Base and Cation Effects on the Suzuki Cross-Coupling of Bulky Arylboronic Acid with Halopyridines: Synthesis of Pyridylphenols

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Strong base and large size cation have been shown to accelerate the rate and the yield of Suzuki coupling of a sterically bulky boronic acid with halopyridines in DME for the synthesis of pyridylphenols.

Introduction

Palladium-mediated cross-coupling reactions of organic electrophiles with organometallics (Li, Mg, Cu, Zn, Zr, Al, Sn, and B) and heteroatoms are versatile methods for the formation of carbon−carbon bonds.[1] Notable among these are the Stille[2] and the Suzuki coupling[3] which are based on reactions between aryl halides and aryl stannanes and arylboronic acids, respectively, in the presence of catalytic amount of Pd(0). These routes are highly valuable for the synthesis of biaryls and in particular regarding unsymmetrical cases. Both methods are compatible with a variety of functional groups. Stille coupling allows the use of neutral reaction conditions. Suzuki coupling offers the advantages of being largely unaffected by the presence of water and yielding nontoxic byproducts. As a consequence, they have been used extensively in the synthesis of natural products,[4] nucleoside analogues,[5] liquid crystals,[6] porphyrins,[7,8] and polymers.[9]

Pyridylphenols are an potentially important but less explored class of ligands[10] for metal complex formation[11] and have been synthesized previously from tedious routes.[10] Our interest in asymmetric catalysts using metal complexes of chiral pyridylphenols[12,13] has prompted us to utilize transition metal catalyzed cross-couplings for the synthesis. We now report the successful synthesis of pyridylphenols as well as the base and cation effects on the Suzuki coupling of a sterically bulky boronic acid with halopyridines in nonaqueous solvent.

Result and Discussion

One of the target pyridylphenols was 2-(3-methyl-2-pyridyl)-3,5-di-*tert*-butylphenol (**8a**). Initially, Stille coupling between the nucleophilic (3-methyl-2-pyridyl)-tributlystannane and the electrophilic aryl bromide **3** was employed but proved unsuccessful with debromination product obtained (Scheme 1). (3-Methyl-2-pyridyl)tributlystannane was not reactive enough possibly due to its weaker nucleophilicity and steric hindrance. The nucleophilic partner was then switched from the pyridine to the phenol. Kumada cross coupling[14] of the Grignard regeant of **3** with 2-bromo-3-methylpyridine **5a** using Ni(Ph$_3$P)$_2$Cl$_2$ catalyst did not, however, result in any cross-coupled product. Therefore, Suzuki cross-coupling reaction was then attempted.

Synthesis of Arylboronic Acid. The arylboronic acid **4** was synthesized from commercially available and inexpensive 3,5-di-*tert*-butylphenol **1**. Phenol **1** was monobrominated with Br_2 in CS_2 to afford 2-bromo-3,5-di-*tert*-butylphenol (**2**) in 94% yield (Scheme 2).[15] Phenol **2** was further methylated with dimethyl sulfate to produce 2-bromo-3,5-di-*tert*-butylanisole (**3**) in 88% yield.[16] Bromide **3** was subjected to metal−halogen exchange with ^{n}BuLi and was then quenched with B(OMe)$_3$ and finally hydrolyzed in aqueous Na_2CO_3 to afford **4** in 74% yield. In the preparation of boronic acid **4**,[13] it was found that the general method of acid hydrolysis[17] proved unsuccessful to yield the desired product **4**. The dimethyl borate intermediate leading to **4** might be either too electron rich or too bulky to be hydrolyzed in acidic medium. Initially, biphasic alkaline hydrolysis (aq

(1) For leading references: (a) Morita, D. K.; Stille, J. K.; Norton, J. R. *J. Am. Chem. Soc.* **1995**, *117*, 8576. (b) Goodson, F. E.; Wallow, T. I.; Novak, B. N. *J. Am. Chem. Soc.* **1997**, *119*, 12441. (c) Standorth, S. P. Tetrahedron **1988**, *54*, 263.

(2) (a) Stille, J. K. *Angew. Chem., Int. Ed. Engl.* **1986**, *98*, 508. (b) Mitchell, T. N. *Synthesis* **1992**, 803.

(3) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457.

(4) (a) Charette, A. B.; De Freitas-Gil, R. P. *Teterhedron Lett.* **1997**, *38*, 2909. (b) Uenishi, J.-i.; Beau, J.-M.; Armstrong, R. W.; Kishi, Y. *J. Am. Chem. Soc.* **1987**, *109*, 4756.

(5) Rbe, S.; Miyaura, N.; Suzuki, A. *Bull. Chem. Soc. Jpn.* **1992**, *65*, 2863.

(6) (a) Goodby, J. W.; Hird, M.; Toyne, K. J.; Watson, T. *J. Chem. Soc., Chem. Commun.* **1994**, 1701. (b) Campi, E. M.; Jackson, W. R.; Maruccio, S. M.; Naeslund, C. F. M. *J. Chem. Soc., Chem. Commun.* **1994**, 2395.

(7) Lin, V. S.-Y.; Therein, M. J.; *Chem. Eur. J.* **1995**, *1*, 645.

(8) (a) Chan, K. S.; Zhou, X.; Au, M. T.; Tam, C. Y. *Tetrahedron* **1995**, *51*, 3129. (b) Zhou, X.; Tse, M. K.; Wan, T. S. M.; Chan, K. S. *J. Org. Chem.* **1996**, *61*, 3590. (c) Zhou, X.; Chan, K. S. *J. Org. Chem.* **1998**, *63*, 99.

