

Palladium–Imidazol-2-ylidene Complexes as Catalysts for Facile and Efficient Suzuki Cross-Coupling Reactions of Aryl Chlorides with Arylboronic Acids

Chunming Zhang, Jinkun Huang,
Mark L. Trudell,*[†] and Steven P. Nolan*[†]

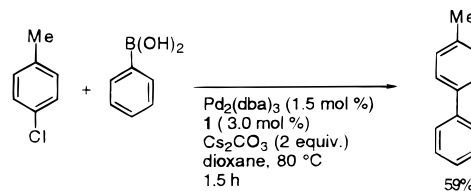
Department of Chemistry, University of New Orleans,
New Orleans, Louisiana 70148

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The palladium-catalyzed Suzuki cross-coupling reaction of aryl bromides, aryl iodides, and pseudohalides (e.g. triflates) is a general method employed for the formation of C–C bonds.¹ The use of aryl chlorides as chemical feedstock in coupling chemistry has proven difficult but would economically benefit a number of industrial processes.^{2,3} The use of phosphine ligands in organometallic chemistry and catalysis is widespread.⁴ Recently, Buchwald⁵ and Fu⁶ have reported phosphine-modified palladium-mediated Suzuki coupling reactions which employ inexpensive aryl chlorides as substrates. The use of bulky phosphine (P^tBu₃) or phosphine-containing moiety (PCy₂) in ancillary ligation was shown to be fundamental in triggering the observed catalytic behavior.

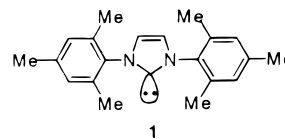
Nucleophilic N-heterocyclic carbenes, the imidazol-2-ylidenes or so-called “phosphine mimics”, have attracted considerable attention as possible alternatives for the widely used phosphine ligands in homogeneous catalysis.^{7,8} The primary advantage of these ligands appears to be that they do not dissociate from the metal center, as a result an excess of the ligand is not required in order to prevent aggregation of the catalyst to yield the bulk metal.⁸ The application of these ligands in palladium-catalyzed Heck reactions,^{9–13}

Scheme 1



rhodium carbene complexes in hydrosilylation,¹⁴ and ruthenium carbene catalysts in olefin metathesis^{15,16a} has opened new opportunities in catalysis.

Recently we examined the solution calorimetry of transition metal-centered ligand substitution involving nucleophilic N-heterocyclic carbenes.¹⁶ This class of ligands exhibited a considerable stabilizing effect in organometallic systems.^{8,17} An understanding of ligand stereoelectronic effects provided by the thermochemical investigations led to the use of this ligand class in a ring-opening/closing metathesis system. Herrmann and co-workers have reported Suzuki cross-coupling activity of carbene ancillary ligands involving aryl bromides and activated aryl chlorides.¹⁸ In view of the stereoelectronic phosphine factors required in the report of Fu and Littke⁶ and results from the thermochemical studies which more clearly defined the electron-donating ability (better donating than PCy₃) and steric demand (larger than PCy₃) of the carbene ligands, 1,3-bis-(2,4,6-trimethylphenyl)imidazol-2-ylidene (**1**, IMes)¹⁹ was examined as a potential ancillary ligand in Suzuki cross-coupling reactions of aryl chlorides and arylboronic acids.



In our initial experiments we observed that the coupling of 4-chlorotoluene and phenylboronic acid (1.5 equiv) in the presence of 1.5 mol % of Pd₂(dba)₃, 3.0 mol % of the carbene **1**,¹⁹ and Cs₂CO₃ in dioxane at 80 °C proceeded to give 4-phenyltoluene in 59% isolated yield (Scheme 1). The reaction proceeded rapidly with complete consumption of the aryl chloride as observed by TLC within 1.5 h.

Since imidazol-2-ylidene carbenes are considerably less stable to air and moisture than the corresponding imidazolium salts, to avoid the preparation and isolation of the carbene **1** we sought to develop a protocol in which the carbene ligand **1** would be generated in situ from salt **2**. When the coupling reaction of 4-chlorotoluene with phenylboronic acid was performed with **2** under the same general conditions, the product 4-phenyltoluene was isolated in 96% yield (Table 1, entry 5). This result represents a significant improvement over the procedure employing the nucleophilic carbene **1** in terms of both isolated yield and ease of execution.

