803 cm^{-1}; NMR ($CDCl_3$) δ 1.00–2.53 (m, 11 H), 2.80–3.13 (m, 2 H), 3.20 (br s, 1 H), 3.88 (dt, 1 H, J = 4 and 8 Hz). Anal. (picrate) Calcd for $C_{14}H_{18}O_8N_4$: C, 45.41; H, 4.90; N, 15.12. Found: C, 45.64; H, 5.01; N, 14.70.

Synthesis of 9. To a solution of **7** (1.41 g, 10 mmol) and triethylamine (1.7 mL, 12 mmol) in CH_2Cl_2 (20 mL) was added methanesulfonyl chloride (1.38 g, 12 mmol) at 0 °C, and the mixture was stirred for 3 h at room temperature. After the usual workup, the product **9** was isolated by column chromatography on silica gel (85% yield).

9: mp 86–87 °C; IR (KBr) 1690, 1300, 1290, 1170, 1040, 1000, 990, 980, 900, 860, 830, 810, 750 cm^{-1}; NMR ($CDCl_3$) δ 1.40–1.79 (m, 1 H), 1.83–2.46 (m, 3 H), 2.97 (d, 2 H, J = 9 Hz), 2.90–3.26 (m, 1 H), 3.09 (s, 3 H), 3.63 (dt, 1 H, J = 7 and 12 Hz), 4.01 (dt, 1 H, J = 6 and 9 Hz), 4.99 (dt, 1 H, J = 6 and 9 Hz). Anal. Calcd for $C_8H_{13}O_4NS$: C, 43.82; H, 5.98; N, 6.39; S, 14.60. Found: C, 43.71; H, 5.90; N, 6.37; S, 14.63.

Synthesis of 12. A mixture of **9** (1.1 g, 5 mmol), KCN (0.78 g, 12 mmol), and AcOH (0.3 g, 5 mmol) in DMF (8 mL) and water (2 mL) was stirred for 4 h at 60 °C. After the solvent was removed, the product **12** was extracted with ethyl acetate from the residue and isolated by column chromatography on silica gel (76% yield).

12: IR (neat) 3500, 2250, 1700, 1335, 1255, 1210, 1190, 1120, 1100, 1040, 990, 920, 795 cm^{-1}; NMR ($CDCl_3$) δ 1.67–4.00 (m, 10 H). Anal. Calcd for $C_8H_{10}ON_2$: C, 63.98; H, 6.71; N, 18.66. Found: C, 63.44; H, 6.76; N, 18.34.

Synthesis of 13. A mixture of **12** (0.45 g, 3 mmol) and $Ba(OH)_2 \cdot 8H_2O$ (3.16 g, 10 mmol) in water (20 mL) was refluxed for 4 h. After water was removed, methanol (20 mL) was added and HCl gas was introduced to the solution until saturation. The solution was stirred for 12 h at room temperature. After evaporation of methanol to remove HCl, methanol (20 mL) and an excess amount of $NaHCO_3$ were added, and the mixture was stirred for 4 h at 50 °C. Methanol was removed and then the residue was extracted with ethyl acetate:ethanol = 10:1. The product was isolated by column chromatography on silica gel (60% yield).

13: mp 53–54 °C; IR (KBr) 1740, 1680, 1215, 1180, 1110, 1050, 880, 815, 780, 670 cm^{-1}; 400-MHz ^{1}H NMR ($CDCl_3$) δ 1.68 (dt, 1 H, J = 9.34 and 12.7 Hz), 2.10–2.15 (m, 3 H), 2.39–2.48 (m, 2 H), 2.56 (ddd, 1 H, J = 1.59, 8.79, and 11.3 Hz), 2.76–2.87 (m, 1 H), 3.13–3.20 (m, 1 H), 3.68 (dt, 1 H, J = 7.76 and 11.3 Hz), 3.77 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 26.00 (t), 31.70 (t), 34.30 (t), 36.05 (t), 41.63 (t), 52.63 (q), 73.48 (s), 174.23 (s), 174.88 (s). Anal. Calcd for $C_9H_{13}O_3N$: C, 59.00; H, 7.15; N, 7.65. Found: C, 58.99; H, 7.29; N, 7.56.

Synthesis of 14. To a suspension of LAH (0.15 g, 4 mmol) in THF (10 mL) was added **13** (0.366 g, 2 mmol), and the mixture was refluxed for 3 h. After the usual workup, **14** was isolated by Kugelrohr distillation (100 °C/20 mm) in quantitative yield.

14: mp (picrate) 254–255 °C; IR (neat) 3400, 1260, 1230, 1190, 1090, 1050, 1025, 840, 700 cm^{-1}; NMR ($CDCl_3$) δ 1.37–2.03 (m, 8 H), 2.33–3.17 (m, 4 H), 3.26 (s, 2 H), 3.38 (br s, 1 H). Anal. (picrate) Calcd for $C_{14}H_{18}O_8N_4$: C, 45.52; H, 4.90; N, 15.13. Found: C, 45.41; H, 4.93; N, 15.01.

