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New Catalysts for Suzuki−Miyaura Coupling Reactions of Heteroatom-Substituted Heteroaryl Chlorides

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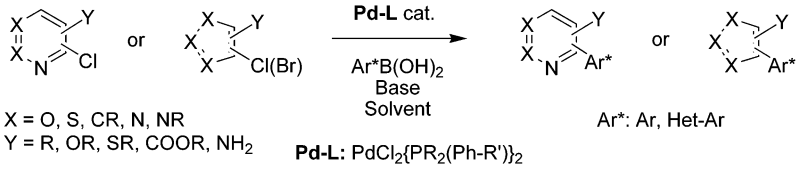

The new air-stable $PdCl_2\{PR_2(Ph\text{-}R')\}_2$ complexes, readily prepared from commercial reagents, exhibit unique efficiency as catalysts for the Suzuki−Miyaura coupling reactions of a variety of heteroatom-substituted heteroaryl chlorides with a diverse range of aryl/heteroaryl boronic acids. The coupling reactions catalyzed by the new complexes exhibit high product yields (88−99%) and high catalyst turnover numbers (up to 10 000 TON).

Introduction

The Suzuki−Miyaura coupling reaction represents one of the most widely utilized methods in organic syntheses.[1] Recent pioneering advances in the development of efficient catalysts have significantly extended the scope of the reaction to include aryl chlorides as coupling partners.[2] Many catalysts for the cross-coupling reactions of aryl chlorides with a range of steric and electronic substitution patterns are now extensively developed. However, catalysts for the general and efficient cross-coupling reactions of heteroatom-substituted heteroaryl chlorides remain underdeveloped.[3]

The cross-coupling reactions of heteroatom-substituted heteroaryl chlorides are of significance to the pharmaceutical industry because of comparatively lower cost of heteroaryl chloride raw materials and the prevalence of heteroatom-substituted heterobiaryls in biologically relevant targets. However, the cross-coupling reactions of such substrates are generally considered to be problematic because these substrates can bind to the metal center and deactivate the catalyst.[4] In the past, heteroaryl halides with heteroatom substituents with labile protons such as −OH, −COOH, −SH, and $-NH_2$ were generally found to be unsuitable coupling partners,[4−8] and required protection/deprotection strategies.[8a] Recently, $PdCl_2(PPh_3)_2$ and $Pd(OAc)_2$/D^{t}BPF catalysts (D^{t}BPF = 1,1′-bis(di-*tert*-butylphosphino)ferrocene) were reported to offer improved results compared to the Pd-L catalysts with electron-rich bulky monodentate phosphine ligands such as P^{t}Bu$_3$ and PCy_2(biphenyl), but high catalyst loadings (5 mol %) were typically required.[4a,b] It was shown that Pd-L catalysts with bulky

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(2) Leading references: (a) Barder, T. E.; Walker, S. D.; Martinelli, J. R.; Buchwald, S. L. *J. Am. Chem. Soc.* **2005**, *127*, 4685−4696. (b) Walker, S. D.; Barder, T. E.; Martinelli, J. R.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2004**, *43*, 1871−1876. (c) Yin, J.; Rainka, M. P.; Zhang, X-X.; Buchwald, S. L. *J. Am. Chem. Soc.* **2002**, *124*, 1162−1163. (d) Kirchhoff, J. H.; Dai, C.; Fu, G. C. *Angew. Chem., Int. Ed.* **2002**, *41*, 1945−1947. (e) Liu, S-Y.; Choi, M. J.; Fu, G. C. *Chem. Commun.* **2001**, 2408−2409. (f) Kataoka, N.; Shelby, Q.; Stambuli, J. P.; Hartwig, J. F. *J. Org. Chem.* **2002**, *67*, 5553−5566. (g) Zapf, A.; Jackstell, R.; Rataboul, F.; Reirmeier, T.; Monsees, A.; Fuhrmann, C.; Shaikh, N.; Dingerdissen, U.; Beller, M. *Chem. Commun.* **2004**, 38−39. (h) Harkal, S.; Rataboul, F.; Zapf, A.; Fuhrmann, C.; Riermeier, T.; Monsees, A.; Beller, M. *Adv. Synth. Catal.* **2004**, *346*, 1742−1748. (i) Zapf, A.; Ehrentraut, A.; Beller, M. *Angew. Chem., Int. Ed.* **2000**, *39*, 4153−4155. (j) Bei, X.; Turner, H. W.; Weinberg, W. H.; Guram, A. S.; Petersen, J. L. *J. Org. Chem.* **1999**, *64*, 6797−6803. (k) Bei, X.; Crevier, T.; Guram, A. S.; Jandeleit, B.; Powers, T. S.; Turner, H. W.; Uno, T.; Weinberg, W. H. *Tetrahedron Lett.* **1999**, *40*, 3855−3858. (l) Bedford, R. B.; Cazin, C. S. J.; Hazelwood, S. L. *Angew. Chem., Int. Ed.* **2002**, *41*, 4120−4122. (m) Bedford, R. B.; Cazin, C. S. J. *Chem. Commun.* **2001**, 1540−1541. (n) Li, G. Y.; Zheng, G.; Noonan, A. F. *J. Org. Chem.* **2001**, *66*, 8677−8678. (o) Gstottmayr, C. W. K.; Bohm, V. P. W.; Herdtweck, E.; Grosche, M.; Herrmann, W. A. *Angew. Chem., Int. Ed.* **2002**, *41*, 1363−1365. (p) Navarro, O.; Kaur, H.; Mahjoor, P.; Nolan, S. P. *J. Org. Chem.* **2004**, *69*, 3173−3180. (q) Navarro, O.; Kelly, R. A., III; Nolan, S. P. *J. Am. Chem. Soc.* **2003**, *125*, 16194−16195. (r) Colacot, T. J.; Shea, H. A. *Org. Lett.* **2004**, *6*, 3731−3734. (s) Dai, Q.; Gao, W.; Liu, D.; Kapes, L. M.; Zhang, X. *J. Org. Chem.* **2006**, *71*, 3928−3934.

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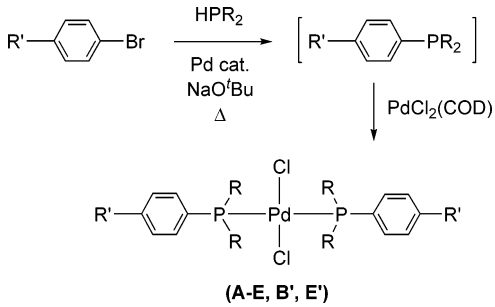
SCHEME 1. Syntheses of $PdCl_2\{PR_2(Ph\text{-}R')\}_2$ Complexes



monodentate phosphine ligands were more susceptible to deactivation by heteroatom-containing reaction substrates.[4b]

As part of our effort to develop efficient and scalable processes to pharmaceutically relevant targets, we are interested in the Suzuki−Miyaura coupling reactions of certain bulky heteroatom-substituted heteroaryl chlorides with aryl/heteroaryl boronic acids. Our study of the state-of-the-art Pd-L catalysts under typical conditions afforded results that were not optimum for the syntheses of specific target molecules of interest. We therefore initiated studies to investigate new Pd-L catalysts. In particular, we studied new dialkylphenylphosphines in which the phenyl is unsubstituted at the ortho position (unlike the Buchwald dialkylphenylphosphine ligands in which the phenyl is substituted with another phenyl group at the ortho position). Herein, we describe in full the syntheses, characterization, and activity of new $PdCl_2\{PR_2(Ph\text{-}R')\}_2$ complexes, and their scope and limitations as catalysts for the Suzuki−Miyaura coupling reactions of heteroatom-containing reaction substrates.

Results

Syntheses and Characterization of $PdCl_2\{PR_2(Ph\text{-}R')\}_2$ Complexes. The $PdCl_2\{PR_2(Ph\text{-}R')\}_2$ complexes **A**−**E** (R = ^{t}Bu) with gradual increase in the basicity of the phosphine ligands were prepared (Figure 1).[9] Additionally, the cyclohexyl analogues **B′** and **E′** (R = Cy) were also prepared for comparison (Figure 1). The complexes were readily prepared in two steps from commercially available reagents (Scheme 1).[10] The palladium-catalyzed cross-coupling reaction of inexpensive aryl bromides with HPR_2 afforded the desired dialkylphenylphosphines, which were reacted with $PdCl_2$(COD) to afford the desired air-stable $PdCl_2\{PR_2(Ph\text{-}R')\}_2$ complexes.

