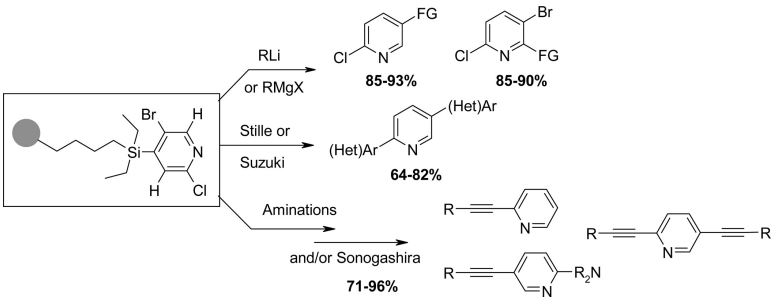
JOURNAL OF combinatorial CHEMISTRY

Article

Solid Phase Synthesis of Pyridine-Based Derivatives from a 2-Chloro-5-Bromopyridine Scaffold

Philippe Pierrat, Philippe C. Gros, and Yves Fort

J. Comb. Chem., **2005**, 7 (6), 879-886• DOI: 10.1021/cc050054a • Publication Date (Web): 18 August 2005



More About This Article

Additional resources and features associated with this article are available within the HTML version:

- Supporting Information
- Access to high resolution figures
- Links to articles and content related to this article
- Copyright permission to reproduce figures and/or text from this article

View the Full Text HTML

Journal of Combinatorial Chemistry is published by the American Chemical Society.
1155 Sixteenth Street N.W., Washington, DC 20036

Solid Phase Synthesis of Pyridine-Based Derivatives from a 2-Chloro-5-Bromopyridine Scaffold

Philippe Pierrat, Philippe C. Gros,* and Yves Fort

Synthèse Organométallique et Réactivité, UMR 7565, Faculté des Sciences, Université Henri Poincaré, Boulevard des Aiguillettes, BP 239, 54506 Vandoeuvre-lès-Nancy, France

Received April 27, 2005

2-Chloro-5-bromopyridine was immobilized on polystyrene via selective introduction of a traceless silicon linker at the C-4 position. A useful scaffold was thus obtained, as demonstrated by efficient and selective reactions with polar and transition organometallic reagents, opening a new access to pyridine-based libraries of synthons and chromophores.

The need for acceleration of drug and material discovery has urged chemists to design fast and efficient processes to obtain highly diversely functionalized compounds. In this context, the solid-phase modification of immobilized scaffolds has emerged as a powerful methodology for the automated production of small molecule libraries.[1] Functional pyridines are important compounds involved in many application fields. Although pyridine libraries have been prepared in solution,[2] only a few examples have been reported on the solid phase,[3] which may be due to a lack of selective methodologies for the clean binding and the traceless cleavage of the sensitive pyridine units. 2,5-Disubstituted pyridines are of particular interest due to their applications in the pharmaceutical[4] and nonlinear optics[5] fields. As a potential starting scaffold, 2-chloro-5-bromopyridine displays numerous reactive sites for diversity introduction via a wide range of chemical transformations, such as metal−halogen exchanges, ortholithiations, organometallic couplings, or S_NAr (Figure 1).[6] Moreover, the C−Br and the C−Cl bonds could be expected to react differently toward nucleophiles or under metal catalysis. Thus, we decided to study the reactivity of such a valuable potent scaffold for the preparation of functional pyridine libraries, and we focused our attention on polystyrene-bound 2-chloro-5-bromopyridine **B** (Figure 1).

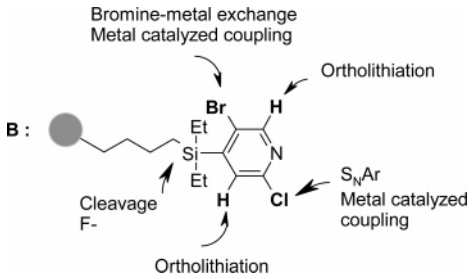
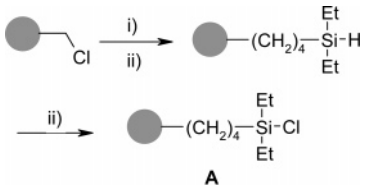


Figure 1. Potential reactive sites in immobilized 2-chloro-5-bromopyridine.

We opted for a silicon-based traceless linker,[7] since it was known to be stable under a wide range of conditions and easily cleaved with fluoride anions. In addition, the silicon may act as a protecting group of the C-4 position of the pyridine ring. Thus, the chlorosilyl resin **A** was first prepared using the procedure of Porco and Hu[4c] (Scheme 1). After reaction of the Merrifield resin (2% DVB cross-linked) with allylmagnesium chloride, rhodium-catalyzed hydrosilylation with diethylsilane followed by chlorination with chlorohydantoin gave **A** in good yield.[8]

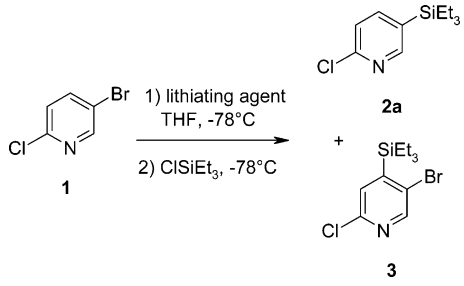
Then, we had to prepare selectively the 4-lithio-2-chloro-5-bromopyridine to introduce the silyl resin at C-4. Taking into account the acidity of H-4, its deprotonation could compete with the usual bromine−lithium exchange and lead

Scheme 1. Preparation of Chlorosilyl Resin **A**[a]



[a] (i) AllylMgCl (2.5 equiv), toluene, 60 °C, 12 h. (ii) $RhCl(PPh_3)_3$ (0.4%), Et_2SiH_2 (2.5 equiv), N_2, r.t., 12 h. (iii) 1,3-Dichloro-5,5-dimethylhydantoin (3 equiv), N_2, CH_2Cl_2, r.t., 1.5 h.

Table 1. Selective Introduction of a Silyl Group at C-4 in **1**



lithiating agent (equiv)	*t* (min)	**2a** (%)[a]	**3** (%)[a]
LTMP (3.2)	60	-	80[b]
n-BuLi (1.2)	30	90	
s-BuLi (1)	30		75[c]
t-BuLi (1)	5		78[c]

[a] Isolated yields after column chromatography. [b] The reaction was incomplete. [c] GC yield > 99%, loss of material upon isolation due to partial instability.

* To whom correspondence should be addressed. E-mail: Philippe.Gros@sor.uhp-nancy.fr.

