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New Air-Stable Catalysts for General and Efficient Suzuki–Miyaura Cross-Coupling Reactions of Heteroaryl Chlorides

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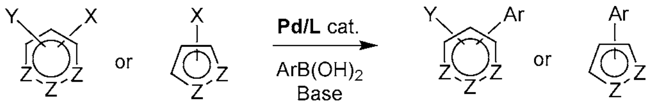
ABSTRACT



X = Cl, Br
Y = OR, SR, NH$_2$
Z = N, S, C

Pd/L: PdCl$_2${P^{t}Bu$_2$(*p*-NMe$_2$-Ph)}$_2$

New air-stable PdCl$_2${P^{t}Bu$_2$(*p*-R-Ph)}$_2$ (R = H, NMe$_2$, CF$_3$,) complexes represent simple, general, and efficient catalysts for the Suzuki–Miyaura cross-coupling reactions of aryl halides including five-membered heteroaryl halides and heteroatom-substituted six-membered heteroaryl chlorides with a diverse range of arylboronic acids. High product yields (89–99% isolated yields) and turn-over-numbers (10 000 TON) are observed.

The Suzuki−Miyaura cross-coupling reaction has emerged as one of the most powerful, attractive, and widely utilized methods for the construction of carbon−carbon bonds.[1] Notably, the pioneering development of novel and highly efficient Pd/L catalysts from the groups of Buchwald,[2] Fu,[3] Hartwig,[4] Beller,[5] Guram/Bei,[6] Bedford,[7] Li,[8] Herrmann,[9] Nolan,[10] and Colacot[11] has significantly extended the scope of the reaction to include aryl chlorides as coupling partners. Although catalysts for cross-coupling reactions of aryl chlorides with a range of electronic and steric properties are now extensively developed, catalysts for general cross-coupling reactions of heteroaryl halides, and particularly five-

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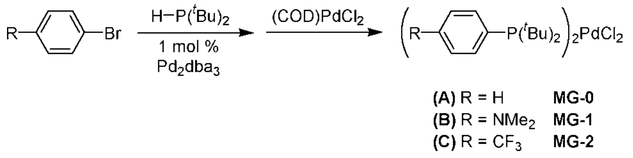
membered heteroaryl halides and six-membered heteroaryl chlorides bearing heteroatom substituents (such as −SR, $-NH_2$, and −OR), remain underdeveloped.[12−14]

The Suzuki−Miyaura cross-coupling reaction of heteroaryl chlorides with heteroatom substituents is of interest to the pharmaceutical industry for the preparation of biologically active compounds. Historically, however, these substrates have been found to be problematic coupling partners. The ineffectiveness of these substrates has been attributed to the potential binding nature of such substrates to the metal center resulting in the formation of inactive (substrate)$_n$−metal complexes.[14] Recently, the groups of Bryce[13] and Itoh[14] have reported the Suzuki−Miyaura cross-coupling reactions of heteroaryl chlorides bearing a primary amine group using $PdCl_2(PPh_3)_2$ and $Pd(OAc)_2$/D^{t}BPF catalysts, respectively, although high catalyst loadings of 5 mol % were typically required. The electron-rich bidentate D^{t}BPF ligand-based Pd/L catalyst was found to be more general and effective compared to the monodentate PPh_3, ^{t}Bu$_3$P, and biphenyl-PR_2 (R = Cy, ^{t}Bu) ligand-based Pd/L catalysts purportedly because of the ability of the chelating D^{t}BPF ligand to inhibit the formation of inactive (substrate)$_n$−metal complexes.[14] However, the Buchwald group has recently reported a successful example of a Pd/L-catalyzed Suzuki−Miyaura cross-coupling reaction of a NH_2-substituted chloropyridine with pyridin-3-ylboronic acid using a monodentate sulfonated S-PHOS ligand.[15]

As part of our efforts to develop efficient processes to biologically active compounds, we were interested in the Suzuki−Miyaura cross-coupling reactions of heteroaryl halides. The state-of-the-art Pd/L catalysts including Pd/D^{t}BPF under typical conditions were found to be practically unattractive for the synthesis of specific targets of interest. Therefore, we initiated a study for the development of new and improved catalysts for the cross-coupling reactions of heteroaryl halides. Herein, we report our preliminary results which include the synthesis, characterization, and reactivity of new air-stable $PdCl_2\{P^tBu_2(p\text{-R-Ph})\}_2$ (R = H (**A**), NMe_2 (**B**), CF_3 (**C**)) complexes[16] and the utility of $PdCl_2\{P^tBu_2(p\text{-NMe}_2\text{-Ph})\}_2$ (**B**) as a simple, general, and highly active catalyst for the efficient Suzuki−Miyaura cross-coupling reactions of aryl halides including six-membered heteroaryl chlorides with −SR, $-NH_2$, and −OR substituents and five-membered heteroaryl halides.

