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PII: DOI: Reference:	S0040-4039(15)30250-1 http://dx.doi.org/10.1016/j.tetlet.2015.10.053 TETL 46882
To appear in:	Tetrahedron Letters
Received Date:	30 July 2015
Revised Date:	13 October 2015
Accepted Date:	15 October 2015



Please cite this article as: Zhao, G., Zhang, K., Wang, L., Li, J., Zou, D., Wu, Y., Wu, Y., Efficient synthesis of diarylmethane derivatives by PdCl₂ catalyzed cross-coupling reactions of benzyl chlorides with aryl boronic acids in aqueous medium, *Tetrahedron Letters* (2015), doi: http://dx.doi.org/10.1016/j.tetlet.2015.10.053

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Efficient synthesis of diarylmethane derivatives by PdCl₂ catalyzed cross-coupling reactions of benzyl chlorides with aryl boronic acids in aqueous medium

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ARTICLE INFO

ABSTRACT

Article history: Received Received in revised form Accepted Available online The research provides a simple and efficient method for preparing diarylmethane derivatives using the cross-coupling reaction of benzyl chlorides and aryl boronic acids catalyzed by palladium chloride in DMF aqueous solution without additional ligand.

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Keywords: Diarylmethane derivatives Suzuki reaction Simple catalytic system

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Introduction

Palladium catalyzed Suzuki-Miyaura cross-coupling reaction has become an important method for the construction of carboncarbon bond.^[1] In recent years, several simple Suzuki-Miyaura catalytic systems without traditional ligand were applied to synthesize biaryl derivatives. For examples, LeBlond and coworkers first reported Pd/C as effective catalyst for the cross coupling reaction using aryl chlorides as substrates.^[2] They indicated that solvent effected on the pathway of homo- and cross-coupling of aryl chlorides, and found the solvent system DMA/H₂O (20/1) favored the cross-coupling pathway of aryl chlorides to obtain the Suzuki cross-coupling product selectively. Liu and coworkers developed the palladium acetate-catalyzed ligand-free Suzuki reaction in aqueous.^[3] They discovered that Pd(OAc)₂-H₂O-acetone catalytic system is highly active for the mono-Suzuki coupling reaction, and Pd(OAc)₂-H₂O-DMF system more suitable for the synthesis of polyaryls. Deng and coworkers found that the combination of Pd(OAc)₂, MeONa, alcohols was also effective to catalyze the cross coupling reaction of aryl halides and aryl boronic acids.^[4] The group of Liu Chun reported a kind of N,O-bidentate ligand formed from EtOH and DMA via the hydrogen bond which was effective for Suzuki reaction of aryl chlorides.^[5] And in the next year, their group developed a catalytic system of PdCl₂ in DMF-H₂O solvent in presence of K₂CO₃ for the cross coupling of aryl bromides and aryl boronic acids.^[6] These previous studies indicated that both solvent and base had a fundamental influence on Suzuki-Miyaura reaction, and suitable combination of different solvents and bases could promote the Suzuki-Miyaura reaction.

Diarylmethanes are one of privileged structural components ubiquitously found in pharmaceuticals and biologically active compounds^[7], and they are also subunits in supramolecular host structures^[8]. Most recently, the palladium catalyzed cross-coupling reactions of benzyl halides with aryl boronic acids have proved to be very powerful for construction of these compounds^[9]. But few aforementioned simple Suzuki-Miyaura catalytic systems without traditional ligand were applied to prepare diarylmethane derivatives.

Bandger and coworkers^[10] had described that ligand-free palladium catalyzed cross-coupling reactions of aryl boronic acids with benzyl halides using acetone:water (3:1) as the solvent at room temperature. However, their conditions were effective on the coupling reaction between benzyl bromides and aryl boronic acids, but had no effect on more available benzyl chloride. Herein, we report that PdCl₂ could catalyze the cross-coupling reaction of benzyl chlorides and aryl boronic acids in DMF aqueous solution under air to prepare diarylmethanes derivatives.