Registry No. **3a**, 83541-81-5; **3b**, 113089-13-7; **3c**, 88817-76-9; **3d**, 85235-39-8; **3e**, 113089-14-8; **3f**, 41844-71-7; **3g**, 113089-15-9; **4a**, 113089-16-0; **5a**, 113089-17-1; **5b**, 113089-18-2; **5c**, 113089-19-3; **5d**, 113089-20-6; *syn*-**5e**, 113089-40-0; *anti*-**5e**, 113089-21-7; *syn*-**5f**, 113089-41-1; *anti*-**5f**, 113089-22-8; *syn*-**5g**, 113089-42-2; *anti*-**5g**, 113158-89-7; **6a**, 113089-23-9; **6b**, 113089-24-0; **6c**, 113089-25-1; **6d**, 113089-26-2; **6e**-*cis*, 113089-28-4; **6e**-*trans*, 113089-27-3; **6f**-*cis*, 113089-30-8; **6f**-*trans*, 113089-29-5; **6g**-*cis*, 113158-91-1; **6g**-*trans*, 113158-90-0; **7**, 108910-03-8; **8**, 63121-28-8; **8** picrate, 113089-33-1; **9**, 113089-35-3; (±)-**12**, 113089-36-4; (±)-**13**, 113089-37-5; (±)-**14**, 113089-38-6; (±)-**14** picrate, 113089-39-7; **15**, 113089-31-9; **16**, 113089-32-0; **16** picrate, 113089-34-2; **17**, 113158-92-2; **18**, 108866-41-7; **18** picrate, 113158-93-3; CCl_3COOCH_3, 598-99-2; $CHCl_2COOCH_3$, 116-54-1.

Catalyzed Metalation Applied to 2-Methoxypyridine

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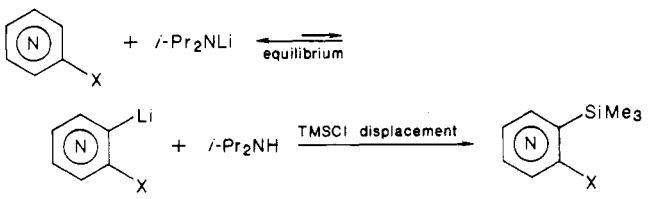
Directed ortho lithiation of 2-methoxypyridine (**1**) has been regioselectively achieved at position 3 by using methyllithium catalyzed by a small amount of diisopropylamine. This metalation methodology, called "catalyzed metalation", gave good results whereas other metalation routes failed. This allowed the convenient synthesis of various 3-substituted 2-methoxypyridines of general interest.

In recent years, metalation of aromatic systems has been successfully developed and it quickly appeared as a powerful functionalization method in aromatic synthesis. Different metalation conditions have been found in order to improve lithiation yields and selectivity. Some laboratories have been interested in the directed lithiation of monosubstituted pyridines using alkyllithium (*n*- or *sec*-butyllithium, methyllithium) or lithium dialkylamides (lithium diisopropylamide or lithium 2,2,6,6-tetramethyl-1-piperidine...).[1-27]

Scheme I



The alkoxy group has been extensively used as ortho-directing substituent for lithiation in the homoaromatic

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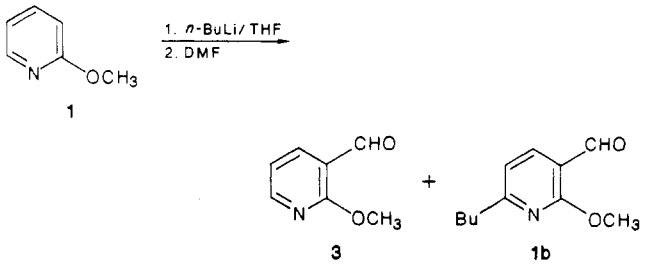
0022-3263/88/1953-1367$01.50/0

Table I. Metalation of 2-Methoxypyridine by Equilibrium Displacement[a]

solvent	θ, °C	yield of 2, %
THF	−70	0
THF	−20	15
THF	−10	25
THF	0	95
THF	25	100
Et_2O	0	0

[a] A reaction time of 2 h and a threefold excess of LDA and TMSCl have been used.

Scheme II



and electron-rich heteroaromatic series, but it possesses a poor activation ability toward metalation, compared to other substituents.[28,29]

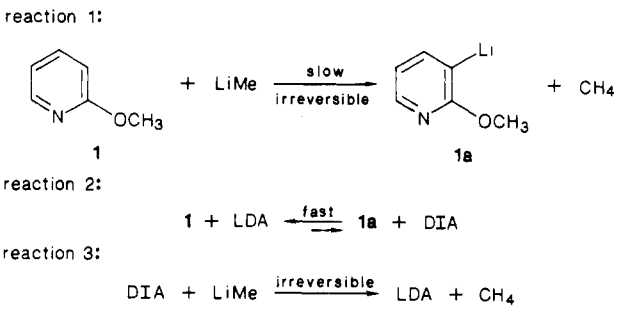
In the π-deficient aromatic series, such as pyridine or quinoline, few successful metalations of monoalkoxy derivatives have been reported. Metalation is only possible when there is an activated position[12,14,15] or when no competitive addition can occur.[30] Thus, for example, 3-ethoxypyridine undergoes metalation at the 2-position[12] when *n*-butyllithium–TMEDA chelate in tetrahydrofuran (THF) at −40 °C is used.

We now describe a convenient metalation methodology called "catalyzed metalation" which has been successfully applied to 2-methoxypyridine (1), whereas classical metalation conditions failed (*n*-butyllithium or LDA).

Results

Metalation of 2-methoxypyridine (1) by lithium diisopropylamide (LDA) is an equilibrium (Scheme I) which can be displaced by the presence of an electrophile such as chlorotrimethylsilane (Scheme I and Table I). Quantitative deprotonation has been achieved by using a threefold excess of LDA and chlorotrimethylsilane in THF at room temperature. However, this methodology could not be applied to electrophilic reagents other than TMSCl,

Scheme III



due to their own reactivity toward LDA.

