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Dabco as an Inexpensive and Highly Efficient Ligand for Palladium-Catalyzed Suzuki–Miyaura Cross-Coupling Reaction

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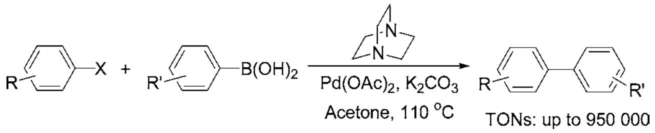
ABSTRACT



An inexpensive and highly efficient Pd(OAc)$_2$/Dabco catalytic system has been developed for the cross-coupling of aryl halides with arylboronic acids. A combination of Pd(OAc)$_2$ and Dabco (triethylenediamine) was observed to form an excellent catalyst, which affords high TONs (turnover numbers; TONs up to 950 000 for the reaction of PhI and *p*-chlorophenylboronic acid) for Suzuki–Miyaura cross-coupling of various aryl iodides and bromides with arylboronic acids.

Biaryls are versatile intermediates in organic synthesis and a recurring functional group in many natural products and bioactive compounds.[1] As a result, considerable effort has been directed toward the development of efficient and selective methods for the synthesis of biaryls.[2−11] The Suzuki−Miyaura cross-coupling reaction represents one of the most widely used processes for the synthesis of biaryls.[2c,4−11] Phosphine ligands are generally used to complex and activate the palladium species, and excellent results have been reported for the palladium-catalyzed Suzuki−Miyaura cross-coupling reaction.[2c,4−6] However, phosphine ligands are sensitive to air, which places significant limits on their synthetic applications.[6] Therefore, the development

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(9) For recent representative papers on diazabutadiene−palladium catalysts, see: (a) Grasa, G. A.; Hillier, A. C.; Nolan, S. P. *Org. Lett.* **2001**, *3*, 1077. (b) Palencia, H.; Garcia-Jimenez, F.; Takacs, J. M. *Tetrahedron Lett.* **2004**, *45*, 3849.

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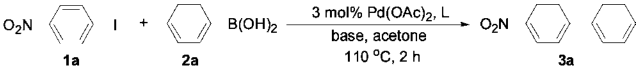
of phosphine-free palladium catalysts would be significant.[7−11] Although simple amines as bases are generally used in cross-coupling reactions and display some properties as ligands to stabilize the reactive palladium intermediates,[12] only two papers have reported the use of simple amines as ligands combined with Pd(0) to efficiently catalyze Suzuki−Miyaura cross-coupling reaction.[11] Compared with primary and secondary amines, however, the use of tertiary amines as ligands showed no activity or low activity for the reaction. Here, we report that $Pd(OAc)_2$/Dabco (a tertiary amine) is a stable, inexpensive, and highly efficient catalyst system for the Suzuki−Miyaura reaction of aryl halides and arylboronic acids.

We first tested the catalytic activity of $Pd(OAc)_2$/Dabco in the Suzuki−Miyaura reaction between 1-iodo-4-nitrobenzene **1a** and phenylboronic acid **2a**, and the results are summarized in Table 1. High yields were observed for the coupling reaction when using Dabco as the ligand. In the absence of Dabco, 70% yield of the corresponding coupling product **3a** was obtained for 2 h when the reaction of **1a** with **2a** proceeded by using 3 mol % $Pd(OAc)_2$ and 3 equiv of K_2CO_3 in acetone at 110 °C, whereas in the presence of 6 mol % Dabco, the yield of **3a** was increased to 100%. But only 45% yield of **3a** was isolated after 2 h when Dabco (3 equiv) was used as the base. In the presence of 3 mol % $Pd(OAc)_2$, 6 mol % Dabco, and 3 equiv of Cs_2CO_3, a yield identical to that of K_2CO_3 was obtained. In H_2O, a low yield (42%) of **3a** was isolated after 2 h.

