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18-Crown-6 promoting Pd/C-catalyzed crosscoupling reaction of aryl bromides and arylboronic acids in aqueous media

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Pd/C-catalyzed Suzuki–Miyaura cross-coupling between aryl bromides and arylboronic acids in 50% methanol aqueous solution proceeded smoothly in the presence of 18-crown-6. Various aryl bromides bearing electron-withdrawing groups and electron-donating groups coupled with arylboronic acid in high yields. In addition, the catalyst could be recycled five times without loss of activity. Copyright © 2012 John Wiley & Sons, Ltd.

Supporting information may be found in the online version of this article.

Keywords: Pd/C; 18-crown-6; Suzuki–Miyaura reaction; recycle; biaryl

Introduction

The palladium-catalyzed Suzuki-Miyaura coupling reaction^[1-5] between aryl halides and arylboronic acids is one of the most important carbon-carbon bond-forming processes in synthetic organic chemistry.^[6-10] In the past few years, great advances have been made in developing active and efficient catalysts by modifying traditional ligands and discovering new ones.[11-13] However, these ligands and Pd precursors are expensive and the palladium catalysts are usually not reusable. To overcome these difficulties, the application of a reusable palladiumcatalvzed Suzuki- Mivaura cross-coupling reaction has been developed.^[14,15] Palladium on carbon (Pd/C) is one of the most frequently used catalysts in industrial applications because of its high catalytic activity, low cost and easy removal from the reaction mixture.^[16,17] The first example of a Pd/C-catalyzed Suzuki reaction was reported by Marck and coworkers in 1994.^[18] Initially, Pd/C was considered as a heterogeneous catalyst for the Suzuki reaction, enabling straightforward removal of the catalyst from the reaction mixture by passing through a filter.^[19,20] However, Conlon has reported that the Suzuki reaction proceeds by a homogeneous pathway when using Pd/C as the catalyst.^[21] The group of Chen also reported that leached/dissolved Pd species are the true active species and Pd absorbed on active carbon has no heterogeneous contribution to the reaction.^[22] In recent years, further interesting examples of Suzuki reactions catalyzed by Pd/C have been reported.^[23-32] Andrus reported a novel bis-phenanthryl NHC ligand for the efficient coupling of aryl chlorides at room temperature with KF/18-crown-6 in THF.^[30] Sajiki and coworkers developed a ligand-free Pd/C-catalyzed system in which aryl bromides were coupled with various arylboronic acids in good yields at room temperature, but the aryl bromides bearing electron-donating groups, such as methoxy, showed lower reactivity and took longer to go to completion.^[31] Mayur V. Khedkar and coworkers found that coupling between aryl halides and arylboronic acids was effective using Pd/C and K_2CO_3 in anisole without other ligands or promoters, but the protocols were limited to the more reactive aryl iodides and required high temperatures.^[32]

Herein, we report an efficient Pd/C-catalyzed Suzuki reaction of aryl bromides and arylboronic acids promoted by 18-crown-6. This method was applied to a wide variety of substrates under mild conditions. In particular, the catalyst could be recovered and recycled five times without loss of activity.

Results and Discussion

Upon preliminary investigation, it was found that the reaction of aryl bromides and arylboronic acids proceeded smoothly to give coupled biaryls in the presence of Pd/C. The addition of 18-crown-6 could improve the effectiveness of the catalyst for the Suzuki reaction. Initially, the reaction conditions were optimized starting from 4-bromonitrobenzene and phenylboronic acid catalyzed by Pd/C with varying amounts of 18-crown-6, as shown in Table 1.

The reaction was completed in 12 h in the absence of 18-crown-6 (Table 1, entry 1). Increasing the amount of 18-crown-6 from 0.5 equiv. to 1.0 equiv., resulting in a remarkable acceleration of the rate and reaction time, was reduced to 1 h (Table 1, entries 2 and 3). Further increasing the amount of 18-crown-6 did not cause a reduction in the reaction time

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Table 1. Effect of the amount of 18-crown-6 on the Suzuki reaction ^a					
	O ₂ NBr +B(OH) ₂	10% Pd/C (2 mol% <u>18-Crown-6</u> 50% MeOH 45°C K_2CO_3 O_2N			
Entry	18-crown-6 (equiv.)	Time (h) ^b	Yield (%) ^c		
1	0	12	90		
2	0.5	6	96		
3	1.0	1	98		
4	2.0	1	97		
^a Reaction conditions: 4-bromonitrobenzene (0.5 mmol), phenylboronic acid (0.6 mmol), K ₂ CO ₃ (1.0 mmol), 10 wt% Pd/C(2 mol%, 0.01 mmol), 50%					

methanol (4 ml), 45°, the reaction was monitored by thin-layer chromatography.