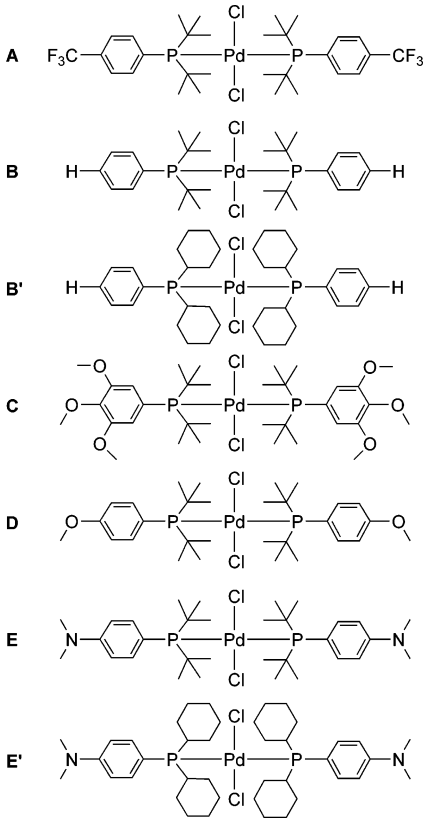


FIGURE 1. New $PdCl_2\{PR_2(Ph\text{-}R')\}_2$ complexes.

The complexes **A**−**E**, **B′**, and **E′** were characterized by spectroscopy and elemental analysis. The ^{31}P NMR spectra of the complexes showed single downfield-shifted resonance for the phosphine ligands (compared to free phosphine) consistent with the binding of the phosphine ligands to the palladium center. Elemental analyses for the complexes were also consistent with the indicated structural formulas. The ^{1}H NMR spectrum of complex **E** in the presence of an internal standard unambiguously confirmed the presence of two phosphine ligands on the palladium center. Additionally, the $-CH_3$ resonance for the ^{t}Bu group in the ^{1}H NMR spectrum of complex **E** appears as a 1:2:1 triplet (overlapping doublet of doublet) with a broader middle peak establishing the trans orientation of the two phosphine ligands on the palladium center.[11] The Raman spectrum of complex **E** showed a Pd−Cl stretch at 295 cm^{-1}.

(3) Recently, others and we have communicated the development of catalysts and conditions for more general and efficient Suzuki−Miyaura coupling reactions of heteroatom-substituted heteroaryl chlorides; see: (a) Kudo, N.; Perseghini, M.; Fu, G. C. *Angew. Chem., Int. Ed.* **2006**, *45*, 1282−1284. (b) Billingsley, K. L.; Anderson, K. W.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2006**, *45*, 3484−3488. (c) Guram, A. S.; King, A. O.; Allen, J. G.; Wang, X.; Schenkel, L. B.; Chan, J.; Bunel, E. E.; Faul, M. M.; Larsen, R. D.; Martinelli, M. J.; Reider, P. J. *Org. Lett.* **2006**, *8*, 1787−1789. (d) Billingsley, K.; Buchwald, S. L. *J. Am. Chem. Soc.* **2007**, *129*, 3358−3366.

(4) For other examples of direct Suzuki−Miyaura coupling reactions of NH_2-substituted heteroaryl chlorides; see: (a) Thompson, A. E.; Hughes, G.; Batsanov, A. S.; Bryce, M. R.; Parry, P. R.; Tarbit, B. *J. Org. Chem.* **2005**, *70*, 388−390. (b) Itoh, T.; Mase, T. *Tetrahedron Lett.* **2005**, *46*, 3573−3577. (c) Cooke, G.; de Cremiers, H. A.; Rotello, V. M.; Tarbit, B.; Vanderstraeten, P. E. *Tetrahedron* **2001**, *57*, 2787.

(5) The Suzuki−Miyaura coupling reaction of NH_2-substituted chloropyridine with pyridin-3-ylboronic acid with more efficient Pd-sulfonated S-PHOS ligand catalyst was reported recently; see: Anderson, K. W.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2005**, *44*, 6173−6177.

(6) The cross-coupling reactions of NH_2-substituted heteroaryl tosylates have been described; see: Gunda, P.; Russon, L. M.; Lakshman, M. K. *Angew. Chem., Int. Ed.* **2004**, *43*, 6372−6377.

(7) For Suzuki−Miyaura coupling reactions of NH_2-substituted heteroaryl bromides and aryl halides, see citations in refs 3b and 4.

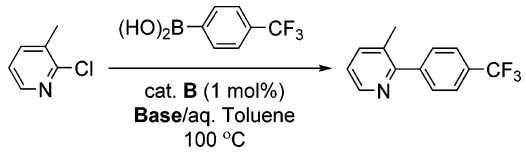
(8) Protection/deprotection strategies were employed for the Suzuki−Miyaura coupling of 3-amino-2-chloropyridine, see: (a) Caron, S.; Massett, S. S.; Bogle, D. E.; Castaldi, M. J.; Braish, T. F. *Org. Process Res. Dev.* **2001**, *5*, 254−256. For Pd-L-catalyzed Suzuki coupling reaction of COOH-substituted bromopyridines, see: (b) Meier, P.; Legraverant, S.; Muller, S.; Schaub, J. *Synthesis* **2003**, 551−554. For related Negishi coupling of heteroatom-substituted aryl chlorides and amino-chloropyridines, see: (c) Miller, J. A.; Farrell, R. P. *Tetrahedron Lett.* **1998**, *39*, 6441−6444.

(9) The complex **B** has been reported previously; see: Mann, B. E.; Shaw, B. L.; Slade, R. M. *J. Chem. Soc. A* **1971**, 2976−2980.

(10) The PCy_2Ph ligand used in the preparation of complex **B′** was purchased from Aldrich Chemical Co. and used as such. The complex **B** was also prepared as shown in Scheme 1. For alternate synthesis of complex **B**, see ref 9.

(11) The *trans*-$PdCl_2(PR_3)_2$ structures are generally observed with most small to moderate sized monodentate phosphine ligands. Trans structure was confirmed for complex **B** previously, similarly based on ^{1}H NMR and IR data, see ref 9.

TABLE 1. Influence of Base on $PdCl_2\{P^tBu_2(Ph\text{-}H)\}_2$ (B)-Catalyzed Cross-Coupling Reaction[a]



entry	base	conv (%)
1	KOAc	>99
2	$Na_2CO_3.H_2O$	96
3	CsF	>99
4	K_2CO_3	>99
5	Cs_2CO_3	>99
6	K_3PO_4	>99
7	NaO^{t}Bu	93
8	Cy_2NH	92
9	$NaHCO_3$	40
10	KF·HF	79
11	$KHCO_3$	57

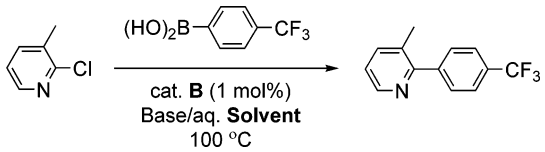
[a] Reaction conditions: heteroaryl chloride (1.0 equiv), aryl boronic acid (1.5 equiv), base (2.0 equiv), 10% aqueous solvent (3−4 mL/mmol), reaction time (6 h). The conversions are based on GCMS A% conversion of the starting heteroaryl chloride to the desired product in the presence of an internal standard.

The characterization data are most consistent with the depicted *trans*-$PdCl_2\{PR_2(Ph\text{-}R')\}_2$ structures shown in Figure 1.[11]

Catalytic Activity of $PdCl_2\{PR_2(Ph\text{-}R')\}_2$ Complexes for Suzuki−Miyaura Coupling Reactions. The $PdCl_2\{PR_2(Ph\text{-}R')\}_2$ complexes were evaluated as catalysts for Suzuki−Miyaura coupling reactions. Initial studies were performed with complex **B** in which the phenyl is unsubstituted (R′ = H). A variety of bases were investigated for the reaction of 2-chloro-3-methylpyridine with 4-trifluoromethylphenylboronic acid, using 1 mol % of catalyst **B** in aqueous toluene at 100 °C. Many different bases were found to promote high conversions (Table 1). Bases such as KOAc, CsF, K_2CO_3, Cs_2CO_3, and K_3PO_4 were particularly efficient and exhibited high conversions to the desired product. Similarly, a variety of aqueous solvents were investigated for the same model reaction in the presence of KOAc and CsF bases, both of which showed optimum results in toluene solvent. An interesting influence of solvent on reaction conversion was observed (Table 2). With KOAc base, the highest reaction conversions to the desired product were observed in *n*-butanol and acetonitrile solvents. With CsF base, the highest reaction conversions to the desired product were observed in *p*-dioxane and acetonitrile solvents. These results indicate that the catalyst performance is strongly influenced by base and solvent combinations and a variety of combinations can be used. However, optimum base/solvent combinations are also likely to be dependent on the nature of the reaction substrates.