Metalation by "accumulation" of the lithio derivative was effective with alkyllithiums. It is then possible to increase the concentration of the 3-lithio-2-methoxypyridine (**1a**) before adding an electrophilic reagent such as DMF. However, metalation by *n*-butyllithium was not chemoselective and competitive nucleophilic addition at C-6 occurred, leading to a mixture of 2-methoxy-3-pyridinecarboxaldehyde (**3**) and 6-butyl-2-methoxy-3-pyridinecarboxaldehyde (**1b**) (Scheme II, Table II). It should be noted that addition of butyllithium on 2-methoxypyridine (1) has been studied by Thomas.[27] We found that metalation could be selectively achieved with methyllithium, but yields remained rather low (Table II).

On the other hand, reaction of methyllithium catalyzed by 5% of diisopropylamine gave good results with 2-methoxypyridine (1). It is then possible to obtain a high concentration of the 3-lithio-2-methoxypyridine (**1a**) in the reaction mixture without side reactions such as protonation by the solvent, nucleophilic addition, or ring opening. Under these conditions, dimethylformamide can be reacted with the lithio derivative. The resulting 3-formyl-2-methoxypyridine (**3**) was easily separated from the reaction mixture and identified[31,32] (see Table II).

The best metalation conditions were obtained in THF at 0 °C for 3 h with 1.8 equiv of methyllithium and 0.05 equiv of diisopropylamine. Aldehyde **3** could then be obtained in a 50% yield whereas deuterolysis (DCl/THF) showed a 70% deprotonation yield. At 20 °C, slightly higher yields of **3** were obtained, but no 2-methoxypyridine was recovered, likely due to ring opening on either 2-methoxypyridine or its lithio derivative, which led to the formation of tarry products.

Reaction of other electrophiles such as aldehydes, ketones, chlorotrimethylsilane, alkyl iodides, bromine, iodine, and ethylene oxide, as well as 1,3,5-trioxane, led to the corresponding 3-substituted 2-methoxypyridines in rather correct yields as shown in Tables III–V. Electrophilic reagents were added to the cooled lithiation mixture (−70 °C), in order to avoid side reaction of the basic medium on the electrophiles (deprotonation, alkylation, halogen–lithium exchange...).

Discussion

A metalation reaction can be explained by two extreme mechanisms: metalation by "accumulation" of the lithio derivative or metalation by "equilibrium displacement" imposed by electrophilic reagent.[4,10,11,33]

In the case of metalation by "equilibrium displacement" (see Scheme I), fast competitive interaction between

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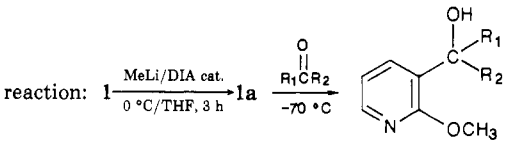
Table II. Metalation of 2-Methoxypyridine by "Catalyzed Metalation"[a]

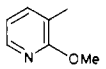
run	metalating reagent	θ, °C	rctn time, h	DIA[b]	metalation yield,[c] %	addition products, %
1	MeLi	0	1.5	yes	45	0
2	MeLi	0	3	yes	50	0
3	MeLi	0	3	no	5	0
4	MeLi	20	1	yes	55	0
5	MeLi	20	3	yes	55	0
6	MeLi	20	3	no	30	0
7	*n*-BuLi	0	1	yes	50	10
8	*n*-BuLi	10	1	yes	45	10
9	*n*-BuLi	20	1	yes	40	15
10	*n*-BuLi	20	1	no	40	15
11	*n*-BuLi/TMEDA	0	3	yes	40	25

[a] For runs 7–11, no 2-methoxypyridine is recovered. In runs 1–3, decomposition results. [b] The amount of DIA is 5% with respect to 2-methoxypyridine. [c] As established by reaction with DMF to give 3-formyl-2-methoxypyridine.

Table III. Carbonyl Electrophiles

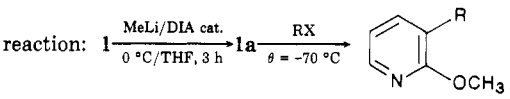


4-14

	R_1	R_2	yield, %		R_1	R_2	yield, %
4	H	Me	50	11	H		50[b]
5	Me	Me	45				
6	Me	Et	40				
7	Et	Et	20	12		$-(CH_2)_4-$	25
8	H	C_5H_{11}	45	13		$-(CH_2)_5-$	40[c]
9	H	$C_8H_{16}CH{=}CH_2$	40	14		$-(CH_2)_7-$	15
10	H	$CH{=}CHC_3H_7$	45[a]				

[a] Ten percent of the *E* isomer of $H_3CCH(OH)CH{=}CHC_3H_7$ (**10a**) is also obtained. [b] 1-(2-Methoxy-3-pyridyl)ethanol is formed (5%). [c] 1-Methylcyclohexanol (10%) (**13a**).

Table IV. Alkyl Halides



	X	R	yield, %
2	Cl	TMS	45[a]
15	I	Me	55
	Br	$CH_2CH{=}CH_2$	0[b]

[a] 3,6-Dihydro-2-methoxy-6-methylpyridine (trace). [b] 2-Methoxy-3-methylpyridine (25%) is formed instead of the expected product.

