Magnetically Recoverable Pd/Fe₃O₄-Catalyzed Stille Cross-Coupling Reaction of Organostannanes with Aryl Bromides

Aviraboina Siva Prasad[†,‡,*] **and Bollikonda Satyanarayana**[†]

[†]*Process Research and Development, CTO-1, Dr. Reddy's Laboratories Ltd., Bollaram, Hyderabad, Andhra Pradesh, India*
[‡]*Institute of Science and Technology, Jawaharlal Nehru Technological University, Kukatpally, Hyderabad 500072,*
*Andhra Pradesh, India.* [*]*E-mail: avirasp@drreddys.com*

The efficient formation of carbon-carbon bonds is among the most crucial transformations in synthetic chemistry. The palladium-catalyzed aryl-aryl cross-coupling (*e.g.*, Suzuki, Negishi, Kumada, Hiyama, and Stille coupling)[1] reaction is one such route to form C-C bonds. Among the different coupling reactions, the potentially most attractive method is Stille cross-coupling[3] of aryl halides with organostannane reagents because the ready availability of organostannane reagents, their air- and moisture-stability and has found wide application in natural product synthesis, carbohydrate chemistry, and biological research.[4] The formed biaryl moiety is also an important structural motif in great number of biologically active compounds and functional molecules.[2]

Generally, phosphine ligands are used to complex and activate the palladium species, and excellent results have been reported for the palladium-catalyzed Stille cross-coupling reaction.[5] However, phosphine ligands are undesirable because of their toxicity and air as well as moisture sensitive with conversion to, for example, phosphine oxide species. However, few phosphine free *N*-based ligands, have been used in the Stille cross-coupling reaction.[6] Although these methods are encouraging, there is a considerable scope for improvement as the non-reusability of the precious palladium precludes wide synthetic applications in the industry. In view of the above, it is desirable to develop a ligand-free and reusable catalytic system for the Stille cross-coupling with wide substrate scope.

Heterogeneous catalysis is particularly attractive as it allows the production and ready separation of large quantities of products with the use of a small amount of catalyst. Magnetic nanoparticles are a class of nanostructured materials of current interest, due largely to their advanced technological and medical applications, envisioned or realized.[7] Among the various magnetic nanoparticles under investigation, Fe₃O₄ nanoparticles are arguably the most extensively studied[8] and emerged as promising supports for immobilization metal nanoparticles. The potential advantage of Fe₃O₄-supported metal catalysts is it can be separated from the reaction medium by an external permanent magnet without using any filtration or centrifugation. Recently Palladium nanoparticles supported on Fe₃O₄ have been the
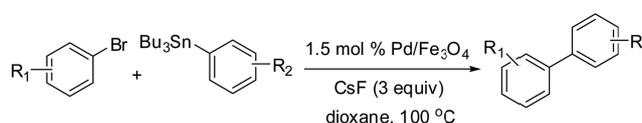
Scheme 1

subject of interest of several groups and widely used in a variety of organic reactions.[9]

In the present work, we report our investigations on the application of Fe₃O₄ supported Pd(0) nanoparticles (Pd/Fe₃O₄) for the Stille cross-coupling of aryl halides under ligand free conditions (Scheme 1).

Results and Discussion

Pd/Fe₃O₄ was prepared according to literature[9b] and the amount of palladium in the catalyst was determined with an inductively coupled plasma, atomic emission spectroscopy (ICPAES) instrument and Palladium content was measured as 0.14 mmolg⁻¹. The TEM images of both the fresh and used catalyst, it is seen that the average size of Fe₃O₄ nanoparticles is in the range of 20-25 nm in diameter and palladium nanoparticles of about 2-3 nm and are dispersed on Fe₃O₄ nanoparticles (Fig. 1). Furthermore, the TEM image (Fig. 1(b)) clearly confirms no change in the morphology even after five cycles.

In an endeavor to identify the best catalytic system for the Stille cross-coupling various bases in combination with different solvents were investigated using 4-bromoanisole as aryl halide and tributylphenylstannane as the organostannane. Among the different bases (K₂CO₃, K₃PO₄, NaOAc, NaOH,
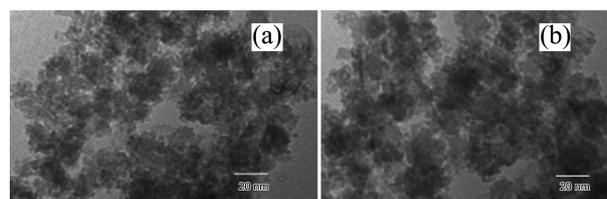

Figure 1. TEM images of Pd/Fe₃O₄ nanoparticles (a)-fresh catalyst and (b) catalyst after five cycles.