Results and Discussion

In preliminary studies, of 4the reaction (chloromethyl)benzonitrile with phenyl boronic acid was chosen as a model reaction for optimization. Firstly, the impact of different solvents and bases was investigated and are summarized in Table 1. When the reaction was carried out in DMF, a 72% yield of target product was obtained (Table 1, entry 1). It is well known that a suitable amount of water may improve Suzuki-Miyaura reactions due to the increase of dissolved base and gave the best result with 96% cross coupling product yield (Table 1, entry 4). Decreasing or increasing the ratio of DMF/H₂O led to declined yields (Table 1, entries 1-9). Several different solvents were also tested under similar conditions but all gave inferior results compared to DMF (Table 1, entries 4 vs 10-18). The study of different bases showed that K2CO3 delivered the desired product in higher yield (Table 1, entries 4 vs 20-27). No product was detected without base (Table 1, entry 19).

Table 1. Screening of solvent, base for the cross-coupling reaction of 4-(chloromethyl)benzonitrile with phenyl boronic acid.^a

	CI + (B(OH)2 PdCl2, 90 °C	
	NC' V	Base, Solver	" NC' V V
Entry	Base	Solvent	Yield% ⁶
1	K_2CO_3	DMF	72
2	K_2CO_3	DMF/H ₂ O(6:1)	93
3	K_2CO_3	DMF/H ₂ O(5:1)	94
4	K_2CO_3	DMF/H ₂ O(4:1)	96
5	K_2CO_3	DMF/H ₂ O(3:2)	70
6	K_2CO_3	DMF/H ₂ O(1:1)	53
7	K_2CO_3	DMF/H ₂ O(2:3)	26
8	K_2CO_3	DMF/H ₂ O(1:4)	9
9	K ₂ CO ₃	H_2O	7
10	K ₂ CO ₃	DMA/H ₂ O(4:1)	89
11	K ₂ CO ₃	NMP/H ₂ O(4:1)	51
12	K ₂ CO ₃	Ethanol/H2O(4:1)	8
13	K ₂ CO ₃	Methanol/H ₂ O(4:1)	9
14	K ₂ CO ₃	Dioxane/H ₂ O(4:1)	Trace
15	K_2CO_3	THF/H ₂ O(4:1)	N. R.
16	K_2CO_3	MeCN/H ₂ O(4:1)	5
17	K_2CO_3	Toluene/H ₂ O(4:1)	N. R.
18	K_2CO_3	Acetone/H ₂ O(4:1)	Trace
19		DMF/H ₂ O(4:1)	N. R.
20	Na ₂ CO ₃	DMF/H ₂ O(4:1)	85
21	Et ₃ N	DMF/H ₂ O(4:1)	57
22	CH ₃ COONa	DMF/H ₂ O(4:1)	66
23	NaOH	DMF/H ₂ O(4:1)	44
24	Cs_2CO_3	DMF/H ₂ O(4:1)	80
25	NaHCO ₃	DMF/H ₂ O(4:1)	84
26	t-BuOK	DMF/H ₂ O(4:1)	19
27	K ₃ PO ₄	DMF/H ₂ O(4:1)	59

^a Reaction conditions: 4-(chloromethyl)benzonitrile (0.5 mmol), phenyl boronic acid (0.6 mmol), PdCl₂ (3 mol%), base (1.0 mmol), solvent (5 ml), 90 °C, 1 h, under air. ^b Yields were determined by GC-MS using n-dodecane as an internal standard.

