Available online at www.sciencedirect.com

SCIENCE DIRECT®

Tetrahedron Letters 45 (2004) 6959–6962

Tetrahedron Letters

Palladium catalyzed ligand-free Suzuki cross-coupling reactions of benzylic halides with aryl boronic acids under mild conditions

B. P. Bandgar,* Sampada V. Bettigeri and Jaywant Phopase

Organic Chemistry Research Laboratory, School of Chemical Sciences, Swami Ramanand Teerth Marathwada University, Vishnupuri, Nanded 431 606, India

Received 29 April 2004; revised 7 July 2004; accepted 16 July 2004
Available online 10 August 2004

Abstract—A highly efficient Suzuki cross-coupling reaction between benzylic halides and aryl boronic acids using palladium chloride as catalyst in acetone:water (3:1) as the solvent system has been developed. High yields of products, mild reaction conditions and short reaction times in the absence of ligand are important features of this method.

The palladium catalyzed Suzuki–Miyaura cross-coupling reaction[1] between aryl boronic acids and aryl halides or triflates has proved to be a very popular and versatile method for forming the carbon–carbon single bonds of biaryls.[2] Diarylmethane derivatives are important building blocks in organic synthesis because of their industrial applications. Organoboron reagents exhibit greater functional group compatibility than organozinc or Grignard reagents. Moreover, the innocuous nature of boronic acids, which are generally non-toxic and thermally air- and moisture-stable, is a practical advantage of the Suzuki reaction relative to other coupling processes. However, the procedure generally suffers from high catalyst loading due to the fast decomposition of the catalyst. In recent years, several thermally stable palladium catalysts have been successfully used for the Suzuki reaction,[3] but most of the results, which have been described with these catalysts were obtained for the coupling of aryl halides. With these catalysts, relatively few results have been reported for the coupling of benzylic halides.[4–6] Most of the results described involve drastic conditions, specific ligands[4–6] and popular but unstable catalysts.[5,6]

Negishi and co-workers had earlier reported Pd(0)- and Ni(0)-catalyzed syntheses of unsymmetrical diarylmethanes via the corresponding benzylzinc bromides or benzylmagnesium chlorides with aryl bromides or iodides.[7] There are other instances in which Pd(0)-catalyzed couplings of benzylic halides under Stille-type conditions have been reported.[8] Bransdsma and co-workers[9] evaluated benzyl–aryl cross-couplings for the synthesis of various tetrachlorobenzyltoluenes using four different transition metal catalysts with a number of different aryl metal compounds. However, they did not employ Suzuki–Miyaura conditions. Longer reaction times (20–48 h), drastic conditions (130 °C) and low yields are the disadvantages associated with some of the reported methods involving Suzuki cross-coupling reactions. In this communication, we report ligand-free palladium catalyzed cross-coupling reactions of aryl boronic acids with benzyl halides in acetone:water (3:1) as the solvent system at room temperature (Scheme 1).

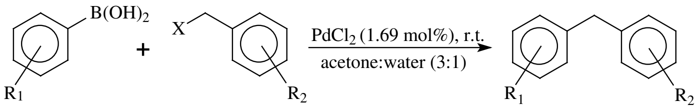
The catalytic study (Table 1) showed that in the absence of catalyst, there was no reaction even after stirring the reaction mixture for 24 h and benzyl iodide was quantitatively recovered. Formation of a trace amount of the corresponding diphenylmethane was observed when the reaction was performed in the presence of 0.56 and 0.81 mol% of $PdCl_2$ as catalyst. Moderate yields (54% and 66%) of the diphenylmethane were obtained in the presence of 1.12 and 1.40 mol% of $PdCl_2$. However, with 1.69 mol% of $PdCl_2$ the reaction was complete in a short time (0.8 h) and an excellent yield of diphenylmethane was obtained (97%). It is important to note that when the amount of catalyst is increased from 1.69 to 2.25 or 2.82 mol%, the yield of the product did not improve

---

Keywords: Suzuki cross-coupling reactions; Catalyst; Aryl boronic acids; Benzylic halides; Diarylmethanes.