The comparative performance of catalysts **A**−**E**, **B**′, **E**′, and $PdCl_2(D^tBPF)$ was evaluated by using the reaction of 2-chloro-*m*-xylene with *p*-tolylboronic acid as a model reaction (Table 3). The reaction conditions employed 1 mol % of catalyst in the presence of K_2CO_3 base and dioxane/water (10/1 v/v) solvent at 100 °C. The catalysts **A**−**E**, **B**′, and **E**′ showed good conversions (entries 1−7) whereas the $PdCl_2(D^tBPF)$ catalyst showed very poor conversion (entry 8). For catalysts **A**−**E**, the performance exhibited a correlation between the basicity of the phosphine ligand and the catalyst activity. The catalyst activity gradually increased with gradual increase in basicity of the phosphine ligand coordinated to the palladium center. The

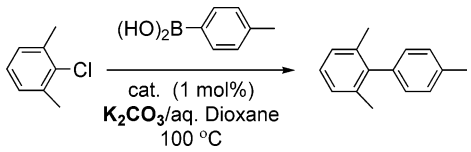
TABLE 2. Influence of Solvent on $PdCl_2\{P^tBu_2(Ph\text{-}H)\}_2$ (B)-Catalyzed Cross-Coupling Reaction[a]



entry	solvent	conv (%)
	KOAc base	
1	*p*-dioxane	74
2	BuOH	>99
3	DME	trace
4	DMAC	trace
5	CH_3CN	>99
	CsF base	
6	*p*-dioxane	>99
7	BuOH	95
8	DME	44
9	DMAC	97
10	CH_3CN	>99

[a] Reaction conditions: heteroaryl chloride (1.0 equiv), aryl boronic acid (1.5 equiv), base (2.0 equiv), 10% aqueous solvent (3−4 mL/mmol), reaction time (6 h). The conversions are based on GCMS A% conversion of the starting heteroaryl chloride to the desired product in the presence of an internal standard.

TABLE 3. Evaluation of $PdCl_2\{PR_2(Ph\text{-}R')\}_2$ Catalysts for Cross-Coupling Reactions of Aryl Chloride[a]



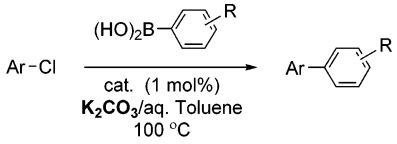
entry	catalyst	conv (%)
1	**A**	65
2	**B**	67
3	**B**′	71
4	**C**	75
5	**D**	85
6	**E**	90
7	**E**′	84
8	$PdCl_2(D^tBPF)$	16

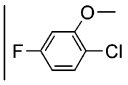
[a] Reaction conditions: aryl chloride (1.0 equiv), aryl boronic acid (1.5 equiv), K_2CO_3 (2.0 equiv), 10% aqueous 1,4-dioxane (3−4 mL/mmol), reaction time (5 h). The conversions are based on GCMS A% conversion of starting aryl chloride to the desired product in the presence of an internal standard.

catalyst **A** with an electron-withdrawing substituent on the phenyl (R′ = CF_3) showed the lowest conversion, while the catalyst **E** with an electron-donating substituent on the phenyl (R′ = NMe_2) showed the highest conversion. The *tert*-butyl and cyclohexyl analogues (**B** vs **B**′, **E** vs **E**′) showed essentially comparable performance, while catalyst **B**′ showed slightly higher conversion than **B**, and **E** showed slightly higher conversion than **E**′ for this reaction. However, the performance of the *tert*-butyl and the cyclohexyl analogues of $PdCl_2\{PR_2(Ph\text{-}R')\}_2$ catalysts is also likely to be influenced by the nature of the reaction substrates.

The catalysts **B**−**E** were further investigated for the reactions of selected heteroatom-containing aryl/heteroaryl chlorides with aryl boronic acids (Table 4). All reactions showed good conversions establishing the compatibility of the catalysts to heteroatom-containing reaction substrates. For the reaction of

TABLE 4. Evaluation of $PdCl_2\{P^tBu_2(Ph\text{-}R')\}_2$ Catalysts for Cross-Coupling Reactions of Aryl and Heteroaryl Chlorides with Arylboronic Acids[a]



Entry	Ar-X	R	Cat.	Conv.(%)
1		*p*-Me	**C**	73
2		*p*-Me	**D**	88
3		*p*-Me	**E**	95
4		*p*-CF_3	**B**	> 99
5		*p*-Me	**B**	> 99
6		o-Me	**B**	> 99
7		*p*-Me	**E**	> 99
8		*p*-Me	**E**	> 99[b]

[a] Reaction conditions: aryl/heteroaryl chloride (1.0 equiv), aryl boronic acid (1.5 equiv), K_2CO_3 (2.0 equiv), 10% aqueous toluene (3−4 mL/mmol), reaction time (12 h). The conversions are based on GCMS A% conversion of starting aryl/heteroaryl chloride to the desired product in the presence of an internal standard. [b] 0.1 mol % catalyst.

2-chloro-5-fluoroanisole with *p*-tolylboronic acid (entries 1−3), catalyst **E** showed better conversion than catalysts **D** and **C**, which is consistent with the catalyst activity trend described above. The catalyst **B** efficiently catalyzed the reaction of 2-chlorothiophene with aryl boronic acids bearing both electron-poor and electron-rich substituents (entries 4−6). The reaction of 2-chloro-3-aminopyridine with *p*-tolylboronic acid was efficient even in the presence of 0.1 mol % of catalyst **E** (entry 8), conclusively establishing the compatibility of the catalysts to heteroatom-containing reaction substrates including amino-substituted pyridines.

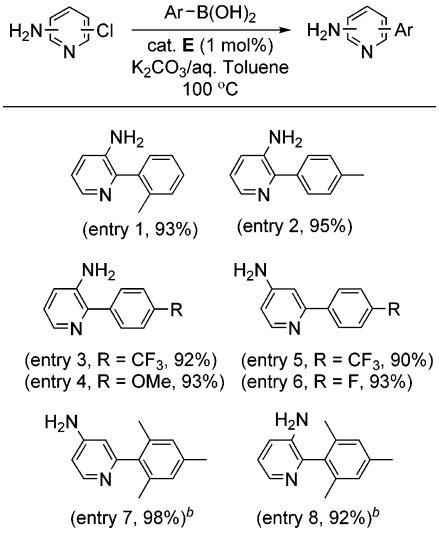
Utility of the $PdCl_2\{P^tBu_2(Ph\text{-}NMe_2)\}_2$ Catalyst (E) for Suzuki−Miyaura Coupling Reactions of Heteroatom-Containing Substrates. The utility of complex **E** for the general Suzuki−Miyaura coupling reactions of heteroatom-substituted heteroaryl chlorides was further explored. The catalyst **E** efficiently catalyzed the reactions of a variety of NH_2-substituted chloropyridines with a range of aryl boronic acids to afford the desired products in high isolated yields (Table 5). The reactions were all efficient irrespective of the position of the free NH_2 group on the pyridine ring and the electronic nature of the aryl boronic acids (entries 1−6). A crowded aryl boronic acid with two ortho substituents also participated effectively (entries 7 and 8).

The catalyst **E** efficiently catalyzed the reactions of other heteroatom-substituted six-membered heteroaryl chlorides with aryl boronic acids (Table 6). The heteroaryl chlorides based on other heterocycles such as pyrimidines and pyridazines, and other heteroatom substituents such as −OMe, −SMe, and −C(O)OMe reacted effectively with a variety of arylboronic acids to afford the desired products in high isolated yields.

The catalyst **E** also efficiently catalyzed the reactions of heteroatom-substituted six-membered heteroaryl chlorides with heteroaryl boronic acids (Table 7). A range of heteroaryl boronic acids participated effectively to afford the desired products in high isolated yields. Similarly, the reactions of five-membered heteroaryl halides (chlorides and bromides) with both aryl- and heteroaryl boronic acids proceeded efficiently (Table 8).[12]

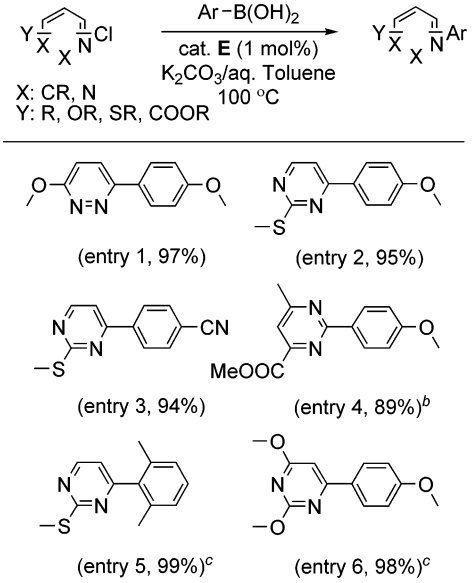
The catalyst **E** also effectively catalyzed the reaction of NH_2-substituted pyridines with aryl and heteroaryl boronate esters

TABLE 5. $PdCl_2\{P^tBu_2(Ph\text{-}NMe_2)\}_2$ (E)-Catalyzed Reactions of Aminochloropyridines with Arylboronic Acids[a]



[a] Reaction conditions: heteroaryl chloride (1.0 equiv), aryl boronic acid (1.2−1.5 equiv), K_2CO_3 (2.0 equiv), 10% aqueous toluene (3−4 mL/mmol), reaction time (8−12 h). The yields correspond to isolated products of greater than 95% purity based on NMR, GCMS, and/or HPLC analysis. [b] 2 mol % catalyst.