10.1021/cc050054a CCC: $30.25
Published on Web 08/18/2005

Scheme 2. Preparation of Resin **B**

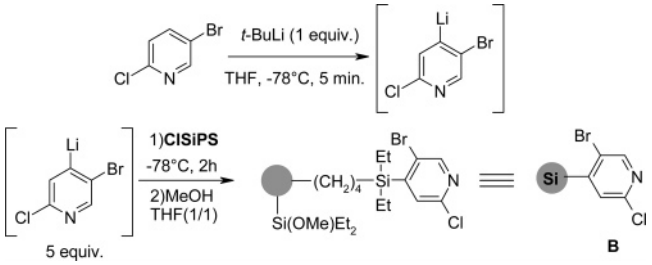
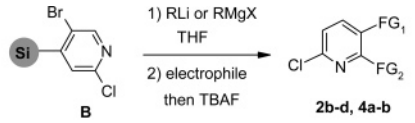
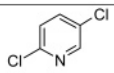
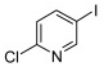
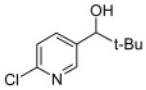
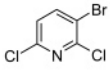
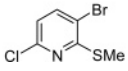


Table 2. Reaction of **B** with Polar Organometallic Reagents



Entry	Reagent	Electrophile	Product		Purity after cleavage%[a]	Isolated yield%[b]
1[c]	BuLi	C_2Cl_6		**2b**	93	85
2[c]	BuLi	I_2		**2c**	90	90
3[d]	iPrMgCl	t-BuCHO		**2d**	90	93
5[e]	LDA	C_2Cl_6		**4a**	89	85
6[e]	LDA	MeSSMe		**4b**	91	90

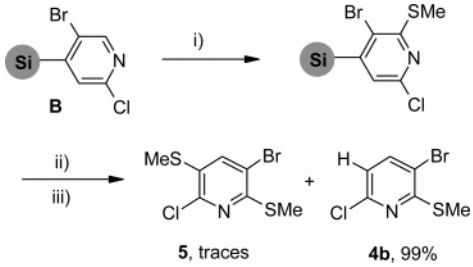
[a] Purity determined by GC/MS after cleavage from the support with TBAF (4 equiv) in THF for 1 h and filtration through a pad of silica. [b] Isolated yield after column chromatography (calculated from loading of **B**). [c] BuLi (4 equiv), −78 °C, 3 h then electrophile (4 equiv), −78 °C. [d] ^{i}PrMgCl (8 equiv), r.t., 8 h then *t*-BuCHO (10 equiv). [e] LDA (6 equiv), −78 °C, 3 h then electrophile (8 equiv), −78 °C.

to silylation at C-4, so 2-chloro-5-bromopyridine **1** was reacted with a range of lithium agents, and the medium was quenched with $ClSiEt_3$ to mimic further reaction with **A** (Table 1).

As shown, branched alkyllithiums gave the clean lithiation at C-4 instead of the classical bromine−lithium exchange. In addition, although 3.2 equiv of LTMP was necessary, a stoichiometric amount of *t*-BuLi promoted complete C-4 silylation in a very short contact time.[9] Such reaction was found to be the cleanest way for substrate immobilization, avoiding all competitive consumption of chlorosilyl moieties during the grafting step. Thus, 4-lithio-2-chloro-5-bromopyridines were first generated with *t*-BuLi and reacted with **A**, yielding the expected resin **B**. Residual chlorosilanes were consumed by methanolysis (Scheme 2). Elemental analysis (nitrogen content) indicated a loading of 1.4 mmol/g (70% yield for four steps from Merrifield resin). The treatment of **B** with TBAF in THF yielded 2-chloro-5-bromopyridine **1** quantitatively.[10]

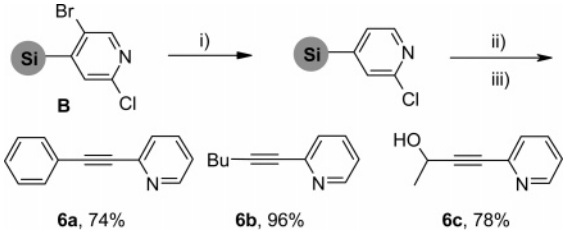
Then we turned to the chemical modifications of the immobilized scaffold. We first studied the reaction with lithium and magnesium reagents. We investigated the

Scheme 3. Attempted Sequential Ortholithiation of **B**[a]



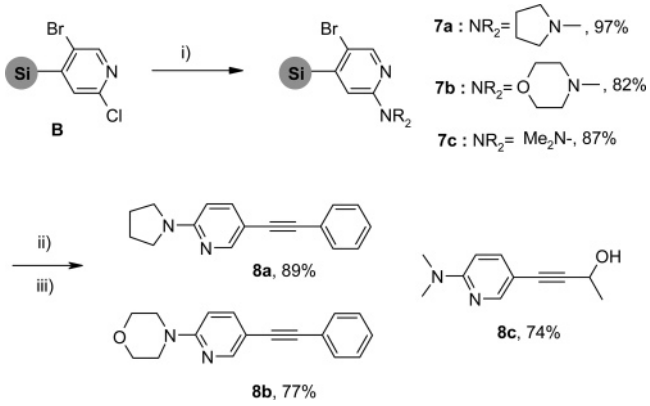
[a] (i) LDA (5 equiv) or LTMP (5 equiv), −78 °C, THF, 3 h then MeSSMe (4 equiv), −78 °C. (ii) Same as i. (iii) TBAF, THF.

Scheme 4. Preparation Monoalkynylpyridines[a]



[a] (i) BuLi (4equiv), −78 °C, 3 h then H_2O (4 equiv), −78 °C to r.t. (ii) Alkyne (2 equiv), 5% $PdCl_2(PPh_3)_2$, 10% CuI, Et_3N (2 equiv), DMF reflux, 12h. (iii) TBAF (4 equiv), THF, r.t., 4 h.

Scheme 5. Preparation of Aminopyridyl Alkynes[a]

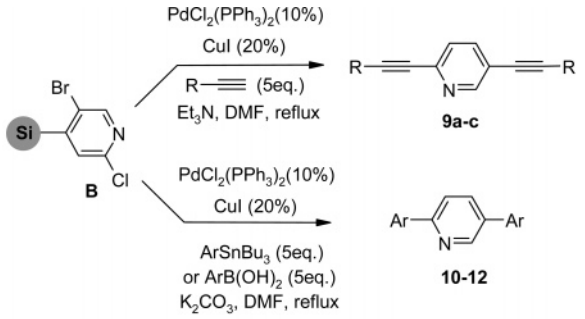


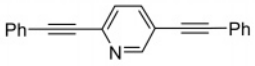
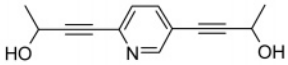
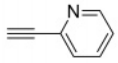
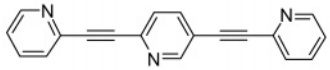
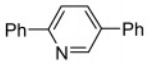
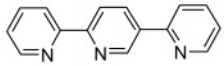
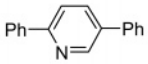
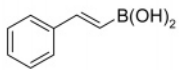
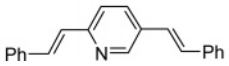
[a] (i) Pyrrolidine or morpholine or benzylamine (5 equiv), DMF, 100 °C, overnight. (ii) Phenylacetylene (2 equiv) or 2-butynol (2 equiv) for **8c**, $PdCl_2(PPh_3)_2$ (5%), CuI (10%.), piperidine reflux, 24 h. (iii) TBAF (4 equiv), THF, r.t., 2 h.

bromine-metal exchange and the ortholithiation (Table 2). Clean reactions were obtained, and the substrate was quantitatively metalated in each case. Bromine−lithium exchange afforded 2,5-disubstituted pyridines in high yield and purity using 4 equiv of *n*-BuLi. The magnesation with ^{i}PrMgCl led to the expected pyridylcarbinol in high yield; however, although the reaction could be conveniently run at room temperature, 8 equiv was required to complete the exchange. A high selectivity was obtained by reaction with LDA. As expected, the silane acted as a protecting group for the C-4 position, and lithiation occurred at the more acidic and less hindered position, that is, alpha to nitrogen, providing a clean source of 2,3,6-trisubstituted derivatives.