(9) (a) Kim, Y. H.; Webster, W. W. *J. Am. Chem. Soc.* **1990**, *112*, 4592. (b) Wallow, T. I. Novak, B. M. *J. Am. Chem. Soc.* **1991**, *113*, 7411. (c) Lamba, J. J. S. Tour, J. M. *J. Am. Chem. Soc.* **1994**, *116*, 11723. (d) Hodge, P.; Power, G. A.; Rabjohns, M. A. *J. Chem. Soc., Chem. Commun.* **1997**, 73. (e) Miller, T. M.; Neeman, T. X.; Zayas, R.; Bair, H. E. *J. Am. Chem. Soc.* **1992**, *114*, 1018.

(10) (a) Riggio, v. G.; Hopff, W. H.; Hoffman, A. A. Waser, P. G. *Helv. Chim. Acta* **1983**, *66*, 1039. (b) Baker, R. W. Rea, S. O.; Sargent, M. V.; Schenkelaars, E. M. C.; Skelton, B. W.; White, A. H. *Tetrahedron: Asymmetry* **1994**, *5*, 45.

(11) Ganis, P.; Saporito, A.; Vitagliano, A. *Inorg. Chem. Acta* **1988**, *142*, 75.

(12) Zhang, H. C.; Chan, K. S. *Tetrahedron Lett.* **1996**, *37*, 1043.

(13) Zhang, H. C.; Xue, F.; Mak, T. C. W.; Chan, K. S. *J. Org. Chem.* **1996**, *61*, 8002.

(14) Kumada, M. *Pure Appl. Chem.* **1980**, *52*, 669.

(15) (a) Lam, F.; Chan, K. S.; Liu, B. J. *Tetrahedron Lett.* **1995**, *35*, 6261. (b) Yoshifuji, M.; An, D. L.; Toyota, K.; Yasunami, M. *Chem. Lett.* **1993**, 2069.

(16) Furniss, B. S.; Hannaford, A. J.; Smith, P. W. G.; Tatchell, A. R. *Vogel's Textbook of Practical Organic Chemistry*, 5th ed.; Longman: Essen, UK, 1989; p 981.

(17) Seeman, W.; Johnson, J. R. *J. Am. Chem. Soc.* **1931**, *53*, 711.

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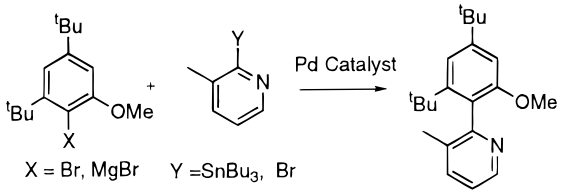
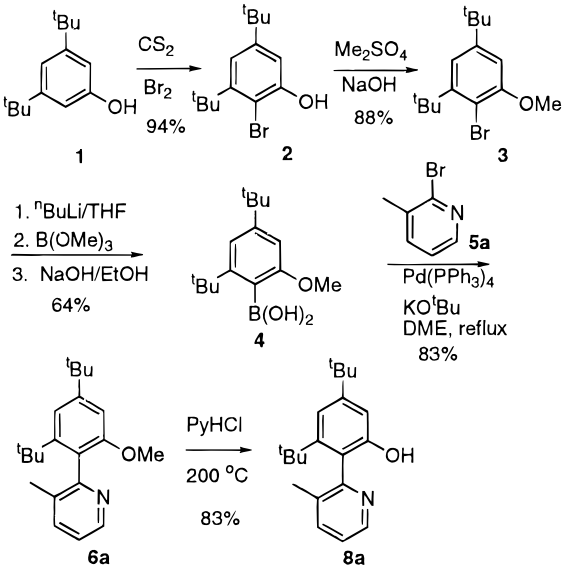
Scheme 1



Scheme 2



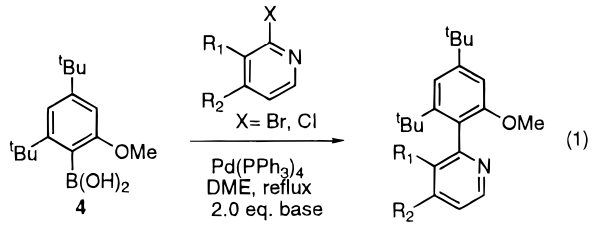
Na_2CO_3/C_6H_6, reflux) was found to be effective to give the desired boronic acid **4** in 2 d. Finally, a monophasic alkaline hydrolysis using NaOH/EtOH proved to be most effective with the arylboronic acid being obtained in just 10 min to give 64% of **4**.

Suzuki Cross-Coupling Reaction. During our initial synthetic effort for compound **6a**, we did not observe any coupling products using the typical Suzuki reaction conditions with either Na_2CO_3 or NaOEt.[18] It is notable that nucleophilic substitution of halopyridine was not a major interfering reaction. Over 70% of **4** was recovered from the synthesis of **6a** using Na_2CO_3 while a complex reaction mixture formed with the use of NaOEt. Arylboronic acids with sterically hindered[19] or electron-withdrawing substitutents[20] have been known to be less successful due to the steric hindrance or competitive hydrolytic deboronation. The modified Suzuki coupling reaction conditions by Gronowitz[20] was employed to suppress deboronation by using glycol dimethyl ether (DME) as the solvent.

