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Ligand-free palladium catalysis of aryl coupling reactions facilitated by grinding

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Abstract—Ligand-free palladium-catalysed Suzuki coupling reactions and homo-couplings of boronic acids have been facilitated by grinding. The reactions are rapid (10–30 min) and can be performed without the need to exclude air and moisture. © 2003 Elsevier Science Ltd. All rights reserved.

Biaryl units constitute important building blocks in natural products and advanced materials.^{1,2} The palladium-mediated cross-coupling reaction between aryl halides and arylboronic acids (the Suzuki reaction) has proven to be a versatile and highly useful method for the preparation of biaryl-containing molecules.³ A variety of catalysts have been prepared and screened for activity in the reaction including palladium N-heterocyclic carbene complexes⁴ and a wide range of palladium phosphine compounds.⁵ There have been a number of recent reports on ligand-free,^{6,7} solventfree,^{7,8} aqueous-phase^{6,9,10} and microwave-assisted¹¹ Suzuki coupling reactions. Another biaryl-forming reaction of interest is the palladium catalysed homocoupling of boronic acids to form symmetrical biaryls. Again, as well as using phosphine-ligated palladium catalysts^{12,13} there have been a number of recent reports on developments of ligand-free¹³⁻¹⁵ and aqueousphase^{14,15} methods.

We report here the ligand-free palladium-mediated Suzuki coupling of aryl halides, in particular bromides, and the homocoupling of boronic acids. We show that it is possible to perform these reactions rapidly by using triethylamine as a base and grinding the reaction mixture. The reactions are performed without the need to use dry reagents or anaerobic conditions. The use of grinding as a synthetic tool is a topic of increasing interest within the chemistry community, this being reflected in the number of recent reviews¹⁶ and communications^{17–20} on the subject. The Pd(PPh₃)₄

catalysed Suzuki reaction using ball-milling has been investigated previously.⁸ The authors report that the formation of the Suzuki-coupled product is often accompanied by a significant quantity of biphenyl, generated by homo-coupling of phenylboronic acid. As a result they use two equiv. of boronic acid for their Suzuki coupling reactions to stop the homo-coupling being a limiting factor. In addition, the reaction conditions used work well only for a limited number of substrates. We wanted to explore the possibility of forming exclusively either Suzuki coupled product or boronic acid homo-coupled product. Secondly, we wanted to increase the substrate scope of the Suzuki reaction using grinding and reduce the stoichiometric ratio of aryl halide to boronic acid from 1:2 to 1:1.

Table 1. Optimisation of conditions for Suzuki couplingof 4-bromotoluene and phenylboronic $acid^{a,22}$

B(OH)2

Br	+ () ''' [Pa]	
Entry	Reaction conditions	Yield (%) ^b
1	$Pd(OAc)_2$, b=Na ₂ CO ₃ , g.t.=30 min	12
2	$PdCl_2$, $b = Na_2CO_3$, $g.t. = 30 min$	9
3	$Pd(OAc)_2$, $b = Na_2CO_3$, g.t. = 1 h	14
4	$Pd(OAc)_2$, b = NEt ₃ , g.t. = 30 min	95
5	$PdCl_2$, b=NEt ₃ , g.t.=30 min	79
6	$Pd(OAc)_2$, b = NEt ₃ , g.t. = 10 min	95
7	$Pd(OAc)_2$, b = NEt ₃ , t = 16 h ^c	60

^a 1 mmol aryl halide, 1 mmol PhB(OH)₂, 3 mmol base, 4.5 mol% Pd salt. b=base, g.t.=grind time, t=reaction time.

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^b Isolated yields.

[°] Stirred in a test tube.

Our starting point was to develop a set of working conditions for the Suzuki coupling reaction. Using 4bromotoluene as the aryl halide and phenylboronic acid as the coupling partner, we screened a range of palladium compounds (Pd(OAc)₂, PdCl₂ and Pd₂(dba)₃) and mineral bases (Na₂CO₃, NaOH, KF) in the reaction using a grinding time of 30 min. Reactions were performed in a hardened-steel vial with steel shot-ball cones. Working on a 1 mmol scale of aryl halide and boronic acid, 4.5 mol% catalyst and 3 mmol base, we found that it was possible to generate up to 12% of the desired biaryl (Table 1, entries 1–3). The yield did not improve on extending the grinding time, increasing the catalyst loading or varying the intensity of the grinding.

