JOC Article

First Regioselective Ortho-Lithiation Induced by a 2-Chloropyridyl Group Complexation

Yves Fort* and Alain L. Rodriguez

Synthèse Organique et Réactivité, UMR CNRS-UHP 7565, Faculté des Sciences, Université Henri Poincaré-Nancy I, BP 239, 54506, Vandoeuvre-Lès-Nancy, France

yves.fort@sor.uhp-nancy.fr

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It is shown that *t*-BuLi in Et_2O promotes an exclusive regioselective metalation of 2-aryl-6-chloropyridine compounds at the aromatic ortho position demonstrating that the 2-chloropyridyl moiety may be considered as a directing group. This functionally directed metalation group was successfully used for the selective lithiation of substituted aromatics and for the straightforward preparation of new N,P ligands.

Introduction

The recognition by Hauser in 1962[1] that the dimethylaminomethyl group could facilitate the direct ortho-metalation (DoM effect)[2a] of unreactive aromatics provided the impetus for a large body of work aimed at exploiting the synthetic utility of complexing effects. Aryl, vinyl, and even unactivated alkyl compounds can be metalated when suitable chelation is provided.[2] Chelation effects have been used to prepare useful lithium compounds but also to provide structural rigidity to control the stereochemistry of the formation of lithium reagents.[3] Despite the importance of these effects, there are relatively few studies on the efficient lithiation of aromatic and heteroaromatic groups assisted by the intramolecular pyridine nitrogen atom complexation.[4] In fact, nucleophilic lithiated reagents generally attack the pyridine ring even at low temperature.[5] Singh has recently reported that 2-(3-thienyl)pyridine can be easily deprotonated at the C-α position of the thienyl ring.[6] This regioselective deprotonation was interpreted as the consequence of an intramolecular pyridyl group coordination and a strong acidity of hydrogens on the thienyl ring. A similar DoM effect of the pyridine nitrogen atom in ortho-lithiation of 2,6-diphenylpyridine and 2-alkyl-6-phenylpyridine compounds has been previously reported.[7] However, such metalations were often not selective and the absence of functionality on the pyridine ring prevented all modifications of the pyridinic structure. To the best of our knowledge, Kauffmann was the only one to report an example in a heteroaromatic series of a lithiation at the ortho position of a functional pyridyl group.[8] Nevertheless, whatever the basic system used, the metalation of 2-chloro-6-(2-thienyl)pyridine was still not selective at the C-γ position on the thienyl ring.

Herein, we describe for the first time the selective and direct mono-metalation based on the intramolecular functionalized pyridyl group complexation, thus providing a convenient access to useful synthons and new electron-releasing N,P ligands.[9]

Results and Discussion

In connection with the study of Kauffmann,[8] we introduced chlorine at the C-6 position of 2-phenylpyridine. Three sites of metalation could be envisioned for 2-chloro-6-phenylpyridine (**1**,[10] Scheme 1). At first, the 2-chloropyridyl group has the potential to act as a directing metalation group (DMG) by a complex-induced proximity effect (CIPE)[11] thereby directing lithiation to the ortho-positon of the adjacent phenyl ring. The nitro-

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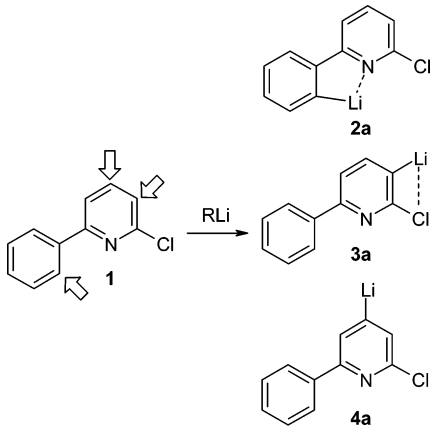
SCHEME 1



gen atom should subsequently ensure stabilization of the formed lithiated intermediate **2a**.

Nevertheless, competition could result from lithiation at the position ortho to the chlorine atom conducting to **3a**. In addition, as reported by Radinov for chloropyridine compounds,[12] a metalation at the acidic para position of the pyridinic nitrogen atom also could be considered providing the lithiated intermediate **4a**. Finally, it was hoped that the nucleophilic substitution of the chlorine atom could be avoided by use of low reaction temperature and a nonnucleophilic base.

In a preliminary study, we examined various basic reagents for the deprotonation of **1**. The selective production of the ortho-lithiated intermediate **2a** versus **3a** and **4a** was evaluated by condensation of MeSSMe as an electrophile, producing **2b**, **3b**, and **4b**, respectively (Figure 1). The main results obtained are reported in Table 1.

As expected with the nonnucleophilic lithium amides,[13] a selective metalation at the C-3 position of **1** was efficiently obtained in the presence of an excess of LiTMP in THF at −78 °C (entry 1), while no reaction was detected in Et_2O (entry 3). The same behavior was obtained with 2 equiv of *n*-BuLi in THF at −78 °C (entry 2). It must be noted that raising the temperature to only 0 °C produced traces of Cl−Bu nucleophilic substitution.

