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Use of Polymer-Supported Pd Reagents for Rapid and Efficient Suzuki Reactions Using Microwave Heating

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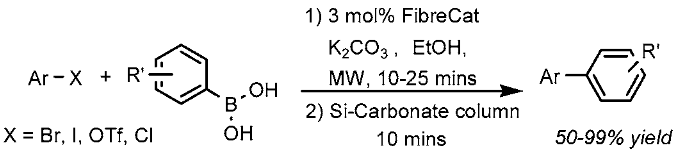
ABSTRACT



A rapid and efficient Suzuki coupling protocol has been developed utilizing polymer-supported palladium catalysts and microwave irradiation. It is also shown that solid-phase extraction of excess boronic acids can be rapidly and conveniently accomplished by utilization of a silica-supported carbonate base.

The palladium-catalyzed cross coupling of aryl halides with boronic acids (Suzuki reaction) is one of the most versatile and commonly utilized reactions for the construction of carbon−carbon bonds, in particular for the formation of biaryls.[1] The biaryl motif is an important pharmacophore in many biologically active compounds,[2] and as such the Suzuki reaction is widely utilized by medicinal chemists in the hit to lead and lead optimization stages of drug discovery. Its popularity has been further enhanced due to the increasing availability of organoboronic reagents, a broad range of functional group tolerance, and the low toxicity of inorganic byproducts. The Suzuki reaction is generally performed in organic solvents such as toluene, DMF, or THF in the presence of inorganic bases and homogeneous Pd catalysts such as $Pd(PPh_3)_4$ or $Pd(PPh_3)_2Cl_2$. One of the major problems encountered when performing Suzuki reactions in automated or semiautomated parallel synthesis results from the use of these homogeneous palladium catalysts. The Pd residues may clog probes and frits that are used to filter and transfer reaction mixtures. In addition, removal of Pd and associated ligands from the resulting product is not always easily accomplished, resulting in tedious workups.

Supported Pd catalysts are becoming increasingly popular since the heterogeneous Pd can be easily filtered upon completion of the reaction.[3] They are also generally air stable and easy to store and handle, making them highly amenable for both routine and automated synthesis.

Recent advances in microwave heating have greatly impacted many aspects of chemical synthesis, including applications for transition-metal-catalyzed reactions.[4] It has been demonstrated that the use of microwave heating can dramatically cut down reaction times, increase product purity and yields, and allow precise control of reaction parameters, all of which are crucial factors to consider when developing reaction protocols for both routine synthetic transformations and parallel synthesis.

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[1] For recent reviews, see: (a) Hassan, J.; Sévignon, M.; Gozzi, C.; Schulz, E.; Lemaire, M. *Chem. Rev.* **2002**, 102, 1359−1470. (b) Kotha, S.; Lahiri, K.; Kashinath, D. *Tetrahedron* **2002**, 58, 9633−9695. (c) Littke, A. F.; Fu, G. C. *Angew. Chem., Int. Ed. Engl.* **2002**, *41*, 4126−4211. (d) Suzuki, A. *J. Organomet. Chem.* **1999**, *576*, 147−168.

[2] Hajduk, P. J.; Bures, M.; Praestgaard, J.; Fesik, S. W. *J. Med. Chem.* **2000**, *43*, 3443−3447.

[3] Recent examples include: (a) Yamada, Y. M.; Takada, K.; Takahashi, H.; Ikegami, S. *Org. Lett.* **2002**, *4*, 3371−3374. (b) Mubofu, E. B.; Clark, J. H.; Macquarrie, D. J. *Green Chem.* **2001**, *3*, 23−25. (c) Zhang, T. Y.; Allen, M. J. *Tetrahedron Lett.* **1999**, *40*, 5813−5816.

[4] For recent reviews, see: (a) Lidström, P.; Tierney, J.; Wathey, B.; Westman, J. *Tetrahedron* **2001**, *57*, 9225−9283. (b) Larhed, M.; Moberg, C.; Hallberg, A. *Acc. Chem. Res.* **2002**, *35*, 717−727. (c) Lew, A.; Krutzik, P. O.; Hart, M. E.; Chamberlin, A. R. *J. Comb. Chem.* **2002**, *4*, 95−105. (d) Perreux, L.; Loupy, A. *Tetrahedron* **2001**, *57*, 9199−9223.