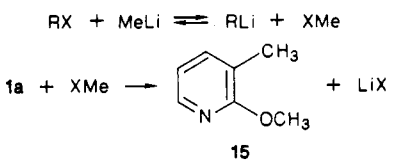
Table V. Other Electrophiles

	electrophile	substituent	θ, °C	yield, %
16	DCl–D_2O/THF	D	−70	70
17	oxirane	CH_2CH_2OH	0	50
18	Br_2	Br	−60	15[a]
19	I_2	I	−60	30[b]
20	1,3,5-trioxane	CH_2OH	25	20[c]

[a] The temperature rose from −60 to −40 °C on addition of Br_2. 2-Methoxy-3-methylpyridine (30%) and the 4-bromo isomer (not isolated) are formed. [b] The temperature rose from −60 to −40 °C on addition of I_2. 2-Methoxy-3-methylpyridine is formed (10%). [c] Slightly different conditions have been used in this case, and 3-deuterio-2-methoxypyridine is identified.

metalating reagent and electrophilic reagent must be avoided: this is illustrated when LDA and TMSCl are used. Metalation of 2- and 3-bromopyridines[4,11,33] and 2-fluoropyridine[10] could be achieved when TMSCl and the monohalopyridine were introduced into a solution of LDA in THF at −70 °C, leading to the corresponding (trimethylsilyl)pyridines. This metalation method was also successfully used by Martin[34] on benzonitriles, by Corey[16] on ketones and esters, by Kress[35] on 5-bromopyrimidine, and by Brandsma[20,21] on pyridine itself. However, few other electrophiles than TMSCl can be reacted under these conditions.

Scheme IV[a]



15

[a] R = Br, I, CH_3, $CH_2CH{=}CH_2$; X = Br or I.

Metalation by alkyllithiums is irreversible, but the deprotonation rate may be slow. In contrast, lithium amides produce a fast but reversible deprotonation, and in many cases, the lithio derivative is formed only at low concentration. So coupling the irreversible but slow reaction of an alkyllithium to the catalytic effect of a lithium amide allowed favorable metalation conditions. This methodology has been first used by Snieckus[36] and by Rickborn[37] and us.[33] It has been successfully studied by us in the case of 2-methoxypyridine (1).

Reaction of methyllithium catalyzed by 5% of diisopropylamine (DIA) gives fast overall deprotonation due to the combination of reactions 2 and 3 (Scheme III). Fast reaction of methyllithium with the small amount of free diisopropylamine allows constant regeneration of LDA and displacement of equilibrium 2 in favor of the lithiopyridine formation. A 70% lithiation yield was obtained as shown by the deuterolysis experiment.

With other electrophiles, some competitive reactions can occur such as deprotonation of enolizable carbonyl electrophiles.

Methylation of pyridine at position 3 was observed when the electrophile was bromine, iodine, or allyl bromide, and 3-methyl-2-methoxypyridine (**15**) could be isolated. This can be explained by a fast exchange between the reagent and methyllithium, followed by reaction of the resulting methyl halide with the 3-lithiopyridine **1a** (Scheme IV).

When bromine was used as electrophile, 3-bromo-2-methoxypyridine (**18**) was formed, which then underwent further metalation and isomerization into 4-bromo-2-methoxypyridine. This is due to a "halogen dance" reaction, as previously described with other bromopyridines at low temperature.[38] The same isomerization was not

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observed with iodine. "Halogen dance" occurs when catalytic amounts of an o-dihalo derivarive is formed,[3,5,39] which is likely not feasible with iodine, due to steric hindrance.

Conclusion

"Catalyzed metalation" has allowed metalation of 2-methoxypyridine, which has not been possible by other metalation routes. The metalation rate is increased by adding a catalytic quantity of diisopropylamine to methyllithium. The thermodynamically favorable, but slow, metalation by methyllithium can now occur at a sufficient rate to overcome competition with side reactions, and good concentration of the lithiated species can be obtained.

3-Substituted 2-methoxypyridines were conveniently prepared in a one-step sequence from the easily available 2-methoxypyridine. The metalation reaction is very clean and is only limited, when bromo or iodo electrophiles are used, by a competitive methylation at C-3, due to the formation of methyl halides. This metalation method is of great interest when metalation is difficult, particularly in the case of poor ortho-directing substituents.

Experimental Section

Commercial n-butyllithium and methyllithium reagents were employed as received. Diisopropylamine (DIA) was dried over calcium hydride, distilled, and stored on calcium hydride. 2-Methoxypyridine was distilled just before use (colorless liquid). Tetrahydrofuran (THF) was dried over benzophenone–sodium complex, distilled, treated with a small amount of n-butyllithium, then redistilled, and stored under argon. Reactions were carried out under dry argon.

^{1}H NMR spectra were recorded on a Varian EM 360 L spectrometer, in $CDCl_3$ solvent with tetramethylsilane (TMS) as internal standard. IR spectra were recorded on a Beckman IR 4250 spectrometer (film for liquids; KBr disk for solids). Elemental analyses were performed on a Carlo Erba 1106 instrument. Melting points were obtained on a Kofler apparatus and are uncorrected.

General Procedures for Metalation. The reactions were performed in a 500-mL three-necked flask equipped with a mechanical stirrer, a thermometer, an isobar funnel, and a rubber septum under dry argon. Freshly distilled THF (200 mL) was introduced in the flask.

Metalation by "Equilibrium Displacement". n-BuLi (1.6 M in hexane; 216 mmol, 135 mL) was added to THF at −40 °C followed by a solution of DIA (346 mmol, 35 g) in THF. The temperature was allowed to rise slowly to 0 °C for 0.25 h. The reaction mixture was then kept at the desired temperature. 2-Methoxypyridine (69 mmol, 7.5 g in 20 mL of THF) was first added at −30 °C, and then chlorotrimethylsilane (138 mmol, 15 g in 20 mL of THF) was only introduced dropwise at the desired temperature and then reacted over 2 h (see Table I); the reaction mixture was then hydrolyzed.

