst, which greatly facilitates the work-up. Moreover water is an economical and environmentally friendly solvent which, under appropriate conditions, also allows new reactions such as carbohydroxy palladation⁶ as well as recycling the catalyst.

Keywords: Suzuki coupling; water-soluble catalyst; recycling.

Previously we have described the Suzuki cross-coupling of a wide range of arylboronic acids or esters with aryl or vinyliodides and shown that diisopropylamine is a very effective base in this medium.⁷ The principal drawback to this protocol lies in its use of expensive aryliodide electrophiles. We envisaged an extension to arylbromides and arylchlorides, which are attractive because of their low cost and wide availability. Recently, we have shown that a water-soluble Ni(0) catalyst formed from NiCl₂(dppe) and TPPTS catalyzed the cross-coupling of a variety of arylchlorides and arylboronic acids to afford good yields of biaryls⁸ (Scheme 1). Here, we wish to report our recent results in Suzuki cross-coupling of arylbromides carried out with the water-soluble catalyst Pd/TPPTS.⁹





Catalyst performance was optimized in the reaction of 2-bromobenzaldehyde with phenylboronic acid. It was found that the nature of the palladium source, $Pd(OAc)_2$ or $PdCl_2$, has no influence on the course of the reaction. The optimal TPPTS/Pd(OAc)_2 ratio was 3:1; 1 equiv. of the phosphine being used to reduce Pd(II) to Pd(0) and the others to stabilize the palla-

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dium.¹⁰ The homogeneity of the reaction mixture was crucially important to the success of the reaction and disopropylamine was found to be the base of choice (Scheme 2).



Scheme 2.

Representative cross-coupling reactions using both electron-rich and electron-poor bromoarenes were investigated under these optimized conditions.¹¹ The results are summarized in Table 1.

Table 1. Scope of Suzuki cross-couplings of arylbromides

Entry	R	Time (h)	Yield (GC conversion %)
1	2-OHC	4	92 (100)
2	4-OHC	0.5	90 (100)
3	4-Ph-CO	1	80 (100)
4	3-Cl	1	78 (87)
5	4-Cl	2	82 (100)
6	4-CH ₃	1	53 (100)
7	2-HO	72	60 (72)
6	2-MeO	2	75 (64)
8	2,4-diMeO	3	68 (84)
9	$2 - H_2 N$	12	64 (100)

It is clear that the cross-coupling is efficient over a broad spectrum of *ortho-* and *para*-substituted aryl bromides and that variations in electronic nature of the

substituents are nicely tolerated. The reaction times are short, except in the cases of 2-bromophenol and 2-bromoaniline, where some chelation to palladium may be occurring (entries 7 and 9). The reaction was chemospecific for aryl bromide in the presence of the corresponding chloride (entries 4 and 5).

As shown in Table 2, the Suzuki coupling of heteroarylbromides with phenylboronic acid is completed in good yield within 8 h (entries 1 and 2). The slightly lower conversions observed when electron-donating substituents are present could be improved by employing longer reaction times and more polar solvents such as NMP (entry 4). Under these conditions, it was possible to generate excellent yields of biaryls having three *ortho*-substituents which are difficult to prepare using the Suzuki coupling in anhydrous conditions (entry 6).

ortho-Biaryls have peculiar biological activity which may reflect the ability of the gauche conformation, (generated by intermolecular repulsions) to interact with proteins; consequently, they show a rather broad band of pharmacological activity. The value of our process is exemplified in a two-step synthesis of xenalipin (Scheme 3), a non-natural product which reduces cholesterol and triglyceride levels in plasma.^{12,13} Coupling of 2-bromobenzaldehyde with 4-trifluoromethylphenyl boronic acid under our standard afforded 2-(4-trifluoromethylphenyl)conditions benzaldehyde in 73% yield within 4 h. Xenalipin was then obtained straightforwardly in a second step through mild KMnO₄ oxidation in 73% yield. This result may be compared with our earlier procedure employing a Suzuki coupling of diazonium and tetrafluoroborate salts.⁴ With the new protocol, the 2-(4trifluoromethyphenyl)benzaldehyde intermediate was efficiently prepared in a shorter time (5 min).