On an other hand, whereas *n*-BuLi, *s*-BuLi, MeLi, or PhLi did not work in Et_2O (entries 4−7), we were pleased to observe a selective deprotonation at the ortho position of the phenyl group with *t*-BuLi (entry 8).[14] This result is of particular interest since, to the best of our knowledge, even the well-known transition metal-catalyzed C−H bond activation with the aid of an intramolecular

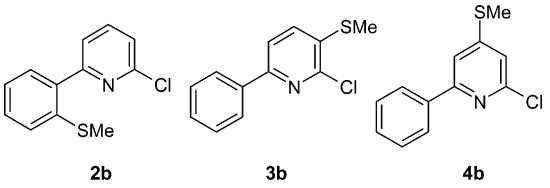


FIGURE 1.

TABLE 1. Conditions for Selective Deprotonation of 1[a]

entry	base (equiv)	solvent	conditions	result[b]
1	LiTMP (3)	THF	−78 °C, 3 h	**3b** (78)
2	*n*-BuLi (2)	THF	−78 °C, 3 h	**3b** (72)
3	LiTMP (3)	Et_2O	−78 °C, 3 h	n.r.[c]
4	*n*-BuLi (2)	Et_2O	−78 °C, 3 h	n.r.[c]
5	MeLi (1)	Et_2O	−78 °C, 3 h	n.r.[c]
6	PhLi (1)	Et_2O	−78 °C, 3 h	n.r.[c]
7	*s*-BuLi (1)	Et_2O	−78 °C, 3 h	n.r.[c]
8	*t*-BuLi (1)	Et_2O	−78 °C, 3 h	**2b** (42) **1** (36)
9	*t*-BuLi (1.4)	Et_2O/cumene[d]	−78 °C, 3 h	**2b** (62) **1** (17)
10	*t*-BuLi (1.4)	THF/cumene[e]	−78 °C, 3 h	**3b** (33) **4b** (29)

[a] All reactions performed on 1 mmol of **1**. [b] Isolated yields are given in parentheses. [c] n.r.: no reaction. [d] Et_2O/cumene ratio: 1/1 [e] THF/cumene ratio: 1/1.

chelation of the pyridyl group does not tolerate the presence of a chlorine atom on the pyridinic substrates.[15]

We next found that the use of 1.4 equiv of *t*-BuLi in a mixture of Et_2O/cumene gave the single product **2b** in 62% yield (entry 9). One portion of cumene in Et_2O increased at −78 °C the solubility of starting material, without loss of regioselectivity in the metalation. Note that, whatever the reaction time, the temperature of lithiation, and the amount of *t*-BuLi, we were unable to increase the conversion of **1**. A dramatic solvent effect was also observed in the regioselective lithiation obtained with *t*-BuLi. When the metalation was performed in THF instead of Et_2O, the desired deprotonation did not occur at all. Indeed a mixture of lithiated products at the ortho and meta position of the chlorine atom (producing **3b** and **4b**, respectively) was obtained (entry 10). The THF effect could be subsequently attributed to the inhibition of the preequilibrium complex **A** formation by external coordination (Scheme 2). Consequently, 2-chloro-6-phenylpyridine was deprotonated at the position ortho to the chlorine atom as a consequence of its DoM effect, and at the acidic para position of the pyridine ring. It then may be assumed that the complexation of the nitrogen atom is crucial for the orientation of the metalation.

To substantiate the importance of the chlorine atom in the metalation of **1**, we replaced this substituent with methoxy and 1-pyrrolidinyl to afford 2-methoxy-6-phenylpyridine (**5**) and 2-phenyl-6-(1-pyrrolidinyl)pyridine (**6**).[16] As a consequence of the methoxy group directing

(10) 2-Chloro-6-phenylpyridine (**1**) was prepared via a direct lithiation at the C-6 position of the 2-phenylpyridine with 3 equiv of the *n*-BuLi−LiDMAE superbase, see: Gros, Ph.; Fort, Y. *Eur. J. Org. Chem*. **2002**, 3375.

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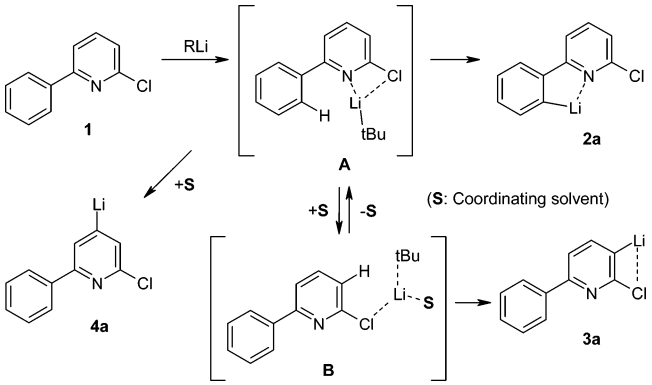
(16) A nucleophilic substitution and a *N*-arylamination by Nickel clusters catalyzed by **1** afforded respectively compounds **5** and **6**; see: (a) Desmarets, C.; Schneider, R.; Fort, Y. *Tetrahedron Lett*. **2000**, *41*, 2875. (b) Desmarets, C.; Schneider, R.; Fort, Y. *Tetrahedron Lett*. **2001**, *42*, 247. (c) Brenner, E.; Schneider, R.; Fort, Y. *Tetrahedron Lett*. **2000**, *41*, 2881. (d) Brenner, E.; Schneider, R.; Fort, Y. *Tetrahedron* **1999**, *55*, 12829.