Metalation by "Accumulation" of the Lithio Derivative. n-BuLi (1.6 M in hexane; 72 mmol, 45 mL) or methyllithium (1.6 M in Et_2O; 120 mmol, 75 mL) was added to THF at −40 °C. 2-Methoxypyridine (66.7 mmol, 7.3 g in 20 mL of THF) was added dropwise at −40 °C, and then the reaction mixture was allowed to stand at the required temperature (see Table I). After the lithio derivative formation, dimethylformamide (69 mmol, 5.0 g in 20 mL of THF) was introduced at −40 °C over 0.17 h. The temperature was kept for 0.75 h at −40 °C and then cooled to −70 °C. The reaction mixture was hydrolyzed with a large excess of $HCl/H_2O/THF$ (exotherm). Water (500 mL) was added.

"Catalyzed Metalation". Methyllithium (1.6 M in Et_2O; 120 mmol, 75 mL) was added to THF at −40 °C. Pure 2-methoxypyridine (66.7 mmol, 7.3 g) was added at −40 °C. The mixture became yellow on addition of DIA (1.43 mmol, 0.2 mL) and was allowed to stand at 0 °C for 3 h. The electrophilic reagent was then added at the temperature mentioned in the product description. The solution was hydrolyzed at −70 °C with a large excess of $HCl/H_2O/THF$.

General Treatment of the Reaction Mixture. After the electrophilic reagent had reacted, the reaction mixture was hydrolyzed by a large excess of concentrated HCl/THF, treated with 500 mL of water and diethyl ether (Et_2O) (if necessary, the reaction mixture was first treated with potassium carbonate), saturated with sodium chloride, and then extracted several times with Et_2O. The organic layer was dried over anhydrous magnesium sulfate ($MgSO_4$), concentrated, and then distilled. Sometimes further purification (distillation or recrystallization) was necessary.

2-Methoxy-3-(trimethylsilyl)pyridine (2). Pure **2** was obtained by vacuum distillation to afford a colorless liquid: bp 55 °C (3 Torr); ^{1}H NMR δ 0.25 (s, 9 H), 3.9 (s, 3 H), 6.75 [dd, 1 H, J = 7.0 Hz and J = 5.0 Hz, H(5)], 7.6 [dd, 1 H, J = 7.0 Hz and J = 2.0 Hz, H(4)], 8.1 [dd, 1 H, J = 5.0 Hz and J = 2.0 Hz, H(6)]; IR (neat) 2945, 1570, 1452, 1384, 1247, 1022, 852, 840 cm^{-1}. Anal. Calcd for $C_9H_{15}NOSi$: C, 59.62; H, 8.34; N, 7.73. Found: C, 59.31; H, 8.29; N, 7.41.

3-Formyl-2-methoxypyridine (3). This compound has already been described in ref 32. When HCOOEt was used (−70 °C for 1 h), **3** was formed together with bis(2-methoxy-3-pyridyl)methanol (**11**). When DMF was used (−40 °C for 0.75 h), **3** was isolated. Both with HCOOEt and DMF, another aldehyde **1b** was isolated.

6-Butyl-3-formyl-2-methoxypyridine (1b): bp 105 °C (3 Torr); ^{1}H NMR δ 0.95 (m, 3 H), 1.45 (m, 4 H), 2.75 (t, 2 H), 4.05 (s, 3 H), 6.65 [d, 1 H, J = 8.0 Hz, H(5)], 8.0 [d, 1 H, J = 8.0 Hz, H(4)], 10.3 (s, 1 H, CHO).

1-(2-Methoxy-3-pyridyl)ethanol (4). Acetaldehyde was added at −70 °C with stirring for 0.5 h. Pure **4** was obtained after distillation: bp 95 °C (3 Torr); ^{1}H NMR δ 1.4 (d, 3 H, J = 7.0 Hz, CH_3), 3.75 (s, 1 H, OH), 3.9 (s, 3 H, OCH_3), 4.95 (q, 1 H, J = 7.0 Hz, CH), 6.8 [dd, 1 H, J = 7.0 Hz and J = 5.0 Hz, H(5)], 7.6 [dd, 1 H, J = 7.0 Hz and J = 2.0 Hz, H(4)], 7.95 [dd, 1 H, J = 5.0 Hz and J = 2.0 Hz, H(6)]; IR (neat) 3360, 2970, 1695, 1468, 1450, 1412, 1248, 1080, 1020, 780 cm^{-1}. Anal. Calcd for $C_8H_{11}NO_2$: C, 62.73; H, 7.24; N, 9.14. Found: C, 62.42; H, 7.21; N, 9.38.

2-(2-Methoxy-3-pyridyl)propan-2-ol (5). Acetone was added at −70 °C with stirring for 1 h. Pure **5** was obtained by distillation: bp 85–90 °C (3 Torr); ^{1}H NMR δ 1.6 (s, 6 H, CH_3), 3.9 (s, 1 H, OH), 4.0 (s, 3 H, OCH_3), 6.8 [dd, 1 H, J = 8.0 Hz and J = 5.0 Hz, H(5)], 7.6 [dd, 1 H, J = 8.0 Hz and J = 2.0 Hz, H(4)], 8.0 [dd, 1 H, J = 5.0 Hz and J = 2.0 Hz, H(6)]; IR (neat) 3420, 2980, 1588, 1465, 1450, 1405, 1250, 1082, 1060, 1020, 780 cm^{-1}. Anal. Calcd for $C_9H_{13}NO_2$: C, 64.65; H, 7.84; N, 8.38. Found: C, 64.41; H, 7.84; N, 8.04.

