Palladium-Catalyzed Selective Cross-Coupling between 2-Bromopyridines and Aryl Bromides

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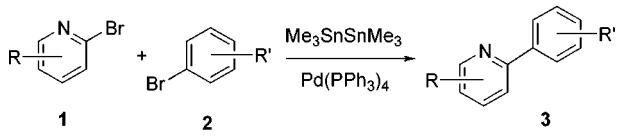
Palladium-catalyzed coupling reactions between two aromatic groups, such as the Stille coupling,[2] are widely utilized in organic synthesis. Intermolecular coupling of 2-halopyridines to other aryl halides has attracted considerable interest. Most methods involve a stepwise process in which anions are generated from one aryl halide either through bromo−lithium exchange with *n*-butyllithium[3] or *tert*-butyllithium[4−6] or Grignard reaction with magnesium metal.[6,7] The anions formed are thus quenched with trialkyltin halides to form arylstannanes[3] or exchanged with zinc chloride to form arylzinc halides.[4−6] The arylstannanes or arylzinc halides are then coupled with the other aryl halide catalyzed by palladium to form the cross-coupled products. Many functional groups are not tolerated during anion generation.

Two one-pot selective cross-coupling procedures between 2-pyridyl and aryl groups have been reported. The first selective cross-coupling[8] was reported between equal molar amounts of 2-pyridyl triflate and a variety of aryl bromides in the presence of 1 equiv of hexamethylditin catalyzed by palladium. The cross-coupled 2-arylpyridines were obtained in 35−68% yields. Another selective cross-coupling was an electrochemical process[9] in which a nickel-catalyzed electroreduction of a one to one mixture of aryl halides and either 2-chloro- or 2-bromopyridine provided 2-arylpyridines in 30−80% yields. For both processes, the selectivity originated from different reactivity of the two starting materials. However, for both methods, no substituent was present on the 2-pyridyl ring.

As a part of our ongoing effort in a combinatorial approach to couple 2-pyridyl groups with a variety of substituents to aryl groups also with a variety of substituents, we developed a one-pot, selective intermolecular cross-coupling between 2-bromopyridines and aryl bromides using hexamethylditin catalyzed by palladium(0). An intramolecular version of this reaction, a cross-coupling between 2-bromopyridines and aryl bromides in the same molecule, is known in the literature.[10,11] Here, however, selectivity is not an issue. For the intermolecular coupling, the level of selectivity depends on the reactivity difference between 2-bromopyridines and aryl bromides. Tilley et al.[12] showed that 2,5-dibromopyridine underwent a regioselective palladium-catalyzed coupling reaction with terminal acetylenes and arylzinc halides to provide the corresponding 2-alkynyl-5-bromo- and 2-aryl-5-bromopyridines. The result suggests that the bromide at the 2-position in 2,5-dibromopyridine is significantly more reactive in palladium-catalyzed coupling reactions than the 5-bromide. This result was further reinforced by the work done by Kelly et al.[13] in the reactivity studies of pyridines doubly substituted with bromine and triflate. It was found that regardless of the leaving group the 2-position was more reactive than the 3-position of the pyridine in a palladium-catalyzed coupling reaction.

On the basis of these results, we took advantage of the high reactivity of 2-bromopyridines and studied their coupling reaction with aryl bromides. We now report a selective, one-pot cross-coupling between 2-bromopyridines and aryl bromides in the presence of 1 equiv of hexamethylditin catalyzed by palladium. 2-Bromo-



pyridine derivatives are commercially available or can be readily made. The method is promising toward applications in combinatorial synthesis, and a variety of electron-withdrawing substituents are tolerated on the pyridyl ring. The isolated yields of cross-coupled products after column chromatography are shown in Table 1.

