Coupling Reactions

DOI: 10.1002/anie.200600493

A Highly Active Catalyst for Suzuki–Miyaura Cross-Coupling Reactions of Heteroaryl Compounds**

*Kelvin L. Billingsley, Kevin W. Anderson, and Stephen L. Buchwald**

In the past two decades, the Suzuki–Miyaura cross-coupling reaction has evolved into one of the most widely employed carbon–carbon bond-forming processes.[1,2] Its impact on organic synthesis is largely attributed to the fact that it provides a general and applicable method for the formation of biaryls, which are found in polymers,[3] biologically active compounds,[4] ligands,[5] and various materials.[6] In recent years, work by numerous groups has resulted in the production of highly active catalyst systems, which allow for couplings to occur with more challenging substrates, such as unactivated aryl chlorides and hindered boronic acids.[7]

Despite these advances, limitations of the method, to date, include its inability to maintain the efficacy exhibited in simple aryl–aryl bond formation when employing nitrogen heterocycles as one or both of the coupling partners (e.g., heteroaryl halides and/or heteroaryl boronic acids/esters).[8] Nitrogen-based heterocycles are ubiquitous in biologically active compounds, but inclusion of these heterocyclic motifs have been particularly detrimental to catalyst activity when palladium is used.[4] In addition, for exceptionally challenging substrates, such as chloroaminopyridines and chloroaminopyrimidines, protection of the free $-NH_2$ group or the need to employ chelating ligands, which prevent competitive binding of the substrate, have been reported to be essential to the success of the transformation.[9,10] Given the importance of the Suzuki–Miyaura reaction, particularly in the area of drug development, an efficient method for the coupling of nitrogen-containing heterocyclic substrates would make a significant impact.

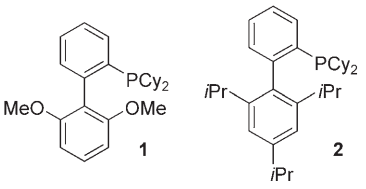
Herein, we report that extremely active catalysts composed of Pd and dialkylbiphenylphosphino ligands **1** or **2** provide a general system for the Suzuki–Miyaura reaction of

[*] K. L. Billingsley, K. W. Anderson, Prof. Dr. S. L. Buchwald
Department of Chemistry, Room 18-490
Massachusetts Institute of Technology
Cambridge, MA 02139 (USA)
Fax: (+1) 617-253-3297
E-mail: sbuchwal@mit.edu

[**] We thank the National Institutes of Health (GM 46059) and the National Cancer Institute (Cancer Training Grant GM 5-T32-CAO9112-30) for support of this work. We are grateful to Merck, Amgen, and Englehard ($Pd(OAc)_2$) for additional support. The Bruker Advance 400 MHz instrument used was purchased with funding from the National Institutes of Health (GM 1S10RR13886-01).

Supporting information for this article is available on the WWW under http://www.angewandte.org or from the author.

challenging heterocyclic substrates, such as aminoheteroaryl halides (chloroaminopyridines and chloroaminopyrimidines) and/or heteroaryl boronic acids/esters (e.g., 3- and 4-pyridineboronic acids, pyrrole boronate esters, and indole boronic acids). After our work was completed, Fu and co-workers reported that a catalyst system comprised of Pd/PCy_3 (Cy = cyclohexyl) was particularly effective in coupling aryl/heteroaryl halides and heteroaryl boronic acids.[11]