KF, CsF) and solvents (toluene, dioxane, water, DMF) screened, CsF and dioxane proved to be efficient for the Pd/Fe₃O₄ catalyzed stille coupling and the scope and generality of the reaction established with different aryl halides and tributylarylstannanes to obtain the corresponding biaryls as shown in Table 1.

When we used a variety of neutral, electron-rich, and electron-poor bromoarenes and tributylphenylstannanes to investigate the synthetic scope of the reaction, the corresponding biaryls were isolated in good to excellent yields. Unsubstituted as well as 4-methyl, 4-methoxy, 3-methoxy substituted bromobenzenes underwent smooth reaction with good yields when compared to 2-methyl and 2-methoxy bromobenzenes (Table 1, entries 1-7). Furthermore, the reaction was extended to other aryl halides such as 4-fluoro, 4-chloro and 4-acetyl bromobenzenes to generate biaryl products in good to excellent yields (Table 1, entries 8-10). We next turned our attention to Stille cross-coupling of substituted aryl tributylstannanes and irrespective of the electronic nature of the substituent all of them underwent the reaction smoothly to give the corresponding products in good yields except tributyl(*o*-tolyl)stannane (Table 1, entries 11-15).

Given the remarkably high levels of catalytic activity displayed with Pd/Fe₃O₄, we investigated its use for the preparation of hindered biaryls. In this study we used 2-bromo-3,4,5-trimethoxy benzaldehyde as a aryl halide, as the resulting products were useful for the preparation of number of bioactive compounds such as allocolchicines, Stegnacine and eupomatilones[10] and the results are summari-

Teble 2. Pd/Fe₃O₄ catalyzed Stille cross-coupling of 2-bromo-3,4,5-trimethoxybenzaldehyde with different tributylarylstannanes[a]
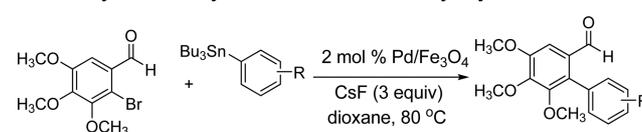
Entry	R	Time	Yield (%)
1	H	24	85
2	4-OCH₃	24	91
3	4-COOCH₃	24	78
4	4-COCH₃	24	81

[a]Reaction conditions: 2-bromo-3,4,5-trimethoxybenzaldehyde (1 mmol), tributylarylstannane (1.2 mmol), Pd/Fe₃O₄ (1.5 mol % of Pd), CsF (3 equiv), dioxane (3 mL) stirred at 80 °C.

zed in Table 2. 2-Bromo-3,4,5-trimethoxy benzaldehyde underwent the cross-coupling reaction with different aryl tributylstannanes smoothly and gave the desired product in good yield (Table 2, entries 1-4).

Encouraged by these results, we next investigated the scope of the reaction with respect to the tributyl(vinyl)-stannane substrate and various aryl bromides, including the deactivated bromoarenes as shown in Table 3. Various aryl bromides, including the 5-bromo-1,2,3-trimethoxybenzene, were readily converted to the corresponding coupled products in moderate to good yields (Table 3, entries 1-5).

To check the reusability of the catalyst, as can be seen from Table 3, the reaction was performed with 4-bromo-anisole and tributylphenylstannane under the optimized

Table 1. Pd/Fe₃O₄ catalyzed Stille cross-coupling of different bromoarenes with different tributylarylstannanes[a]

Entry	R₁	R₂	Time (h)	Yield (%)
1	H	H	16	86
2	4-OCH₃	H	20	81
3	3-OCH₃	H	20	83
4	2-OCH₃	H	24	72
5	3,4-OCH₂O	H	18	85
6	4-CH₃	H	18	80
7	2-CH₃	H	24	70
8	4-Cl	H	16	85
9	4-F	H	16	83
10	4-COCH₃	H	14	91
11	4-CH₃	4-CH₃	18	82
12	4-CH₃	4-OCH₃	18	80
13	4-CH₃	2-CH₃	18	74
14	4-CH₃	2-OCH₃	18	68
15	4-CH₃	3,4-OCH₂O	18	80

[a]Reaction conditions: aryl bromide (1 mmol), tributylarylstannane (1.2 mmol), Pd/Fe₃O₄ (1.5 mol % of Pd), CsF (3 equiv), dioxane (3 mL) stirred at 100 °C.