Secondly, the impact of catalyst loading, reaction temperature, reaction time was also studied. As shown in Table 2, 1 mol% of PdCl₂ could satisfy the reaction and gave excellent yield of product after 1 h (Table 2, entries 3-6), and the reaction couldn't proceed without catalyst (Table 2, entry 1). When the reaction was scaled up to 10 mmol scale, even 0.2 mol% PdCl₂ could efficiently catalyze the model reaction with a 93% yield of the product by prolonged the reaction time to 3 h (Table 2, entry 2). Decreasing the reaction temperature from 90 °C to 25 °C the vields were decreased (Table 2, entries 3 vs 7-8). Moreover, the vield was not further improved evidently by increasing the temperature from 90 °C to 110 °C (Table 2, entry 3 vs 9). So the subsequent experiments were carried out at 90 °C. Additionally, time optimization revealed that the reaction gave excellent yield after 1 h. When the reaction time was prolonged to 2 hours, the yield did not increase (Table 2, entries 3, 10, 11). Finally, the

optimum reaction condition is 1.0 mol% of $PdCl_2$ in presence of K_2CO_3 in DMF/H₂O (4:1) for 1 h at 90 °C under air.

Table 2. Screening of catalyst loading, reaction temperature, reaction time for the cross-coupling reaction of 4- (chloromethyl)benzonitrile with phenyl boronic acid.^a

NC $CI + CI + CI + COH_2 + CO$				
Entry	$PdCl_2 (mol\%)$	Temp. (°C)	Time (h)	Yield% ^b
1		90	1	N. R.
2	0.2	90	3	93°
3	1.0	90	1	96
4	2.0	90	1	95
5	3.0	90	1	96
6	4.0	90	1	97
7	1.0	25	1	52
8	1.0	60	1	88
9	1.0	110	1	97
10	1.0	90	0.5	86
11	1.0	90	2	96

^a Reaction conditions: 4-(chloromethyl)benzonitrile (0.5 mmol), phenyl boronic acid (0.6 mmol), PdCl₂, K₂CO₃ (1.0 mmol), DMF/H₂O (4:1, 5 ml), under air. ^b Yields were determined by GC-MS using n-dodecane as an internal standard. ^c Reaction conditions: 4-(chloromethyl)benzonitrile (10 mmol), phenyl boronic acid (12 mmol), PdCl₂ (0.2 mol%), K₂CO₃ (20 mmol), DMF/H₂O (4:1, 50 ml), under air.

After establishing the optimized reaction conditions, the reaction of benzyl chlorides and aryl boronic acids bearing electron-donating and electron-withdrawing substituents at the aromatic ring were investigated. Four general trends could be seen from Table 3: 1). Most reactions proceed smoothly to give the corresponding products in moderate to good yields. 2) The position of substituents have little effect on the reaction yields (Table 3, entries 1, 2; 8, 9, 10; 15, 16; 20, 21; 23, 24), and they all gave the desired products in good isolated yields. 3) Benzyl chlorides with electron-withdrawing substituents or aryl boronic acids with electron-donating substituents tend to give better yields (Table 3, entries 1, 6, 18, 22). 4) The process tolerates a variety of functional groups that are available for further functionalization. In addition, halogen substituents such as fluoro, chloro could survive the mild reaction conditions (Table 3, entries 3, 13, 15, 16, 23, 24), but substrates with aryl bromide unit gave the byproduct of biaryl derivatives which is an explanation of their low corresponding yields (Table 3, entries 7, 17).

Table 3. The cross-coupling of various benzyl chlorides and aryl boronic acids under optimized reaction conditions.^a

		K ₂ CO ₃ , DMF/H ₂ O (4:1)	
Entry	R ₁	R_2	Yield% ^b
1	4-CN	Н	90
2	2-CN	Н	88
3	4-Cl	Н	85
4	4-NO ₂	Н	77
5	4-COOCH ₃	Н	58
6	4-OCH ₃	Н	30
7	4-Br	Н	36
8	4-CH ₃	Н	87

9	3-CH ₃	Н	90
10	2-CH ₃	Н	83
11	Н	Н	92 ^c
12	Н	4-OCH ₃	84
13	Н	4-F	81
14	4-CN	4-COCH ₃	74
15	4-CN	4-F	69
16	4-CN	3-F	50
17	4-CN	4-Br	36
18	4-CN	4-CN	46
19	4-CN	3-CF ₃	51
20	4-CN	2-CH ₃	83
21	4-CN	4-CH ₃	87
22	4-CN	4-OCH ₃	90
23	4-Cl	3-COCH ₃	75
24	2-Cl	3-COCH ₃	73

