mp 164–165 °C. The ^1H NMR spectral data is given in Table II.

Acknowledgment. Acknowledgment is made to the donors of the Petroleum Research Fund, administered by the American Chemical Society, for support of this research.

Registry No. *m*-$BrC_6H_4CH_3$, 591-17-3; *p*-$BrC_6H_4CH_3$, 106-38-7; *o*-$BrC_6H_4CH_3$, 95-46-5; *p*-$BrC_6H_4NO_2$, 586-78-7; *m*-$BrC_6H_4NO_2$, 585-79-5; *p*-$IC_6H_4CH_3$, 624-31-7; Me-5-Br-2,4-$I_2C_6H_2$, 123568-17-2; Me-4-Br-2,5-$I_2C_6H_2$, 123568-18-3; Me-6-Br-2,3,4,5-I_4C_6, 123568-19-4; Me-5-Br-2,3,4,6-I_4C_6, 123568-20-7; Me-2,5-Br_2-4-IC_6H_2, 123568-21-8; NO_2-4-Br-3,5-$I_2C_6H_2$, 6311-50-8; NO_2-3-Br-4,5-$I_2C_6H_2$, 98137-95-2; I_6C_6, 608-74-2; 1,2,4,5-$I_4C_6H_2$, 636-31-7; 1,4-$I_2C_6H_4$, 624-38-4; 1,2-$I_2C_6H_4$, 615-42-9; HO-2,4,6-$I_3C_6H_2$, 609-23-4; $CH_3I_5C_6$, 64349-91-3; Me-2,4,5-$I_3C_6H_2$, 32704-10-2; Me-2-Br-4,5-$I_2C_6H_2$, 123568-22-9; HO_2C-2,3,4,5,6-I_5C_6, 64385-02-0; HO_2C-3,4,5-$I_3C_6H_2$, 2338-20-7; NO_2-3,4,5-$I_3C_6H_2$, 53663-23-3; $MeO_2CCH{=}CH_2$, 96-33-3; HC≡CPh, 536-74-3; $CH_2{=}CHPh$, 100-42-5; $CH_2{=}CHCH(OH)CH_3$, 598-32-3; $(CH_3)_3SiC{\equiv}CH$, 1066-54-2; $HOC(CH_3)_2C{\equiv}CH$, 115-19-5; $Pd(OAc)_2$, 3375-31-3; $Pd(PPh_3)_2Cl_2$, 13965-03-2; (*E*)-2,5-Br_2-4-CH_3-1-$(CH_3O_2CCH{=}CH)C_6H_2$, 123568-23-0; N-O_2-4-Br-3,5-$(CH_3O_2CCH{=}CH)_2C_6H_2$, 123568-24-1; 1,2,4,5-$(CH_3O_2CCH{=}CH)_4C_6H_2$, 123568-25-2; 1,2,4-$(CH_3O_2CCH{=}CH)_3C_6H_3$, 123568-26-3; 1,4-$(CH_3O_2CCH{=}CH)_2C_6H_4$, 7549-44-2; 1,2,3,4,5,6-$(C_6H_5C{\equiv}C)_6C_6$, 110846-75-8; 1,2,4,5-$(C_6H_5C{\equiv}C)_4C_6H_2$, 25634-84-8; 1,2-$(CH_3O_2CCH{=}CH)_2C_6H_4$, 61198-30-9; HO-2,4,6-$(C_6H_5C{\equiv}C)_3C_6H_2$, 123568-27-4; Me-2,3,4,5,6-$(C_6H_5C{\equiv}C)_5C_6$, 123568-28-5; Me-2,4,5-$(CH_3O_2CCH{=}CH)_3C_6H_2$, 123568-29-6; Me-2,4,5-$(C_6H_5C{\equiv}C)_3C_6H_2$, 123568-30-9; 3-Br-4-$CH_3C_6H_3CH{=}CHC_6H_5$, 123568-31-0; 4-Br-3-$CH_3C_6H_3CH{=}CHC_6H_5$, 123568-32-1; 1,3-$(CH_3O_2CCH{=}CH)_2$-4-Br-6-$CH_3C_6H_2$, 123568-33-2; 1,4-$(C_6H_5C{\equiv}C)_2$-5-Br-2-$CH_3C_6H_2$, 123568-34-3; $(CH_3COCH_2C-H_2)$-2,5-Br_2-4-$CH_3C_6H_2$, 123568-35-4; $(CH_3O_2CCH{=}CH)$-2,5-$(C_6H_5CH{=}CH)_2$-4-$CH_3C_6H_2$, 123568-36-5; HO_2C-2,3,4,5,6-$(C_6H_5C{\equiv}C)_5C_6$, 123568-37-6; HO_2C-3,4,5-$(C_6H_5C{\equiv}C)_3C_6H_2$, 123568-38-7; 1,2,3-$(C_6H_5C{\equiv}C)_3$-5-$NO_2C_6H_2$, 123568-39-8; 1,2,3-$((CH_3)_3SiC{\equiv}C)_3$-5-$NO_2C_6H_2$, 123568-40-1; 1,3-$(C_6H_5C{\equiv}C)_2$-2-Br-5-$NO_2C_6H_2$, 123568-41-2; 1,3-$(HOC(CH_3)_2C{\equiv}C)_2$-2-Br-5-$NO_2C_6H_2$, 123568-42-3; 1,3-$(CH_3O_2CCH{=}CH)_2$-2-$(HOC-(CH_3)_2C{\equiv}C)$-5-$NO_2C_6H_2$, 123568-43-4; 1,2-$(C_6H_5C{\equiv}C)_2$-3-Br-5-$NO_2C_6H_2$, 123568-44-5; $Me(CH_3O_2CCH{=}CH)_2C_6H_3$, 123568-47-8; $I_5C_6NO_2$, 59875-34-2; NO_2-3,5-$(CH_3O_2CCH{=}CH)_2C_6H_3$, 20883-29-8; NO_2-2-Br-3,4,5,6-I_4C_6, 123568-45-6; NO_2-3-Br-2,4,5,6-I_4C_6, 123568-46-7.