We decided to change the base from an inorganic salt to a liquid organic base, choosing triethylamine. We wanted to maintain the threefold molar excess of the base as compared to the aryl halide and boronic acid but this meant that the reaction mixture was now liquid. In order to be able to use a grinding methodology we needed to bulk-up the mixture with an inert solid to make a paste. We chose as this bulking agent NaCl, addition of which to the mixture of 4-bromotoluene and phenylboronic acid (1 mmol of each), 4.5 mol% $Pd(OAc)_2$ and 3 equiv. NEt₃ to make a paste, followed by 30 min grinding resulted in an isolated yield of 4-phenyltoluene of 95%. The reaction was performed in a hardened-steel vial with one large ball. Variation of reaction conditions showed us that the grinding time could be reduced from 30 min to 10 min with no drop in product yield (Table 1, entries 4-6). We wanted to compare the results obtained by grinding the reaction mixture with those obtained by simply stirring the mixture. We performed a control experiment, stirring a mixture of 4-bromotoluene, phenylboronic acid, $Pd(OAc)_2$ and NEt_3 in a flask for 10 min and found that there was little product formed. However, if the mixture is stirred overnight then a 60% yield of product is obtained (Table 1, entry 7). This result is interesting in itself and shows that the use of triethylamine as a base has potential for application in room temperature Suzuki reactions simply using stirring. Clearly one of the key roles of the grinding is simply to mix the reagents thoroughly and rapidly, speeding up the reaction. Concomitant with this will be localised heating of the reaction mixture, this perhaps also accelerating the reaction. Of interest is that heating the stirred reaction mixture results in a decrease in product yield. We term our methodology as being *facilitated by grinding* rather than invoking a mechanical activation effect.

Having found suitable conditions for the reaction, we screened a range of aryl bromides in the $Pd(OAc)_2$ mediated Suzuki coupling reaction with phenylboronic acid (Table 2, entries 1–10). The data shows that the methodology is general, a variety of bromides reacting with phenylboronic acid in good yields. Sterically hindered aryl bromides can be coupled using this method but the yields are lower than their non-hindered analogues. We also screened representative aryl iodides and chlorides in the reaction (Table 2, entries 11–13). Under our conditions aryl chlorides could not be coupled and aryl iodides gave incomplete conversion, even with extended grinding times. Similar problems with aryl iodides have been reported in the literature previously.^{10,21} Fu and co-workers show that addition of AgBF₄ can speed up Suzuki couplings involving aryl

Table 2. Suzuki cross-couplings facilitated by grinding^{a,23}



Entry	Aryl halide	Isolated yield, %
1	Br	96
2	Br NO ₂	97
3	Br	92
4	Br	95
5	Br	51
6	Br	79
7	Br	77
8	MeO Br	33
9	Br	95
10	Br CO ₂ Me	93
11 ^b		20
12 ^{b,c}		67
13 ^b	c,	2

^a 1.0 equiv. ArX, 1.0 equiv. PhB(OH)₂, 3.0 equiv. NEt₃, 4.5 mol% Pd(OAc)₂, NaCl added to form a damp paste, grinding for 10 min. Isolated yields of compounds, characterised by comparison of ¹H and ¹³C NMR spectra with authentic samples or literature data.

^c With 3 equiv. AgBF₄ added.

