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Palladium and nickel catalysed Suzuki cross-coupling of sterically hindered aryl bromides with phenylboronic acid

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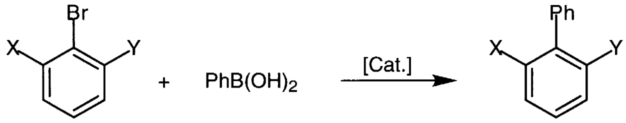
Abstract

Nickel and palladium catalysts for the Suzuki cross-coupling of aryl halides bearing two *ortho* substituents with phenylboronic acid have been developed and used for the synthesis of sterically hindered biaryls. © 2000 Elsevier Science Ltd. All rights reserved.

Keywords: Suzuki cross-coupling; biaryls; palladium; nickel; steric hindrance.

Palladium and nickel mediated cross-coupling reactions have evolved into versatile methods for carbon–carbon bond formation.[1,2] Of particular interest is the coupling of aryl halides and aryl boronic acids, the so-called Suzuki reaction (Scheme 1), due to the fact that the biaryl unit and its homologues are found in natural products, polymers, liquid crystals and advanced materials.[3,4] The coupling of di-*ortho* substituted boronic acids with aryl halides has been reported previously.[5] It is however not easy to prepare these sterically hindered acids and so our attention has been focused on coupling di-*ortho* substituted aryl halides with simple boronic acids. In this letter we describe two methods by which Suzuki cross-couplings of sterically crowded aryl bromides and phenylboronic acid proceed in good yield using commercially available reagents.



Scheme 1.

The palladium complex, $Pd_2(dba)_3$ [dba=dibenzylideneacetone], when used in the presence of a tertiary phosphine ligand and a base, has been shown to behave as an active catalyst for Suzuki coupling reactions.[6,7] As a starting point for our studies, we decided to develop this catalyst mixture for synthesis of sterically hindered biaryls from phenylboronic acid and aryl bromides bearing alkyl and aryl groups in

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the two *ortho* positions. The coupling reaction between 2,6-dimethylbromobenzene and phenylboronic acid to form 2,6-dimethylbiphenyl (**1**) was studied first.[8] As shown in Tables 1 and 2, the best results are obtained using 3 mol% $Pd_2(dba)_3$, 6 mol% trimethyl phosphite and two equivalents of K_3PO_4 in dioxane, heating the reaction mixture at 95°C for 8 h. This is in contrast to previous investigations showing that, when coupling less sterically demanding aryl halides with $Pd_2(dba)_3$, the use of tributyl phosphine and Cs_2CO_3 gives the best results.[3] We find that, using P^tBu_3, poor yields of sterically crowded biaryl are obtained. We rationalise our observations in terms of the difference in cone angle[9] between P^tBu_3 (182°) and $P(OMe)_3$ (107°) and hence the distance to which the Pd complex can approach the aryl halide; the $P(OMe)_3$ complex being able to access and react with the sterically hindered halide, the P^tBu_3 not.

Table 1
Effect of P-donor ligand on the Pd-catalysed Suzuki cross-coupling of 2,6-dimethyl bromobenzene with phenylboronic acid to form **1**[a)]

P-donor ligand	Yield (%)
PPh_3	0
dppf[b)]	0
PEt_3	30
$P(OEt)_3$	37
$P(OMe)_3$	82

[a)] Using 3 mol-% $Pd_2(dba)_3$, 6 mol-% P-donor ligand and 2 equiv K_3PO_4 in dioxane, heating at 95 °C for 8 h.
[b)] dppf = 1,2-bisdiphenylphosphino ferrocene.

Table 2
Effect of base on the Pd-catalysed Suzuki cross-coupling of 2,6-dimethyl bromobenzene with phenylboronic acid to form **1**[a)]

Base	Yield (%)
Na_2CO_3	5
K_2CO_3	5
Cs_2CO_3	53
K_3PO_4	82

[a)] Using 3 mol-% $Pd_2(dba)_3$, 6 mol-% $P(OMe)_3$ and 2 equiv base in dioxane, heating at 95 °C for 8 h.

To develop the synthetic protocol and also identify possible limits of steric hindrance beyond which the reaction would not occur, we studied the coupling of 2-ethyl-6-methylbromobenzene,[10,11] 2,6-diethylbromobenzene, 4-bromobiphenyl,[12] and 9-bromoanthracene[13] with phenylboronic acid, using the $Pd_2(dba)_3/P(OMe)_3$ catalyst mixture with the aim of forming 2-ethyl-6-methylbiphenyl (**2**), 2,6-diethylbiphenyl (**3**), *o*-terphenyl (**4**) and 9-phenylanthracene (**5**), respectively (Table 3).

Our route to substituted biaryls offers a significant improvement over previously reported methods. It is not necessary to use aryl phosphines where, in addition to their steric bulk retarding the process, unwanted by-products are often formed by reaction of ligand-bound phenyl groups with the boronic acid.[14] It is not necessary to use labilised aryl triflates or mesylates in order to get a reasonable yield of product, nor is it necessary to use other metal transfer agents such as arylmagnesium halides.[5,15] As a consequence it is possible to form the desired biaryl, quickly, efficiently and from simple, unmodified, starting materials.