Upon increasing the strength of base, boronic acid **4** underwent a Suzuki cross coupling with 2-bromo-3-methylpyridine **5a**,[21] in the presence of 2.0 equiv of KO^{t}Bu and 5 mol % of $Pd(Ph_3P)_4$ in DME to produce **6a** in 83% yield. Finally, compound **6a** was demethylated by pyridine hydrochloride under N_2 to afford **8a** in 83% yield (Scheme 2).

To verify the generality of base effect on this reaction, less bulky halopyridines **5b**,**c** also were reacted with **4** (eq 1, Table 1). A strong base effect on the cross coupling

Table 1. Suzuki Cross Couplings of Arylboronic Acids with Halopyridines



5a. R_1=Me, R_2=H, X=Br
5b R_1=R_2=H, X=Br
5c R_1-R_2=$(CH)_4$, X=Cl

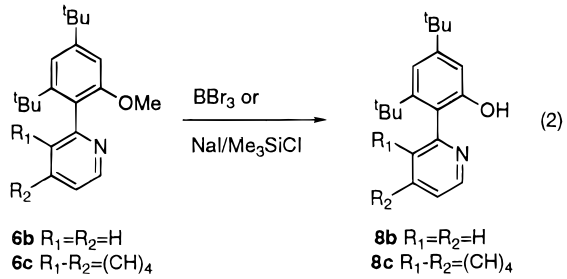
6a R_1=Me, R_2=H
6b R_1=R_2=H
6c R_1-R_2=$(CH)_4$

	% yield (reaction time, h)		
base	**6b**	**6a**	**6c**
Na_2CO_3	26 (90)	0 (90)	0 (90)
NaOH	40 (140)	22 (24)	44 (26)
NaOEt[a]	74 (4)	0 (12)	45 (26)
KO^{t}Bu[b]	86 (4)	83 (16)	77 (10)

[a] 2.0 M in EtOH. [b] 2.0 M in ^{t}BuOH.

in DME was observed. The reactions of the extremely sterically bulky arylboronic acid **4** with halopyridines **5a**−**c** using the standard base (Na_2CO_3) produced either no desired products or very low yields with extended reaction time. Upon increasing the strength of base from NaOH, NaOEt to KO^{t}Bu (2 equiv), both the yields of products and the rates of the reactions increased.

The demethylation of anisoles **6b,c** were achieved with BBr_3 or NaI/TMSCl to give **8b,c** respectively. in good yields (eq 2).



6b R_1=R_2=H
6c R_1-R_2=$(CH)_4$

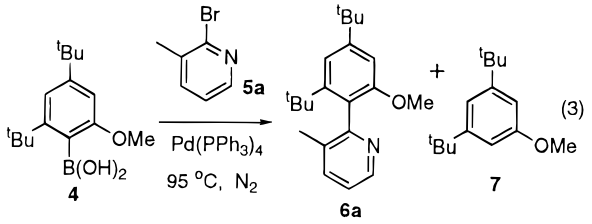
8b R_1=R_2=H
8c R_1-R_2=$(CH)_4$

In an effort to optimize reaction conditions, we have further discovered a cation effect on this Suzuki reaction (eq 3, Table 2). The reaction gave a better yield of **6a** in a homogeneous medium with the addition of ^{t}BuOH to dissolve KO^{t}Bu than in a heterogeneous medium without the addition of ^{t}BuOH (entries 1, 4, and 5). The rate of formation of **8a** was decreased when NaO^{t}Bu, freshly prepared in situ from Na/^{t}BuOH, was used, with the yield remaining unchanged when the same batch of Pd catalyst was used. Some competitive deboronation product **7** was observed (entry 1). (Different batches of commerically available $Pd(Ph_3P)_4$ affected the rate and yields of **6a** slightly.) Most surprisingly, addition of 18-crown-6 to KO^{t}Bu *decreased both the yield and rate of the formation of* ***6a*** (entries 3 and 4). Weaker bases with large size cations (Cs and Ba) proved to be inferior to KO^{t}Bu (entries 6 and 7).

The base and cation effect can be rationalized according to the mechanism shown in Scheme 3. Two equivalents of base are required in this catalytic cycle.[3] One equivalent is used to react with arylboronic acid and the other is used to react with arylpalladium halide to give pal-

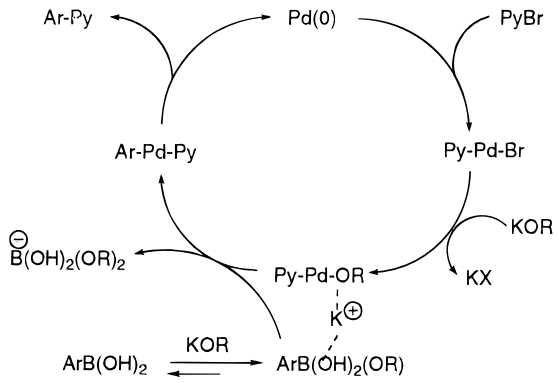
(18) Watanabe, T.; Miyaura, N.; Suzuki, A. *Synlett* **1992**, *207*, 6.
(19) Thompson, W. J.; Gandino, J. *J. Org. Chem.* **1984**, *49*, 5237.
(20) Gronowitz, S.; Bobosic, V.; Lawitz, K. *Chem. Scripta* **1984**, *23*, 120.
(21) Case, F. H. *J. Am. Chem. Soc.* **1946**, *68*, 2074.