(14) Herrmann, W. A.; Goossen, L. T.; Köcher, C.; Autus, G. R. *J. Organomet. Chem., Int. Ed. Engl.* **1996**, *35*, 2805–2807.

(15) Weskamp, T.; Schattenmann, W. C.; Spiegler, M.; Herrmann, W. A. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 2490–2493.

(16) (a) Huang, J.; Stevens, E. D.; Nolan, S. P.; Petersen, J. L. *J. Am. Chem. Soc.* **1999**, *121*, 2674–2678. (b) Huang, J.; Schanz, H.-J.; Stevens, E. D.; Nolan, S. P. *Organometallics* **1999**, *18*, in press.

(17) Voges, M. H.; Rømming, C.; Tilset, M. *Organometallics* **1999**, *18*, 529–533.

(18) Herrmann, W. A.; Reisinger, C.-P.; Spiegler, M. *J. Organomet. Chem.* **1998**, *557*, 93–96.

(19) Arduengo, A. J., III; Dias, H. V. R.; Harlow, R. L.; Kline, M. *J. Am. Chem. Soc.* **1992**, *114*, 5530–5534.

[†] M.L.T.: email mtrudell@uno.edu; tel (504) 280-733; fax (504) 280-6860. S.P.N.: email snolan@uno.edu; tel. (504) 280-6445; fax (504) 280-6860.

(1) (a) For a review, see: Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457–2483. (b) For more recent palladium-based catalyzed couplings of aryl chlorides, see: Hamann, B. C.; Hartwig, J. F. *J. Am. Chem. Soc.* **1998**, *120*, 7369–7370. (c) Reetz, M. T.; Lohmer, G.; Schwickardi, R. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 481–483. (d) Littke, A. F.; Fu, G. C. *J. Org. Chem.* **1999**, *64*, 10–11.

(2) Cornils, B.; Herrmann, W. A., Eds. *Applied Homogeneous Catalysis with Organometallic Compounds*; VCH: Weinheim, 1996.

(3) (a) *Chem. Eng. News* **1998**; June 1, 24. (b) *Chem. Eng. News* **1998**; July 13, 71.

(4) (a) Collman, J. P.; Hegedus, L. S.; Norton, J. R.; Finke, R. G. *Principles and Applications of Organotransition Metal Chemistry*; University Science Books: Mill Valley, CA, 1987. (b) Parshall, G. W.; Iftel, S. *Homogeneous Catalysis*; J. Wiley and Sons: New York, 1992. (c) Pignolet, L. H., Ed. *Homogeneous Catalysis with Metal Phosphine Complexes*; Plenum: New York, 1983.

(5) Old, D. W.; Wolfe, J. P.; Buchwald, S. L. *J. Am. Chem. Soc.* **1998**, *120*, 9722–9723.

(6) Littke, A. F.; Fu, G. C. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 3387–3388.

(7) (a) Regitz, M. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 725–728. (b) Arduengo, A. J., III; Krafczyk, R. *Chem. Zeit.* **1998**, *32*, 6–14.

(8) Herrmann, W. A.; Köcher, C. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2163–2187.

(9) Herrmann, W. A.; Elison, M.; Fisher, J.; Köcher, C.; Autus, G. R. *J. Organomet. Chem., Int. Ed. Engl.* **1995**, *34*, 2371–2373.

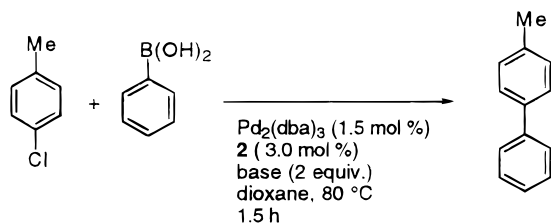
(10) Herrmann, W. A.; Brossmer, C.; Beller, M.; Fischer, H. DE 4,421,730 (Hoechst, AG), 1994; DE 4,421,753 (Hoechst, AG), 1994.