Coupling of 2-bromopyridine and phenyl bromide (entry a) gave a 45% yield of the desired cross-coupled product, 2-phenylpyridine, together with trace quantities of homo-coupled products, biphenyl and 2,2′-bipyridyl. The coupling of 2-bromopyridine and 3-bromopyridine yielded predominantly cross-coupled product (entry b), in agreement with the observation that the 2-pyridyl position is more reactive. The reactions of 6-bromonicotinaldehyde (entry c) and 6-bromo-2-pyridinecarbaldehyde (entry d) were subjected to extensive product distribution analysis. ^{1}H NMR analysis of the crude reaction mixtures revealed that the ratios of the desired cross-coupled product to the homo-coupled bipyridyl dialdehyde were 6.5:1 and 4:1, respectively. In addition, a small quantity of biphenyl was also isolated (<15% mole of the cross-coupled products). The reaction of 2-bromonicotinaldehyde (entry h) gave a much lower

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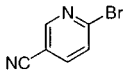
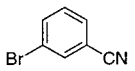
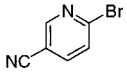
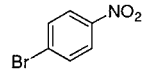
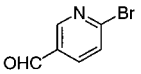
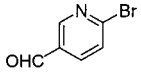
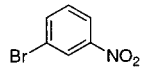
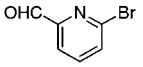
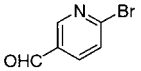
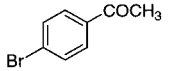
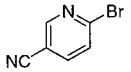
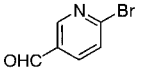
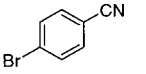
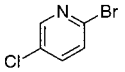
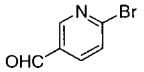
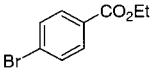
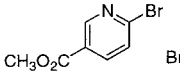
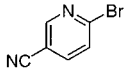
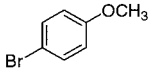
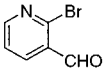
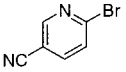
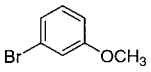
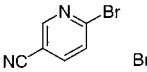
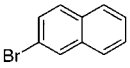
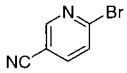
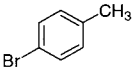
Table 1. Cross-Coupling between 2-Bromopyridines and Aryl Bromides

Entry	2-bromopyridine	ArBr	Yield (%)[a]	Entry	2-bromopyridine	ArBr	Yield (%)[a]
a			45	j			59
b			59	k			67
c			57	l			56
d			61	m			56
e			52	n			61
f			53	o			53
g			60	p			34[c]
h			25[b]	q			42[c]
i			53	r			33[c]

[a] Isolated yield. [b] Incomplete reaction. [c] Tris(dibenzylidineacetone)dipalladium(0) and tri-*tert*-butylphosphine were used instead of tetrakis(triphenylphosphine)palladium(0).

yield, probably due to steric hindrance. The desired cross-coupled product was obtained in 25% yield, together with a substantial quantity of biphenyl and some unreacted 2-bromonicotinaldehyde.

We then studied coupling reactions between 6-bromonicotinonitrile or 6-bromonicotinaldehyde with substituted phenyl bromides (entries i−r). The general trend is that the yields are higher when phenyl bromide is substituted with electron-withdrawing groups (entries j−o). This is expected because electron-withdrawing groups make the aryl bromide more electron-deficient and thus facilitate the oxidative addition to Pd(0). For phenyl bromides substituted with electron-donating groups (3- and 4-bromoanisole and 4-bromotoluene), the desired coupled products were obtained in much lower yields (31−40%). A byproduct, 6-phenylnicotinonitrile, was isolated in substantial quantity (10−40%). This byproduct, not observed in other reactions, probably was formed due to internal aryl exchange[14,15] with triphenylphosphine ligand as a result of the low reactivity of the electron-rich phenyl bromides. We successfully eliminated this byproduct by using tris(dibenzylidineacetone)-dipalladium(0) and tri-*tert*-butylphosphine[16] instead of tetrakis(triphenylphosphine)palladium(0). To our delight, no major byproduct was observed under these modified conditions (entries p−r). The desired products were obtained as the major products, albeit in moderate yields.