2-(2-Methoxy-3-pyridyl)butan-2-ol (6). The electrophile used was 2-butanone and reacted at −70 °C for 1 h: bp 95–100 °C (3 Torr); ^{1}H NMR δ 0.8 (t, 3 H, J = 8.0 Hz, CH_3CH_2), 1.55 (s, 3 H, CH_3), 1.9 (q, 2 H, J = 8.0 Hz, CH_2CH_3), 3.6 (s, 1 H, OH), 4.0 (s, 3 H, OCH_3), 6.85 [dd, 1 H, J = 8.0 Hz and J = 5.0 Hz, H(5)], 7.6 [dd, 1 H, J = 8.0 Hz and J = 2.0 Hz, H(4)], 8.05 [dd, 1 H, J = 5.0 Hz and J = 2.0 Hz, H(6)]; IR (neat) 3440, 2970, 1585, 1464, 1405, 1250, 1020, 780 cm^{-1}. Anal. Calcd for $C_{10}H_{15}NO_2$: C, 66.27; H, 8.34; N, 7.73. Found: C, 65.95; H, 8.19; N, 7.56.

3-(2-Methoxy-3-pyridyl)pentan-3-ol (7). 3-Pentanone was added at −70 °C, with stirring for 1 h, to afford **7** as a liquid, which was purified by vacuum distillation: bp 95–100 °C (3 Torr); ^{1}H NMR δ 0.7 (t, 6 H, J = 8.0 Hz, CH_3CH_2), 1.95 (m, 4 H, J = 8.0 Hz, CH_2CH_3), 3.4 (s, 1 H, OH), 3.95 (s, 3 H, OCH_3), 6.8 [dd, 1 H, J = 8.0 Hz and J = 5.0 Hz, H(5)], 7.6 [dd, 1 H, J = 8.0 Hz and J = 2.0 Hz, H(4)], 8.0 (dd, 1 H, J = 5.0 Hz and J = 2.0 Hz, H(6)]; IR (neat) 3400, 2970, 1585, 1460, 1405, 1240, 1090, 1025, 785 cm^{-1}. Anal. Calcd for $C_{11}H_{17}NO_2$: C, 67.66; H, 8.78; N, 7.17. Found: C, 67.26; H, 9.01; N, 6.96.

1-(2-Methoxy-3-pyridyl)hexanol (8). Hexanal was added at −70 °C (reaction time 1 h) to afford **8** as a liquid, purified by vacuum distillation: bp 125–135 °C (3 Torr); ^{1}H NMR δ 0.9 (m, 3 H), 1.35 (m, 6 H), 1.65 (m, 2 H), 3.2 (s, 1 H, OH), 3.9 (s, 3 H, OCH_3), 4.75 (t, 1 H, CH), 6.8 [dd, 1 H, J = 8.0 Hz and J = 5.0 Hz, H(5)], 7.6 [dd, 1 H, J = 8.0 Hz and J = 2.0 Hz, H(4)], 7.95

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[dd, 1 H, J = 5.0 Hz and J =2.0 Hz, H(6)]; IR (neat) 3360, 2950, 2930, 2860, 1595, 1465, 1412, 1250, 1025, 780 cm^{-1}. Anal. Calcd for $C_{12}H_{19}NO_2$: C, 68.87; H, 9.15; N, 6.69. Found: C, 68.66; H, 9.10; N, 6.67.

1-(2-Methoxy-3-pyridyl)-10-undecen-1-ol (9). 10-Undecenal was added at −70 °C (1 h) to afford **9** as a liquid: bp 170–175 °C (3 Torr); ^{1}H NMR δ 1.3–2.0 (m, 16 H, C_8H_{16}), 3.2 (s, 1 H, OH), 3.95 (s, 3 H, OCH_3), 4.6–6.2 (m, 4 H, CH and CH=CH_2), 6.8 [dd, 1 H, J = 8.0 Hz and J = 5.0 Hz, H(5)], 7.0 [dd, 1 H, J = 8.0 Hz and J = 2.0 Hz, H(4)], 8.0 [dd, 1 H, J = 5.0 Hz and J = 2.0 Hz, H(6)]; IR (neat) 3380, 2920, 2850, 1592, 1465, 1412, 1248, 1022, 910, 780 cm^{-1}. Anal. Calcd for $C_{17}H_{27}NO_2$: C, 73.61; H, 9.81; N, 5.05. Found: C, 73.47; H, 9.79; N, 5.07.

1-(2-Methoxy-3-pyridyl)-(*E*)-2-hexen-1-ol (10). The *E* isomer of 2-hexenal was added at −70 °C, with stirring for 1 h, to afford 10% of the *E* isomer of 3-hepten-2-ol (**10a**)[40] and 45% of **10**, which was purified by vacuum distillation: bp 125–130 °C (3 Torr); ^{1}H NMR δ 0.9 (m, 3 H, C_3H_7), 1.4 (m, 2 H, C_3H_7), 2.0 (m, 2 H, C_3H_7), 3.4 (s, 1 H, OH), 4.0 (s, 3 H, OCH_3), 5.3 (m, 1 H, CH), 5.7 (m, 2 H, vinyl CH), 6.85 [dd, 1 H, J = 8.0 Hz and J = 5.0 Hz, H(5)], 7.65 [dd, 1 H, J = 8.0 Hz and J = 2.0 Hz, H(4)], 8.0 [dd, 1 H, J = 5.0 Hz and J = 2.0 Hz, H(6)]; IR (neat) 3360, 2950, 2920, 2870, 1592, 1465, 1410, 1250, 1085, 1022, 965, 780 cm^{-1}. Anal. Calcd for $C_{12}H_{17}NO_2$: C, 69.54; H, 8.27; N, 6.76. Found: C, 69.40; H, 8.12; N, 6.81.