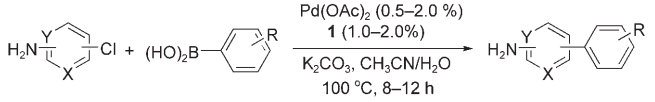


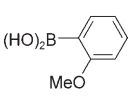
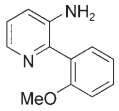
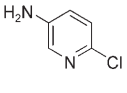
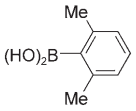
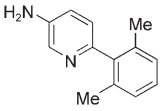
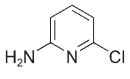
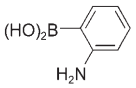
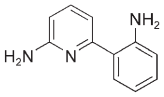
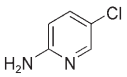
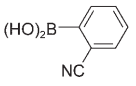
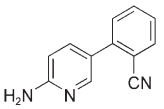
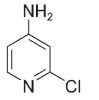
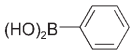
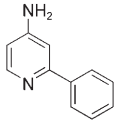
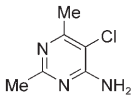
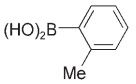
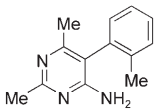
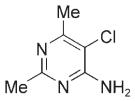
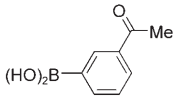
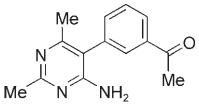
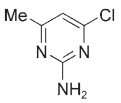
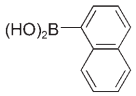
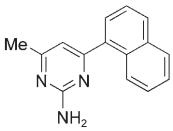
Only a few reports can be found on the successful Suzuki–Miyaura coupling of substrates that possess unprotected amino groups on a heteroaryl moiety.[9,12] Traditionally, to circumvent the problems associated with this functional group array, the free amino group is protected prior to the cross-coupling process and must, correspondingly, be deprotected following the organometallic reaction.[10] Past studies suggest that binding of the free $-NH_2$ group to the metal center can retard the catalytic cycle; therefore, the basicity of the aminoheteroaryl moiety should directly correlate to the efficacy of the Pd-catalyzed process (Scheme 1).[9a,13] Although previous reports suggest that chelating ligands are a necessity for the efficient coupling of unprotected aminoheteroaromatic compounds,[9a] our group has established that Suzuki–Miyaura reactions that employ the dialkylmonophosphino biaryl **1** as the supporting ligand display unprecedented reactivity while maintaining a broad substrate scope. Thus, in our initial studies, we utilized a catalyst based upon $Pd(OAc)_2$/**1** for the coupling of aryl boronic acids with chloroaminoheterocycles.

A catalyst system that employs **1** as the supporting ligand proved to be highly active for the cross-coupling of a range of chloroaminopyridines and chloroaminopyrimidines with aryl boronic acids that possess functional groups. For example, the reaction of 3-amino-2-chloropyridine with 2-methoxyphenylboronic acid smoothly produced the desired biaryl in 99% yield (Table 1, entry 1). In addition, the sterically hindered 2,6-dimethylphenylboronic acid reacted in 82% yield with 5-amino-2-chloropyridine (Table 1, entry 2), and similarly electron-deficient boronic acids also react in good yield under the derived conditions (Table 1, entry 4). Also, it is interesting to note that 4-amino-2-chloropyridine, which is the most basic among these substrates, reacts in excellent yield with phenylboronic acid (Table 1, entry 5). To the best of our knowledge, this result represents the highest yielding Suzuki–Miyaura coupling with a highly basic chloroaminopyridine.[9a]

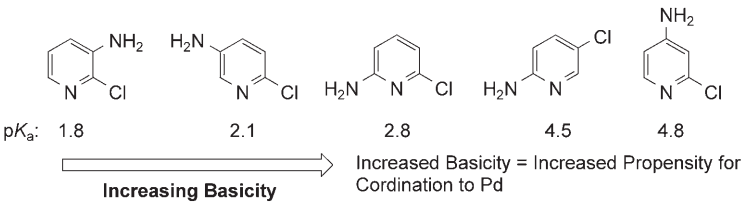
Similar to the results found for chloroaminopyridines, the $Pd(OAc)_2$/**1** catalyst system was highly active for the couplings of chloroaminopyrimidines (Table 1, entries 6–8). These reactions proceed in greater than 90% yield for both sterically encumbered heteroaryl halides and aryl boronic acids. In addition, the reaction of the electron-deficient boronic acid, 3-acetylphenylboronic acid, with the 4-amino-5-chloro-2,6-dimethylpyrimidine proceeds smoothly to produce the highly substituted heterobiaryl in