* Corresponding author. Tel.: +91-2462-229242/3; fax: +91-2462-229245; e-mail: bandgar_bp@yahoo.com

0040-4039/$ - see front matter © 2004 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2004.07.073



R_1= H, OMe, OCH_2Ph, R_2 = H, NO_2, F, Cl, Br, I, X = Cl, Br, I

Scheme 1.

Table 1. Catalytic study of Suzuki cross-coupling reactions between benzene boronic acids (1 mmol) and benzyl iodide (1 mmol)

Entry	Catalyst, $PdCl_2$ (mol%)	Reaction time (h)	Yield (%)
1	0	24	—
2	0.56	24	—
3	0.81	24	—
4	1.12	24	54
5	1.40	24	66
6	1.69	0.8	97
7	2.25	0.8	96
8	2.25	24	96
9	2.82	24	96

even after stirring the reaction mixture for 24 h (Table 1, entries 7 and 8).

Applying the optimized conditions, we studied the Suzuki cross-coupling reaction of benzyl bromide with phenyl boronic acid, which furnished an excellent yield of diphenylmethane **2a** (95%) in 2.5 h (Table 2, entry 1). However, the coupling reaction of benzyl iodide with phenyl boronic acid gave a better yield (97%) in a shorter reaction time (0.8 h) (entry 2). There was no coupling reaction between benzyl chloride and phenyl boronic acid even after stirring the reaction mixture for 24 h (entry 20). Next, the coupling reaction was examined with several substituted benzyl bromides and substituted aryl boronic acids in the presence of catalyst (Table 2). Even *o*-xylene and *p*-xylene dibromides underwent smooth Suzuki cross-couplings giving good to excellent yields of products, although, longer reaction times were required for the coupling of these dibromides with vari-

Table 2. Palladium catalyzed Suzuki cross-coupling reactions of aryl boronic acids with benzyl halides

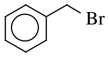
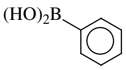
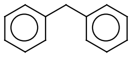
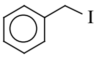
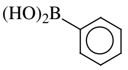
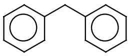
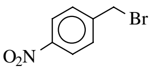
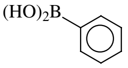
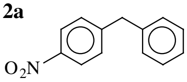
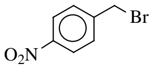
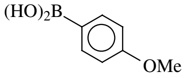
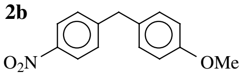
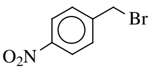
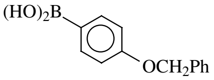
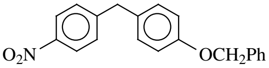
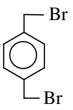
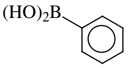
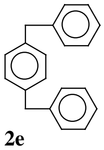
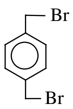
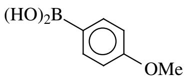
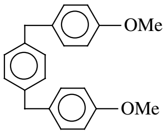
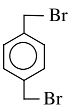
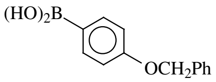
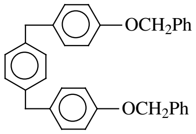
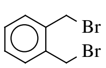
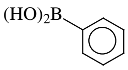
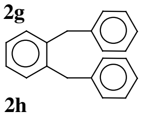
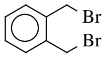
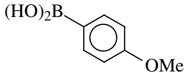
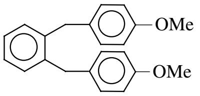
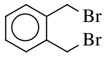
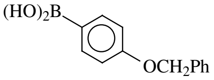
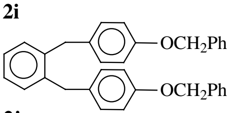
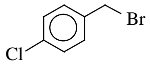
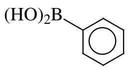
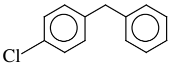
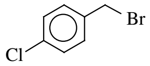
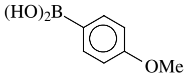
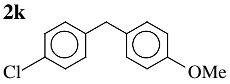
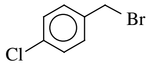
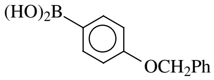
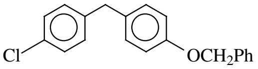
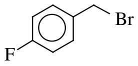
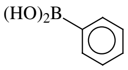
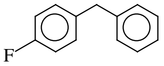
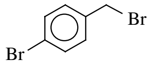
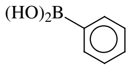
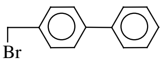
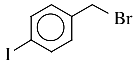
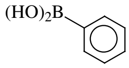
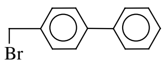
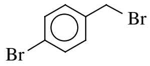
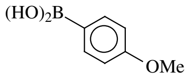
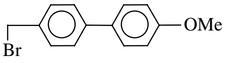
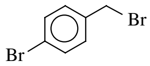
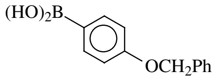
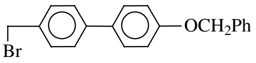
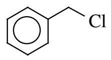
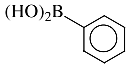
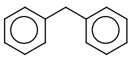
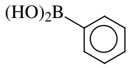
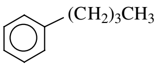
Entry	Benzyl halide	Borornic acid	Product	Time (h)	Yield[a] (%)
1			 **2a**	2.5	95
2			 **2a**	0.8	97
3			 **2b**	2.4	94
4			 **2c**	3.0	92
5			 **2d**	2.0	95
6			 **2e**	4.0	85
7			 **2f**	4.5	84
8			 **2g**	6.0	75
9			 **2h**	7.0	80

