REGIOSELECTIVE *ORTHO*-LITHIATION OF HALOPYRIDINES. SYNTHESES OF *ORTHO*-DISUBSTITUTED PYRIDINES AND A CONVENIENT GENERATION OF 3,4-PYRIDYNE†

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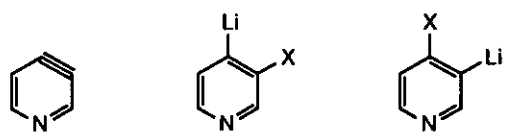
Abstract–The regioselective *ortho*-lithiation of 3-chloro- (**4**), 3-fluoro- (**7**), 3-bromo- (**10**), 2-chloro- (**22**), and 4-chloropyridine (**25**) with lithium diisopropylamide affords, after quenching with various electrophiles, the corresponding *ortho*-disubstituted pyridines in yields from 16-96%. Halogen-metal exchange between 4-iodo-3-chloropyridine (**6a**) and *tert*-butyllithium or *n*-butyllithium provides a convenient generation of 3,4-pyridyne (**1**), which is trapped in a Diels-Alder reaction with furan and 2,5-dimethylfuran to give **31** and **32** (24-38%).

Heteroatom-facilitated metalation reactions have had a major impact on the design and execution of organic synthesis over the past decade, particularly those reactions involving aromatic and heteroaromatic substrates.[1,2] In connection with a synthetic approach to the ellipticine (6*H*-pyrido[4,3-*b*]carbazole) family of antitumor alkaloids, we desired to generate and trap 3,4-pyridyne (**1**) in a Diels-Alder reaction.[3] At that time, the only two techniques for generating and efficiently trapping **1** with dienes (e.g., furan) involved tedious, multi-step syntheses of 3,4-pyridyne precursors.[4,5] Following the completion of the present research, there have appeared in the literature several other good methods for the generation of 3,4-pyridyne (**1**).[6]



1 **2** **3**

†This paper is dedicated to Professor Ted Taylor in celebration of his 70th birthday, with affection and admiration from a fellow Vermonter.

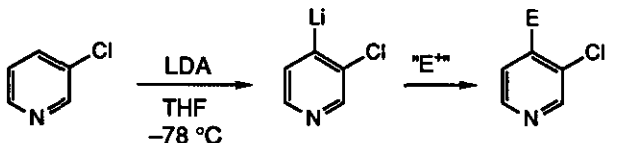
Other methods for the generation of **1**, involving the treatment of 3- and 4-halopyridines with amide and dialkylamide bases, give very poor yields of Diels-Alder adducts; instead, the major products arise from nucleophilic addition to **1**.[7,8] We felt that this problem could be circumvented by generating an *ortho*-metalated halopyridine (**2**) or (**3**) in the absence of nucleophiles, i.e., by halogen-metal exchange of an appropriate 3,4-dihalopyridine. Elimination of LiX from **2** or **3** would generate 3,4-pyridyne (**1**). This protocol is excellent for the formation and trapping of benzyne and other arynes.[9]

The relative kinetic acidity of pyridine (C-4 > C-3 > C-2 : 12, 9.3, 1.0)[10] combined with the greatly increased kinetic acidity of the *ortho* hydrogens in halobenzenes[11,12] suggested that it would be feasible to metalate regioselectively the C-4[13] position of the readily available 3-halopyridines as a route to 3,4-dihalopyridines. Although the regioselective C-4 lithiation of 3-chloropyridine with *n*-butyllithium was reported in 1972,[7d] the yields of 3,4-disubstituted pyridines were lowered by formation of C-2 product and by addition of the alkyllithium to the pyridine ring. Therefore, we chose to explore lithium diisopropylamide (LDA) as the base in this reaction.[14]

Following the completion of the present work, Quéguiner and co-workers have reported extensive studies on the metalation chemistry of halopyridines.[15]

RESULTS AND DISCUSSION

Regioselective Lithiation of Halopyridines. Treatment of 3-chloropyridine (**4**) with LDA (THF, –78 °C) results in the regioselective lithiation of the C-4 position to give 3-chloro-4-lithiopyridine (**5**). Quenching this solution with a variety of electrophiles, at low temperatures to forestall premature 3,4-pyridyne formation, gives the 3,4-disubstituted pyridines (**6**) in 16-96% yields. Our results are tabulated in the Table. The structures of **6a-h** were established by spectral and analytical data, including ^{13}C nmr. In some cases, direct comparison with literature data was possible.



4 5

6a E = I
6b E = TMS
6c E = PhS
6d E = PhCHOH
6e E = Ph_2COH
6f E = Me_2COH
6g E = Br
6h E = SO_2Ph

Similarly, both 3-fluoro- (**7**) and 3-bromopyridine (**10**) are metalated at C-4 with LDA to give the respective anions (**8**) and (**11**), respectively. Quenching these species at low temperatures affords the corresponding 3,4-

Table. Reactions of 2-Halo-3-lithio, 3-Halo-4-lithio, and 3-Lithio-4-halopyridines with Electrophiles

Pyridine Anion	Electrophile	Product	% Yield[a]
5	I_2	3-Chloro-4-iodopyridine (**6a**)	65
5	Me_3SiCl	3-Chloro-4-trimethylsilylpyridine (**6b**)	96
5	PhSSPh	3-Chloro-4-thiophenylpyridine (**6c**)	75
5	PhCHO	1-Phenyl-1-(3-chloro-4-pyridyl)methanol (**6d**)	57
5	Ph_2CO	1,1-Diphenyl-1-(3-chloro-4-pyridyl)methanol (**6e**)	65
5	Me_2CO	2-(3-Chloro-4-pyridyl)-2-propanol (**6f**)	28[b]
5	Br_2	3-Chloro-4-bromopyridine (**6g**)	16[c]
5	$PhSO_2Cl$	3-Chloro-4-phenylsulfonylpyridine (**6h**)	80[d]
8	I_2	3-Fluoro-4-iodopyridine (**9a**)	50
8	Me_3SiCl	3-Fluoro-4-trimethylsilylpyridine (**9b**)	87
11	PhSSPh	3-Bromo-4-thiophenylpyridine (**12a**)	61
11	MeCHO	1-(3-Bromo-4-pyridyl)ethanol (**12b**)[e]	79
11	PhCOMe	1-(3-Bromo-4-pyridyl)-1-phenylethanol (**12c**)	36
11	**15**	**16**	81
11	**17**	**18**	57
19	Me_3SiCl	2-Chloro-3-trimethylsilylpyridine (**24**)	74
22	Me_3SiCl	3-Trimethylsilyl-4-chloropyridine (**27**)	92

[a]Yields refer to isolated (distilled, recrystallized, chromatographed, or sublimed) product.