10.1021/ol048972p CCC: $27.50

Although microwave-assisted Suzuki reactions have been reported,[5] there are few reports on the use of polymer-supported Pd catalysts in Suzuki reactions.[6] Wishing to take full advantage of the complementary nature of these powerful tools, we have investigated the use of several commercially available polymer-supported Pd catalysts in microwave-assisted Suzuki reactions. Herein we report our findings on the application of polymer-supported Pd catalysts such as FibreCat (Figure 1)[7,8] and PS−PPh$_3$−Pd[9] in microwave-accelerated Suzuki reactions.

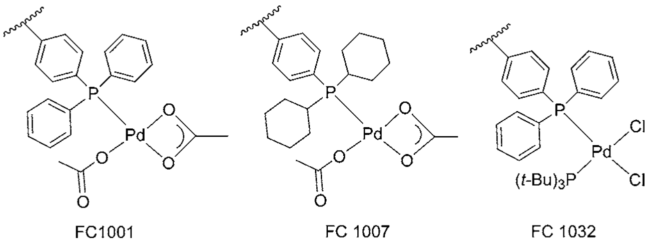
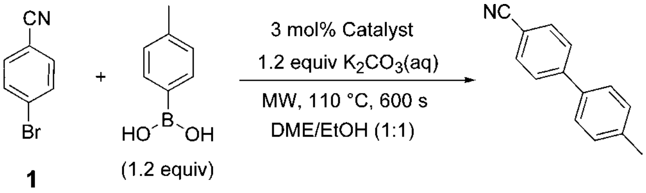


Figure 1. Polyethylene-Supported FibreCat Pd Catalysts.

Compound **1** (Table 1) was initially selected for our model study. Under microwave heating conditions, both FC 1001 and PS−PPh$_3$−Pd afforded excellent conversion to the Suzuki product, as verified by ^{1}H NMR and LC/MS, with low loading of the catalyst (3 mol %) and short reaction times (110 °C, 600 s).[10] A simple filtration through Si-carbonate[11] and chromatographic purification afforded the final product in excellent yield and purity.[12]

Table 1. Microwave-Assisted Suzuki Reaction with Polymer-Supported Pd

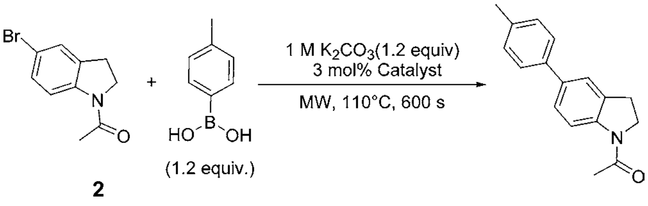


entry	catalyst	conversion[a] (isolated yield)
1	FC 1001	100% (99%)
2	PS−PPh$_3$−Pd	97% (90%)

[a] Determined by ^{1}H NMR and LC/MS.

Encouraged by these results, and wanting to investigate the general scope of the method, we picked compound **2** to carry out additional studies (Table 2). Under microwave heating conditions with K$_2$CO$_3$ as the base in DME/EtOH (1:1), good conversions were observed when either PdCl$_2$(PPh$_3$)$_2$, FC 1001, or PS−PPh$_3$−Pd (Table 2, entries 1−3) was used. Increasing the amount of boronic acid did not improve the conversion. The reaction was found to be insensitive to water content, which was varied from 0 to 50% of the total solvent volume. It was found that utilizing K$_2$CO$_3$ as the base gave the best yields. Inferior conversions were observed when other bases were used, including Na$_2$CO$_3$, organic amines, and various polymer-supported bases. After screening different solvent systems, it was observed that increasing amounts of DME decreased the reaction efficiency (Table 2, entry 4). Optimal reaction conditions were obtained using 3 mol % catalyst and heating to 110 °C

Table 2. Suzuki Coupling Reaction of 5-Bromobenzolidine with Various Catalytic Systems



entry	catalyst	solvent	conversion[a]
1	PdCl$_2$(PPh$_3$)$_2$	DME/EtOH (1:1)	88%
2	PS−PPh$_3$−Pd	DME/EtOH (1:1)	81%
3	FC 1001	DME/EtOH (1:1)	85%
4	FC 1001	DME/EtOH (7:2)	50%
5	FC 1001	EtOH	97%
6	FC 1001	EtOH	100%[b]
7	FC 1007	EtOH	100%
8	FC 1032	EtOH	100%

[a] Determined by ^{1}H NMR and LC/MS. [b] Microwave, 900 s, 110 °C.