^a Reaction conditions: substituted benzyl chloride (0.5 mmol), substituted phenyl boronic acid (0.6 mmol), PdCl₂ (1.0 mol%), K₂CO₃ (1.0 mmol), DMF/H₂O (4:1, 5 ml), 1 h, 90 °C, under air. ^b Isolated yields. ^c GC-MS yield.

This research showed the present catalytic system was effective on the coupling reaction between benzyl chloride and aryl boronic acid. To gain insight into the interaction among our catalytic system, the catalytic system was reinvestigated in the absence of reaction substrates (Table 4 and Figure 1). As can be seen from Figure 1, the direct phenomenon of vessel 4 and 6 were much different from others. Lots of Pd black deposited onto the wall of vessel 6, obtaining colorless and transparent solution, which in accordance with our former experimental results that in the presence of suitable amount of H₂O the model reaction could be accomplished in an hour due to the improved solubility of K_2CO_3 as well as the rapid generation of Pd(0). Whereas, the phenomenon of vessel 4 was a little out of our expectation that almost all PdCl₂ combined with K₂CO₃ generating light yellow solid and separating with upper layer colorless and transparent solution. In order to satisfy our curiosity, the solid complex was separated out and used to catalyze the model reaction in pure DMF without additional PdCl₂ and K₂CO₃, and it works well after prolonged the reaction time to 2 hours. It could also be reused two times with 96% yields of corresponding product respectively. Further ¹H NMR and IR analysis revealed that DMF was also included in the solid complex (see the Supporting Information) to form а possible complex of $(PdCl_2)_x(K_2CO_3)_v(DMF)_z$. On the basis of the literature report, DMF may function as the following three kinds of roles in organometallic chemistry. 1) Aprotic solvent. 2) Weak ligand^[11]. 3) Reducing agent. More recently, DMF was also applied into preparing metal nanoparticles, with respect to its temperaturedependent reducing ability as well as possible weakly interaction with metal through the carbonyl oxygen.^[12] So in the optimum reaction condition, DMF possibly played as a crucial role for the success of the coupling. It is not only an aprotic solvent but also weak ligand for the catalytic cycle. By combination of suitable ratio of DMF and H₂O, it is also played as a reducing agent to generate highly active Pd(0). And the Pd(0) may works in soluble palladium clusters form surrounded by DMF according to the literature reports.^[13]

Table 4. The reinvestigation of our catalytic system without reaction substrates ^a

reaction substrates.					
Entry	PdCl ₂	DMF	H_2O	K_2CO_3	

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4				100	•
1	3 mg	5 ml			
2	3 mg		5 ml		
3	3 mg	4 ml	1 ml		
4	3 mg	5 ml		138 mg	
5	3 mg		5 ml	138 mg	
6	3 mg	4 ml	1 ml	138 mg	
9 4 11 1	. 11	1 1 00	0 9 11 1 1		-

^a All above studies were carried out at 90 °C, 1h, under air.



Figure 1 the corresponding phenomenon of Table 4

Conclusion

To sum up, we have developed a simple and efficient method to prepare diarylmethane derivatives in good yields under mild experimental conditions. Various functional groups that are available for further functionalization could survive in our catalytic system. DMF functions as solvent and weak ligand in our catalytic system. Further study about the scope, mechanism and synthetic applications of our catalytic system is ongoing.

Acknowledgments

We are grateful to the Natural Science Foundation of China (20772114, 21172200), Research Program of Fundamental and Advanced Technology of Henan Province (122300413203), and Technology Research and Development Funds of Zhengzhou (141PRCYY516) for financial support.