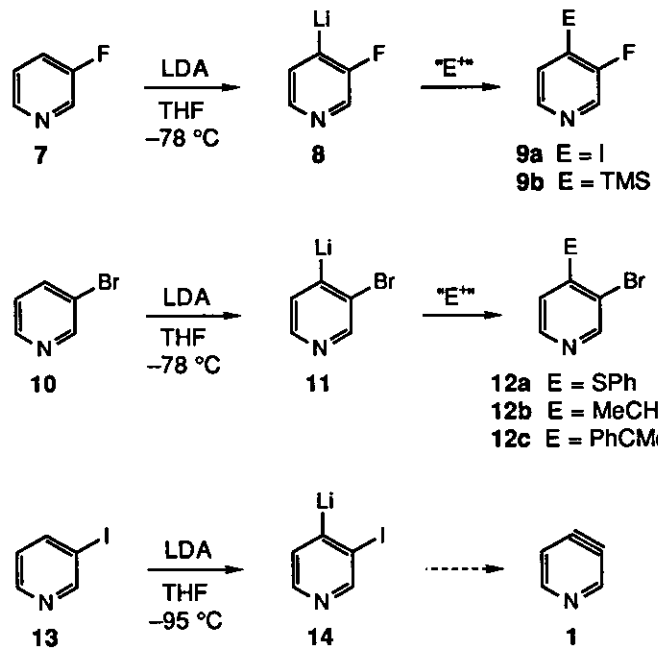
[b]The predominant pathway appears to be enolate formation, resulting in recovered 3-chloropyridine (**4**).

[c]An extremely exothermic reaction accounts for the low yield due to decomposition of **5**.

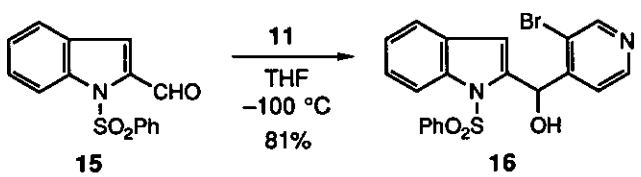
[d]Crude yield only, but tlc indicated a pure material and ^1H nmr was consistent with the assigned structure. Attempted purification by distillation, crystallization or column chromatography repeatedly resulted in total decomposition for reasons which remain puzzling.

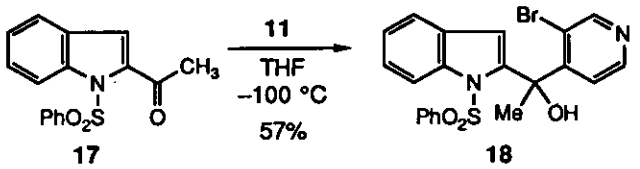
[e]Unfortunately, no analytical data were obtained for this compound; spectra support the assigned structure.

disubstituted pyridines (**9**) and (**12**), respectively, in good yields (Table). In contrast, the attempted metalation of 3-iodopyridine (**13**) with LDA at –95 °C failed to give the 3,4-disubstituted pyridine after quenching with electrophiles. Instead, a dark polymer material formed immediately at –95 °C after the addition of LDA, suggesting the rapid decomposition of the presumed 3-iodo-4-lithiopyridine (**14**) to 3,4-pyridyne (**1**).



The reactions of 3-bromo-4-lithiopyridine (**11**) with 1-phenylsulfonylindole-2-carboxaldehyde (**15**) and 1-phenylsulfonyl-2-indolyl methyl ketone (**17**) afford the expected **16** and **18** in 81% and 57% yields, respectively. The only other materials isolated from the latter reaction are ketone (**17**) (38%) and 3-bromopyridine (**10**), apparently resulting from enolate formation, as is observed in the reaction between **11** and acetophenone.

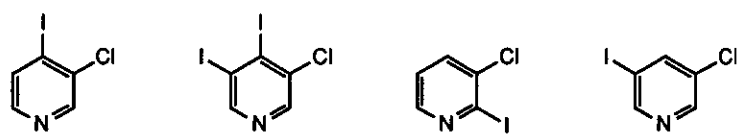




17 18

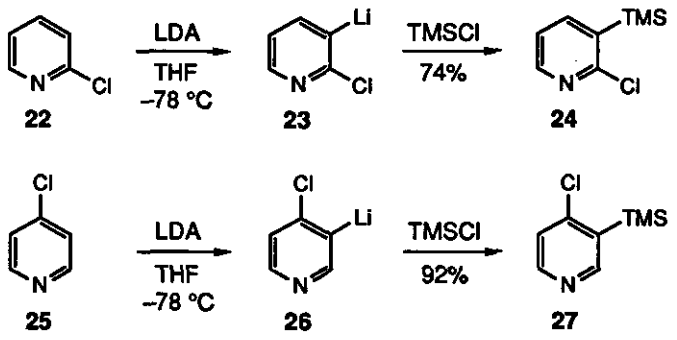
The stability of these 3-halo-4-lithiopyridines appears to be in the predictable order:[9,16] **8** >> **5** > **11** >> **14**, as judged by visual decomposition of each reaction mixture. The 3-fluoro-4-lithiopyridine (**8**) is exceptionally stable and only succumbed to being quenched with iodine at about –30 °C. The lithiochloropyridine (**5**) is stable for at least one hour at –78 °C, but rapidly decomposes at higher temperatures. The bromo species (**11**) is stable for 10-15 min at –78 °C, and, in fact, must be cooled to –100 °C prior to quenching. As already noted, the iodo species (**14**) is apparently only fleetingly stable at –95 °C. As Quéguiner has shown, at higher temperature these lithiohalopyridines rearrange or suffer ring opening.[15]

To establish the precise regiochemistry of this lithiation reaction, we carefully examined the composition of the reaction mixture obtained by quenching 3-chloro-4-lithiopyridine (**5**) with iodine. This crude product was subjected to medium pressure preparative liquid chromatography[17] to yield 3-chloro-4-iodopyridine (**6a**) (93%), 3-chloro-4,5-diiodopyridine (**19**) (3%), and an inseparable mixture of 2-iodo-3-chloropyridine (**20**) (2%) and 3-chloro-5-iodopyridine (**21**) (2%). These compounds were readily identified by their ^{1}H nmr and mass spectra. Assuming that the diiodide (**19**) is formed by a hydrogen-metal exchange reaction between 3-chloro-4-lithiopyridine (**5**) and 3-chloro-4-iodopyridine (**6a**), then the true regiolithiation of 3-chloropyridine (**4**) is 96% at H-4 and 2% each at H-2 and H-5. This is in qualitative agreement with the kinetic acidity data.[13]



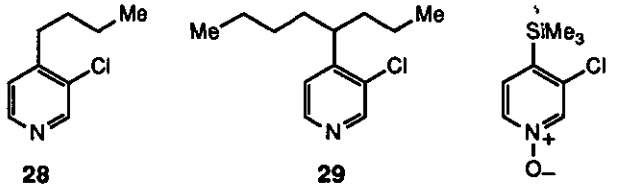
6a **19** **20** **21**

Regioselective *ortho*-lithiation of 2-chloro- (**22**) and 4-chloropyridine (**25**) can also be effected with LDA (THF, –78 °C) to generate **23** and **26**, respectively. Quenching at –78 °C with chlorotrimethylsilane gives the corresponding **24** and **27** in good to excellent yields. There is a high degree of regioselectivity observed in these two metalation reactions, but the precise regiolithiation of **22** and **25** remains to be established.



22 23 24 25 26 27

Reaction of 3-chloro-4-lithiopyridine (**5**) with *n*-butyl iodide is complicated by deprotonation of the initial product and a subsequent second alkylation. Thus, the products obtained in this reaction are 3-chloro-4-*n*-butylpyridine (**28**) and 3-chloro-4-(4-*n*-octyl)pyridine (**29**).