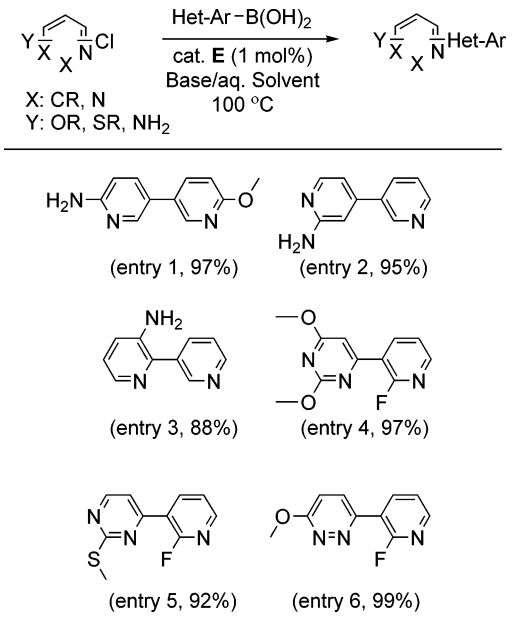
TABLE 6. $PdCl_2\{P^tBu_2(Ph\text{-}NMe_2)\}_2$ (E)-Catalyzed Reactions of Other Six-Membered Heteroaryl Chlorides with Arylboronic Acids[a]



[a] Reaction conditions: heteroaryl chloride (1.0 equiv), heteroaryl boronic acid (1.2−1.5 equiv), K_2CO_3 (2.0 equiv), 10% aqueous toluene (3−4 mL/mmol), reaction time (12−24 h). The yields correspond to isolated products of greater than 95% purity based on NMR, GCMS, and/or HPLC analysis. [b] 0.01 mol % catalyst, anhydrous toluene solvent. [c] 0.1 mol % catalyst.

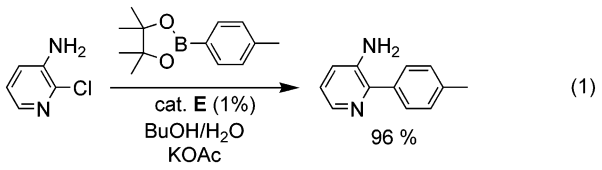
(12) Leading references for the cross-coupling reactions of five-membered heteroaryl halides: (a) Charles, M. D.; Shultz, P.; Buchwald, S. L. *Org. Lett.* **2005**, *7*, 3965−3968. (b) Hooper, M. W.; Utsunomiya, M.; Hartwig, J. F. *J. Org. Chem.* **2003**, *68*, 2861−2873.

TABLE 7. $PdCl_2\{P^tBu_2(Ph\text{-}NMe_2)\}_2$ (E)-Catalyzed Reactions of Six-Membered Heteroaryl Chlorides with Heteroarylboronic Acids[a]

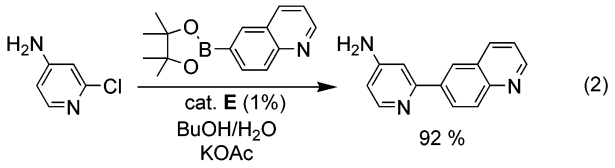


[a] Reaction conditions: heteroaryl chloride (1.0 equiv), aryl boronic acid (1.2−1.5 equiv), base (2.0−3.0 equiv; KOAc for entries 1, 4, and 6, K_3PO_4 for entries 2 and 3, and $KHCO_3$ for entry 5), 10% aqueous solvent (3−4 mL/mmol, *n*-butanol for entry 1, 1,4-dioxane for entries 2−4, and CH_3CN for entries 5 and 6), reaction time (5.0−20.0 h). The yields correspond to isolated products of greater than 95% purity based on NMR, GCMS, and/or HPLC analysis.

(eqs 1 and 2), indicating both boronate esters and boronic acids to be suitable and complementary coupling partners.



(1)

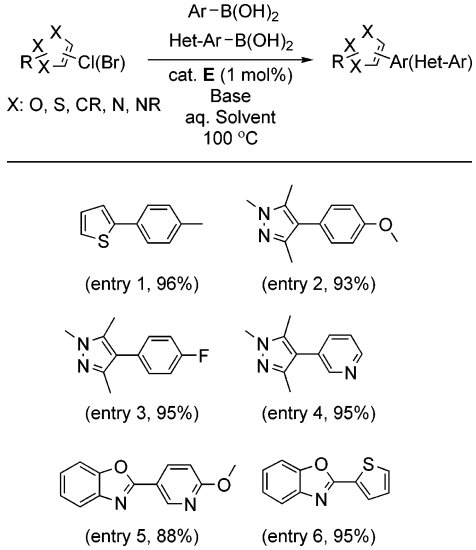


(2)

Catalyst Turnover Numbers (TONs). While 1 mol % of catalysts (100 TONs) was typically employed to study and establish the scope of the new catalysts for Suzuki−Miyaura coupling reactions, lower catalyst loadings to achieve higher TONs were briefly investigated with catalyst **E** in some cases.[13] Catalyst TONs were found to be dependent on the nature of the reaction substrates. For aryl boronic acids, TONs of 1000−10000 were observed particularly with electron-rich aryl boronic acids and electron-poor heteroaryl chloride coupling partners (entries 4−6, Table 6). A TON of 850 was observed for the reaction of 2-chloropyridin-4-amine with 4-fluorophenylboronic acid. For heteroaryl boronic acids, TONs of 200−500 were observed for reactions tested under low catalyst loading conditions. A TON of 490 was observed for the reaction of 6-chloro-2,4-dimethoxypyrimidine with 2-fluropyridin-3-ylboronic acid; a TON of 250 was observed for the reaction of 4-chloro-2-(methylthio)pyrimidine with 2-fluropyridin-3-ylboronic acid; and a TON of 500 was observed for the reaction of 2-chlorobenzoxazole with 6-methoxypyridin-3-ylboronic acid. The reaction of 2-chlorobenzonitrile with *p*-tolylboronic acid was found to proceed to completion in the presence of only 0.01 mol % (TON 10 000) of catalyst **E** to afford the desired industrially significant intermediate, OTBN (*o*-tolylbenzonitrile), in high yield.[3c]

(13) The catalyst TONs were investigated under otherwise typical reaction conditions without further optimizations. For experiments with heteroaryl boronic acids, 0.1 mol % catalyst **E** was employed, and the TONs were determined from calibrated HPLC product area %.

TABLE 8. $PdCl_2\{P^tBu_2(Ph\text{-}NMe_2)\}_2$ (E)-Catalyzed Reactions of Five-Membered Heteroaryl Halides with Aryl- and Heteroarylboronic Acids[a]

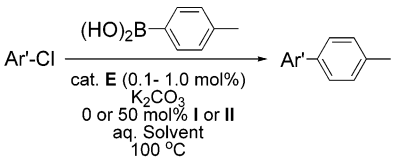


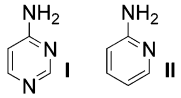
[a] Reaction conditions: heteroaryl halide (1.0 equiv; halide = Cl for entries 1, 5, and 6, halide = Br for entries 2−4), aryl boronic acid (1.2−1.5 equiv), base (2.0 equiv; K_3PO_4 for entries 1−5, KOAc for entry 6), 10% aqueous solvent (3−4 mL/mmol; 1,4-dioxane), reaction time (5−12 h). The yields correspond to isolated products of greater than 95% purity based on NMR, GCMS, and/or HPLC analysis.

Deactivation Studies of $PdCl_2\{P^tBu_2(Ph\text{-}NMe_2)\}_2$ Catalyst (E). The results summarized above clearly establish that catalyst **E** is not prone to deactivation by heteroatom-containing substrates. To further establish the stability of catalysts **E**, selected reactions were performed in the presence of potentially deactivating chelating substrates such as 4-aminopyrimidine and 2-aminopyridine. For the reactions of 2-chloro-*m*-xylene and 3-amino-2-chloropyridine with *p*-tolylboronic acid (Table 9), catalyst **E** was found to efficiently catalyze the reactions even in the presence of 50 mol % of the chelating substrates. Comparable conversions were observed in the presence and absence of the added chelating substrates. The results indicate that catalyst **E** has a high tolerance to chelating substrates under the described reaction conditions.

