of some of the phenyl resonances may be ambiguous). For **28** (Z = 3',4'-CH_2CH_2O): δ 203.5 (s, C^+), 182.6 (s, C4'), 152.7, 147.2 (d, C6'), 142.5, 137.4 (d, C2'), 140.7 (s, PhC_i), 137.9 (d, PhC_p), 136.9 (s, C1'), 135.5, 135.3 (s, C3'), 135.1 (d, PhC_o), 134.7 (d, PhC_o), 130.3 (d, PhC_m), 116.5, 115.2 (d, C5'), 79.7 (t, CH_2O), 27.2 (t, CH_2-C), 27.2 (q, CH_3). For **29** (Z = 3',4'-CH_2CH_2O): δ 183.9 (s, C4'), 179.5 (d, $C1^+$), 156.7, 149.2 (d, C6'), 141.1, 139.1 (d, C2'), 138.3 (s, C1'), 135.4 (s, C3'), 118.4, 116.8 (d, C5'), 80.9 (t, CH_2O), 27.3 (t, CH_2), 139.9, 137.7, 134.2, 131.6 (Ph). For **29** (Z = 3'-CF_3): δ 201.9 (d, $C1^+$), 146.3 (m, C4'), 144.7 (d, C6'), 139.9 (m, C2'), 138.8 (s, C1'), 135.0 (q, J = 36 Hz, C3'), 133.9 (d, C5'), 123.6 (q, J = 273 Hz, CF_3), 154.8, 151.8, 143.4, 134.6, 133.9, 137.1 (s, Ph). For **29** (Z = 3',5'-$(CF_3)_2$): δ 201.2 (d, $C1^+$), 141.3 (d, C2',6'), 139.8 (s, C1'), 135.6 (q, J = 35 Hz, C3',5'), 123.1 (q, J = 274 Hz, CF_3), (C4' not observed), 158.8, 154.5, 146.3, 135.5, 134.9, 137.0 (s, Ph).

Preparation of Alcohol Precursors. The alcohol precursors were prepared by standard Grignard reactions of the corresponding ketone with the appropriate bromo- or iodobenzene. The 3',4'-(ethylenoxy)phenyl (3',4'-CH_2CH_2O) derivatives were prepared by the method of Brown and Gundu Rao from the corresponding ketone and 5-lithio-2,3-dihydrobenzofuran.[58] The physical constant data for these precursors are summarized in Table VI. All new compounds gave satisfactory analytical data (±≤0.3%). The ^{13}C NMR spectral data for all of the precursors were in accordance with the assigned structures. All of the parent ketones used for the Grignard reactions are commercially available except for nortricyclanone and *endo*-5,6-trimethylene-2-norbornanone. These ketones were prepared by following the procedures developed in our laboratories.[21a,63]

(58) Brown, H. C.; Gundu Rao, C. *J. Org. Chem.* **1979**, *44*, 133-136.
(59) Takeuchi, K.; Kurosaki, T.; Okamoto, K. *Tetrahedron* **1980**, *36*, 1557-1563.
(60) Brown, H. C.; Gundu Rao, G.; Vander Jagt, D. L. *J. Am. Chem. Soc.* **1979**, *101*, 1780-1783.
(61) Brown, H. C.; Vander Jagt, D. L. *J. Am. Chem. Soc.* **1969**, *91*, 6850-6852.
(62) Stelt, C van der; Funcke, A. B. H.; Nauta, W. T. *Arzneim.-Forsch.* **1964**, *14*, 964.
(63) Brown, H. C.; Rothberg, I.; Vander Jagt, D. L. *J. Org. Chem.* **1972**, *37*, 4098-4100.

Regioselective Metalation Reactions of Some Substituted (Methoxymethoxy)arenes

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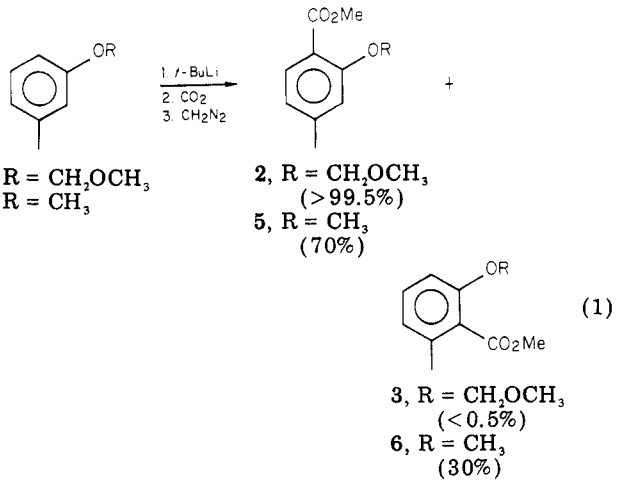
The methoxymethoxy substituent acts as a relatively strong ortho-directing group in hydrogen-metal exchange reactions. However, the directing effects are influenced by the metalation medium, thus permitting an unusual degree of control of the site of metalation. In conjunction with weak ortho-directing groups, the metalation ortho to the methoxymethoxy group can be directed to either of the ortho positions by controlling the electron-donating capacity of the metalating solvent. In strongly donating solvents the 1,2,4-substitution pattern will arise from a meta-substituted methoxymethoxy arene, while in nondonating solvents the 1,2,3-substitution is favored. In addition, the methoxymethoxy group serves also to enhance the rate of metalation and to stabilize the aryl-metalated products so that some competing addition reactions are suppressed.

The wide variety of transformations possible via organolithium intermediates make them crucially important in synthetic chemistry.[1] In the elaboration of aromatic systems they are becoming increasingly more prevalent due to the development of substituents capable of directing the introduction of the metal in a predictable manner.[2-8] For example, treatment of an arene bearing an ortho-directing group with an alkyllithium reagent results in metalation regioselectively in the ortho positions. A number of ortho-directing groups have been investigated, their directing capability frequently being compared to the methoxy group which is considered to be of intermediate ortho-directing capacity.[9] Strong directing groups are SO_2NR_2,[9] SONHR,[9] $CONR_2$,[10] CONHR,[9] CH_2NR_2,[9] OCH_2OCH_3,[11] NHCOR,[12] $NHCO_2R$,[13] CSNHR,[14] and oxazolines.[15,16] Weaker ortho-directing groups include NR_2, CF_3, F,[9] SR,[17] and some other groups which have shown ortho-directing capabilities such as CH_2OH,[18] $CH(OR)_2$,[19] and imidazolidines.[20]