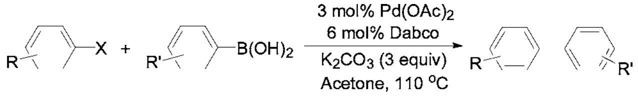
Table 1. Palladium-Catalyzed Suzuki−Miyaura Reaction of 1-Iodo-4-nitro-benzene **1a** and Phenylboronic Acid **2a**[a]

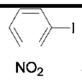
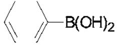
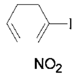
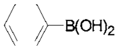
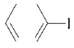
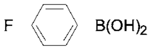
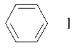
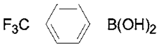
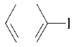
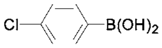
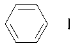
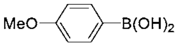
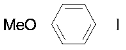
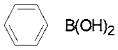
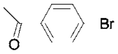
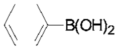
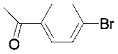
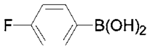
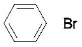
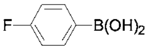
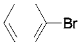
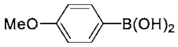
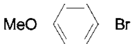
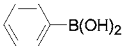
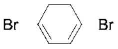
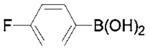
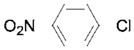
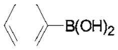
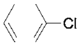
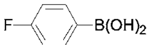


entry	solvent	base	Dabco (equiv)	isolated yield (%)
1	acetone	K_2CO_3	0	70
2	acetone	K_2CO_3	0.06	100
3	acetone	0	3.00	45
4	acetone	Cs_2CO_3	0.06	98
5	H_2O	K_2CO_3	0.06	42

[a] Unless otherwise indicated, the reaction conditions were as follows: **1** (0.5 mmol), **2** (0.7 mmol), $Pd(OAc)_2$ (3 mol %), Dabco, and K_2CO_3 (3 equiv) in acetone (5 mL) at 110 °C for 2 h.

Table 2. $Pd(OAc)_2$/Dabco-Catalyzed Cross-Coupling of Aryl Halides with Arylboronic Acids



entry	ArX	ArB(OH)$_2$	yield (%)[b]
1	 (**1b**)	 (**2a**)	95 (**3b**)
2	 (**1c**)	 (**2a**)	96 (**3c**)
3	 (**1d**)	 (**2b**)	97 (**3d**)
4	 (**1d**)	 (**2c**)	100 (**3e**)
5	 (**1d**)	 (**2d**)	100 (**3f**)
6	 (**1d**)	 (**2e**)	97 (**3g**)
7	 (**1e**)	 (**2a**)	100 (**3g**)
8[c]	 (**1f**)	 (**2a**)	92 (**3h**)
9[d]	 (**1f**)	 (**2b**)	100 (**3i**)
10	 (**1g**)	 (**2b**)	94 (**3d**)
11	 (**1g**)	 (**2e**)	95 (**3g**)
12	 (**1h**)	 (**2a**)	97 (**3g**)
13[e]	 (**1i**)	 (**2b**)	69 (**3j**)
14[f]	 (**1j**)	 (**2a**)	18 (**3a**)
15	 (**1k**)	 (**2b**)	—

[a] Unless otherwise indicated, the reaction conditions were as follows: **1** (0.5 mmol), **2** (0.7 mmol), $Pd(OAc)_2$ (3 mol %), Dabco (6 mol %), and K_2CO_3 (3 equiv) in acetone (5 mL) at 110 °C for 2 h. [b] Isolated yield. [c] For 4 h. [d] For 3.5 h. [e] **1i** (0.25 mmol). [f] For 18 h.

As shown in Table 2, the palladium-catalyzed Suzuki−Miyaura reaction with the Dabco ancillary ligand proved to be exceptionally active. Various aryl iodides and aryl bromides, including the deactivated aryl bromides, were readily converted to the corresponding coupled products in excellent yields. It is worth noting that this reaction was performed without the protection of inert gas. It is interesting that coupling of 1,4-dibromobenzene **1j** with *p*-fluorophenylboronic acid **2b** was carried out smoothly to afford terphenyl **3j** in 69% yield. Unfortunately, the $Pd(OAc)_2$/Dabco catalytic system was less effective for the reaction of aryl chlorides. The reaction of activated aryl chloride **1j** with **2a** afforded 18% yield of the corresponding coupled product **3a** after 18 h. An attempt to couple chlorobenzene **1k** with **2b** was not successful.

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(10) For recent representative papers on other phosphine-free ligand-palladium catalysts, see: (a) Tao, B.; Boykin, D. W. *Tetrahedron Lett.* **2002**, *43*, 4955. (b) Alonso, D. A.; Nájera, C.; Pacheco, M. C. *Org. Lett.* **2000**, *2*, 1823. (c) Botella, L.; Nájera, C. *Angew. Chem., Int. Ed.* **2002**, *41*, 179. (d) Bedford, R. B.; Cazin, C. S. *Chem. Commun.* **2001**, 1540. (e) Alonso, D. A.; Nájera, C.; Pacheco, M. C. *J. Org. Chem.* **2002**, *67*, 5588 and references cited therein. (f) de Vries, A. H. M. Mulders, J. M. C. A.; Mommers, J. H. M.; Henderickx, H. J. W.; de Vries, J. G. *Org. Lett.* **2003**, *5*, 3285 and references cited therein.

