ORGANIC
LETTERS

2005
Vol. 7, No. 11
2101−2104

Suzuki Coupling of Aryl Chlorides with Phenylboronic Acid in Water, Using Microwave Heating with Simultaneous Cooling

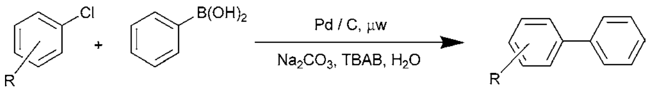
Riina K. Arvela and Nicholas E. Leadbeater*

Department of Chemistry, University of Connecticut, Unit 3060, 55 North Eagleville Road, Storrs, Connecticut 06269-3060

nicholas.leadbeater@uconn.edu

Received February 17, 2005

ABSTRACT

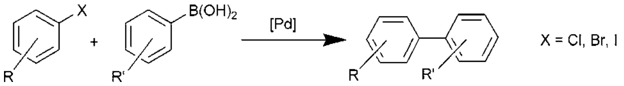


Microwave heating used in conjunction with simultaneous cooling

We present here a methodology for the Suzuki coupling of aryl chlorides with phenylboronic acid using Pd/C as a catalyst, water as a solvent, and microwave heating. We show that simultaneous cooling in conjunction with microwave heating prolongs the lifetime of the aryl chloride substrates during the course of the reaction and, as a result, yields of the desired biaryl as well as overall recovery of material can be increased.

The Suzuki reaction (palladium-catalyzed cross coupling of aryl halides with boronic acids) is well-known as being one of the most versatile and utilized reactions for the selective construction of carbon−carbon bonds, in particular for the formation of biaryls (Scheme 1).[1] While aryl iodides and bromides are the more reactive substrates in the reaction, it is aryl chlorides which are cheaper and more readily available. As a result, significant research effort has been focused on the preparation and use of catalysts capable of activating aryl chloride substrates.[2] Complexes bearing bulky phosphines,[3] *N*-heterocyclic carbenes,[4] or palladacyclic complexes[5] have been found to be particularly active.

Scheme 1



Research in our group has focused around the use of water as a solvent in conjunction with microwave heating for performing organic transformations. Water offers practical advantages over organic solvents. It is cheap, readily available, nontoxic, and nonflammable. As well as being energy efficient, microwaves can also enhance the rate of reactions and in many cases improve product yields. The interest in the areas is evidenced by the large number of papers and reviews appearing in the literature in the past few years.[6−8]

---

(1) For recent reviews see: (a) Bellina, F.; Carpita, A.; Rossi, R. *Synthesis* **2004**, 2419. (b) Pershichini, P. J. *Curr. Org. Chem.* **2003**, *7*, 1725. (c) Hassan, J.; Sévignon, M.; Gozzi, C.; Schulz E.; Lemaire, M. *Chem. Rev.* **2002**, *102*, 1359. (d) Kotha, S.; Lahiri, S.; Kashinath, D. *Tetrahedron* **2002**, *58*, 9633.

(2) For a general review see: Littke, A. F.; Fu, G. *Angew. Chem., Int. Ed.* **2002**, *41*, 4176.

(3) For recent representative examples see: (a) Smith, R. C.; Woloszynek, R. A.; Chen, W. Z.; Ren, T.; Protasiewicz, J. D. *Tetrahedron Lett.* **2004**, *45*, 8327. (b) Colacot T. J.; Shea, H. A. *Org. Lett.* **2004**, 6, 3731. (c) Milne J. E.; Buchwald, S. L. *J. Am. Chem. Soc.* **2004**, *126*, 13028. (d) Tewari, A.; Hein, M.; Zapf, A.; Beller, M. *Synthesis* **2004**, 935.

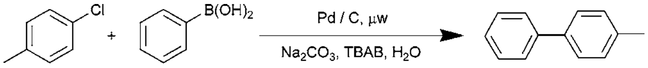
(4) For reviews see: (a) Peris, E.; Crabtree, R. H. *Coord. Chem. Rev.* **2004**, *248*, 2239. (b) Crudden, C. M.; Allen, D. P. *Coord. Chem. Rev.* **2004**, *248*, 2247. (c) Hillier, A. C.; Grasa, G. A.; Viciu, M. S.; Lee, H. M.; Yang C. L.; Nolan, S. P. *J. Organomet. Chem.* **2002**, *653*, 69. (d) Jafarpour, L.; Nolan, S. P. *Adv. Organomet. Chem.* **2001**, *46*, 181.