(1) Wakefield, B. J. "The Chemistry of Organolithium Compounds"; Pergamon Press: New York, 1974. Gschwend, H. W.; Rodriguez, H. R. *Org. React.* **1979**, *26*, 1-360. Slocum, D. W.; Jennings, C. A. *J. Org. Chem.* **1976**, *41*, 3653. Abicht, H.-P.; Issleib, K. *Z. Chem.* **1977**, *17*, 1. Marburg, S.; Tolman, R. L. *J. Heterocycl. Chem.* **1980**, *17*, 1333. Semmelhack, M. F.; Bisaha, J.; Czarny, M. *J. Am. Chem. Soc.* **1979**, *101*, 768. Snieckus, V. *Heterocycles* **1980**, *14*, 1649.
(2) Ronald, R. C. *Tetrahedron Lett.* **1976**, *4413*-4416.
(3) Baldwin, J. E.; Blair, K. W. *Tetrahedron Lett.* **1978**, 2559-2562. Forbes, I.; Pratt, R. A.; Raphael, R. A. *Ibid.* **1978**, 3965.
(4) Narzsimhan, N. S.; Mali, R. S.; Barve, M. V. *Synthesis* **1979**, 906-909.
(5) Trost, B. M.; Rivers, G. T.; Gold, J. M. *J. Org. Chem.* **1980**, *45*, 1835-1838.
(6) Kraus, G. A.; Pezzonite, J. O. *J. Org. Chem.* **1979**, *44*, 2480-2482.
(7) Buchi, G.; Chu, P. S. *J. Org. Chem.* **1978**, *43*, 3717-3719.
(8) Harris, T. D.; Neuschwander, B.; Boekelheide, V. *J. Org. Chem.* **1978**, *43*, 727-730.
(9) Slocum, D. W.; Jennings, C. A. *J. Org. Chem.* **1976**, *41*, 3653-3664.
(10) Beak, P.; Brown, R. A. *J. Org. Chem.* **1977**, *42*, 1823-1824. de Silva, S. O.; Reed, J. N.; Snieckus, V. *Tetrahedron Lett.* **1978**, 5099-5102. de Silva, S. O.; Snieckus, V. *Ibid.* **1978**, 5103-5106. de Silva, S. O.; Ahmad, I.; Snieckus, V. *Ibid.* 5107-5110.
(11) Christensen, H. *Synth. Commun.* **1975**, *5*, 65-78. Townsend, C. A.; Bloom, L. M. *Tetrahedron Lett.* **1981**, 3923.
(12) Fuhrer, W.; Gschwend, H. W. *J. Org. Chem.* **1979**, *44*, 1133-1136.
(13) Muchowski, J. M.; Venuti, M. C. *J. Org. Chem.* **1980**, *45*, 4798-4801.
(14) Fritt, J. J.; Gschwend, H. W. *J. Org. Chem.* **1976**, *41*, 4029-4031.
(15) Meyers, A. I.; Mihelich, E. D. *J. Org. Chem.* **1975**, *40*, 3158-3159.
(16) Meyers, A. I.; Lztomski, K. *J. Org. Chem.* **1979**, *44*, 4464-4466.
(17) Cabiddu, S.; Melis, S.; Piras, P. P.; Sotgiu, F. *J. Organomet. Chem.* **1979**, *182*, 155-163.
(18) Meyer, N.; Seebach, D. *Chem. Ber.* **1980**, *113*, 1304-1319; *Angew. Chem. Int. Ed. Engl.* **1978**, *17*, 521.
(19) Plaumann, H. P.; Key, B. A.; Rodrigo, R. *Tetrahedron Lett.* **1979**, 4921-4924.

0022-3263/82/1947-2101$01.25/0

All of the aforementioned directing groups can be very selective for metalation at the ortho positions. However, with many of these groups, problems are encountered in the lack of discrimination between nonequivalent ortho positions[9,21] or between the ring positions and other acidic sites within the substrate.[12,14,20,22-24] In some cases the directing group or even the aromatic nucleus may be subject to nucleophilic attack by the metalation reagent.[1,9,10,12,19] When the methoxymethoxy substituent is employed as a directing group, substantial selectivity toward metalation can be obtained. This directing group increases the discrimination between ortho positions, and in many cases favors metalation over addition reactions to sensitive groups. For example, in a preliminary report it was shown that litiation of 3-methyl-1-(methoxymethoxy)benzene (1) occurred rapidly in excellent yield and afforded >99.5% of the less hindered ortho isomer 2 upon carbonation[2] (eq 1). In addition, this group effected



1, R = CH_2OCH_3
4, R = CH_3

2, R = CH_2OCH_3 (>99.5%)
5, R = CH_3 (70%)

3, R = CH_2OCH_3 (<0.5%)
6, R = CH_3 (30%)

(1)

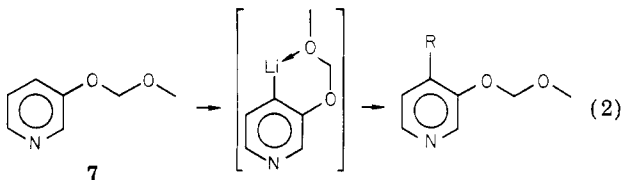
substantial activation of the aromatic ring toward metalation over that usually observed for a methoxy group.[25]

Phenols are readily converted to methoxymethyl ethers by treatment of the phenoxides with chloromethyl ether[26] or by acid-catalyzed exchange ketalization with methylal (dimethoxymethane) with 4-Å molecular sieves to remove methanol from the dichloromethane azeotrope.[27] When the methoxymethyl group is no longer needed, it can easily be removed by mild acid-catalyzed hydrolysis or methanolysis. Thus, these derivatives are ideal for reactions involving metalations of phenolic compounds and constitute an attractive alternative to electrophilic substitution[28] especially if ortho substitution is desired.

This report discusses features of the methoxymethoxy group that make it unique among ortho-directing groups and summarizes some of our investigations on their utility for arene metalations.[29] The methoxymethoxy group is of modest strength when compared to some of the strong ortho-directors, but it is strong enough to exert a substantial directing influence, so that systems usually susceptible to nucleophilic attack may be successfully metalated. More importantly, however, this group permits a remarkable degree of control of the regioselectivity of metalation between nonequivalent ortho centers, and in some cases allows selection of either of two possible ortho substitutions.

Results and Discussion

Nucleophilic addition of the alkyllithium metalating species to the aromatic nucleus is a competing reaction in the metalation of certain arenes. This is especially true in the case of pyridines which cannot usually be metalated directly. The lithio derivatives of pyridines usually are prepared by halogen–metal exchange.[1,30] With a methoxymethoxy substituent, however, the deprotonation reaction is greatly enhanced and good yields of ring-metalated products can be obtained. Treatment of 3-(methoxymethoxy)pyridine 7 with *tert*-butyllithium in ether at −78 °C for 15 min afforded a bone-white powder. Quenching with D_2O afforded an 88% yield of deuterated product 8 (eq 2) in which >95% of the deuterium was



7

8, R = D
9, R = I

(2)

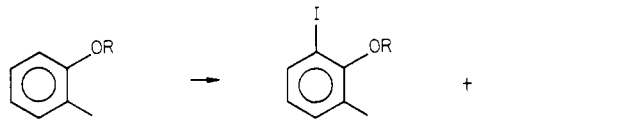
incorporated in the C-4 position. The C-4 and C-5 protons of 7 overlap in a complex multiplet between δ 7.6 and 7.0. After metalation and deuteration this multiplet collapsed to a doublet at δ 7.2 that integrated for a single proton. The integration of the C-2 and C-6 protons relative to the methoxymethyl resonances remained constant; however, the meta coupling of the C-2 proton with the C-4 protons was removed by the deuteration. These results indicate that metalation had occurred almost exclusively at C-4.

Quenching lithiated 7 with ethylene iodochloride[31] produced a 90% yield of 4-iodo-3-(methoxymethoxy)-pyridine (9) after chromatography on silica gel. In addition, two other fractions were obtained in 3% and 4% yields. These were the products from C-2 metalation and nucleophilic attack of the ring, respectively. The most comparable metalation of a pyridine is the 4-oxazolinyl group of Meyers.[32] Treatment of 4-oxazolinylpyridine with methyllithium afforded good yields of metalated product; however, the use of the more reactive butyllithiums resulted in nucleophilic attack on the pyridine ring. Other reports of the direct metalation of pyridines are for polychlorinated systems[33] or systems with more than one orthodirecting or carbanion stabilizing groups.[34]