SCHEME 2

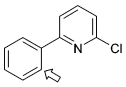
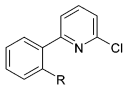
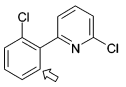
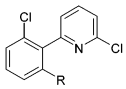
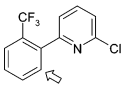
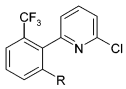
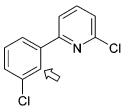
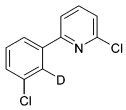


effect, *t*-BuLi efficiently accomplished in Et_2O/cumene a lithiation at the C-3 position on the pyridine ring. This result contrasted with those obtained with **1**. An explanation could be a difference of strength in lithium complexation between Cl and MeO. Since the O−Li interaction is assumed to be stronger than that of chlorine, the methoxy group more strongly competes in lithium complexation with the pyridine nitrogen than the chlorine atom. The consequence is a delivery of *tert*-butyllithium at the ortho position of the methoxy group. In the case of 2-phenyl-6-(1-pyrrolidinyl)pyridine (**6**), no reaction occurred with the addition of *t*-BuLi. This pronounced difference between **6** and **1** implies the governance of the deprotonation not only by the complex induced proximity effects but also by the acidification of hydrogens due to the presence of an electron-withdrawing chlorine atom on the pyridine ring in **1**. In addition, the steric effect could also intervene.

After determining the best conditions for selective lithiation of **1** at the ortho position of the phenyl group, we demonstrated the scope of the 2-chloropyridyl DMG by preparing a series of ortho-substituted 2-chloro-6-phenylpyridine compounds (Table 2). The versatility of our methodology was clearly demonstrated by introducing various functionalities efficiently at the ortho position (entries 4−9). Compounds **2e**−**g**,**i**,**j** were particularly attractive since they bear potentially reactive functional groups.

We also investigated the deprotonation of other related 2-aryl-6-chloropyridines (entries 10−13). As in the case of **1**, **2g**, **9**, and **11** were exclusively deprotonated at the position ortho to the 2-chloropyridyl group. This regioselective aromatic metalation involves a stronger ortho-directing effect of the 2-chloropyridyl group compared to the DoM effect of the chlorine atom[13] or to the ortho- and sometimes para-directing effects of the trifluoromethyl group (entries 10−12).[17] An additive effect between the pyridyl group and the chlorine atom can explain the observed regioselectivity with compound **11** (entry 13). The total consumption of reagents **2g**, **9**, and **11** during the lithiation could result from the acidification of hydrogens induced by the presence of electron-withdrawing groups on the phenyl ring.

TABLE 2. Selective Metallation of Chloropyridine Compounds in Et_2O/Cumene (1/1) at −78 °C with 1.4 equiv of *t*-BuLi[a]

Entry	Substrate	E^+	Product		Yield(%)[b]
					
1[c]	**1**	MeSSMe	R : SMe	**2b**	62
2[d]	**1**	MeOD	D	**2c**	76
3[c]	**1**	Me_2SO_4	Me	**2d**	45
4[c]	**1**	PhCHO	PhCHOH	**2e**	53
5[c]	**1**	(*c*-Pr)$_2$CO	(*c*-Pr)$_2$C(OH)	**2f**	55
6[c]	**1**	C_2Cl_6	Cl	**2g**	44
7[c]	**1**	Me_3SiCl	$SiMe_3$	**2h**	60
8[c]	**1**	Bu_3SnCl	$SnBu_3$	**2i**	51
9[c]	**1**	$ClPPh_2$	PPh_2	**2j**	41
					
10	**2g**	C_2Cl_6	R : Cl	**7**	69
11	**2g**	Bu_3SnCl	$SnBu_3$	**8**	76
12[e]					
	9	MeSSMe	R : SMe	**10**	89
13[f]					
	11	MeOD		**12**	84

[a] All reactions performed on 1 mmol of substrate. [b] Isolated yields after chromatography on silica gel. [c] 14−21% of **1** recovered. [d] Deuterium content: 83% (^{1}H NMR). [e] The lithiation was performed at −50 °C. [f] Deuterium content: 95% (^{1}H NMR).