(5) For reviews see: (a) Bedford, R. B.; Cazin, C. S. J.; Holder, D. *Coord. Chem. Rev.* **2004**, *248*, 2283. (b) Chincilla, R.; Nájera, C.; Yus, M. *Chem. Rev.* **2004**, *104*, 2667. (c) Bedford, R. B. *Chem. Commun.* **2003**, 1787.

10.1021/ol0503384 CCC: $30.25

We have studied the Suzuki reaction extensively and found that it is possible to perform couplings of aryl bromides in neat water using microwave heating with as little as 50 ppb palladium as a catalyst.[9−12] The reaction involves the use of tetrabutylammonium bromide (TBAB) as a phase transfer agent. Although when using 0.4 mol % of $Pd(OAc)_2$ as a catalyst it is possible to couple some aryl chlorides, yields are moderate at best. A review of the literature shows that this is generally found to be the case for nonactivated substrates whenever simple palladium sources such as $Pd(OAc)_2$, $PdCl_2$, and palladium on carbon (Pd/C) are used as catalysts either in water or in water/organic solvent mixtures.[13−21] Yields can be improved by using palladacyclic complexes,[22] palladium complexes of phosphine oxides,[23] or di(2-pyridyl)methylamine-based palladium complexes[24] as catalyst precursors. An objective of our recent work has been to develop a methodology for Suzuki couplings of aryl chlorides in water but using just simple palladium sources as catalysts. We report our initial results here.

Table 1. Coupling of 4-chlorotoluene with Phenylboronic Acid[a]



entry	temp (°C)	simultaneous cooling	product (mmol)	material recovered (mmol)	
				4-chlorotoluene	total
1	120	no	0.40	0.23	0.63
2	100	no	0.19	0.19	0.38
3	135	no	0.56	0.08	0.64
4	150	no	0.61	0.10	0.71
5	120	yes	0.75	0.07	0.82
6	100	yes	0.40	0.12	0.52
7	135	yes	0.71	0.10	0.81
8	150	yes	0.56	0.19	0.75

[a] Reactions were run in a sealed tube, using 1 mmol of 4-chlorotoluene, 1.3 mmol of phenylboronic acid, 1 mol % of Pd/C, 3.7 mmol of Na_2CO_3, 1 mmol of TBAB, and 2 mL of water. An initial microwave irradiation of 300 W was used, the temperature being ramped from room temperature to the target temperature where it was then held until a total reaction time of 10 min had elapsed. Temperature was measured with a fiber-optic device inserted into the reaction vessel.

We decided to focus attention on the use of Pd/C. This has been used quite extensively as a catalyst for Suzuki couplings in aqueous media as well as in organic solvents.[25] Choice of cosolvent turns out to be very important, especially when using aryl chlorides as substrates. The first report of the use of Pd/C for the coupling in aqueous media was by a group from Hoffmann La Roche.[13] They showed that aryl iodides and bromides can be effectively coupled in mixtures of water and organic solvents, primarily ethanol. By changing the cosolvent from ethanol to dimethylacetamide (DMA), it is possible to favor the Suzuki cross coupling as opposed to homocoupling pathway when using Pd/C with aryl chlorides as substrates.[14] With those bearing electron-withdrawing groups, yields of between 79% and 95% are obtained with 5 mol % of Pd/C and a 20:1 mixture of DMA:water after 24 h. With those bearing electron-neutral or electron-donating functionalities longer times (48 h) or higher catalyst loadings (15 mol % of Pd/C) are required to obtain even moderate yields of the desired products. Low catalyst loadings can be sufficient when using Pd/C in NMP/water mixtures, *p*-chloroacetophenone being coupled with phenylboronic acid in high yields within 2 h at 120 °C with use of 0.05−0.25 mol % of Pd/C.[15,16] However, this was the only aryl chloride substrate cited.

To study reaction parameters, we used 4-chlorotoluene as a substrate (Table 1). A 40% yield of the desired biaryl was obtained when using phenylboronic acid as the coupling partner, water as the solvent, sodium carbonate as the base, 1 mol % of Pd/C as the catalyst, TBAB as a phase transfer agent, and microwave heating (Table 1, entry 1). We heated

---

(6) For a recent review see: Kappe, C. O. *Angew. Chem., Int. Ed.* **2004**, *43*, 6250.