Current Limitations. While catalyst **E** efficiently catalyzed the Suzuki−Miyaura coupling reactions of a range of reaction substrates, the reactions of certain substrates were found to be inefficient under the reaction conditions investigated. These include reactions of alkyl boronic acids with both aryl and heteroaryl chlorides, the reactions of pyrazole boronate ester with chloro-aminopyridines, the reactions of 2-chlorobenzothia-

TABLE 9. Deactivation Studies of Complex E-Catalyzed Suzuki−Miyaura Reactions[a]





Entry	Ar'-Cl	I or II	Conv.(%)
1		0	94
2		50 mol% I	> 90
3		50 mol% II	> 90
4		0	> 99
5		50 mol% I	> 99
6		50 mol% II	> 99

[a] Reaction conditions: aryl or heteroaryl chloride (1.0 equiv), aryl boronic acid (1.5 equiv), K_2CO_3 (1.5−2.0 equiv), 10% aqueous solvent (3−4 mL/mmol), reaction time (entries 1−3, 10 h; entries 4−6, 20 h), catalyst loading (Pd %: entries 1−3, 1 mol %; entries 4−6, 0.1 mol %), and solvent (entries 1−3, aq toluene; entries 4−6, aq *p*-dioxane). The conversions are based on GCMS A% conversion of the starting heteroaryl chloride to the desired product in the presence of an internal standard.

zole with heteroaryl boronic acids, and the reactions of chloropurine with heteroaryl boronic acids.

Discussion

The new air-stable $PdCl_2\{PR_2(Ph\text{-}R')\}_2$ complexes are readily prepared in two steps from the cross-coupling reactions of commercially available aryl bromides and dialkylphosphine reagents followed by the reactions of the generated phosphines with $PdCl_2(COD)$. The new complexes catalyze the Suzuki−Miyaura coupling reactions of a variety of substrates. The coupling reactions are influenced by the nature of the base and solvent employed; however, a number of base and solvent combinations provide good results. The performance of $PdCl_2\{PR_2(Ph\text{-}R')\}_2$ catalysts is influenced by the electronic properties of the phosphine ligands coordinated to the palladium center. For Suzuki−Miyaura coupling reactions, the catalyst activity increases with the increase in basicity of the phosphine ligand. Thus, while all catalysts exhibit good ability to catalyze the coupling reactions, catalyst **E** and **E′** with the most electron-rich phosphine ligands, in particular, show the highest activity. The catalyst **E** efficiently catalyzes the Suzuki−Miyaura coupling reactions of a variety of heteroatom-substituted heteroaryl chlorides with a range of aryl and heteroaryl boronic acids. Many diverse electronic and steric substitution patterns on both coupling partners are well tolerated. The catalyst turnover numbers (TONs) are influenced by the nature of the reaction substrates. For aryl boronic acids, catalyst TONs up to 10 000 are achieved particularly with electron-rich aryl boronic acids and electron-poor aryl/heteroaryl chlorides. For heteroaryl boronic acids, catalyst TONs up to 500 are achieved. However, sterically demanding reaction susbtrates require higher catalyst loadings (TON 50−100).

The efficiency of the new $PdCl_2\{PR_2(Ph\text{-}R')\}_2$ complexes, in particular complexes **D**, **E**, and **E′**, as catalysts for Suzuki−Miyaura coupling reactions of heteroatom-substituted heteroaryl chlorides can be ascribed to the unique combination of electronic and steric properties of the new phosphine ligands. The electron-rich nature of the new phosphine ligands promotes the oxidative addition of the C−Cl bond,[14] while the steric properties of the new phosphine ligands appear to be particularly favorable for the coupling reactions of heteroatom-containing substrates.

In comparison to the previously reported catalysts $(PdCl_2(PPh_3)_2$[4a] and $PdCl_2(D^tBPF)$[4b] for the Suzuki−Miyaura coupling reactions of heteroatom-containing substrates, the new $PdCl_2\{PR_2(Ph\text{-}R')\}_2$[3c] catalysts and the recently reported Pd_2dba_3/PCy_3[3a,15] and Pd_2dba_3/PR_2biphenyl[3b] catalysts provide a significant advance. Owing to the specific combination of ligand electronic and steric properties, the new $PdCl_2\{PR_2(Ph\text{-}R')\}_2$ catalysts provide unique substrate scope, product yields, and catalyst turnovers for the cross-coupling reactions of heteroatom-substituted heteroaryl chlorides.

Conclusions

The new air-stable $PdCl_2\{PR_2(Ph\text{-}R')\}_2$ complexes **A**−**E**, **B′**, and **E′** are readily available in two simple steps from commercially available starting materials.[16] The complexes efficiently catalyze the Suzuki−Miyaura coupling reactions of a variety of heteroatom-substituted heteroaryl chlorides with a diverse range of aryl- and heteroaryl-boronic acids. The exceptional performance of the catalysts for the cross-coupling reaction of heteroatom-substituted heteroaryl chlorides is attributed to the unique combination of electronic and steric properties of the new monodentate phosphine ligands. The new ligands and new metal−ligand complexes are currently being explored for other pharmaceutically relevant applications.

Experimental Section

Syntheses of $PdCl_2\{PR_2(Ph\text{-}R')\}_2$ Complexes (A: R = ^{t}Bu, R′ = *p*-CF_3; B: R = ^{t}Bu, R′ = H; B′: R = Cy, R′ = H; C: R = ^{t}Bu, R′ = 3,4,5-tri-OMe; D: R = ^{t}Bu, R′ = *p*-OMe; E: R = ^{t}Bu, R′ = *p*-NMe_2; E′: R = Cy, R′ = *p*-NMe_2). The syntheses were typically performed on a 4.0−5.0 mmol scale of the aryl halide. A toluene or xylene solution of dialkylphosphine (1.0 equiv), aryl bromide (1.0 equiv), NaO^tBu (1.5 equiv), and Pd_2dba_3 (1 mol %) was stirred at 90− 30 °C for 12 h. The reaction was cooled to ambient temperature and filtered through a short silica gel plug. The silica gel plug was rinsed with toluene or dioxane. The combined filtrate was concentrated under vacuum and the residue was dissolved in THF. Alternatively, the combined filtrate was used as such. The $PdCl_2(COD)$ (0.35−0.40 equiv) complex was added as a solid and the reaction mixture was stirred at ambient temperature for 12 h. For complex **B′**, a 2:1 reaction mixture of commercially available PCy_2Ph and $PdCl_2(COD)$ in THF was stirred at ambient temperature for 12 h. The reaction mixture was filtered, and the yellow solid was washed with pentane and dried under

(14) The electronic properties of the new ligands (particularly in complexes **D**, **E**, and **E′**) are likely to be comparable to P^tBu_3 and PR_2(biphenyl) ligands because of the presence of an electron-donating group in the para position of the phenyl ring. However, sterically, the new ligands are likely to be somewhat smaller than the P^tBu_3 and PR_2(biphenyl) ligands.

(15) For earlier examples of related Pd-PCy_3 catalysts for general Suzuki−Miyaura coupling reactions, see: (a) Shen, W. *Tetrahedron Lett.* **1997**, *38*, 5575−5578. (b) Wallace, D. J.; Chen, C. Y. *Tetrahedron Lett.* **2002**, *43*, 6987−6990.

(16) The new $PR_2(Ph\text{-}R')$ ligands and $PdCl_2\{PR_2(Ph\text{-}R')\}_2$ complexes are named as "A-Phos" and $(A\text{-}Phos)_2PdCl_2$, respectively, for example, complexes **E** and **E′** are referred to as "$(A\text{-}^{ta}Phos)_2PdCl_2$" and "$(A\text{-}^{ca}Phos)_2PdCl_2$", respectively.

vacuum. The desired complexes were typically obtained in about 85% isolated yields.

$PdCl_2\{P^tBu_2(Ph\text{-}p\text{-}CF_3)\}_2$ (A): ^{1}H NMR ($CDCl_3$) δ 8.00 (br s, 4H), 7.59 (br d, J = 7.9, 4H), 1.62 (br t, J_{PH} = 7.0 Hz, 36H). ^{31}P NMR ($CDCl_3$) δ 55.7. ^{19}F NMR ($CDCl_3$) δ −63.4. Elemental Anal. Calcd: C 47.54, H 5.85. Found: C 47.57, H 6.05. Raman (cm^{-1}) 297.9 (Pd−Cl).

$PdCl_2\{P^tBu_2(Ph)\}_2$ (B): ^{1}H NMR (CD_2Cl_2) δ 7.9−7.8 (m, 4H), 7.36−7.30 (m, 6H), 1.56 (br. t, J_{PH} = 6.9 Hz, 36H). ^{31}P NMR (CD_2Cl_2) δ 54.4. Raman (cm^{-1}) 300.9 (Pd−Cl).