Table 2 (*continued*)

Entry	Benzyl halide	Borornic acid	Product	Time (h)	Yield[a] (%)
10			 **2i**	10.0	70
11			 **2j**	15.0	67
12			 **2k**	3.0	87
13			 **2l**	3.0	90
14			 **2m**	3.5	85
15			 **2n**	3.0	91
16			 **3a**	1.0	93
17			 **3a**	0.5	94
18			 **3b**	1.25	88
19			 **3c**	1.5	92
20				24	N.R.
21	$CH_3(CH_2)_3Br$			24	N.R.

N.R.: No reaction.

[a] Yields of isolated, pure products.

ous aryl boronic acids (Table 2, entries 6–11). It is interesting to note that benzyl bromides and iodides underwent smooth coupling with aryl boronic acids whereas halogens such F and Cl present on the aromatic ring remained unaffected (Table 2, entries 12–15). However, aromatic bromides and iodides underwent the Suzuki cross-coupling reaction selectively in the presence of benzyl bromides (Table 2, entries 16–19). Attempts to react alkyl bromides with aryl boronic acids did not afford any trace of the cross-coupled product even after stirring the reaction mixture for 24h.

In conclusion, we have developed a highly efficient method for the synthesis of diarylmethanes using a ligand-free Suzuki cross-coupling reaction.

Typical procedure: A mixture of phenyl boronic acid (1mmol), potassium carbonate (2.5mmol), 4-nitrobenzyl iodide (1mmol) in acetone–water (3:1, 10mL) was stirred at room temperature until the reaction mixture became homogeneous. Then, the mixture was cooled in an ice bath and $PdCl_2$ (3mg, 1.69mol%) was added at 0°C under a nitrogen atmosphere. Stirring was continued at room temperature until completion of the reaction (TLC). The solvent was removed under reduced pressure and the product was extracted with diethyl ether. Removal of the solvent under vacuum furnished a crude product, which was further purified by column chromatography using silica gel and 100% petroleum ether.