^clsolated yield.

(Table 1, entry 4). Therefore, 1.0 equiv. of 18-crown-6 was selected as the additive in this catalytic system.

Although the reason for the difference in catalyst activity is not clear, it might be caused by the high concentration of leached Pd in the reaction mixture. Firstly, the oxygen atom on 18-crown-6 could bind to the palladium adsorbed on the active carbon support and remove it from the solution. Secondly, 18-crown-6 could help to stabilize Pd in solution. Therefore, the function of 18-crown-6 is similar to the phase transfer catalyst and ligands in the reaction

Generally, base is an important factor in the cross-coupling reaction.^[33] Various bases were evaluated for the model crosscoupling reaction of 4-bromonitrobenzene with phenylboronic acid. The results are summarized in Table 2 and show that K₂CO₃ (Table 2, entry 1) gave better results than other bases (Table 2, entries 2-6). Therefore, K₂CO₃ was selected as the effective base in this catalytic system.

Further investigations were carried out to examine the influence of the solvent on the same model reaction. The results are summarized in Table 3. Both methanol and 50% methanol aqueous solution (Table 3, entries 1 and 2) gave satisfactory yields; 50% methanol aqueous solution gave an excellent result, whereas the use of pure H₂O gave quite a poor result (Table 3, entry 3). On the other hand, dioxane, acetone and DMF, usually used as solvents in the Suzuki reactions, resulted in low yields (Table 3, entries 4-6). In addition, small amounts of benzene and phenol were observed in the reactions formed by protodeboronation of phenylboronic acid.

Next, we applied the optimized conditions for the Suzuki crosscoupling reaction of a range of aryl halides with arylboronic acids in the presence of 2 mol% Pd/C at 45 °C in 50% methanol agueous solution. As illustrated in Table 4, various aryl bromides containing an electron-withdrawing group such as 4-NO2 and 4-CHO, and electron-donating groups such as 4-OCH₃, reacted smoothly with phenylboronic acid to provide the corresponding cross-coupling products in high yields (Table 4, entries 1-4). Regarding the aryl boronic acid, the coupling reaction using electron-rich aryl boronic acid proceeded quite efficiently relative to non-substituted phenylboronic acids. (Table 4, entries 5-9). For example, 3,4-dimethoxyphenylboronic acid underwent Suzuki coupling with 4-bromonitrobenzene to afford the desired product in 99% yield in 0.5 h (Table 4, entry 5). Noticeably, the crosscoupling reaction of ortho-substituted aryl bromides gave the expected biaryl derivatives in high yield (Table 4, entry 9). As far

Table 2. Effect of base on the Suzuki reaction ^a				
	O_2N Br + $B(OH)_2$	10% Pd/C (2 mol%) base (2.5 equiv) solvent,45°C 18-Crown-6 (1 equiv)	>	
Entry	Base	Time (h)	Yield (%) ^b	
1	K ₂ CO ₃	1	98	
2	Na ₂ CO ₃	1	89	
3	NaOH	1	46	
4	NaHCO ₃	1	52	
5	Cs ₂ CO ₃	1	63	
6	Et ₃ N	2	25	

^aReaction conditions: 4-bromonitrobenzene (0.5 mmol), phenylboronic acid (0.6 mmol), 10 wt% Pd/C(2 mol%, 0.01 mmol), base (1.0 mmol), 18-crown-6 (0.5 mmol), 50% methanol (4 ml), 45 °C.

^bIsolated yield.

^bCompletion time.

Table 3. Effect of different solvents on the Suzuki reaction^a

	O ₂ N Br + B(OH) ₂	$10\% \text{ Pd/C (2 mol%)}$ $18\text{-Crown-6(1 equiv)}$ Solvent K ₂ CO ₃ 45°C	
Entry	Solvent	Time (h)	Yield (%)
1	MeOH	3	94 ^b
2	50%MeOH	1	98 ^b
3	H ₂ O	12	5 ^c
4	Dioxane	6	33 ^c
5	Acetone	6	22 ^c
6	DMF	6	28 ^c

^aReaction conditions: 4-bromonitrobenzene (0.5 mmol), phenylboronic acid (0.6 mmol), 10 wt% Pd/C(2 mol%, 0.01 mmol), 18-crown-6 (0.5 mmol), K₂CO₃ (1.0 mmol), solvent (4 ml), 45 $^{\circ}$ C.