Table 1: Suzuki–Miyaura coupling of chloroaminoheterocycles using ligand **1**.[a]



Entry	Aryl chloride	Boronic acid	Product	Yield [%][b]
1				99
2				82
3				95
4				79[c]
5				92
6				97
7				96
8				92[c]

[a] Reaction conditions: heteroaryl halide (1.0 equiv), aryl boronic acid (1.2–1.5 equiv), K_2CO_3 (2.0–3.0 equiv), CH_3CN (1.5 mL mmol^{-1} halide), H_2O (1.0 mL mmol^{-1} halide), cat. = $Pd(OAc)_2$, L/Pd = 2:1. [b] Yield of isolated product based upon an average of two runs. [c] Reaction was conducted using K_3PO_4 and 1,4-dioxane (2.5 mL mmol^{-1} halide).

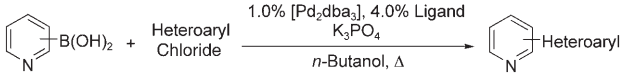


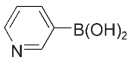
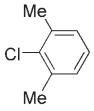
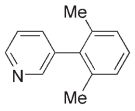
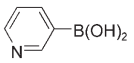
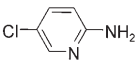
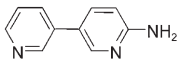
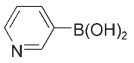
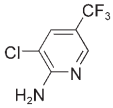
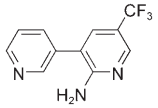
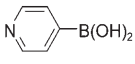
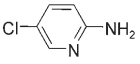
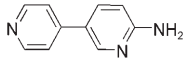
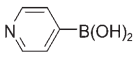
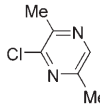
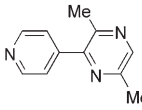
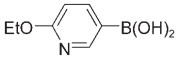
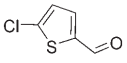
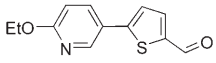
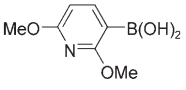
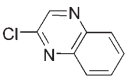
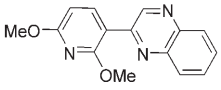
Scheme 1. Basicity of selected aminopyridines.

96% yield (Table 1, entry 7). This protocol corresponds to the only method whereby chloroaminopyrimidines are coupled to hindered aryl boronic acids.

Pyridines are the most common heterocyclic motif found in pharmaceutically active compounds.[14] Thus, preparative methods of pyridine derivatives remain an essential research topic in organic synthesis. Despite efforts by numerous groups, pyridine-derived boronic acids have proved to be a particularly difficult class of substrate for the Suzuki–Miyaura reaction.[11,15] The $Pd(OAc)_2$/**1** catalyst system provided good yields for the reaction of pyridine boronic acids with activated heteroaryl chlorides. For example, the reaction of 3-chloro-2,5-dimethylpyrazine with 4-pyridineboronic acid provided an 83% yield of the desired heterobiaryl (Table 2, entry 5).

Table 2: Suzuki–Miyaura coupling of pyridine boronic acids using ligands **1** or **2**.[a]



Entry	Boronic acid	Aryl chloride	Product	Ligand	*T* [°C]	Yield [%][b]
1				**2**	100	81
2				**2**	120	95
3				**2**	120	95
4				**2**	120	95
5				**1**	100	83[c,d]
6				**2**	100	91
7				**2**	100	91[e]

[a] Reaction condiitons: aryl or heteroaryl chloride (1.0 equiv), boronic acid (1.5 equiv), K_3PO_4 (2.0 equiv), *n*-butanol (2 mL mmol^{-1} halide), cat. = [Pd_2dba_3], L/Pd = 2:1. [b] Yield of isolated product based upon an average of two runs. [c] $Pd(OAc)_2$ was used instead of [Pd_2dba_3]. [d] Reaction was conducted in *s*-butanol. [e] Reaction was conducted in *tert*-amyl alcohol.