28 29 30

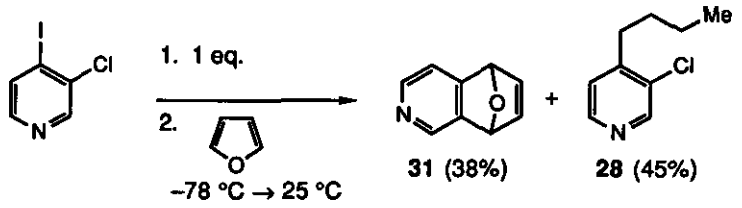
Interestingly, 3-chloro-4-trimethylsilylpyridine (**6b**) and its *N*-oxide (**30**), prepared by *m*-chloroperbenzoic acid (*m*-CPBA) oxidation of **6b**, do not undergo aromatic electrophilic *ipso*-desilylation, even under forcing conditions. Thus, treatment of **6b** with iodine monochloride in refluxing CCl_4 for 28 h or with neat benzaldehyde (130 °C, 5 h) resulted in no reaction. Moreover, *N*-oxide (**30**) was inert to ICl (CCl_4, reflux, 22 days), and 3-fluoro-4-trimethylsilylpyridine (**9b**) was impervious to the action of MeLi.

Attempts to lithiate pyridine itself using the standard conditions imparted a bright canary yellow color to the reaction mixture, but no substituted pyridines could be isolated after the addition of various electrophiles. Meth-Conn had earlier isolated 2,2'-bipyridine from the reaction of pyridine with LDA (Et_2O, various temperatures).[18]

Generation of 3,4-Pyridyne and Diels-Alder Trapping.

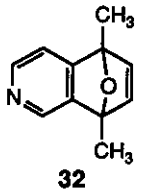
Treatment of 3-chloro-4-iodopyridine (**6a**) with 1 equiv. of *n*-butyllithium (THF, –78 °C) generates 3-chloro-4-lithiopyridine (**5**). Furan was added to the reaction mixture at –78 °C and it was allowed to warm slowly to room temperature. Workup gave the desired Diels-Alder adduct (**31**) in 38% yield, along with 3-chloro-4-*n*-butylpyridine (**28**) in 45% yield, which is presumably formed by the alkylation of **5** by *in situ* generated *n*-butyl iodide. In

addition, a considerable amount of dark polymer was present, probably initiated by the reaction of 3,4-pyridyne (**1**), which is highly susceptible to nucleophilic addition, with its precursor lithiochloropyridine (**5**).



31 (38%) **28** (45%)

The alkylation problem (cf. **28**) was circumvented by employing *tert*-butyllithium (2 equiv.,[19] –95 °C) for the halogen-metal exchange reaction. Under these conditions, cycloadduct (**31**) was isolated in 33% purified yield and no alkylated products were found. Unfortunately, the dark polymer was again present. We designed and had constructed a low-temperature-controlled, inverse-addition apparatus[20] that would allow for the instantaneous generation of 3,4-pyridyne (**1**) in a medium relatively free of its nucleophilic precursor (**5**), but rich in diene trap. Thus, treatment of **6a** with *tert*-BuLi (2 equiv., –100 °C) in the upper reaction vessel generated **5**, which is stable for at least 2 h at –100 °C. This solution was then added slowly over 1 h to a solution of excess furan in dry THF at various temperatures (20 to –30 °C) above that required for the elimination of LiCl from **5**. Under these conditions, none of the usual dark polymer formed, but the yield of cycloadduct (**31**) was about the same as in earlier experiments. A similar reaction with 2,5-dimethylfuran as trap gave **32** in 24% purified yield.



32

Although the generation and trapping of 3,4-pyridyne from 3-chloro-4-lithiopyridine by a halogen-metal exchange protocol from 3-chloro-4-iodopyridine remains to be optimized, it is gratifying that the basic purpose for the use of this apparatus[20] was successful in obstructing the formation of the otherwise ubiquitous 3,4-pyridyne polymer. Furthermore, the yields of furan Diels-Alder cycloadducts (**31**) and (**32**), combined with the ease of preparation of precursor (**6a**), makes this method of 3,4-pyridyne generation compare favorably with other, newer procedures.[6]

EXPERIMENTAL

General. Melting points were determined in open capillaries with a Mel-Temp Laboratory Devices apparatus and are uncorrected. Elemental analyses were performed by Atlantic Microlabs, Atlanta, GA. Infrared (ir) spectra were recorded on a Perkin-Elmer 599 instrument. ^{1}H Nmr spectra were routinely obtained at 60 MHz with a Hitachi Perkin-Elmer R-24 spectrometer and, in certain cases, with a JEOL-FX60Q Fourier transform NMR spectrometer. Chemical shifts are reported in parts per million downfield from tetramethylsilane as the internal reference. ^{13}C Nmr spectra were measured on a JEOL-FX60Q Fourier transform NMR spectrometer operating at 15 MHz. High resolution ^{1}H nmr (360 MHz) and ^{13}C nmr (90 MHz) spectra were generously supplied by the Regional NMR Center, Colorado State University, Fort Collins, CO. High resolution mass spectra were obtained at the NIH Regional Facility at the Massachusetts Institute of Technology by Dr. Catherine E. Costello. Low resolution mass spectra were determined on a Finnigan EI-CI gas chromatograph-mass spectrometer. Medium pressure liquid chromatography was performed on an apparatus modeled after that originally designed by Meyers.[17] Thin layer chromatography (tlc) was performed on precoated (0.2 mm) silica gel 60 F_{254} plastic sheets (E. Merck). Spots were visualized under 254 nm ultraviolet light and/or by spraying with a solution of 3% aqueous ceric ammonium sulfate in 10% sulfuric acid followed by brief heating. The alkyllithium reagents were purchased from Aldrich and standardized by titration against 2,5-dimethoxybenzyl alcohol.[21] Tetrahydrofuran was distilled from sodium/benzophenone and diisopropylamine and 2,2,6,6-tetramethylpiperidine were distilled over sodium hydride. The halopyridine compounds were observed by tlc using 95:5 ethyl acetate (EtOAc)-triethylamine (Et_3N) to develop the plates. For many of the lithiation procedures, a 3-neck round-bottomed flask fitted with an internal thermometer, magnetic stirring bar, argon inlet adapter, and rubber serum cap was found to be most convenient. All reactions were performed in oven-dried (130 °C) glassware under prepurified argon or nitrogen.

3-Chloro-4-lithiopyridine (5). To a magnetically stirred solution of dry diisopropylamine (3.70 ml, 26.4 mmol) in dry THF (20 ml) under N_2 at –78 °C was added *via* syringe *n*-BuLi (1.60 M in hexane; 16.5 ml, 26.4 mmol). This solution of LDA was stirred at –78 °C for 20 min and then treated dropwise over 10-15 min (keeping the internal temperature below –70 °C) with a solution of 3-chloropyridine (3.00 g, 2.51 ml, 26.4 mmol) in dry THF (5 ml). The resulting lithiopyridine (5) partially precipitated as a colorless solid in a light yellow-orange solution. The mixture was stirred for 20-30 min at –78 °C and then quenched *in situ* with the electrophiles listed in the Table and as described below.