Table 2. Cation Effect of Suzuki Cross Coupling Reaction



	time	base	solvent	% yield of **6a**	% yield of **7**
1	15 min	KO^{t}Bu	^{t}BuOH/DME	61	18
2	5.5 h	NaO^{t}Bu	^{t}BuOH/DME	60	18
3	45 min	KO^{t}Bu	18C-6/^{t}BuOH/DME	30	38
4	16 h	KO^{t}Bu	18C-6/DME	32	30
5	6 h	KO^{t}Bu	DME	27	22
6	116 h	Cs_2CO_3	^{t}BuOH/DME	20	29
7	5d	$Ba(OH)_2$	^{t}BuOH/DME	0	0

Scheme 3



ladium alkoxy intermediate via ligand substitution. Since arylboronic acids are weak acids (pK_a of phenyl boronic acid = 8.8),[9b] base either attacks the electrophilic boron or abstracts a proton of the boronic acid. In either possibility, the nucleophilicity of the resultant boronate anion or the equilibrium concentration of the anion will be increased and more reactive toward the pyridyl alkoxyl palladium formed via the oxidative addition of pyridyl halides and ligand substitution with base. Stronger base will enhance the rate of the transmetalation step similar to that observed with increasing base strength to increase the rate and the yields of products. A similiar base effect for other weaker bases has been reported earlier by Suzuki.[18] The extremely strong K^{t}OBu base has also been utilized successfully in DME by Charette in cyclopropane synthesis while other base−solvent combinations were either ineffective or less efficient.[4a]

The effect of the cation is surprising. The rate of the reaction increased with the size of the cation. Addition of 18-crown-6 did not increase the rate as expected through an increase in base strength through better solvation of the cation.[22] Presumably, the large size potassium cation (1.44 Å)[23] may template the nucleophilic attack of boronate to the palladium pyridyl alkoxy intermediate via the interaction of the alkoxy oxygen atom and possibly the pyridyl nitrogen with the potassium ion with minimal steric crowding in the transition state of transmetalation or reductive elimination.[1b,2,23] The smaller size of sodium caton (1.12 Å)[24] gave a slower rate presumbly due to more steric crowding in the transition state. Addition of 18-crown-6 destroyed the templated, rate-accelerated transmetalation even though the base strength may be stronger.[22,25] This kind of cation-accelerated Suzuki cross-coupling reaction, though less prominent, has also been observed in the reaction of phenylboronic acid with methyl 4-bromophenylacetate.[26] The yields of coupled product using CsF, KF, and Bu_4NF were 95, 91, and 90%, respectively. Tl(OH), whose ionic radius is 1.54 Å and is a strong base,[24] has also been shown to accelerate the Suzuki cross-coupling reactions.[4b,27] In the intromolecular[23] and intermolecular[28] ortho-arylation of phenols, the effect of cation size on yields of products was the following: Li_2CO_3 < Na_2CO_3 < K_2CO_3 < Cs_2CO_3. An explantion was suggested that the larger cations are better solvated, resulting in a more nucleophilic, " naked" phenolate anion. It may well be understood that a cation templating effect was operating in addition to increasing base strength as shown in this study.

In conclusion, we have shown that in comparison with Kumada coupling, the unique Suzuki cross couplings between the extremely sterically bulky arylboronic acid **4** with halopyridines have been successfully carried out using the strong base KO^{t}Bu to give highly hindered pyridylphenols. Stronger base and a larger size cation increase the rates and the yields of the coupling. Further studies on the general scope of the reaction are continuing.

Experimental Section

Unless otherwise noted, all materials were obtained from commercial suppliers and used without further purification. Tetrahydrofuran (THF) and diethyl ether (Et_2O) were distilled from sodium benzophenone ketyl immediately prior to use. Hexane was distilled over calcium chloride. Toluene was distilled from sodium, and dichloromethane was distilled over calcium hydride. Thin-layer chromatography was performed on precoated silica gel plates. Silica gel (70−230 and 230−400 mesh) was used for column chromatography.

Melting points were uncorrected. IR spectra were recorded as neat films on KBr plates. ^{1}H NMR spectra were recorded at 250, 300, or 500 MHz. Spectra were referenced internally to the residual proton resonance in $CDCl_3$ (δ 7.24 ppm), or with tetramethylsilane (TMS, δ 0.00 ppm) as internal standard. Chemical shifts (δ) were reported as part per million (ppm) in δ scale downfield from TMS. Coupling constant (J) were reported in hertz (Hz). ^{13}C NMR spectra were obtained at 62.89, 75, or 125 MHz and referenced to the residual $CHCl_3$ (δ 77.00 ppm) in $CDCl_3$. Mass spectra were recorded either at electron ionization or at FAB mode using *m*-nitrobenzyl alcohol (NBA) as the matrix. Elemental analyses were performed by the Medac Ltd., Department of Chemistry, Brunel University, U.K.

2-Bromo-3,5-di-*tert*-butylphenol (2). To a solution of 3,5-di-*tert*-butylphenol (**1**) (30 g, 0.15 mol) in CS_2 (50 mL) at 0 °C

(22) Hennings, D. D.; Iwasa, S.; Rawal, V. H. *J. Org. Chem.* **1997**, *62*, 2.

(23) Generation of a rate-determining step in Suzuki cross coupling is not universal. Suggestion of the rate-determining step (a) in reduction−elimination: Aliprantis, A. O.; Canary, J. W. *J. Am. Chem. Soc.* **1994**, *116*, 6985; (b) in transmetalation; ref 1b.