We finally examined structural modifications of the pyridine ring using the C−Cl bond as a source of further functionalizations. In this context, the useful synthon **2j** led us to investigate its reactivity for the preparation of new N,P ligands. As shown in Scheme 3, according to our previous work on Nickel cluster-catalyzed arylamination,[18] the reaction of **2j** with pyrrolidine efficiently gave the new N,P,N ligand **13**. Palladium-catalyzed cross-couplings could also be performed since **2j** efficiently coupled in the presence of CsF[19] with naphthylboronic acid to produce **14** in good yield. Finally, the substitution reaction with sodium ethanethiolate in DMF afforded the new mercapto ligand **15** in good yield.

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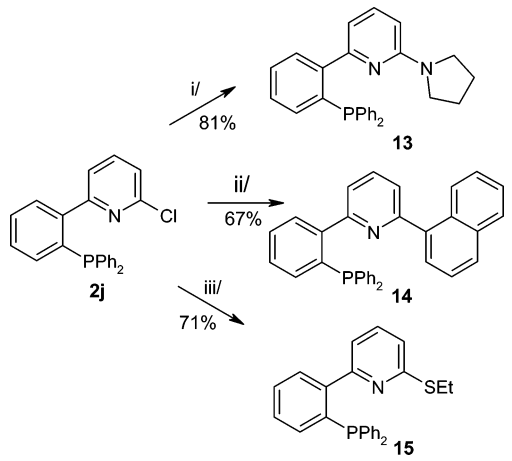
SCHEME 3[a]



[a] Reagents and conditions: (i) Pyrrolidine, 10 mol % of $Ni(OAc)_2$, NaH/t-AmONa, THF, reflux. (ii) Naphthyl-$B(OH)_2$, CsF, 10 mol % of $Pd(PPh_3)_2Cl_2$, DME, reflux. (iii) EtSNa, DMF, rt then 50 °C.

In conclusion, we have shown that the 2-chloropyridyl group may be used as a directing ortho-metalation group in an aromatic series allowing a regioselective lithiation process. Subsequent functionalization of the C−Cl bond provided an efficient method for the straightforward synthesis of useful synthons and new N,P ligands. Further investigations to extend the scope of this reaction are currently in progress.

Experimental Section

General Methods. ^1H and ^{13}C NMR spectra were recorded at 400 and 50 MHz, respectively (excepted for compound **2g**, which was recorded at 200 and 50 MHz, respectively), with $CDCl_3$ as solvent and TMS as internal standard for ^1H NMR. ^{31}P NMR spectra were recorded at 162 MHz. GC/MS (EI) spectra was recorded on a HP5871 spectrometer.

Materials and Solvents. Et_2O, THF, DME, and cumene were distilled from sodium−benzophenone and stored on sodium wire before use. DMF was distilled from calcium hydride immediately prior to use. *t*-BuLi was used as a 1.5 M solution in pentane. *n*-BuLi was used as a 1.6 M solution in hexanes. Crushed $Ni(OAc)_2 \cdot 4H_2O$ was dried under vaccum (50 mmHg) at 110 °C for 15 h. Sodium hydride (65% in mineral oil) was used after three washings with THF under nitrogen.

General Procedure for Ortho-Lithiation of 2-Aryl-6-chloropyridine. A solution of 2-chloro-6-phenylpyridine (191 mg, 1 mmol) in diethyl ether (2 mL) and cumene (2 mL) was cooled at −78 °C. *t*-BuLi (0.93 mL, 1.4 mmol) was then added dropwise under a nitrogen atmosphere. After 3 h of stirring at −78 °C, the appropriate electrophile (2 mmol) was added dropwise. The temperature was then allowed to raise to 20 °C. Hydrolysis was performed at this temperature with H_2O (5 mL). The aqueous phase was first extracted with diethyl ether (10 mL) and then with dichloromethane (10 mL). After drying ($MgSO_4$), filtration, and evaporation of solvents the crude product was purified by column chromatography on silica gel.

2-Chloro-6-[2-(methylsulfanyl)phenyl]pyridine (2b). Column chromatography (8:2 hexanes/AcOEt) yielded **2b** (146 mg, 62%) as a yellow solid, mp 69−72 °C; ^1H NMR δ_H 2.39 (s, 3H), 7.23 (td, J = 7.6 and 1.2 Hz, 1H), 7.31 (dd, J = 7.6 and 0.8 Hz, 1H), 7.34 (br d, J = 7.6 Hz, 1H), 7.39 (td, J = 7.6 and 1.2 Hz, 1H), 7.44 (dd, J = 7.6 and 1.2 Hz, 1H), 7.51 (br d, J = 7.6 Hz, 1H), 7.72 (t, J = 7.6 Hz, 1H); ^{13}C NMR δ_C 16.5, 122.6, 122.7, 125.0, 126.3, 129.3, 130.0, 137.4, 138.2, 138.6, 150.6, 158.7. MS (EI) *m*/*z* 237 (2), 235 (55), 222 (34), 220 (100), 200 (4), 184 (19). Anal. Calcd for $C_{12}H_{10}ClNS$: C, 61.14; H, 4.28; N, 5.94. Found: C, 60.89; H, 4.52; N, 6.05.

