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Aerobic ligand-free Suzuki coupling catalyzed by in situ-generated palladium nanoparticles in water

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ABSTRACT

A simple and efficient procedure for Suzuki coupling of aryl bromides/iodides with aryl- and alkylboronic acids catalyzed by in situ-generated palladium(0) nanoparticles in water without any ligand in open air to produce a variety of functionalized biaryls and alkyl-aryls has been developed. The boronic acids act here as the reducing agent for the formation of Pd nanoparticles. The reactions are remarkably fast (5 min) and high yielding. The catalyst is recyclable up to three runs without loss of efficiency.

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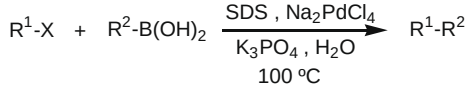
Since the first report of palladium-catalyzed Suzuki coupling of aryl halides with arylboronic acids,[1] this reaction has undergone a tremendous growth, and is considered one of the most powerful tools for the construction of an aryl–aryl bond, in particular for the formation of biaryls, structural units found in natural products, pharmaceuticals, and advanced materials.[2] The catalysis by metal nanoparticles is of considerable current interest as these semi-heterogeneous catalysts usually show enhanced catalytic efficiency because of their better ability to transfer electrons and large surface area-to-volume ratio.[3] In addition, they also offer the general advantages of heterogeneous catalysts of easy recovery and recyclability.[3] A variety of palladium nanoparticles-catalyzed Suzuki reactions, such as naphthidine di(radical cations)-stabilized palladium nanoparticles in dioxane,[4a] in situ-generated palladium nanoparticles in PEG-400 without any ligand,[4b] dendrimer-stabilized Pd nanoparticles in H_2O/EtOH,[4c] and Pd nanoparticles supported on polyaniline nanofibers in water,[4d] have been developed among others.[4] However, many of these procedures used expensive and complex ligands or supports, and with a few exceptions, most reactions involved hazardous organic solvents. Also several of these reactions are sluggish requiring at least 24 h for completion. The use of an eco-friendly reaction medium, minimization of steps, better yields, and faster reaction remained constant challenges in the context of green chemistry.[5,6] As a part of our program to explore palladium nanoparticles for carbon–carbon bond formation,[7] we report here a one-pot Suzuki coupling reaction catalyzed by in situ-generated Pd(0) nanoparticles in water without a conventional ligand (Scheme 1).

To optimize the reaction conditions, a series of experiments under varied conditions in terms of surfactants, base, reaction temperature, and reaction time for a model coupling reaction of 4-bromoanisole and phenylboronic acid were carried out as illustrated in Table 1. It was found that the best results in terms of yields and reaction time were obtained using sodium dodecyl sulfate (SDS)/K_3PO_4 at 100 °C in water (Table 1, entry 5), K_3PO_4 acts here as a base as well as a stabilizer.[8]

We also found that a representative coupling of 4-bromoacetophenone and phenylboronic acid in water at 100 °C furnished the best yield (96%) compared to other organic solvents such as DMF, toluene, and THF under identical conditions (Table 2).

Thus, in a general experimental procedure under optimized conditions, arylboronic acid (1.2 mmol) was added to a stirred solution of Na_2PdCl_4 (2.5 mol %), K_3PO_4 (1.5 mmol), and SDS (0.5 mmol) in water followed by aryl bromide (1 mmol) at room temperature in the open air. The reaction mixture was heated at



Scheme 1.

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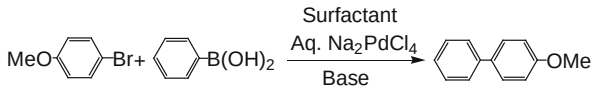
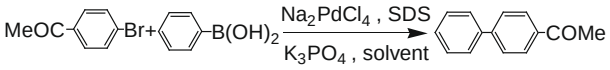
Table 1
Standardization of reaction conditions



Entry	Surfactant	Base	Temp (°C)	Time	Yield (%)
1	SDS	K_2CO_3	27	5 h	37
2	SDS	K_3PO_4	25	5 h	72
3	SDS	KF	28	5 h	20
4	SDS	NaOAc	25	5 h	21
5	**SDS**	**K_3PO_4**	**100**	**5 min**	**95**
6	—	K_3PO_4	100	20 min	75
7	—	K_3PO_4	25	5 h	63
8	TBAB	K_3PO_4	100	5 min	85