$PdCl_2\{PCy_2(Ph)\}_2$ (B′): ^{1}H NMR (C_6D_6) δ 7.90 (m, 4H), 7.29−7.18 (m, 6H), 2.93−1.16 (m, 44H). ^{31}P NMR (C_6D_6) δ 41.9. Elemental Anal. Calcd: C 59.55, H 7.50. Found: C 59.38, H 7.01.

$PdCl_2\{P^tBu_2(Ph\text{-}3,4,5\text{-}tri\text{-}OMe)\}_2$ (C): ^{1}H NMR (C_6D_6) δ 7.41 (t, J_{PH} = 4.7 Hz, 4H), 3.93 (s, 6H), 3.71 (s, 12H), 1.76 (br t, J_{PH} = 6.8 Hz, 36 H). ^{31}P NMR (C_6D_6) δ 69.4. Elemental Anal. Calcd: C 50.91, H 7.29. Found: C 50.74, H 7.03.

$PdCl_2\{P^tBu_2(Ph\text{-}p\text{-}OMe)\}_2$ (D): Isolated material contained 1,4-dioxane (0.25 mol equiv). ^{1}H NMR (C_6D_6) δ 8.06−8.02 (p, J = 4.3 Hz, 4H), 6.85 (d, J = 8.6 Hz, 4H), 3.32 (s, 6H), 1.77 (br t, J = 6.8, 36H). Elemental Anal. Calcd: C 53.28, H 7.45. Found: C 53.36, H 7.03.

$PdCl_2\{P^tBu_2(Ph\text{-}p\text{-}NMe_2)\}_2$ (E): ^{1}H NMR ($CDCl_3$) δ 7.5 (br s, 4H), 6.42 (d, J = 8.3 Hz, 4H), 2.75 (s, 12H), 1.38 (t, J_{PH} = 6.6 Hz, 36H). ^{31}P NMR ($CDCl_3$) δ 52.1. Elemental Anal. Calcd: C 54.28, H 7.97. Found: C 53.17, H 7.58. Raman (cm^{-1}) 295.8 (Pd−Cl).

$PdCl_2\{PCy_2(Ph\text{-}p\text{-}NMe_2)\}_2$ (E′): ^{1}H NMR (C_6D_6) δ 7.91 (m, 4H), 6.64 (d, J = 8.8, 4H), 3.03−1.28 (m, 44H), 2.52 (s, 12H). ^{31}P NMR (C_6D_6) δ 39.2. Elemental Anal. Calcd: C 59.15, H 7.94. Found: C 58.85, H 7.63.

General Procedure for the Suzuki−Miyaura Coupling Reactions. All Suzuki−Miyaura coupling reactions (Tables 1−9, eqs 1 and 2) were typically performed on a 1.0 mmol scale of the aryl halide. A mixture of aryl halide (1.0 equiv), aryl boronic acid/ester (1.2−1.5 equiv), base (2.0−3.0 equiv), and catalyst (0.01−2.0 mol %) in aqueous solvent (∼3−4 mL for 1.0 mmol starting substrate, ∼10% water) was stirred at 80−100 °C in screw-capped glass vials for 5−20 h. The reaction was cooled to ambient temperature and extracted in organic solvent (ether or dichloromethane). The organic extract was subjected to an aqueous workup (when product stability permitted, 1 N NaOH was used to facilitate removal of excess boronic acid), dried over anhydrous Na_2SO_4, and concentrated under vacuum. The crude material was purified by column chromatography on silica gel with hexanes and hexanes/ethyl acetate or 5% methanol in ethyl acetate as eluents. High TON experiments were stirred at 80−100 °C for 24 h. Additional details are provided in the schematics and text.

2-(*o*-Tolyl)-3-pyridinamine (Table 5, entry 1). This compound was isolated as a white solid (93% yield) from the reaction of 2-chloropyridin-3-amine and *o*-tolylboronic acid with the general procedure. ^{1}H NMR ($CDCl_3$) δ 8.08 (d, J = 4.5 Hz, 1H), 7.29−7.26 (m, 4H), 7.08−7.00 (m, 2H), 3.59 (s br, 2H), 2.17 (s, 3H). ^{13}C NMR ($CDCl_3$) δ 146.0, 140.3, 139.2, 137.4, 136.7, 130.7, 129.1, 128.5, 126.3, 123.2, 121.9, 19.3.

2-(*p*-Tolyl)-3-pyridinamine (Table 5, entry 2). This compound was isolated as a white solid (95% yield) from the reaction of 2-chloropyridin-3-amine and *p*-tolylboronic acid with the general procedure. ^{1}H NMR ($CDCl_3$) δ 8.1 (d/d, J = 4.1/1.8 Hz, 1H), 7.55 (d, J = 8.2 Hz, 2H), 7.26 (d, J = 7.8 Hz, 2H), 7.04 − 6.98 (m, 2H), 3.84 (s br, 2H), 2.39 (s, 3H). ^{13}C NMR ($CDCl_3$) δ 145.1, 140.0, 139.9, 138.0, 135.7, 129.4, 128.3, 122.8, 122.6, 21.3.

2-{4-(Trifluoromethyl)phenyl}-3-pyridinamine (Table 5, entry 3). This compound was isolated as a white solid (92% yield) from the reaction of 2-chloropyridin-3-amine and 4-(trifluoromethyl)phenylboronic acid with the general procedure. ^{1}H NMR ($CDCl_3$) δ 8.12 (d/d, J = 4.5/1.6 Hz, 1H), 7.81 (d, J = 8.0 Hz, 2H), 7.71 (d, J = 8.3 Hz, 2H), 7.10 − 7.02 (m, 2H), 3.85 (s br). ^{13}C NMR ($CDCl_3$) δ 143.1, 142.3, 140.2, 140.2, 130.1 (q, $^2J_{CF}$ = 32.5 Hz), 128.9, 125.7 (q, $^3J_{CF}$ = 3.5 Hz), 123.8, 123.2, 124.2 (q, $^1J_{CF}$ = 272 Hz).

2-(4-Methoxyphenyl)-3-pyridinamine (Table 5, entry 4). This compound was isolated as a white solid (93% yield) from the reaction of 2-chloropyridin-3-amine and 4-methoxyphenylboronic acid with the general procedure. ^{1}H NMR ($CDCl_3$) δ 8.08 (d/d, J = 3.7/1.1 Hz, 1H), 7.60 (d, J = 8.4 Hz, 2H), 7.01−6.96 (m, 4H), 3.85 (s br, 2H, partially overlapped), 3.82 (s, 3H). ^{13}C NMR ($CDCl_3$) δ 159.5, 144.8, 140.1, 139.8, 131.1, 129.8, 122.7, 122.6, 114.2, 55.4.

2-{4-(Trifluoromethyl)phenyl}-4-pyridinamine (Table 5, entry 5). This compound was isolated as a white solid (90% yield) from the reaction of 2-chloropyridin-4-amine and 4-(trifluoromethyl)phenylboronic acid with the general procedure. ^{1}H NMR ($CDCl_3$) δ 8.31 (d, J = 5.4 Hz, 1H), 8.0 (d, J = 8.2 Hz, 2H), 7.67 (d, J = 8. Hz2, 2H), 6.93 (s, 1H), 6.51 (br d, J = 5.5 Hz, 1H), 4.39 (br s, 2H). ^{13}C NMR ($CDCl_3$) δ 156.8, 153.7, 150.3, 143.2, 130.5 (q, $^2J_{CF}$ = 32.2 Hz), 127.2, 125.5 (q, $^3J_{CF}$ = 3.5 Hz), 124.3 (q, $^1J_{CF}$ = 272 Hz), 109.0, 106.9.

2-(4-Fluorophenyl)-4-pyridinamine (Table 5, entry 6). This compound was isolated as a white solid (93% yield) from the reaction of 2-chloropyridin-4-amine and 4-fluorophenylboronic acid with the general procedure. ^{1}H NMR ($CDCl_3$) δ 7.46−7.42 (m, 2H), 7.14−7.10 (m, 2H), 6.97−6.92 (m, 3H), signal for NH_2 protons not observed. ^{13}C NMR ($CDCl_3$) δ 161.3 (d, $^1J_{CF}$ = 246.0 Hz), 142.3, 129.6 (d, $^3J_{CF}$ = 3.4 Hz), 127.0, 126.58, 126.54 (d, $^3J_{CF}$ = 7.8 Hz), 123.73, 122.1, 114.76 (d, $^2J_{CF}$ = 21.5 Hz).

2-Mesityl-4-pyridinamine (Table 5, entry 7). This compound was isolated as a white solid (98% yield) from the reaction of 2-chloropyridin-4-amine and mesitylboronic acid with the general procedure. ^{1}H NMR ($CDCl_3$) δ 8.02 (d, J = 5.5 Hz, 1H), 6.75 (s, 2H), 6.23 (d, J = 5.4 Hz, 1H), 6.20 (s, 1H), 4.57 (s br, 2H), 2.17 (s, 3H), 1.90 (s, 6H). ^{13}C NMR ($CDCl_3$) δ 159.0, 152.7, 148.4, 137.1, 135.9, 134.5, 127.0, 109.1, 106.8, 20.0, 18.9.