(7) For other reviews on the general area of microwave-promoted organic synthesis see: (a) Lidström, P.; Tierney, J. P.; Wathey, B.; Westman, J. *Tetrahedron* **2001**, *57*, 9225. (b) Caddick, S. *Tetrahedron* **1995**, *51*, 10403.

(8) A number of books on microwave-promoted synthesis have been published recently: (a) Lidström, P.; Tierney, J. P., Eds. *Microwave-Assisted Organic Synthesis*; Blackwell, Oxford, UK, 2005 (b) Loupy, A., Ed. *Microwaves in Organic Synthesis*; Wiley-VCH: Weinheim, Germany, 2002. (c) Hayes, B. L. *Microwave Synthesis*: *Chemistry at the Speed of Light*; CEM Publishing: Matthews, NC, 2002.

(9) (a) Leadbeater, N. E.; Marco, M. *J. Org. Chem.* **2003**, *68*, 5660. (b) Leadbeater, N. E.; Marco, M. *Angew. Chem., Int. Ed.* **2003**, *42*, 1407. (c) Leadbeater, N. E.; Marco, M. *J. Org. Chem.* **2003**, *68*, 888. (d) Leadbeater, N. E.; Marco, M. *Org. Lett.* **2002**, *4*, 2973.

(10) Arvela, R. K.; Leadbeater, N. E.; Sangi, M. S.; Williams, V. A.; Granados, P.; Singer, R. D. *J. Org. Chem.* **2005**, *70*, 161.

(11) For reports of microwave-couplings in organic solvents or solvent free, see: (a) Hallberg, A.; Larhed, M. *J. Org. Chem.* **1996**, *61*, 9582. (b) Wang, Y.; Sauer, D. R. *Org. Lett.* **2004**, *6*, 2793. (c) Kabalka, G. W.; Wang, L.; Pagni, R. M.; Hair C. M.; Namboodiri, V. *Synthesis* **2003**, 217 (d) Kabalka, G. W.; Pagni, R. M.; Wang, L.; Namboodiri, V.; Hair, C. M. *Green Chem.* **2000**, *2*, 120.

(12) For reports of microwave-promoted Suzuki couplings in water, see: (a) Blettner, C. G.; Konig, W. A.; Stenzel, W.; Schotten T. *J. Org. Chem.* **1999**, *64*, 3885. (b) Han, J. W.; Castro, J. C.; Burgess, K. *Tetrahedron Lett.* **2003**, *44*, 9359. (c) Appukkuttan, P.; Orts, A.; Chandran, R. P.; Goeman, J. L.; Van der Eycken, J.; Dehaen, W.; Van der Eycken, E. *Eur. J. Org. Chem.* **2004**, 3277. (d) Gong, Y.; He, W. *Org. Lett.* **2002**, *4*, 3803. (e) Namboodiri, V. V.; Varma, R. S. *Green. Chem.* **2001**, *3*, 146. (f) Zhang, W.; Chen, C. H.-T.; Lu, Y.; Nagashima, T. *Org. Lett.* **2004**, *6*, 1473. (g) Solodenko, W.; Schön, U.; Messinger, J.; Glinschert, A.; Kirschning, A. *Synlett* **2004**, 1699.

(13) Marck, G.; Villiger, A.; Buchecker, R. *Tetrahedron Lett.* **1994**, *35*, 3277.

(14) LeBlond, C. R.; Andrews, A. T.; Sun, Y.; Sowa, J. R. *Org. Lett.* **2001**, *3*, 1555.

(15) Heidenreich, R. G.; Köhler, K.; Krauter, J. G. E.; Pietsch, J. *Synlett* **2002**, 1118.

(16) Gruber, M.; Chouzier, S.; Köhler, K.; Djakovitch, L. *Appl. Catal. A* **2004**, *265*, 161.

(17) Conlon, D. A.; Pipik, B.; Ferdinand, S.; LeBlond, C. R.; Sowa, J. R.; Izzo, B.; Collins, P.; Hom, G.-J.; Williams, J. M.; Shi, Y.-J.; Sun, Y. *Adv. Synth. Catal.* **2003**, *345*, 931.

(18) Sakurai, H.; Tsukuda, T.; Hirao, T. *J. Org. Chem.* **2002**, *67*, 2721.