We then investigated the abstraction of the residual H-3 proton, exploiting the orthodirecting power of the chlorine atom, so reaction of entry 6 was repeated, omitting the cleavage step. After filtration, washing, and drying, the resin was subsequently reacted with LDA or with the more basic

Table 3. Preparation of 2,5-Disubstituted Pyridines



Entry	Reagents	Product		Purity after cleavage[a]	Isolated yield%[b]
1[d]			**9a**	91	65
2[d]			**9b**	87	76
3[d]			**9c**	88	71
4[b]	$PhSnBu_3$		**10**	91	82
5[b]	$2\text{-}PyrSnBu_3$		**11**	87	76
6[c]	$PhB(OH)_2$		**10**	88	64
7[c]			**12**	89	69

[a] Purity determined by GC/MS after cleavage from the support with TBAF (4 equiv) in THF for 1 h and filtration through a pad of silica. [b] Isolated yield after column chromatography (calculated from loading of **B**).

LTMP and quenched with MeSSMe (Scheme 3). Unfortunately, the expected tetrasubstituted product **3** was only detected in trace amount by GC/MS, and **2b** was obtained in 99% yield, even using large excesses of base or extended reaction times. An explanation could be the steric hindrance generated by the silyl group of the linker impeding the approach of the hindered lithiating agents. Indeed, a deuteration experiment with MeOD as electrophile did not reveal any detectable incorporation of deuterium (^{1}H NMR), indicating the absence of metalation.

We next investigated the reactivity of the C−Cl bond. We first examined the ability of the template to give 2-alkynylpyridines. The C−Br bond which was necessary for the immobilization step (Scheme 2) had to be first reduced. **B** was thus treated with *n*-BuLi under the conditions of Table 2 (entry 1), followed by hydrolysis. An intermediate cleavage revealed the quantitative reduction. The resin was then submitted to a range of Sonogashira couplings, which occurred quantitatively, leading to the expected compounds **6a**−**c** in good yields (Scheme 4).

Due to the numerous applications of aminopyridines, especially in the pharmaceutical field, the ability of the starting scaffold to react with amines was examined. The C−Cl bond was found to be sufficiently electrophilic to react selectively with amines, avoiding competitive reaction with the C−Br bond and use of Pd or Ni-catalysts, so **B** was simply heated in DMF in the presence of an excess of the appropriate amine. After cleavage, the corresponding aminopyridines were obtained in excellent yields (Scheme 5). Interestingly, reaction with benzylamine led to dimethylamino pyridine **7c** instead of the expected introduction of a benzylamino group. This could be explained by a prior reaction of benzylamine with DMF leading to formation of dimethylamine, which then reacted with the C−Cl bond.[11]

The available C−Br bond was then subjected to a Sonogashira coupling to prepare a range of chromophores.[3b] The reaction was first attempted under classical Pd-catalyzed conditions in DMF with Et_3N as a base, and no coupling was observed, so the reaction was performed using piperidine as solvent and base to avoid probable palladium complexation by immobilized aminopyridines. Under these conditions, clean couplings occurred, providing **8a**−**c** in high overall yields and purities (90−91%). This good result also revealed the ability of piperidine to swell the polystyrene resin, which is not usual for secondary amines.

Then we examined the reactivity of C−Cl and C−Br bonds in Sonogashira, Suzuki, and Stille couplings. Exploratory experiments rapidly showed that both the bonds exhibited similar reactivity. Whatever the conditions used to attempt monofunctionalization, a significant amount of

disubstituted product (7−45%) was obtained in addition to the two monosubstituted derivatives. We then decided to focus on the preparation of 2,5-disubstituted compounds by using an excess of the coupling partner (5 equiv) (Table 3). Under these conditions, the two halogens were substituted quantitatively, leading to the expected products in good yields and purities.

Conclusion

We have demonstrated that 2-chloro-5-bromopyridine immobilized on a Merrifield resin is a versatile scaffold, especially for preparation of diverse pyridine-based compounds, such as polyhalogenated synthons and conjugated chromophores, potentially active for nonlinear optics. Organometallic reagents were found to be efficient tools, providing cleanly functional products in high yields and purities. Taking into account an increasing demand for polyfunctional pyridine libraries, many works still have to be carried out to design and investigate the reactivity of new heterocyclic scaffolds on the solid phase.

Experimental Section

Procedure for the Selective C-4 Silylation of 1. A solution of 2-chloro-5-bromopyridine **1** (386 mg, 2 mmol) in THF (6 mL) was cooled to −78 °C, and *t*-BuLi (1.17 mL, 2 mmol) was added dropwise under nitrogen. After 5 min at −78 °C, the brown solution was treated with a solution of triethylchlorosilane (3 mmol, 0.55 mL) in THF (4 mL). After 1 h at −78 °C, the reaction medium was allowed to warm to room temperature and stirred for 1 h. The mixture was finally hydrolyzed at 0 °C with H_2O (10 mL). The aqueous layer was then extracted with ether, and the organic layer was dried ($MgSO_4$). After evaporation of the solvents under reduced pressure, the crude product was purified by column chromatography using hexane/AcOEt (90:10) as eluents, yielding silane **3** (477 mg, 78%) as a colorless oil. ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 0.96$ (bs, 15 H), 7.28 (s, 1H), 8.42 (s, 1H). ^{13}C NMR (50 MHz, $CDCl_3$): $\delta = 2.4$, 6.9, 126.3, 131.4, 149.8, 150.7, 150.2. GC/MS (EI) *m*/*z* (%): 278 (24.5), 276 (20.1), 250 (20), 248 (16), 224 (19.4), 222 (69), 220 (55.6), 168 (13.1), 140 (22.9), 109 (49), 104 (100), 77 (77.8), 63 (61), 53 (34). Anal. Calcd for $C_{11}H_{17}$BrClNSi: C, 43.08; H, 5.59; N, 4.57. Found: C, 42.97; H, 5.48; N, 4.51.