Table 3. Pd/Fe₃O₄ catalyzed Stille cross-coupling of different bromoarenes with tributyl(vinyl)stannane[a]
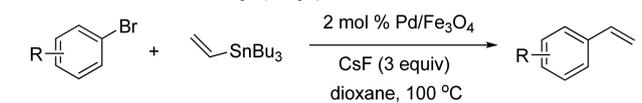
Entry	Aryl halide	Product	Time	Yield (%)
1			24	81
2			24	75
3			24	76
4			36	52
5			24	80
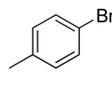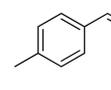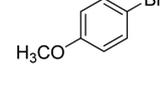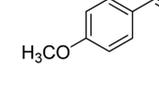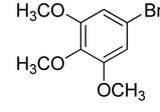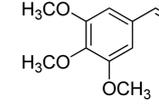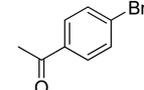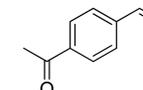
[a]Reaction conditions: Aryl bromide (1 mmol), tributyl(vinyl)stannane (1.2 mmol), Pd/Fe₃O₄ (1.5 mol % of Pd), CsF (3 equiv), dioxane (3 mL) stirred at 100 °C.

Notes

Bull. Korean Chem. Soc. **2012**, Vol. 33, No. 8   2791

Table 4. Recovery and reuse of Pd/Fe$_3$O$_4$ catalyst for the Stille cross-coupling of 4-bromoanisole with tributylphenylstannanes

Yield (%)					Average yield (%)
First	Second	Third	Fourth	Fifth	
81	76	75	76	73	76

[a]Reaction conditions: 4-bromoanisole (1 mmol), tributylphenylstannane (1.2 mmol), Pd/Fe$_3$O$_4$ (1.5 mol % of Pd), CsF (3 equiv), dioxane (3 mL) stirred at 100 °C.

reaction conditions. The catalyst was separated from the reaction mixture by applying external magnetic field and reused for five times without significant loss of catalytic activity.

Conclusions

In conclusion, we have developed a simple and efficient method for the Stille cross-coupling of bromoarenes with different organostannane reagents using magnetically recoverable Pd/Fe$_3$O$_4$ under ligand free conditions. The catalyst is completely magnetically recoverable because of the superparamagnetic behaviour of Fe$_3$O$_4$ and the efficiency of the catalyst remains unaltered even after 5 cycles. The operational simplicity and the mild reaction conditions add to the value of this method as a practical alternative to the Stille cross-coupling.

Experimental

Preparation of the Pd/Fe$_3$O$_4$ Catalyst. 1 g of dopamine-functionalized Fe$_3$O$_4$ nanoparticles[9b] were dispersed in water and NaPdCl$_4$ solution in water was added to the mixture to get 10 wt % of Pd. Diluted solution of hydrazine monohydrate was added drop wise to adjust the pH to 9. The reaction mixture was stirred overnight at room temperature and then allowed to settle. The product Pd/Fe$_3$O$_4$ was washed several times with water, centrifuged and dried at room temperature.

Typical Experimental Procedure. Aryl bromide (1 mmol), Organostannane (1.2 mmol), CsF (3 mmol), Pd/Fe$_3$O$_4$ catalyst (1.5 mol % of Pd) and dioxane (3 mL) was taken in a round-bottomed flask and stirred at 100 °C for appropriate time. After completion of the reaction (monitored by TLC) the catalyst was easily separated from the reaction mixture with an external magnet. After removing the solvent, the crude material was chromatographed on silica gel using hexane-ethyl acetate mixture as eluent to afford the pure product. The spectroscopic data of all known compounds were identical to those reported in the literature.

Reuse of Catalyst. After completion of the reaction the catalyst was recovered by filtration and washed several times with ethyl acetate and then ether and dried for further reuse. The catalyst showed consistent activity for five cycles.

Spectroscopic data for the selected compounds:

5-Phenylbenzo[*d*][1,3]dioxole (Table 1, entry 5): ^{1}H

NMR (300 MHz, CDCl$_3$) δ 5.98 (s, 2H), 6.84 (d, 1H, *J* = 7.1 Hz), 7.09-7.13 (m, 2H), 7.26 (t, 1H, *J* = 7.9 Hz), 7.36 (t, 2H, *J* = 7.2 Hz), 7.46 (d, 2H, *J* = 7.9 Hz). ^{13}C NMR (75 MHz, CDCl$_3$) δ 21.1, 101.2, 107.5, 108.6, 120.3, 126.7, 129.4, 135.4, 136.5, 137.9, 146.9, 148.1. EI MS (*m/z*): 198 (M$^+$).