Lithiation of Methoxypyridines Directed by α-Amino Alkoxides

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The addition of methoxypyridinecarboxaldehydes to certain lithium dialkylamides gave α-amino alkoxides in situ that were ring-lithiated with alkyllithium bases. Alkylation and hydrolysis on workup provided ring-substituted methoxypyridinecarboxaldehydes via a one-pot reaction. The one-pot methylation of isomeric methoxypyridinecarboxaldehydes was examined. The regioselectivity of the lithiation–methylation was dependent on the aldehyde, the amine component of the α-amino alkoxide, and the metalation conditions. When lithiated *N,N,N'*-trimethylethylenediamine was used as the amine component of the α-amino alkoxide, methylation generally occurred ortho to the aldehyde function. The analogous reactions using lithium *N*-methylpiperazide as the amine component gave substitution next to the methoxy group. Several new methylated methoxypyridinecarboxaldehydes were prepared in a regioselective manner by using this one-pot procedure.

Despite the susceptibility of pyridines to nucleophilic attack by alkyllithium bases, directed lithiation has recently evolved as a useful method for regioselective substitution of the pyridine ring.[2] A variety of ortho-directing groups have been utilized to effect regiospecific metalation into an ortho position of pyridine. Directing groups include $CONR_2$,[3] CONHR,[3] oxazolines,[4] pivaloylamino,[5] $OCONEt_2$,[6] OR,[7] OCH_2OR,[8] halogen,[9] and SO_2NR_2.[10] Carbonyl-derived directing groups prepared from pyridinecarboxaldehydes have not been investigated. Due to a need for substituted methoxypyridinecarboxaldehydes in our laboratories, we decided to study the lithiation of methoxypyridines directed by α-amino alkoxides.

The addition of aromatic aldehydes to certain lithium dialkylamides gives α-amino alkoxides that can be ring-lithiated with alkyllithiums. Alkylation and hydrolysis on workup provides ortho-substituted aryl aldehydes via a one-pot reaction. This methodology works well for the one-pot substitution of benzaldehyde derivatives[11] as well

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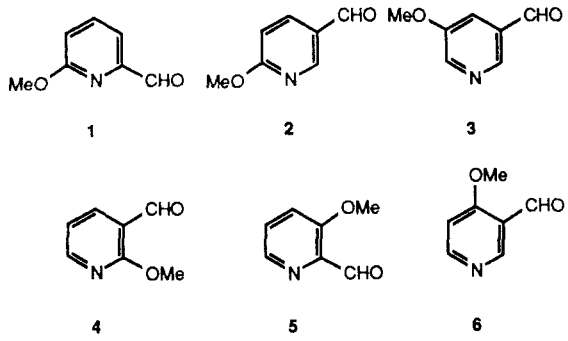
as for heterocyclic aromatic aldehydes,[12] i.e., various thiophene-, furan-, pyrrole-, and indolecarboxaldehydes. The directing power of an α-amino alkoxide group can be altered by simply varying the amine component, allowing regioselective control during the lithiation of a diactivated aromatic ring.[11,12] Since an α-amino alkoxide's ortho-directing ability is due to a chelation effect and not a strong inductive effect, it was not clear that the regioselective control inherent in this methodology could be utilized in the pyridine series, as competing nucleophilic attack of the alkyllithium base on the pyridine nucleus may occur. In this report we describe our studies on the directed lithiation of various α-amino alkoxides prepared in situ from methoxypyridinecarboxaldehydes.

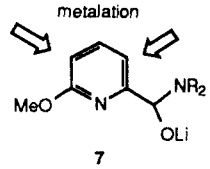
Results and Discussion

Synthesis of Methoxypyridinecarboxaldehydes. The required methoxypyridinecarboxaldehydes were prepared in two steps from commercially available dibromopyridines or from methoxypyridines in one step via directed lithiation. Treatment of 2,6-dibromopyridine with sodium methoxide in methanol gave 6-bromo-2-methoxypyridine, which on lithium–halogen exchange and formylation with dimethylformamide (DMF) provided 6-methoxy-2-pyridinecarboxaldehyde (1). In an analogous