Preparation of Resin B. A dry 250-mL, three-necked flask was charged with 10 g of Merrifield resin (Merrifield's peptide resin, 2% cross-linked DVB, 2 mmol of Cl/g, 20 mmol) and purged with argon for 20 min. After introduction of anhydrous toluene (80 mL), the suspension was stirred for 5 min to swell the resin. Allylmagnesium chloride (25 mL, 2.0 M in THF, 50 mmol) was then added slowly via a syringe, and the reaction mixture was stirred at room temperature for 30 min. The suspension was then heated to 60 °C for 12 h, and the mixture was allowed to cool to room temperature. The resin was then filtered, washed with THF (100 mL), and transferred into a reactor containing 120 mL of THF/1 N HCl (3:1). After heating to 45 °C for 12 h, the resin was filtered and washed twice with THF, MeOH, and Et_2O. After drying under vacuum for 12 h, the white olefin resin (9.8 g) was obtained. IR (cm^{-1}): 1639 (C═C), the C−Cl stretch at 1265 cm^{-1} from starting Merrifield resin was absent.

A dry 250-mL, three-necked flask was charged with 10 g (20 mmol) of dry olefin resin. The vessel was then purged with argon for 20 min, then toluene (200 mL) was added. After 5 min of stirring and addition of $RhCl(PPh_3)_3$ (74 mg, 0.4 mol %), Et_2SiH_2 (6.4 mL, 50.0 mmol) was introduced dropwise via a syringe at room temperature. The mixture was then stirred for 2 h, and the resin was filtered and washed thrice with toluene, THF, and Et_2O. The resin was then dried under vacuum at room temperature to give the corresponding white silane resin (10.6 g). IR (cm^{-1}), 2100 (Si−H), 1229 (Si−C).

To 10 g of the silane resin (20 mmol) was added 1,3-dichloro-5,5-dimethylhydantoin (12 g, 60 mmol) in 200 mL of dry DCM under argon. The mixture was then stirred for 1.5 h at room temperature. (*Note*: The concentration of the chlorinating agent should be ∼0.3 M. It is important to use this concentration for the complete chlorination of the silane.) The resin was then washed thrice with dry DCM (300 mL) and dry THF (300 mL) under argon. The resin was then immediately suspended in 200 mL of anhydrous THF and cooled to −78 °C. A solution of 5 equiv of 2-chloro-5-bromo-4-lithiopyridine (generated by treating 2-chloro-5-bromopyridine (19.3 g, 100 mmol) with 1 equiv of *t*-BuLi (1.7 M in pentane, 58.8 mL) at −78 °C for 5 min in 500 mL of THF was then transferred via a cannula. After 1 h at −78 °C, the reaction mixture was allowed to warm to room temperature for 12 h. The mixture was then cooled to 0 °C and treated dropwise with MeOH (200 mL). The resulting mixture was then washed thrice with THF (200 mL), THF/H_2O (1:1) (200 mL), THF (200 mL), DCM (200 mL), and Et_2O (200 mL) and dried under vacuum for 12 h to give the brown pyridine containing resin **B** (13.85 g). Anal. Found: C, 74.06; H, 7.42; N, 1.96 (1.4 mmol N /g, 70%).

General Procedure for Cleavage from Resin. Polystyrene resin (750 mg, 1 mmol) was placed in a 10-mL, round-bottom flask equipped with a magnetic stirrer, then TBAF (4 mmol, 4 mL of a 1 M solution in THF) was added. The reaction medium was stirred for 1 h at room temperature, and 10 mL of water was added to the mixture. The resin was then filtered and washed with H_2O (2 × 10 mL), THF (2 × 10 mL), and Et_2O (2 × 10 mL). The filtrate was then extracted with Et_2O, and the organic layer was dried ($MgSO_4$) and passed through a pad of silica. After evaporation of solvents under reduced pressure, the crude product was purified by column chromatography.

General Procedure for Bromine−Lithium Exchange. A suspension of resin **B** (750 mg, 1 mmol) in anhydrous THF (10 mL), under nitrogen, was cooled to −78 °C, and *n*-BuLi (1.6 mL, 2.5 M in hexane, 4 mmol) was added dropwise. After 3 h at this temperature, the solution was treated with a solution of the appropriate electrophile (4 mmol) in THF (10 mL). The reaction medium was then allowed to warm to room temperature overnight, and the mixture was hydrolyzed at 0 °C with H_2O (10 mL). The resin was then filtered and washed with H_2O (2 × 10 mL), THF (2 × 10 mL), and Et_2O (2 × 10 mL) and dried under

vacuum for 12 h. The cleavage and treatment described above gave compounds **2b** and **2c**.

2,5-Dichloropyridine (2b).[12] 125 mg (85%), white solid, mp 59 °C (lit.[13] 59−62 °C), eluent hexane/AcOEt (90:10). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.29 (dd, J = 8 and 0.7 Hz, 1H), 7.63 (dd, J = 8 and 2.5 Hz, 1H), 8.35 (d, J = 0.7 Hz, 1H). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 125.1, 132, 138.4, 148.40, 148.42, 151.7. MS (EI); *m*/*z* (%): 149 [M^+ + 1] (64), 147 [M^+ − 1] (100), 112 (77), 85 (13), 76 (35), 51 (9.8).

2-Chloro-5-iodopyridine (2c).[14] 215 mg (90%), yellow solid, mp 97 °C, eluent hexane/AcOEt (90:10). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.14 (dd, J = 8.5 and 0.7 Hz, 1H), 7.9 (dd, J = 9 and 2 Hz, 1H), 8.6 (d, J = 0.7 Hz, 1H). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 90.7, 126.1, 146.7, 150.9, 155.6. MS (EI); *m*/*z* (%): 240 [M^+ + 1] (5.3), 239 [M^+] (100), 127 (19), 112 (75), 85 (37), 76 (53).

General Procedure for Bromine−Magnesium Exchange. A suspension of resin **B** (750 mg, 1 mmol) in anhydrous THF (5 mL), under nitrogen, was cooled to 0 °C, and ^{i}PrMgCl (4 mL of a 2 M solution in THF, 8 mmol) was added dropwise. The reaction medium was then allowed to warm to room temperature (6 h). The mixture was then cooled to 0 °C and treated with *t*-BuCHO (860 mg, 10 mmol) and allowed to warm to room temperature overnight. The hydrolysis was realized with water (10 mL) at 0 °C. The resin was then filtered and washed with H_2O (2 × 10 mL), THF (2 × 10 mL), and Et_2O (2 × 10 mL) and dried under vacuum for 12 h. Cleavage, treatment, and column chromatography (hexane/AcOEt (80:20) gave **2d**[15] (186 mg, 93%) as a white solid, mp 125 °C (lit.[16] 122−123 °C). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.91 (s, 9H), 4.43 (s, 1H), 7.28 (d, J = 8 Hz, 1H), 7.66 (dd, J = 8 and 2.4 Hz, 1H), 8.25 (d, J = 2.4 Hz, 1H). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 25.5, 35.6, 79.2, 123.3, 136.4, 137.9, 148.7, 152.2. MS (EI); *m*/*z* (%): 184 (1.5), 145 (30), 144 (19), 143 (100), 142 (44), 78 (19), 57 (31).