(24) Cotton, F. A.; Wilkinson, G. *Advanced Inorganic Chemsitry*, 5th ed.; John Wiley and Sons: New York, 1988.

(25) Addition of 18-crown-6 to NaO^{t}Bu in Pd-catalyzed amination accelerated the rate of the rate; a different origin may be possible. Wolfe, J. P.; Buchwald, S. L. *J. Org. Chem.* **1997**, *62*, 6066.

(26) Wright, S. W.; Hageman, D. L.; McClure, L. D. *J. Org. Chem.* **1994**, *59*, 6095.

(27) Anderson, J.; Namli, H. *Synlett* **1995**, 765.

(28) Satoh, T.; Kawamura, Y.; Miura, M.; Nomura, M. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 1740.

was added bromine (7.7 mL, 0.15 mol) in CS_2 (7.5 mL) dropwise during a period of 2 h, and the resulting brown solution was stirred for another 1 h at room temperature. Saturated $Na_2S_2O_3$ solution (20 mL) was added, and the solution was stirred for 30 min. The organic layer was separated, the aqueous layer was extracted with CH_2Cl_2 (50 mL × 2), and the combined organic extracts were washed with water and brine and dried over Na_2SO_4. After removal of solvent, the light yellow residue was recrystallized from CH_2Cl_2−hexane to give colorless crystals (40 g, 94%); mp 113−115 °C (lit.[15] 114.5−115.5 °C); R_f = 0.41 (hexane/ethyl acetate = 1:2); ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.29 (s, 9 H), 1.51 (s, 9 H), 5.92 (s, 1 H), 6.97 (d, 1 H, J = 2.3 Hz), 7.04 (d, 1 H, J = 2.3 Hz); MS (EI): *m*/*z* (relative intensity) 285 (M^+, 11); IR (neat): 3502 cm^{-1}.

2-Bromo-3,5-di-*tert*-butylanisole (**3**). A solution of sodium hydroxide (2.64 g, 66 mmol) in 30 mL of water was added to 2-bromo-3,5-di-*tert*-butylphenol (**2**) (9.5 g, 33 mmol). After the mixture was cooled to 0 °C, Me_2SO_4 (6.2 mL, 66 mmol) was then added dropwise within 2 h. The mixture was further heated at 65 °C for another 2 h before cooling down to room temperature. The reaction mixture was extracted with CH_2Cl_2 (25 mL × 3). The extracts were washed with brine and dried over $MgSO_4$. After removal of the solvent, the residue was distilled in vacuo to give 2-bromo-3,5-di-*tert*-butylanisole (**3**) as a colorless liquid (88−90 °C/0.02 mmHg) which solidified as colorless crystals (8.8 g, 88%) upon standing for a while; mp 46−48 °C (lit.[15] 47.5−48 °C); R_f = 0.39 (hexane); ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.32 (s, 9 H), 1.54 (s, 9 H), 3.89 (s, 3 H), 6.83 (d, 1 H, J = 2.2 Hz), 7.12 (d, 1 H, J = 2.2 Hz); MS (EI): *m*/*z* (relative intensity) 299 (M^+, 43).

2,4-Di-*tert*-butyl-6-methoxyphenylboronic Acid (**4**). ^{n}Butyllithium (1.6 M in hexane, 25 mL, 40 mmol) was added to a solution of 2-bromo-3,5-di-*tert*-butylanisole (**3**) (12 g, 40 mmol) in THF (20 mL) at −78 °C under nitrogen. The mixture was stirred for 1 h and then transferred to a solution of $B(OMe)_3$ (9.1 mL, 80 mmoL) in THF (10 mL) at −78 °C under nitrogen. It was allowed to warm to room temperature and stirred overnight, and HCl (10%, 20 mL) was added to the mixture and stirred for 10 min. The organic layer was separated, and the aqueous phase was extracted with ether (50 mL × 3). The combined organic phase was washed with brine. After removing of solvent, the residue was redissolved in benzene (60 mL). A solution of Na_2CO_3 (8.5 g, 80 mmol) in water (40 mL) was added, and then the mixture was refluxed for 24 h. Benzene was rotary-evaporated, and the remaining aqueous layer was extracted with ether (30 mL × 3). The ether layer was then washed with brine and dried over $MgSO_4$. The solvent was removed, and the residue was recrystallized from ether/hexane to give 2,4-di-*tert*-butyl-6-methoxyphenylboronic acid (**4**) as colorless crystals (7.8 g, 74%); mp 164−166 °C; R_f = 0.29 (hexane:ethyl acetate = 3:1); ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.32 (s, 9 H), 1.42 (s, 9 H), 3.81 (s, 3 H), 4.78 (brs, 2H), 6.76 (d, 1H, J = 1.6 Hz), 7.11 (d, 1 H, J = 1.6 Hz); FABMS: *m*/*z* (relative intensity) 264 (M^+, 46); IR (neat): 3316 cm^{-1}. Anal. Calcd for $C_{15}H_{25}OB$: C, 68.20; H, 9.54. Found: C,68.26; H, 9.76.

An improved hydrolysis was performed as follows. After rotary evaporation of the ethereal extract, the residue was added to NaOH (3.2 g, 80 mmol) in EtOH (60 mL) and stirred at room temperature for 10 min. After rotary evaporation of solvent, he aqueous phase was extracted with ether (50 mL × 3). The combined organic phase was washed with water and brine and dried (Na_2SO_4). After filtration and rotary evaporation, the residue was recrystallized from ether/hexane to give 64% yield of **4**.

