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Convenient and Efficient Suzuki–Miyaura Cross-Coupling Catalyzed by a Palladium/Diazabutadiene System

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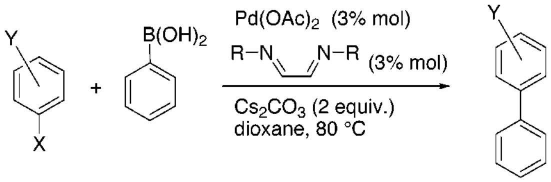
ABSTRACT



A $Pd(OAc)_2$/diazabutadiene system has been developed for the catalytic cross-coupling of aryl halides with arylboronic acids. A combination of the diazabutadiene DAB-Cy (1, *N*,*N*′-dicyclohexyl-1,4-dizabutadiene) and $Pd(OAc)_2$ was found to form an excellent catalyst for the Suzuki–Miyaura cross-coupling of various aryl bromides and activated aryl chlorides with arylboronic acids.

The Suzuki−Miyaura cross-coupling reaction, involving the coupling of an arylboronic acid with an organohalide, has proven to be an extremely useful synthetic tool in organic synthesis.[1] Although palladium complexes bearing tertiary phosphine ligands are commonly employed[1a,2] in Suzuki−Miyaura cross-couplings, these catalysts are often sensitive to air oxidation and therefore require air-free handling in order to minimize ligand oxidation. Nucleophilic *N*-heterocyclic carbenes, the imidazol-2-ylidenes, have recently been used as ancillary ligands for Suzuki−Miyaura cross-coupling reactions with great success.[3]

In the specific area of coupling chemistry, catalytic systems that contain supporting ligations other than tertiary phosphine represent a scarcely explored area of investigation. Recently, a Pd(II) cyclometalated imine catalyst able to mediate both Suzuki[4] and Heck[5] reactions has been reported by Milstein. Unfortunately, this system requires high reaction temperatures and leads to products in modest yields. On the basis of the Milstein report, we thought a well-known family of ligands, the diazabutadienes, might possibly mediate the Suzuki−Miyaura reaction. The chelating nature of these ligands might also assist in stabilizing catalytic species. Ligands containing the 1,4-diaza-1,3-butadiene skeleton, α-diimines, (DAB-R, Scheme 1) have been known for quite some time.[6] The coordination versatility of these ligands, a consequence of the flexibility of the NCCN backbone and the strong σ-donor and π-acceptor properties, reflects a very important feature of DAB-R−metal complexes.[7] Few investigations have focused on the influence of DAB-R as a

Scheme 1. Diazabutadiene Ligands

R = aryl and alkyl

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[1] (a) For a review, see: Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457−2483. (b) Suzuki, A. *Metal-Catalyzed Cross-Coupling Reactions*; Diederich, F., Stang, P. J., Eds.; Wiley-VCH: Weinheim, 1998; pp 49−97 and references therein. (c) Hamann, B. C.; Hartwig, J. F. *J. Am. Chem. Soc.* **1998**, *120*, 7369−7370. (d) Reetz, M. T.; Lohmer, G.; Schwickardi, R. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 481−483. (e) Littke, A. F.; Fu, G. C. *J. Org. Chem.* **1999**, *64*, 10−11.

[2] Applications of phosphine ligands in homogeneous catalysis: (a) Parshall, G. W.; Ittel, S. *Homogeneous Catalysis*; J. Wiley and Sons: New York, 1992. (b) Pignolet, L. H., Ed. *Homogeneous Catalysis with Metal Phosphine Complexes*; Plenum: New York, 1983.