2-Chloro-6-(2-deuteriophenyl)pyridine (2c). Column chromatography (9:1 hexanes/AcOEt) yielded **2c** (144 mg, 76%, deuterium content: 83%) as a white solid, mp 36−38 °C; ^1H NMR δ_H 7.23 (dd, J = 7.6 and 1.0 Hz, 1H), 7.41−7.46 (m, 3H), 7.62 (dd, J = 7.7 and 1.0 Hz, 1H), 7.67 (t, J = 7.8 Hz, 1H), 7.98 (br d, J = 7.5 Hz, 1H); ^{13}C NMR δ_C 118.5, 122.4, 126.8, 128.6, 129.6, 137.5, 139.1, 151.1, 157.9. MS (EI) *m*/*z* 192 (34), 191 (44), 190 (100), 155 (49), 128 (29). Anal. Calcd for $C_{11}DH_7ClN$: C, 69.30; H, 3.70; N, 7.35. Found: C, 69.14; H, 4.41; N, 7.24.

2-Chloro-6-(2-methylphenyl)pyridine (2d). Column chromatography (9:1 hexanes/AcOEt) yielded **2d** (92 mg, 45%) as a pale oil; ^1H NMR δ_H 2.30 (s, 3H), 7.28−7.34 (m, 4H), 7.35 (d, J = 7.6 Hz, 1H), 7.41 (br d, J = 7.2 Hz, 1H), 7.73 (t, J = 7.6 Hz, 1H); ^{13}C NMR δ_C 20.4, 122.3, 122.6, 126.1, 128.8, 129.8, 131.0, 136.0, 138.9, 139.0, 150.8, 160.7. MS (EI) *m*/*z* 205 (14), 204 (36), 203 (46), 202 (100), 168 (21), 167 (26), 166 (22). Anal. Calcd for $C_{12}H_{10}ClN$: C, 70.77; H, 4.95; N, 6.88. Found: C, 70.58; H, 4.74; N, 6.73.

[2-(6-Chloro-2-pyridinyl)phenyl](phenyl)methanol (2e). Column chromatography (8:2 hexanes/AcOEt) yielded **2e** (157 mg, 53%) as a pale oil; ^1H NMR δ_H 5.86 (br s, 2H), 7.14 (br t, J = 7.2 Hz, 1H), 7.21 (d, J = 8.0 Hz, 1H), 7.24, (t, J = 7.2 Hz, 2H), 7.27 (br d, J = 7.6 Hz, 2H), 7.32 (d, J = 7.6 Hz, 1H), 7.35−7.37 (m, 1H), 7.40−7.43 (m, 2H), 7.45−7.47 (m, 1H), 7.65 (t, J = 7.6 Hz, 1H); ^{13}C NMR δ_C 74.2, 122.3, 122.4, 126.1, 126.5, 127.6, 127.9, 129.6, 130.4, 130.5, 138.3, 139.7, 143.6, 149.5, 160.2. MS (EI) *m*/*z* 297 (33), 296 (33), 295 (100), 260 (5), 241 (52), 218 (32), 216 (32). Anal. Calcd for $C_{18}H_{14}ClNO$: C, 73.10; H, 4.77; N, 4.74. Found: C, 73.29; H, 4.61; N, 4.45.

[2-(6-Chloro-2-pyridinyl)phenyl](dicyclopropyl)-methanol (2f). Column chromatography (8:2 hexanes/AcOEt) yielded **2f** (155 mg, 55%) as an orange solid, mp 104−106 °C; ^1H NMR δ_H 0.24−0.29 (m, 2H), 0.30−0.39 (m, 2H), 0.41−0.47 (m, 2H), 0.60−0.66 (m, 2H), 1.04−1.11 (m, 2H), 7.28 (dd, J = 7.6 and 1.2 Hz, 1H), 7.32 (d, J = 8.0 Hz, 1H), 7.36 (dd, J = 7.6 and 0.8 Hz, 1H), 7.43 (d, J = 8.0 Hz, 1H), 7.46 (td, J = 8.0 and 1.2 Hz, 1H), 7.77 (t, J = 7.6 Hz, 1H), 8.08 (dd, J = 8.0 and 0.8 Hz, 1H); ^{13}C NMR δ_C 1.5, 2.1, 21.2, 73.0, 122.1, 123.0, 126.6, 127.7, 128.6, 132.2, 138.4, 139.6, 147.4, 149.1, 163.9. MS (EI) *m*/*z* 284 (1), 282 (3), 260 (32), 259 (17), 258 (100), 216 (30). Anal. Calcd for $C_{18}H_{18}ClNO$: C, 72.11; H, 6.05; N, 4.67. Found: C, 72.15; H, 6.17; N, 4.69.