2-Bromo-3-methylpyridine (**5a**).[21] HBr (48%) (39.5 mL) was added to a three-neck flask, fitted with a dropping funnel, a mechanical stirrer, and a low temperature thermometer. It was cooled to 0 °C in an ice−salt bath. 2-Amino-3-methylpyridine (8.0 mL, 80 mmol) was then added over a period of 10 min with the solution maintained at 0 °C. Bromine (12 mL, 0.23 mol) was then added within 1 h. Sodium nitrite (14 g, 0.20 mol) in water (20 mL) was introduced dropwise over 2 h, and the solution was kept at 0 °C. Stirring was continued for another 30 min. Sodium hydroxide (30 g, 0.75 mol) in water (30 mL) was then added. Potassium hydroxide pellets (5.0 g, 90 mmol) were added, and the reaction mixture was allowed to stand for 1 h. After filtration, the ether was removed, and the residue was submitted to vacuum distillation (45 °C/0.15 mmHg) to give 2-bromo-3-methylpyridine (3.6 g, 26%) as a colorless liquid. ^{1}H NMR (250 MHz, $CDCl_3$) δ 2.39 (s, 3 H), 7.18 (m, 1 H), 7.52 (d, 1 H, J = 7.5 Hz), 8.20 (d, 1 H, J = 3.6 Hz).

1-Chloroisoquinoline (**5c**).[29] Phosphoryl chloride (28 mL, 0.30 mol) was added to a solution of isoquinoline *N*-oxide (14.5 g, 0.10 mol) in $CHCl_3$ (50 mL). The reaction mixture was refluxed for 2 h and was then cooled to room temperature. The resulting orange solution was poured onto ice. Concentrated aqueous ammonia was then added until the solution was basic. It was separated, and the aqueous layer was extracted with CH_2Cl_2 (50 mL × 2). The combined organic extracts were dried over Na_2SO_4 and then concentrated in vacuo to give a brown oil. Vacuum distillation (100−101 °C/0.10 mmHg) afforded 1-chloroisoquinoline (14.3 g, 84%) as a colorless solid; mp 35−37 °C (lit.[29] 37−38 °C); R_f = 0.52 ($CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.56 (d, 1 H, J = 5.5 Hz), 7.64−7.74 (m, 2 H), 7.76 (d, 1 H, J = 6.7 Hz), 8.22−8.30 (m, 2 H).

3,5-Di-*tert*-butyl-2-(3′-methyl-2′-pyridyl)anisole (6a). A mixture of 2-bromo-3-methylpyridine (172 mg, 1 mmol) and palladium tetrakis(triphenylphosphine) (58 mg, 0.05 mmol) in DME (3 mL) was degassed for three times by freeze−pump−thaw method (three cycles) and then gently heated and stirred in a nitrogen atmosphere until the suspension disappeared. Afterward, 3,5-di-*tert*-butyl-6-methoxyphenylboronic acid (264 mg, 1 mmol) and potassium *tert*-butoxide (224 mg, 2 mmol) in *tert*-butyl alcohol (0.5 mL) were added sucessively. The mixture was degassed for three times again by freeze−pump−thaw method (three cycles) and refluxed at 95 °C for 15 min under nitrogen. After being cooled to room temperature, the suspension was filtered through Celite to give a solution, and the Celite was washed with dichloromethane (20 mL). The solvent was removed at reduced pressure, and the extract was purified by column chromatography on silica gel by hexane/ethyl acetate = 6:1 as eluent to obtain 3,5-di-*tert*-butyl-2-(3′-methyl-2′-pyridyl)anisole as a white solid (201 mg, 64% yield); mp = 114−115 °C, hexane/ethyl acetate = 6:1, R_f = 0.4, ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.09 (s, 9H), 1.33 (s, 9 H), 2.06 (s, 3 H), 3.60 (s, 3 H), 6.80 (d, 1 H, J = 1.9 Hz), 7.11 (dd, 1 H, J = 4.8, 7.5 Hz), 7.19 (d, 1 H, J = 1.9 Hz), 7.44 (d, 1 H, J = 6.8 Hz), 8.44 (d, 1 H, J = 4.6 Hz); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 19.2, 31.4, 31.9, 35.0, 36.9, 55.8, 106.2, 117.0, 121.7, 126.0, 134.0, 136.2, 145.6, 148.1, 151.1, 156.9, 159.2. FABMS: *m*/*z* (relative intensity) (M^+, 20); HRMS (matrix, NBA) calcd for $C_{21}H_{29}NO{\cdot}H^+$ 312.2322, found 312.2296. **3,5-Di-*tert*-butylanisole**[30] **(7)** was also obtained as colorless liquid R_f = 0.8, hexane/ethyl acetate = 20:1, in 18% yield.^{1}H NMR (300 MHz, $CDCl_3$) δ 1.32 (s, 18 H), 3.82 (s, 3 H), 6.77 (s, 2 H), 7.03 (s, 1 H).

The experiement using NaO^{t}Bu was caried out as follows. Na (46 mg, 2.0 mmol) was refluxed in ^{t}BuOH (0.7 mL) for 3 h under N_2. The solution was transferred to the reaction mixture similiar to that with KO^{t}Bu. The reaction was carried out likewise in 5.5 h to give **6a** in 60% yield together with 18% yield of **7**.