Table 2
Standardization of solvent for Suzuki cross-coupling



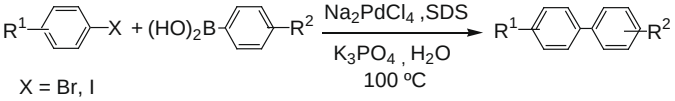
Entry	Solvent	Temp (°C)	Time (min)	Yield (%)
1	DMF	100	5	52
2	Toluene	100	5	52
3	THF	100	5	30
4	H_2O	100	5	96

100 °C (oil bath) for 5 min. Extraction with ethyl acetate and purification (recrystallization/chromatography) provided the pure product. All of these products are known compounds, and were easily identified by comparison of their spectroscopic (^{1}H NMR and ^{13}C NMR) data with those reported (see references in Table 3).

To confirm the formation of Pd nanoparticles and determine their properties, an extract from the reaction of 4-bromoanisole and phenylboronic acid in the presence of SDS (100 °C) after 5 min showed the formation of nanoparticles of the size of 6–8 nm by a TEM (transmission electron microscope) image (Fig. 1) and EDS (energy dispersive X-ray spectroscopy) confirmed the presence of Pd nanoparticles (Fig. 2). The UV spectra showed the presence of a peak at 425 nm corresponding to Pd(II) of aqueous solution of Na_2PdCl_4 before the start of the reaction and the disappearance of this peak with the progress of the reaction after 2 min indicating complete formation of Pd(0) nanoparticles, and their presence till the end of the reaction (Fig. 3).

A wide range of aryl bromides and iodides with varied substituents underwent cross coupling with several diversely substituted phenylboronic acids and alkylboronic acids by this procedure to produce the corresponding biaryls and alkyl–aryls. The results are summarized in Table 3. Most of these reactions were very fast being completed in 5 min. The presence of an electron-withdrawing or electron-donating group on the aromatic ring of aryl halides did not affect the reactivity and yields of products. Aryl iodides (Table 3, entries 1, 18, and 24) and aryl bromides participated in this reaction leaving chlorides and fluorides unreactive (Table 3, entries 9–12, and 22). The substituted phenylboronic acids (Table 3, entries 6, 8, 11, 12, 14, 17, 19, and 23) also coupled with aryl halides readily. The alkylboronic acids (Table 3, entries 26–28) underwent reactions by this procedure to produce the corresponding alkyl–aryls without any difficulty. The sensitive heteroaryl halides (Table 3, entries 24 and 25) bearing pyridyl and thienyl moieties produced the corresponding aryl-heteroaryl-coupled products in high yields. The position (*o, m, and p*) of substituents on the aromatic rings of aryl halides and phenylboronic acids did not have any appreciable effect on the progress of the reaction. Several functional groups

Table 3
Pd nanoparticles-catalyzed cross coupling of arylhalides and aryl or alkyl boronic acids



Entry	R^1	R^2	Time (min)	Yield[a] (%)	Ref.
1*	H	H	5	96	4c
2	H	H	5	92	4c
3	2-OCH_3	H	5	92	4d
4	3-OCH_3	H	5	94	4a
5	4-OCH_3	H	5	95	4f
6	4-OCH_3	3-CH_3	5	96	9
7	4-CH_3	H	5	96	4f
8	4-CH_3	4-CH_3	5	92	10
9	4-F	H	5	92	4f
10	4-Cl	H	5	94	14
11	4-Cl	3-CH_3	5	95	12
12	4-Cl	4-CHO	5	95	13
13	3-CHO	H	5	94	4e
14	2-CHO	4-CHO	5	92	14
15	2-COH_3	H	5	96	15
16	4-CN	H	5	95	4f
17	4-NO_2	3-CH_3	5	94	16
18*	3-CF_3	H	5	94	17
19		3-CH_3	5	96	12
20		4-CHO	5	90	18
21	4-HO	3-CH_3	5	92	19
22	4-F	3-Cl	5	84	20
23	4-CH_3	4-$COCH_3$	5	88	21
24*		H	5	92	22
25		H	10	88	23
26	4-$COCH_3$	^{n}Bu–$B(OH)_2$	5	86	24
27	4-CHO	CH_3–$B(OH)_2$	15	75	25
28	4-CN	CH_3–$B(OH)_2$	25	70	25

[a] Yields refer to those of purified isolated products characterized by spectroscopic data (IR, ^{1}H NMR, and ^{13}C NMR).
* Indicates X = I.

such as OCH_3, Cl, F, CHO, $COCH_3$, CN, NO_2, CF_3, and OH were compatible in this reaction, and thus this procedure provided an easy access to functionalized biaryls. Particularly, the biphenyls containing highly manipulable groups such as CHO, $COCH_3$, CN, and NO_2 (Table 3, entries 14–17, 20, 23, and 26) in either one or both rings are very useful in organic synthesis.