3-Chloro-4-iodopyridine (6a). A magnetically stirred solution of **5** (prepared from **4**, 3.00 g, 26.4 mmol) was treated over 10 min under N_2 with a solution of iodine (6.70 g, 26.4 mmol) in dry THF (15 ml) keeping the internal temperature below –65 °C. The reaction mixture was allowed to warm to 5 °C over 4-5 h, poured into 8% aqueous sodium bisulfite (100 ml), and extracted with Et_2O (3 x 150 ml). The combined organic extracts were washed with 8% aqueous sodium bisulfite (50 ml), 5% aqueous $NaHCO_3$ (50 ml), H_2O (75 ml), and brine (2 x 125 ml), dried (K_2CO_3), and concentrated in vacuo to give 7.50 g of crude **6a** as a brown solid. Sublimation at 50-60 °C/2 Torr gave 4.08 g (65%) of **6a** as colorless needles, mp 100-102 °C. A portion of this material (1.50 g) was dissolved in CH_2Cl_2 (5 ml) and subjected to medium pressure liquid chromatography over silica gel with CH_2Cl_2 elution to give the following ratios of separated products: 3-chloro-4-iodopyridine (**6a**) (93%; mp 105.5-106 °C (lit.,[22] mp 105-106 °C)); 3-chloro-4,5-diiodopyridine (**19**) (3%; mp 150-151 °C); and an inseparable mixture of 2-iodo-3-chloropyridine (**20**) and 3-chloro-5-iodopyridine (**21**) (4%; *ca.* 55:45 by their cleanly separated ^1H nmr signals). For **6a**: ir (KBr) 1545, 1445, 1385, 1270, 1130, 835, 748, 720 cm^{-1}; ^1H nmr ($CDCl_3$) δ 8.57 (1 H, s), 8.06 (1 H, d, J = 5 Hz), 7.75 (1 H, d, J = 5 Hz); ^{13}C nmr ($CDCl_3$) δ 148.3, 147.1, 137.0, 134.6, 108.9; ms *m/z* 239 (M^+, 44%), 204, 127, 112 (83%), 85, 76 (31%), 50 (100%); uv (MeOH) λ_{max} 241, 272 nm. For **19**: ^1H nmr ($CDCl_3$) δ 7.84 (broad s); ms *m/z* 365 (M^+, 22%), 238, 127, 111, 85, 76 (100%). For **20** and **21**: ^1H nmr ($CDCl_3$) δ 8.33 (1 H, d of d, J = 5 and 2 Hz), 7.70 (1 H, d of d, J = 7 and 2 Hz), 7.25 (1 H, d of d, J = 5 and 7 Hz); 8.76 (1 H, d, J = 2 Hz), 8.58 (1 H, d, J = 2 Hz), 8.07 (1 H, d of d, J = 2 and 2 Hz). The mass spectrum of the mixture of **20** and **21** showed *m/z* 239 (M^+, 55%), 204, 127, 112 (100%), 85, 76, 50.

3-Chloro-4-trimethylsilylpyridine (6b). A magnetically stirred solution of **5** (prepared from **4**, 3.00 g, 26.4 mmol) was treated over 5-10 min under N_2 with a solution of freshly distilled chlorotrimethylsilane (3.60 ml, 28.4 mmol) in dry THF (15 ml) maintaining the internal temperature below –65 °C. The reaction mixture was allowed to warm to room temperature overnight, partially concentrated in vacuo, poured into 5% aqueous $NaHCO_3$ (100 ml), and extracted with Et_2O (3 x 100 ml). The combined organic extracts were washed with H_2O (1 x 75 ml), and brine (2 x 75 ml), dried (K_2CO_3), and concentrated in vacuo to afford 5.37 g of a light pink oil. Distillation gave 4.72 g (96%) of **6b** as a colorless liquid: bp 75-77 °C/1 Torr; ir (neat film) 3075, 2970, 2915, 1579, 1470, 1395, 1255, 1183, 1127, 1085, 1030, 840, 725, 622, 565 cm^{-1}; ^1H nmr ($CDCl_3$) δ 8.55 (1 H, s), 8.50 (1 H, d, J = 5 Hz), 7.32 (1 H, d, J = 5 Hz), 0.40 (9 H, s); ^{13}C nmr ($CDCl_3$) δ 148.5, 147.9, 146.5, 138.3,

129.2, 1.54; uv (95% EtOH) λ_{max} 272 nm. Anal. Calcd for $C_8H_{12}NClSi$: C, 51.73; H, 6.51; N, 7.54; Cl, 19.09. Found: C, 51.67; H, 6.60; N, 7.51; Cl, 19.05.

3-Chloro-4-thiophenylpyridine (6c). A magnetically stirred solution of **5** (prepared from **4**, 3.00 g, 26.4 mmol) was treated over 10 min under N_2 with a solution of diphenyl disulfide (5.77 g, 26.4 mmol) in dry THF (25 ml) maintaining the internal temperature below –65 °C. The reaction mixture was allowed to warm to room temperature overnight, poured into 6% aqueous sodium bisulfite (100 ml), and extracted with Et_2O (4 x 100 ml). The combined extracts were washed with cold 2 N aqueous NaOH (3 x 75 ml), H_2O (2 x 50 ml), and brine (2 x 75 ml), dried (K_2CO_3), and concentrated in vacuo to give 6.10 g of a viscous orange-brown oil which crystallized when triturated with 2:1 hexane-Et_2O (15 ml). After standing in the cold for 7 days, 5.65 g of tan crystals were collected and then recrystallized (3x) from 5:1 hexane-Et_2O (with activated charcoal decolorization the initial time). A final recrystallization from hexane gave 4.38 g (75%) of analytically pure **6c** as colorless crystals in two crops: mp 52.5-53.0 °C; ir (KBr) 3045, 1560, 1450, 1400, 1275, 1130, 1080, 1025, 820, 750, 685, 595, 490 cm^{-1}; ^1H nmr ($CDCl_3$) δ 8.45 (1 H, s), 8.18 (1 H, d, J = 5 Hz), 7.58 (5 H, s), 6.55 (1 H, d, J = 5 Hz); ^{13}C nmr ($CDCl_3$) δ 149.3, 148.8, 146.9, 135.6, 129.9, (2 C's), 127.9, 127.7, 120.0; uv (95% EtOH) λ_{max} 218, 262 nm. Anal. Calcd for $C_{11}H_8NClS$: C, 59.59; H, 3.64; N, 6.32; Cl, 15.99; S, 14.46. Found: C, 59.59; H, 3.65; N, 6.32; Cl, 15.99; S, 14.42.

1-Phenyl-1-(3-chloro-4-pyridyl)methanol (6d). A magnetically stirred solution of **5** (prepared from **4**, 3.00 g, 26.4 mmol) was treated over 10 min under N_2 with a solution of freshly distilled benzaldehyde (2.94 g, 27.7 mmol) in dry THF (20 ml) keeping the internal temperature below –70 °C. The reaction mixture was warmed to 40 °C over 45 min and quenched with an aqueous solution of NH_4Cl (1.41 g) in H_2O (20 ml). The mixture was allowed to warm to room temperature, poured into H_2O (100 ml), and extracted with Et_2O (3 x 100 ml). The combined extracts were washed with H_2O (1 x 25 ml), and brine (2 x 100 ml), dried (K_2CO_3), and concentrated in vacuo to afford 7.20 g of an amber oil which crystallized when triturated with hexane (25 ml). After standing in the cold for 24 h, the product was collected by filtration, washed with hexane, and dried to provide 3.27 g (57%) of analytically pure **6d** as fluffy white crystals: mp 140-140.5 °C; ir ($CHCl_3$) 3605, 2990, 1585, 1450, 1397, 1160, 1017, 694, 651, 598 cm^{-1}; ^1H nmr (DMSO-d_6) δ 8.64 (1 H, d, J = 5.5 Hz), 8.60 (1 H, s), 7.87 (1 H, d, J = 5.5 Hz), 7.38 (5 H, s), 6.43 (1 H, d, J = 4 Hz), 6.09 (1 H, d, J = 4 Hz); ^{13}C nmr ($CDCl_3$) δ 149.9, 148.9, 147.6, 140.7, 129.9, 128.5, 128.2, 127.0, 121.9, 71.8. Anal. Calcd for $C_{12}H_{10}NOCl$: C, 65.61; H, 4.59; N, 6.38; Cl, 16.14. Found: C, 65.69; H, 4.64; N, 6.39; Cl, 16.08.