2-Mesityl-3-pyridinamine (Table 5, entry 8). This compound was isolated as a white solid (92% yield) from the reaction of 2-chloropyrdin-3-amine and mesitylboronic acid with the general procedure. ^{1}H NMR ($CDCl_3$) δ 7.98 (d, J = 4.5 Hz, 1H), 6.92 (d/d, J = 8.0/5.0 Hz, 1H), 6.84 (d, J = 8.0 Hz, 1H), 6.82 (s, 2H), 3.45 (s br, 2H), 2.20 (s, 3H), 1.88 (s, 6H). ^{13}C NMR ($CDCl_3$) δ 145.8, 140.5, 139.4, 137.6, 136.5, 133.8, 128.6, 122.8, 121.3, 21.2, 19.4.

3-Methoxy-6-(4-methoxyphenyl)pyridazine (Table 6, entry 1). This compound was isolated as a white solid (97% yield) from the reaction of 3-chloro-6-methoxypyridazine and 4-methoxyphenylboronic acid with the general procedure. ^{1}H NMR ($CDCl_3$) δ 7.96 (d, J = 8.8 Hz, 2H), 7.72 (d, J = 9.2 Hz, 1H), 7.27−6.99 (m, 3H), 4.17 (s, 3H), 3.86 (s, 3H). ^{13}C NMR ($CDCl_3$) δ 164.0, 160.8, 154.9, 128.8, 127.8, 126.6, 117.7, 114.4, 55.4, 54.8.

4-(4-Methoxyphenyl)-2-methylthiopyrimidine (Table 6, entry 2). This compound was isolated as a white solid (95% yield) from the reaction of 4-chloro-2-(methylthio)pyrimidine and 4-methoxyphenylboronic acid with the general procedure. ^{1}H NMR ($CDCl_3$) δ 8.45 (d, J = 5.3 Hz, 1H), 8.05 (d, J = 9.0 Hz, 2H), 7.26 (d, J = 5.8 Hz, 1H), 6.97 (d, J = 9.0 Hz, 2H), 3.85 (s, 3H), 2.62 (s, 3H). ^{13}C NMR ($CDCl_3$) δ 172.5, 163.3, 162.2, 157.4, 128.8, 128.7, 114.3, 111.0, 55.5, 14.2.

4-{2-(Methylthio)pyrimidin-4-yl}benzonitrile (Table 6, entry 3). This compound was isolated as an off-white solid (94% yield) from the reaction of 4-chloro-2-(methylthio)pyrimidine and 4-cyanophenylboronic acid with the general procedure. ^{1}H NMR ($CDCl_3$) δ 8.64 (d, J = 5.3 Hz, 1H), 8.20 (d, J = 8.6 Hz, 2H), 7.79 (d, J = 8.4 Hz, 2H), 7.40 (d, J = 5.3 Hz, 1H), 2.65 (s, 3H). ^{13}C NMR ($CDCl_3$) δ 173.5, 161.8, 158.3, 140.5, 132.7, 127.8, 118.4, 114.5, 112.2, 14.3.

Methyl 2-(4-Methoxyphenyl)-6-methylpyrimidine-4-carboxylate (Table 6, entry 4). This compound was isolated as an off-white solid (89% yield) from the reaction of methyl 2-chloro-6-methylpyrimidine-4-carboxylate and 4-methoxyphenylboronic acid

with the general procedure except (i) anhydrous toluene was used as solvent and (ii) 0.01 mol % of catalyst was used. ^{1}H NMR ($CDCl_3$) δ 8.47 (d, J = 8.8 Hz, 2H), 7.63 (s, 1H), 6.98 (d, J = 8.6 Hz, 2H), 4.02 (s, 3H), 3.86 (s, 3H), 2.63 (s, 3H). ^{13}C NMR ($CDCl_3$) δ 169.5, 165.5, 164.8, 162.1, 154.9, 130.2, 129.8, 117.3, 113.9, 55.4, 53.1, 24.6.

4-(2,6-Dimethylphenyl)-2-(methylthio)pyrimidine (Table 6, entry 5). This compound was isolated as a colorless oil (99% yield) from the reaction of 4-chloro-2-(methylthio)pyrimidine and 2,6-dimethylphenylboronic acid with the general procedure except 0.1 mol % of catalyst was used. ^{1}H NMR ($CDCl_3$) δ 8.47 (d, J = 4.9 Hz, 1H), 7.12 (t, J = 7.6 Hz, 1H), 7.01 (d, J = 7.5 Hz, 2H), 6.80 (d, J = 5.0 Hz, 1H), 2.47 (s, 3H), 2.01 (s, 6H). ^{13}C NMR ($CDCl_3$) δ 171.9, 166.8, 156.1, 136.9, 134.2, 127.6, 126.8, 116.1, 19.2, 13.1.

2,4-Dimethoxy-6-(4-methoxyphenyl)pyrimidine (Table 6, entry 6). This compound was isolated as an off-white solid (98% yield) from the reaction of 6-chloro-2,4-dimethoxypyrimidine and 4-methoxyphenylboronic acid with the general procedure except 0.1 mol % of catalyst was used. ^{1}H NMR ($CDCl_3$) δ 8.02 (d, J = 8.6 Hz, 2H), 6.97 (d, J = 8.6 Hz, 2H), 6.7 (s, 1H), 4.07 (s, 3H), 3.99 (s, 3H), 3.86 (s, 3H). ^{13}C NMR ($CDCl_3$) δ 172.5, 165.6, 165.4, 161.7, 129.3, 128.6, 114.0, 95.9, 55.4, 54.7, 53.9.

5-(6-Methoxypyridin-3-yl)pyridin-2-amine (Table 7, entry 1). This compound was isolated as a white solid (97% yield) from the reaction of 5-chloropyridin-2-amine and 6-methoxypyridin-3-ylboronic acid with the general procedure. ^{1}H NMR ($CDCl_3$) δ 8.27 (d/d, J = 8/2.3 Hz, 2H), 7.70 (d/d, J = 8.6/2.6 Hz, 1H), 7.59 (d/d, J = 8.6/2.5 Hz, 1H), 6.80 (d, J = 8.6 Hz, 1H), 6.58 (d, J = 8.4 Hz, 1H), 4.53 (br s, 2H), 3.97 (s, 3H). ^{13}C NMR ($CDCl_3$) δ 163.4, 157.7, 146.1, 144.2, 136.8, 136.2, 127.4, 124.2, 110.9, 108.6, 53.5.

4-(Pyridin-3-yl)pyridin-2-amine (Table 7, entry 2). This compound was isolated as an off-white solid (95% yield) from the reaction of 4-chloropyridin-2-amine and pyridin-3-ylboronic acid with the general procedure. ^{1}H NMR ($CDCl_3$) δ 8.84 (s, 1H), 8.65 (d, J = 3.5 Hz, 1H), 8.17 (d, J = 5.0 Hz, 1H), 7.87 (d, J = 7.5 Hz, 1H), 7.34−7.45 (m, 1H), 6.86 (d, J = 5.0 Hz, 1H), 6.69 (s, 1H), 4.68 (br s, 2H). ^{13}C NMR ($CDCl_3$) δ 158.3, 149.1, 148.2, 147.3, 146.3, 133.6, 133.4, 122.9, 111.6, 105.4.

2-(Pyridin-3-yl)pyridin-3-amine (Table 7, entry 3). This compound was isolated as a white solid (88% yield) from the reaction of chloropyridin-3-amine and pyridin-3-ylboronic acid with the general procedure. ^{1}H NMR ($CDCl_3$) δ 8.96 (s, 1H), 8.63 (d, J = 4.0 Hz, 1H), 8.15 (d, J = 3.5 Hz, 1H), 8.03 (d, J = 7.5 Hz, 1H), 7.40−7.42 (m, 1H), 7.05−7.17 (m, 2H), 3.79 (s br, 2H). ^{13}C NMR ($CDCl_3$) δ 147.2, 146.9, 139.0, 138.1, 138.1, 133.9, 132.2, 121.4, 121.3, 120.8.

4-(2-Fluoropyridin-3-yl)-2,6-dimethoxypyrimidine (Table 7, entry 4). This compound was isolated as an off-white solid (97% yield) from the reaction of l-chloro-2,4-dimethoxypyrimidine and 2-fluoropyridin-3-ylboronic acid with the general procedure. ^{1}H NMR ($CDCl_3$) δ 8.92−8.99 (m, 1H), 8.53 (d, J = 5.0 Hz, 1H), 7.60−7.57 (m, 1H), 7.02 (s, 1H), 4.31 (s, 3H), 4.26 (s, 3H). ^{13}C NMR ($CDCl_3$) δ 172.7, 165.2, 161.2 (d, J_{CF} = 244 Hz), 159.1 (d, J_{CF} = 7.8 Hz), 148.8 (d, J_{CF} = 15.6 Hz), 141.2, 121.9 (d, J_{CF} = 4.3 Hz), 119.8 (d, J_{CF} = 25.2 Hz), 101.7 (d, J_{CF} = 13.9 Hz), 54.8, 54.1.