Action of 3-Formyl-2-methoxypyridine. Compound **3** was allowed to react at −70 °C for 1 h. Under these conditions, 50% of bis(2-methoxy-3-pyridyl)methanol[32] (**11**) was formed along with 1-(2-methoxy-3-pyridyl)ethanol (**4**) (5%) and unreacted electrophile was recovered. **11**: bp 170–180 °C (3 Torr); mp 105 °C (from heptane–Et_2O).

1-(2-Methoxy-3-pyridyl)cyclopentanol (12). Cyclopentanone was added at −70 °C, with stirring for 1 h, to give **12**, which was purified by vacuum distillation: bp 110 °C (3 Torr); ^{1}H NMR δ 2.0 (s, 8 H, cyclopentyl), 3.3 (s, 1 H, OH), 4.0 (s, 3 H, OCH_3), 6.8 [dd, 1 H, J = 8.0 Hz and J = 5.0 Hz, H(5)], 7.6 [dd, 1 H, J = 8.0 Hz and J = 2.0 Hz, H(4)], 8.0 [dd, 1 H, J = 5.0 Hz and J = 2.0 Hz, H(6)]; IR (neat) 3420, 2950, 1586, 1462, 1450, 1405, 1247, 1020, 780 cm^{-1}. Anal. Calcd for $C_{11}H_{15}NO_2$: C, 68.37; H, 7.82; N, 7.25. Found: C, 68.29; H, 7.79; N, 7.00.

1-(2-Methoxy-3-pyridyl)cyclohexanol (13). The action of cyclohexanone at −70 °C for 1 h led to 10% of 1-methylcyclohexanol (**13a**)[41] and 40% of **13**, which was purified by distillation: bp 125 °C (3 Torr); ^{1}H NMR δ 1.5–2.0 (m, 10 H, cyclohexyl), 3.6 (s, 1 H, OH), 4.0 (s, 3 H, OCH_3), 6.8 [dd, 1 H, J = 8.0 Hz and J = 2.0 Hz, H(5)], 7.6 [dd, 1 H, J = 8.0 Hz and J = 2.0 Hz, H(4)], 8.0 [dd, 1 H, J = 5.0 Hz and J = 2.0 Hz, H(6)]; IR (neat) 3430, 2925, 2850, 1582, 1460, 1448, 1403, 1240, 1020, 778 cm^{-1}. Anal. Calcd for $C_{12}H_{17}NO_2$: C, 69.54; H, 8.27; N, 6.76. Found: C, 69.42; H, 8.08; N, 7.07.

1-(2-Methoxy-3-pyridyl)cyclooctanol (14). Cyclooctanone was added at −70 °C, with stirring for 1 h, to afford **14**, which was purified by vacuum distillation and by recrystallization from acetone/water: bp 145 °C (3 Torr); mp 145 °C; ^{1}H NMR δ 1.3–2.5 (m, 14 H, cyclooctyl), 3.9 (s, 1 H, OH), 4.0 (s, 3 H, OCH_3), 6.8 [dd, 1 H, J = 8.0 Hz and J = 5.0 Hz, H(5)], 7.6 [dd, 1 H, J = 8.0 Hz and J = 2.0 Hz, H(4)], 8.0 [dd, 1 H, J = 5.0 Hz and J = 2.0 Hz, H(6)]; IR (KBr disk) 3400, 2910, 1580, 1460, 1402, 1245, 1020, 1015, 787, 775 cm^{-1}. Anal. Calcd for $C_{14}H_{21}NO_2$: C, 71.46; H, 9.00; N, 5.95. Found: C, 66.44; H, 9.12; N, 5.51 (this analysis is in agreement with $C_{14}H_{21}NO_2{\cdot}H_2O$ calcd C, 66.37; H, 9.15; N, 5.53).

3-Methyl-2-methoxypyridine (15).[42] This other method of preparation of compound **15** using methyl iodide as the electrophile gave a 55% yield at −60 °C for 1 h. Compound **15** was purified by distillation: bp 40 °C (3 Torr); ^{1}H NMR δ 2.15 (s, 2 H, CH_3), 3.95 (s, 3 H, OCH_3), 6.7 [dd, 1 H, J = 7.5 Hz and J = 5.5 Hz, H(5)], 7.3 [dd, 1 H, J = 7.5 Hz and J = 2.0 Hz, H(4)], 8.0 [dd, 1 H, J = 5.5 Hz and J = 2.0 Hz, H(6)]; IR (neat) 2950, 1595, 1470, 1450, 1405, 1307, 1255, 1190, 1115, 1025, 785 cm^{-1}. Anal. Calcd for C_7H_9NO: C, 68.27; H, 7.37; N, 11.37. Found: C, 67.89; H, 7.48; N, 11.04. This compound was also isolated when allyl bromide was added at −70 °C for 0.5 h.

3-Deuterio-2-methoxypyridine (16). Compound **16** was prepared by the action of DCl/D_2O at −70 °C for 0.5 h. In this case, the electrophile was added slowly to the reaction mixture. Compound **16** was obtained by distillation together with 2-methoxypyridine: bp 75–80 °C (70 Torr); ^{1}H NMR δ 3.9 (s, 3 H, OCH_3), 6.8 [dd, 1 H, J = 8.0 Hz and J = 5.0 Hz, H(5)], 7.5 [m, 1 H, H(4)], 8.15 [dd, 1 H, J = 5.0 Hz and J = 2.0 Hz, H(6)].