1,1-Diphenyl-1-(3-chloro-4-pyridyl)methanol (6e). A magnetically stirred solution of **5** (prepared from **4**, 3.00 g, 26.4 mmol) was treated with a solution of benzophenone (5.05 g, 27.7 mmol) in dry THF (20 ml) according to the procedure used for **6d**. After the mixture was warmed to room temperature and poured into H_2O (50 ml), much precipitate had appeared which did not dissolve when a 2:1 mixture of Et_2O-CH_2Cl_2 (150 ml) was added. The precipitate was collected by filtration, washed sequentially several times with H_2O and Et_2O, and thoroughly dried to afford 4.52 g (58%) of analytically pure **6e** as a white powder, mp 210-211 °C. An additional 0.56 g (7%) of **6e** was obtained from the organic extracts according to the procedure used for **6d**, mp 203-207 °C. The combined yield of **6e** was 5.08 g, 65%; ir (KBr) 3160, 1574, 1396, 1280, 1185, 1025, 830, 733, 690, 634, 574 cm^{-1}; ^1H nmr (DMSO-d_6) δ 8.61 (1 H, s), 8.56 (1 H, d, J = 5 Hz), 7.34 (10 H, s), 7.25 (1 H, d, J = 5 Hz), 6.80 (1 H, br s). Anal. Calcd for $C_{18}H_{14}NOCl$: C, 73.09; H, 4.77; N, 4.73; Cl, 11.98. Found: C, 72.91; H, 4.83; N, 4.67; Cl, 11.84.

2-(3-Chloro-4-pyridyl)-2-propanol (6f). A magnetically stirred solution of **5** (prepared from **4**, 3.00 g, 26.4 mmol) was treated over 10 min under N_2 with a solution of freshly distilled (from Drierite) acetone (1.61 g, 27.7 mmol) in dry THF (10 ml) keeping the internal temperature below –75 °C. The reaction mixture was warmed to –20 °C over 3 h and quenched with an aqueous solution of NH_4Cl (1.41 g) in H_2O (20 ml). The mixture was allowed to warm to room temperature, poured into H_2O (100 ml), and, after saturating the aqueous phase with NaCl, extracted with Et_2O (4 x 75 ml) and then $CHCl_3$ (2 x 50 ml). The combined extracts were washed with brine (1 x 75 ml), dried (K_2CO_3), and concentrated in vacuo to afforded 4.33 g of a light amber oil. The ^1H nmr spectrum of this crude material indicated 3-chloropyridine (**4**) and **6f** in an integrated ratio of 63:37, respectively. After removing most of the 3-chloropyridine at 25 °C/0.35 Torr, the viscous residue (2.36 g) was triturated with 9:1 hexane-Et_2O (10 ml) to afford 1.25 g (28%) of **6f** as colorless crystals, mp 66-68 °C. Recrystallization from hexane gave the analytical sample: mp 77-78 °C; ir ($CHCl_3$) 3605, 3295, 2985, 1595, 1468, 1408, 1374, 1336, 1225, 1166, 1041, 962, 851 cm^{-1}; ^1H nmr (DMSO-d_6) δ 8.55 (1 H, s, 8.54 (1 H, d, J = 5.5 Hz), 7.83 (1 H, d, J = 5.5 Hz), 5.55 (1 H, s), 1.63 (s, 6 H); ^{13}C nmr ($CDCl_3$) δ 153.6, 150.7, 148.1, 128.8, 121.2, 72.4, 28.6. Anal. Calcd for $C_8H_{10}NOCl$: C, 55.99; H, 5.87; N, 8.16; Cl, 20.66. Found: C, 55.82; H, 5.87; N, 8.14; Cl, 20.61.

3-Chloro-4-bromopyridine (6g). A magnetically stirred solution of **5** (prepared from **4**, 3.00 g, 26.4 mmol) was treated over 5-10 min under N_2 with a cold solution of bromine (4.22 g, 26.4 mmol) in dry THF (15 ml) resulting in an extremely exothermic reaction. The mixture was allowed to warm to room temperature and

worked up as for **6a**. Sublimation of the crude product at 60-80 °C/20 Torr gave 0.80 g (16%) of **6g** as colorless crystals: mp 69-70 °C (lit.,[22] mp 71-72 °C); ir ($CHCl_3$) 1550, 1460, 1390, 1260, 1025, 825 cm^{-1}; ^1H nmr ($CDCl_3$) δ 8.56(1 H, s), 8.24 (1 H, d, J = 5 Hz), 7.54 (1 H, d, J = 5 Hz); uv (MeOH) λ_{max} 228, 269 nm.

3-Chloro-4-phenylsulfonylpyridine (6h). A magnetically stirred solution of **5** (prepared from **4**, 3.00 g, 26.4 mmol) was treated over 1-2 min under N_2 with a –78 °C solution of freshly distilled $PhSO_2Cl$ (3.60 ml, 27.7 mmol) in dry THF (20 ml) from a jacketed constant-addition funnel while maintaining the internal temperature below –60 °C. The reaction mixture was warmed to room temperature overnight, poured into 5% aqueous $NaHCO_3$ (75 ml) and extracted with Et_2O (4 x 80 ml). The combined extracts were washed with H_2O (1 x 50 ml), and brine (2 x 75 ml), dried (K_2CO_3), and concentrated in vacuo to afford 5.38 g (80%) of a light reddish oil which crystallized on standing overnight under N_2. The ^1H nmr spectrum indicated a very clean product consistent with **6h**. However, the material could not be further purified due to its instability: ^1H Nmr ($CDCl_3$) δ 8.61 (1 H, s), 8.50 (1 H, d, J = 5 Hz), 8.47 (2 H, d, J = 9 Hz), 8.09 (1 H, m), 7.85-7.52 (2 H, m), 7.38 (1 H, d, J = 5 Hz).

3-Fluoro-4-lithiopyridine (8). To a magnetically stirred solution of dry diisopropylamine (1.85 ml, 13.2 mmol) in dry THF (10 ml) under N_2 at –78 °C was added *via* syringe *n*-BuLi (1.60 M in hexane; 8.25 ml, 13.2 mmol). This solution of LDA was stirred at –78 °C for 20 min and then treated dropwise over 5 min with a solution of 3-fluoropyridine (**7**) (1.28 g, 13.2 mmol) in dry THF (3 ml). The resulting **8** partially precipitated as a colorless solid in a bright yellow solution. The mixture was stirred for 30 min at –78°C and then quenched *in situ* with the electrophiles listed in the Table and as described below.