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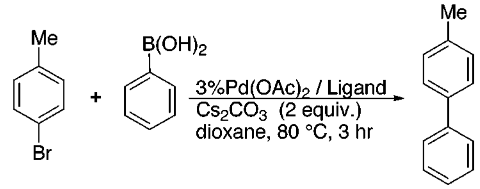
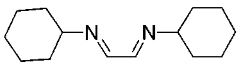
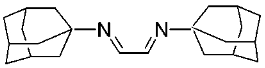
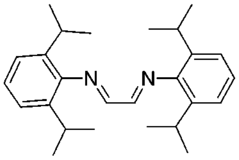
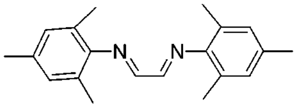
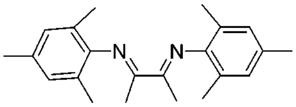
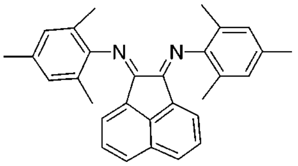
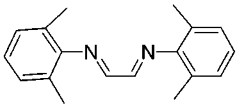
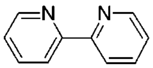
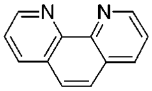
Table 1. Influence of DAB-R Ligands on the Palladium-Catalyzed Cross-Coupling Reaction of 4-Bromotoluene with Phenylboronic Acid[a]



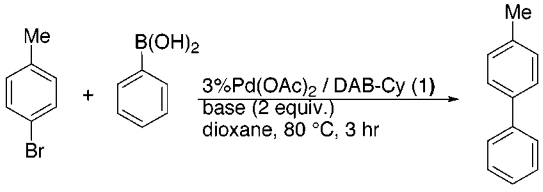
entry	ligand	yield[b,c,d]
1	No L	30
2	 **(1)**	99
3	 **(2)**	93
4	 **(3)**	80
5	 **(4)**	85
6	 **(5)**	78
7	 **(6)**	79
8	 **(7)**	60
9		13
10		NR

[a] Reaction conditions: 1.0 mmol of 4-bromotoluene, 1.5 mmol of phenylboronic acid, 2 mmol of Cs_2CO_3, 3.0 mol % $Pd(OAc)_2$, 3.0 mol % ligand, 3 mL odioxane, 80 °C, 3 h. [b] Isolated yields. [c] All reactions were monitored by GC. [d] Yields are average of two runs.

supporting ligand in catalytic processes. The most notable exceptions have been the use of metal−diimine complexes to mediate olefin polymerization[8] and alkyne cyclotrimerization[9] processes.

We now wish to report an additional use of these ligands in the efficient catalytic cross-coupling of aryl halides with arylboronic acids using a combination of $Pd(OAc)_2$/diazabutadiene (DAB-R) as the catalytic system.

Table 2. Effect of Base on $Pd(OAc)_2$/DAB-Cy (**1**)-Catalyzed Cross-Coupling of 4-Bromotoluene with Phenylboronic Acid[a]



entry	base	yield[b,d]
1	none	nr
2	Na_2CO_3	nr
3	$Ca(OH)_2$	nr
4	NaOMe	nr
5	$K(O^tBu)$	10[c]
6	TBAF	11[c]
7	KOMe	14[c]
8	$Ba(OH)_2$	44
9	K_2CO_3	63
10	KF	78
11	CsF	87
12	Cs_2CO_3	99

[a] Reaction conditions: 1.0 mmol of aryl bromide, 1.5 mmol of phenylboronic acid, 2 mmol of base, 3.0 mol % $Pd(OAc)_2$, 3.0 mol % DAB-Cy, 3 mL of dioxane, 80 °C. [b] Isolated yields. [c] GC yields. [d] All reactions were monitored by GC. Yields are average of two runs.