^b Grinding time of 30 min.

iodides. To see if this would increase the rate of couplings in our reaction we screened a range of silver salts as additives using 4-iodotoluene and phenylboronic acid as substrates. We found that the yield of biaryl could be increased from 20 to 67% by addition of 1.5 equiv. of AgBF₄. When using 3 equiv. of AgNO₃, we found that together with formation of the Suzuki product, we also obtained significant quantities of homo-coupled product deriving from the phenylboronic acid. We believed that this may open up the possibility of preparing symmetrical biaryls from boronic acids and so repeated the reaction in the absence of aryl halide, this giving biphenyl in 72% yield. We then screened other boronic acids in the Pd(OAc)₂-mediated homo-coupling reaction (Table 3). The data show that moderate to good yields of the desired products were obtained. De-activated boronic acids can be coupled using the methodology but only in low yields. Again it is possible to perform the reaction by stirring the mixture instead of grinding but yields are lower even after extended reaction times.

In summary, Suzuki coupling and boronic acid homocoupling reactions facilitated by grinding have been reported. Good yields of biaryls have been formed from phenylboronic acid and a range of aryl bromides. The reactions are rapid, the catalyst used simple, and they are performed without the need to exclude air and moisture. A number of boronic acids have been homocoupled using the same reaction conditions but with

Table 3. Boronic acid homo-couplings facilitated by $\operatorname{grinding}^{a,24}$



^a Reaction conditions: 1.0 equiv. R-B(OH)₂, 3.0 equiv. NEt₃, 4.5 mol% Pd(OAc)₂, 3.0 equiv. AgNO₃, NaCl added to form a damp paste, grinding for 30 min. Isolated yields of compounds, characterised by comparison of ¹H and ¹³C NMR spectra with authentic samples or literature data.

silver nitrate as an additive. Work to extend the scope of the reactions is currently underway.

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- 22. Grinding experiments were performed using a Retsch[®] Mixer Mill Type MM 200 (http://www.retsch.de/ index.php). Samples were loaded into 10 ml capacity screw cap stainless steel grinding jars. The vibration frequency of the mixer mill was set to 30 Hz (1800 rpm). Stirring experiments were performed in small test tubes which, after loading with the reagents, were sealed with a septum to prevent evaporation.
- 23. General procedure for Suzuki couplings of aryl bromides and phenylboronic acid: A grinding jar was loaded with aryl bromide (1 mmol), phenylboronic acid (122 mg, 1 mmol), Pd(OAc)₂ (10 mg, 0.045 mmol, 4.5 mol %) and triethylamine (300 mg, 0.41 ml, 3 mmol). NaCl was added slowly to the reaction mixture with agitation with a spatula until a damp paste was formed. The consistency of the paste was such that no liquid remained in the grinding jar but the granules of NaCl clung to the spatula when lifted from the mixture, this taking roughly 2 g

NaCl. A grinding ball was then added, the jar closed and placed into the mixer mill and the reaction mixture ground for 10 min. After grinding, the jar was then opened cautiously to avoid loss of material attached to the lid. All the material inside the jar was scraped into a conical flask and the jar rinsed with water and then ether and the washings placed with the scrapings. Water (30 ml) and ether (30 ml) were added to the flask and the entire contents transferred to a separating funnel. HCl (40 ml, 2 M) was added and after agitation, the organic layer was separated, dried over anhydrous MgSO₄, filtered and concentrated by rotary evaporation. In initial screening experiments yields were determined by ¹H NMR analysis using 1,2-dichloroethene as an internal standard. For isolation of products, in the cases where the starting aryl halide was a liquid unreacted aryl halide was firstly removed by heating the crude residue whilst under a vacuum on a Schlenk line. Products were purified by recrystallization, or flash chromatography on silica gel using hexane or hexane/ethyl acetate as eluent.

24. General procedure for homo-couplings of boronic acids: A grinding jar was loaded with boronic acid (1 mmol), Pd(OAc)₂ (10 mg, 0.045 mmol, 4.5 mol %), AgNO₃ (3 mmol, 510 mg) and triethylamine (300 mg, 0.41 ml, 3 mmol). NaCl was added slowly to the reaction mixture with agitation with a spatula until a damp paste was formed. The consistency of the paste was such that no liquid remained in the grinding jar but the granules of NaCl clung to the spatula when lifted from the mixture. A grinding ball was then added, the jar closed and placed into the mixer mill and the reaction mixture ground for 30 min. The grinding jar was then opened and the contents worked up in an identical manner to the Suzuki reactions.