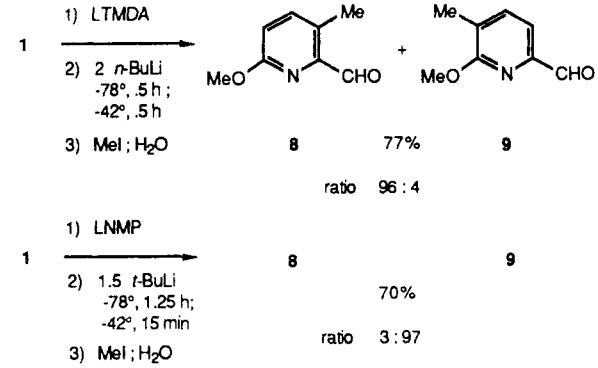


fashion, 2,5-dibromopyridine was converted to 5-bromo-2-methoxypyridine, which was treated with *n*-butyllithium and DMF to give 6-methoxy-3-pyridinecarboxaldehyde (2). Monosubstitution of 3,5-dibromopyridine was achieved using sodium methoxide in DMF. Subsequent lithium–halogen exchange at −100 °C and formylation gave 5-methoxy-3-pyridinecarboxaldehyde (3) in good yield. Directed lithiation of 2-, 3-, and 4-methoxypyridine using mesityllithium as the base and subsequent formylation with DMF gave 2-methoxy-3-pyridinecarboxaldehyde (4), 3-methoxy-2-pyridinecarboxaldehyde (5), and 4-methoxy-3-pyridinecarboxaldehyde (6), respectively.[7c]

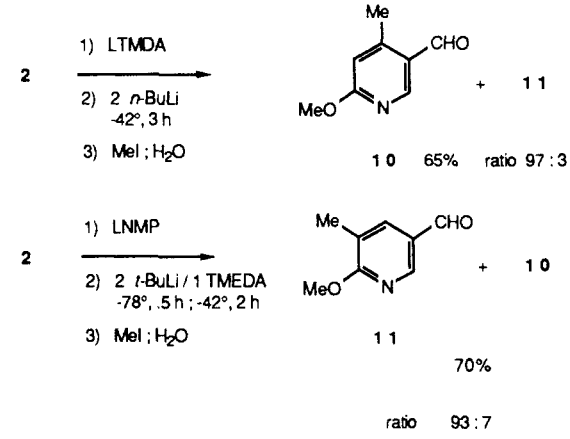
Directed Lithiation Studies. The α-amino alkoxides were prepared by addition of the pyridinecarboxaldehyde to lithiated *N,N,N'*-trimethylethylenediamine (LTMDA) or lithium *N*-methylpiperazide (LNMP) in tetrahydrofuran (THF) at −78 °C. The α-amino alkoxide 7, formed



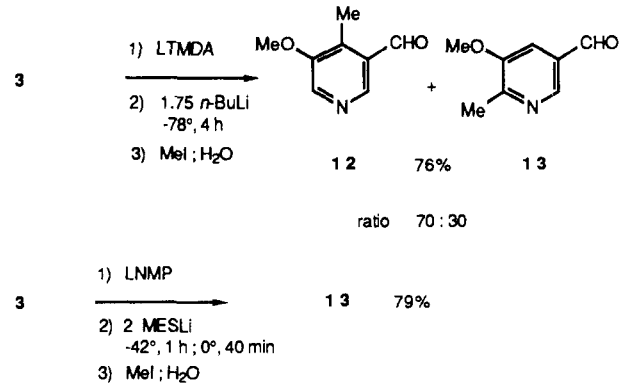
in situ from pyridinecarboxaldehyde 1, has two sites, C-3 and C-5, where lithiation may occur. We anticipated that regioselective metalation could be achieved at either position by varying the amine component of the α-amino alkoxide. Reaction of 1 with LTMDA followed by lithiation with *n*-butyllithium and methylation gave a 77% yield of aldehydes 8 and 9 in a ratio of 96:4. The regioselectivity can be reversed by changing the amine component. Treatment of 1 with LNMP, *tert*-butyllithium, and methyl iodide gave a 70% yield of 8 and 9 in a ratio of 3:97.



We next investigated the methylation of pyridinecarboxaldehyde 2. The α-amino alkoxide formed from 2 and LTMDA was lithiated and methylated to give the C-4 and C-5 substituted pyridines 10 and 11 in a ratio of 97:3. The analogous reaction of 2 with LNMP and *tert*-butyllithium gave mainly C-5 methylated pyridine 11. Lithiation–methylation at C-2 was not observed.



The metalation of pyridinecarboxaldehyde 3 using LTMDA and *n*-butyllithium led to a 70:30 mixture of C-4 and C-6 methylated pyridines 12 and 13. We were unable to find conditions to improve the ratio of products in favor of C-4 substitution. A highly regioselective C-6 methylation was obtained, however, by using LNMP as the amine component and mesityllithium[13] (MESLi) as the base. In this manner pyridinecarboxaldehyde 13 was isolated as the sole product in 79% yield. Substitution at C-4 occurred when pyridinecarboxaldehyde 4 was treated with LTMDA,



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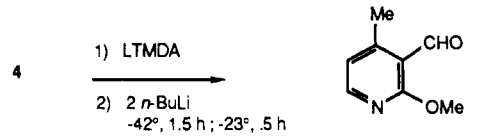
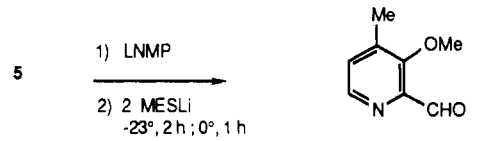
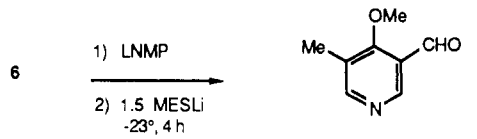
n-butyllithium, and methyl iodide. An 82% yield of substituted pyridine 14 was isolated as the sole product.