In conclusion, we have demonstrated a selective, one-pot intermolecular cross-coupling reaction between 2-bromopyridines and aryl bromides using hexamethylditin and palladium catalyst. 2-Bromopyridine derivatives are commercially available or can be readily made. The desired phenylpyridines can be easily separated from the homo-coupled products, the main side products. The method is promising toward applications in combinatorial synthesis, and the desired cross-coupled products can be obtained in moderate to good yields.

Experimental Section

General. All reactions were conducted under a nitrogen atmosphere with magnetic stirring. All reagents and solvents were commercial grade. Column chromatography was performed on Baker silica gel (40 μm). Melting points are uncorrected. NMR spectra were recorded in $CDCl_3$ at 400 MHz for ^1H with TMS as the internal standard and at 100 MHz for ^{13}C with the solvent as the internal standard. Electrospray mass spectra were recorded on Micromass Platform or Micromass Quattro. Electron impact mass spectra were recorded by ionization at 70 eV.

6-Bromonicotinonitrile (1e). 6-Chloronicotinonitrile (1.38 g, 10 mmol) was heated at 145 °C in phosphorus tribromide (15 mL) for 32 h. After cooling, the mixture was concentrated in vacuo. To the residue was added phosphorus tribromide (15 mL),

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and the mixture was heated at 145 °C for another 32 h. After cooling, the mixture was concentrated in vacuo, and an ice−water mixture (50 mL) was added. Sodium bicarbonate was added to neutralize the mixture, and the product was extracted with ethyl acetate (3 × 50 mL). The combined organic extracts were washed with brine and dried over magnesium sulfate. The solvent was removed in vacuo, and the residue was chromatographed (hexanes−ethyl acetate) to give 1.49 g (81%) of 6-bromonicotinonitrile as a white solid: mp 116−118 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66 (d, J = 11.0 Hz, 1H), 7.80 (dd, J = 3.1, 11.0 Hz, 1H), 8.67 (d, J = 3.1 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 109.2, 115.7, 128.7, 140.7, 146.6, 152.8. Electrospray MS m/z 183.0, 185.0 ($M + H^+$). Anal. Calcd for $C_6H_3BrN_2$: C, 39.38; H, 1.65; N, 15.31. Found: C, 39.22; H, 1.82; N, 15.17.

General Procedure of the Cross-Coupling. A mixture of 2-bromopyridine **1** (1 mmol), aryl bromide **2** (1 mmol), tetrakis(triphenylphosphine)palladium(0) (110 mg, 0.1 mmol), and hexamethylditin (327 mg, 1 mmol) in anhydrous 1,4-dioxane (10 mL) was refluxed under nitrogen for 18 h. The starting 2-bromopyridine was totally consumed as shown by TLC and mass spectroscopic analysis. The reaction time was not optimized. For entries p−r, tris(dibenzylidineacetone)dipalladium(0) (61 mg, 0.05 mmol) and tri-*tert*-butylphosphine (61 mg, 0.3 mmol) were used instead of tetrakis(triphenylphosphine)palladium(0). The solvent was removed, and the residue was then separated using flash column chromatography over silica gel eluting typically with hexanes−ethyl acetate, providing the coupled product **3**. Yields are given in Table 1. Compounds **3a**−**3h** are known in the literature.[17−23]

6-(2-Naphthyl)nicotinonitrile (3i): mp 165−167 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57 (m, 2H), 7.90 (m, 1H), 8.01 (m, 4H), 8.15 (dd, J = 1.8, 8.4 Hz, 1H), 8.56 (d, J = 1.3 Hz, 1H), 9.00 (dd, J = 0.9, 2.1 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 107.8, 117.0, 120.2, 124.1, 126.8, 127.5, 127.7, 127.8, 128.9, 129.0, 133.3, 134.3, 134.6, 139.9, 152.5, 160.4. Electrospray MS m/z 231.1 ($M + H^+$). Anal. Calcd for $C_{16}H_{10}N_2$: C, 83.46; H, 4.38; N, 12.17. Found: C, 83.14; H, 4.75; N, 12.20.

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Supporting Information Available: Full characterization data for compounds **3j**−**3r**. This material is available free of charge via the Internet at http://pubs.acs.org.

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