^bIsolated yield.

^cNot completed.

Table 4. Pd/C-catalyzed Suzuki–Miyaura cross-coupling between aryl bromides and arylboronic acids ^a				
	R_1 Br + (HO) ₂ B-	Pd/C(2mol %) 	OH R1 R2	
Entry	R ₁	R ₂	Time (h) ^b	Yield (%) ^c
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17	4-NO ₂ 4-CHO 4-OMe 3-OMe, 4-OMe 4-NO ₂ 4-CHO 4-OMe 3,4-OCH ₂ O- 2-NO ₂ , 4-OMe 4-NO ₂ 4-CHO 4-OMe 3,4-OCH ₂ O- 2-NO ₂ , 4-OMe 3,4-OCH ₂ O- 2-NO ₂ , 4-OMe 4-NO ₂ 4-OMe 3-OMe 3-OMe 3-OMe	H H H 3-OMe, 4-OMe 3-OMe, 4-OMe 3-OMe, 4-OMe 3-OMe, 4-OMe 3-OMe, 4-OMe 4-CF ₃ 4-CF ₃ 2-Me, 5-Me	1 1 2 4 0.5 0.5 1 3 5 3 3 5 8 8 8 8 8 8 2 3 5	99 98 97 97 99 99 98 91 91 96 95 94 92 91 88 98 92 24
18	3-OMe, 4-OMe 3,4-OCH ₂ O-	2-Me, 5-Me 2-Me, 5-Me	5	84 86
20 21 22	4-NO ₂ 4-NO ₂ 4-CHO	2-Me, 5-Me 4-CF ₃ 4-CF ₃	6 3 3	34" 22 ^d 26 ^d
23 24	4-NO ₂ 4-NO ₂	4-CF ₃ 4-CF ₃	3 3	90 ^e 28 ^f

^aReaction conditions: aryl bromides (0.5 mmol), aryl boronic acid (0.6 mmol), 10 wt% Pd/C (2 mol%, 0.01 mmol), K₂CO₃ (1.0 mmol), 18-crown-6 (0.5 mmol), 50% methanol aqueous solution (4 ml), 45 °C.

^bCompletion time.

^clsolated yield.

^dWithout addition of 18-crown-6.

^e18-Crown-6 (0.1 equiv.) was added to the mixture with an incubation period of 30 min.

^f18-Crown-6 (0.1equiv.) was added to the mixture without an incubation period.

as we know, aryl boronic acids bearing electron-withdrawing groups usually shows lower reactivity in the Suzuki reaction.^[25,34] Very few papers, to the best of our knowledge, have reported that high yields were achieved with arylboronic acids bearing strong electron-withdrawing groups. In this catalytic system, 4-(trifluoromethyl)phenylboronic acid coupled with various aryl bromides bearing electron-withdrawing groups and electrondonating groups gave high yields (Table 4, entries 10-15). For example, 4-(trifluoromethyl)phenylboronic acid reacted with 4-bromonitrobenzene to afford the product in 98% yield in 3 h (Table 4, entry 10). However, the Suzuki reaction between 4-bromonitrobenzene and 4-(trifluoromethyl)phenylboronic acid did not go to completion without the addition of 18-crown-6 (Table 4, entry 21). Steric hindrance of the ortho-substituted arylboronic acids did not affect the reaction progress in this system. 2,5-Dimethylphenylboronic acid coupled with various aryl bromides in high yields (Table 4, entries 16-19). For example, 2,5-dimethylphenylboronic acid reacted with 4-bromonitrobenzene to afford the product in 98% yield in 2 h (Table 4, entry 16). By contrast, only 34% yield was achieved without the addition of 18-crown-6 (Table 4, entry 20). In addition, we tried to carry out the Suzuki coupling of aryl chlorides with phenylboronic acid in this system. Unfortunately, no desired product was obtained when 4-chloronitrobenzene was coupled with phenylboronic acid at 80 °C using a catalyst loading of 5 mol%.

