[Chem. Pharm. Bull. 33(3)1016—1022(1985)]

ortho-Directed Lithiation of (2-Methoxy)ethoxy- and (2-Dimethylamino)ethoxy-arenes

AKIMORI WADA,* SHŌICHI KANATOMO, and SOTOO NAGAI

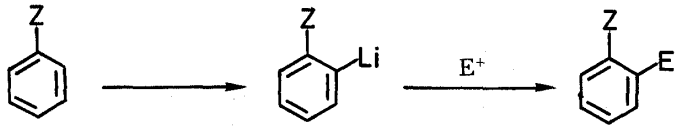
School of Pharmacy, Hokuriku University, Ho-3, Kanagawa-machi, Kanazawa, Ishikawa 920–11, Japan

(Received June 20, 1984)

ortho-Directed lithiation of a number of (2-methoxy)ethoxy- and (2-dimethylamino)ethoxy-arenes has been investigated. Lithiation of these compounds followed by treatment with various electrophiles afforded *ortho*-substituted products in moderate to excellent yields.

Keywords——*ortho*-directed lithiation; (2-methoxy)ethoxyarene; (2-dimethylamino)ethoxy-arene; regioselectivity

The formation of regiospecifically *ortho*-metalated aromatics by deprotonation, as illustrated for substituted benzenes in Chart 1, has been shown to be a very useful reaction in organic synthesis.[1] Although a number of *ortho*-directing substituents have so far been investigated, the methoxymethoxy group was recently found to be a most effective directing group because of strong coordination to the lithium atom by both oxygen atoms.[2] In this paper, we describe the capability of the (2-methoxy)ethoxy[3] and (2-dimethylamino)ethoxy groups for *ortho*-directed lithiation, and the reaction of lithiated intermediates with various electrophiles.



Z=SO_2Y, CONHR, CH_2NR_2
OR, NHAr, NRAr, NR_2

Chart 1

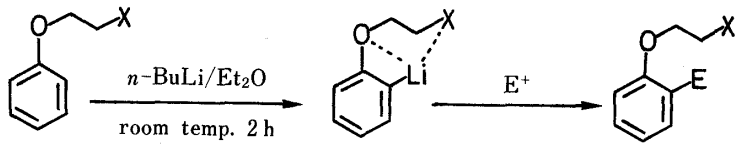
The starting materials, (2-methoxy)ethoxy- (**2a**, **c**, **d**) and (2-dimethylamino)ethoxy-arenes (**2b**), were prepared from the corresponding hydroxyarenes by the usual method except for the pyridine derivative (**2e**), which was obtained by condensation of 4-chloropyridine hydrochloride (**3**) with 2-methoxyethanol in the presence of 2 eq of sodium metal in 29% yield (Chart 2).

Treatment of **2a** and **2b** with 1.2 eq of *n*-butyllithium in ether for 2 h gave the *ortho*-lithiated derivatives (**4a** and **4b**) as colorless precipitates, which were quenched with *N*,*N*-dimethylformamide (DMF) to afford 2-formylated benzenes (**5a** and **5'a**) in 62 and 76% yields, respectively (Chart 3). The reactivity of *ortho*-lithiated benzenes (**4a** and **4b**) with various electrophiles such as benzaldehyde, methyl iodide, carbon dioxide, and trimethylsilyl chloride was investigated, and the results are summarized in Table I. In the reaction of **2b** with methyl iodide, carbon dioxide, and trimethylsilyl chloride, a complex mixture was obtained and *ortho*-substituted products could not be isolated (runs 8—10). The yields of *ortho*-substituted products in the case of the (2-dimethylamino)ethoxy group (runs 6, 7) were better

1 **2a**: R=H, X=OMe, Y=CH; **2b**: R=H, X=NMe_2, Y=CH; **2c**: R=Me, X=OMe, Y=CH; **2d**: R=H, X=OMe, Y=N — 3 — **2e**

Chart 2

than those in the case of the (2-methoxy)ethoxy group (runs 1, 2). These results can be explained by the consideration that the coordination of the lithium atom with the nitrogen atom is stronger than that with the oxygen atoms in the lithiated structure of **4**. This view is supported by the fact that lithiation of 4-methoxy-*N*,*N*-dimethylbenzylamine followed by condensation with benzophenone regioselectively afforded the *ortho*-substituted product with respect to the amine.[4]



2a: X=OMe; **2b**: X=NMe_2 — **4a**: X=OMe; **4b**: X=NMe_2 — **5a**: X=OMe, E=CHO; **5b**: X=OMe, E=CH(OH)Ph; **5c**: X=OMe, E=Me; **5d**: X=OMe, E=CO_2H; **5e**: X=OMe, E=$SiMe_3$; **5'a**: X=NMe_2, E=CHO; **5'b**: X=NMe_2, E=CH(OH)Ph