The air-stable $PdCl_2\{P^tBu_2(p\text{-R-Ph})\}_2$ (**A**−**C**) complexes were readily prepared in two steps from commercially available inexpensive reagents (Scheme 1).[17] The selected aryl bromides were reacted with di-*tert*-butylphosphine in the presence of the Pd_2dba_3 catalyst and a base to afford the desired phosphine ligands, which were then reacted with the $PdCl_2(COD)$ complex to afford the desired palladium complexes **A**−**C**. The complexes were characterized by ^1H and ^{31}P NMR. Elemental analysis and ^{31}P NMR studies of mixtures (1:1 molar ratio) of $PdCl_2(PPh_3)_2$ with **A**, **B**, and

Scheme 1. Synthesis of New Palladium/Phosphine Complexes



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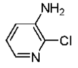
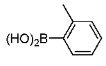
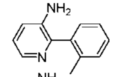
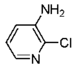
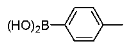
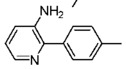
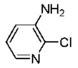
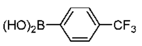
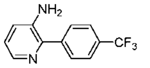
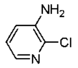
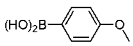
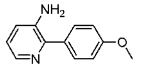
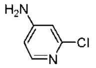
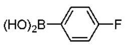
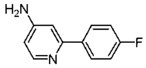
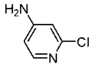
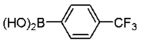
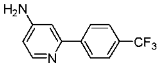
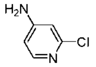
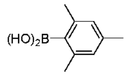
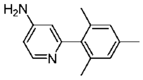
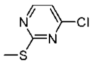
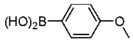
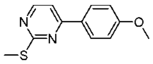
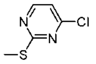
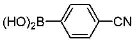
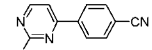
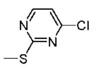
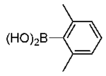
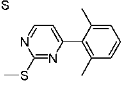
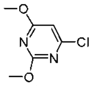
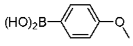
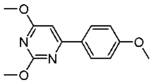
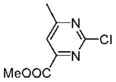
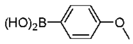
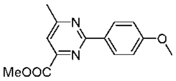
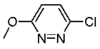
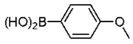
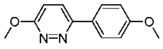
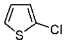
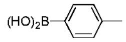
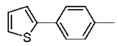
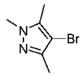
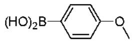
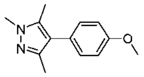
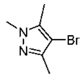
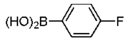
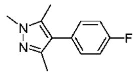
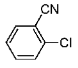
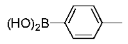
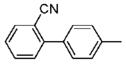
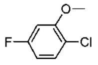
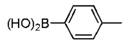
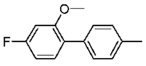
1				93
2				95
3				92
4				93
5				93[b]
6				90
7				98[c]
8				95
9				94
10				99[d,i]
11				98[d]
12				89[e,f]
13				97
14				96
15				93[g]
16				95[g]
17				94[e,g]
18				99[h]

[a] Reaction conditions: Ar−X (1.0 equiv), Ar−B(OH)$_2$ (1.2 equiv), K_2CO_3 (2.0 equiv), catalyst **B** (1.0 mol %), toluene/water (10−20% water), reflux for 12 h. Yields correspond to % isolated product. [b] 860 TON observed at lower catalyst loading. [c] 2 mol % of catalyst. [d] 0.1 mol % of catalyst. [e] 0.01 mol % of catalyst. [f] Anhyd toluene. [g] K_3PO_4 base. [h] GC-MS. [i] For comparison, 1.0−1.2 mol % of catalyst was required for complete conversion with $Pd(OAc)_2$/*s*-PHOS and $PdCl_2$(D^{t}BPF) catalysts under otherwise identical conditions.

C, respectively, confirmed the presence of two phosphine ligands in each of the palladium complexes **A**−**C**.

The cross-coupling reaction of 3-methyl-2-chloropyridine with 4-(trifluoromethyl)phenylboronic acid in the presence of catalyst **A** was studied to identify suitable bases and solvents. In toluene solvent, the bases K_2CO_3, K_3PO_4, KOAc, Cs_2CO_3, CsF, and Na_2CO_3 were found to be the best. The solvent/base combinations of butanol/KOAc, 1,4-dioxane/CsF, and acetonitrile/CsF were also found to be suitable.