 Table 2. Suzuki cross-coupling of a variety of arylbromides and boronic acids

Entry	Aryl Bromide	Boronic acid	Product	Time (h)	Yield (GC conversion %)
1	⟨ N →Br	(HO) ₂ B	$\sum_{n} - \sum_{n}$	8	75 (83)
2		(HO) ₂ B		8	87 (100)
3	CN Br	(HO) ₂ B		1	92 (100)
4	MeO -Br	(HO) ₂ B	MeO	4 72	84 (76) 93 (93) ^a
5	CI-Br	(HO) ₂ B-F		3	96 (100)
6	Br	(HO) ₂ B		0.75	89 (93)
		/	/		

" Reaction performed in NMP (N-methylpyrrolidone)



Scheme 3.

The effect of lowering of catalyst loading was also studied under our standard conditions in the model coupling of 4-bromobenzaldehyde and boronic acid (Scheme 4).



Scheme 4.

Reducing the mole fraction of palladium from 5×10^{-2} mol Pd to 1×10^{-2} mol still gave a quantitative yield with no increase in the reaction time (Table 3, entry 1). However, a small fall in conversion was observed after 4 h when using 1×10^{-3} mol of catalyst (entry 2). The turnover number at 10^{-4} mol concentrations is good (6400), thus proving that our water-soluble catalyst is competitive with the most recent methods which generally use palladacycles (entry 4).¹⁴ It is also noteworthy

Table 3. Suzuki with low catalyst loading^a

Entry	Pd (mol)	Time (h)	Conversion (%) ^b	TON
1	0.01	0.5	100	100
2	0.001	4	88	880
3	10^{-4}	22	64	6400
4	10^{-5}	17	3	

^a Reaction conditions: 1 mmol arylbromide, 1.2 equiv. boronic acid, [arylbromide]=2.5 M.

^b Conversion was determined by GC.

Table 4. Parameters relating to the recycling of the water-soluble catalyst^a

that homocoupling reactions were suppressed (<1% GC). 15

Finally, it was possible to recycle the catalyst for use in the same coupling reaction by using 5 mol% Pd and 4 equiv. of TPPTS to increase catalyst stability (Table 4).

Table 4 shows that a decrease in the degree of conversion only appears in the fourth generation catalyst. Reaction times increased upon recycling, perhaps because of the accumulation of salts in the mixture.

To conclude, a water-soluble palladium catalyst has been shown to have high efficiency and turnover numbers for the Suzuki coupling of a wide range of aryl bromides to boronic acids. Furthermore, the catalyst can be recycled three times without loss of activity.

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References

- 1. Review: Stanfort, S. P. *Tetrahedron* **1998**, *54*, 263–303 and references cited therein.
- For recent reviews, see: (a) Miyaura, N.; Suzuki, A. *Chem. Rev.* 1995, 95, 2457–2483; (b) Suzuki, A. In *Metalcatalyzed Cross-coupling Reactions*; Diederich, F.; Stang, P. J., Eds.; Wiley-VCH: New York; 1998; pp. 49–97; (c) Stanforth, S. P. *Tetrahedron* 1998, 54, 263–303.