Chart 3

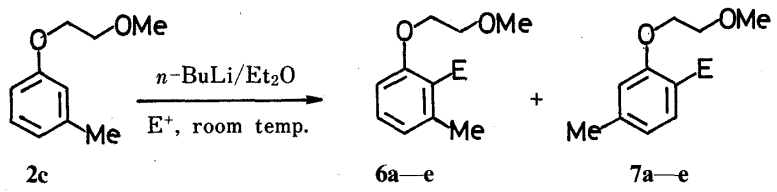
TABLE I. Reaction of **2** with *n*-BuLi and Electrophiles

Runs	Substrate	Electrophile	Condition[a]	Product	Yield[b] (%)
1	**2a**	DMF	A	**5a**	62
2	**2a**	PhCHO	A	**5b**	29
3	**2a**	MeI	A	**5c**	68
4	**2a**	CO_2	B	**5d**	70
5	**2a**	Me_3SiCl	A	**5e**	43
6	**2b**	DMF	A	**5'a**	76
7	**2b**	PhCHO	A	**5'b**	49
8	**2b**	MeI	A	Complex mixture[c]	
9	**2b**	CO_2	B		
10	**2b**	Me_3SiCl	A		

a) A: room temp., 0.5 h. B: −70 °C→room temp., 2 h. *b*) Isolated yield. *c*) *o*-Substituted product (**5'**) was not present.

The regioselectivity in *ortho*-directed lithiation is a significant problem for synthetic application. Therefore we investigated the lithiation of unsymmetrically 1,3-disubstituted benzene (**2c**). Lithiation of **2c** followed by condensation with methyl iodide gave a mixture of two possible isomers, the 1,2,3- and 1,2,5-trisubstituted products (**6a** and **7a**), in a ratio of

58 : 42 (Chart 4). The ratio of the two isomers was determined by gas-liquid chromatographic (GC) analysis. The results with other electrophiles are summarized in Table II. Generally, the ratio of **6** decreased with increase in the bulkiness of the electrophiles. In the reaction with trimethylsilyl chloride, **7e** was obtained selectively and the corresponding **6e** was not detected at all (run 5).



2c **6a—e** **7a—e**

a: E=Me
b: E=CO_2Me
c: E=CHO
d: E=CH(OH)Ph
e: E=$SiMe_3$

Chart 4

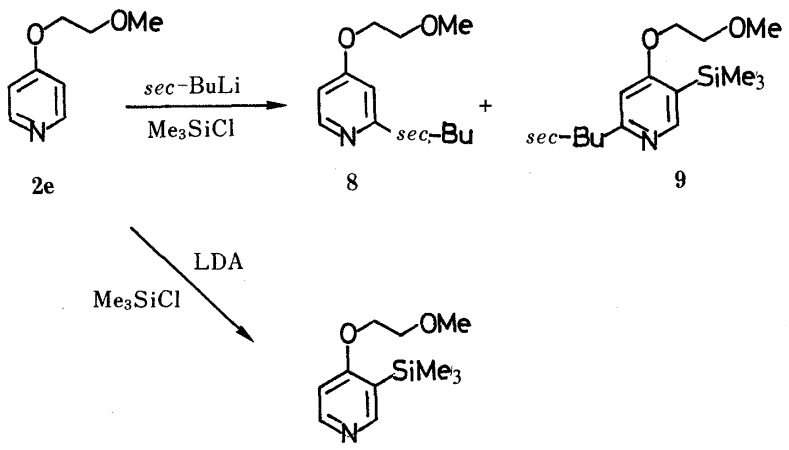
TABLE II. Reaction of **2c** with Electrophiles

Runs	Electrophile	Condition[a]	Yield[b] (%)	Product ratio[c] **6** : **7**
1	MeI	A	59	**6a** : **7a** = 42 : 58
2	CO_2	B	45[d]	**6b** : **7b** = 39 : 61
3	DMF	A	47	**6c** : **7c** = 35 : 65
4	PhCHO	A	36	**6d** : **7d** = 33 : 67
5	Me_3SiCl	A	32	**6e** : **7e** = 0 : 100

a) A: room temp., 0.5 h. B: −70 °C→room temp., 2 h. *b*) Isolated yield as a mixture of **6** and **7**. *c*) Determined by GC analysis. *d*) After treatment with diazomethane.

It is well known that the lithio derivatives of pyridines are usually prepared by halogen–metal exchange reaction,[5] because nucleophilic addition of the alkyllithium occurs to the C=N bond.[1,6] However, a few examples are known of *ortho*-directed lithiation of monosubstituted pyridines,[2,7] and there are some reports on polychlorinated system[8] or systems with more than one *ortho*-directing or carbanion-stabilizing group.[9] Therefore, we focused our attention on *ortho*-directed lithiation of (2-methoxyethoxy)pyridines. Treatment of **2e** with *sec*-butyllithium and subsequent quenching with trimethylsilyl chloride at −70 °C afforded the 2-*sec*-butylpyridine (**8**) and 2-*sec*-butyl-5-trimethylsilylpyridine (**9**) in 29 and 11% yields, respectively. The silylated product (**9**) was presumably obtained *via* lithiation at the less hindered *ortho* position of **8** followed by quenching with trimethylsilyl chloride. The structure of **9** was easily determined from its proton nuclear magnetic resonance (^{1}H-NMR)spectrum, which showed two singlets at 8.38 and 6.58 ppm due to two aromatic protons. In order to avoid alkylation during the reaction, we next chose lithium diisopropylamide (LDA) as a lithiating reagent because of its lower nucleophilicity. Similar treatment of **2e** with LDA followed by trimethylsilyl chloride gave the *ortho*-substituted product (**10**) in 14% yield (Chart 5). The yield of **10** was increased to 39% by using 2 eq of LDA. On the other hand, the reaction of **2d** with LDA and trimethylsilyl chloride afforded only a complex mixture and no *ortho*-substituted products were detected.