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[5] For recent examples, see: (a) Larhed, M.; Hallberg, A. *J. Org. Chem.* **1996**, *61*, 9582−9584. (b) Leadbeater, N. E.; Marco, M. *J. Org. Chem.* **2003**, *68*, 888−892. (c) Leadbeater, N. E.; Marco, M. *J. Org. Chem.* **2003**, *68*, 5660−5667. (d) Leadbeater, N. E.; Marco, M. *Org. Lett.* **2002**, *4*, 2973−2976. (e) Gong, Y.; He, W. *Org. Lett.* **2002**, *4*, 3803−3805.

[6] (a) Choudary, B. M.; Madhi, S.; Chowdari, N. S.; Kantam, M. L.; Sreedhar, B. *J. Am. Chem. Soc.* **2002**, *124*, 14127−14136. (b) Fenger, I.; Drian, C. L. *Tetrahedron Lett.* **1998**, *39*, 4287−4290. (c) Yamada, Y. M.; Takeda, K.; Takahashi, H.; Ikegami, S. *J. Org. Chem.* **2003**, *68*, 7733−7741. (d) Uozumi, Y.; Danjo, H.; Hayashi, T. *J. Org. Chem.* **1999**, *64*, 3384−3388. (e) Zhang, W.; Chen, C. H.-T.; Lu, Y.; Nagashima, T. *Org. Lett.* **2004**, *6*, 1473−1476.

[7] Johnson Matthey. http://www.chemicals.matthey.com (accessed July 4, 2004).

[8] Colacot, T. J.; Gore, E. S.; Kuber, A. *Organometallics* **2002**, *21*, 3301−3304.

[9] Argonaut Technologies. http://www.argotech.com (accessed July 4, 2004).

[10] Microwave reactions were carried out on a Emrys Optimizer (http://www.personalchemistry.com). Wattage was automatically adjusted so as to maintain the desired temperature.

[11] SiliCycle, Inc. http://www.silicycle.com (accessed July 4, 2004).

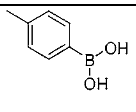
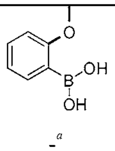
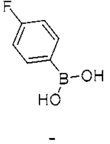
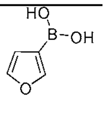
[12] **Representative Procedure.** A Smith Process vial (2−5 mL) was charged with a stir bar, 0.2 mmol (36.4 mg) of 4-bromobenzonitrile, 0.24 mmol (32.6 mg) of *p*-tolylboronic acid, and 2 mL of ethanol. A solution of 1 M K$_2$CO$_3$ (0.24 mL) was added to the solution followed by the polymer-supported Pd (3 mol % Pd) catalyst. The reaction vessel was sealed and heated to 110 °C for 600 s under microwave irradiation. After cooling, the reaction mixture was transferred to a prepacked column of Si-carbonate (2 g, 0.79 mmol/g), which had been conditioned with MeOH/CH$_2$Cl$_2$ (1:1), and the elutant was collected via gravity filtration. The column was then washed with MeOH/CH$_2$Cl$_2$ (1:1) (3 × 3 mL). The elutants were combined, concentrated, and purified by flash chromatography (silica, hexane/ethyl acetate, 0−10% gradient) to afford 38.3 mg (99%) of analytically pure 4′-methyl-biphenyl-4-carbonitrile.

for 10−15 min in EtOH with K_2CO_3 as the base (Table 2, entries 5−8).

Unlike the homogeneous system (Table 2, entry 1), the supported Pd reactions were much cleaner, usually yielding a colorless solution upon completion of the reaction. Analysis of the crude reaction mixture by LC-MS showed a single peak corresponding to the product with no observable phosphine byproducts. With $PdCl_2(PPh_3)_2$, a brown solution was obtained after heating and triphenylphosphine oxide was detected in the crude LC/MS.[13] FC 1007 and FC 1032,[14] which are more reactive than FC 1001, gave quantitative conversions with shorter reaction times (Table 2, entries 5−8).[15] All of the reactions were performed under ambient atmosphere in sealed microwave tubes, and no observable difference was found when the reaction was carried out under nitrogen. This allows for easy sample preparation and is advantageous for automated parallel synthesis as compared to the use of homogeneous Pd Suzuki catalysts, most of which are air sensitive to various extents.