4-(2-Fluoropyridin-3-yl)-2-(methylthio)pyrimidine (Table 7, entry 5). This compound was isolated as a white solid (92% yield) from the reaction of 4-chloro-2-(methylthio)pyrimidine and 2-fluoropyridin-3-ylboronic acid with the general procedure. ^{1}H NMR ($CDCl_3$) δ 8.71 (t, J = 8.8 Hz, 1H), 8.61 (d, J = 5.5 Hz, 1H), 8.33 (s, 1H), 7.56 (d, J = 3.5 Hz, 1H), 7.33−7.42 (m, 1H), 2.62 (s, 3H). ^{13}C NMR ($CDCl_3$) δ 172.3, 161.2 (d, J_{CF} = 243 Hz), 158.1, 158.0 (d, J_{CF} = 7.8 Hz), 149.5 (d, J_{CF} = 15.6 Hz), 141.2, 122.1, 119.4 (d, J_{CF} = 26.0 Hz), 115.5 (d, J_{CF} = 13.0 Hz), 14.2.

3-(2-Fluoropyridin-3-yl)-6-methoxypyridazine (Table 7, entry 6). This compound was isolated as a white solid (99% yield) from the reaction of 3-chloro-6-methoxypyridazine and 2-fluoropyridin-3-ylboronic acid with the general procedure. ^{1}H NMR ($CDCl_3$) δ 8.60−8.70 (m, 1H), 8.31 (d, J = 4.5 Hz, 1H), 7.97 (d/d, J = 9.5/2.0 Hz, 1H), 7.35−7.45 (m, 1H), 7.10 (d, J = 9.0 Hz, 1H), 4.21 (s, 3H). ^{13}C NMR ($CDCl_3$) δ 164.4, 160.5 (d, J_{CF} = 240 Hz), 150.4 (d, J_{CF} = 6.1 Hz), 148.4 (d, J_{CF} = 15.6 Hz), 140.9, 130.0 (d, J_{CF} = 11.3 Hz), 122.3, 119.4 (d, J_{CF} = 26.8 Hz), 117.3, 55.0.

2-(*p*-Tolyl)thiophene (Table 8, entry 1). This compound was isolated as a white solid (96% yield) from the reaction of 2-chlorothiophene and *p*-tolylboronic acid with the general procedure. ^{1}H NMR ($CDCl_3$) δ 7.48 (d, J = 8.2 Hz, 2H), 7.24 (d, J = 3.5 Hz, 1H), 7.2 (d, J = 5 Hz, 1H), 7.15 (d, J = 7.9 Hz, 2H), 7.03 (d/d, J = 5.1/3.6 Hz, 1H), 2.33 (s, 3H). ^{13}C NMR ($CDCl_3$) δ 144.6, 137.3, 131.6, 129.5, 127.9, 125.8, 124.2, 122.6, 21.2.

4-(4-Methoxyphenyl)-1,3,5-trimethyl-1*H*-pyrazole (Table 8, entry 2). This compound was isolated as a white solid (93% yield) from the reaction of 4-bromo-1,3,5-trimethylpyrazole and 4-methoxyphenylboronic acid with the general procedure. ^{1}H NMR ($CDCl_3$) δ 7.15 (d, J = 8.6 Hz, 2H), 6.94 (J = 8.6 Hz, 2H), 3.82 (s, 3H), 3.76 (s, 3H), 2.22 (s, 3H), 2.20 (s, 3H). ^{13}C NMR ($CDCl_3$) δ 158.1, 145.0, 136.0, 130.5, 126.6, 118.8, 113.9, 55.3, 36.0, 12.4, 10.2.

4-(4-Fluorophenyl)-1,3,5-trimethyl-1*H*-pyrazole (Table 8, entry 3). This compound was isolated as a white solid (95% yield) from the reaction of 4-bromo-1,3,5-trimethylpyrazole and 4-fluorophenylboronic acid with the general procedure. ^{1}H NMR ($CDCl_3$) δ 7.10 (d/d. J = 8.8/5.7 Hz, 2H), 6.99 (t, J = 8.8 Hz, 2H), 3.69 (s, 3H), 2.13 (s, 3H), 2.12 (s, 3H). ^{13}C NMR ($CDCl_3$) δ 160.5 (d, J = 244 Hz), 143.9, 135.1, 129.9 (d, J = 7.7 Hz), 129.2 (d, J = 2.6 Hz), 117.3, 114.2 (d, J = 20.7 Hz), 35.0, 11.3, 9.1. ^{19}F NMR ($CDCl_3$) δ −116.

3-(1,3,5-Trimethyl-1*H*-pyrazol-4-yl)pyridine (Table 8, entry 4). This compound was isolated as an off-white solid (95% yield) from the reaction of 4-bromo-1,3,5-trimethylpyrazole and pyridine-3-ylboronic acid with the general procedure. ^{1}H NMR ($CDCl_3$) δ 8.50−8.52 (m, 2H), 7.57 (d, J = 8.0 Hz, 1H), 7.33 (d/d, J = 7.5, 5.0 Hz, 1H), 3.80 (s, 3H), 2.25 (s, 6 H). ^{13}C NMR ($CDCl_3$) δ 150.3, 147.3, 145.2, 136.7, 136.5, 130.2, 123.4, 115.6, 36.1, 12.4, 10.2.

2-(6-Methoxypyridin-3-yl)benzo[*d*]oxazole (Table 8, entry 5). This compound was isolated as an off-white solid (88% yield) from the reaction of 2-chlorobenzoxazole and 6-methoxypyridin-3-ylboronic acid by using the general synthetic procedure with a modified workup procedure where the product was precipitated by adding water to the reaction mixture in dioxane. The precipitated product was washed with water (5 mL) and cold pentane (1 mL) and dired under vacuum. ^{1}H NMR ($CDCl_3$) δ 9.04 (br s, 1H), 8.36 (br d, J = 11.0 Hz, 1H), 7.75 (br s, 1H), 7.56 (br s, 1H), 7.34 (m, 2H), 6.88 (d, J = 8.8 Hz, 1H), 4.03 (s, 3H). ^{13}C NMR ($CDCl_3$) δ 166.0, 161.4, 150.6, 147.2, 142.0, 137.5, 125.0, 124.7, 119.8, 117.1, 111.4, 110.5, 54.0.

2-(Thiophen-2-yl)benzo[d]oxazole (Table 8, entry 6). This compound was isolated as a white solid (95% yield) from the reaction of 2-chlorobenzooxazole and 2-thiopheneboronic acid with the general procedure. ^{1}H NMR ($CDCl_3$) δ 7.89 (d, J = 4.0 Hz, 1H), 7.67−7.78 (m, 1 H), 7.49−7.58 (m, 2H), 7.28−7.37 (m, 2H), 7.11−7.21 (m, 1H). ^{13}C NMR ($CDCl_3$) δ 159.1, 150.4, 142.0, 130.3, 130.0, 129.7, 128.3, 125.1, 124.8, 119.8, 110.5.

2-(*p*-Tolyl)-3-pyridinamine (Eq 1). This compound was isolated as a white solid (96% yield) from the reaction of 2-chloro-3-pyridinamine and 4,4,5,5-tetramethyl-2-*p*-tolyl-1,3,2-dioxaborolane with the general procedure. Isolated material contained some 2,3-dimethylbutane-2,3-diol. The ^{1}H and ^{13}C NMR data matched that of entry 2, Table 5.

2-(Quinolin-6-yl)pyridine-4-amine (Eq 2). This compound was isolated as a white solid (92% yield) from the reaction of 2-chloro-4-pyridinamine and 6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-quinoline with the general procedure. ^{1}H NMR (CD_3OD) δ 8.88 (d, J = 4.0 Hz, 1H), 8.45 (d, J = 8.0 Hz, 1H), 8.35 (s, 1 H), 8.19

(d, 8.6, 1H), 8.12 (d, 6.1, 2H), 7.60−7.57 (dd, J = 8.2, 4.2 Hz, 1H), 7.14 (s, 1H), 6.66 (d, J = 5.5 Hz, 1H), $-NH_2$ protons not observed. ^{13}C NMR ($CDCl_3$) δ 157.1, 155.5, 150.6, 147.5, 147.2, 137.6, 136.9, 128.5, 128.4, 128.3, 126.4, 121.8, 108.0, 107.0.

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Supporting Information Available: Detailed experimental procedures and characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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