Although a number of sterically crowded biaryls can be formed using the $Pd_2(dba)_3/P(OMe)_3$ catalyst mixture, we find that a limit comes when both *ortho* substituents on the aryl halide are equal to or more

Table 3
Scope of the $Pd_2(dba)_3/P(OMe)_3$-catalysed Suzuki cross-coupling of sterically hindered aryl bromides[a)]

X [b)]	Y [b)]	Product	Yield (%)
Me	Me	**1**	80
Me	Et	**2**	54
Et	Et	**3**	0
H	Ph	**4**	72
-(CH)-[c)]	-(CH)-[c)]	**5**	59

[a)] Using 3 mol-% $Pd_2(dba)_3$, 6 mol-% $P(OMe)_3$ and 2 equiv. K_3PO_4 in dioxane, heating at 95 °C for 8 h. [b)] X and Y refer to *ortho* substituents as shown in Scheme 1. [c)] 9-bromoanthracene.

sterically demanding than ethyl groups. This may attribute to the difficulty of the catalyst to get close enough to the aryl halide for the initial oxidative addition to occur. This led us to look at some nickel catalysts for the synthesis of **1**–**5**. We felt that, using nickel complexes such as $Ni(dppf)Cl_2$ [dppf=1,1′-bis-diphenylphosphino ferrocene] and $Ni\{P(OMe)_3\}_2Cl_2$, it may be possible to facilitate the coupling of more sterically demanding aryl halides.[16] As the results in Table 4 show, this is unfortunately not the case. As with the palladium system, sterically crowded biaryls can be formed but the limit to this comes at the same point.[17] A key advantage of the nickel catalysts over the $Pd_2(dba)_3/P(OMe)_3$ mixture is the much greater ease of separation of product from catalyst mixture at the end of the reaction. As the nickel complex added is the catalyst for reaction, the addition of free phosphine or phosphite is not necessary as it is in the case of $Pd_2(dba)_3$. Other advantages of the nickel systems include the air stability, cost and ease of preparation of the catalyst, all of which are important when considering the scale-up of the reaction.

Table 4
Scope of the nickel catalysed Suzuki cross-coupling of sterically hindered aryl bromides[a)]

X [b)]	Y [b)]	Product	Yield (%)	
			$Ni(dppf)Cl_2$	$Ni(P(OMe)_3\}_2Cl_2$
Me	Me	**1**	52	78
Me	Et	**2**	41	70
Et	Et	**3**	0	0
H	Ph	**4**	57	66
-(CH)-[c)]	-(CH)-[c)]	**5**	52	65

[a)] Using 5 mol-% nickel complex, 6 mol-% P-donor ligand and 2 equiv. K_3PO_4 in dioxane, heating at 95 °C for 8 h. [b)] X and Y refer to *ortho* substituents as shown in Scheme 1. [c)] 9-bromoanthracene.

In summary, we have developed catalyst mixtures for the Suzuki cross-coupling of aryl halides bearing two *ortho* substituents with phenylboronic acid. Our catalyst systems, which employ readily available components, allow for the synthesis of sterically crowded biaryls in good yields and open up new routes for the synthetic chemist when attempting to prepare compounds containing this structural motif, including a range of natural products.

Acknowledgements

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11. Preparation of 2-ethyl-6-methylbiphenyl (**2**): Method as with **1** but using 2-ethyl-6-methylbromobenzene (537 g, 2.7 mmol) as the aryl halide. **2** (286 mg) was recovered in 56% yield. ^1H NMR ($CDCl_3$, 250 MHz): δ 1.23 (t, 3H), 2.25 (s, 3H), 2.75 (q, 2H), 7.21 (m, 2H), 7.25 (m, 2H), 7.35 (m, 2H), 7.49 (m, 1H), 7.51 (m, 1H). MS (ES) *m/z* 196 (calcd 196.2).
12. Preparation of *o*-terphenyl (**4**): Method as with **1** but using 2-bromobiphenyl (629 mg, 0.45 ml, 2.7 mmol) as the aryl halide. **4** (447 mg) was recovered in 72% yield. ^1H NMR ($CDCl_3$, 250 MHz): δ 7.4 (m, 4H), 7.16 (m, 10H). MS (ES) *m/z* 230 (calcd 230.3). Mp 56°C (lit. 56–58°C).
13. Preparation of 9-phenylanthracene (**5**): Method as with **1** but using 9-bromoanthracene (693 mg, 2.7 mmol) as the aryl halide. **5** (404.6 mg) was recovered in 59% yield. ^1H NMR ($CDCl_3$, 250 MHz): δ 8.42 (m, 1H), 7.95 (m, 2H), 7.62 (m, 2H), 7.51 (m, 4H), 7.42 (m, 3H), 7.3 (m, 2H). MS (ES) *m/z* 254 (calcd 254.3). Mp 154°C (lit 153–155°C).
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