The present results suggest that both (2-methoxy)ethoxy and (2-dimethylamino)ethoxy groups are useful for *ortho*-directed lithiation, and can be summarized as follows: 1) in the



2e 8 9

10

Chart 5

benzene system (2-methoxy)ethoxy and (2-dimethylamino)ethoxy groups are rather strong *ortho*-directing groups, and their *ortho*-lithiation-directing effects are between those of methoxy and methoxymethoxy groups based on a comparison of the yields of corresponding reactions,[2,10] 2) in the pyridine system, *ortho*-lithiation is possible by using lithiating reagents having low nucleophilicity such as LDA, and this should also be applicable to other nitrogen-containing heteroaromatics.

Experimental

All melting and boiling points are uncorrected. Infrared (IR) absorption spectra were recorded on a JASCO IRA-2 spectrometer and NMR spectra on a JEOL JNM-MH-100 spectrometer (with tetramethylsilane as an internal standard). Mass spectra (MS) were obtained with a JEOL JMS-100 instrument with a direct inlet system. GC was obtained on a Shimadzu GC-4 CM with a 3 mm × 2 m glass column packed with 1.5% OV-17 on Shimalite W (201 D). Column chromatography was carried out on Merck Silicagel 60.

General Procedure for Preparation of 2-Methoxyethoxy- and 2-Dimethylaminoethoxyarenes (2a—e)——A solution of hydroxyarene (**1**) (30 mmol) in ether (10 ml) was added dropwise to a stirred suspension of NaH (50%, 1.45 g, 30 mmol) in ether (60 ml) and DMF (20 ml) at room temperature under nitrogen. The resulting mixture was stirred for 10 min, then a solution of 1-bromo-2-ethoxyethane (4.2 g, 30 mmol) in ether (10 ml) was added. (In the case of 1-bromo-2-dimethylaminoethane hydrobromide (3.4 g, 15 mmol), the solid was added through a funnel.) The reaction mixture was stirred for 15 h, and then poured into 50 ml of water. The aqueous layer was separated and extracted with ether (30 ml × 2). The extract was washed with 10% NaOH, water, and aqueous NaCl. The ethereal layer was dried with Na_2SO_4 and concentrated *in vacuo*. The crude product was purified by distillation *in vacuo*.

(2-Methoxyethoxy)benzene (2a)——This was prepared from phenol (2.8 g, 30 mmol) and 1-bromo-2-ethoxyethane (4.2 g, 30 mmol) in 38% yield (1.7 g), bp 108—110 °C (25 mmHg). *Anal.* Calcd for $C_9H_{12}O_2$: C, 71.02; H, 7.95. Found: C, 71.25; H, 7.82. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1595, 1585. NMR ($CDCl_3$) δ: 7.6—6.9 (5H, m, ArH), 4.17 (2H, dd, J=6, 7 Hz, CH_2), 3.79 (2H, dd, J=6, 7 Hz, CH_2), 3.48 (3H, s, OMe). MS m/z: 152 (M^+).

(2-Dimethylaminoethoxy)benzene (2b)——This was prepared from phenol (1.0 g, 10 mmol) and 1-bromo-2-dimethylaminoethane hydrobromide (1.15 g, 5 mmol) in 78% yield (0.64 g), bp 65—68 °C (10 mmHg). *Anal.* Calcd for $C_{10}H_{15}NO$: C, 72.69; H, 9.14; N, 8.48. Found: C, 72.88; H, 9.01; N, 8.19. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1590, 1580. NMR ($CDCl_3$) δ: 7.6—6.9 (5H, m, ArH), 4.11 (2H, t, J=6 Hz, CH_2), 2.72 (2H, t, J=6 Hz, CH_2), 2.31 (6H, s, NMe_2). MS m/z: 165 (M^+).

1-(2-Methoxyethoxy)-3-methylbenzene (2c)——This was prepared from *m*-cresol (3.4 g, 32 mmol) and 1-bromo-2-methoxyethane (4.2 g, 30 mmol) in 52% yield (2.6 g), bp 122—125 °C (27 mmHg). *Anal.* Calcd for $C_{10}H_{14}O_2$: C, 72.26; H, 8.49. Found: C, 72.15; H, 8.45. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1595, 1590, 1580. NMR ($CDCl_3$) δ: 7.27 (1H, br t, J=9 Hz, ArH), 7.0—6.7 (2H, m, ArH), 6.87 (1H, s, ArH), 4.15 (2H, dd, J=6, 7 Hz, CH_2), 3.81 (2H, dd, J=6, 7 Hz, CH_2), 3.48 (3H, s, OMe), 2.35 (3H, s, Me). MS m/z: 166 (M^+).