14 82%



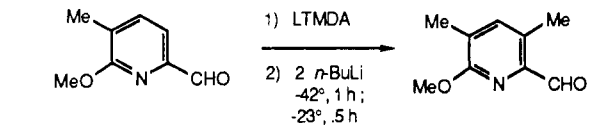
15 67%



16 82%

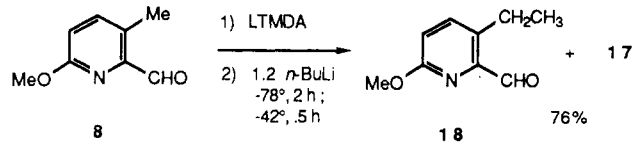
Mesityllithium was effective at lithiating the C-4 position of the α-amino alkoxide derived from pyridine **5** and LNMP. Methylation and workup gave 3-methoxy-4-methyl-2-pyridinecarboxaldehyde (**15**) in 67% yield. Regiospecific substitution of pyridinecarboxaldehyde **6** at C-5 was achieved using LNMP and mesityllithium. We were unable to induce metalation at C-2 by using LTMDA as the amine component.

To determine if methylated methoxypyridinecarboxaldehydes could be further substituted using this methodology, we prepared an α-amino alkoxide from pyridine **9** and LTMDA. Lithiation with *n*-butyllithium and methylation gave a 67% yield of the tetrasubstituted pyridine **17**.



9 17 67%

The analogous reaction of the α-amino alkoxide derived from pyridinecarboxaldehyde **8** and LTMDA gave alkylation mainly on the C-3 methyl group. A mixture of products **18** and **17** were obtained in a ratio of 94:6, demonstrating the α-amino alkoxide's ability to direct lateral metalation as well as ring lithiation.

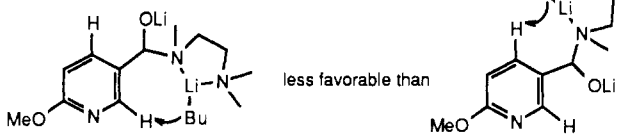


8 18 76%

ratio 94:6

Conclusion

Lithiation of pyridines directed by α-amino alkoxides has been shown to be effective for the substitution of various methoxypyridinecarboxaldehydes. The procedure utilizes a convenient one-pot reaction, which has an obvious advantage over the more classical multistep ortho-directing methodologies. A high degree of regioselective control is achieved in many cases by simply changing the amine component of the α-amino alkoxide. The lack of success in obtaining an α-amino alkoxide directed lithiation at C-2 is interesting. A C-3 methoxy or ethoxy group directs lithiation to C-2,[7] while chelating C-3 ortho-directing groups such as $-OCH_2OMe$ and $-OCONR_2$ effect metalation at C-4.[6,8] Because the C–N bonds of a pyridine ring are shorter than the ring C–C bonds, some of the bond angles are distorted from 120°. In pyridine, for example, the C-4, C-3, H-3 bond angle is 121.36°, whereas the C-2, C-3, H-3 angle is 120.11°.[14] This small distortion might affect the angle of intramolecular attack onto the C-2 or C-4 hydrogen by the alkyllithium base, which is chelated to a C-3 directing group (i.e., **19** and **20**). This may cause C-2 lithiation via complex **19** to be less favorable than the analogous attack at the C-4 hydrogen via complex **20**.[15] Further study is needed to support this hypothesis.



19 20

The methodology presented in this paper is useful for the regioselective preparation of substituted alkoxypyridines, which are valuable precursors to pyridones and pyridinols,[16] as well as synthetically useful dihydropyridones.[17]

Experimental Section

All reactions were performed in oven-dried glassware under a N_2 atmosphere. Tetrahydrofuran (THF) was dried by distillation from sodium benzophenone ketyl prior to use. *N,N,N'*-Trimethylethylenediamine, *N*-methylpiperazine, and dimethylformamide (DMF) were distilled from calcium hydride and stored over 3-Å molecular sieves under N_2. Other solvents and reagents from commercial sources were generally stored over 3-Å molecular sieves and used without further purification.

Melting points were determined with a Thomas-Hoover capillary melting point apparatus and are uncorrected. NMR spectra were recorded on a Varian XL-300 or an IBM AF 80 spectrometer. Radial preparative-layer chromatography (Radial PLC) was carried out by using a Chromatotron (Harris Associates, Palo Alto, CA). Elemental analyses were carried out by M-H-W laboratories, Phoenix, AZ. Infrared spectra were recorded on a Perkin-Elmer Model 7500 spectrometer. Gas–liquid chromatography (GC) was performed on a Hewlett-Packard Model 5880A gas chromatograph equipped with a 30 m × 0.25 mm FSOT column packed with OV-101. The 2,4-dinitrophenylhydrazones were prepared by using a modified method published by Behforouz.[18]

6-Bromo-2-methoxypyridine. 6-Bromo-2-methoxypyridine was prepared by a variation of the literature procedure.[19] To

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a stirred solution of 2,6-dibromopyridine (17.42 g, 74 mmol) in anhydrous MeOH (50 mL) was added NaOMe (28.6 mL of 25% NaOMe in MeOH, 125 mmol). The mixture was refluxed for 25 h and then poured into cold 5% $NaHCO_3$ (50 mL). The mixture was extracted with ether (3 × 30 mL), and the organic layer was concentrated. Ether (50 mL) was added to the remaining liquid, and the mixture was washed with brine (40 mL). The organic layer was dried (K_2CO_3) and concentrated, and the residue was Kugelrohr distilled (85–95 °C/15 mmHg) to give 10.11 g (73%) of 6-bromo-2-methoxypyridine as a clear liquid: IR (neat) 2953, 1596, 1582, 1558, 1472, 1413, 1298, 1022, 857 cm^{-1}; ^1H NMR (80 MHz, $CDCl_3$) δ 3.89 (s, 3 H), 6.63 (d, 1 H, J = 8 Hz), 6.99 (d, 1 H, J = 8 Hz), 7.37 (t, 1 H, J = 8 Hz); ^{13}C NMR (20 MHz, $CDCl_3$) δ 54.3, 109.5, 120.3, 138.8, 140.5, 163.9.