From the standpoint of green chemistry, low loading of additive would be desirable. Simeone has reported an efficient system catalyzed by palladium on carbon and the amount of ligand can be significantly decreased by incorporating an incubation period.^[25] Thus we designed experiments whereby low levels of 18-crown-6 (0.1equiv.) are added to the reaction mixture after a short incubation period. We were surprised to find that the reaction between 4-bromonitrobenzene and 4-(trifluoromethyl) phenylboronic acid proceeded quite efficiently to afford the product in 90% yield with only 0.1 equiv. of 18-crown-6 added to the reaction mixture after an incubation time of 30 min (Table 4, entry 23). On the other hand, only 28% yield was achieved without incubation time (Table 4, entry 24).

We next examined the reuse of Pd/C in the coupling of 4-bromonitrobenzene with phenylboronic acid. The results are

summarized in Table 5 and show that Pd/C could be recycled five times without loss of activity. After the fifth run, Pd/C was filtered through a 0.45 μ m filter and the filtrates were analyzed by inductively coupled plasma (ICP) for palladium. ICP analysis showed that less than 1 ppm leached Pd existed in the filtrate after catalyst removal. These results show that after the reaction was completed almost all the dissolved palladium species can redeposit on the support, and be easily separated from the reaction mixture, which is consistent with the reports by Chen and coworkers.^[22]

In conclusion, we have developed a mild and efficient protocol for Pd/C-catalyzed Suzuki–Miyaura cross-coupling reaction. The addition of 18-crown-6 can promote the reaction. The method allows for the preparation of a wide variety of biaryl derivatives with excellent yields. Furthermore, the Pd/C catalyst could be recycled five times without loss of activity.

Experimental

General Information

Unless otherwise stated, all the reactions were carried out in air. All aryl bromide and arylboronic acids were purchased from Aladdin, Alfa, and used without purification. Pd/C was purchased from Kaida Chemical Co. Ltd. The bases and solvents were purchased from Kermel Chemical Co. Ltd. NMR spectra were recorded on a Bruker Avance 400 spectrometer. Chemical shifts are reported in ppm relative to TMS. The Pd analysis was performed by ICP-MS (Thermo Electron, XSeries II). All products were isolated by short chromatography on a silica gel (200–300 mesh) column using petroleum ether (60–90 °C).

General Procedure for the Suzuki-Miyaura Cross-Coupling Reaction

Aryl bromide (0.5 mmol), arylboronic acid (0.6 mmol), K_2CO_3 (1.0 mmol ,138 mg), 10 wt% Pd/C(0.01 mmol, 24 mg), 18-crown-6 (0.5 mmol, 132 mg) and MeOH (2 ml) and H_2O (2 ml) were added to a test tube, and the reaction mixture was stirred at 45 °C in air. After a certain period, the reaction mixture was diluted with H_2O



^aReaction conditions: 4-bromonitrobenzene (0.5 mmol), phenylboronic acid (0.6 mmol), K₂CO₃ (1.0 mmol), 10 wt% Pd/C(2 mol%, 0.01 mmol), 18-crown-6 (0.5 mmol) and 50% MeOH (4 ml), 45°.

^bCompletion time.

^cIsolated yield.

(10 ml) and EtOAc (10 ml) and passed through a membrane filter. The filtrate was separated into two layers and the aqueous layer was extracted with EtOAc (2×10 ml). The combined organic layers were washed with brine (10 ml), dried over MgSO₄, and concentrated *in vacuo*. The crude product was purified by column chromatography on silica gel using petroleum ether to afford pure product. All of the isolated products were gave satisfactory ¹H NMR data (see supporting information).

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References

- [1] N. Miyaura, A. Suzuki, Chem. Rev. 1995, 95, 2457.
- [2] A. Suzuki, J. Organomet. Chem. **1999**, 576, 147.
- [3] S. Kotha, K. Lahiri, D. Kashinath, Tetrahedron 2002, 58, 9633.
- [4] G. Altenhoff, R. Goddard, C. W. Lehmann, F. Glorius, Angew. Chem. Int. Ed. 2003, 42, 3690.
- [5] M. Eckhardt, G. C. Fu, J. Am. Chem. Soc. 2003, 125, 13642.
- [6] J. Li, W. Liu, Org. Lett. **2004**, *6*, 28091.
- [7] I. Nakamura, Y. Yamamoto, Chem. Rev. 2004, 104, 2127.
- [8] S. Schweizer, J. M. Becht, C. DrianLe, *Adv. Synth. Catal.* 2007, *349*, 1150.
 [9] G. B. Smith, G. C. Dezeny, D. L. Hughes, A. O. King, T. R. Verhoeven, *J.*
- Org. Chem. **1994**, *59*, 8151. [10] C. Nicolaou, C. N. C. Boddy, S. Brase, N. Winssinger, Angew. Chem. Int.
- Ed. **1999**, *38*, 2096.
- [11] Z.-Y. Tang, Y. Lu, Q.-S. Hu, Org. Lett. 2003, 5, 293.
- [12] T. E. Barder, S. D. Walker, J. R. Martinelli, S. L. Buchwald, J. Am. Chem. Soc. 2005, 127, 4685.
- [13] V. A. Kozlov, D. V. Aleksanyan, Y. V. Nelyubina, K. A. Lyssenko, P. V. Petrovskii, A. A. Vasil'ev, I. L. Odinets, *Organometallics* **2011**, *30*, 2920.