2-Chloro-6-(2-chlorophenyl)pyridine (2g). Column chromatography (8:2 hexanes/CH_2Cl_2) yielded **2g** (99 mg, 44%) as a yellow oil; ^1H NMR δ_H 7.30 (dd, J = 8.4 and 2.0 Hz, 1H), 7.32−7.36 (m, 2H), 7.43−7.48 (m, 1H), 7.56−7.63 (m, 2H), 7.70 (t, J = 8.0 Hz, 1H); ^{13}C NMR δ_C 122.9, 123.3, 127.0, 129.9, 130.1, 131.6, 132.0, 137.6, 138.4, 150.9, 157.1. MS (EI) *m*/*z* 227 (7), 226 (5), 225 (43), 223 (66), 190 (32), 188 (100). Anal. Calcd for $C_{11}H_7Cl_2N$: C, 58.96; H, 3.15; N, 6.25. Found: C, 58.74; H, 3.42; N, 6.07.

2-Chloro-6-[(2-trimethylsilyl)phenyl]pyridine (2h). Hydrolysis was performed with a 2 M aqueous solution of NaOH. Column chromatography (9:1 hexanes/AcOEt) yielded **2h** (157 mg, 60%) as a yellow oil; ^1H NMR δ_H 0.13 (s, 9H), 7.33 (d, J = 7.6 Hz, 1H), 7.46−7.50 (m, 4H), 7.73 (t, J = 7.6 Hz, 1H), 7.77−7.79 (m, 1H); ^{13}C NMR δ_C 0.7, 121.3, 122.4, 127.9, 128.7, 128.8, 135.6, 139.0, 139.8, 145.3, 150.4, 162.1. MS (EI) *m*/*z* 262 (1), 248 (36), 247 (20), 246 (100), 216 (2). Anal. Calcd for $C_{14}H_{16}ClNSi$: C, 64.22; H, 6.16; N, 5.35. Found: C, 64.16; H, 6.12; N, 5.33.

2-Chloro-6-[(2-tributylstannyl)phenyl]pyridine (2i). Column chromatography (9:1 hexanes/AcOEt) yielded **2i** (243 mg, 51%) as a pale oil; ^1H NMR δ_H 0.81 (t, J = 7.2 Hz, 9H), 0.97−0.99 (m, 6H), 1.22−1.29 (m, 6H), 1.36−1.42 (m, 6H), 7.25 (dd, J = 7.8 and 0.6 Hz, 1H), 7.37−7.40 (m, 2H), 7.59 (d, J = 7.2 and 0.6 Hz, 1H), 7.67−7.71 (m, 3H); ^{13}C NMR δ_C 11.8, 13.6, 27.4, 29.1, 120.0, 122.4, 127.7, 128.2, 128.3, 137.8, 139.2, 143.4,

144.2, 150.8, 161.1. Anal. Calcd for $C_{23}H_{34}ClNSn$: C, 57.71; H, 7.16; N, 2.93. Found: C, 57.38; H, 7.39; N, 2.72.

2-Chloro-6-[2-(diphenylphosphino)phenyl]pyridine (2j). The reaction was treated with 1.4 mmol of $ClPPh_2$. Column chromatography (7:3 benzene/hexanes) yielded **2j** (157 mg, 41%) as a yellow viscous oil; ^{1}H NMR δ_H 7.11 (br dd, J = 7.6 and 4.0 Hz, 1H), 7.15 (d, J = 7.6 Hz, 1H), 7.25−7.37 (m, 12H), 7.42 (td, J = 7.6 and 1.2 Hz, 1H), 7.52 (t, J = 7.6 Hz, 1H), 7.58 (ddd, J = 7.6, 4.4 and 1.2 Hz, 1H); ^{13}C NMR δ_C 122.4, 122.5, 128.2, 128.3, 128.4, 128.7, 129.7, 133.9, 134.1, 137.2, 137.6, 138.1, 144.0, 150.3, 159.4; ^{31}P NMR δ_P −13.4. MS (EI) *m*/*z* 375 (4), 374 (7), 373 (15), 298 (33), 297 (32), 296 (100), 221 (3), 220 (5), 219 (11).

2-Chloro-6-(2,6-dichlorophenyl)pyridine (7). Column chromatography (8:2 hexanes/CH_2Cl_2) yielded **7** (179 mg, 69%) as a pale oil; ^{1}H NMR δ_H 7.17 (d, J = 8.0 Hz, 1H), 7.18 (t, J = 8.0 Hz, 1H), 7.28 (dd, J = 8.0 and 0.8 Hz, 1H), 7.29 (br d, J = 8.0 Hz, 2H), 7.68, (t, J = 8.0 Hz, 1H); ^{13}C NMR δ_C 123.76, 123.78, 128.2, 130.3, 134.6, 137.1, 139.1, 151.1, 155.7. MS (EI) *m*/*z* 259 (34), 257 (37), 224 (63), 222 (100), 187 (32). Anal. Calcd for $C_{11}H_6Cl_3N$: C, 51.10; H, 2.34; N, 5.42. Found: C, 51.42; H, 2.57; N, 5.32.