3-Fluoro-4-iodopyridine (9a). A magnetically stirred solution of **8** (prepared from **7**, 1.28 g, 13.2 mmol) was treated over 5 min under N_2 with a solution of iodine (3.35 g, 13.2 mmol) in dry THF (10 ml). The reaction mixture was allowed to warm to room temperature overnight, poured into 3% aqueous sodium thiosulfate (100 ml), and extracted with Et_2O (3 x 100 ml). The combined organic extracts were washed with H_2O (1 x 50 ml), and brine (2 x 50 ml), dried (K_2CO_3), and concentrated in vacuo to afford 2.94 g of crude **9a** as a dark oily solid. Sublimation at 20-25 °C/20 Torr gave 1.47 g (50%) of pure **9a** as colorless needles: mp 80-81 °C (lit.,[23] mp 87 °C); ir ($CHCl_3$) 3000, 1570, 1478, 1415, 1280, 825, 648, 615, 585, 560 cm^{-1}; ^1H nmr ($CDCl_3$) δ 8.30 (1 H, s), 8.05 (1 H, m), 7.79-7.58 (1 H, m).

3-Fluoro-4-trimethylsilylpyridine (9b). A magnetically stirred solution of **8** (prepared from **7**, 1.28 g, 13.2 mmol) was treated over 5 min under N_2 with a solution of freshly distilled TMSCl (1.80 ml, 14.2 mmol) in

dry THF (7 ml) keeping the internal temperature below –60 °C. The reaction mixture was allowed to warm to room temperature overnight, poured into 5% aqueous $NaHCO_3$ (100 ml), and extracted with Et_2O (3 x 100 ml). The combined extracts were washed with H_2O (1 x 50 ml), and brine (2 x 50 ml), dried (K_2CO_3), and concentrated in vacuo to afford 2.99 g of a pale yellow oil. Distillation gave 1.93 g (87%) of **9b** as a colorless liquid: bp 40-42 °C/0.5 Torr; ir (neat) 3070, 2980, 2920, 1538, 1485, 1412, 1270, 1235, 1205, 1100, 1060, 850, 765, 728, 625 cm^{-1}; ^1H nmr ($CDCl_3$) δ 8.5-8.3 (2 H, m), 7.30 (1 H, m), 0.35 (s, 9 H); ^{13}C nmr ($CDCl_3$) δ 172.0, 155.3, 144.9, 144.6, 137.9, 136.0, 128.9, 128.4, 1.65. Anal. Calcd for $C_8H_{12}NFSi$: C, 56.76; H, 7.15; N, 8.27. Found: C, 56.66; H, 7.19; N, 8.27.

3-Bromo-4-lithiopyridine (11). To a magnetically stirred solution of dry diisopropylamine (3.70 ml, 26.4 mmol) in dry THF (25 ml) under argon at –78 °C was added *via* syringe *n*-BuLi (1.60 M in hexane; 16.5 ml, 26.4 mmol). This solution of LDA was stirred at –78 °C for 20 min and then treated over 5 min neat *via* syringe with 3-bromopyridine (4.17 g, 2.54 ml, 26.4 mmol) keeping the internal temperature below –75 °C. The resulting lithiopyridine (**11**) appeared as a cloudy light orange suspension. The mixture was immediately cooled to –90 °C, maintained at –80 to –90 °C for 20 min, and then quenched *in situ* with the electrophiles listed in the Table and as described below.

3-Bromo-4-thiophenylpyridine (12a). A magnetically stirred solution of **11** (prepared from **10**, 4.17 g, 26.4 mmol) was treated over 3-5 min under argon with a solution of diphenyl disulfide (5.77 g, 26.4 mmol) in dry THF (25 ml) maintaining the internal temperature below –65 °C (very exothermic reaction). The reaction mixture was allowed to warm to room temperature overnight, poured into 6% aqueous sodium bisulfite (100 ml), and extracted with Et_2O (3 x 125 ml). The combined extracts were washed with 6% aqueous sodium bisulfite (1 x 100 ml), 2 N aqueous NaOH (3 x 50 ml), H_2O (2 x 75 ml), and brine (2 x 75 ml), dried (K_2CO_3), and concentrated in vacuo to afford 8.24 g of a brown viscous oil. The ^1H nmr spectrum of this material indicated **12a** and a considerable amount of diphenyl disulfide. This crude product was then dissolved in Et_2O (150 ml) and extracted with cold 3 N aqueous HCl (3 x 75 ml). The combined acidic portions were basified with solid KOH to pH 8-9 and extracted with Et_2O (3 x 125 ml). The combined Et_2O extracts were washed with H_2O (2 x 75 ml), and brine (2 x 75 ml), dried (K_2CO_3), and concentrated in vacuo to give 4.93 g of a red brown oil. Column chromatography over silica gel with 2:1 hexane-Et_2O provided 4.29 g (61%) of **12a** as an amber oil which slowly crystallized under N_2 in the cold, mp 48.5-49.5 °C. Recrystallization from hexane gave the analytical sample as colorless prisms: mp 53.5-54 °C; ir (KBr) 3045, 1560, 1445, 1400, 1275, 1080, 1020, 825 cm^{-1};

^{1}H nmr ($CDCl_3$) δ 8.52 (1 H, s), 8.18 (1 H, d, J = 5 Hz), 7.53 (5 H, s), 6.50 (1 H, d, J = 5 Hz); ^{13}C nmr ($CDCl_3$) δ 151.5, 150.7, 147.4, 135.7, 130.1 (2 C's), 128.5, 120.4, 118.1; uv (95% EtOH) λ_{max} 220, 260 nm. Anal. Calcd for $C_{11}H_8NBrS$: C, 49.64; H, 3.03; N, 5.26; Br, 30.02; S, 12.05. Found: C, 49.60; H, 3.07; N, 5.26; Br, 30.00; S, 12.04.

1-(3-Bromo-4-pyridyl)ethanol (12b). A magnetically stirred solution of **11** (prepared from **10**, 4.17 g, 26.4 mmol) was treated under argon at –90 °C neat *via* syringe over 5 min with freshly distilled acetaldehyde (1.90 ml, 34.0 mmol) maintaining the internal temperature below –75 °C. The mixture was allowed to stir at –90 °C for 1 h, warmed to –20 °C over 30 min, and then poured into an aqueous solution of NH_4Cl (1.60 g) in H_2O (100 ml). The aqueous phase was saturated with NaCl and extracted with CH_2Cl_2 (4 x 100 ml). The combined organic extracts were washed with brine (2 x 50 ml), dried (K_2CO_3), and concentrated in vacuo to afford 6.66 g of a dark orange oil. Column chromatography over florisil with 1:1 hexane-benzene gave initially, trace amounts of 3-bromopyridine (**10**) and other nonpolar oils. Elution with EtOAc then afforded 4.23 g (79%) of **12b** as a light amber viscous oil which crystallized under N_2 in the cold: mp 74-75 °C; ir ($CHCl_3$) 3610, 3260, 2985, 1588, 1450, 1400, 1370, 1250, 1163, 1015, 902, 842, 611, 572 cm^{-1}; ^{1}H nmr ($CDCl_3$) δ 8.43 (1 H, s), 8.32 (1 H, d, J = 5.5 Hz), 7.52 (1 H, d, J = 5.5 Hz), 5.56 (1 H, br s), 5.06 (1 H, q, J = 6 Hz), 1.42 (3 H, d, J = 6 Hz); ms *m/z* 203, 201 (M^+), 188, 186, 160, 158, 122, 106, 78 (100%), 51. An elemental analysis was not obtained for this compound.