- [14] T. Suzuka, T. Nagamine, K. Ogihara, M. Higa, *Catal. Lett.* **2010**, *139*, 85.
- [15] Y. Kitamura, S. Sako, A. Tsutsui, Y. Monguchi, T. Maegawa, Y. Kitade, H. Sajiki, Adv. Synth. Catal. 2010, 352, 718.
- [16] F.-X. Felpin, T. Ayad, S. Mitra, Eur. J. Org. Chem. 2006, 2679.
- [17] M. Gruber, S. Chouzier, K. Koehler, L. Djakovitch, Appl. Catal. A: General 2004, 265, 161.
- [18] G. Marck, A. Villiger, R. Buchecker, *Tetrahedron Lett.* **1994**, *35*, 3277.
 [19] D. Gala, A. Stamford, J. Jenkins, M. Kugelman, *Org. Proc. Re. Dev.* **1997**, *1*, 163.
- [20] R. G. Heidenreich, K. Kohler, J. G. E. Krauter, J. Pietsch, Synlett 2002, 1118.
- [21] D. A. Conlon, B. Pipik, S. Ferdinand, C. R. LeBlond, J. R. Sowa, B. Izzo, P. Collins, G.-J. Ho, J. M. Williams, Y.-J. Shi, Y. K. Sun, *Adv. Synth. Catal.* **2003**, *345*, 931.
- [22] J. S. Chen, O. N. Vassylyev, A. P. Panarello, J. G. Khinast, Appl. Catal. A: General 2007, 325, 76.
- [23] Y. Kitamura, S. Sako, T. Udzu, A. Tsutsui, T. Maegawa, Y. Monguchi, H. Sajiki, *Chem. Commun.* 2007, 5069.
- [24] Y. Kitamura, A. Sakurai, T. Udzu, T. Maegawa, Y. Monguchi, H. Sajiki, *Tetrahedron* 2007, 63, 10596.
- [25] P. Simeone, J. R. Sowa, Tetrahedron 2007, 63, 12646.
- [26] P.-P. Zhang, X.-X. Zhang, H.-X. Sun, R.-H. Liu, B. Wang, Y.-H. Lin, *Tetrahedron Lett.* **2009**, *50*, 4455.
- [27] A. Arcadi, G. Cerichelli, M. Chiarini, M. Correa, D. Zorzan, Eur. J. Org. Chem. 2003, 4080.
- [28] G. Lu, R. Franzen, Q. Zhang, Y. J. Xua, Tetrahedron Lett. 2005, 46, 4255.
- [29] M. Lysén, K. Köhler, Synthesis 2006, 4, 0692.
- [30] C. Song, Y. D. Ma, Q. Chai, C. Q. Ma, W. Jiang, M. B. Andrus, *Tetrahedron* 2005, 61, 7438.
- [31] T. Maegawa, Y. Kitamura, S. Sako, T. Udzu, A. Sakurai, A. Tanaka, Y. Kobayashi, K. Endo, U. Bora, T. Kurita, A. Kozaki, Y. Monguchi, H. Sajiki, *Chem. Eur. J.* **2007**, *13*, 5937.
- [32] V. Khedkar, P. J. Tambade, Z. S. Qureshi, B. M. Bhanage, Eur. J. Org. Chem. 2010, 6981.
- [33] C. Liu, Q. J. Ni, F. Y. Bao, J. S. Qiu, Green Chem. 2011, 13, 1260.
- [34] L. X. Yin, J. Liebscher, Chem. Rev. 2007, 107, 133.