6-Methoxy-2-pyridinecarboxaldehyde (1). To a stirred solution of 6-bromo-2-methoxypyridine (1.01 g, 5.40 mmol) in THF (20 mL) at −78 °C was added *n*-BuLi (5.61 mmol). After 1 h, DMF (0.472 g, 6.00 mmol) was added, and the mixture was allowed to stir for 30 min at −78 °C. The cold mixture was poured directly into a stirred aqueous solution of 5% $NaHCO_3$ (50 mL) and extracted with ether (3 × 25 mL). The combined organic extracts were washed with brine and dried (K_2CO_3). The mixture was filtered and concentrated. The crude product was purified by radial PLC (silica gel, 5% EtOAc–hexanes) followed by Kugelrohr distillation [bp 99–105 °C/20 mmHg (lit.[20] bp 103–104 °C/20 mmHg)] to give 574 mg (78%) of **1** as an oil: IR (neat) 2955, 2829, 1719, 1704, 1600, 1474, 1333, 1276 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.03 (s, 3 H), 6.98 (d, 1 H, J = 8.4 Hz), 7.57 (d, 1 H, J = 7.2 Hz), 7.74 (dd, 1 H, J = 8.4, 7.2 Hz), 9.97 (s, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 53.15, 115.01, 115.92, 138.71, 150.08, 164.02, 192.50; DNP mp 216–219 °C.

5-Bromo-2-methoxypyridine. 5-Bromo-2-methoxypyridine was prepared by a variation of the literature procedure.[19] To a stirred solution of 2,5-dibromopyridine (10.94 g, 46 mmol) in anhydrous MeOH (25 mL) was added NaOMe (50 mL of 25% NaOMe in MeOH, 210 mmol). The mixture was refluxed for 7 h and then poured into cold stirred 5% $NaHCO_3$ (75 mL). The mixture was extracted with ether (4 × 30 mL) and washed with brine (3 × 30 mL). The organic layer was dried ($MgSO_4$), filtered, and concentrated. The crude product was purified by Kugelrohr distillation (65–70 °C/3.5 mmHg) to give 7.96 g (92%) of a clear liquid: IR (neat) 2984, 2946, 1572, 1451, 1339, 1293, 1262, 1009, 799 cm^{-1}; ^1H NMR (80 MHz, $CDCl_3$) δ 3.88 (s, 3 H), 6.59 (d, 1 H, J = 8.8 Hz), 7.56 (d, 1 H, J = 8.8 Hz), 8.18 (s, 1 H); ^{13}C NMR (20 MHz, $CDCl_3$) δ 53.76, 111.79, 112.69, 141.00, 147.70, 163.10.

6-Methoxy-3-pyridinecarboxaldehyde (2). To a stirred solution of 5-bromo-2-methoxypyridine (1.63 g, 8.69 mmol) in THF (25 mL) at −78 °C was added *n*-BuLi (9.10 mmol). After 1 h, DMF (1.27 g, 17.4 mmol) was added and stirring was continued for 30 min at −78 °C. The cold mixture was poured directly into a stirred aqueous solution of 5% $NaHCO_3$ (50 mL) and extracted with ether (3 × 25 mL). The combined organic extracts were washed with brine and dried (K_2CO_3). The mixture was filtered and concentrated to give a yellow solid (1.21 g). The crude product was recrystallized from hexanes to give 1.00 g (84%) of **2** as a light yellow solid: mp 50.5–51.5 °C (hexanes); IR (neat) 2993, 2952, 2837, 1696, 1605, 1568, 1495, 1363, 1291, 1222, 1016, 838 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.04 (s, 3 H), 6.85 (d, 1 H, J = 9 Hz), 8.07 (d, 1 H, J = 9 Hz), 8.64 (s, 1 H), 9.96 (s, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 54.07, 111.84, 126.50, 137.20, 152.63, 167.47, 189.26.

5-Bromo-3-methoxypyridine. Sodium methoxide in MeOH (20.5 mL, 95 mmol) was stirred under reduced pressure (15 mmHg) at 65 °C for 30 min. The remaining solid was placed under a N_2 atmosphere and dissolved in DMF (60 mL). Solid 3,5-dibromopyridine (15 g, 63 mmol) was added, and the mixture was stirred at 63–68 °C. After 4 h, additional NaOMe/MeOH solution (7 mL, 32 mmol) was added. The reaction mixture was allowed to stir at 63–68 °C for 12 h, then poured into H_2O (80 mL), and extracted with ether (6 × 20 mL). The combined organic extracts were washed with brine (50 mL) and dried ($MgSO_4$). The mixture was filtered and concentrated to give a yellow solid. The crude product was purified by radial PLC (silica gel, 10% EtOAc–hexanes) followed by recrystallization (hexanes) to give 8.78 g (78%) of 5-bromo-3-methoxypyridine as a light yellow solid. The residue from the mother liquid was purified by radial PLC (silica gel, 5% EtOAc–hexanes) to give an additional 1.27 g (11%) of product: IR (neat) 3045, 3010, 2940, 1577, 1557, 1457, 1418, 1313, 1266, 1009, 858 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.86 (s, 3 H), 7.36 (s, 1 H), 8.25 (s, 1 H), 8.29 (s, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 55.45, 120.02, 122.78, 135.85, 142.46, 155.64; mp 34–35 °C (hexanes). Anal. Calcd for C_6H_6BrNO: C, 38.33; H, 3.22; N, 7.45. Found: C, 38.18; H, 3.26; N, 7.28.