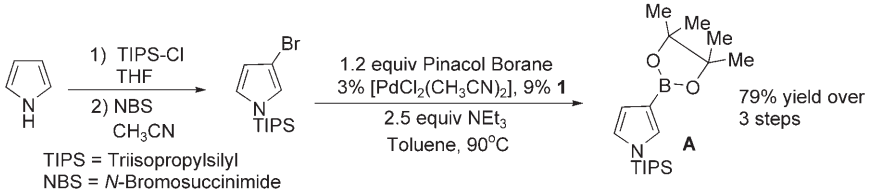
However, the catalyst proved to be far less efficacious for the reaction of unactivated aryl and heteroaryl chlorides.

We have established that a catalyst system based upon [Pd_2dba_3] (dba = dibenzylideneacetone) and the more-hindered ligand **2** afforded good-to-excellent yields for the cross-coupling of a variety of aryl and heteroaryl chlorides with pyridine-based boronic acids. We speculate that use of **2** maximizes the concentration of [$L_1Pd(Ar)X$] (X = halide) intermediates, which may be particularly important in these cases. Pyridine boronic acids reacted efficiently with sterically hindered aryl chlorides, as the coupling of 2-chloro-*m*-xylene with 3-pyridineboronic acid provided the biaryl in 81% yield (Table 2, entry 1). In addition, a range of aminopyridines was effectively coupled in excellent yield to 3- and 4-pyridineboronic acids (Table 2, entries 2–4). Similarly, commercially available alkoxypyridine boronic acids reacted in greater than 90% yield with an electron-deficient heteroaryl chloride (Table 2, entry 6). This protocol represents a general method for the coupling of pyridine-derived boronic acids with heteroaryl chlorides.

The first report of a pyrrole boronic acid was in 1991,[16] and currently a limited number of citations are found on the synthesis and utility of pyrrole-based boronic acids and borane derivatives.[17] As pyrroles are found in a variety of biological systems, we found this lack of precedent to be of particular interest. We discovered that employing a boronate ester instead of the boronic acid allowed for facile purification of the pyrrole reagent and its increased stability under the reaction conditions. Thus, **A** was synthesized in 79% yield from pyrrole by protection, selective bromination, and subsequent palladium-catalyzed boronation (Scheme 2).

Initial studies that employed pyrrole boronate esters proved to be unsuccessful as significant reduction of the aryl halide was detected. However, the addition of extraneous water to the reaction mixture minimized the amount of by-product and increased the overall yield. These conditions proved to be highly efficient for the coupling with heteroaryl bromides and activated heteroaryl chlorides at low catalyst loadings. The reaction of **A** with 5-bromoindole (Table 2, entry 1) and 2-bromopyridine (Table 2, entry 2) smoothly produced the heterobiaryls in greater than 90% yield at Pd loading of 0.25 mol%. In addition, **A** was also coupled to 2-bromothiophene in nearly quantitative yield with relatively high turnover numbers (Table 2, entry 3).

To examine the differences between the 2- and 3-boronated positions of the pyrrole unit, *N*-Boc-pyrrole-2-boronic acid (Boc = *tert*-butoxycarbonyl) was prepared by the known directed metalation strategy.[18] Significant dimerization or protodeboronation of the boronic acid was not readily detected under these conditions in contrast to what was previously repor-



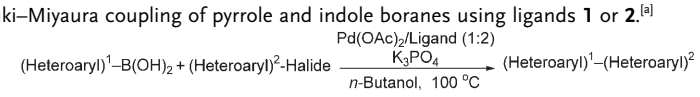
Scheme 2. Synthesis of *N*-(TIPS)-3-pyrrole pinacol borane.