^a Yield (%) determined by GC

- For coupling reactions of aryl chlorides in organic medium, see: Stürmer, R. Angew. Chem., Int. Ed. 1999, 38, 3307–3308; For early examples, see: (a) Old, D. W.; Wolfe, J. P.; Buchwald, S. L. J. Am. Chem. Soc. 1998, 120, 9722–9723; Wolfe, J. P.; Singer, R. A.; Yang, B. H.; Buchwald, S. L. J. Am. Chem. Soc. 1999, 121, 9550–9561; (b) Littke, A. F.; Dai, C.; Fu, G. C. J. Am. Chem. Soc. 2000, 122, 4020–4028; (c) Weskamp, T.; Bohm, V. P. W.; Herrmann, W. A. J. Organomet. Chem. 1999, 585, 348– 352.
- 4. (a) Darses, S.; Jeffery, T.; Brayer, J.-L.; Demoute, J.-P.; Genêt, J.-P. *Tetrahedron Lett.* 1996, 37, 3857–3860; (b) Darses, S.; Jeffery, T.; Brayer, J.-L.; Demoute, J.-P.; Genêt, J.-P. *Bull. Soc. Chim. Fr.* 1996, 133, 1095–1102; (c) Darses, S.; Brayer, J.-L.; Demoute, J.-P.; Genêt, J.-P. *Tetrahedron Lett.* 1997, 38, 4393–4396; (d) Darses, S.; Michaut, G.; Genêt, J.-P. *Eur. J. Org. Chem.* 1999, 1875–1883.
- For reviews, see: Genêt, J.-P.; Savignac, M. J. Organomet. Chem. 1999, 576, 305–317; Genêt, J.-P.; Savignac, M.; Lemaire-Audoire, S. In IUPAC Monographs Chemistry for the 21st Century; Murahashi, S.-I.; Davies, S. G., Eds. Transition metal catalysed reactions, 1999, pp. 55 and references cited therein.
- Galland, J.-C.; Savignac, M.; Genêt, J.-P. *Tetrahedron* Lett. 1997, 38, 8695–8698.
- Genêt, J.-P.; Lindquist, A.; Blart, E.; Mouriès, V.; Savignac, M. *Tetrahedron Lett.* 1995, *36*, 1443–1446.
- (a) Galland, J.-C.; Savignac, M.; Genêt, J.-P. *Tetrahedron Lett.* **1999**, *40*, 2323–2326; (b) Galland, J.-C.; Dias, S.; Savignac, M.; Genêt, J.-P. *Tetrahedron* **2001**, to be published.
- 9. Dupuis, C. Ph.D.; Université Pierre et Marie Curie: Paris, December 1999.
- 10. Amatore, C.; Blart, E.; Genêt, J.-P.; Jutand, A.; Lemaire-

Audoire, S.; Savignac, M. J. Org. Chem. 1995, 60, 6829-6839.

- 11. Typical procedure: Water and acetonitrile were degassed under vacuum. Pd(OAc)₂ (5 mol%, 0.025 mmol, 5.6 mg), TPPTS (15%; 0.075 mmol, 128 mg of a 33% wt solution in water) and 0.16 mL of water were placed in a flask under argon and warmed at 60°C for 15 min. A solution of 4-bromobenzaldehyde (1 equiv., 0.5 mmol, 58 µL) and phenylboronic acid (1.2 equiv., 0.6 mmol, 73 mg) in 0.5 mL of acetonitrile was added in the flask. Diisopropylamine (2.5 equiv., 1.25 mmol, 175 µL) was then added in the flask and the resulting mixture was stirred 4 h at 80°C. Reaction progress was monitored by GC and when the reaction was completed, the mixture was quenched with 5 mL of saturated NaCl solution and extracted by 3×5 mL of ethyl acetate. The organic layers were combined, dried over MgSO₄, filtered and concentrated in vacuo. Purification of crude product by flash chromatography on silica gel afforded 77 mg of 4-phenylbenzaldehyde (85%) as a solid. $F = 56^{\circ}C$; ¹H NMR (CDCl₃, 200 MHz, δ ppm): 7.44–7.56 (3H, m); 7.67 (2H, dd); 7.73 (2H, d); 7.98 (2H, d); 10.1 (1H, s, CHO); ¹³C (CDCl₃, 50 MHz, d ppm): 127.3; 127.6; 128.4; 128.9; 130.2; 135.1; 139.6; 147.1; 191.8 (CHO).
- Bell, L. N.; Burke, M. T.; Hodgson, Jr., G. L.; Shumaker, T. K. *Eur. Pat. Appl.* EP 59, 983 (1982).
- Koch, K.; Chambers, R. J.; Biggers, M. S. Synlett 1994, 347–348.
- (a) Beller, M.; Fischer, H.; Hermann, A.; Öfele, K.; Brossmer, C. Angew. Chem., Int. Engl. 1995, 34, 1848– 1849; (b) Albisson, D. A.; Bedford, R. B.; Laurence, S. E.; Scully, P. N. J. Chem. Soc., Chem. Commun. 1998, 2095–2096; (c) Bedford, R. B.; Welch, S. J. Chem. Soc., Chem. Commun. 2001, 129–130.
- Moreno-Mañas, M.; Pérez, M.; Pleixats, R. J. Org. Chem. 1996, 61, 2346–2351.