3,5-Di-*tert*-butyl-2-(2′-pyridyl)anisole (6b). A mixture of 2-bromopyridine (**5a**) (79 mg, 0.50 mmol) and 5 mol % of $Pd(Ph_3P)_4$ (30 mg, 0.025 mmol) in DME (5 mL) was stirred under N_2 for 20 min. Then 2,4-di-*tert*-butyl-6-methoxyphenylboronic acid (**4**) (1.32 g, 0.5 mmol) in DME (0.5 mL) and 2.0 equiv of potassium *tert*-butoxide (112 mg, 1.0 mmol) in *tert*-butyl alcohol (0.5 mL) were added successively. The reaction mixture was deoxygenated by the freeze−pump−thaw method (three times, −196 °C to 25 °C) and was then refluxed for 4 h under N_2 until no starting material was left as monitored by TLC. After cooling to room temperature, the mixture was

(29) Alcock, N. W.; Brown, J. M.; Hulmes, D. I. *Tetrahedron: Asymmetry* **1993**, *4*, 743.

filtered and the precipitate was washed with CH_2Cl_2. The filtrates were concentrated by rotary evaporation to give a brown oil, and it was then redissolved in CH_2Cl_2 (30 mL), washed with water and brine, and dried over $MgSO_4$. Concentration using a rotary evaporator and subsequent chromatography on silica gel using hexane/ethyl acetate (6:1) as the eluent afforded 3,5-di-*tert*-butyl-2-(2′-pyridyl)anisole (**6b**) (127 mg, 86%) as colorless crystals; mp 105−107 °C (hexane/CH_2Cl_2); R_f = 0.25 (hexane/ethyl acetate = 6:1); ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.12 (s, 9 H), 1.36 (s, 9 H), 3.63 (s, 3 H), 6.85 (d, 1 H, J = 1.5 Hz), 7.18−7.31 (m, 3 H), 7.65 (t, 1 H, J = 7.6 Hz), 8.64 (dd, 1 H, J = 1.7, 5.4 Hz), ^{13}C NMR (125 MHz, $CDCl_3$): δ 31.4, 32.4, 35.1, 36.9, 56.0, 106.3, 116.5, 121.4, 127.0, 127.2, 134.9, 148.3, 148.5, 151.4, 157.5, 159.5; FABMS: *m*/*z* (relative intensity) 297 (M^+, 100). Anal. Calcd for $C_{20}H_{27}NO$: C, 80.75; H, 9.16; N, 4.71. Found: C, 80.52; H, 9.26; N, 4.68.

3,5-Di-*tert*-butyl-2-(2′-isoquinolinyl)anisole (6c). A similiar procedure as that used in the preparation of **6a:** 2-Chloroisoquinoline (**5c**) was used as the halopyridine, and the reaction was refluxed for 10 h. After usual workup, 3,5-di-*tert*-butyl-2-(2′-isoquinolinyl)anisole (**6c**) was obtained as colorless crystals in 77% yield; mp 106−108 °C (hexane/CH_2Cl_2); R_f = 0.36 (hexane/ethyl acetate = 6:1); ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.01 (s, 9 H), 1.40 (s, 9 H), 3.48 (s, 3 H), 6.88 (s, 1 H), 7.30 (s, 1 H), 7.38 (t, 1 H, J = 7.3 Hz), 7.58 (m, 3 H), 7.78 (d, 1 H, J = 8.0 Hz), 8.60 (d, 1 H, J = 5.8 Hz); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 32.1, 32.9, 35.8, 37.6, 56.6, 107.0, 117.7, 120.2, 125.4, 127.1, 128.4, 130.1, 130.6, 136.2, 142.3, 150.0, 152.4, 158.5, 162.1; FABMS: *m*/*z* (relative intensity) (M^+, 100). Anal. Calcd for $C_{24}H_{29}NO$: C, 82.94; H, 8.42; N, 4.03. Found: C, 82.83; H, 8.53; N, 3.91.

3,5-Di-*tert*-butyl-2-(3′-methyl-2′-pyridyl)phenol (8a). Pyridine (11.8 mL, 145 mmol) was added to 37% of hydrochloride acid (12.1 mL, 145 mmol), and the mixture was stirred and heated at 200 °C for 30 min. Then water was removed by distillation at 220 °C to give a white solid of pyridinium hydrochloride.[31] 3,5-Di-*tert*-butyl-2-(3′-methyl-2′-pyridyl)anisole (**6a**) (3.5 g, 11 mmol) was then added, and the mixture was heated to 200 °C for 12 h under N_2. After cooling to room temperature, water (40 mL) was added. The reaction mixture was neutralized with aqueous sodium hydroxide and was extracted with CH_2Cl_2 (50 mL × 3). The extracts were washed with brine and dried over $MgSO_4$. After the solvent was removed, the residue was purified by flash chromatography with a solvent mixture of hexane/ethyl acetate (3:1) as the eluent to afford 3,5-di-^{t}butyl-(3′-2′-methylpyridyl)phenol (**8a**) as colorless crystals (2.7 g, 83%): mp 162−164 °C ($CHCl_3$); R_f = 0.21 (hexane/ethyl acetate = 3:1); ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.11 (s, 9 H), 1.32 (s, 9 H), 2.14 (s, 3 H), 4.60 (brs, 1 H), 6.84 (s, 1 H), 7.16 (s, 1 H), 7.21−7.26 (m, 1 H), 7.59 (d, 1 H, J = 7.5 Hz), 8.49 (d, 1 H, J = 4.1 Hz); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 19.2, 31.3, 32.0, 34.8, 37.0, 110.9, 117.1, 122.8, 123.3, 134.8, 137.7, 146.9, 148.1, 152.0, 152.6, 157.8; FABMS: *m*/*z* (relative intensity) 297 (M^+, 58); IR (neat): 3057 cm^{-1}. Anal. Calcd for $C_{20}H_{27}NO$: C, 80.75; H, 9.16; N, 4.71. Found: C, 80.27; H, 9.26; N, 4.60.