3-(2-Methoxyethoxy)pyridine (2d)——This was prepared from 3-hydroxypyridine (2.0 g, 20 mmol) and 1-bromo-2-ethoxyethane (2.8 g, 20 mmol) in 11% yield (350 mg), bp 105—115 °C (5 mmHg). *Anal.* Calcd for $C_8H_{11}NO_2$: C,

62.72; H, 7.24; N, 9.14. Found: C, 62.88; H, 7.05; N, 9.23. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1580, 1570. NMR ($CDCl_3$) δ: 8.5—8.2 (2H, m, ArH), 7.4—7.2 (2H, m, ArH), 4.22 (2H, dd, J=5, 6.5 Hz, CH_2), 3.81 (2H, dd, J=5, 6.5 Hz, CH_2), 3.48 (3H, s, OMe). MS m/z: 153 (M^+).

4-(2-Methoxyethoxy)pyridine (2e)——4-Chloropyridine hydrochloride (**3**) (4.5 g, 30 mmol) was added to a stirred solution of 2-methoxyethanol (50 ml) containing sodium 2-methoxyethoxide (60 mmol) at room temperature under nitrogen. The resulting mixture was stirred for 12 h, and the solvent was removed *in vacuo*. Water (50 ml) was added to the residue, and the mixture was extracted with ether (30 ml × 3). The combined extract was washed with 10% NaOH, water, and aqueous NaCl. The ethereal layer was dried over Na_2SO_4 and concentrated *in vacuo*. The residue was distilled to afford **2e** (1.35 g, 29%), bp 100—105 °C (5 mmHg). *Anal.* Calcd for $C_8H_{11}NO_2$: C, 62.72; H, 7.24; N, 9.14. Found: C, 62.68; H, 7.24; N, 8.99. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1580, 1560. NMR ($CDCl_3$) δ: 8.6—8.4 (2H, m, ArH), 7.9—6.8 (2H, m, ArH), 4.24 (2H, dd, J=5, 6 Hz, CH_2), 3.85 (2H, dd, J=5, 6 Hz, CH_2), 3.51 (3H, s, OMe). MS m/z: 153 (M^+).

General Procedure for Lithiation of 2-Methoxyethoxy- and 2-Dimethylaminoethoxyarenes and Reaction with Electrophiles——A 1.5 M solution of *n*-BuLi in hexane (0.8 ml, 1.2 mmol) was added dropwise to a solution of **2** (1.0 mmol) in anhydrous ether (5 ml) at room temperature. After the reaction mixture had been maintained for 2 h at the same temperature, a solution of an appropriate electrophilic reagent in anhydrous ether (2 ml) was added. The reaction mixture was stirred under the conditions indicated in Table I and then quenched with saturated aqueous NH_4Cl. The organic layer was separated and the aqueous layer was extracted with ether (15 ml × 3). The combined organic layer was washed with saturated aqueous NaCl and dried over Na_2SO_4. The solvent was evaporated off to afford the crude product. In the case of **2c**, the crude product was purified by column chromatography on silica gel (with $CHCl_3$ as the eluting solvent) to give a mixture of **6** and **7**. This was analyzed by GC.

2-(2-Methoxyethoxy)benzaldehyde (5a)——This was prepared from **2a** (155 mg, 1.0 mmol), *n*-BuLi (0.8 ml, 1.2 mmol), and DMF (150 mg, 2.0 mmol), bp 120—125 °C (3 mmHg, bath temperature). *Anal.* Calcd for $C_{10}H_{12}O_3$: C, 66.65; H, 6.71. Found: C, 66.32; H, 6.83. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1680, 1600. NMR ($CDCl_3$) δ: 10.54 (1H, s, CHO), 7.94 (1H, dd, J=8, 2.5 Hz, ArH), 7.64 (1H, dt, J=8, 2.5 Hz, ArH), 7.3—7.0 (2H, m, ArH), 4.28 (2H, dd, J=7, 8 Hz, CH_2), 3.83 (2H, dd, J=7, 8 Hz, CH_2), 3.48 (3H, s, OMe). MS m/z: 180 (M^+).

1-[2-(2-Methoxyethoxy)phenyl]-1-phenylmethanol (5b)——This was prepared from **2a** (300 mg, 1.97 mmol), *n*-BuLi (1.6 ml, 2.4 mmol), and PhCHO (210 mg, 2.0 mmol), bp 220—235 °C (3 mmHg, bath temperature). *Anal.* Calcd for $C_{16}H_{18}O_3$: C, 74.39; H, 7.02. Found: C, 74.10; H, 6.99. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3400, 1595, 1585. NMR ($CDCl_3$) δ: 7.7—6.8 (9H, m, ArH), 6.04 (1H, br s, CH), 4.08 (2H, dd, J=5, 6 Hz, CH_2), 3.75 (1H, br s, OH), 3.63 (2H, dd, J=5, 6 Hz, CH_2), 3.44 (3H, s, OMe). MS m/z: 258 (M^+).

