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Palladium-Catalyzed Cross-Coupling Reactions of Pyridylboronic Acids with Heteroaryl Halides Bearing a Primary Amine Group: Synthesis of Highly Substituted Bipyridines and Pyrazinopyridines

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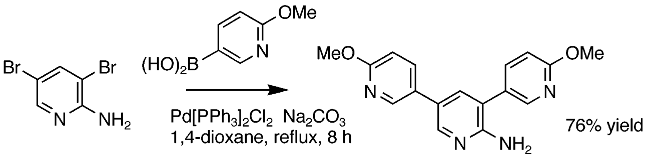

A range of halogenated aromatics and heteroaromatics bearing a primary amine group are shown to be suitable substrates for Suzuki cross-coupling reactions with arylboronic acids and pyridylboronic acids under standard conditions, without the need for protection/deprotection steps. New amino-substituted arylpyridines, bipyridines, and pyrazinopyridines have thereby been obtained. Conditions for the efficient syntheses of 2-methoxy-5-pyridylboronic acid **1** and 2-methoxy-3-pyridylboronic acid **2** in ca. 75 g batches have been defined. A 2-fold reaction of 2-amino-5-bromopyrazine with 2,5-dimethoxy-1,4-benzenediboronic acid affords 1,4-dimethoxy-2,5-bis[2-(5-aminopyrazyl)]benzene **31**. The X-ray crystal structures of **1** and **31**·DMF are reported.

The Suzuki–Miyaura protocol for palladium-catalyzed cross-coupling of aryl/heteroaryl boronic acids (or esters) with aryl/heteroaryl halides is of paramount importance for the synthesis of biaryl and heterobiaryl systems.[1] It is often stated that compounds bearing labile protons (especially primary amines, carboxylic acids, and alcohols) are not suitable coupling partners in these reactions,[2] thereby necessitating additional protection/deprotection steps. For instance, no product was obtained from attempted Suzuki reactions on 2-chloropyridin-3-carboxamide, and 2-chloro-3-hydroxypyridine gave only a very low yield of cross-coupled product.[3] 3-Iodoanthranilic acid failed to react with a range of arylboronic acids.[4] More recently, Caron et al. reported that attempted Suzuki reaction between phenylboronic acid and 2-chloro-3-aminopyridine was unsuccessful, although the acetamide and benzaldehyde imine derivatives reacted in high yield.[5]

It is notable, therefore, that Meier et al. have recently reported Suzuki coupling reactions of *unprotected* bromopyridylcarboxylic acids with formylphenylboronic acid.[2] We now report our studies on halogenated aromatics and heteroaromatics bearing a primary amine group as substrates for Suzuki couplings. There are only isolated examples in the literature of successful reactions in the presence of NH$_2$ groups, and many of these are low yielding. Substrates include 2-amino-3-bromoquinoxaline,[6] 2-bromo-5-halopyridazine,[7] 6-chloro-2,4-diaminopyrimidine,[8] 4-chloroaniline,[9] and 2-bromo-5-aminopyrazine.[10] Hitherto there is no report of a systematic study using the same catalyst and reaction conditions while varying the amino-containing substrate and the arylboronic acids.

We chose to develop the chemistry of 2-methoxy-5-pyridylboronic acid **1** and 2-methoxy-3-pyridylboronic acid **2** in these reactions as there is widespread interest in pyridylboronic acid derivatives and their derived libraries of aryl/heteroarylpyridines (Chart 1).[10–12] Examples of reactions of 2-chloro-5-pyridylboronic acid **3**

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(5) Caron, S.; Massett, S. S.; Bogle, D. E.; Castaldi. M. J.; Braish, T. F. *Org. Proc. Res. Dev.* **2001**, *5*, 254. In this paper, no information was given about the reaction conditions or the catalyst used for the attempted Suzuki coupling between phenylboronic acid and 2-chloro-3-aminopyridine. The conditions reported for the successful reaction of the acetamide derivative are as follows: aq Na$_2$CO$_3$, toluene/ethanol/water, Pd[PPh$_3$]$_4$, reflux, 8 h. In contrast to this paper, using our standard conditions given in Table 1, we obtained 3-amino-2-phenylpyridine in 86% yield from the reaction of phenylboronic acid and 2-chloro-3-aminopyridine.

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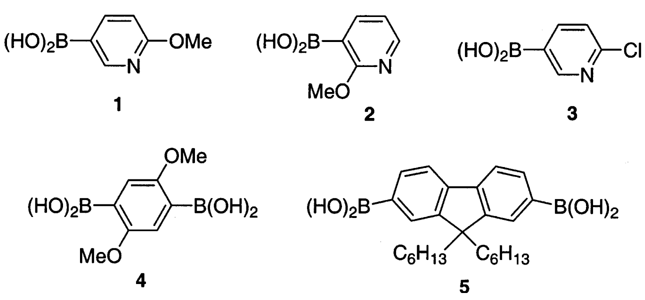
CHART 1. Structures of Boronic Acids Used in This Study



and the aryldiboronic acids **4** and **5** are included for comparison. We have previously published small-scale syntheses of **1**[10] and **2**[11i] (250–350 mg batches) in 65% and 13% yields, respectively, using lithium–halogen exchange (for **1**) and directed *ortho*-metalation reactions[13] (for **2**). After much experimentation, we have now optimized procedures which afford ca. 75 g batches of analytically pure **1** and **2** in 65% and 58% yields, respectively. The X-ray crystal structure of **1** is reported in the Supporting Information.