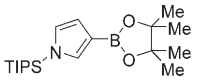
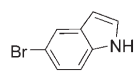
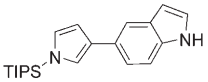
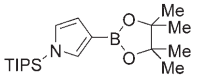
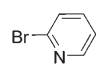
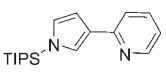
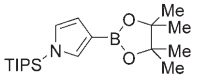
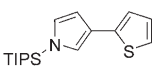
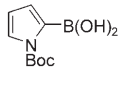
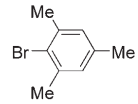
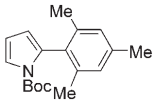
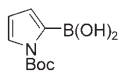
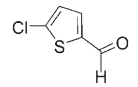
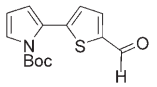
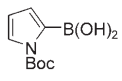
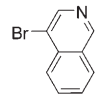
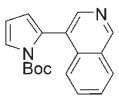
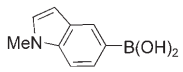
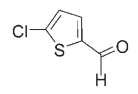
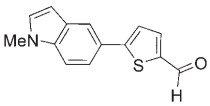
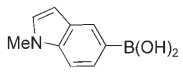
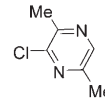
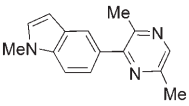
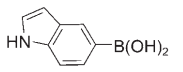
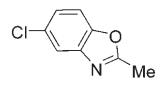
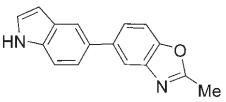
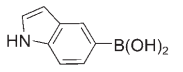
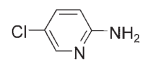
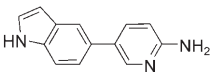
ted.[17b] Under the standard conditions, *N*-Boc-pyrrole-2-boronic acid was combined with the sterically encumbered substrate 2-bromomesitylene to afford the desired product in 89% yield (Table 3, entry 4). In addition, this boronic acid reacted in good yield with a variety of heteroaryl halides. The coupling of *N*-Boc-pyrrole-2-boronic acid with 5-chloro-2-thiophene carboxaldehyde and 4-bromoisoquinoline afforded the heterobiaryls in 84 and 95% yield, respectively (Table 3, entries 5 and 6). This method is the first general protocol through which 2- and 3-pyrrole organoboranes may serve as the nucleophilic component in the Suzuki–Miyaura reaction.

Indoles have been of interest for over a century because of the biological activity displayed by many of its derivatives.[19] Several studies have been conducted on the reactivity of indole-derived boronic acids under Suzuki–Miyaura conditions.[20] However, to date, there are only a few general methods for the cross-coupling of these derivatives with heteroaryl chlorides.[11] The reaction of 5-indoleboronic acid with a range of heteroaryl chlorides proceeded in good-to-excellent yields. The $Pd(OAc)_2$/**1** catalyst system was highly active for the reaction of activated heteroaryl chlorides. The coupling of *N*-methyl-5-indoleboronic acid with 5-chloro-2-thiophene carboxaldehyde resulted in 96% yield of the biaryl at a Pd loading of 0.25 mol% (Table 3, entry 7). In addition, this indole boronic acid smoothly reacted with 3-chloro-2,5-dimethylpyrazine to afford the heterobiaryl in 90% yield (Table 3, entry 8). As suggested in other reports, no significant difference in reactivity for the unprotected heteroaryl boronic was observed.[21] 5-Indoleboronic acid was coupled to several unactivated heteroaryl chlorides in $\geq$75% yield (Table 3, entries 9 and 10). In these cases, the temperature of the reaction had to be raised to 120 °C to facilitate the complete conversion of the heteroaryl chloride. The reaction of 5-indoleboronic acid with 5-chlorobenzoxazole and 2-amino-5-chloropyridine produced the desired heterobiaryl in 91 and 77% yields, respectively (Table 3, entries 9 and 10). This protocol represents the only current method by which indole boronic acids can be coupled to unactivated heteroaryl chlorides.

In summary, we have demonstrated that use of catalysts comprised of Pd and ligands **1** or **2** provide highly stable and active catalysts for the Suzuki–Miyaura coupling of pyridine, pyrrole, and indole boronic acids/esters. We also have shown that this catalyst is not inhibited by the presence of highly basic aminopyridines or aminopyrimidines, again demonstrating its high catalytic activity. Further work in applying these catalytic systems to a wider array of heteroaryl substrates will be reported in due course.