General Procedure for Ortholithiation with LDA. A solution of diisopropylamine (0.84 mL, 6 mmol) in THF (40 mL) was cooled to −40 °C, and *n*-BuLi (2.4 mL, 2.5 M in hexane, 6 mmol) was added dropwise under nitrogen. The reaction medium was allowed to warm to 0 °C, stirred for 30 min, and then cooled to −78 °C. Resin **B** (750 mg, 1 mmol) was added slowly via a solid addition funnel, and the dark mixture was stirred for 3 h. The reaction medium was then treated at −78 °C with the appropriate electrophile (8 mmol) in THF (10 mL), and the medium was allowed to warm to room temperature (12 h). The hydrolysis was realized at 0 °C with H_2O (40 mL). The resin was then filtered and washed with H_2O (2 × 10 mL), THF (2 × 10 mL) and Et_2O (2 × 10 mL) and dried under vacuum for 12 h. The cleavage and treatment described above gave compounds **4a** and **4b**.

3-Bromo-2, 6-dichloropyridine (4a). 193 mg (85%), white gummy solid, eluent hexane/AcOEt (90:10). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.30 (d, J = 8 Hz, 1H), 7.94 (d, J = 8 Hz, 1H). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 118.9, 126.3, 143.3, 150.1, 155.7. MS (EI); *m*/*z* (%): 382 (33), 380 (11), 303 (100), 301 (60), 222 (23), 151 (9), 75 (14). Anal. Calcd for $C_5H_2BrCl_2N$: C, 26.47; H, 0.89; N, 6.17. Found: C, 26.52; H, 0.91; N, 6.13.

3-Bromo-6-chloro-2-methylsulfanylpyridine (4b). 213 mg (90%), white gummy solid, eluent hexane/AcOEt (95:5). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 2.56 (s, 3H), 6.9 (d, J = 8.2 Hz, 1H), 7.62 (d, J = 8.2 Hz, 1H). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 14.8, 117.2, 120.0, 141.2, 149.6, 158.5. MS (EI); *m*/*z* (%): 239 [M^+] (42), 237 (31), 160 (32), 158 (100), 112 (17), 64 (10). Anal. Calcd for $C_6H_5BrClNS$: C, 30.21; H, 2.11; N, 5.87; S, 13.44. Found: C, 29.92; H, 2.09; N, 5.78; S, 13.41.

Preparation of Monoalkynylpyridines 6a−c. The bromine lithium exchange was performed on resin **B** as described above, except that H_2O (10 mL) was added as electrophile. After the usual filtration and washings, the resin was submitted to Sonogashira coupling as follows. A mixture of $PdCl_2(PPh_3)_2$ (35 mg, 0.05 mmol), CuI (19 mg, 0.1 mmol), and Et_3N (2 mL) in DMF (10 mL) was stirred under nitrogen. The resin **(**1 mmol) and the appropriate alkyne (2 mmol) were added to the mixture, which was then heated to reflux for 24 h. The mixture was then cooled to room temperature, and the resin was filtered and washed with NH_4OH (2 × 10 mL), H_2O (2 × 10 mL), THF (2 × 10 mL), and Et_2O (2 × 10 mL) and dried under vacuum for 12 h. The cleavage and treatment described above gave compounds **6a−c**.

2-Phenylethynylpyridine (6a).[16] 132 mg (74%), yellow solid, mp 34 °C, eluent hexane/AcOEt (80:20). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.24 (dd, J = 7 and 6 Hz, 1H), 7.37−7.38 (m, 3H), 7.53 (d, J = 8 Hz, 1H), 7.61 (dd, J = 6 and 2 Hz, 2H), 7.68 (td, J = 7.5 and 2 Hz, 1H), 8.62 (d, J = 6 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 88.9, 89.6, 122.6, 123.1, 127.6, 128.7, 129.3, 132.4, 136.6, 143.7, 150.4. MS (EI); *m*/*z* (%): 180 [M^+ + 1] (12), 179 [M^+] (100), 178 [M^+ − 1] (34), 151 (10), 76 (17).

2-Hex-1-ynylpyridine (6b).[17] 152 mg (96%), yellow oil, eluent hexane/AcOEt (70:30). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.88 (t, J = 7.2 Hz, 3H), 1.40−1.59 (m, 4H), 2.38 (t, J = 6.9 Hz, 2H), 7.14 (dd, J = 7.8 and 5 Hz, 1H), 7.34 (d, J = 7.8 Hz, 1H), 7.57 (td, J = 7.8 and 5 Hz, 1H), 8.51 (d, J = 7 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 12.6, 18.1, 21.1, 29.5, 79.6, 89.9, 121.3, 125.8, 135.0, 143.0, 148.8. MS (EI); *m*/*z* (%): 159 [M^+] (30), 158 [M^+ − 1] (38), 144 (35), 130 (100), 117 (88), 89 (39), 78 (20), 51 (17).

4-Pyridin-2-yl-but-3-yn-2-ol (6c).[18] 141 mg (78%), yellow oil, eluent AcOEt. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.57 (d, J = 6.6 Hz, 3H), 4.83 (q, J = 6.5 Hz, 1H), 5.53 (s, 1H), 7.18 (dd, J = 6.8 and 5 Hz, 1H), 7.37 (d, J = 7.8 Hz, 1H), 7.61 (dd, J = 7.8 and 6.8 Hz, 1H), 8.52 (d, J = 5 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 23.7, 57.6, 82.0, 92.3, 112.7, 122.6, 126.8, 136.1, 142.5, 149.2.

Preparation of Aminopyridylalkynes 8a−c. (a) Procedure for Amination. The resin **B** (750 mg, 1 mmol) was swelled in DMF (10 mL), and the appropriate amine (5 mmol) was added to the reaction medium, which was then heated to reflux for 24 h. After cooling, resin was filtered and washed with H_2O (2 × 10 mL), THF (2 × 10 mL), and Et_2O (2 × 10 mL) and dried under vacuum for 12 h. The cleavage and treatment described above gave the aminopyridines **6a−c**.

5-Bromo-2-pyrrolidin-1-yl-pyridine (7a).[19] 220 mg (97%), white solid, mp 71 °C, eluent hexane/AcOEt (90:10). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 2.00 (t, J = 6.4 Hz, 4H), 3.40 (t, J = 6.4 Hz, 4H), 6.25 (d, J = 9 Hz, 1H), 7.47 (dd, J = 9 and 2.4 Hz, 1H), 8.15 (d, J = 2.4 Hz, 1H). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 25.9, 47.2, 105.8, 108.2, 139.5, 148.9, 156.1. MS (EI); *m*/*z* (%): 228 [$M^+ + 1$] (38), 227 [M^+] (13), 226 [$M^+ - 1$] (39), 199 (97), 197 (100), 158 (19), 118 (11), 78 (33), 70 (64), 51 (18).

5-Bromo-2-morpholin-1-yl-pyridine (7b).[6d] 199 mg (82%), yellow solid, mp 77 °C, eluent hexane/AcOEt (80:20). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 3.46 (t, J = 5 Hz, 4H), 3.81 (t, J = 5 Hz, 4H), 6.53 (d, J = 9.1 Hz, 1H), 7.56 (dd, J = 9 and 2.4 Hz, 1H), 8.21 (d, J = 2.3 Hz, 1H). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 45.9, 66.9, 108.61, 108.64, 140.2, 148.9, 159.4. MS (EI); *m*/*z* (%): 244 [$M^+ + 1$] (35), 243 [M^+] (28), 242 [$M^+ - 1$] (37), 213 (51), 211 (50), 185 (45), 158 (97), 157 (100), 78 (63), 51 (22).