On the basis of our previous experience in Pd/imidazolium salt catalyzed Suzuki−Miyaura reaction,[3e] we observed that the coupling of 4-bromotoluene and phenylboronic acid in the presence of 3 mol % of $Pd(OAc)_2$, 3 mol % DAB-Mes (**4**), and Cs_2CO_3 in dioxane, at 80° C, proceeded to give 4-methylbiphenyl in 85% isolated yield (Table 1, entry 5). Investigation of other diazabutadiene ligands led to the observation that alkyl-diazabutadienes (Table 1, entries 2 and 3) are superior supporting ligands for the Pd-catalyzed Suzuki reaction compared to aryl-diazabutadienes (Table 1, entries 4−8). This reactivity trend is in agreement with the stronger donating ability of alkyl substituents, making the ligand more electron-rich. Other bis(nitrogen donor) ligands were inves-

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(3) (a) Regitz, M. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 725−728. (b) Arduengo, A. J., III; Krafczyc, R. *Chem. Zeit.* **1998**, *32*, 6−14. (c) Herrmann, W. A.; Kocher, C. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2163−2187. (d) Herrmann, W. A.; Reisinger, C. P.; Spiegler, M *J. Organomet. Chem.* **1998**, *557*, 93−96. (e) Zhang, C.; Huang, J.; Trudell, M. T.; Nolan, S. P. *J. Org. Chem.* **1999**, *64*, 3804−3805. (f) Böhm, V. P. W.; Gstömayr, C. W. K.; Weskamp. T.; Herrmann, W. A. *J. Orgamomet. Chem.* **2000**, *595*, 186−190.

(4) Weissman, H.; Milstein, D. *Chem. Commun.* **1999**, 1901−1902.

(5) Ohff, M.; Ohff, A.; Milstein, D. *Chem. Commun.* **1999**, 357−358.

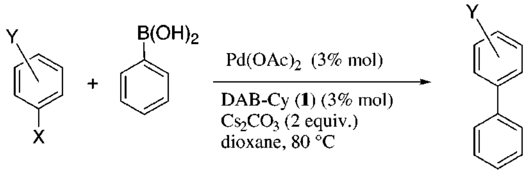
(6) van Koten, G.; Vrieze, K. *Adv. Organomet. Chem.* **1982**, *21*, 151−239 and references cited.

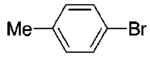
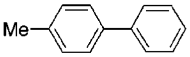
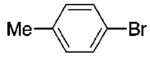
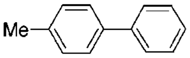
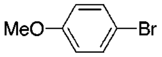
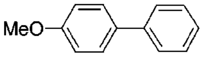
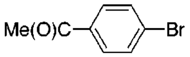
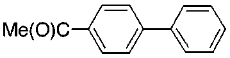
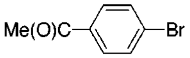
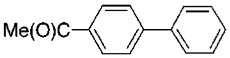
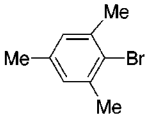
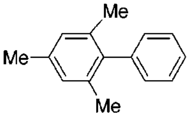
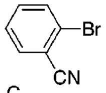
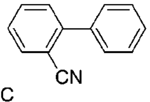
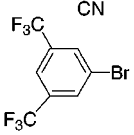
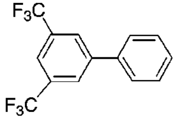
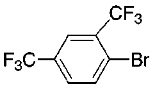
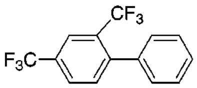
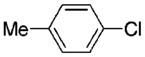
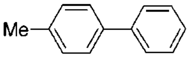
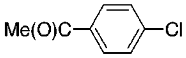
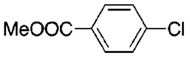
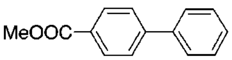
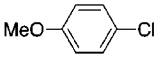
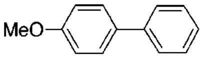
(7) (a) Mathur, P.; Ghosh, S.; Sarkar, A.; Rheingold, A. L.; Guzei, I. A. *J. Organomet. Chem.* **1998**, *566*, 159−164. (b) Lehmann, J. F.; Urquhart, S. G.; Ennis, L. E.; Hitchcock, A. P.; Hatano, K.; Gupta, S.; Denk, M. K. *Organometallics* **1999**, *18*, 1862−1872. (c) Greulich, S.; Kaim, W.; Stange, A.; Stoll, H.; Fiedler, J.; Zalis, S. *Inorg. Chem.* **1996**, *35*, 3998−4002. (d) Breuer, J.; Fruhauf, H.-W.; Smeets, W. J. J.; Spek, A. L. *Inorg. Chim. Acta* **1999**, *291*, 438−447.