1-(2-Methoxyethoxy)-2-methylbenzene (5c)——This was prepared from **2a** (155 mg, 1.0 mmol), *n*-BuLi (0.8 ml, 1.2 mmol), and MeI (420 mg, 3.0 mmol), bp 95—100 °C (3 mmHg, bath temperature). *Anal.* Calcd for $C_{10}H_{14}O_2$: C, 72.26; H, 8.49. Found: C, 71.98; H, 8.54. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1600. NMR ($CDCl_3$) δ: 7.5—6.8 (4H, m, ArH), 4.12 (2H, dd, J=6, 7 Hz, CH_2), 3.75 (2H, dd, J=6, 7 Hz, CH_2), 3.45 (3H, s, OMe), 2.25 (3H, s, Me). MS m/z: 166 (M^+).

2-(2-Methoxyethoxy)benzoic Acid (5d)——This was prepared from **2a** (155 mg, 1.0 mmol), *n*-BuLi (0.8 ml, 1.2 mmol), and excess solid carbon dioxide, bp 160—170 °C (5 mmHg, bath temperature). *Anal.* Calcd for $C_{10}H_{12}O_4$: C, 61.21; H, 6.17. Found: C, 61.43; H, 5.93. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3300, 1720. NMR ($CDCl_3$) δ: 9.21 (1H, s, CO_2H), 8.17 (1H, dd, J=9, 2.5 Hz, ArH), 7.64 (1H, dt, J=9, 2.5 Hz, ArH), 7.3—7.0 (2H, m, ArH), 4.39 (2H, dd, J=6, 7 Hz, CH_2), 3.86 (2H, dd, J=6, 7 Hz, CH_2), 3.46 (3H, s, OMe). MS m/z: 196 (M^+).

1-(2-Methoxyethoxy)-2-trimethylsilylbenzene (5e)——This was prepared from **2a** (300 mg, 1.97 mmol), *n*-BuLi (1.6 ml, 2.4 mmol), and trimethylsilyl chloride (300 mg, 3.0 mmol), bp 135—140 °C (7 mmHg, bath temperature). *Anal.* Calcd for $C_{12}H_{20}O_2Si$: C, 64.23; H, 8.98. Found: C, 64.03; H, 9.08. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1590, 1565. NMR ($CDCl_3$) δ: 7.6—6.8 (4H, m, ArH), 4.15 (2H, dd, J=6, 7 Hz, CH_2), 3.78 (2H, dd, J=6, 7 Hz, CH_2), 3.45 (3H, s, OMe), 0.26 (9H, s, $SiMe_3$). MS m/z: 224 (M^+).

2-(2-*N*,*N*-Dimethylamino)ethoxybenzaldehyde (5'a)——This was prepared from **2b** (170 mg, 1.0 mmol), *n*-BuLi (0.8 ml, 1.2 mmol), and DMF (150 mg, 2.0 mmol), bp 120—130 °C (8 mmHg, bath temperature). *Anal.* Calcd for $C_{11}H_{15}NO_2$: C, 68.31; H, 7.82; N, 7.25. Found: C, 68.48; H, 8.01; N, 7.08. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1680, 1590. NMR ($CDCl_3$) δ: 10.49 (1H, s, CHO), 7.92 (1H, dd, J=8, 2.5 Hz, ArH), 7.62 (1H, dt, J=8, 2.5 Hz, ArH), 7.2—6.9 (2H, m, ArH), 4.21 (2H, t, J=6 Hz, CH_2), 2.80 (2H, t, J=6 Hz, CH_2), 2.34 (6H, s, NMe_2). MS m/z: 193 (M^+).

1-[2-(2-*N*,*N*-Dimethylaminoethoxy)phenyl]-1-phenylmethanol (5'b)——This was prepared from **2b** (90 mg, 0.54 mmol), *n*-BuLi (0.4 ml, 0.6 mmol), and PhCHO (55 mg, 0.52 mmol), mp 81—83 °C (MeOH). *Anal.* Calcd for $C_{17}H_{21}NO_2$: C, 75.24; H, 7.80; N, 5.16. Found: C, 75.08; H, 7.74; N, 5.23. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3600, 1590, 1580. NMR ($CDCl_3$) δ: 7.4—6.6 (9H, m, ArH), 5.86 (1H, s, CH), 5.84 (1H, s, OH), 3.99 (2H, t, J=6 Hz, CH_2), 2.54 (2H, t, J=6 Hz, CH_2), 2.18 (6H, s, NMe_2). MS m/z: 271 (M^+).