1-(3-Bromo-4-pyridyl)-1-phenylethanol (12c). A magnetically stirred solution of **11** (prepared from **10**, 4.17 g, 26.4 mmol) was treated under argon at –100 °C neat *via* syringe over 2 min with acetophenone (3.33 g, 27.7 mmol) keeping the internal temperature below –85 °C. The mixture was stirred at –90 °C for 2 h, warmed to –20 °C over 1 h, and then worked up according to the procedure used for **12b** to afford 9.69 g of an amber oil. The ^{1}H nmr spectrum of this material showed **12c**, in addition to a considerable amount of 3-bromopyridine and acetophenone. After removing most of the latter two components at 30 °C/0.2 Torr, the residue was triturated with 2:1 hexane-Et_2O (30 ml) and allowed to stand in the cold for 2 h. The product was collected by filtration, washed with Et_2O, and dried (70 °C/0.5 Torr) to give 2.65 g (36%) of analytically pure **12c** as a colorless powder: mp 146-148 °C; ir ($CHCl_3$) 3605, 3560, 3240, 2990, 1581, 1448, 1400, 1372, 1328, 1158, 1017, 908, 835 cm^{-1}; ^{1}H nmr ($CDCl_3$) δ 8.50 (1 H, s), 8.45 (1 H, d, J = 5 Hz), 7.93 (1 H, d, J = 5 Hz), 7.32 (5 H, s), 4.14 (1 H, s), 2.00 (3 H, s); ^{13}C nmr ($CDCl_3$) δ 154.4, 153.2, 148.2, 144.8, 128.2, 127.5, 125.9, 122.6, 120.0, 76.3, 27.6; ms *m/z* 279, 277 (M^+), 264 (100%), 262, 198, 186, 184, 159, 157, 129, 121, 105. Anal.

Calcd for $C_{13}H_{12}NOBr$: C, 56.14; H, 4.35; N, 5.04; Br, 28.73. Found: C, 56.20; H, 4.38; N, 5.02; Br, 28.70.

1-[1-Phenylsulfonylindol-2-yl]-1-(3-bromo-4-pyridyl)methanol (16). A magnetically stirred solution of 3-bromo-4-lithiopyridine (**11**) (prepared from **10**, 0.864 g, 5.47 mmol) in dry THF (20 ml) was treated under Ar at –100 °C with a solution of 1-phenylsulfonylindole-2-carboxaldehyde (**15**)[20] (1.30 g, 4.56 mmol) in dry THF (10 ml) over 5 min maintaining the internal temperature below –78 °C. The reaction mixture was allowed to stir at –90 °C for 1.5 h, warmed to –75 °C, and quenched with a solution of NH_4Cl (0.29 g) in H_2O (20 ml). The mixture was allowed to warm to room temperature, poured into H_2O (150 ml), and extracted with CH_2Cl_2 (3 x 100 ml). The organic extracts were washed with brine (2 x 100 ml), dried (Na_2SO_4), and concentrated in vacuo to afford 2.98 g of a dark orange oil. Chromatography over florisil (Et_2O; 2:1 Et_2O-acetone) gave 1.64 g (81%) of **16** as a foamy white solid (R_f, 0.33, 95:5 EtOAc-Et_3N). Crystallization from 1:1:1 Et_2O-$CHCl_3$-acetone gave the analytical sample: mp 153-154 °C; ir ($CHCl_3$) 3580, 2990, 1585, 1448, 1365, 1295, 1166, 1144, 1085, 1020, 915, 816 cm^{-1}; ^1H nmr ($CDCl_3$) δ 8.65 (1 H, s), 8.62 (1 H, d, J = 5 Hz), 8.3-7.1 (10 H, m), 6.47 (1 H, d, J = 4 Hz), 5.91 (1 H, s), 4.51 (1 H, d, J = 4 Hz); ^{13}C nmr ($CDCl_3$) δ 151.4, 148.7, 148.6, 140.3, 138.5, 137.3, 134.0, 129.3, 128.4, 126.6, 125.5, 123.9, 123.3, 121.4, 120.7, 114.4, 111.6, 67.3; uv (95% EtOH) λ_{max} 218, 253 nm. Anal. Calcd for $C_{20}H_{15}N_2O_3BrS$: C, 54.19; H, 3.41; N, 6.32; Br, 18.02; S, 7.23. Found: C, 54.11; H, 3.41; N, 6.30; Br, 18.00; S, 7.22.

1-[1-Phenylsulfonylindol-2-yl]-1-(3-bromo-4-pyridyl)ethanol (18). A magnetically stirred solution of 3-bromo-4-lithiopyridine (**11**) (prepared from **10**, 3.32 g, 21.05 mmol) in dry THF (60 ml) was treated under Ar at –100 °C with a solution of 1-phenylsulfonyl-2-indolyl methyl ketone (**17**)[24] (5.25 g, 17.5 mmol) in dry THF (35 ml) over 5 min maintaining the internal temperature below –90 °C. The reaction mixture was kept below –80 °C for 1.5 h, warmed to 10 °C over 3.5 h, and quenched with 5% aqueous NH_4Cl (150 ml). The mixture was diluted with brine (100 ml) and extracted with CH_2Cl_2 (4 x 125 ml). The organic extracts were washed with brine (1 x 200 ml), dried (K_2CO_3), and concentrated in vacuo to afford 10.18 g of a dark orange oil which was further dried at 60 °C/0.2 Torr for 2 h to remove 3-bromopyridine (**10**). The resulting light tan solid (7.15 g) was flash chromatographed over silica gel. Initial elution with CH_2Cl_2 provided 1.98 g (38%) of recovered ketone (**17**) and subsequent elution with 1:1 CH_2Cl_2-EtOAc gave 4.56 g (57%; 91% based on recovered **17**) of **18** as an off-white solid, mp 175-178 °C. Recrystallization from $CHCl_3$ gave the analytical sample as colorless crystals: mp 184-185 °C; ir (KBr) 3160, 1594, 1451, 1377, 1294, 1176, 1129, 1074, 1024, 933, 835, 760 cm^{-1}; ^1H nmr

($CDCl_3$) δ 8.48 (1 H, d, J = 5 Hz), 8.3-7.9 (2 H, m), 7.9-7.1 (9 H, m), 7.02 (1 H, s), 5.21 (1 H, br s), 2.00 (3 H, s); ^{13}C nmr ($CDCl_3$) δ 153.23, 153.18, 147.9, 143.1, 138.3, 138.0, 133.4, 128.8, 128.2, 125.5, 125.3, 123.9, 122.8, 121.4, 118.6, 114.9, 114.5, 73.0, 29.3; ms *m/z* 458, 456 (M^+), 443, 441, 377, 317, 315, 300, 219, 186, 184, 144, 89, 77 (100%); uv (EtOH) λ_{max} 223, 255, 292 (sh) nm. Anal. Calcd for $C_{21}H_{17}N_2O_3BrS$: C, 55.15; H, 3.75; N, 6.13; Br, 17.47; S, 7.01. Found: C, 55.07; H, 3.76; N, 6.13; Br, 17.45; S, 7.00.