2-(2-Methoxy-3-pyridyl)ethanol (17). Ethylene oxide was added at 0 °C, with stirring for 1.5 h, to afford **17**, which was then purified by distillation: bp 110 °C (3 Torr); ^{1}H NMR δ 2.8 (t, 2 H, CH_2), 3.5 (s, 1 H, OH), 3.85 (t, 2 H, CH_2), 3.95 (s, 3 H, OCH_3), 6.75 [dd, 1 H, J = 7.5 Hz and J = 5.5 Hz, H(5)], 7.4 [dd, 1 H, J = 7.5 Hz and J = 2.0 Hz, H(4)], 7.95 [dd, 1 H, J = 5.5 Hz and J = 2.0 Hz, H(6)]; IR (neat) 3360, 2950, 1594, 1465, 1412, 1310, 1255, 1110, 1045, 1020, 785 cm^{-1}. Anal. Calcd for $C_8H_{11}NO_2$: C, 62.73; H, 7.24; N, 9.14. Found: C, 62.63; H, 7.15; N, 9.31.

3-Bromo-2-methoxypyridine (18).[43] Neat bromine was introduced into the reaction mixture at −70 °C. During the addition of the electrophile, the temperature increased from −70 to −40 °C. After complete addition, the mixture was allowed to stand at −60 °C for 0.5 h. Besides 3-bromo-2-methoxypyridine (bp 70–75 °C (3 Torr)), 3-methyl-2-methoxypyridine was also isolated. (In the ^{1}H NMR spectrum of the crude product, 4-bromo-2-methoxypyridine seemed to be present but could not be isolated.)

3-Iodo-2-methoxypyridine (19). Iodine in THF was introduced slowly; the temperature of the reaction mixture rose from −70 to −40 °C. After addition of the electrophile, the reaction mixture was kept at −60 °C for 0.5 h. Before extraction, the solution was treated with sodium thiosulfate until bleaching. Compound **19** was purified by distillation: bp 85 °C, (3 Torr); ^{1}H NMR δ 3.95 (s, 3 H, OCH_3), 6.6 [dd, 1 H, J = 7.5 Hz and J = 5.0 Hz, H(5)], 8.0 [m, 2 H, H(4) and H(6)]; IR (neat) 2960, 1584, 1470, 1406, 1300, 1260, 1075, 1030, 1010, 790, 760 cm^{-1}. Anal. Calcd for C_6H_6INO: C, 30.66; H, 2.57; N, 5.96. Found: C, 30.35; H, 2.57; N, 6.12. 3-Methyl-2-methoxypyridine (10%) was also isolated from the reaction mixture.

(2-Methoxy-3-pyridyl)methanol (20). The electrophile used was 1,3,5-trioxane. The metalation conditions were slightly different from those used with the other electrophiles. An excess of methyllithium was needed to cleave the 1,3,5-trioxane. We used 160 mL (256 mmol) of methyllithium and 6.5 g (72.2 mmol) of electrophile, which was introduced immediately. The reaction mixture was allowed to stand at 25 °C for 2 h before hydrolysis with C_2H_5OD. 3-Deuterio-2-methoxypyridine was isolated besides **20**, which was purified by distillation: bp 95 °C (3 Torr); ^{1}H NMR δ 3.7 (s, 1 H, OH), 3.9 (s, 3 H, OCH_3), 4.6 (s, 2 H, CH_2), 6.8 [dd, 1 H, J = 7.5 Hz and J = 5.5 Hz, H(5)], 7.55 [dd, 1 H, J = 7.5 Hz and J = 2.0 Hz, H(4)], 7.95 [dd, 1 H, J = 5.5 Hz and J = 2.0 Hz, H(6)], IR (neat) 3300, 2950, 1595, 1590, 1465, 1415, 1310, 1255, 1045, 1020, 780 cm^{-1}. Anal. Calcd for $C_7H_9NO_2$: C, 60.42; H, 6.52; N, 10.07. Found: C, 60.29; H, 6.38; N, 9.87.

Registry No. **1**, 1628-89-3; **1b**, 112219-56-4; **2**, 112197-01-0; **3**, 71255-09-9; **4**, 112197-02-1; **5**, 112197-03-2; **6**, 112197-04-3; **7**, 112197-05-4; **8**, 112197-06-5; **9**, 112197-07-6; **10**, 112197-08-7; **10a**, 67077-39-8; **11**, 71255-10-2; **12**, 112197-09-8; **13**, 112197-10-1; **13a**, 590-67-0; **14**, 112197-11-2; **15**, 19230-59-2; **15** (4-bromo isomer), 112197-12-3; **16**, 112197-13-4; **17**, 112197-14-5; **18**, 13472-59-8; **19**, 112197-15-6; **20**, 112197-16-7; 10-undecanal, 112-45-8; (*E*)-2-hexenal, 6728-26-3; cyclopentanone, 120-92-3; cyclohexanone, 108-94-1; cyclooctanone, 502-49-8; 3,6-dihydro-2-methoxy-6-methylpyridine, 112197-17-8; oxirane, 75-21-8; 1,3,5-trioxane, 110-88-3.

(40) This compound **10a** results from the reaction of the excess of methyllithium on the electrophile: bp 50 °C (3 Torr); ^{1}H NMR ($CDCl_3$) δ 0.9 (m, 3 H, C_3H_7), 1.2 (d, 3 H, CH_3), 2.0 (m, 2 H, C_3H_7), 2.7 (s, 1 H, OH), 4.25 (m, 2 H, C_3H_7), 5.6 (m, 2 H, vinyl CH).

(41) This compound **13a** was formed by the reaction between the excess of methyllithium and cyclohexanone: bp 40 °C (3 Torr); ^{1}H NMR ($CDCl_3$) δ 1.2 (s, 3 H, CH_3), 1.5–2.3 (m, 11 H, cyclohexyl and OH).

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(43) This compound has already been prepared by Spinner and White (Spinner, E.; White, J. C. B. *J. Chem. Soc. B* **1966**, 991) and by us (ref 38).