References and notes

- 1. Miyaura, N.; Suzuki, A. Chem. Rev. **1995**, 95, 2457–2483.
- LeBlond, C. R.; Andrews, A. T.; Sun, Y. K.; Sowa, J. R. Org. Lett. 2001, 10, 1555–1557.
- Liu, L. F.; Zhang, Y. H.; Xin, B. W. J. Org. Chem. 2006, 71, 3994– 3997.
- 4. Deng, C. L.; Guo, S. M.; Xie, Y. X.; Li, J. H. Eur. J. Org. Chem. 2007, 1457–1462.
- 5. Yang, W. B.; Liu, C.; Qiu, J. S. Chem. Commun. 2010, 46, 2659–2661.
- Liu, C.; Ni, Q. J.; Bao, F. Y.; Qiu, J. S. Green Chem. 2011, 13, 1260–1266.
- (a) Wai, J. S.; Egbertson, M. S.; Payne, L. S.; Fisher, T. E.; Embrey, M. W.; Tran, L. O.; Melamed, J. Y.; Langford, H. M.; Guare, J. P.; Zhuang, L. H.; Grey, V. E.; Vacca, J. P.; Holloway, M. K.; Naylor-Olsen, A. M.; Hazuda, D. J.; Felock, P. J.; Wolfe, A. L.; Stillmock, K. A.; Schleif, W. A.; Gabryelski, L. J.; Young, S. D. J. Med. Chem. 2000, 43, 4923–4926; (b) Long, Y. Q.; Jiang, X. H.; Dayam, R.; Sanchez, T.; Shoemaker, R.; Sei, S.; Neamati, N. J. Med. Chem. 2004, 47, 2561–2573; (c) Ohtake, Y.; Sato, T.; Kobayashi, T.; Nishimoto, M.; Taka, N.; Takano, K.; Yamamoto, K.; Ohmori, M.; Yamaguchi, M.; Takami, K.; Yeu, S. Y.; Ahn, K.

H.; Matsuoka, H.; Morikawa, K.; Suzuki, M.; Hagita, H.; Ozawa, K.; Yamaguchi, K.; Kato, M.; Ikeda, S. J. Med. Chem. 2012, 55, 7828–7840; (d) Rische, T.; Eilbracht, P. Tetrahedron 1999, 55, 1915–1920.