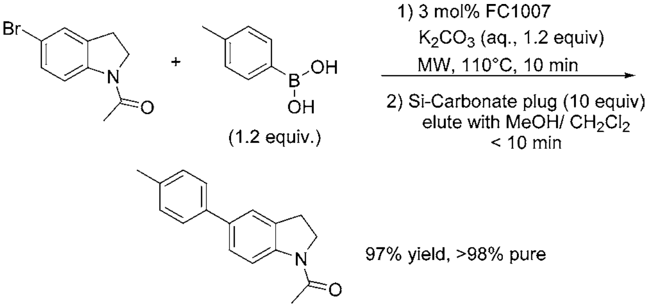
Solid-phase extraction (SPE) techniques have proven to be useful for scavenging a wide range of excess reagents and reaction side-products, including boronic acids.[16] SPE is especially well suited for parallel synthesis since in many cases a simple filtration will remove undesired materials, thereby greatly simplifying reaction workup. It has been found that the use of silica-supported reagents in SPE can greatly decrease the time required for byproduct sequestration.[17] Therefore, Si-carbonate was studied for its effectiveness in scavenging boronic acids. For these experiments, the desired amount of Si-carbonate was packed into a short column and subsequently prewetted with MeOH. A solution of boronic acid in EtOH was passed through the Si-carbonate column by gravity filtration and washed with additional MeOH. Compound **1** was added to the boronic acid solution and used as an internal standard to determine the amount of boronic acid in the eluted material by LC/MS and ^1H NMR. As seen in Table 3, it was found that 10 equiv of Si-carbonate efficiently scavenged the boronic acid completely in a single flow-through. Other solvents can be used effectively in combination with MeOH. The complete scavenging process takes less than 10 min and is effective with a range of boronic acids. This process greatly reduces reaction workup time, which is one of the bottlenecks in analogue synthesis. When the desired conversion is quantitative, and after SPE scavenging of excess boronic acid, no further purification is needed. As is shown in Scheme 1, application of the microwave-accelerated FibreCat-catalyzed Suzuki reaction followed by Si-carbonate SPE afforded the biaryl Suzuki product after 20 min in high yield and purity. The process can be easily adapted to automation and, in turn, utilized to prepare Suzuki libraries via parallel syntheses.

Table 3. Scavenging of Boronic Acids with a Si-Carbonate Plug

Si-carbonate	amount of boronic acid scavenged			
				
1 equiv	< 5%	-[a]	-	-
3 equiv	< 50%	-	-	-
10 equiv	100%	100%	100%	100%

[a] Not determined.

Scheme 1. Microwave-Accelerated Suzuki Reaction Utilizing FC 1007 and Si-Carbonate



With a convenient protocol in hand, we examined the scope of this method, and the results are summarized in Table 4. It was found that both electron-rich and electron-deficient boronic acids afforded the desired product in good to excellent yields. In addition, this method efficiently couples a wide range of aryl halides, including aryl bromides (entries 1−3), activated aryl chlorides (entries 4−5), and iodides (entries 6−8), affording excellent isolated yields. Aryl triflates can also be accommodated (entry 9). Aryl chlorides with electron-donating groups are generally challenging substrates for Suzuki coupling reactions. Under these conditions, moderate yields were obtained with inactivated aryl chlorides when the most reactive FibreCat, FC 1032, was used (entries 10 and 11). Many of the entries in Table 4 showed quantitative conversion by LC-MS and crude ^1H NMR. In those cases, passing the crude mixtures through a plug of Si-carbonate as described previously afforded the pure products without the need for further purification.

In summary, we have developed a rapid, efficient, and general Suzuki coupling reaction protocol that utilizes

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(13) Trace amounts (<35 ppm) of Pd were observed (ICP analysis) in some crude reaction products prepared with the supported catalysts. The leached Pd was eliminated during the flash chromatography step.

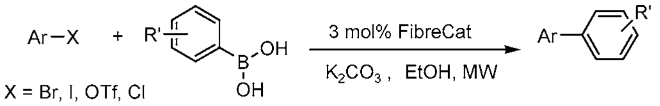
(14) FC 1032 is referred to as “Tuna Cat” in ref 8.