2-Chloro-3-trimethylsilylpyridine (24). A magnetically stirred solution of LDA (26.4 mmol) in dry THF (20 ml) was prepared as described for **5** and then treated at –78 °C under N_2 with a solution of 2-chloropyridine (**22**) (3.00 g, 2.51 ml, 26.4 mmol) in dry THF (6 ml). The resulting **23** precipitated as a colorless solid in a light yellow solution. The mixture was stirred for 1 h at –78 °C and then quenched over 2-3 min with a solution of TMSCl (3.60 ml, 28.4 mmol) in dry THF (10 ml) maintaining the internal temperature below –78 °C. The reaction mixture was allowed to warm to room temperature overnight and then worked up according to the procedure used for **6b** to afford 6.14 g of a light amber oil. Distillation gave 3.62 g (74%) of **24** as a colorless liquid, bp 54-62 °C/0.4 Torr. Redistillation gave the analytical sample: bp 56-60 °C/0.3 Torr; ir (neat) 3045, 2960, 2905, 1560, 1418, 1367, 1250, 1201, 1120, 1058, 1039, 845, 766, 650 cm^{-1}; ^1H nmr ($CDCl_3$) δ 8.31 (1 H, d of d, J = 5 and 2.5 Hz), 7.78 (1 H, d of d, J = 7 and 2.5 Hz), 7.14 (1 H, d of d, J = 7 and 5 Hz), 0.37 (9 H, s); ^{13}C nmr ($CDCl_3$) δ 156.7, 149.8, 144.6, 134.9, 121.7, 1.5. Anal. Calcd for $C_8H_{12}NClSi$: C, 51.73; H, 6.51; N, 7.54; Cl, 19.09. Found: C, 51.86; H, 6.52; N, 7.53; Cl, 19.02.

3-Trimethylsilyl-4-chloropyridine (27). A magnetically stirred solution of LDA (26.4 mmol) in dry THF (20 ml) was prepared as described for **5** and then treated at –78 °C under N_2 with a solution of 4-chloropyridine (**25**) (3.00 g, 26.4 mmol) in dry THF (5 ml). The resulting lithiopyridine (**26**) precipitated as a colorless solid in a light yellow-orange solution. The mixture was stirred for 45 min at –78 °C and then quenched over 5-10 min with a solution of TMSCl (3.60 ml, 28.4 mmol) in dry THF (10 ml) maintaining the internal temperature below –65 °C. The reaction mixture was allowed to warm to room temperature overnight and then worked up according to the procedure used for **6b** to afford 6.18 g of a light amber oil. Distillation gave 4.50 g (92%) of **27** as a colorless liquid. Redistillation gave the analytical sample: bp 52 °C/0.65 Torr; ir (neat) 3050, 2970, 2910, 1555, 1470, 1450, 1390, 1260, 1208, 1179, 1123, 1074, 1050, 1030, 845, 765, 737, 692, 624, 565 cm^{-1}; ^1H nmr ($CDCl_3$) δ 8.55 (1 H, s), 8.43 (1 H, d, J = 5.5 Hz), 7.21 (1 H, d, J = 5.5 Hz), 0.40 (9 H, s); ^{13}C nmr ($CDCl_3$) δ 155.2, 151.0, 150.6, 133.5, 124.3, 1.2. Anal. Calcd for $C_8H_{12}NClSi$: C, 51.73; H, 6.51; N, 7.54; Cl, 19.09. Found: C, 51.91; H, 6.54; N, 7.51; Cl, 18.99.

5,8-Epoxy-5,8-dihydroisoquinoline (31). To a magnetically stirred solution of 3-chloro-4-iodopyridine (**6a**) (1.30 g, 5.42 mmol) in dry THF (25 ml) under N_2 at –95 °C was added *tert*-BuLi (2.00 M in pentane; 5.50 ml, 11.0 mmol). There immediately resulted a bright red color and, after 20 min at –95 °C, furan (4.0 ml, 55 mmol) was added *via* syringe. The reaction mixture was allowed to warm to –25 °C over 2 h, maintained at this temperature for 1 h, and then allowed to warm to room temperature overnight. The dark polymeric material was filtered and washed well with Et_2O. The organic portions (300 ml) were washed with saturated aqueous $NaHCO_3$ (1 x 100 ml) and the aqueous phase was extracted further with CH_2Cl_2 (1 x 75 ml). The combined organic portions were then washed with brine (2 x 100 ml), dried (K_2CO_3), and concentrated in vacuo to afford 0.58 g of a dark oil. Distillation gave 0.26 g (33%) of **31** as a light amber liquid (R_f, 0.30, 95:5 EtOAc-Et_3N): bp 92-100 °C/0.25 Torr (lit.,[7c] bp 100 °C/4 Torr); ir ($CHCl_3$) 3100, 1620, 1410, 1280, 995, 965, 830, 805, 790 cm^{-1}; ^1H nmr ($CDCl_3$) δ 8.35 (1 H, s), 8.20 (1 H, d, J = 5 Hz), 7.20 (1 H, d, J = 5 Hz), 6.95 (2 H, s), 5.75 (1 H, s), 5.65 (1 H, s); uv (MeOH) λ_{max} 239, 267 nm.

5,8-Epoxy-5,8-dimethyl-5,8-dihydroisoquinoline (32). To a solution of 3-chloro-4-iodopyridine (**6a**) (1.659 g, 6.923 mmol) in dry THF (65 ml) under argon at –100 °C and mechanically stirred in the upper reaction vessel[20] was added *tert*-BuLi (2.10 M in pentane; 6.59 ml, 13.8 mmol) *via* syringe over 2 min keeping the internal temperature below –80 °C. The bright red solution which resulted was stirred at –95 °C for 5 min and then slowly dripped into a –2 °C solution of freshly distilled 2,5-dimethylfuran (7.50 ml, 70.5 mmol) in dry THF (10 ml) over 25 min. The rate of addition was controlled such that the internal temperature of the bottom reaction vessel was *ca.* –2 °C throughout the addition. The reaction mixture was stored at 0 °C for 20 min and then allowed to warm to room temperature overnight. After 5% aqueous $NaHCO_3$ (150 ml) was added, the mixture was extracted with Et_2O (3 x 125 ml) and then CH_2Cl_2 (1 x 100 ml). The combined extracts were washed with H_2O (1 x 75 ml), and brine (2 x 150 ml), dried (K_2CO_3), and concentrated in vacuo to afford 1.26 g of a dark oil. Chromatography over activity III basic Al_2O_3 with 9:1 CH_2Cl_2-hexane provided 0.278 g (24%) of **32** as a colorless solid: (R_f, 0.38, 95:5 EtOAc-Et_3N) mp 80-81 °C (lit.,[7c] mp 92 °C); ir (KBr) 3065, 2975, 2935, 1603, 1444, 1422, 1390, 1319, 1162, 1147, 865, 842, 725, 661, 629, 587 cm^{-1}; ^1H nmr ($CDCl_3$) δ 8.33 (1 H, s), 8.29 (1 H, d, J = 5 Hz), 7.08 (1 H, d, J = 5 Hz), 6.75 (2 H, s), 1.90 (3 H, s), 1.85 (3 H, s); ^{13}C nmr ($CDCl_3$) δ 162.3, 147.4, 147.3, 147.0, 145.6, 138.0, 113.9, 88.2, 87.9, 15.0, 14.7.

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