4'-Methoxy-4-methyl-biphenyl (Table 1, entry 12): ^{1}H NMR (300 MHz, CDCl$_3$) δ 2.38 (s, 3H), 3.82 (s, 3H), 6.90 (d, 2H, *J* = 9.0 Hz), 7.16 (d, 2H, *J* = 8.3 Hz), 7.38 (d, 2H, *J* = 8.3 Hz), 7.44 (d, 2H, *J* = 9.0 Hz). ^{13}C NMR (75 MHz, CDCl$_3$) δ 21.0, 55.3, 114.1, 126.5, 127.9, 129.4, 133.7, 136.3, 137.9, 158.8. EI MS (*m/z*): 198 (M$^+$).

4,4',5,6-Tetramethoxybiphenyl-2-carbaldehyde (Table 2, entry 2): ^{1}H NMR (300 MHz, CDCl$_3$) δ 3.53 (s, 3H), 3.85 (s, 3H), 3.94 (s, 3H), 3.96 (s, 3H), 6.94 (d, 2H, *J* = 8.3 Hz), 7.23 (d, 2H, *J* = 8.7 Hz), 7.31 (s, 1H), 9.62 (s, 1H). ^{13}C NMR (75 MHz, CDCl$_3$) δ 55.2, 55.9, 60.8, 61.0, 105.1, 113.4, 124.5, 129.6, 132.3, 134.2, 151.2, 152.8, 159.3, 191.4. ESI MS (*m/z*): 303 (M + H).

1,2,3-Trimethoxy-5-vinylbenzene (Table 3, entry 4): ^{1}H NMR (300 MHz, CDCl$_3$) δ 3.85 (s, 3H), 3.86 (s, 3H), 3.88 (s, 3H), 5.13 (dd, 1H, *J* = 10.9 Hz, 0.8 Hz), 5.62 (dd, 1H, *J* = 17.6 Hz, 0.8 Hz), 6.67 (s, 2H), 6.69 (dd, 1H, *J* = 17.6 Hz, 10.9 Hz). ^{13}C NMR (75 MHz, CDCl$_3$) δ 56.1, 60.7, 60.8, 104.5, 113.6, 133.4, 136.5, 138.1, 153.3. EI MS (*m/z*): 194 (M$^+$).

References

1. (a) Miyaura, N.; Yamada, K.; Suzuki, A. *Tetrahedron Lett.* **1979**, 3437. (b) Baba, S.; Negishi, E. *J. Am. Chem. Soc.* **1976**, *98*, 6729. (c) Dai, C.; Fu, C. *J. Am. Chem. Soc.* **2001**, *123*, 2719. (d) Tamao, K.; Sumitani, K.; Kumada, M. *J. Am. Chem. Soc.* **1972**, *94*, 4374. (e) Hatanaka, Y.; Hiyama, T. *J. Org. Chem.* **1988**, *53*, 920. (f) Stille, J. K. *Pure Appl. Chem.* **1985**, *57*, 1771.
2. (a) Stille, J. K. *Angew. Chem., Int. Ed.* **1986**, *25*, 508. (b) Farina, V.; Krishnamurthy, V.; Scott, W. *J. Org. React.* **1997**, *50*, 1. (c) Hassa, J.; Svignon, M.; Gozzi, C.; Schulz, E.; Lemaire, M. *Chem. Rev.* **2002**, *102*, 1359.
3. (a) Nicolaou, K. C.; Li, Y.; Sugita, K.; Monenschein, H.; Guntupali, P.; Mitchell, H. J.; Fylaktakidou, K. C.; Vourloumis, D.; Giannakakou, P.; O'Brate, A. *J. Am. Chem. Soc.* **2003**, *125*, 15443. (b) Kadota, I.; Takamura, H.; Sato, K.; Ohno, A.; Matsuda, K.; Yamamoto, Y. *J. Am. Chem. Soc.* **2003**, *125*, 46. (c) Kuribayashi, T.; Gohya, S.; Mizuno, Y.; Satoh, S. *J. Carbohyd. Chem.* **1999**, *18*, 383. (d) Nicolaou, K. C.; King, N. P.; Finlay, M. R. V.; He, Y.; Roschangar, F.; Vourloumis, D.; Vallberg, H.; Sarabia, F.; Ninkovic, S.; Hepworth, D. *Bioorg. Med. Chem.* **1999**, *7*, 665.
4. (a) Schmidt, U.; Leitenberger, V.; Griesser, H.; Schmidt, J.; Meyer, R. *Synthesis* **1992**, 1248-1254. (b) Markham, A.; Goa, K. L. *Drugs* **1997**, *54*, 299-311. (c) Croom, K. F.; Keating, G. M. *Am. J. Cardiovasc. Drugs* **2004**, *4*, 395-404. (d) Sharpe, M.; Jarvis, B.; Goa, K. L. *Drugs* **2001**, *61*, 1501-1529. (e) Matheron, M. E.; Porchas, M. *Plant Dis.* **2004**, *88*, 665-668. (f) Poetsch, E. *Kontakte* **1988**, *2*, 15.
5. (a) Littke, A. F.; Fu, G. C. *Angew Chem., Int. Ed.* **1999**, *38*, 2411. (b) Littke, A. F.; Schwarz, L.; Fu, G. C. *J. Am. Chem. Soc.* **2002**, *124*, 6343. (c) Netherton, M. R.; Fu, G. C. *Org. Lett.* **2001**, *3*, 4295. (d) Su, W.; Urgaonkar, S.; Verkade, J. G. *Org. Lett.* **2004**, *6*, 1421. (c) Su, W.; Urgaonkar, S.; McLaughlin, P. A.; Verkade, J. G.