5-Methoxy-3-pyridinecarboxaldehyde (3). To a stirred solution of 5-bromo-3-methoxypyridine (4.09 g, 22.9 mmol) in THF (100 mL) at −100 °C was added *n*-BuLi (25.2 mmol) over 10 min. The solution was allowed to stir for an additional 20 min at −100 °C, and then DMF (2.3 mL, 29.8 mmol) was added. The mixture was stirred for 30 min, allowing the temperature to slowly warm to −60 °C. The cold mixture was then poured directly into brine (100 mL) and extracted with ether (3 × 40 mL). The combined organic extracts were dried (K_2CO_3), filtered, and concentrated. The crude product was purified by radial PLC (silica gel, 10% EtOAc–hexanes) to give 2.19 g (73%) of **3** as a light yellow solid: IR (neat) 2943, 2844, 1708, 1693, 1588, 1473, 1428, 1321, 1282, 1253, 1175 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.93 (s, 3 H), 7.62 (s, 1 H), 8.56 (s, 1 H), 8.67 (s, 1 H), 10.11 (s, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 55.59, 116.16, 131.86, 144.53, 144.86, 156.00, 199.51; mp 33–34 °C (hexanes/CCl_4). Anal. Calcd for $C_7H_7NO_2$: C, 61.31; H, 5.15; N, 10.21. Found: C, 61.17, H, 5.22; N, 10.35.

2-Methoxy-3-pyridinecarboxaldehyde (4). To a stirred solution of *tert*-butyllithium (8.19 mmol, 4.96 mL of a 1.65 M solution in pentane) in 20 mL of THF at −78 °C was added dropwise 2-bromomesitylene (0.60 mL, 3.9 mmol). After this stirred for 1 h, 2-methoxypyridine (0.32 mL, 3.0 mmol) was added dropwise, and the mixture was warmed to 0 °C and stirred for 1 h. The homogeneous solution was warmed to room temperature and stirred for an additional 1 h. This solution was cooled to −78 °C and *N,N*-dimethylformamide (0.35 mL, 4.5 mmol) was added in one portion and stirred for 1 h. Acetic acid (6.0 mmol, 0.35 mL) was added, and the solution was warmed to room temperature. Saturated aqueous $NaHCO_3$ (20 mL) was added, and the mixture was extracted with three 20-mL portions of diethyl ether. The combined organic layers were washed with brine, dried over $MgSO_4$ for 15 min, filtered through Celite, and concentrated in vacuo. The crude product was purified by radial PLC (silica gel, EtOAc–hexanes) to give 0.257 g (63%) of **4** as an oil: ^1H NMR (300 MHz, $CDCl_3$) δ 10.38 (s, 1 H), 8.39 (dd, 1 H, J = 5.0 and 2.0 Hz), 8.12 (dd, 1 H, J = 8.0 and 2.0 Hz), 7.02 (m, 1 H, J = 8.0, 5.0 and 1.0 Hz), 4.08 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 189.1, 164.4, 152.8, 137.5, 118.8, 117.2, 53.8; IR (neat) 3004, 2964, 2869, 1684, 1654, 1584, 1474, 1422, 1394, 1114, 1269, 1204, 1115, 1034, 883, 824, 794, 692 cm^{-1}. Anal. Calcd for $C_7H_7O_2N$: C, 61.31; H, 5.14; N, 10.21. Found: C, 61.40; H, 5.14; N, 10.28.

3-Methoxy-2-pyridinecarboxaldehyde (5). To a stirred solution of *tert*-butyllithium (8.01 mmol, 4.40 mL of a 1.82 M solution in pentane) in 20 mL of THF at −78 °C was added dropwise 2-bromomesitylene (0.60 mL, 3.9 mmol). After this stirred for 1 h, 3 methoxypyridine (0.30 mL, 3.0 mmol) was added dropwise. The solution was warmed to −23 °C, stirred for 3 h, and then cooled again to −78 °C. *N,N*-Dimethylformamide (0.35 mL, 4.5 mmol) was added, and the resulting solution was stirred at −78 °C for 1 h. The reaction was quenched at −78 °C with 20 mL of brine and extracted with ether. The combined organic layers were washed with brine, dried over K_2CO_3, and concentrated. The crude product was purified by radial PLC (silica gel, EtOAc/EtOH) to give 0.350 g (85%) of **5**, which was subsequently recrystallized (benzene/cyclohexane) to give a white solid: mp 67–68 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 10.35 (s, 1 H), 8.41 (d, 1 H, J = 4.0 Hz), 7.55–7.35 (m, 2 H), 3.98 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 190.3, 157.8, 141.9, 140.9, 128.7, 120.1, 55.7; IR (KBr) 3077, 2991, 2960, 2876, 1694, 1577, 1470, 1432, 1395, 1297, 1255, 1189, 1158, 1114, 1066, 1007, 925, 857, 807, 738, 658 cm^{-1}. Anal. Calcd for $C_7H_7NO_2$: C, 61.31; H, 5.14; N, 10.21. Found: C, 61.36; H, 5.16; N, 10.24.