1-(2-Methoxyethoxy)-2,3-dimethylbenzene (6a) and 1-(2-Methoxyethoxy)-2,5-dimethylbenzene (7a)——These compounds were prepared from **2c** (160 mg, 0.96 mmol), *n*-BuLi (0.8 ml, 1.2 mmol), and MeI (420 mg, 3.0 mmol). GC (180 °C) analysis indicated that **6a** and **7a** were present in a ratio of 42 : 58. Their retention times were 2.5 and 2.1 min, respectively. Analytical samples were obtained by medium-pressure column chromatography on silica gel (C_6H_6 : $CHCl_3$ = 5 : 1). **6a**: *Anal.* Calcd for $C_{11}H_{16}O_2$: C, 73.30; H, 8.95. Found: C, 73.17; H, 9.19. IR $\nu_{max}^{CHCl_3}$ cm^{-1}:

1590. NMR ($CDCl_3$) δ: 6.99 (1H, t, J=8 Hz, ArH), 6.74 (1H, d, J=8 Hz, ArH), 6.60 (1H, d, J=8 Hz, ArH), 4.05 (2H, dd, J=6, 7 Hz, CH_2), 3.72 (2H, dd, J=6, 7 Hz, CH_2), 3.43 (3H, s, OMe), 2.24 (3H, s, Me), 2.15 (3H, s, Me). MS m/z: 180 (M^+). **7a**: *Anal.* Calcd for $C_{11}H_{16}O_2$: C, 73.30; H, 8.95. Found: C, 73.53; H, 8.93. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1600, 1570. NMR ($CDCl_3$) δ: 6.96 (1H, d, J=8 Hz, ArH), 6.63 (1H, d, J=8 Hz, ArH), 6.60 (1H, s, ArH), 4.03 (2H, dd, J=5, 7 Hz, CH_2), 3.70 (2H, dd, J=5, 7 Hz, CH_2), 3.42 (3H, s, OMe), 2.29 (3H, s, Me), 2.19 (3H, s, Me). MS m/z: 180 (M^+).

Methyl 2-(Methoxyethoxy)-6-methylbenzoate (6b) and Methyl 2-(2-Methoxyethoxy)-4-methylbenzoate (7b)——These compounds were prepared by the reaction of **2c** (150 mg, 0.91 mmol) with *n*-BuLi (0.7 ml, 1.05 mmol) and excess solid carbon dioxide, followed by treatment with diazomethane. GC (200 °C) analysis indicated that **6b** and **7b** were present in a ratio of 39 : 61. Their retention times were 4.0 and 4.9 min, respectively. Analytical samples were obtained by medium-pressure column chromatography on silica gel (C_6H_6 : AcOEt = 10 : 1). **6b**: Exact MS Calcd for $C_{12}H_{16}O_4$: 224.104. Found: 224.105. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1720, 1590. NMR ($CDCl_3$) δ: 7.29 (1H, t, J=8 Hz, ArH), 6.88 (1H, d, J=8 Hz, ArH), 6.84 (1H, d, J=8 Hz, ArH), 4.17 (2H, dd, J=5, 6 Hz, CH_2), 3.89 (3H, s, OMe), 3.76 (2H, dd, J=5, 6 Hz, CH_2), 3.42 (3H, s, OMe), 2.29 (3H, s, Me). **7b**: Exact MS Calcd for $C_{12}H_{16}O_4$: 224.104. Found: 224.104. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1715, 1610. NMR ($CDCl_3$): 7.77 (1H, d, J=8.5 Hz, ArH), 6.85 (1H, s, ArH), 6.83 (1H, d, J=8.5 Hz, ArH), 4.19 (2H, dd, J=5, 6 Hz, CH_2), 3.85 (3H, s, OMe), 3.83 (2H, dd, J=5, 6 Hz, CH_2), 3.46 (3H, s, OMe), 2.36 (3H, s, Me).

2-(2-Methoxyethoxy)-6-methylbenzaldehyde (6c) and 2-(2-Methoxyethoxy)-4-methylbenzaldehyde (7c)——These compounds were prepared from **2c** (150 mg, 0.91 mmol), *n*-BuLi (0.7 ml, 1.05 mmol), and DMF (150 mg, 2.0 mmol). GC (190 °C) analysis indicated that **6c** and **7c** were present in a ratio of 35 : 65. Their retention times were 4.7 and 5.4 min, respectively. Analytical samples were obtained by medium-pressure column chromatography of silica gel (C_6H_6 : $CHCl_3$ = 5 : 1). **6c**: Exact MS Calcd for $C_{11}H_{14}O_3$: 194.094. Found: 194.094. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1680, 1600, 1580. NMR ($CDCl_3$) δ: 10.68 (1H, s, CHO), 7.44 (1H, t, J=8.5 Hz, ArH), 6.88 (2H, d, J=8.5 Hz, ArH), 4.24 (2H, dd, J=5, 6 Hz, CH_2), 3.82 (2H, dd, J=5, 6 Hz, CH_2), 3.47 (3H, s, OMe), 2.59 (3H, s, Me). **7c**: Exact MS Calcd. for $C_{11}H_{14}O_3$: 194.094. Found: 194.093. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1670, 1600, 1575. NMR ($CDCl_3$) δ: 10.37 (1H, s, CHO), 7.82 (1H, d, J=8 Hz, ArH), 6.91 (1H, d, J=8 Hz, ArH), 6.86 (1H, s, ArH), 4.26 (2H, dd, J=5, 6 Hz, CH_2), 3.86 (2H, dd, J=5, 6 Hz, CH_2), 3.46 (3H, s, OMe), 2.41 (3H, s, Me).