The standard conditions for the Suzuki coupling reactions were sodium carbonate (aqueous 1 M) as base and bis(triphenylphosphino)palladium dichloride as catalyst (5 mol %) in 1,4-dioxane at reflux for 8 h. The conditions of the reaction shown in entry 7 were varied to establish the optimum mol % of catalyst and reaction time. Using 1, 5, and 10 mol % catalyst gave product **23** in 37, 69, and 67% yields, respectively. With varying reaction times using 5 mol % catalyst the following product yields were obtained: 2 h gave 32% yield; 8–48 h gave 67–69% yields. Yields were independent of the base used (Na_2CO_3, K_2CO_3, Cs_2CO_3, or Ba_2CO_3). The results presented in Table 1 show that many reactions proceed in high yields in the presence of primary amine groups, thereby directly affording new amino-substituted biaryl/heteroaryl systems without the need for any protection/deprotection steps.

The following points are noteworthy. Entries 1 and 2 establish that the reactions are efficient with bromobenzene derivatives bearing an amine substituent. It is known that some π-deficient heteroaryl chlorides are reactive partners in Suzuki reactions,[3,8,11l] although generally the bromide analogues are preferred if they are readily available. A comparison of entries 3–6 shows that 3-amino-2-chloropyridine **8** (entries 3 and 4) is especially efficient and is a better substrate than the isomers **9** and **10**, respectively. It can be envisaged that the amino group will coordinate to an incoming palladium atom of the catalyst and the high yield with **8** can be ascribed to steric factors in the complexed intermediate facilitating displacement of the *ortho* halogen.[14] Indeed, **8** also reacted with phenyl- and 4-methoxyphenylboronic acids to give the expected cross-coupled products in >80% yields.[15] Entries 7–10 using substrates **11** and **12** demonstrate that more highly-functionalized amino-substituted bipyridines can also be obtained in synthetically viable yields. The methoxy group *ortho* to the boronic acid (compound **2**) does not sterically hinder the reaction. The acetamide derivative **13** reacted in similar high yield to give **27** (entry 11).

The reactions have been extended to 2-amino-5-bromopyrazine **14** which reacts in moderate yields with the pyridylboronic acids **1**–**3** (entries 12–14) to provide the novel pyrazinylpyridine derivatives **28**–**30**. Entry 14 establishes that 2-chloro-5-pyridylboronic acid **3** shows comparable reactivity to the methoxy analogues **1** and **2**. It is known that Suzuki cross-couplings of arylboronic acids and less-reactive (electron-rich) chloroaromatics proceed in the presence of $\mathrm{P}^t\mathrm{Bu}_3/[\mathrm{Pd}_2(\mathrm{dba})_3]$ (dba = dibenzylideneacetone) under conditions where $[\mathrm{Pd}_2(\mathrm{dba})_3]$ alone is ineffective,[9] and we have shown that product yields using 2,3-dichloro-4-pyridylboronic acid and 2,6-dichloro-3-pyridylboronic acid with 3-bromoquinoline are significantly increased using $\mathrm{P}^t\mathrm{Bu}_3/\mathrm{Pd}[\mathrm{PPh}_3)_2\mathrm{Cl}_2$ compared to $\mathrm{Pd}[\mathrm{PPh}_3]_2\mathrm{Cl}_2$ alone.[15] However, addition of $\mathrm{P}^t\mathrm{Bu}_3$ (10 mol %) to the reaction mixture had no effect on selected lower yielding reactions in Table 1.

Entries 15–18 extend the reaction to 2-fold couplings by using the diboronic acid derivatives **4** and **5** (entries 15 and 16) or dihalo reagents **15** and **16** (entries 17 and 18) to yield products **31**–**34** in good or moderate yields, demonstrating that this protocol is applicable to the synthesis of extended amino-substituted tri- and tetraarylene structures.