4-Methoxy-3-pyridinecarboxaldehyde (6). To a stirred solution of *tert*-butyllithium (8.01 mmol, 4.40 mL of a 1.82 M solution in pentane) in 20 mL of THF at −78 °C was added dropwise 2-bromomesitylene (0.60 mL, 3.9 mmol). After this

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stirred for 1 h, 4-methoxypyridine (0.30 mL, 3.0 mmol) was added dropwise. This solution was warmed to −23 °C, stirred for 3 h, and then cooled again to −78 °C. *N,N*-Dimethylformamide (0.35 mL, 4.5 mmol) was added, and the solution was stirred at −78 °C for 1 h. The reaction was quenched at −78 °C with 20 mL of brine and extracted with ether. The combined organic layers were dried over K_2CO_3. Concentration gave the crude product which was purified by radial PLC (silica gel, EtOAc/EtOH) to give 0.317 g (77%) of **6** as a solid, which was further purified for elemental analysis by recrystallization (CCl_4) to give white crystals: mp 65.5–67.5 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.46 (s, 1 H), 8.90 (s, 1 H), 8.65 (d, 1 H, J = 6.0 Hz), 6.95 (d, 1 H, J = 6.0 Hz), 4.01 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 188.6, 166.6, 155.9, 150.7, 120.4, 107.1, 55.8; IR (KBr) 3105, 3079, 2985, 2951, 2886, 2849, 2770, 1679, 1586, 1500, 1488, 1439, 1396, 1314, 1278, 1205, 1170, 1061, 1018, 932, 841, 822, 745, 660 cm^{-1}. Anal. Calcd for $C_7H_7NO_2$: C, 61.31; H, 5.14; N, 10.21. Found: C, 61.11; H, 5.09; N, 10.01.

General Procedure for Methylation of Methoxypyridinecarboxaldehydes. To a stirred solution of the secondary amine (*N,N,N'*-trimethylethylenediamine or *N*-methylpiperazine, 2.4 mmol) in 10 mL of THF was added *n*-BuLi (2.2 mmol) at −78 °C. After 15 min, the appropriate methoxypyridinecarboxaldehyde (2 mmol) was added, and the mixture was stirred at −78 °C for 15 min. The indicated base was added and stirred at the indicated temperatures and times. Methyl iodide (10 mmol) was added at −78 °C, and the mixture was allowed to come to room temperature (30 min). The solution was poured into vigorously stirred cold brine (25 mL) and extracted with ether (3 × 25 mL). The organic extracts were dried (K_2CO_3) and concentrated. The crude products were purified by radial PLC (EtOAc-hexanes).

Spectral Data. 6-Methoxy-3-methyl-2-pyridinecarboxaldehyde (8): IR (neat) 2945, 2820, 1711, 1606, 1483, 1341, 1272, 796 cm^{-1}; ^{1}H NMR (80 MHz, $CDCl_3$) δ 2.55 (s, 3 H), 3.99 (s, 3 H), 6.83 (d, 1 H, J = 8.4 Hz), 7.47 (d, 1 H, J = 8.4 Hz), 10.06 (s, 1 H); ^{13}C NMR (20 MHz, $CDCl_3$) δ 18.03, 53.87, 115.57, 129.14, 143.28, 146.92, 162.79, 195.38; mp 52.5–54 °C (hexanes). Anal. Calcd for $C_8H_9NO_2$: C, 63.57; H, 6.00; N, 9.27. Found: C, 63.53; H, 6.08; N, 9.12.

6-Methoxy-5-methyl-2-pyridinecarboxaldehyde (9): IR (KBr) 3011, 2955, 2841, 1695, 1597, 1463, 1277, 1243, 1027 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.28 (s, 3 H), 4.05 (s, 3 H), 7.49 (d, 1 H, J = 7.2 Hz), 7.54 (d, 1 H, J = 7.2 Hz), 9.94 (s, 1 H); ^{13}C NMR (20 MHz, $CDCl_3$) δ 16.50, 53.83, 116.04, 127.65, 138.96, 148.82, 162.96, 193.06; DNP mp 222–224 °C (EtOH). Anal. Calcd for $C_8H_9NO_2$: C, 63.57; H, 6.00; N, 9.27. Found: C, 63.21; H, 5.83; N, 9.12.

6-Methoxy-4-methyl-3-pyridinecarboxaldehyde (10): IR (KBr) 3026, 1695, 1613, 1554, 1446, 1362, 1255, 1147 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.61 (s, 3 H), 4.01 (s, 3 H), 6.60 (s, 1 H), 8.51 (s, 1 H), 10.07 (s, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.85, 53.85, 112.90, 125.38, 151.42, 155.25, 166.60, 190.58; mp 91–92 °C (hexanes). Anal. Calcd for $C_8H_9NO_2$: C, 63.57; H, 6.00; N, 9.27. Found: C, 63.31; H, 6.02, N, 9.13.

6-Methoxy-5-methyl-3-pyridinecarboxaldehyde (11): IR (neat) 2989, 2953, 1694, 1605, 1484, 1408, 1381, 1268, 1141, 1016 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.24 (s, 3 H), 4.06 (s, 3 H), 7.88 (s, 1 H), 8.47 (s, 1 H), 9.93 (s, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 15.79, 54.30, 122.10, 126.73, 136.35, 150.39, 166.19, 189.81; mp 56–56.5 °C (hexanes). Anal. Calcd for $C_8H_9NO_2$: C, 63.57; H, 6.00; N, 9.27. Found: C, 63.69; H, 5.94; N, 9.30.