2-Chloro-6-[2-chloro-6-(tributylstannyl)phenyl]pyridine (8). Column chromatography (8:2 hexanes/CH_2Cl_2) yielded **8** (389 mg, 76%) as a pale oil; ^{1}H NMR δ_H 0.74−0.78 (m, 6H), 0.83 (t, J = 7.2 Hz, 9H), 1.21−1.28 (m, 6H), 1.33−1.41 (m, 6H), 7.27 (dd, J = 7.6 and 7.2 Hz, 1H), 7.31 (dd, J = 7.6 and 0.8 Hz, 1H), 7.38 (dd, J = 7.6 and 1.2 Hz, 1H), 7.48 (br d, J = 7.2 Hz, 2H), 7.68 (t, J = 7.6 Hz, 1H); ^{13}C NMR δ_C 10.9, 13.6, 27.3, 29.0, 123.1, 124.5, 129.1, 129.8, 133.0, 135.4, 138.1, 144.0, 147.1, 151.3, 159.9. Anal. Calcd for $C_{23}H_{33}Cl_2NSn$: C, 53.84; H, 6.48; N, 2.73.: Found: C, 53.65; H, 6.58; N, 2.82.

2-Chloro-6-[2-(methylsulfanyl)-6-(trifluoromethyl)-phenyl]pyridine (10). Column chromatography (8:2 hexanes/CH_2Cl_2) yielded **10** (271 mg, 89%) as a yellow oil; ^{1}H NMR δ_H 2.36 (s, 3H), 7.25 (br d, J = 7.6 Hz, 1H), 7.36 (dd, J = 8.0 and 0.8 Hz, 1H), 7.46 (d, J = 2.8 Hz, 1H), 7.47 (d, J = 6.4 Hz, 1H), 7.52 (br dd, J = 6.4 and 2.8 Hz, 1H), 7.73 (t, J = 7.6 Hz, 1H); ^{13}C NMR δ_C 16.1, 122.3 (CH, J_{C-F} = 5.3 Hz), 123.6 (CF_3, J_{C-F} = 273.9 Hz), 123.7, 123.8 (CH, J_{C-F} = 1.5 Hz), 128.6, 129.1, 129.2 (C_q, J_{C-F} = 30.5 Hz), 131.8, 136.1 (broad signal), 138.8, 141.1, 150.8, 155.9. MS (EI) *m*/*z* 303 (2), 290 (35), 288 (100), 268 (18).

2-Chloro-6-[2-deuterio-3-chlorophenyl]pyridine (12). Column chromatography (8:2 hexanes/CH_2Cl_2) yielded **12** (189 mg, 84%, deuterium content: 95%) as a white solid, mp 90−92 °C; ^{1}H NMR δ_H 7.27 (dd, J = 7.8 and 0.7 Hz, 1H), 7.38 (d, J = 3.8 Hz, 1H), 7.39 (d, J = 5.0 Hz, 1H), 7.60 (dd, J = 7.8 and 0.8 Hz, 1H), 7.70 (t, J = 7.8 Hz, 1H), 7.85 (dd, J = 4.9 and 4.0 Hz, 1H); ^{13}C NMR δ_C 118.7, 123.2, 125.0, 126.9, 129.6, 130.0, 134.9, 139.5, 151.5, 156.4. MS (EI) *m*/*z* 226 (63), 224 (100), 191 (28), 189 (57), 154 (31). Anal. Calcd for $C_{11}DH_6Cl_2N$: C, 57.11; H, 7.19; N, 16.65. Found: C, 57.40; H, 7.16; N, 16.26.

2-[2-(Diphenylphosphino)phenyl]-6-(1-pyrrolidinyl)-pyridine (13). A solution of *t*-AmOH (36 mg, 0.4 mmol) and pyrrolidine (284 mg, 4 mmol) in THF (1 mL) was added to a suspension of NaH (62 mg, 2.6 mmol) in THF (3 mL) and the mixture was heated to 63 °C. 2,2′-Bipyridine (94 mg, 0.6 mmol) was added followed by dried $Ni(OAc)_2$ (36 mg, 0.2 mmol) and the reflux was maintained for 1.5 h. To the dark suspension thus obtained was added a solution of chloropyridine (**2j**, 374 mg, 1 mmol) and styrene (21 mg, 0.2 mmol) in THF (0.5 mL) and the mixture was heated for 5 h. After cooling at room temperature, hydrolysis with water (1 mL), and dilution with ether, the mixture was filtered, dried ($MgSO_4$), and concentrated. The crude material was purified by chromatography on silica gel (7:3 benzene/hexanes, then benzene) to yield **13** (320 mg, 81%) as a viscous oil. ^{1}H NMR δ_H 1.71−1.78 (m, 4H), 3.02−3.08 (m, 4H), 6.21 (d, J = 8.4 Hz, 1H), 6.66 (d, J = 8.4 Hz, 1H), 7.07 (ddd, J = 7.7, 4.0, and 1.2 Hz, 1H), 7.21−7.30 (m, 11H), 7.33 (td, J = 7.5 and 1.2 Hz, 1H), 7.40 (t, J = 8.4 Hz, 1H), 7.60 (ddd, J = 7.5, 4.3, and 1.2 Hz, 1H); ^{13}C NMR δ_C 25.5, 46.4, 104.7, 111.5, 127.9, 128.0, 128.1, 128.7, 129.6, 133.9, 135.4, 135.5, 136.9, 139.6, 147.8, 148.3, 156.4, 158.2; ^{31}P NMR δ_P −14.5. MS (EI) *m*/*z* 408 ($M^{\bullet+}$, 10), 331 (100), 332 (25), 204 (11), 183 (10).