(20) Harris, T. D.; Roth, G. P. *J. Organomet. Chem.* **1979**, *44*, 2004–2007.
(21) Shirley, D. A.; Harmon, T. E.; Cheng, C. F. *J. Organomet. Chem.* **1974**, *69*, 327–344.
(22) Harmon, T. E.; Shirley, D. A. *J. Org. Chem.* **1974**, *39*, 3164–3165.
(23) Viswanathan, G. T.; Wilke, C. A. *J. Organomet. Chem.* **1973**, *54*, 1–7.
(24) Ludt, R. E.; Crowther, G. P.; Hauser, C. R. *J. Org. Chem.* **1970**, *35*, 1288–1296.
(25) Ronald. R. C. *Tetrahedron Lett.* **1975**, 3973–3974.
(26) Fieser, L. F.; Fieser, M. "Reagents for Organic Synthesis"; Wiley: New York, 1967; Vol. 1, pp 132–135.
(27) Yardley, J. P.; Fletcher, H., 3rd. *Synthesis* **1976**, 233–244.
(28) For comprehensive reviews of electrophilic substitution reactions see: Olah, G. A., Ed. "Freidel–Crafts and Related Reactions"; Wiley-Interscience: New York, 1963–1965; Vol. 1–4. Stock, L. "Aromatic Substitution Reactions"; Prentice-Hall: Englewood Cliffs, NJ, 1968.
(29) Winkle, M. R.; Ronald, R. C. Northwest Regional Meeting of the American Chemical Society, June 14, 1979; American Chemical Society: Washington, DC, 1979; Abstract 138.
(30) Gilman, H.; Spatz, S. M. *J. Org. Chem.* **1951**, *16*, 1485. Wibaut, J. P.; de Jonge, A. P.; van der Voort, H.; Otto, P. *Recl. Trav. Chim. Pays-Bas* **1951**, *70*, 1054. Murray, A., III; Foreman, W. W.; Langham, W. *J. Am. Chem. Soc.* **1948**, *70*, 1037. Parham, W. E.; Piccirilli, R. M. *J. Org. Chem.* **1977**, *42*, 257.
(31) Ronald, R. C.; Lansinger, J. M. *J. Chem. Soc., Chem. Commun.* **1979**, 124–125.
(32) Meyers, A. I.; Gabel, R. A. *Tetrahedron Lett.* **1978**, 227–230; *Heterocycles* **1978**, *11*, 133.
(33) Cook, J. D.; Wakefield, B. *J. Chem. Soc. C* **1969**, 1973–1978.

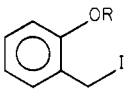
Recently, Katritzky has reported the litiation of 2-(aminocarbonyl)pyridines.[35]

Metalation of arenes that have benzylic protons flanked by ortho-directing groups is complicated by competing ring and benzylic deprotonations.[12,14,20,22-24] Selectivity for the ring positions is rare. For example, 2-methylanisole **10a** affords 42% ring metalation and 58% benzylic metalation with *tert*-butyllithium in cyclohexane. In contrast, the methoxymethoxy substituent affords excellent selectivity for the ring position. Treatment of 2-(methoxymethoxy)toluene (**10**) with *tert*-butyllithium in hexane results in the rapid formation of an off-white precipitate, which after iodination in THF with ethylene iodochloride afforded 3-iodo-2-(methoxymethoxy)toluene (**11**) in 87% yield (eq 3). None of the benzylic iodide **11a** or products



10, R = CH_2OCH_3
10a, R = Me

11, R = CH_2OCH_3 (>99%), R = Me (42%)



11a, R = CH_2OCH_3 (nil), R = Me (58%)

(3)

from it were detected by either GLC or TLC, indicating that the methoxymethoxy directing group is highly selective for ring metalation over benzylic metalation.

The most dramatic effects of the methoxymethoxy directing group are observed in cases where the selection of either of two ortho positions may be controlled by the metalating conditions. Few examples of this kind of regioselective control for aromatic metalation are known. The best examples are perhaps the metalation of 1-methoxynaphthalene, which occurred primarily at C-2 with *n*-butyllithium/TMEDA in cyclohexane and at C-8 with *tert*-butyllithium/cyclohexane–pentane,[36] and the metalation of 4-methoxy-(dimethylamino)benzene, which with *n*-butyllithium resulted in exclusive reaction ortho to the amino function but with *n*-butyllithium/TMEDA selected the positions ortho to the methoxy group.[9] However, (methoxymethoxy)benzenes that also have a weak ortho-directing group with a meta orientation can be selectively metalated at either of the two nonequivalent orthopositions by changing the metalating conditions (metalating agent and solvent system). By far, changes in the solvent system have the most profound effect upon the site of metalation. In general, hindered metalating agents and strongly electron-donating solvents tend to favor the ortho site farthest away from the weak ortho-directing group, while nondonating solvents and nonhindered metalating agents favor the ortho-position between the two directing substituents. These observations are contrary to some of the generalizations of some other workers that solvent compositions usually have little effect upon the orientation of metalation[1] and that ortho-directing groups meta to one another usually function in concert to direct introduction of the metal between them.[37]

When *N,N*-dimethyl-3-(methoxymethoxy)aniline (**12**) was treated with *tert*-butyllithium in ether, the metalated derivative formed rapidly as an off-white precipitate. Quenching a THF solution with ethylene iodochloride resulted in a 79% yield of iodides **13** and **14** which were shown by GLC to be in a ratio of 99:1, respectively. Quite unexpectedly the major product in this case resulted from reaction at what would appear to be the least activated of the methoxymethoxy ortho centers. That this unexpected ratio does not arise entirely from steric effects was demonstrated when the reaction was repeated by using *n*-butyllithium in ether. Although the selectivity obtained was not quite so favorable (82:18), the direction of the selectivity for the 1,2,4-isomer was maintained. These results contrast remarkably with the metalations run in hexane only. The reaction in this solvent to form the metalated product was much slower; however, upon treatment with ethylene iodochloride the GLC showed that the ratio had been completely reversed and that 98% of the product was isomer **14** and only 2% was the product **13**. Note that the metalation of *m*-anisidine affords only products corresponding to **14**.

The regioselection is also possible with other substituents meta to the methoxymethoxy group. The hydroxymethyl group and the dialkoxymethyl group behave similarly. With *n*-butyllithium in benzene, 3-(methoxymethoxy)benzyl alcohol (**15**) is metalated exclusively in the position between the substituents. Regioselectivity for this position has been observed previously with the analogous 3-methoxybenzyl alcohol.[5,38] However, in the case of **15** the metalation is considerably more rapid and produces much higher selectivity. When a powerful electron-donor solvent mixture was employed, metalation occurred primarily at the other position ortho to the methoxymethoxy directing group. By use of *tert*-butyllithium in ether–TMEDA the ratio of **16** to **17** was shifted to 85:15.

The carboxaldehyde function masked as an acetal also permits regiocontrol of metalation. The dioxane (1,3-propanediol acetal) was superior to the dioxolane (ethylene glycol acetal) because the dioxolane tends to undergo a fragmentation reaction under the metalation conditions that affords the carboxylate anion and ethylene. Acyclic acetals are also satisfactory. Reaction of 2-[3-(methoxymethoxy)phenyl]-1,3-dioxane (**18**) with *tert*-butyllithium in cyclohexane afforded after iodination the isomeric iodides **19** and **20** in a 78% yield. The results of these metalation reactions are summarized in Table I.

With more powerful ortho-directing groups the possibilities for regioselection are limited. Metalation of 3-(methoxymethoxy)anisole with *tert*-butyllithium in hexane affords a 3:97 ratio of **22** and **23** in 78% yield. In ether the ratio changes to 41:59, but it does not seem feasible to obtain **22** as the major product. Oddly, addition of TMEDA caused the ratio to become less favorable for **22**. Although, temperature does not seem to have an effect on most of the metalations, due to the instability of TMEDA in the presence of *tert*-butyllithium, metalations could not be run at higher temperatures, and if in this case higher temperatures would have been beneficial, they were unavailable.

(34) Ferles, M.; Silhanova, A. *Collect. Czech. Chem. Commun.* **1979**, *44*, 3137. Gribble, G.; Saulnier, M. *Tetrahedron Lett.* **1980**, 4137. Epsatajn, J.; Berski, Z.; Brzezinski, J.; Jozwiak, A. *Ibid.* **1980**, 4739. Wantanabe, M.; Snieckus, V. *J. Am. Chem. Soc.* **1980**, *102*, 1457–1461. Tamura, Y.; Fujita, M.; Chen, L.-C.; Inoue, M.; Kifa, Y. *J. Org. Chem.* **1981**, *46*, 3564–3567.