5-Methoxy-4-methyl-3-pyridinecarboxaldehyde (12): IR (KBr) 2960, 1692, 1585, 1489, 1422, 1294, 1270, 1011, 909, 713 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.56 (s, 3 H), 3.98 (s, 3 H), 8.37 (s, 1 H), 8.62 (s, 1 H), 10.33 (s, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 10.51, 56.50, 129.85, 136.45, 137.57, 146.04, 154.18, 191.82; mp 70.5–71.5 °C (hexanes). Anal. Calcd for $C_8H_9NO_2$: C, 63.57; H, 6.00; N, 9.27. Found: C, 63.66; H, 6.06; N, 9.27.

5-Methoxy-6-methyl-3-pyridinecarboxaldehyde (13): IR (KBr) 2978, 2860, 1689, 1595, 1392, 1152 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.57 (s, 3 H), 3.91 (s, 3 H), 7.51 (s, 1 H), 8.52 (s, 1 H), 10.05 (s, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.10, 55.40, 112.32, 130.81, 144.56, 154.27, 156.30, 190.58; mp 75.5–76.5 °C (hexanes). Anal. Calcd for $C_8H_9NO_2$: C, 63.57; H, 6.00; N, 9.27. Found: C, 63.38; H, 6.02; N, 9.19.

2-Methoxy-4-methyl-3-pyridinecarboxaldehyde (14): IR (neat) 2988, 2953, 2869, 1686, 1590, 1564, 1476, 1377, 1302, 1083 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.59 (s, 3 H), 4.04 (s, 3 H), 6.77 (d, 1 H, J = 5.1 Hz), 8.16 (d, 1 H, J = 5.1 Hz), 10.54 (s, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.79, 53.84, 117.16, 120.87, 150.79, 152.42, 165.78, 191.47; mp 29.5–30 °C (hexanes). Anal. Calcd for $C_8H_9NO_2$: C, 63.57; H, 6.00; N, 9.27. Found: C, 63.68; H, 5.89; N, 9.15.

3-Methoxy-4-methyl-2-pyridinecarboxaldehyde (15): IR (neat) 2933, 2832, 1715, 1585, 1561, 1473, 1263, 1224, 1002 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.30 (s, 3 H), 3.84 (s, 3 H), 7.28 (d, 1 H, J = 4.8 Hz), 8.35 (d, 1 H, J = 4.8 Hz), 10.15 (s, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 15.19, 62.34, 130.09, 142.80, 144.78, 145.24, 157.33, 191.04; mp 42.5–44 °C (hexanes). Anal. Calcd for $C_8H_9NO_2$: C, 63.57; H, 6.00; N, 9.27. Found: C, 63.76; H, 6.00; N, 9.18.

4-Methoxy-5-methyl-3-pyridinecarboxaldehyde (16): IR (KBr) 2897, 1703, 1678, 1574, 1480, 1404, 1269, 1228, 1153, 996, 821 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.34 (s, 3 H), 4.01 (s, 3 H), 8.57 (s, 1 H), 8.83 (s, 1 H), 10.38 (s, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.09, 62.61, 123.84, 126.88, 150.32, 157.09, 166.77, 189.07; mp 64.5–66 °C (hexanes). Anal. Calcd for $C_8H_9NO_2$: C, 63.57; H, 6.00; N, 9.27. Found: C, 63.51; H, 6.04; N, 9.29.

3,5-Dimethyl-6-methoxy-2-pyridinecarboxaldehyde (17): IR (KBr) 2961, 2924, 2832, 1696, 1561, 1478, 1416, 1356, 1277, 1117 cm^{-1}; ^{1}H NMR (80 MHz, $CDCl_3$) δ 2.21 (s, 3 H), 2.50 (s, 3 H), 4.00 (s, 3 H), 7.23 (s, 1 H), 10.01 (s, 1 H); ^{13}C NMR (20 MHz, $CDCl_3$) δ 16.09, 17.74, 53.66, 126.38, 129.17, 142.76, 144.76, 160.84, 194.92; mp 84.5–85.5 °C (hexanes). Anal. Calcd for $C_9H_{11}NO_2$: C, 65.44; H, 6.71; N, 8.48. Found: C, 65.21; H, 6.79; N, 8.35.

3-Ethyl-6-methoxy-2-pyridinecarboxaldehyde (18): IR (neat) 2975, 1711, 1603, 1482, 1337, 1271, 1030 cm^{-1}; ^{1}H NMR (80 MHz, $CDCl_3$) δ 1.19 (t, 3 H, J = 7.5 Hz), 3.01 (q, 2 H, J = 7.5 Hz), 3.99 (s, 3 H), 6.86 (d, 1 H, J = 8.4 Hz), 7.53 (d, 1 H, J = 8.4 Hz), 10.06 (s, 1 H); ^{13}C NMR (20 MHz, $CDCl_3$) δ 15.58, 24.24, 53.86, 115.84, 135.54, 141.85, 146.50, 162.70, 195.12; DNP mp 180–184 °C (EtOH). Anal. Calcd for $C_9H_{11}NO_2$: C, 65.44; H, 6.71; N, 8.48. Found: C, 65.45; H, 6.66, N, 8.57.

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