(5-Bromopyridin-2-yl)-dimethylamine (7c).[20] 175 mg (87%), yellow solid, mp 39 °C (lit.[21] 40−41 °C) eluent hexane/AcOEt (90:10). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 3.04 (s, 6H), 6.38 (d, J = 9.1 Hz, 1H), 7.46 (dd, J = 9.1 and 2.1 Hz, 1H), 8.15 (d, J = 2.1 Hz, 1H). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 37.6, 105.4, 106.6, 138.8, 147.8, 157.3. MS (EI); *m*/*z* (%): 202 [M^+] (54), 201 [$M^+ - 1$] (11), 187 (63), 185 (66), 173 (96), 171 (100), 158 (41), 119 (11), 78 (71), 51 (42).

(b) Procedure for Sonogashira Coupling of Immobilized Aminopyridines. A mixture of $PdCl_2(PPh_3)_2$ (35 mg, 0.05 mmol) and CuI (18 mg, 0.1 mmol) in piperidine (10 mL) was stirred under nitrogen. The resin bearing aminopyridine (1 mmol) and appropriate alkyne (2 mmol) were added to the suspension, which was heated to reflux for 24 h. The mixture was then cooled to room temperature, and the resin was filtered and washed with NH_4OH (2 × 10 mL), H_2O (2 × 10 mL), THF (2 × 10 mL), and Et_2O (2 × 10 mL) and dried under vacuum for 12 h. The cleavage and treatment described above gave the aminopyridyl alkynes **8a**−**c**.

5-Phenylethynyl-2-pyrrolidin-1-yl-pyridine (8a). 220 mg (89%), yellow solid mp 125 °C, eluent hexane/AcOEt (50:50). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 2.0 (t, J = 2.9 Hz, 4H), 3.50 (t, J = 3 Hz, 4H), 6.35 (d, J = 8.8 Hz, 1H), 7.31−7.34 (m, 3H), 7.50 (d, J = 6.5 Hz, 2H), 7.56 (dd, J = 9 and 2.1 Hz,1H), 8.34 (d, J = 2 Hz, 1H). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 25.5, 46.9, 87.7, 88.4, 106.3, 123.6, 127.8, 128.3, 131.3, 139.8, 150.9. MS (EI); *m*/*z* (%): 249 [$M^+ + 1$] (11), 248 [M^+] (74), 220 (20), 219 (100), 179 (15), 124 (5.9), 109 (13), 91 (15.7), 70 (19.3). Anal. Calcd for $C_{17}H_{16}N_2$: C, 82.21; H, 6.49; N, 11.28. Found: C, 81.92; H, 6.24; N, 11.34.

5-Phenylethynyl-2-morpholin-1-yl-pyridine (8b). 203 mg (77%), yellow solid, mp 135 °C, eluent hexane/AcOEt (70:30). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 3.53 (t, J = 5 Hz, 4H), 3.78 (t, J = 5 Hz, 4H), 6.54 (d, J = 9 Hz, 1H), 7.28−7.30 (m, 3H), 7.45−7.48 (m, 2H), 7.57 (dd, J = 9 and 2.2 Hz, 1H), 8.34 (d, J = 2.2 Hz, 1H). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 44.9, 66.3, 86.9, 89.7, 105.6, 108.9, 123.1, 127.7, 128.1, 131.1, 139.8, 150.9, 157.8. MS (EI); *m*/*z* (%): 264 [M^+] (100), 233 (57), 219 (42), 207 (48), 179 (87), 152 (22), 89 (31), 76 (32). Anal. Calcd for $C_{17}H_{16}N_2O$: C, 77.25; H, 6.10; N, 10.60. Found: C, 75.59; H, 6.23; N, 10.45.

2-(Dimethylamine)-pyridine-3-yl-but-2-yn-3-ol (8c). 140 mg (74%), brown solid, mp 108 °C, eluent hexane/AcOEt (70:30). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.53 (d, J = 6.8 Hz, 3H), 3.08 (s, 6H), 4.74 (q, J = 6.8 Hz, 1H), 6.42 (d, J = 9 Hz, 1H), 7.43 (dd, J = 8.9 and 2.2 Hz, 1H), 8.28 (d, J = 2.2 HZ, 1H). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 24.3, 37.9, 58.2, 81.3, 91.6, 104.9, 106.3, 139.6, 150.8, 162.4. Anal. Calcd for $C_{11}H_{14}N_2O$: C, 69.45; H, 7.42; N, 14.72. Found: C, 69.15; H, 7.12, N, 14.95.

General Procedure for One-Pot Preparation of Dialkynylpyridines 9a−c. A mixture of $PdCl_2(PPh_3)_2$ (70 mg, 0.1 mmol), CuI (38 mg, 0.2 mmol), and Et_3N (4 mL) in DMF (10 mL) was stirred under nitrogen. The resin **B** (750 mg, 1 mmol) and the appropriate alkyne (5 mmol) were added to the mixture, which was then heated to reflux for 24 h. The mixture was then cooled to room temperature, and the resin was filtered and washed with NH_4OH (2 × 10 mL), H_2O (2 × 10 mL), THF (2 × 10 mL), and Et_2O (2 × 10 mL) and dried under vacuum for 12 h. The cleavage and treatment described above gave compounds **10a**−**c**.

2,5-Diphenylethynylpyridine (9a). 181 mg (65%), yellow solid, mp 157 °C, eluent hexane/AcOEt (90:10). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.36−7.40 (m, 6H), 7.5−7.63 (m, 5H), 7.79 (dd, J = 8 and 2 Hz, 1H), 8.76 (d, J = 2 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 87.0, 89.5, 92.2, 95.3, 120.4, 123.4, 127.4, 129.4, 129.5, 130, 130.2, 132.7, 133.1, 139.4, 142.9, 153.4. MS (EI); *m*/*z* (%): 280 [$M^+ + 1$] (24), 279 [M^+] (100), 250 (5.2), 126 (17), 76 (2.2). Anal. Calcd for $C_{21}H_{13}N$: C, 90.30; H, 4.69; N, 5.01. Found: C, 89.99; H, 4.63; N, 4.77.

4-[6-(3-Hydroxybut-1-ynyl)-pyridin-3-yl]-but-3-yn-2-ol (9b). 163 mg (76%), yellow oil, eluent AcOEt. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.55 (d, J = 6.9 Hz, 3H), 1.57 (d, J = 6.5 Hz, 3H), 4.77 (q, J = 6.5 Hz, 2H), 7.35 (d, J = 8 Hz, 1H), 7.65 (dd, J = 8 and 1.5 Hz, 1H), 8.6 (d, J = 1.5 Hz, 1H). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 24.3, 24.5, 58.8, 59.0, 80.6, 83.1, 93.8, 96.8, 119.6, 126.6, 139.2, 141.8, 152.6. Anal. Calcd for $C_{13}H_{13}NO_2$: C, 72.54; H, 6.09; N, 6.51; O, 14.87. Found: C, 72.96; H, 5.84; N, 6.42.