(8) (a) Johnson, L. K.; Killian, C. M.; Brookhart, M. S. *J. Am. Chem. Soc.* **1995**, *117*, 6414−6416. (b) Killian, C. M.; Tempel, D. J.; Johnson, L. K.; Brookhart, M. S. *J. Am. Chem. Soc.* **1996**, *118*, 11664−11665. (c) Tempel, D. J.; Johnson, L. K.; Huff, R. L.; White, P. S.; Brookhart, M. S. *J. Am. Chem. Soc.* **2000**, *122*, 6686−6700 and references cited.

(9) van der Poel, H.; van Koten, G.; Kokkes, M.; Stam, C. H. *Inorg. Chem.* **1981**, *20*, 2941−2950.

Table 3. Pd(OAc)$_2$/DAB-Cy (**1**)-Catalyzed Cross-Coupling of Aryl Halides with Phenylboronic Acid[a]



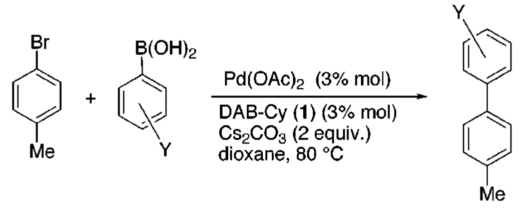
entry	aryl halide	product	time (h)	yield(%)[b,g]
1			3	99
2			5	90[c]
3			5	95
4			1	98
5			20	99[d]
6			4	97
7			1	98
8			2	95
9			21	98
10			4.5	20[e,f]
11			4	98[e]
12			5	85[e]
13			24	35[e,f]

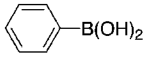
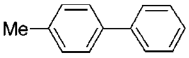
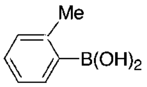
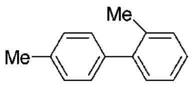
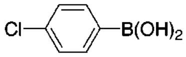
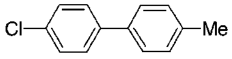
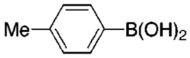
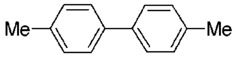
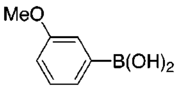
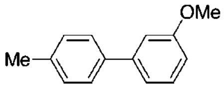
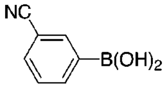
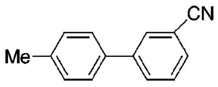
[a] Reaction conditions: 1.0 mmol of aryl halide, 1.5 mmol of phenylboronic acid, 2 mmol of Cs$_2$CO$_3$, 3.0 mol % Pd(OAc)$_2$, 3.0 mol % DAB-Cy, 3 mL of dioxane, 80 °C. [b] Isolated yields. [c] The reaction was performed in the air. [d] The reaction was performed using Pd(OAc)$_2$ only. [e] The reaction was performed at 100 °C. [f] GC yield. [g] All reactions were monitored by GC. Yields are average of two runs.

tigated, but considering the electronic argument presented above, it was not surprising to observe a poorer performance of the commercially available ligands 2,2′-bipyridyl (Table 1, entry 9) and 1,10-phenanthroline (Table 1, entry 10).

An investigation of the influence of the base suggested that Cs$_2$CO$_3$ was the reagent of choice. In turn, K$_2$CO$_3$, an effective base for the cyclopalladated-imine catalyst for the Suzuki–Miyaura reaction,[4] proved to be less effective, leading to a 63% isolated yield (Table 2, entry 9). Other bases such as Na$_2$CO$_3$, Ca(OH)$_2$, NaOMe, K(O^{t}Bu), KOMe, and Ba(OH)$_2$ proved to be ineffective for the cross-coupling of 4-bromotoluene with phenylboronic acid (Table 2, entries 2–5, 7, 8). Moreover, KF, a very effective additive for Pd(dba)$_2$/(^{t}Bu)$_3$P-catalyzed Suzuki–Miyaura reaction,[10] also proved to be less effective in the present system.