In general, the reactions are very clean and high yielding. The aqueous layer containing the catalyst after work up was recycled for three subsequent runs without an appreciable loss of efficiency.

As indicated by UV studies, Pd(II) was reduced to Pd(0) by phenylboronic acid during the reaction. It was also confirmed by a blank experiment adding phenylboronic acid to a solution of Na_2PdCl_4 in water without using SDS and aryl halide, where the solution turned black immediately indicating the formation of Pd(0). A similar reduction of palladium(II) acetate by phenylboronic acid was also observed by Jin.[4b] It is believed that Pd(0) is the catalytic species and that the reaction proceeds through the usual interaction of aryl halide and Pd(0) to form the aryl-palladiumhalide complex **1,** which then couples with arylboronic acid to give the aryl-Pd(II) intermediate **2,** and finally provides the biaryl product via the

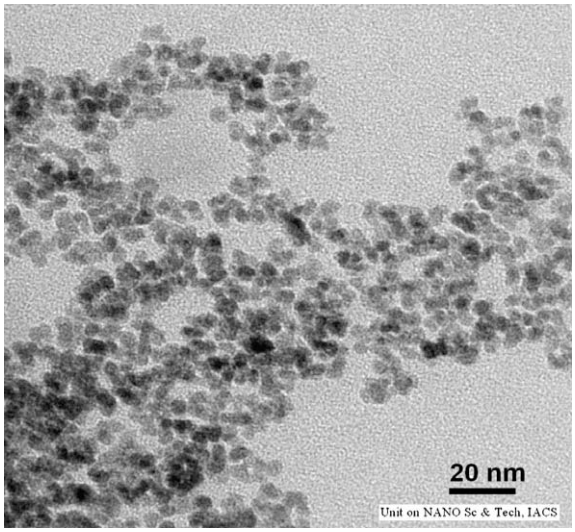


Figure 1. TEM image Pd nanoparticles.

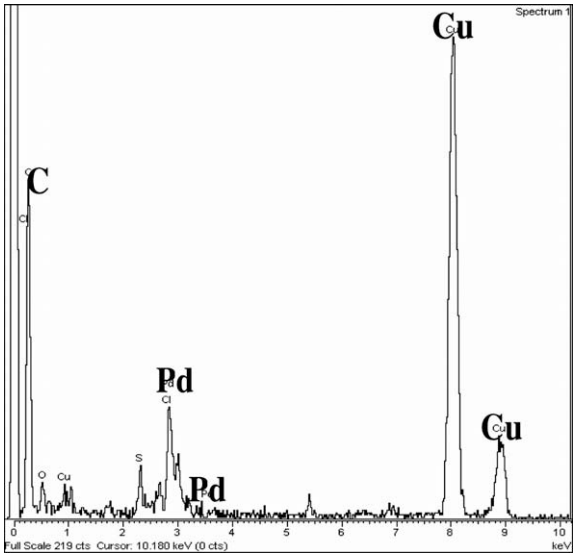


Figure 2. EDX spectra of PdNP on Cu grid.

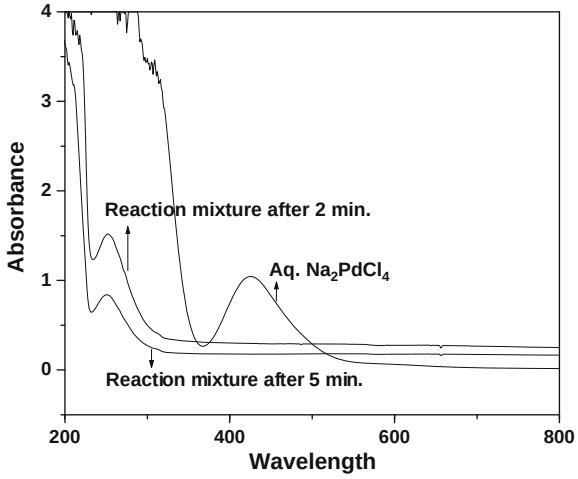
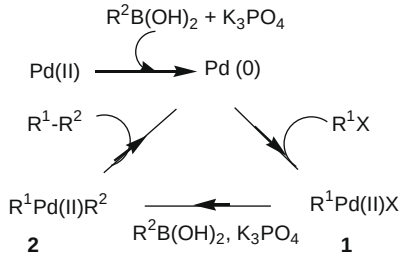


Figure 3. UV spectra of Pd at different stages (0–5 min) of the reaction.