J. Am. Chem. Soc. **2004**, *126*, 16433. (d) Zhou, W. J.; Wang, K. H.; Wang, J. X. *J. Org. Chem.* **2009**, *74*, 5599.

6. (a) Grasa, G. A.; Nolan, S. P. *Org. Lett.* **2001**, *3*, 119. (b) Li, J. H.; Liang, Y.; Xie, Y. X. *Tetrahedron Lett.* **2005**, *61*, 7283.

7. (a) Yavuz, C. T.; Mayo, J. T.; Yu, W. W.; Prakash, A.; Falkner, J. C.; Yean, S.; Cong, L. L.; Shipley, H. J.; Kan, A.; Tomson, M.; Natelson, D.; Colvin, V. L. *Science* **2006**, *314*, 964. (b) Gao, J.; Zhang, W.; Huang, P.; Zhang, B.; Zhang, X.; Xu, B. *J. Am. Chem. Soc.* **2008**, *130*, 3710. (c) Lu, J.; Yang, S. H.; Ng, K. M.; Su, C. H.; Yeh, C. S.; Wu, Y. N.; Shieh, D. B. *Nanotechnology* **2006**, *17*, 5812. (d) Li, Z.; Wei, L.; Gao, M.; Lei, H. *Adv. Mater.* **2005**, *17*, 1001.

8. (a) Roca, A. G.; Morales, M. P.; O'Grady, K.; Serna, C. J. *Nanotechnology* **2006**, *17*, 783. (b) Zheng, Y. H.; Cheng, Y.; Bao, F.; Wang, Y. S. *Mater. Res. Bull.* **2006**, *41*, 525. (c) Lang, C.; Schueler, D.; Faivre, D. *Macromol. Biosci.* **2007**, *7*, 144. (d) Majewski, P.; Thierry, B. *Crit. Rev. Solid State Mater. Sci.* **2007**, *32*, 203.

9. (a) Yi, K. D.; Lee, S. S.; Ying, Y. J. *Chem. Mater.* **2006**, *18*, 2459. (b) Guin, D.; Baruwati, B.; Manorama, S. V. *Org. Lett.* **2007**, *9*, 1419. (c) Cano, R.; Ramon, D. J.; Yus, M. *Tetrahedron* **2011**, *67*, 5432. (d) Liu, J.; Peng, X.; Sun, W.; Zhao, Y.; Xia, C. *Org. Lett.* **2008**, *10*, 3933. (e) Zhang, R.; Liu, J.; Li, F.; Wu, S.; Xia, C.; Sun, W. *Chinese J. Chem.* **2011**, *29*, 525.

10. (a) Appukkuttan, P.; Eycken, E. V. *Eur. J. Org. Chem.* **2008**, 5867. (b) Wang, R. W. J.; Rebhun, L. I.; Kupchan, S. M. *Cancer Research* **1977**, *37*, 3071. (c) Joncour, A.; Decor, A.; Liu, J. M.; Tran Huu Dau, M. E.; Baudoin, O. *Chem. Eur. J.* **2007**, *13*, 5450.