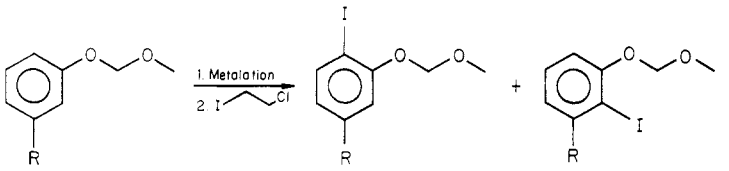
(35) Katritzky, A.; Rahimi-Rastgoo, S.; Ponkshe, N. *Synthesis* **1981**, 127.

(36) Shirley, D. A.; Cheng, C. F. *J. Organomet. Chem.* **1969**, 251–252.

(37) Slocum, D. W.; Sugarman, D. I.; "Polyamine-Chelated Alkali Metal Compounds"; Langer, A. W., Ed.; American Chemical Society: Washington, DC, 1974, p 232.

(38) Uemura, M.; Tokuyema, S.; Sakan, T. *Chem. Lett.* **1975**, 1195–1198.

Table I



I

I	R	conditions	% yield	% 1,2,4-isomer (compd no.)	% 1,2,3-isomer (compd no.)
1	Me	*t*-BuLi, pentane, 0 °C	95	99.5 (2)	0.5 (3)
12	NMe_2	*t*-BuLi, Et_2O, 0 °C	78	99 (13)	1 (14)
		n-BuLi, Et_2O, 0 °C	44	82 (13)	18 (14)
		n-BuLi, hexane, room temp	44	2 (13)	98 (14)
		t-BuLi, hexane, room temp		57 (13)	43 (14)
15	CH_2OH	*n*-BuLi, benzene, room temp	78	nil (16)	100 (17)
		n-BuLi, Et_2O, 0 °C	79	19 (16)	81 (17)
		t-BuLi, benzene, room temp	80	40 (16)	60 (17)
		t-BuLi, Et_2O, 0 °C	72	59 (16)	41 (17)
		n-BuLi, TMEDA, Et_2O, 0 °C	67	70 (16)	30 (17)
		t-BuLi, TMEDA, Et_2O, −78 °C	68	85 (16)	15 (17)
18		*n*-BuLi, C_6H_{12}, 0 °C	71	0.5 (19)	95 (20)
		t-BuLi, C_6H_{12}, 0°C	78	8 (19)	92 (20)
		t-BuLi, Et_2O, 0 °C	85	50 (19)	50 (20)
		n-BuLi, TMEDA, Et_2O, −78 °C	10	50 (19)	50 (20)
		t-BuLi, TMEDA, Et_2O, −78 °C	76	90 (19)	10 (20)
		t-BuLi, THF, −78 °C	10	90 (19)	10 (20)
21	OCH_3	*t*-BuLi, hexane, 0 °C	78	3 (22)	97 (23)
		t-BuLi, Et_2O, 0 °C	95	41 (22)	59 (23)
		t-BuLi, TMEDA, Et_2O, −78 °C	93	5 (22)	95 (23)
24	$CONMe_2$	*t*-BuLi, Et_2O-hexane, −78 °C	35	nil (25)	100 (26)
27	COOMe	*t*-BuLi, Et_2O, −78 °C	no metalation		
28	COOH	*t*-BuLi, THF, −78 °C	20		100 (29)
30	C≡N	*t*-BuLi, Et_2O, −78 °C	no metalation		

Although the methoxymethoxy group exerts a strong activating effect toward metalation, it is not sufficient to completely suppress the addition of the metalating agent to carbonyl groups. The methoxymethoxy arenes **24**, **27**, **28**, and **30** bearing the $CONMe_2$, COOMe, COOH(Li), and CN groups, respectively, were investigated. Only the $CONMe_2$ and carboxylate groups were somewhat resistant to addition. The dimethylamide **24** and the carboxylate **30** gave small amounts of metalated products which were the expected 1,2,3-substituted isomers. Other metalated isomers, if formed, constituted much less than 0.5% of the metalated product. The ester **27** and the nitrile **30** gave only addition products. While other investigators have avoided the problem of addition to amides by using the more hindered diethylamides or secondary amides that can be deprotonated,[10,39] it is interesting that with the methoxymethoxy group metalation of the dimethylamide occurs to a significant albeit not synthetically useful extent.

The selectivities observed can be rationalized on the basis of solvation effects in which the two substituents interact with the metalating species in noncoordinating solvents to direct the metalation to the site that permits the higher degree of internal solvation. In coordinating solvents only the more powerful methoxymethoxy substituent is involved as a ligand to the metalating species, and the weaker directing group is relegated to acting mainly as a bulky substituent. The presence of two strong directing groups makes the solvent contribution to selectivity of lesser importance. Selection of isomers on a kinetic or thermodynamic basis involving differential solubilities is probably not operable in the present system since both metalated isomers are frequently insoluble, and no isomeration from one isomer to the other was observable even unser conditions where the metalated products are soluble. The absence of isomerization of ring positions is not unusual in aryllithium chemistry.[1,40] Isomerization does occur with some imine-directing groups.[41]

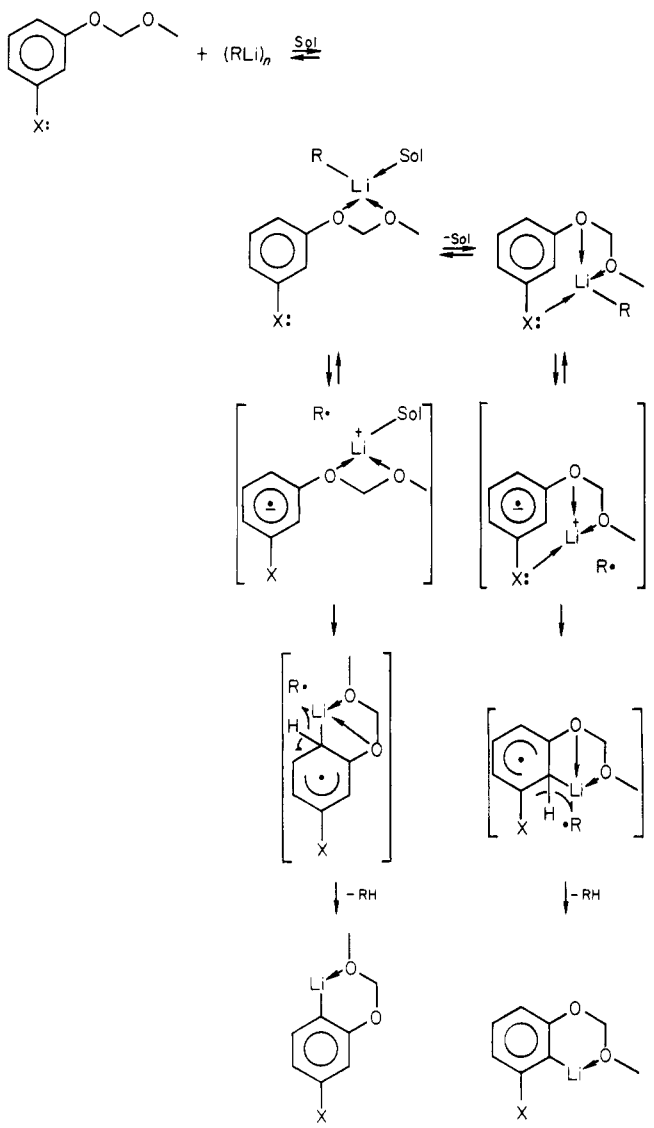
For achievement of the selectivities obtained in the methoxymethoxy systems, the formation of an intermediate complex prior to proton abstraction must occur. This could perhaps be explained on the basis of a protophilic mechanism.[42] However, the insensitivity of these and other systems[21] to steric hinderance, particularly in the metalating base, is inconsistent with the simple approach of the reagent resulting in proton removal. Even 3-*tert*-butylanisole affords 9% of the C-2-metalated product with *tert*-butyllithium.[21] Our results can perhaps best be accommodated by a modification of radical anionic pathway proposed by Shirley and Hendrix[21,43,44] (Scheme I) in which the metalating reagent is first coordinated to the methoxymethoxy group followed by electron transfer and then collapse of the caged radical–radical anion pair with concomitant hydrogen abstraction. In the absence of good solvent ligands coordination by the meta substituent would direct the metalation to the site between the two substituents. With good coordinating solvents the weak meta substituent ligand is not strongly involved in coordination, and metalation occurs at the least hindered site unless a strong directing influence from the meta substituent intervenes.