Scheme 2. Plausible mechanism of Suzuki coupling.

reductive elimination of Pd(II) to Pd(0) as outlined in Scheme 2. It was also found that the reaction did not proceed at all in the absence of Pd nanoparticles.

Recently, we have reported[7c] Pd nanoparticles-catalyzed Hiyama coupling using Na_2PdCl_4/SDS/NaOH/H_2O. Although the present procedure used a similar reagent system, Na_2PdCl_4/SDS/K_3PO_4/H_2O, there are marked differences in the formation and reactivity of Pd nanoparticles. In Hiyama Coupling,[7c] Pd nanoparticles are formed by the reduction of Pd-salt by SDS, whereas in this reaction, the reduction of Pd(II) was done by phenyl/alkylboronic acid, this being a much faster process. All the reactions (Suzuki) proceeded well in the absence of SDS in reasonably good yields (10–15% lower than those in the presence of SDS), and thus SDS is not an essential part of this process. SDS was used to stabilize the Pd nanoparticles and to improve the recyclability of Pd nanoparticles. Tetrabutylammonium bromide, a different stabilizer, was also found to provide results similar to SDS (Table 1, entry 8). On the contrary, in the Hiyama coupling the reaction did not proceed at all in the absence of SDS, which acts as a reducing as well as a stabilizing agent. Moreover, we have been able to successfully use alkylboronic acid forming an aryl–alkyl bond in Suzuki coupling, whereas in the case of the earlier Hiyama coupling,[7c] this reaction did not go with alkylboronic acid. In general, alkylboronic acids are less reactive than arylboronic acids, and thus it is very difficult to achieve aryl–alkyls. Our procedure is efficient and has accomplished these reactions (Table 3, entries 26–28) and provided improved yields in a shorter reaction time (10–25 min compared to 7.5–72 h by a reported procedure[24]).

On comparison of our results with those in some of the recently published procedures using Pd nanoparticles for Suzuki coupling,[4] we find that this procedure provides significant advantages in terms of reaction time, simplicity of operation, and yields of products. In addition, this procedure provides a one-pot operation using in situ-generated Pd nanoparticles, whereas, with one exception,[4b] others use preformed nanoparticles thus making the process two-step.

In conclusion, we have developed a convenient and efficient one-pot procedure for Suzuki coupling of aryl halides and aryl- and alkylboronic acids catalyzed by in situ-generated Pd(0) nanoparticles in water under aerobic and ligand-free conditions. The significant advantages of this procedure are simple operation, reasonably high yields, very fast (5 min) reaction time, easy recovery of the catalyst, and reusability up to three runs without any appreciable loss of efficiency and environment-friendly reaction conditions. Suzuki coupling in the absence of any conventional ligand is also of much significance.

Acknowledgments

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Supplementary data

Supplementary data (Copies of ^{1}H and ^{13}C NMR spectra of all products listed in Table 3) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2008.12.063.