- (a) Conn, M. M.; Rebek, J. *Chem. Rev.* **1997**, *97*, 1647–1668; (b) Ma, J. C.; Dougherty, D. A. *Chem. Rev.* **1997**, *97*, 1303–1324; (c) Jasat, A.; Sherman, J. C. *Chem. Rev.* **1999**, *99*, 931–967; (d) Philp, D.; Stoddart, J. F. *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 1154– 1196.
- (a) Chowdhury, S.; Georghiou, P. E. Tetrahedron Lett. 1999, 40, 9. 7599-7603; (b) Langle, S.; Abarbri, M.; Duchêne, A. Tetrahedron Lett. 2003, 44, 9255–9258; (c) Chahen, L.; Doucet, H.; Santelli, M. Synlett. 2003, 11, 1668-1672; (d) Nobre, S. M.; Wolke, S. I.; da Rosa, R. G.; Monteiro, A. L. Tetrahedron Lett. 2004, 45, 6527-6530; (e) Nobre, S. M.; Monteiro, A. L. Tetrahedron Lett. 2004, 45, 8225-8228; (f) Chang, C. P.; Huang, Y. L.; Hong, F. E. Tetrahedron 2005, 61, 3835-3839; (g) Burns, M. J.; Fairlamb, I. J. S.; Kapdi, A. R.; Sehnal, P.; Taylor, R. J. K. Org. Lett. 2007, 9, 5397-5400; (h) Inés, B.; Moreno, I.; SanMartin, R.; Domínguez, E. J. Org. Chem. 2008, 73, 8448-8451; (i) Fairlamb, I. J. S.; Sehnal, P.; Taylor, R. J. K. Synthesis 2009, 3, 508-510; (j) Zhang, Y. Q. J. *Chem. Research* **2013**, *7*, 375–376; (k) Guan, Z. H.; Li, B. Y.; Hai, G. L.; Yang, X. J.; Li, T.; Tan, B. E. *RSC Adv.* **2014**, *4*, 36437– 36443; (1) Botella, L.; Nájera, C. Angew. Chem. Int. Ed. 2002, 41, 179-181; (m) Botella, L.; Nájera, C. J. Organomet. Chem. 2002, 663, 46-57; (n) Baleizão, C.; Corma, A.; García, H.; Leyva, A. J. Org. Chem. 2004, 69, 439-446; (o) Alacid, E.; Nájera, C. J. Organomet. Chem. 2009, 694, 1658-1665; (p) Nájera, C.; Gil-Moltó, J.; Karlström, S. Adv. Synth. Catal. 2004, 346, 1798-1811; (q) Yu, A. J.; Li, X. D.; Peng, D. P.; Wu, Y. J.; Chang, J. B. Appl. Organometal. Chem. 2012, 26, 301-304; (r) Singh, R.; Viciu, M. S.; Kramareva, N.; Navarro, O.; Nolan, S. P. Org. Lett. 2005, 7, 1829-1832; (s) Kuriyama, M.; Shinozawa, M.; Hamaguchi, N.; Matsuo, S.; Onomura, O. J. Org. Chem. 2014, 79, 5921-5928.
- Bandgar, B. P.; Bettigeri, S. V.; Phopase, J. Tetrahedron Lett. 2004, 45, 6959–6962.
- (a) Young, A. C. M.; Walters, M. A.; Dewan, J. C. Acta Cryst. 1989, C45, 1733–1736; (b) Suzuki, H.; Fukushima, N.; Ishiguro, S. I. Acta Cryst. 1991, C47, 1838–1842; (c) Suzuki, H.; Ishiguro, S. I. Acta Cryst. 1998, C54, 586–588; (d) Morimoto, T.; Nakajima, T.; Sawa, S.; Nakanishi, R.; Imori, D.; Ishitani, O. J. Am. Chem. Soc. 2013, 135, 16825–16828; (e) Senchurova, L. A.; Yustratov, V. P.; Gel'fman, M. I. Zhurnal Neorganicheskoi Khimii 1996, 41, 97–99; (f) Hosokawa, T.; Nomura, T.; Murahashi, S. I. J. Organomet. Chem. 1998, 551, 387-389.
- (a) Pastoriza–Santos, I.; Liz–Marzán, L. M. Langmuir 1999, 15, 948–951; (b) Liu, X. F.; Li, C. H.; Xu, J. L.; Lv, J.; Zhu, M.; Guo, Y. B.; Cui, S.; Liu, H. B.; Wang, S.; Li, Y. L. J. Phys. Chem. C 2008, 112, 10778–10783; (c) Pastoriza-Santos, I.; Liz-Marzán, L. M. Adv. Funct. Mater. 2009, 19, 679–688; (d) Kawasaki, H.; Yamamoto, H.; Fujimori, H.; Arakawa, R.; Inada, M.; Iwasaki, Y. Chem. Commun. 2010, 46, 3759–3761; (e) Aguirre, M. E.; Rodríguez, H. B.; Román, E. S.; Feldhoff, A.; Grela, M. A. J. Phys. Chem. C 2011, 115, 24967–24974; (f) Carpenter, M. K.; Moylan, T. E.; Kukreja, R. S.; Atwan, M. H.; Tessema, M. M. J. Am. Chem. Soc. 2012, 134, 8535–8542.
- (a) de Vries, A. H. M.; Mulders, J. M. C. A.; Mommers, J. H. M.; Henderickx, H. J. W.; de Vreies, J. G. Org. Lett. 2003, 5, 3285– 3288. (b) Reetz, M. J.; de Vries, J. G. Chem. Commun. 2004, 1559– 1563.

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