In summary, this work establishes that a wide range of halogenated aromatics and heteroaromatics bearing a primary amine group are suitable substrates for Suzuki cross-coupling reactions under standard conditions, without the need for protection/deprotection steps which are traditionally considered to be necessary for these reactions to proceed cleanly. This is the first systematic study of such reactions in the presence of a primary NH_2 group. With the exception of reagent **8** (as discussed above), it appears that brominated heterocycles are preferable to the chloro derivatives as coupling partners in these reactions. Highly substituted pyridines, including heteroarylpyridines, continue to attract much attention[16] due to their roles as bioactive compounds, ligands for self-assembly, and building blocks for materials chemistry applications.[17] The presence of the primary amine group offers attractive prospects for further synthetic transformations, as well as applications in supramolecular and coordination chemistry. The oligo(arylene) systems **31**–**34** incorporating electron-deficient pyridine, pyrimidine, and pyrazine units are candidates as electron-transporting molecules in optoelectronic devices.[17]

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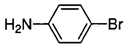
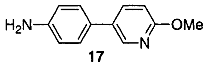
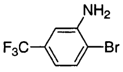
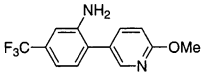
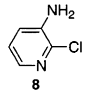
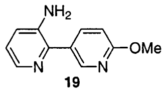
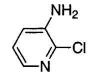
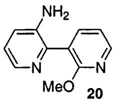
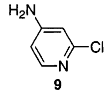
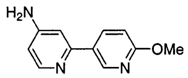
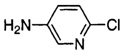
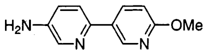
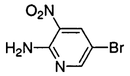
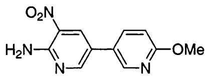
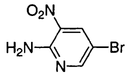
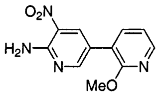
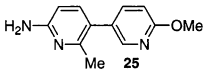
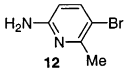
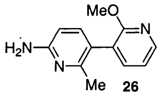
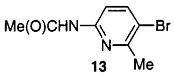
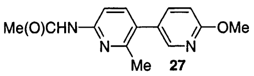
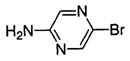
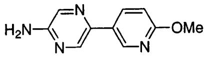
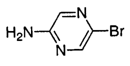
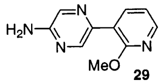
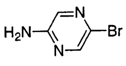
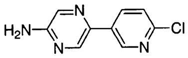
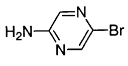
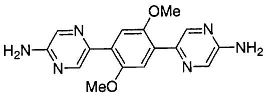
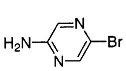
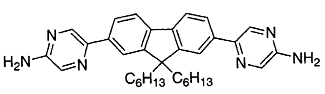
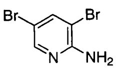
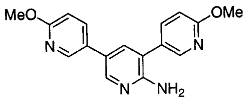
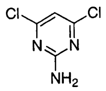
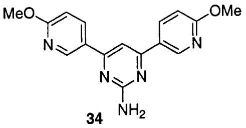
TABLE 1[a]

$\mathbf{1\text{-}5} + \text{R-Y} \xrightarrow{(i)} \mathbf{17\text{-}34}$

Entry	Boronic acid	R-Y	Product	Isolated yield (%)
1	1	 **6**	 **17**	80
2	1	 **7**	 **18**	84
3	1	 **8**	 **19**	82
4	2	 **8**	 **20**	69
5	1	 **9**	 **21**	40
6	1	 **10**	 **22**	40
7	1	 **11**	 **23**	69
8	2	 **11**	 **24**	75
9	1	 **12**	 **25**	73
10	2	 **12**	 **26**	75
11	1	 **13**	 **27**	81
12	1	 **14**	 **28**	60
13	2	 **14**	 **29**	70
14	3	 **14**	 **30**	62
15	4	 **14**	 **31**	56
16	5	 **14**	 **32**	51
17	1	 **15**	 **33**	76
18	1	 **16**	 **34**	35

[a] Reagents: entries 1–14, 17, 18, (i) $Pd[PPh_3]_2Cl_2$, 1,4-dioxane, Na_2CO_3 (1 M), reflux, 8 h; entries 15, 16, (i) $Pd[PPh_3]_4$, THF, Na_2CO_3 (1 M), reflux, 24 h.

Experimental Section

Typical Procedure for the Cross-Coupling Reactions. The boronic acid (1.0 equiv), the aryl halide (0.9 equiv), and $Pd[PPh_3]_2Cl_2$ (ca. 5 mol %) were sequentially added to degassed 1,4-dioxane, and the mixture was stirred at 20 °C for 30 min. Degassed aqueous Na_2CO_3 solution (1 M, 3.0 equiv) was added, and the reaction mixture was heated under argon at reflux for 8 h. Solvent was removed in vacuo, ethyl acetate was added, and the organic layer was washed with brine, separated, and dried over $MgSO_4$. The mixture was purified by chromatography on a silica gel column. On some occasions additional recrystallization was necessary to remove traces of Ph_3PO which coeluted with the desired product. Other compounds isolated were variable amounts of the "self-coupled" boronic acid, e.g., 6,6-dimethoxy-[3,3′]bipyridine (from reactions of **1**) which was usually the first compound to elute, and unreacted arylhalide.

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Supporting Information Available: Full details of synthetic procedures and characterization data for compounds **1**, **2**, and **16**–**34**; X-ray crystallographic data and ORTEP plots for compounds **1** and **31**·DMF and a description of their structures. This material is available free of charge via the Internet at http://pubs.acs.org.

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