The cross-coupling reaction of 2-chloro-*m*-xylene with *p*-tolylboronic acid in the presence of K_2CO_3 base and toluene solvent was used to evaluate the reactivity of catalysts **A**−**C**.[17] The catalyst reactivity was found to be dependent on the electronic properties of the ligands. The catalyst **B** with the most electron-rich phosphine ligand was found to be the best under these anhydrous conditions (6 h, % conversion at 100 °C: **A**, 81; **B**, 94; **C**, 63). Aqueous conditions resulted in further improvement (faster reaction) in performance of catalyst **B**.

The efficacy of catalyst **B** (**MG-1**) for general Suzuki−Miyaura cross-coupling reactions of heteroaryl and aryl halides was further investigated (Table 1).[17] The reactions were conducted with K_2CO_3 or K_3PO_4 base in toluene/water (10−20% water) solvents. Catalyst loadings of 1.0−0.1 mol % were typically employed. The reactions of amino-substituted 2-chloropyridines with arylboronic acids bearing both electron-withdrawing and electron-donating substituents were efficient and afforded the desired products in high yields (entries 1−6). The reaction of 4-amino-2-chloropyridine with the sterically demanding 2,4,6-trimethylphenylboronic acid also afforded the desired product in high yield (entry 7), although a slightly higher catalyst loading was required. In comparison, the previous best conditions for these substrates with Pd/D^{t}BPF and Pd/PPh_3 catalysts required significantly higher catalyst loadings (5 mol %) and only low yields (ca. 40%) were obtained with the 4-amino-2-chloropyridine substrate.[12,13] The reactions of −SMe, −OMe, and −C(O)-OMe-substituted pyrimidines with diverse arylboronic acids went to completion efficiently even at lower catalyst loadings (1.0−0.01 mol %, 100−10 000 TONs) (entries 8−12). The reaction of 3-chloro-6-methoxypyridazine with 4-methoxyphenylboronic acid gave the desired product in high yield (entry 13). The reactions of five-membered heteroaryl halides including 2-chlorothiophene and 1,3,5-trimethyl-4-bromopyrazole with arylboronic acids also proceeded efficiently (entries 14−16). The reactions of traditional aryl chlorides with arylboronic acids were also very successful (entries 17−18). Notably, the reaction of 2-chlorobenzonitrile with *p*-tolylboronic acid proceeded to completion in the presence of only 0.01 mol % of catalyst **B** (10 000 TON) to afford the desired industrially significant intermediate, OTBN (*o*-tolylbenzonitrile), in high yield (entry 17). Turn-over-numbers higher than 10 000 were not investigated in this study.

In conclusion, we have demonstrated that new air-stable $PdCl_2\{P^tBu_2(p\text{-R-Ph})\}_2$ complexes are readily available from simple inexpensive reagents and the complex $PdCl_2\{P^tBu_2(p\text{-NMe}_2\text{-Ph})\}_2$ (**B**, **MG-1**), in particular, represents an efficient and general catalyst for the Suzuki−Miyaura cross-coupling reactions of aryl halides including five-membered heteroaryl halides and heteroatom-substituted six-membered heteroaryl chlorides with a diverse range of arylboronic acids. High product yields (89−99% isolated yields) and turn-over-numbers (up to 10 000 TON) are generally observed. Overall, these results significantly advance the scope of Suzuki−Miyaura cross-coupling reactions and are of tremendous value to the research and development efforts in the pharmaceutical industry. Studies to delineate catalyst structure and activity relationships and to explore catalyst utility for other reactions are currently in progress.

Acknowledgment. Dr. Thomas Colacot of Johnson Matthey is thanked for providing multigram quantities of catalyst **A**.

Note Added after ASAP Publication. There was a change in the presentation of the heteroaryls in the Abstract and TOC graphic in the version published April 1, 2006; the corrected version was published April 4, 2006.

Supporting Information Available: Experimental procedures and characterization data are provided as Supporting Information. This material is available free of charge via the Internet http://pubs.acs.org.

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[12] Leading references to cross-coupling reactions of five-membered heteroaryl halides: (a) Charles, M. D.; Schultz, P.; Buchwald, S. L. *Org. Lett.* **2005**, *7*, 3965−3968. (b) Hooper, M. W.; Utsunomiya, M.; Hartwig, J. F. *J. Org. Chem.* **2003,** *68*, 2861−2873.

[13] Thompson, A. E.; Hughes, G.; Batsanov, A. S.; Bryce, M. R.; Parry, P. R.; Tarbit, B. *J. Org. Chem.* **2005**, *70*, 388−390.

[14] Itoh, T.; Mase, T. *Tetrahedron Lett.* **2005**, *46*, 3573−3577.

[15] Anderson, K. W.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2005**, *44*, 6173−6177.

[16] Complex **A** has been reported previously; see: Mann, B. E.; Shaw, B. L.; Slade, R. M. *J. Chem. Soc. A* **1971**, 2976−2980.

[17] Detailed experimental procedures and characterization data are provided as Supporting Information.