Although this mechanistic proposal accommodates the unusual regioselection observed, we have not been able to

(39) Kende, A. S.; Rizzi, J. P. *J. Am. Chem. Soc.* **1981**, *103*, 4247–4248.

(40) Graybill, B. M.; Shirley, D. A. *J. Org. Chem.* **1966**, *31*, 1221–1225.
(41) Ziegler, F. E.; Fowler, K. W. *J. Org. Chem.* **1976**, *41*, 1564.
(42) Finnegan, R. A.; Alfshull, J. W. *J. Organomet. Chem.* **1967**, *9*, 193–204.
(43) Shirley, D. A.; Hendrix, J. P. *J. Organomet. Chem.* **1968**, *11*, 217–226.
(44) Hendrix, J. P. Ph.D. Dissertation, University of Tennessee, Knoxville, TN, 1965.

Scheme I



observe any radical intermediates directly in the methoxymethoxy system. Shirley and Hendrix have observed ESR signals in the metalation of naphthalene with butyllithium–TMEDA; however, the increased stability of the naphthalenide radical anions may account for these observations in this system and in other polynuclear aromatics.[43] Radical intermediates in the metalation of anisole with lithium in THF or lithium naphthalenide have also been proposed.[45]

The methoxymethoxy substituent displays several features that should make it attractive for use in the synthesis of polysubstituted aromatic compounds. In addition to its versatility as an ortho-directing group for aromatic substitution, it is a convenient and stable phenolic protecting group that is easily introduced and readily removed under mild conditions. Rates of metalation with this group can be greatly enhanced over that of ordinary ethers, and most importantly, it affords a unique type of regiochemical control for substitution of the aromatic ring.

Experimental Section

General Methods. Melting point determinations were made by using a Thomas-Hoover Unimelt apparatus and are uncorrected. Infrared spectra were obtained on a Beckman Model IR 18A or on a Acculab 1 spectrophotometer. Spectra of liquid samples were obtained as films and solids as KBr pellets. Nuclear magnetic resonance spectra were obtained on a Varian Associates Model EM-360 spectrophotometer with tetramethylsilane as an internal standard. Gas chromatograms were obtained on a Packard-Becker Model 417 or a Varian Aerograph Series 1700 gas chromatograph with 3 mm × 2.6 m glass columns packed with 3% OV-17 on 80/100 Chromosorb W HP. Analytical thin-layer chromatograms were run on Merck precoated silica plates with 250-μm layers. Preparative thin-layer chromatograms were run on 20 × 20 cm plates coated with a 1.6-mm layer of Merck silica gel PF 254 on Merck aluminum oxide GF 254 (Type 60/E). Combustion analyses were performed by Galbraith Laboratories.

The solvents were either purchased in small quantities of high purity or were dried and distilled before use. The alkyllithiums were obtained from either Aldrich Chemical Co. or Ventron Corp. The concentrations were determined by the titration method developed in this laboratory.[46]

Preparation of (Methoxymethoxy)arenes. Method A. A 500-mL, three-necked, round-bottomed flask containing a magnetic stir bar was fitted with a reflux condenser and addition funnel. It was flushed with N_2, and 2.6 g of NaH (4.5 g of a 57% mineral oil dispersion, 0.11 mmol) was placed in the flask and washed free of mineral oil with five small portions of petroleum ether. Dry Et_2O (250 mL) and DMF (50 mL) were added. The phenol was dissolved in 50 mL of dry ether and added slowly (over 15 min) to the stirred mixture. The reaction was stirred for an additional 15 min. The chloromethyl methyl ether (9 mL, 0.12 mol) was dissolved in 25 mL of ether and added slowly. The reaction was followed with TLC and was complete within 10–20 min after the addition of chloromethyl methyl ether. The reaction mixture was added to 150 mL of water. The aqueous layer was separated and extracted three times with ether. These ether extractions were added to the organic layer and were washed three times with 10% NaOH, water, and saturated sodium chloride. This was dried with $MgSO_4$ and concentrated under vacuum. The crude product was purified by distillation under vacuum.

Method B. The method of Yardley and Fletcher[27] was employed. The phenol (0.04 mol), dimethoxymethane (16 mL, 0.18 mol), dichloromethane (90 mL), and *p*-toluenesulfonic acid monohydrate (40 mg) was placed in a 250-mL round-bottomed flask. This was fitted with a Soxhlet extractor containing 40 g of 4-Å molecular sieves. A $CaCl_2$ drying tube was attached to the condenser. The reaction was refluxed for 24 h, cooled to room temperature, and treated with 0.5 mL of triethylamine. The reaction was washed twice with 10% NaOH, water, and saturated sodium chloride. The organic phase was dried with $MgSO_4$ and concentrated under vacuum. The crude product was then distilled under vacuum.

Metalation of (Methoxymethoxy)arenes. General Procedure. The (methoxymethoxy)arene was weighed into a small flask (10–25 mL). Internal standards for GC analysis, if used, were added at this time. The flask was sealed with a septum and flushed with N_2. The appropriate solvent was added with a syringe, and the mixture stirred magnetically and cooled to the temperature indicated. The metalating agent was added with a syringe. Usually the metalated product formed as a precipitate. After the specified length of time the reaction was quenched with either D_2O or ethylene iodochloride in THF. In the latter case the THF was used for solubility purposes to ensure rapid reaction.

The reaction mixture was then poured into water and extracted with ether (3×). The combined ethereal extracts were washed twice with water and once with brine, dried with anhydrous $MgSO_4$, and concentrated at reduced pressure to afford the crude reaction product.

3-(Methoxymethoxy)pyridine (7) was prepared by method A by starting with 3-hydroxypyridine (4.7 g, 0.05 mol). The crude product was distilled under vacuum to yield 7: 2.4 g (32%); bp 85–87 °C (15 mm); NMR (CCl_4) δ 3.51 (s, 3 H), 5.23 (s, 2 H), 7.0–7.6 (m, 4 H); IR 3040, 2910, 1570, 1480, 1425, 1230, 1200, 1155, 1085, 1045, 985, 805, 710 cm^{-1} (the last two bands are typical of 3-substituted pyridines).

***N,N*-Dimethyl-3-(methoxymethoxy)aniline** (12) was prepared by method A from 3-(dimethylamino)phenol (6.8 g, 0.05

(45) Screttas, C. G. *J. Chem. Soc., Chem. Commun.* **1972**, 869–870.

(46) Winkle, M. R.; Lansinger, J. M.; Ronald, R. C. *J. Chem. Soc., Chem. Commun.* **1980**, 87–88.

mol). The dark oil which resulted was distilled under vacuum to yield 4.62 g (51%) of pure **12** as a clear liquid: bp 144–145 °C (15 mm); NMR (CCl_4) δ 2.94 (s, 6 H), 3.46 (s, 3 H), 5.13 (s, 2 H), 6.2–7.3 (m, 4 H); IR 3095, 2980, 2900, 1610, 1510, 1360, 1235, 1150, 1080, 1020, 920, 825, 755, 685 cm^{-1}. Analysis was not possible due to the rapid decomposition at room temperature.