2,5-Bispyridine-ethynylpyridine (9c). 201 mg (71%), yellow solid, mp 182 °C, eluent hexane/AcOEt (90:10).^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.31 (m, 2H), 7.57 (d, J = 7.8 Hz, 1H), 7.62−7.65 (m, 2H), 7.71−7.75 (m, 2H), 7.88 (dd, J = 8 and 1.8 Hz, 1H), 8.66 (d, J = 4.3 Hz, 2H), 8.85 (d, J = 1.8 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 88.7, 92.6, 93.4, 95.0, 123.6, 123.8, 127.6, 128.1, 136.6, 139.2, 150.44, 150.47, 153.1. MS (EI); *m*/*z* (%): 284 (100), 283 [$M^+ + 2$] (40), 207 (15), 152 (50), 141 (32), 102 (22), 77 (58), 51 (36). Anal. Calcd for $C_{19}H_{14}N_3$: C, 81.12; H, 3.94; N, 14.94. Found: C, 81.32; H, 4.01; N, 14.76.

General Procedure for Stille Cross-Coupling. A mixture of $PdCl_2(PPh_3)_2$ (70 mg, 0.1 mmol) and CuI (38 mg, 0.2 mmol) in DMF (10 mL) was stirred under nitrogen. Resin **B** (750 mg, 1 mmol) and the appropriate organotin (5 mmol) was added. After refluxing for 24 h, the mixture was cooled to room temperature. The resin was then filtered and washed

with NH_4OH (2 × 10 mL), H_2O (2 × 10 mL), THF (2 × 10 mL), and Et_2O (2 × 10 mL) and dried under vacuum for 12 h. The cleavage and treatment above-described gave compounds **10** and **11**.

2,5-Diphenylpyridine (10).[21] 190 mg (82%), yellow solid, mp 173 °C (lit.[22] 177 °C), eluent hexane/AcOEt (80:20). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 8.94 (d, J = 2.3 Hz, 1H), 8.04 (d, J = 7.0 Hz, 2H), 7.95 (dd, J = 8.3 and 2.3 Hz, 1H), 7.80 (d, J = 8.3 Hz, 1H), 7.63 (d, J = 7.7 Hz, 2H), 7.52−7.38 (m, 6H). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 121.4, 127.9, 128.0, 129.1, 129.8, 130.0, 130.2, 136.2, 142.7, 143.9, 149.2, 154.23. MS (EI); *m*/*z* (%): 232 [M^+ + 1] (17), 231 [M^+] (100), 230 [M^+ − 1] (41), 202 (8), 102 (12), 76 (5), 51 (4).

[2,2′,5′,2″]-Terpyridine (11).[23] 177 mg (76%), yellow solid, mp 156 °C (lit.[24] 157 °C), eluent hexane/AcOEt (50:50). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.28−7.34 (m, 2H), 7.81−7.85 (m, 3H), 8.46−8.54 (m, 3H), 8.72 (d, J = 2.2 Hz, 1H), 8.76 (d, J = 2.2 Hz, 1H), 9.28 (d, J = 1 Hz, 1H). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 121.0, 121.3, 121.7, 123.2, 124.2, 135.0, 135.6, 137.3, 148.0, 149.6, 150.5, 155.0, 156.1, 156.6.

General Procedure for Suzuki Cross-Coupling. To a mixture of $PdCl_2(PPh_3)_2$ (70 mg, 0.1 mmol), CuI (38 mg, 0.2 mmol), and K_2CO_3 (1.3 g, 10 mmol) in DMF (10 mL) under nitrogen were added resin **B** (750 mg, 1 mmol) and the appropriate boronic acid (5 mmol). After refluxing for 24 h, the mixture was then cooled to room temperature, and the resin was filtered and washed with NH_4OH (2 × 10 mL), H_2O (2 × 10 mL), THF (2 × 10 mL), and Et_2O (2 × 10 mL) and dried under vacuum for 12 h. The cleavage and treatment described above gave compounds **10** and **12**.

2,5-Distyrylpyridine (12).[24] 195 mg (69%), yellow solid, mp 202−205 °C (lit.[25] 208 °C), eluent hexane/AcOEt (9:1). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.07 (d, J = 6.4 Hz, 2H), 7.17−7.35 (m, 8H), 7.49 (d, J = 10.8 Hz, 4H), 7.53 (d, J = 6.4 Hz, 1H), 7.76 (dd, J = 8 and 2.2 Hz, 1H), 8.64 (d, J = 2.5 Hz, 1H). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 122.2, 125.0, 126.8, 127.3, 127.8, 128.3, 128.6, 128.9, 129.01, 129.06, 130.4, 131.6, 132.8, 133.2, 136.9, 148.8, 154.7. MS (EI); *m*/*z* (%): 284 [M^+ + 1] (7.6), 283 [M^+] (44), 282 [M^+ + 1] (100), 239 (1), 77 (4).

Acknowledgment. The authors thank FMC Lithium Inc. for a generous gift of alkyllithium reagents.

References and Notes

(1) (a) Gallop, M. A.; Barrett, R. W.; Dower, W.; Fodor, S. P. A.; Gordon, E. M. *J. Med. Chem.* **1994**, *37*, 1233−1385. (b) Thompson, L.; Ellman, J. A. *Chem. Rev.* **1996**, *96*, 555−600. (c) Armstrong, R. W.; Combs, A. P.; Tempest, P. A.; Brown, S. D.; Keating, T. A. *Acc. Chem. Res.* **1996**, *29*, 123−131. (d) Ellman, J. A. *Acc. Chem. Res.* **1996**, *29*, 132−143. Hemkens, P. H.; Ottenheim, H. C.; Rees, D. *Tetrahedron* **1996**, *52*, 4527−4554. (e) Krchnack, V.; Holladay, M. W. *Chem. Rev.* **2002**, *102*, 61−92. (f) Ziegert, R. E.; Toräng, J.; Knepper, K.; Bräse, S. *J. Comb. Chem.* **2005**, *7*, 147−169.

(2) (a) Cotterill, I. C.; Usyatinsky, A. Y.; Arnold, J. M.; Clark, D. S.; Dordick, J. S.; Michels, P. C.; Khmelnitsky, Y. L. *Tetrahedron Lett.* **1998**, *39*, 1117−1120. (b) Bagley, M. C.; Dale, J. W.; Ohnesorge, M.; Xiong, X.; Bower, J. *J. Comb. Chem.* **2003**, *5*, 41−44. (c) Fujimori, T.; Wirsching, P.; Janda, K. D. *J. Comb. Chem.* **2003**, *5*, 625−631. (d) Abbiati, G.; Arcadi, A.; Bianchi, G.; Di Giuseppe, S.; Marinelli, F.; Rossi, E. *J. Org. Chem.* **2003**, *68*, 6959−6966. (e) Bashford, K. E.; Burton, M. B.; Cameron, S.; Cooper, A. L.; Hogg, R. D.; Kane, P. D.; MacManus, D. A.; Matrunola, C. A.; Moody, C. J.; Robertson, A. A. B.; Warne, M. R. *Tetrahedron Lett.* **2003**, *44*, 1627−1629. (f) Martinez-Teipel, B.; Teixido, J.; Pascual, R.; Mora, M.; Pujola, J.; Fujimoto, T.; Borrell, J. I.; Michelotti, E. L. *J. Comb Chem.* **2005**, *7*, 436−448.