2-[2-(Diphenylphosphino)phenyl]-6-(1-naphthyl)pyridine (14). A mixture of chloropyridine **2j** (185 mg, 0.5 mmol), $Pd(PPh_3)_2Cl_2$ (35 mg, 0.05 mmol), and PPh_3 (24 mg, 0.1 mmol) in DME (2 mL)was warmed to form a yellow solution. Naphthylboronic acid (130 mg, 0.75 mmol) and CsF (222 mg, 1.5 mmol) were added and the mixture heated under reflux overnight. After the solution was cooled to room temperature, water (5 mL) and CH_2Cl_2 (10 mL) were added, the organic layer was separated, and the aqueous layer was extracted twice with CH_2Cl_2 (20 mL). The combined organic layers were washed with brine, dried ($MgSO_4$), and evaporated. The crude product was purified by flash chromotography on silica gel (7:3 benzene/hexanes) to yield **14** (155 mg, 67%) as a viscous oil. ^{1}H NMR δ_H 7.08 (ddd, J = 8.0, 4.0, and 0.8 Hz, 1H), 7.17−7.21 (m, 10H), 7.27 (td, J = 7.6 and 1.2 Hz, 1H), 7.32−7.37 (m, 1H), 7.40−7.44 (m, 5H), 7.48 (dd, J = 7.6 and 0.8 Hz, 1H), 7.68 (ddd, J = 7.6, 4.4, and 1.2 Hz, 1H), 7.71 (t, J = 8.0 Hz, 1H), 7.82 (dd, J = 6.8 and 2.0 Hz, 1H), 7.80 (br d, J = 8.4 Hz, 1H), 7.96 (d, J = 8.4 Hz, 1H); ^{13}C NMR δ_C 122.5, 123.3, 125.3, 125.6, 125.8, 126.1, 127.6, 128.1, 128.2, 128.3, 128.4, 128.8, 129.8, 131.2, 133.8, 134.7, 135.8, 135.9, 138.0, 138.4, 146.1, 146.6, 158.1, 159.0; ^{31}P NMR δ_P −14.0.

2-[2-(Diphenylphosphino)phenyl]-6-(ethylsulfanyl)pyridine (15). Sodium ethanethiolate (310 mg, 5 mmol) was added to a stirred solution of chloropyridine **2j** (186 mg, 0.5 mmol) in DMF (2 mL) kept under a nitrogen atmosphere. After 48 h of stirring at room temperature, the reaction medium was heated at 50 °C (1.5 h). After being cooled at room temperature, the reaction mixture was poured on water and extracted with CH_2Cl_2 (20 mL). The combined organic layers were washed with water, dried ($MgSO_4$), and evaporated. The residue was chromatographed on silica gel (7:3 benzene/hexanes, then benzene) to yield **15** (140 mg, 71%) as a viscous oil. ^{1}H NMR δ_H 1.12 (t, J = 7.2 Hz, 3H), 2.73 (q, J = 7.2 Hz, 2H), 7.02 (d, J = 8.0 Hz, 1H), 7.08 (d, J = 7.6, Hz, 1H), 7.10 (ddd, J = 7.6, 4.0, and 0.8 Hz, 1H), 7.23−7.35 (m, 12H), 7.41 (t, J = 8.0 Hz, 1H), 7.56 (ddd, J = 7.6, 4.4, and 1.2 Hz, 1H); ^{13}C NMR δ_C 14.5, 23.9, 119.8, 120.3, 128.2, 128.3, 128.7, 129.7, 133.8, 135.0, 135.6, 146.3, 146.9, 158.4, 159.3; ^{31}P NMR δ_P −14.6. MS (EI) *m*/*z* 399 ($M^{+\cdot}$, 2), 370 (100), 322 (16), 292 (11), 260 (14), 216 (16).

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Supporting Information Available: ^{1}H and ^{13}C NMR spectra for all the new compounds **2j**, **13**, **14**, and **15**. This material is available free of charge via the Internet at http://pubs.acs.org.

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