(11) (a) Tao, B.; Boykin, D. W. *Tetrahedron Lett.* **2003**, *44*, 7993. (b) Tao, B.; Boykin, D. W. *J. Org. Chem.* **2004**, *69*, 4330.

(12) (a) Link, J. T. In *Organic Reaction*; Overman L. E., Ed.; J. Wiley and Sons: 2002; Vol. 60, p 157. (b) Strieter, E. R.; Blackmond, D. G.; Buchwald, S. L. *J. Am. Chem. Soc.* **2003**, *125*, 13978.

The catalytic efficacy of the $Pd(OAc)_2$/Dabco catalytic system in the Suzuki–Miyaura reaction was further evaluated, and the results are summarized in Table 3. For coupling of aryl iodides **1a**, **1d**, and **1e**, including activated aryl iodide **1a** and deactivated aryl iodide **1e** with arylboronic acids **2**, the catalyst loading could be decreased to 0.0001 mol %, and good yields could still be obtained after prolonged heating. For coupling of aryl bromides, the catalytic efficiency decreased to some extent. For example, when the catalyst loading was decreased to 0.01 mol %, activated aryl bromide **1f** and phenylboronic acid **2a** were also efficiently coupled in high yield (85%) for 40 h. Further decreasing the catalyst loading to 0.001 mol % leads to a low yield (11%, TONs = 11 000). The deactivated 4-bromoanisole **1h** was a suitable substrate at a loading of 1 mol % Pd, but not at 0.1 mol %.

Table 3. Screening the Catalytic Efficiency of the $Pd(OAc)_2$/Dabco Catalytic System for the Suzuki–Miyaura Reaction[a]

entry	ArX	$ArB(OH)_2$	Pd (mol %)	time (h)	yield[b] (%)	TON
1	**1a**	**2a**	0.01	4	100	10 000
2	**1a**	**2a**	0.001	5	93	93 000
3	**1a**	**2a**	0.0001	5	92	920 000
4[c]	**1a**	**2a**	0.0001	48	90	900 000
5	**1d**	**2d**	0.0001	14	95	950 000
6	**1e**	**2a**	0.01	14	97	9700
7	**1e**	**2a**	0.001	18	100	100 000
8	**1e**	**2a**	0.0001	24	74	740 000
9	**1f**	**2a**	0.01	40	85	8500
10	**1f**	**2a**	0.001	48	11	11 000
11	**1h**	**2a**	1	12	92	92
12	**1h**	**2a**	0.1	48	42	420
13	**1h**	**2a**	0.01	48	17	1700
14	**1h**	**2a**	0.001	48	9	9000

[a] Unless otherwise indicated, the reaction conditions were as follows: **1** (0.5 mmol), **2** (0.7 mmol), $Pd(OAc)_2$/Dabco (1:2), and K_2CO_3 (3 equiv) in acetone (5 mL) at 110 °C. [b] Isolated yield. [c] **1a** (5 mmol) and **2a** (7 mmol) in acetone (50 mL).

In summary, an inexpensive and highly efficient methodology catalyzed by the $Pd(OAc)_2$/Dabco system has been developed (TONs up to 950 000 for the reaction of PhI and *p*-chlorophenylboronic acid). The use of Dabco as a supporting ligand for the Suzuki–Miyaura cross-coupling reaction emerged as an attractive alternative to the phosphine ligand. Furthermore, the reactions can be readily conducted in air. Currently, further efforts to design achiral and chiral ligands, based on the Dabco skeleton, and extend the application of these ligands in other palladium-catalyzed transformations are underway in our laboratory.

Acknowledgment. We thank the National Natural Science Foundation of China (No. 20202002), Hunan Province Department of Education (NO. 02C211) and Hunan Normal University for financial support.

Supporting Information Available: Analytical data and spectra (^1H and ^{13}C NMR) for all the products **3**; typical procedure for the $Pd(OAc)_2$/Dabco-catalyzed Suzuki–Miyaura reaction. This material is available free of charge via the Internet at http://pubs.acs.org.

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