Table 3: Suzuki–Miyaura coupling of pyrrole and indole boranes using ligands **1** or **2**.[a]



Entry	Boronic acid	Aryl chloride	Product	Ligand	Pd [mol%]	Yield [%][b]
1				**1**	0.25	97[c]
2				**1**	0.25	91[c]
3				**1**	0.25	99[c]
4				**1**	2.0	89
5				**1**	2.0	84
6				**1**	2.0	95
7				**1**	0.25	96
8				**1**	2.0	90[e]
9				**2**	2.0	91[d]
10				**2**	2.0	77[d]

[a] Reaction conditions: aryl or heteroaryl chloride (1.0 equiv), boronic acid (1.5 equiv), K_3PO_4 (2.0 equiv), *n*-butanol (2 mL mmol^{-1} halide), cat. = [Pd_2dba_3], L/Pd = 2:1. [b] Yield of isolated product based upon an average of two runs. [c] [Pd_2dba_3] was used instead of $Pd(OAc)_2$. [d] Reaction was conducted at 120 °C. [e] *s*-Butanol was used as the solvent.

Received: February 6, 2006
Published online: April 26, 2006

Keywords: amines · boronic acids · cross-coupling · heteroaryl halides · Suzuki–Miyaura reaction

[1] A. de Meijere, F. Diederich, Eds. *Metal-Catalyzed Cross-Coupling Reactions*, *Vol. 2*, Wiley-VCH, Weinheim, **2004**.

[2] a) N. Miyaura, *Top. Curr. Chem.* **2002**, *219*, 11; b) A. Suzuki, *Organomet. Chem.* **1999**, *28*, 147.

[3] M. Kertesz, C. H. Choi, S. Yang, *Chem. Rev.* **2005**, *105*, 3448.

[4] a) A. Markham, K. L. Goa, *Drugs* **1997**, *54*, 299; b) R. Capdeville, E. Buchdunger, J. Zimmermann, A. Matter, *Nat. Rev. Drug Discovery* **2002**, *1*, 493; c) J. Boren, M. Cascante, S. Marin, B. Comin-Anduix, J. J. Centelles, S. Lim, S. Bassilian, S. Ahmed, W. N. Lee, L. G. Boros, *J. Biol. Chem.* **2001**, *276*, 37747.

[5] H. Tomori, J. M. Fox, S. L. Buchwald, *J. Org. Chem.* **2000**, *65*, 5334.

[6] S. Lightowler, M. Hird, *Chem. Mater.* **2005**, *17*, 5538.

[7] a) T. E. Barder, S. D. Walker, J. R. Martinelli, S. L. Buchwald, *J. Am. Chem. Soc.* **2005**, *127*, 4685; b) T. E. Barder, S. L. Buchwald, *Org. Lett.* **2004**, *6*, 2649; c) S. D. Walker, T. E. Barder, J. R. Martinelli, S. L. Buchwald, *Angew. Chem.* **2004**, *116*, 1907; *Angew. Chem. Int. Ed.* **2004**, *43*, 1871; d) H. N. Nguyen, X. Huang, S. L. Buchwald, *J. Am. Chem. Soc.* **2003**, *125*, 11818; e) J. Yin, M. P. Rainka, X.-X. Zhang, S. L. Buchwald, *J. Am. Chem. Soc.* **2002**, *124*, 1162; f) R. Singh, M. S. Viciu, N. Kramareva, O. Navarro, S. P. Nolan, *Org. Lett.* **2005**, *7*, 1829; g) A. F. Littke, C. Dai, G. C. Fu, *J. Am. Chem. Soc.* **2000**, *122*, 4020.

[8] a) I. Kondolff, H. Doucet, M. Santelli, *Synlett* **2005**, 2057; b) A. E. Thompson, G. Hughes, A. S. Batsanov, M. R. Bryce, P. R. Parry, B. Tarbit, *J. Org. Chem.* **2005**, *70*, 388; also see references [7a–d].