(19) Gala, D.; Stamford, A.; Jenkins, J.; Kugelman, M. *Org. Proc. Res. Dev.* **1997**, *1*, 163.

(20) Ennis, D. S.; McManus, J.; Wood-Kaczmar, W.; Richardson, J.; Smith, G. E.; Carstairs, A. *Org. Proc. Res. Dev.* **1999**, *3*, 248.

(21) Mori, Y.; Seki, M. *J. Org. Chem*, **2003**, *68*, 1571.

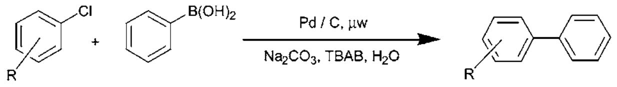
(22) See for example: (a) Chen, C. L.; Liu, Y. H.; Peng, S. M.; Liu, S. T. *Tetrahedron Lett.* **2005**, *46*, 521. (b) Alonso D. A.; Botella, L.; Nájera, C.; Pacheco, C. *Synthesis* **2004**, 1713. (c) Botella, L.; Nájera, C. *J. Organomet. Chem.* **2002**, *663*, 46.

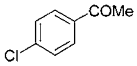
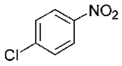
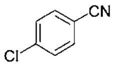
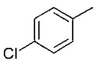
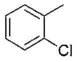
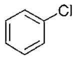
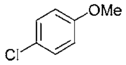
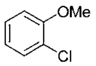
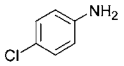
(23) Miao, G.; Ye, P.; Yu, L.; Baldino, C. M. *J. Org. Chem.* **2005**, *70*, 2332.

(24) (a) Nájera, C.; Gil-Moltó J.; Karlström, S. *Adv. Synth. Catal.* **2004**, *346*, 1798. (b) Nájera, C.; Gil-Moltó J.; Karlström, S. *Org. Lett.* **2004**, *5*, 1451.

(25) For a representative example of use of nonaqeous solvent mixtures see: Kabalka, G. W.; Namboodiri, V.; Wang, L. *Chem. Commun.*, **2001**, 775.

Table 2. Coupling of Aryl Chlorides with Phenylboronic Acid[a]



entry	aryl chloride	simultaneous cooling	product (mmol)	aryl chloride recovered (mmol)	total material recovered (mmol)
1		no	0.89	0.05	0.94
		yes	0.90	0.05	0.95
2		no	0.96	0.04	1.00
		yes	0.94	0.01	0.95
3		no	0.79	0.17	0.96
		yes	0.80	0.20	1.00
4		no	0.40	0.23	0.63
		yes	0.75	0.07	0.82
5		no	0.25	0.06	0.31
		yes	0.64	0.01	0.65
6		no	0.59	–[b]	–[b]
		yes	0.65	–[b]	–[b]
7		no	0.36	0.24	0.60
		yes	0.65	0.26	0.91
8[c]		no	0.22	0.53	0.75
		yes	0.48	0.42	0.90
9[c]		no	0.21	0.64	0.85
		yes	0.56	0.36	0.92

[a] Reactions were run in a sealed tube, using 1 mmol of aryl halide, 1.3 mmol of phenylboronic acid, 1 mol % of Pd/C, 3.7 mmol of Na_2CO_3, 1 mmol of TBAB, and 2 mL of water.An initial microwave irradiation of 300 W was used, the temperature being ramped from room temperature to 120 °C where it was then held until a total reaction time of 10 min had elapsed. Temperature was measured with a fiber-optic device inserted into the reaction vessel. [b] It is not possible to quantify exactly the remaining aryl halide due to possible evaporation during the workup procedure [c] Run for a total reaction time of 30 min.

the reaction mixture from room temperature to 120 °C in a sealed tube and then held at this temperature until a total reaction time of 10 min had elapsed. Analysis of the product mixture showed significant loss of material. We suspected that it was the aryl chloride starting material that was being destroyed during the course of the reaction. To confirm this, we repeated the reaction but in the absence of the boronic acid coupling partner and found that all the aryl chloride was lost during the 10 min reaction time. We tried decreasing the reaction temperature to 100 °C in an effort to limit the competitive decomposition of the chlorotoluene but obtained only a 19% yield of the desired product (Table 1, entry 2). Increasing the reaction temperature to 135 °C or 150 °C does lead to an increase in product yield but decomposition of the chlorotoluene is still a major problem (Table 1, entries 3 and 4).