***N,N*-Dimethyl-3-(methoxymethoxy)benzamide (24).** Treatment of 3-hydroxybenzoic acid with DMF and P_2O_5 as previously reported[47] produced *N,N*-dimethyl-3-hydroxybenzamide as a white crystalline solid: mp 127–128 °C (lit.[47] mp 128–130 °C). An 8.3-g sample of the hydroxyamide (0.05 mmol) was converted to the methoxymethyl derivative by method B. However, the conversion to the ether was not high, since after 96 h at reflux 5.3 g of starting material was extracted from the reaction mixture with 10% NaOH. The residue was chromatographed on silica gel and eluted with 85% ethyl acetate–hexane. The fractions containing the amide were yellow. Treatment with activated charcoal (Nuchar C-190) for 12 h yielded a clear colorless oil: 2.2 g (58%); NMR (CCl_4) δ 3.0 (s, 6 H), 3.4 (s, 3 H), 5.22 (s, 2 H), 6.9–7.5 (m, 4 H); IR (neat) 3070, 2930, 1625, 1575, 1480, 1265, 1150, 1180, 1010, 795, 750, 690 cm^{-1}.

3-(Methoxymethoxy)benzonitrile (30). The aldehyde group of 3-hydroxybenzaldehyde was converted to a nitrile by the procedure of van Es.[48] 3-Hydroxybenzaldehyde (6.1 g, 0.05 mol) was added to a solution of hydroxyamine hydrochloride (4.1 g, 0.058 mol) and sodium formate (6.3 g) in formic acid (75 mL). The mixture was heated to reflux for 2 h, water was added, and then the mixture was extracted three times with ethyl acetate. The combined extracts were concentrated at reduced pressure to remove the formic acid. The residue was dissolved in ether (50 mL), washed with water and brine, dried with anhydrous magnesium sulfate, and concentrated to afford a white solid that was recrystallized from hexene and CCl_4: 4.5 g (76%); mp 78–80 °C (lit.[49] mp 78–81 °C).

The 3-hydroxybenzonitrile (4.5 g, 0.038 mol) was converted to the methoxymethyl ether by using method A to afford 5.9 g (97%) of **30** as a colorless liquid: bp 120 °C (3 mm, Kugelrohr); NMR (CCl_4) δ 3.53 (s, 3 H), 5.28 (s, 2 H), 7.2–7.7 (m, 44); IR (neat) 3080, 2960, 2240, (C≡N), 1570, 1475, 1425, 1320, 1245, 1145, 1070, 1005, 920, 785, 690 cm^{-1}.

Methyl 3-(Methoxymethoxy)benzoate (27). 3-Hydroxybenzoic acid (6.9 g, 0.05 mol) was converted to the methyl ester by stirring in methanol (150 mL) containing concentrated H_2SO_4 (3 mL) for 5 h. The reaction mixture was then poured into water (100 mL) and extracted with ether. The combined ethereal extracts were washed with H_2O, 10% aqueous $NaHCO_3$, and brine, dried with anhydrous magnesium sulfate, and concentrated to yield a white solid. This was recrystallized from benzene–ether to yield 7.5 g (98%) of methyl 3-hydroxybenzoate, mp 68–69 °C (lit.[50] mp 69 °C).

Methyl 3-hydroxybenzoate (6.1 g, 0.04 mol) was converted to the methoxymethyl ether by method B. The crude product (5.94 g), a slightly yellow oil, was distilled at 161.5–162.5 °C (24 mm) to afford 5.2 g (66%) of methyl 3-(methoxymethoxy)benzoate (**27**) as a clear colorless liquid: NMR (CCl_4) δ 3.45 (s, 3 H), 3.91 (s, 3 H), 5.26 (s, 2 H), 7.1–7.9 (m, 4 H); IR 3035, 2940, 1720, 1585, 1445, 1270, 1145, 1100, 1060, 1010, 750 cm^{-1}. Anal. Calcd for $C_{10}H_{12}O_4$: C, 61.22; H, 6.16. Found: C, 61.18; H, 5.93.

3-(Methoxymethoxy)benzoic Acid (28). Methyl 3-(methoxymethoxy)benzoate (**27**) (1.1 g, 5.7 mmol) was dissolved in methanol (5 mL) and aqueous 10% NaOH (3 mL). After 4 h the reaction mixture was washed with three portions of ether, acidified with 5% aqueous HCl to pH 3, and extracted four times with ether. The combined extracts from the acidified mixture were washed with brine, dried with anhydrous magnesium sulfate, and concentrated to afford 1.0 g (96%) of white crystalline product: mp 122–123 °C; NMR ($CDCl_3$) δ 3.62 (s, 3 H), 5.38 (s, 2 H), 7.3–8.1 (m, 4 H); IR (Nujol mull) 2930, 1675, 1585, 1455, 1375, 1310, 1230, 1155, 1075, 1010, 990, 915, 760, 680 cm^{-1}.

3-(Methoxymethoxy)benzyl Alcohol (15). Methyl 3-(methoxymethoxy)benzoate (**27**) (2.22 g, 0.011 mol) was dissolved in ether (50 mL) and treated with $LiAlH_4$ (0.22 g, 0.006 mol) in small portions. After the addition was complete, the reaction mixture was stirred for 15 min then quenched with a small amount of saturated aqueous Na_2SO_4. Anhydrous magnesium sulfate was added until all of the water was adsorbed, and a granular precipitate formed. The mixture was filtered and the filtrate concentrated to afford 1.83 g (96%) of **15** as a clear oil: bp 88–90 °C (0.06 mm); NMR (CCl_4) δ 3.50 (s, 3 H), 4.6 (s, 1 H), 5.27 (s, 2 H), 7.0–77 (m, 4 H); IR 3400 (OH) 2940, 2900, 1505, 1485, 1450, 1250, 1150, 1080, 1020, 920, 785, 735, 690 cm^{-1}. Anal. Calcd for $C_9H_{12}O_3$: C, 64.27; H, 7.19. Found: C, 64.02; H, 7.14.

2-[3-(Methoxymethoxy)phenyl]-1,3-dioxane (18). 3-Hydroxybenzaldehyde (6.1 g, 0.05 mol) was acetylated (Ac_2O/py) by a modification of the procedure of Morton and Morge[51] to afford 7.8 g (95%) of 3-acetoxybenzaldehyde as a yellow oil, bp 65–66 °C (0.06 mm) [lit.[51] bp 100 °C (1.0 mm)]. A 7.4-g (0.045 mol) sample of the acetate was refluxed with 1,3-propanediol (7 mL, 0.1 mol) in benzene (50 mL) containing toluene sulfonic acid (0.5 g). Water was removed with a Dean–Stark trap. After 2 h the evolution of water ceased, and the mixture was allowed to cool to ambient temperature. A solution of 10% aqueous NaOH was added and the mixture stirred vigorously for 2 h. The pH was adjusted to 8 with HCl and the mixture extracted with ether (4 × 50 mL). The combined extracts were dried with anhydrous $MgSO_4$ and concentrated to a brown oil. Color was largely removed by washing through a silica gel column (2.5 cm × 15 cm). Concentration of the filtrate produced 6.1 g of solid material. Recrystallization from benzene afford 5.4 g of 2-(3-hydroxyphenyl)-1,3-dioxane: mp 108–109 °C [lit.[52] mp 109–110 °C]; 60% yield from 3-hydroxybenzaldehyde.

A 4.5-g (0.025 mol) sample of the phenol was converted to the methoxymethoxyarene **18** by using method A to afford 4.7 g (84%) after distillation: bp 168–172 °C (4.0 mm); NMR (CCl_4) δ 0.9–1.5 (m, 1 H), 1.7–2.7 (m, 1 H) 3.50 (s, 3 H), 3.6–4.5 (m, 4 H), 5.21 (s, 2 H), 5.44 (s, 1 H), 6.9–7.6 (m, 4 H); IR 3040, 2950, 2840, 1580, 1480, 1445, 1370, 1270, 1240, 1140, 1080, 1010, 790, 670 cm^{-1}. Anal. Calcd for $C_{12}H_{16}O_4$: C, 64.27; H, 7.19. Found: C, 60.30; H, 7.39.