(11) (a) Herrmann, W. A.; Fischer, J.; Elison, M.; Köcher, C. DE 4,447,066 (Hoechst, AG), 1994; DE 4,447,067 (Hoechst, AG), 1994; DE 4,447,068 (Hoechst, AG), 1994. (b) Herrmann, W. A.; Fischer, J.; Elison, M.; Köcher, C. EP 0,719,753 (Hoechst, AG), 1996; EP 0,719,758 (Hoechst, AG), 1996; EP 0,719,953 (Hoechst, AG), 1996.

(12) Herrmann, W. A.; Fischer, J.; Elison, M.; Köcher, C.; Autus, G. R. *J. Chem. Eur. J.* **1996**, *2*, 772–780.

(13) McGuinness, D. S.; Green, M. J.; Cavell, K. J.; Skelton, B. W.; White, A. H. *J. Organomet. Chem.* **1998**, *565*, 165–178.

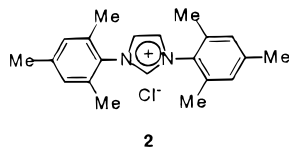
Table 1. Effect of the Base on the Rate of Pd₂(dba)₃/IMes·HCl (2**) Catalyzed Suzuki Cross-Coupling Reactions of 4-Chlorotoluene with Phenylboronic Acid**



entry	base	time (h)	yield (%) ^{a,b}
1	Et ₃ N	24	<5 ^c
2	Na ₂ CO ₃	43	6 ^c
3	KOAc	43	42 ^c
4	K ₂ CO ₃	24	53
5	CsF	2	65
6	Cs ₂ CO ₃	1.5	96

^a Isolated yields. ^b All reactions were monitored by TLC. ^c 4-Chlorotoluene was not completely consumed within the indicated reaction time (TLC).

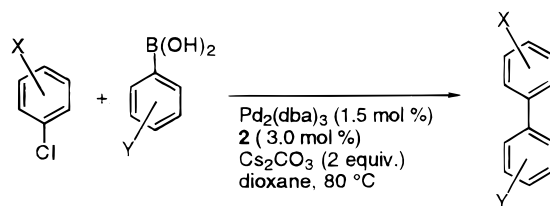
An investigation of the base in situ generation of the carbene ligand **1** from the salt **2** and enhanced catalytic activity revealed that Cs₂CO₃ was the reagent of choice



(Table 1). Other inorganic bases such as Na₂CO₃, KOAc, K₂CO₃, and CsF resulted in longer reaction times for complete consumption of the aryl chloride and afforded moderate to low yields of coupling products. When the organic base triethylamine was employed, the reaction ceased within minutes and precipitation of palladium black was observed.

As illustrated in Table 2, the palladium-catalyzed Suzuki reaction with the ancillary ligand **2** was exceptionally tolerant of a variety of functional groups substituted on the aryl chlorides and arylboronic acids. Electron-donating and electron-withdrawing substituents were both well tolerated by the catalytic system and provided the corresponding coupling products in excellent yields.

Table 2. Functional Group Tolerance of Pd₂(dba)₃/IMes·HCl (2**) Catalyzed Suzuki Cross-Coupling Reactions of Aryl Chlorides with Phenylboronic Acid Derivatives**



entry	X	Y	time (h)	yield (%) ^a
1	4-Me	H	1.5	96
2	4-Me	H	1.5	97 ^b
3	4-Me	4-OMe	1.5	99
4	4-Me	2-Me	1.5	88
5	4-Me	3-OMe	1.5	91
6	H	4-OMe	1.5	99
7	2,5-diMe	H	1.5	89
8	4-OMe	H	1.5	93
9	4-CO ₂ Me	H	1.5	99

^a Isolated yields. ^b 6.0 mol % of **2**.

Use of the imidazolium salt **2** allowing for the in situ generation of IMes **1** is a significant improvement upon existing Suzuki cross-coupling reaction methods. Furthermore, preliminary studies have shown that the use of other imidazolium salts as well as Pd(OAc)₂ can affect the Suzuki cross-coupling reaction of aryl chlorides with arylboronic acids. However, reactions performed with other imidazolium salts required longer times and afforded lower yields, while Pd(OAc)₂ was found to be equally as effective as Pd₂(dba)₃ under the reaction conditions described above. Detailed investigations focusing on imidazol-2-ylidene substituent effects, functional group tolerance, and catalytic activity in this and other coupling transformations are ongoing.

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Supporting Information Available: Experimental procedures. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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