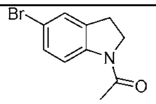
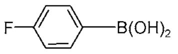
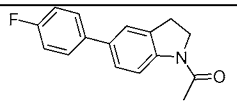
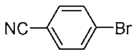
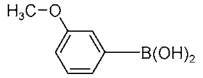
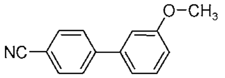
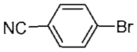
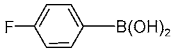
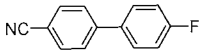
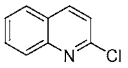
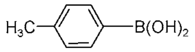
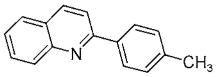
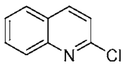
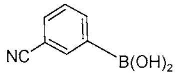
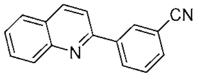
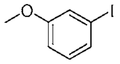
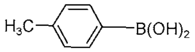
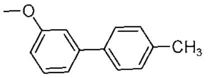
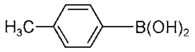
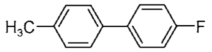
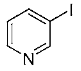
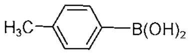
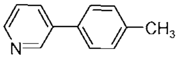
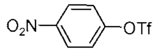
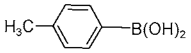
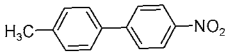
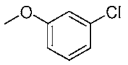
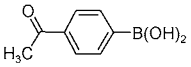
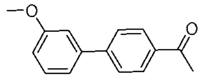
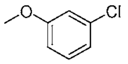
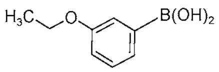
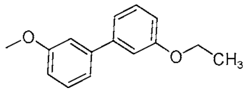
(15) Reaction was incomplete after 8 h when carried out in refluxing EtOH as described in ref 8.

(16) (a) Flynn, D. L.; Devraj, R. V.; Naing, W.; Parlow, J. J.; Weidner, J. J.; Yang, S. *Med. Chem. Res.* **1998**, *8*, 219−243. (b) Flynn, D. L.; Devraj, R. V.; Parlow, J. J. *Curr. Opin. Drug Discovery Dev.* **1998**, *1*, 41−50. (c) Weidner, J. J.; Parlow, J. J.; Flynn, D. L. *Tetrahedron Lett.* **1999**, *40*, 239−242. (d) Lan, P.; Berta, D.; Porco, J. A.; South, M. S.; Parlow, J. J. *J. Org. Chem.* **2003**, *68*, 9678−9686.

(17) Sauer, D. R.; Kalvin, D.; Phelan, K. M. *Org. Lett.* **2003**, *5*, 4721−4724.

Table 4. Suzuki Coupling Reactions Catalyzed by Polymer-Supported Pd under Microwave Irradiation



entry	Ar-X	R'	R-R'	isolated yield (%)[h] (conversion %)
1				90 (95)[a, c, d]
2				98 (100)[a, e]
3				98 (100)[a, e]
4				89 (100)[b, d]
5				95 (100)[b, d]
6				80[c, b, f]
7				83[b, f]
8				89 (100)[b, f]
9				61[c, b, d]
10				50[b, g]
11				61[b, g]

[a] FC 1001 was used. [b] FC 1032 was used. [c] Small amount of dehalogenated product was observed in the crude reaction mixture. [d] Reaction conditions: 1.4 equiv of boronic acid was used. Microwave, 110 °C, 900 s. [e] Reaction conditions: microwave, 110 °C, 600 s. [f] Reaction conditions: microwave, 120 °C, 600 s. [g] Reaction conditions: 1.5 equiv of boronic acid was used. Microwave, 120 °C, 1500 s. [h] Greater than 97% purity by HPLC (ELSD and UV detection) and NMR analysis.

commercially available polymer-supported Pd catalysts and microwave heating. Furthermore, it has been demonstrated that excess boronic acid can be effectively scavenged by Si-carbonate. The protocol is convenient and uses environmentally benign reagents and solvents. In addition, this Suzuki reaction procedure is highly amenable for parallel synthesis and has been successfully used for routine library generation in our laboratories.

Supporting Information Available: General experiment details and analytical characterization. This material is available free of charge via the Internet at http://pubs.acs.org.

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