1-[2-(2-Methoxyethoxy)-6-methylphenyl]-1-phenylmethanol (6d) and 1-[2-(2-Methoxyethoxy)-4-methylphenyl]-1-phenylmethanol (7d)——These compounds were prepared from **2c** (150 mg, 0.91 mmol), *n*-BuLi (0.7 ml, 1.04 mmol), and PhCHO (150 mg, 2.0 mmol). GC (230 °C) analysis indicated that **6d** and **7d** were present in a ratio of 33 : 67. Their retention times were 9.9 and 10.9 min, respectively. Analytical samples were obtained by medium-pressure column chromatography on silica gel (C_6H_6 : AcOEt = 19 : 1). **6d**: *Anal.* Calcd for $C_{17}H_{20}O_3$: C, 74.97; H, 7.40. Found: C, 74.76; H, 7.25. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3450, 1600, 1580. NMR ($CDCl_3$) δ: 7.5—6.6 (8H, m, ArH), 6.10 (1H, d, J=11 Hz, CH), 4.72 (1H, d, J=11 Hz, OH), 4.2—3.9 (2H, m, CH_2), 3.6—3.3 (2H, m, CH_2), 3.32 (3H, s, OMe), 2.40 (3H, s, Me). MS m/z: 272 (M^+). **7d**: *Anal.* Calcd for $C_{17}H_{20}O_3$: C, 74.97; H, 7.40. Found: C, 74.71; H, 7.40. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3450, 1610, 1580. NMR ($CDCl_3$) δ: 7.6—7.3 (5H, m, ArH), 7.08 (1H, d, J=8 Hz, ArH), 6.78 (1H, d, J=8 Hz, ArH), 6.76 (1H, s, ArH), 6.08 (1H, d, J=6 Hz, CH), 4.15 (2H, dd, J=5, 6 Hz, CH_2), 3.88 (1H, d, J=6 Hz, OH), 3.64 (2H, dd, J=5, 6 Hz, CH_2), 3.39 (3H, s, OMe), 2.32 (3H, s, Me). MS m/z: 272 (M^+).

1-(2-Methoxyethoxy)-3-methyl-6-trimethylsilylbenzene (7e)——This was prepared from **2c** (150 mg, 0.91 mmol), *n*-BuLi (0.7 ml, 1.05 mmol), and trimethylsilyl chloride (300 mg, 3.0 mmol). Distillation gave pure **7e**, bp 140—150 °C (7 mmHg, bath temperature). *Anal.* Calcd for $C_{13}H_{22}O_2Si$: C, 65.49; H, 9.30. Found: C, 65.44; H, 9.45. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1595, 1550. NMR ($CDCl_3$) δ: 7.37 (1H, d, J=8 Hz, ArH), 6.91 (1H, d, J=8 Hz, ArH), 6.74 (1H, s, ArH), 4.13 (2H, dd, J=6, 7 Hz, CH_2), 3.81 (2H, dd, J=6, 7 Hz, CH_2), 3.74 (3H, s, OMe), 2.36 (3H, s, Me), 0.25 (9H, s, $SiMe_3$). MS m/z: 272 (M^+).

2-(2-Butyl)-4-(2-methoxyethoxy)pyridine (8) and 2-(2-Butyl)-4-(2-methoxyethoxy)-5-trimethylsilylpyridine (9)——These compounds were prepared from **2e** (150 mg, 1.0 mmol), *sec*-BuLi (1.3 M solution in hexane, 0.9 ml, 1.2 mmol), and Me_3SiCl (300 mg, 3.0 mmol). Analytical samples were obtained by column chromatography on silica gel ($CHCl_3$). **8**: Exact MS Calcd for $C_{12}H_{19}NO_2$: 209.141. Found: 209.141. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1590, 1560. NMR ($CDCl_3$) δ: 8.37 (1H, d, J=5.5 Hz, ArH), 6.64 (1H, s, ArH), 6.63 (1H, d, J=5.5 Hz, ArH), 4.13 (2H, dd, J=5, 6 Hz, CH_2), 3.75 (2H, dd, J=5, 6 Hz, CH_2), 3.42 (3H, s, OMe), 2.72 (1H, m, CH), 1.69 (2H, m, CH_2), 1.25 (3H, d, J=7 Hz, Me), 0.82 (3H, t, J=6.5 Hz, Me). **9**: Exact MS Calcd for $C_{15}H_{27}NO_2Si$: 281.181. Found: 281.181. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1580, 1540. NMR ($CDCl_3$) δ: 8.38 (1H, s, ArH), 6.58 (1H, s, ArH), 4.17 (2H, dd, J=5.5, 6.5 Hz, CH_2), 3.78 (2H, dd, J=5.5, 6.5 Hz, CH_2), 3.45 (3H, s, OMe), 2.75 (1H, m, CH), 1.69 (2H, m, CH), 1.29 (3H, d, J=6.5 Hz, Me), 0.88 (3H, t, J=7 Hz, Me), 0.29 (9H, s, $SiMe_3$).