3-Methoxy-1-(methoxymethoxy)benzene 21 was prepared by method A by starting with 6.2 g of 3-methoxyphenol. The crude product was distilled [bp 123–123.5 °C (17 mm)] to yield 13.8 g (82%) of pure **21**: NMR (CCl_4) δ 3.44 (s, 3 H), 3.74 (s, 3 H), 5.13 (s, 2 H), 6.2–7.5 (m, 4 H); IR 3070, 2940, 1590, 1490, 1280, 1255, 1210, 1185, 1140, 1070, 1035, 1005, 915, 835, 740, 670 cm^{-1}. Anal. Calcd for $C_9H_{12}O_3$: C, 64.27; H, 7.19. Found: C, 64.57; H, 7.43.

Metalation of (Methoxymethoxy)arenes. Metalation of 3-(Methoxymethoxy)pyridine (7). (a) 3-(Methoxymethoxy)-pyridine (**7**; 0.139 g, 1.00 mmol) was metalated in ether (5 mL) at −78 °C with *t*-BuLi (1.1 M in pentane, 0.95 mL; 1.05 mmol). After 0.5 h the reaction was quenched with D_2O (0.5 mL). The crude product was chromatographed on a silica gel preparative plate developed with ether to afford 0.124 g (88%) of 3-(methoxymethoxy)pyridine-*4-d*. By NMR there was 95–100% monodeuteration at C-4.

(b) A sample of **7** (0.166 g, 1.2 mmol) was metalated as above. The anion was quenched with ethylene iodochloride (0.27 g, 1.4 mmol) in THF (1.0 mL). The crude product (310 mg) was chromatographed on a silica gel preparative plate developed with 95% ether–petroleum ether. The major band (284 mg, 90%) and two more mobile minor bands (8 and 7 mg) were removed from the plate. The major band was identified as 4-iodo-3-(methoxymethoxy)pyridine (**9**), and the minor bands were identified as the products of addition of *t*-BuLi and metalation at C-2, respectively. An analytical sample of **9** was prepared by sublimation [48–50 °C (0.25 mm)]. This yielded pure white crystals: mp 62.5–65 °C; NMR δ 3.58 (s, 3 H), 5.36 (s, 2 H), 7.78 (distorted d, 1 H), 8.00 (br, 1 H), 8.44 (br, 1 H); IR 3080, 2900, 1550, 1475, 1410, 1390, 1295, 1150, 1090, 970, 915, 825 cm^{-1}. Anal. Calcd for C, 31.72; H, 3.04; N, 5.29; I, 47.88. Found: C, 31.58; H, 3.00; N, 5.24; I, 48.15.

Metalation of 2-Methyl-1-(methoxymethoxy)benzene (10). 2-Methyl-1-(methoxymethoxy)benzene[11] (**10**; 165 mg, 1.08 mmol) and *n*-hexadecane (86.5 mg, 0.383 mmol) were treated in hexane

(47) Schinbauer, M. *Monatsh. Chem.* **1968**, *99*, 1799–1807.
(48) van Es, T. *J. Chem. Soc.* **1965**, 1564.
(49) Vonwinkel, E.; Bartel, J. *Chem. Ber.* **1974**, *107*, 1221–1227.
(50) Kofler, A., *Mikrochim. Acta* **1980**, 904–911.
(51) Morton, D. R.; Morge, R. A. *J. Org. Chem.* **1978**, *43*, 2093–2101.
(52) Nikles, E. F. *J. Agric. Food Chem.* **1969**, *17*, 939–953.

(3 mL) at 0 °C with *t*-BuLi (0.73 mL, 1.5 M, 1.1 mmol). After 1 h the reaction was quenched with ethylene iodochloride (320 mg, 1.7 mmol) in THF (1 mL) followed by water (1 mL) after about 5 min. The organic phase of the reaction was analyzed by GC (190 °C). The relative areas of the *n*-hexadecane (retention time 2.3 min) and 3-iodo-2-methyl-1-(methoxymethoxy)benzene (**11**, retention time 3.8 min) peaks indicated that an 87% yield of **11** had been produced.

A pure sample of **11** was produced in a reaction similar to the one above, except that no internal standard was added. The crude product was chromatographed on an alumina plate, eluting twice with 4% ether–petroleum ether. This produced a single broad band which was divided into three parts. The bottom third yielded pure **11** as a clear oil: bp 59–60 °C (0.25 mm); NMR (CCl_4) δ 2.37 (s, CH_3), 3.65 (s, 3 H), 5.08 (s, 2 H), 6.80 (t, J = 8.0 Hz, 1 H), 7.21 (d, J = 8.0 Hz, 1 H), 7.71 (d, J = 8.0 Hz, 1 H); IR 3060, 2940, 1560, (w), 1455, 1395, 1260, 1230, 1200, 1160, 1075, 960, 840, 770 cm^{-1}. Anal. Calcd for $C_9H_{11}IO_2$: C, 38, 87; H, 3.99. Found: C, 38.97, H, 3.97.

Metalation of *N,N*-Dimethyl-3-(methoxymethoxy)aniline (12). (a) The aniline **12** (160 mg, 0.88 mmol) was metalated in ether (5 mL) at 0 °C with *t*-BuLi (0.51 mL, 1.9 mmol). After 15 min, the anion was quenched with ethylene iodochloride (210 mg, 1.1 mmol) in THF (2 mL). Gas chromatography (220 °C) of the crude product indicated that the two iodination products, *N,N*-dimethyl-4-iodo-3-(methoxymethoxy)aniline (**13**) and *N,N*-dimethyl-2-iodo-3-(methoxymethoxy)aniline (**14**), were present in a ratio of about 99:1. Iodide **13** had a retention time of 5.6 min, and **14** had a retention time of 3.4 min.

The crude product was chromatographed on a silica gel plate developed with 70% CH_2Cl_2–hexane to afford 11 mg of recovered **12** and 0.210 g (78%) of **13** as a very light green oil which decomposed rapidly: bp 106–109 °C (0.05 mm); NMR (CCl_4) δ 2.96 (s, $N(CH_3)_2$), 3.55 (s, 3 H), 5.23 (s, 2 H), 6.17 (dd, J = 9.0, 3.5 Hz), 6.52 (d, J = 3.5 Hz, 1 H) 7.56 (d, J = 9.0 Hz, 1 H); IR 3040, 2895, 1580, 1485, 1250, 1195, 1140, 1080, 1010, 990, 970, 920, 810, 780 cm^{-1}. Analysis was not possible due to the rapid decomposition.

(b) Metalation of **12** (0.194 g, 1.07 mmol) with *n*-BuLi (0.47 mL, 2.3 M, 1.08 mmol) for 2 h at 0 °C afforded a 82:18 ratio of **13** to **14** and demonstrated that changing the base from *t*-BuLi to *n*-BuLi had little effect on the selectivity of the metalation.

(c) A sample of **12** (175 mg, 0.96 mmol) was metalated in hexane (5 mL) at 0 °C with *n*-BuLi (0.42 mL, 2.3 M, 0.97 mmol). After 0.5 h there was little evidence of reaction, so the mixture was allowed to warm to ambient temperature for 2.5 h and then was quenched with ethylene iodochloride (230 mg, 1.2 mmol) in THF (2 mL). Analysis of the crude product by GC (220 °C) indicated that metalation had proceeded to the extent of about 50% and that the ratio of iodides **13** and **14** was less than 2:98. The crude product (292 mg) was chromatographed on a silica gel plate developed with 70% CH_2Cl_2–hexane to yield 72 mg (41%) of recovered **12** and 0.129 (44%) of iodide **14** as a clear liquid: bp 85–84 °C (0.05 mm); NMR (CCl_4) δ 2.78 (s, $N(CH_3)_2$), 3.53 (s, 3 H), 5.26 (s, 2 H), 6.7–7.0 (m, 2 H), 7.25 (distorted t, J = 8.0 Hz, 1 H); the absorptions at 6.7–7.0 and 7.25 are typical of the ABC pattern found in 1,2,3-trisubstituted benzenes; IR 3060, 2810, 1575, 1450, 1245, 1200, 1145, 1080, 1020, 965, 930, 850, 775, 710 cm^{-1}. Anal. Calcd for $C_{10}H_{14}INO_2$: C, 39.11; H, 4.59; I, 41.32; N, 4.56. Found: C, 39.24; H, 4.45; I, 40.98; N, 4.51.