(3) (a) Tadesse, S.; Bhandari, A.; Gallop, M. A. *J. Comb. Chem.* **1999**, 1, 184−187. (b) Grosche, P.; Holtzel, A.; Walk, T. B.; Trautwein, A. W.; Jung, G. *Synthesis* **1999**, *11*, 1961−1970. (c) Katritzky, A. R.; Chassaing, C.; Barrow, S. J.; Zhang, Z.; Vvedensky, V.; Forood, B. *J. Comb. Chem.* **2002**, *4*, 249−250. (d) Gros, P.; Louërat, F.; Fort, Y. *Org. Lett.* **2002**, *4*, 1759−1761. (e) Louërat, F.; Gros, P.; Fort, Y. *Tetrahedron Lett.* **2003**, *44*, 5613−5616.

(4) (a) Papageorgiu, G. C.; Borer, X. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 1549−1552. (b) Tonder, E.; Olesen, P. H. *Curr. Med. Chem.* **2001**, *8*, 651−674. (c) Zhang, L.; Pavlova, O. A.; Chefer, S. I.; Hall, A. W.; Kurian, V.; Brown, L. L.; Kimes, A. S.; Mukhin, A. G.; Horti, A. G. *J. Med. Chem.* **2004**, *47*, 2453−2465.

(5) (a) Burrow, M. P.; Gray, G. W.; Lacey, D.; Toyne, K. J. *Liq. Cryst.* **1988**, *3*, 1643−1653. (b) Wong, J.; Masson, P.; Nicoud, J.-F. *Polym. Bull.* **1994**, *32*, 265−272. (c) Vasconcelos, U. B.; Dalmolin, E.; Merlo, A. A. *Org. Lett.* **2005**, *7*, 1027−1030.

(6) For references on the selective functionalization of polyhalopyridines in solution phase, see: (a) Tilley J. F.; Zawoiski, S. *J. Org. Chem.* **1988**, *53*, 386−387. (b) Belfrekh, N.; Dietrich-Buchecker, C.; Sauvage, J.-P. *Tetrahedron Lett.* **2001**, *42*, 2779−2781. (c) Barry, P. R.; Wang, C.; Batsanov, A. S.; Bryce, M. R.; Tarbit, B. *J. Org. Chem.* **2002**, *67*, 7541−7543. (d) Ji, J.; Li, T.; Bunnelle, W. H. *Org. Lett.* **2003**, *5*, 4611−4614. (e) Vasconcelos, U. B.; Dalmolin, E.; Merlo, A. A. *Org. Lett.* **2005**, *7*, 1027−1030. (f) Heckmann, G.; Bach, T. *Angew. Chem., Int. Ed.* **2005**, *44*, 1199−1201.

(7) (a) Boehm, T. L.; Showalter, H. D. H. *J. Org. Chem.* **1996**, *61*, 6498−6499. (b) Plunkett, M. J.; Ellman, J. A. *J. Org. Chem.* **1997**, *62*, 2885−2893. (c) Hu, Y.; Porco, J. A.; Labadie, J. W.; Gooding, O. W.; Trost, B. M. *J. Org. Chem.* **1998**, *63*, 4518−4521. (d) Lindsley, C. W.; Hodges, J. C.; Filzen, G. F.; Watson, B. M.; Geyer, A. G. *J. Comb. Chem.* **2000**, *2*, 550−559. (e) Meloni, M.; Brown, R. C. D.; White, P. D.; Armour, D. *Tetrahedron Lett.* **2002**, *43*, 6023−6026.

(8) All the functionalization steps were easily monitored by IR spectroscopy.

(9) This reaction was recently reported by us using the less sterically hindered TMSCl as electrophile. See: Pierrat, Ph.; Gros, Ph.; Fort, Y. *Synlett*, **2004**, *13*, 2319−2322.

(10) No product resulting from bromine scrambling was detected, indicating the stability of the lithio intermediate during the immobilization step. The amount of isolated **1** was in full agreement with elemental analysis.

(11) Such a dimethylamination of chloropyridine has been reported in the presence of DMF and ethanolamines. See: Cho, Y. H.; Park, J. C. *Tetrahedron Lett.* **1997**, *38*, 8331−8334.

(12) Kuwayama, T.; Inoue, S.; Asanuma, G.; Shiono, M. (Kuraray Co., Ltd., Japan). PCT Int. Appl. WO19980319 A1, 1998; *Chem. Abstr.* **128**, *230248*.

(13) Commercially available compound mp obtained from the Aldrich Advancing Science Catalog.

(14) Bouillon, A.; Lancelot, J.-C.; Rault, S. *Tetrahedron* **2002**, *58*, 2885−2890.

(15) Bolm, C.; Ewald, M.; Felden, M.; Schlingloff, G. *Chem. Ber.* **1992**, *125*, 1169−1190.

(16) Lautens, M.; Yoshida, M. *J. Org. Chem.* **2003**, *68*, 762−769.

(17) Novak, Z.; Szabo, A.; Repasi, J.; Kotschy, A. *J. Org. Chem.* **2003**, *68*, 3327−3329.
(18) Schubert, T.; Hummel, W.; Kula, M.-R.; Muller, M. *Eur. J. Org. Chem.* **2001**, 4181−4187.
(19) Takayanagi, M.; Sagi, K.; Nakagawa, T.; Yamanashi, M.; Kayahara, T.; Takehana, S. (Ajinomoto Co., Inc., Japan). PCT Int. Appl. WO 19980723, 1998; *Chem. Abstr.* **129**, 161414.
(20) Paudler, W. W.; Jovanovic, M. V. *J. Org. Chem.* **1983**, *48*, 1064−1069.
(21) Berthiol, F.; Kondolff, I.; Doucet, H.; Santelli, M. *J. Organomet. Chem*. **2004**, *689* (17), 2786−2798.
(22) Kagabu, S.; Ando, C.; Ando, J. *J. Chem. Soc., Perkin Trans. 1* **1994**, *6*, 739−752.
(23) Yanagida, S.; Ogata, T.; Kuwana, Y.; Wada, Y.; Murakoshi, K.; Ishida, A.; Takamuku, S.; Kusaba, M.; Nakashima, N. *J. Chem. Soc., Perkin Trans. 2*, **1996**, *9*, 1963−1969.
(24) Marri, E.; Pannacci, D.; Galiazzo, G.; Mazzucato, U.; Spalletti, A. *J. Phys. Chem. A* **2003**, *107*, 11231−11238.
(25) Siegrist, A.; Meyer, H. R.; Gassman, P.; Moss, S. *Helv. Chim. Acta* **1980**, *63*, 1131−1334.

CC050054A