2b: mp: 80°C; IR (KBr, neat): 854, 1103, 1407, 1535, 1608, 2855, 2922 cm^{-1}; ^{1}H NMR (300MHz, $CDCl_3$): δ 3.8 (s, 2H, Ar–CH_2), 7.5 (d, 2H, $J = 8.6$Hz, Ar–H), 7.8–7.9 (m, 5H, Ar–H), 8.2 (d, 2H, $J = 8.6$Hz, Ar–H). Anal. Calcd for $C_{13}H_{11}NO_2$: C, 73.22; N, 6.56; H, 5.19. Found: C, 73.09; N, 6.50; H, 5.19.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2004.07.073.

References and notes

1. (a) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457; (b) Suzuki, A. *J. Organomet. Chem.* **1999**, *576*, 147; (c) Suzuki, A. *J. Organomet. Chem.* **2002**, *653*, 83; (d) Littke, A. F.; Fu, G. C. *Angew. Chem., Int. Ed.* **2002**, *41*, 4176.
2. (a) Hoye, T. R.; Chen, M. *J. Org. Chem.* **1996**, *61*, 7940; (b) Hensel, V.; Lutzow, K.; Jocob, J.; Gessler, K.; Schluter, A.-D. *Angew. Chem., Int. Ed.* **1997**, *36*, 2654; (c) Schwartz, E. B.; Knobler, C. B.; Cram, D. J. *J. Am. Chem. Soc.* **1992**, *114*, 10775; (d) Mohri, S.-I.; Stefinovic, M.; Snieckus, V. *J. Org. Chem.* **1997**, *62*, 7072.
3. (a) Beller, M.; Fischer, H.; Hermann, W. H.; Ofele, K.; Brossmer, C. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 1848; (b) Albisson, D. A.; Bedford, R. B.; Lawrence, S. E.; Scully, P. N. *Chem. Commun.* **1998**, 2095; (c) Weissman, H.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **1999**, *38*, 2413; (d) Wolfe, J. P.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **1999**, *38*, 2413; (e) Wolfe, J. P.; Singer, R. A.; Yange, B. H.; Buchwald, S. L. *J. Am. Chem. Soc.* **1999**, *121*, 9550.
4. (a) Chowdhury, S.; Georghiou, P. E. *Tetrahedron Lett.* **1999**, *40*, 7599; (b) Maddaford, S. P.; Keay, B. A. *J. Org. Chem.* **1994**, *59*, 6501; (c) Chahen, L.; Doucet, H.; Santelli, M. *Synlett* **2003**, 1168.
5. (a) Snarp, M. J.; Snicckus, V. *Tetrahedron Lett.* **1985**, *26*, 5997; (b) Pernia, G. J.; Kilburn, J. D.; Essex, J. W.; Mortishire-Smith, R. J.; Rowley, M. *J. Am. Chem. Soc.* **1996**, *118*, 10220; (c) Chowdhury, S.; Georghiou, P. E. *Tetrahedron Lett.* **1999**, *40*, 7599; (d) Juteau, H.; Gareau, Y.; Labelle, M.; Sturino, C. F.; Sawyer, N.; Tremblay, N.; Lamontagne, S.; Carriere, M.-C.; Denis, D.; Metters, K. M. *Bioorg. Med. Chem.* **2001**, *9*, 1977; (e) Botella, L.; Najera, C. *Angew. Chem., Int. Ed.* **2002**, *41*, 179.
6. (a) Moreno-Manas, M.; Pujuelo, F.; Pleixats, R. *J. Org. Chem.* **1995**, *60*, 2396; (b) Cortes, J.; Moreno-Manas, M.; Pleixats, R. *Eur. J. Org. Chem.*, **2000**, 239; (c) GooBen, L. *J. Chem. Commun.* **2001**, 669; (d) Liu, X.-X.; Deng, M.-Z. *Chem. Commun.* **2002**, 622.
7. Negishi, E.; King, A. O.; Okukado, N. *J. Org. Chem.* **1977**, *42*, 1821.
8. Kamlage, S.; Sefkow, M.; Peter, M. G. *J. Org. Chem.* **1999**, *64*, 2938, and references cited therein.
9. de Lange, R.-J.; van Hooijdonk, M. J. C. M.; Brandsma, L. *Tetrahedron* **1995**, *60*, 7284.