Table 4. Pd(OAc)$_2$/DAB-Cy (**1**)-Catalyzed Cross-Coupling of 4-Bromotoluene with Various Arylboronic Acids[a]



entry	aryl boronic acid	product	time (h)	yield(%)[b,c]
1			3	99
2			10	86
3			6	99
4			2.5	96
5			24	67
6			24	57

[a] Reaction conditions: 1.0 mmol of 4-bromotoluene, 1.5 mmol of arylboronic acid, 2 mmol of Cs$_2$CO$_3$, 3.0 mol % Pd(OAc)$_2$, 3.0 mol % DAB-Cy, 3 mL of dioxane, 80 °C. [b] Isolated yields. [c] All reactions were monitored by GC. Yields are average of two runs.

As illustrated in Table 3, the palladium-catalyzed Suzuki–Miyaura reaction with the DAB-Cy (**1**) ancillary ligand proved exceptionally active. Not surprisingly the nonactivated aryl bromides (Table 3, entry 3) were easily converted. This reaction could be performed in the air as well but requires longer reaction times (Table 3, entry 2). Moreover, *ortho*-substituted substrates also led to excellent yields (Table 3, entries 6 and 7). The catalytic effect was confirmed by running the standard reaction on 4-bromoacetophenone without ligand. The reaction proceeds, but it requires much longer reaction times compared to the Pd(OAc)$_2$/DAB-R system (Table 3, entries 4 and 5). Activated aryl chlorides led to moderate to high yields when this catalytic system was employed (Table 3, entries 11 and 12). Attempts to couple the electron-neutral 4-chlorotoluene and the electron-rich 4-chloroanisole were not successful. Investigations regarding the steric and electronic properties of diazabutadiene ligands able to activate the aryl chlorides are presently underway.

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(10) Littke, A. F.; Dai, C.; Fu, G. C. *J. Am. Chem. Soc.* **2000**, *122*, 4020–4028.

The effect of varying the aryl boronic acids in the Suzuki−Miyaura cross-coupling reactions was also investigated using 4-bromotoluene as the substrate (Table 4). *para*-Substituted aryl boronic acids led to excellent yields of the desired products (Table 4, entries 3 and 4), while the sterically hindered 2-methylphenylboronic acid required longer reaction time before affording very good yields of the product (Table 4, entry 2). Attempts to couple 4-bromotoluene with *meta*-substituted aryl boronic acids such as 3-cyanophenylboronic acid or 3-methoxyphenylboronic acid resulted in low yields. The lower reaction rate may be explained in terms of the different electronic properties of *meta*-substituted boronic acids.[11]

In summary, an unprecedented, general, and efficient methodology based on the $Pd(OAc)_2$/DAB-R system has been developed. The use of DAB-R as supporting ligands for the Suzuki−Miyaura cross-coupling reaction represents an interesting alternative to existing catalytic systems based on the use of tertiary phosphine ligands. The $Pd(OAc)_2$/DAB-R system is very efficient in the Suzuki−Miyaura cross-coupling reaction of aryl bromides with aryl boronic acids in terms of reactivity, reaction temperature, reaction time, and air-stability. This system represents unprecedented reactivity for a bis(nitrogen) ligand system with regard to reactivity with unactivated and sterically encumbered substrates, as well as activated aryl chlorides. Investigations regarding the utility of $Pd(OAc)_2$/DAB-R systems toward the activation of electron-rich and electron-neutral aryl chlorides, as well as the influence of the steric and electronic factors of DAB-R ligands are ongoing.

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Supporting Information Available: Experimental procedure and references to known compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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[11] March, J. *Advanced Organic Chemistry*; J. Wiley and Sons: New York, 1992; pp 278−286.