We decided to explore the technique of simultaneous cooling while microwave heating. In principle, it allows for higher levels of microwave energy to be introduced into a reaction while maintaining the mixture at a particular temperature by passing a stream of compressed air over the reaction vessel. Recent reports appearing in the literature have suggested that this can result in higher product yields and new pathways that were previously unattainable.[26−28] We have investigated the concept ourselves, looking specifically at the measurement of temperature when using simultaneous cooling and then assessing its use in different synthetic transformations.[29] We found that it is important to monitor the temperature of a reaction mixture accurately and this involves the use of a fiber-optic temperature measurement setup. Using external IR temperature measurement, the temperature recorded is lower than the bulk temperature of the reaction mixture because of the air passing over the reaction vessel.

Using fiber-optic temperature measurement, we performed the Suzuki reaction between 4-chlorotoluene and phenylboronic acid using the same reaction conditions as before but this time with the application of simultaneous cooling. In the same total reaction time (i.e., 10 min) we obtained a 75% yield of the desired biaryl (Table 1, entry 5). This is 35% higher than when simultaneous cooling is not used. This difference could be attributed to the fact that the

---

(26) Chen, J. J.; Deshpande, S. V. *Tetrahedron Lett.* **2003**, *44*, 8873.

(27) Humphrey, C. E.; Easson, M. A. M.; Tierney, J. P.; Turner, N. J. *Org. Lett.* **2003**, *5*, 849.

(28) Katritzky, A. R.; Zhang, Y.; Singh, S. K.; Steel, P. J. *ARKIVOC* **2003**, *15*, 47.

(29) Leadbeater, N. E.; Pillsbury, S. J.; Shanahan, E.; Williams, V. A. *Tetrahedron* **2005**, *61*, 3565.

rate of decomposition of the aryl chloride substrate is lower when using simultaneous cooling thus prolonging its lifetime.

We repeated the reaction at lower and higher bulk temperatures with the addition of simultaneous cooling and found that overall recovery of material was higher and product yields increased or were approximately the same (Table 1, entries 6−8).

We subsequently screened different bases as well as catalyst loadings and, based on our results, we determined that, working on a 1 mmol scale, the optimum conditions were a 1:1.3 molar ratio of 4-chlorotoluene to phenylboronic acid, 1 mol % of Pd/C, 3.7 mmol of Na_2CO_3, 1 mmol of TBAB, 2 mL of water, and heating to 120 °C for a total reaction time of 10 min with simultaneous cooling.

We then screened a representative range of aryl chlorides in the coupling protocol with phenylboronic acid, both with and without the use of simultaneous cooling. The results are presented in Table 2. With substrates bearing electron-withdrawing groups, the effects of simultaneous cooling on the product yield are not significant (Table 2, entries 1−3). We attribute this to the fact that the coupling is faster than the decomposition of the chloride substrate and hence good yields of the desired biaryl are obtained even without simultaneous cooling. With substrates bearing electron-neutral or electron-donating substituents, cooling significantly increases the product yield and the total material recovered at the end of the reaction (Table 2, entries 4−9). Overall, the product yields obtained by using our methodology exceed the best already in the literature for Suzuki couplings of aryl chlorides with simple palladium sources.

We have attempted to identify the decomposition products formed from the aryl chloride starting materials. To achieve this, we ran the reaction without the addition of the boronic acid component and analyzed the product mixture. While we cannot definitively say what the decomposition products are in the reaction currently, we can rule out formation of the corresponding phenol or des-chloro compound.

In summary, we have developed a methodology for the Suzuki coupling of aryl chlorides with phenylboronic acid using palladium on carbon as a catalyst, water as a solvent, and microwave heating. We have investigated the use of simultaneous cooling in conjunction with microwave heating and shown that this prolongs the lifetime of the aryl chloride substrates during the course of the reaction. As a result, with substrates bearing electron-neutral or electron-donating substituents, yields of the desired biaryl can be increased as well as overall recovery of material. We are currently investigating further the substrate scope of the reaction as well as the origins of the effect of simultaneous cooling.

Acknowledgment. The University of Connecticut is thanked for funding.

Supporting Information Available: General experimental details, a typical procedure for the Suzuki coupling reactions, temperature, pressure, and power profiles for a reaction with cooling on and cooling off and spectral data for the coupling products. This material is available free of charge via the Internet at http://pubs.acs.org.

OL0503384