4-(2-Methoxyethoxy)-3-trimethylsilylpyridine (10)——i) This was prepared from **2e** (150 mg, 1.0 mmol), diisopropylamine (100 mg, 1.0 mmol), *n*-BuLi (0.7 ml, 1.1 mmol), and Me_3SiCl (300 mg, 3.0 mmol). The crude product was purified by column chromatography on silica gel ($CHCl_3$) to afford **10** (30 mg, 14%). Exact MS Calcd for $C_{11}H_{19}NO_2Si$: 225.118. Found: 225.119. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1570. NMR ($CDCl_3$) δ: 8.46 (2H, br s, ArH), 6.74 (1H, d, J=6 Hz, ArH), 4.15 (2H, dd, J=5.5, 6.5 Hz, CH_2), 3.78 (2H, dd, J=5.5, 6.5 Hz, CH_2), 3.45 (3H, s, OMe), 0.30 (9H, s, $SiMe_3$).

ii) This was prepared from **2e** (150 mg, 1.0 mmol), diisopropylamine (200 mg, 2.0 mmol), *n*-BuLi (1.4 ml,

2.2 mmol), Me_3SiCl (300 mg, 3.0 mmol) in 39% (87 mg) yield. This was identical with the sample obtained in i).

References and Notes

1) B. J. Wakefield, "The Chemistry of Organolithium Compounds," Pergamon Press, New York, 1974, pp. 112—116; H. W. Gschwend and H. R. Rodriguez, *Org. React.*, **26**, 1 (1979); S. Marburg and R. L. Tolman, *J. Heterocycl. Chem.*, **17**, 1333 (1980); M. F. Semmelhack, J. Bisaha, and M. Czarny, *J. Am. Chem. Soc.*, **101**, 768 (1979); V. Snieckus, *Heterocycles*, **14**, 1649 (1980).
2) M. R. Winkle and R. C. Ronald, *J. Org. Chem.*, **47**, 2101 (1982); C. A. Townsend and L. M. Bloom, *Tetrahedron Lett.*, **22**, 3923 (1981).
3) The lithiation of (2-methoxyethoxy)benzene was reported previously, but this was limited to deuterium exchange: R. A. Ellison and F. N. Kotsonis, *J. Org. Chem.*, **38**, 4192 (1973).
4) D. W. Slocum and C. A. Jenings, *J. Org. Chem.*, **41**, 3653 (1976).
5) H. Gilman and S. M. Spatz, *J. Org. Chem.*, **16**, 1485 (1951); A Murray, W. W. Foreman, and W. Langham, *J. Am. Chem. Soc.*, **70**, 1037 (1948); W. E. Parham and R. M. Piccirilli, *J. Org. Chem.*, **42**, 257 (1977).
6) H. Gilman and H. S. Broadbent, *J. Am. Chem. Soc.*, **70**, 2809 (1948); B. Prijs, A. H. Lutz, and H. Erlenmeyer, *Helv. Chim. Acta*, **31**, 571 (1948).
7) A. I. Meyers and R. A. Gabel, *Tetrahedron Lett.*, **1978**, 227; *idem, Heterocycles*, **11**, 133 (1978); G. W. Gribble and M. G. Saulnier, *Tetrahedron Lett.*, **21**, 4137 (1980); A. R. Katritzky, S. R. Rastgoo, and N. K. Ponkshe, *Synthesis*, **1981**, 127; T. Güngör, F. Marsais, and G. Quéguiner, *ibid.*, **1982**, 499; F. Marsais, G. Le Nard, and G. Quéguiner, *ibid.*, **1982**, 235; E. J. Corey and S. G. Pyne, *Tetrahedron Lett.*, **24**, 3291 (1983); J. A. Turner, *J. Org. Chem.*, **48**, 3401 (1983).
8) J. D. Cook and B. Wakefield, *J. Chem. Soc. (C)*, **1969**, 1973.
9) M. Ferless and A. Silhanova, *Collect. Czech. Chem. Commun.*, **44**, 3137 (1979); G. W. Gribble and M. G. Saulnier, *Tetrahedron Lett.*, **21**, 4137 (1980); J. Epsztajn, Z. Berski, J. Z. Brezezinski, and A. Jozwiak, *ibid.*, **21**, 4739 (1980); M. Watanabe and V. Snieckus, *J. Am. Chem. Soc.*, **102**, 1457 (1980); Y. Tamura, M. Fujita, L.-C. Chen, M. Inoue, and Y. Kita, *J. Org. Chem.*, **46**, 3564 (1981).
10) R. A. Finnegan and J. W. Altchuld, *J. Organomet. Chem.*, **9**, 193 (1967).