3,5-Di-*tert*-butyl-2-(2′-pyridyl)phenol (8b). A solution of anisole **6b** (250 mg, 0.84 mmol) in CH_2Cl_2 (8 mL) was added to a solution of BBr_3[32] (0.08 mL, 0.84 mmol) in CH_2Cl_2 (1 mL) at −78 °C under N_2. The reaction mixture was allowed to warm to rt and stirred overnight. Then H_2O (10 mL) was added, the solution stirred for 10 min, and the organic layer separated. The aqueous layer was neutralized with saturated $NaHCO_3$ to pH = 6 and was then extracted with $CHCl_3$ (10 mL × 3). The combined organic phase was washed with brine and dried over $MgSO_4$. After the solvent was removed, the residue was purified by flash chromatography on silica gel with a mixture of hexane/ethyl acetate (3:1) as the eluent to afford 3,5-di-*tert*-butyl-2-(2′-pyridyl)phenol (**8b**) as colorless crystals (170 mg, 71%): mp 181−183 °C ($CHCl_3$); R_f = 0.23 (hexane/ethyl acetate = 3:1); ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.15 (s, 9 H), 1.32 (s, 9 H), 5.72 (brs, 1 H), 6.85 (d, 1 H, J = 1.8 Hz), 7.17 (d, 1 H, J = 1.8 Hz), 7.30 (t, 1 H, J = 6.1 Hz), 7.41 (d, 1 H, J = 7.7 Hz), 7.73 (t, 1 H, J = 7.7 Hz), 8.69 (d, 1 H, J = 5.0 Hz); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 31.3, 32.8, 34.8, 36.9, 111.0, 116.9, 122.2, 124.3, 127.4, 136.2, 148.6, 149.4, 152.1, 153.6, 158.9; FABMS: *m*/*z* (relative intensity) 283 (M^+, 100); IR (neat): 3250 cm^{-1}; HRMS (matrix, NBA) calcd for $C_{19}H_{25}NO\cdot H^+$ 284.2009, found 284.2001.

3,5-Di-*tert*-butyl-2-(2′isoquinolinyl)phenol (8c). A 10 mL round-bottom flask was charged with 3,5-di-*tert*-butyl-2-(2′-isoquinolinyl)anisole (**6c**) (260 mg, 0.75 mmol) and NaI (330 mg, 2.25 mmol), CH_3CN (2.0 mL) was added to the mixture, the flask was flushed with N_2, and Me_3SiCl (0.29 mL, 2.25 mmol) was then added.[33] The reaction mixture was refluxed for 96 h under N_2. H_2O (5.0 mL) was added to the mixture, and it was extracted with diethyl ether (5.0 mL × 3). The extracts were washed with aqueous $Na_2S_2O_3$ and brine and dried over $MgSO_4$. After the solvent was removed, the residue was purified by flash chromatography with a solvent mixture of hexane/ethyl acetate (3:1) as the eluent to afford 3,5-di-*tert*-butyl-2-(2′-isoquinolinyl)phenol (**8c**) as colorless crystals (217 mg, 87%): mp 122−124 °C ($CHCl_3$); R_f = 0.29 (hexane/ethyl acetate = 3:1); ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.00 (s, 9 H), 1.36 (s, 9 H), 6.87 (d, 1 H, J = 1.8 Hz), 7.25 (d, 1 H, J = 1.8 Hz), 7.49 (t, 1 H, J = 6.6 Hz), 7.68 (m, 3 H), 7.86 (d, 1 H, J = 8.0 Hz), 8.59 (d, 1 H, J = 5.8 Hz); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 31.3, 32.3, 34.8, 37.0, 111.4, 117.0, 120.4, 122.3, 126.7, 127.3, 127.6, 129.8, 130.3, 136.0, 141.8, 149.3, 152.3, 153.5, 160.3; FABMS: *m*/*z* (relative intensity) 333 (M^+, 100); IR (neat): 3056 cm^{-1}; Anal. Calcd for $C_{23}H_{27}NO$: C, 82.83; H, 8.17; N, 4.20. Found: C, 82.49; H, 8.20; N, 4.20.

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(30) Cozort, J. R.; Outlaw, J. F., Jr.; Hawkins, A.; Siegel, S. *J. Org. Chem.* **1983**, *48*, 4190.

(31) McOmie, J. F. W.; Watts, M. L.; West, D. E. *Tetrahedron* **1968**, *24*, 2289.

(32) (a) Holligan, B. M.; Jeffery, J. C.; Norgett, M. K.; Schatz, E.; Ward, M. D. *J. Chem. Soc., Dalton Trans.* **1992**, 3345. (b) Dietrich-Buchecker, C. O.; Sauvage, J. P. *Tetrahedron* **1990**, *46*, 503.

(33) Olah, G. A.; Narang, S. C.; Gupta, B. G. B.; Malhotra, R. *J. Org. Chem.* **1979**, *44*, 1247.