[9] A few direct cross-coupling reactions that involve heteroaryl moieties with unprotected NH_2 groups have been disclosed; see: ref. [8b] and a) T. Itoh, T. Mase, *Tetrahedron Lett.* **2005**, *46*, 3573; b) T. Itoh, K. Sato, T. Mase, *Adv. Synth. Catal.* **2004**, *346*, 1859; c) P. Gunda, L. M. Russon, M. K. Lakshman, *Angew. Chem.* **2004**, *116*, 6532; *Angew. Chem. Int. Ed.* **2004**, *43*, 6372; d) L. A. Agrofoglio, I. Gillaizeau, Y. Saito, *Chem. Rev.* **2003**, *103*, 1875; e) T. Tagata, M. Nishida, *J. Org. Chem.* **2003**, *68*, 9412; f) M. Feuerstein, H. Doucet, M. Santelli, *J. Organomet. Chem.* **2003**, *687*, 327.

[10] For examples in which it was essential to protect the amino-heterocycle, see: a) S. Caron, S. S. Massett, D. E. Bogle, M. J. Castaldi, T. F. Braish, *Org. Process Res. Dev.* **2001**, *5*, 254; b) J. A. Miller, R. P. Farrell, *Tetrahedron Lett.* **1998**, *39*, 6441.

[11] N. Kudo, M. Perseghini, G. C. Fu, *Angew. Chem.*, **2006**, *118*, 1304; *Angew. Chem. Int. Ed.* **2006**, *15*, 1282.

[12] During the production of this manuscript, Guram et al. reported that the use of $[PdCl_2\{PtBu_2(p\text{-}RPh)\}_2]$ ($R = H, NMe_2, CF_3$) were quite effective as catalysts in the Suzuki–Miyaura coupling of amino-heteroaryl/heteroaryl chlorides and aryl boronic acids, see: A. S. Guram, A. O. King, J. G. Allen, X. Wang, L. B. Schenkel, J. Chan, E. E. Bunel, M. M. Faul, R. D. Larsen, M. J. Martinelli, P. J. Reider, *Org. Lett* **2006**, ASAP.

[13] S. Wagaw, S. L. Buchwald, *J. Org. Chem.* **1996**, *61*, 7240.

[14] V. Bonnet, F. Mongin, F. Tre'court, G. Breton, F. Marsais, P. Knochel, G. Que'guiner, *Synlett* **2002**, 1008.

[15] a) M. Ishikura, M. Kamada, M. Terashima, *Heterocycles* **1984**, *22*, 265; b) P. R. Parry, C. Wang, A. S. Batsanov, M. R. Bryce, B. Tarbit, *J. Org. Chem.* **2002**, *67*, 7541; c) G. A. Molander, B. Biolatto, *J. Org. Chem.* **2003**, *68*, 4302; d) C. L. Cioffi, W. T. Spencer, J. J. Richards, R. J. Herr, *J. Org. Chem.* **2004**, *69*, 2210; e) P. B. Hodgson, F. H. Salingue, *Tetrahedron Lett.* **2004**, *45*, 685; f) T. E. Barder, S. L. Buchwald, *Org. Lett.* **2004**, *6*, 2649.

[16] S. Martina, V. Enkelmann, G. Wegner, A. D. Schluter, *Synthesis* **1991**, 613.

[17] a) A. Alzarez, A. Guzmen, A. Ruiz, E. Velards, J. Muchowski, *J. Org. Chem.* **1992**, *57*, 1653; b) C. Johnson, G. Stemp, N. Anand, S. Stephen, T. Gallagher, *Synlett* **1998**, 1025.

[18] B. Bray, P. Mathies, R. Naef, D. Solas, T. Tidwell, D. Artis, J. Muchowski, *J. Org. Chem.* **1990**, *55*, 6317.

[19] *Indoles* (Ed.: W. J. Houlihan), Wiley-Interscience, New York, **1972**.

[20] Y. Yang, A. R. Martin, *Heterocycles* **1992**, *34*, 1395.

[21] M. Prieto, E. Zurita, E. Rosa, L. Munoz, P. Lloyd-Williams, E. Giralt, *J. Org. Chem.* **2004**, *69*, 6812.