References and notes

1. Miyaura, N.; Yanada, K.; Suzuki, A. *Tetrahedron Lett.* **1979**, *20*, 3437–3440.
2. (a) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457–2483; (b) Hassan, J.; Sevignon, M.; Gozzi, C.; Schulz, E.; Lemaire, M. *Chem. Rev.* **2002**, *102*, 1359–1469; (c) Farina, V. *Adv. Synth. Catal.* **2004**, *346*, 1553–1582; (d) Nakamura, I.; Yamamoto, Y. *Chem. Rev.* **2004**, *104*, 2127–2198; (e) Phan, N. T. S.; Vander Sluys, M.; Jones, C. W. *Adv. Synth. Catal.* **2006**, *348*, 609–679.
3. (a) Roucoux, A.; Schulz, J.; Patin, H. *Chem. Rev.* **2002**, *102*, 3757–3778; (b) Astruc, D.; Lu, F.; Aranzaes, J. R. *Angew. Chem., Int. Ed.* **2005**, *44*, 7852–7872; (c) Astruc, D. *Inorg. Chem.* **2007**, *46*, 1884–1894.
4. (a) Desmarets, C.; Omar-Amrani, R.; Walcarius, A.; Lambert, J.; Champagne, B.; Fort, Y.; Schneider, R. *Tetrahedron* **2008**, *64*, 372–381. and references cited therein; (b) Han, W.; Liu, C.; Jin, Z. *Adv. Synth. Catal.* **2008**, *350*, 501–508. and references cited therein; (c) Diallo, A. K.; Ornelas, C.; Salmon, L.; Aranzaes, J. R.; Astruc, D. *Angew. Chem., Int. Ed.* **2007**, *46*, 8644–8648; (d) Gallon, B. J.; Kojima, R. W.; Kaner, R. B.; Diaconescu, P. L. *Angew. Chem., Int. Ed.* **2007**, *46*, 7251–7254; (e) Wu, L.; Li, B. L.; Huang, Y.-Y.; Zhou, H.-F.; He, Y.-M.; Fan, Q.-H. *Org. Lett.* **2006**, *8*, 3605–3608. and references cited therein; (f) Wei, W.; Qin, Y.; Luo, M.; Xia, P.; Wong, M. S. *Organometallics* **2008**, *27*, 2268–2272.
5. Shaughnessy, K. H.; DeVasher, R. B. *Curr. Org. Chem.* **2005**, *9*, 585–604.
6. Anastas, P. T.; Warner, J. C. *Green Chemistry: Theory and Practice*; Oxford University Press: New York, 1998.
7. (a) Ranu, B. C.; Chattopadhyay, K. *Org. Lett.* **2007**, *9*, 2409–2412; (b) Ranu, B. C.; Chattopadhyay, K.; Adak, L. *Org. Lett.* **2007**, *9*, 4595–4598; (c) Ranu, B. C.; Dey, R.; Chattopadhyay, K. *Tetrahedron Lett.* **2008**, *49*, 3430–3432.
8. Kapoor, S.; Joshi, R.; Mukherjee, T. *Chem. Phys. Lett.* **2002**, *354*, 443–448.
9. Yamada, Y. M. A.; Maeda, Y.; Uozumi, Y. *Org. Lett.* **2006**, *8*, 4259–4262.
10. Rammial, T.; Taylor, S. A.; Bender, M. L.; Gorodetski, B.; Lee, P. T. K.; Walsby, C. J.; Clyburne, J. A. C. *J. Org. Chem.* **2008**, *73*, 801–812.
11. Srimani, D.; Sawoo, S.; Sarkar, A. *Org. Lett.* **2007**, *9*, 3639–3642.
12. Uozumi, Y.; Nakai, Y. *Org. Lett.* **2002**, *4*, 2997–3000.
13. Kataoka, N.; Shelby, Q.; Stambuli, J. P.; Hartwig, J. F. *J. Org. Chem.* **2002**, *67*, 5553–5566.
14. Tanaka, M.; Souma, Y. *Chem. Commun.* **1991**, 1551–1553.
15. Baruwati, B.; Guin, D.; Manorama, S. B. *Org. Lett.* **2007**, *9*, 5377–5380.
16. Masllorens, J.; Roglam, A.; Moreno-Manas, N.; Parella, T. *Organometallics* **2004**, *23*, 2533–2540.
17. Fuchibe, K.; Ohshima, Y.; Mitomi, K.; Akiyama, T. *Org. Lett.* **2007**, *9*, 1497–1499.
18. Goodman, S. L.; Holzemann, G.; Sulyok, G. A. G.; Kessler, H. *J. Med. Chem.* **2002**, *45*, 1045–1051.
19. Edsall, R. J., Jr.; Harris, H. A.; Manas, E. S.; Mewshaw, R. E. *Biorg. Med. Chem.* **2003**, *11*, 3457–3474.
20. Antelo Miguez, J. M.; Adrio, L. A.; Sousa-Pedrares, A.; Vila, J. M.; Hii, K. K. *J. Org. Chem.* **2007**, *72*, 7771–7774.
21. Li, F.; Bai, S.; Hor, T. S. A. *Organometallics* **2008**, *27*, 672–677.
22. Proch, S.; Kempe, R. *Angew. Chem., Int. Ed* **2007**, *46*, 3135–3138.
23. Gong, J. F.; Zhang, Y. H.; Song, M. P. *Organometallics* **2007**, *26*, 6487–6492.
24. Najera, C.; Gil-Molto, J.; Karlstrom, S. *Adv. Synth. Catal.* **2004**, *346*, 1798–1811.
25. Pouchert, C. J., II ed.. In *The Aldrich Library of NMR Spectra*; Aldrich Chemical: Milwaukee, USA, 1983; Vol. 1.