Metalation of 3-(Methoxymethoxy)benzyl Alcohol (15). (a) A sample of **15** (164 mg, 0.97 mmol) was metalated in benzene (4 mL) at ambient temperature with *n*-BuLi (0.89 mL, 2.4 M, 2.1 mmol). After 1 h the reaction was treated with ethylene iodochloride (0.27 g, 1.4 mmol) in THF (2.0 mL). Gas chromatography (195 °C) of the crude product showed only starting material **15** (retention time 2.4 min) and 2-iodo-3-(methoxymethoxy)benzyl alcohol (**17**, retention time 11.0 min). The isomeric iodide **16**, 4-iodo-3-(methoxymethoxy)benzyl alcohol, was not present in detectable concentrations. The crude product was chromatographed on a silica gel plate developed with 60% ether–petroleum ether to produce 222 mg of iodide **17** and 32 mg of recovered **15**. This is a 78% isolated yield, or 96% yield based on recovered starting material. Iodide **17** was recrystallized from CH_2Cl_2–hexane to yield white crystals: mp 88.5–91 °C; NMR (CCl_4) 1.98 (br s, OH), 3.55 (s, 3 H), 4.68 (s, 2 H), 5.30 (s, 2 H), 6.9–7.4 (m, 3 H, typical of a 1,2,3-substituted benzene); IR 3310–3100 (OH), 2900, 1590, 1565, 1445, 1250, 1155, 1085, 1010, 920, 765, 700 cm^{-1}. Anal. Calcd for $C_9H_{11}IO_3$: C, 36.76; H, 3.77; I, 43.15. Found: C, 35.80; H, 3.74; I, 43.48.

(b) A sample of **15** (0.152 g, 0.90 mmol) was metalated in ether (2 mL) at −78 °C with a solution of *t*-BuLi (1.0 mL, 2.0 M, 2.0 mmol) and TMEDA (0.35 mL, 2.3 mmol) in ether (3 mL). After 1 h the mixture was allowed to warm to ambient temperature and was then quenched with ethylene iodochloride (0.09 mL, 1.0 mmol) in THF (2.0 mL). Gas chromatography (195 °C) of the crude product indicated that the iodides **16** (retention time 11.6 min) and **17** (retention time 11.0 min) were present in a ratio of 85:15. The crude product was chromatographed on a silica gel plate developed with 60% ether–petroleum ether to afford 153 mg of **16**, 27 mg of **17**, and 36 mg of **15**. This represents a 68% yield of iodides (88% based on recovered starting material). Iodide **16** was obtained as a clear oil: bp 99–101 °C (0.01 mm; bulb to bulb distillation); NMR (CCl_4) δ 3.00 (s, OH), 3.52 (s, 3 H), 4.53 (s, 2 H), 5.24 (s, 2 H), 6.74 (d, J = 8.6, 1 H), 7.06 (s, 1 H), 7.81 (d, J = 8.6 Hz, 1 H); IR 3400 (OH), 2940, 2900, 1585, 1485, 1450, 1250, 1150, 1080, 1020, 920, 785, 735, 690 cm^{-1}. Anal. Calcd for $C_9H_{11}IO_3$: C, 36.76; H, 3.77; I, 43.15. Found: C, 36.96; H, 3.90; I, 43.06.

(c) A sample of **15** (0.169 g, 1.01 mmol) was metalated in ether (2.0 mL) containing TMEDA (0.25 mL) at 0 °C with *n*-BuLi (1.2 mL, 1.7 M, 2.0 mmol). After 1 h ethylene iodochloride (190 mg, 1.0 mmol) in THF (1 mL) was added. The crude product was chromatographed on a silica gel plate developed with 50% ether–petroleum ether. This produced recovered **15** (54 mg) and iodides **16** (112 mg) and **17** (24 mg) and represents a 67% yield of iodinated products based on recovered starting material.

Metalation of 2-[3-(Methoxymethoxy)phenyl]-1,3-dioxane (18). (a) The acetal **18** (0.244 g, 1.09 mmol) was metalated in a mixture of cyclohexane (4.0 mL) and hexane (0.5 mL) at 0 °C with *t*-BuLi (0.64 mL, 1.9 M, 1.2 mmol). After 10 min ethylene iodochloride (310 mg, 1.6 mmol) in THF (2.0 mL) was added. Gas chromatography (220 °C) of the crude material indicated that very little starting material remained and that 2-[2-iodo-3-(methoxymethoxy)phenyl]-1,3-dioxane (**20**) and 2-[6-iodo-3-(methoxymethoxy)phenyl)]-1,3-dioxane (**19**) were present in a ratio of 92:8. The crude product (424 mg) was chromatographed on a silica gel plate developed with 50% ether–petroleum ether and produced two distinct bands. The more polar band contained unreacted **18** and iodide **19**. The other band products 277 mg (72%) of iodide **20** as a white solid. Some decomposition of the product seemed to have taken place during the chromatography, reducing the isolated yield. Recrystallization of **20** from cyclohexane–CH_2Cl_2 produced white crystals: mp 83.5–84.5 °C; NMR (CH_2Cl_2) δ 1.1–1.6 (m, 1 H), 1.8–2.4 (m, 1 H), 3.54 (s, 3 H), 3.7–4.5 (m, 4 H), 5.30 (s, 2 H), 5.63 (s, 1 H), 7.1–7.5 (m, 3 H, typical of a 1,2,3-trisubstituted benzene); IR 3070, 2915, 2850, 1565, 1455, 1430, 1370, 1250, 1145, 1100, 1080, 1035, 995, 785, 770, 705 cm^{-1}. Anal. Calcd for $C_{12}H_{15}IO_4$: C, 41.16; H, 4.32; I, 36.24. Found: C, 41.07; H, 4.59; I, 36.41.

(b) The acetal **18** 234 mg, 1.04 mmol) was metalated as above with *n*-BuLi (0.48 mL, 2.4 M, 1.2 mmol). A gelatinous precipitate formed which was difficult to stir. Ethylene iodochloride in THF was added after 30 min. Gas chromatography (220 °C) indicated that the iodides **20** and **19** were present in a ratio of 95:5. Preparative thin-layer chromatography resulted in a 67% yield of **20**. While these conditions produced slightly better regioselectivity, the overall yield was less than that in the previous reaction.

(c) The acetal **18** (0.229 g, 1.02 mmol) was metalated in a mixture of ether (3.5 mL), hexane (1.5 mL), and TMEDA (0.19 mL, 1.3 mmol) at −78 °C with *t*-BuLi (0.65 mL, 1.9 M, 1.2 mmol). After 20 min ethylene iodochloride (270 mg, 1.4 mmol) in THF (3 mL) was added, and the mixture was allowed to warm to room temperature. Gas chromatography (220 °C) of the crude product indicated that the iodides **19** and **20** were present in a ratio of 90:10. The crude product was chromatographed on a silica gel plate developed with CH_2Cl_2. Two bands appeared. The more polar band was recovered **18**. The less polar band yielded 0.273 g (76%) of a mixture of **19** and **20** as a clear oil. The GC ratio remained at 10:90. Crystallization from cyclohexane–CH_2Cl_2 produced white crystals of pure **19**: mp 58–59 °C; NMR (CCl_4) δ 1.1–1.6 (m, 1 H), 1.8–2.4 (m, 1 H), 3.55 (s, 3 H), 3.6–4.5 (m, 4

H), 5.29 (s, 3 H), 5.39 (s, 1 H), 6.87 (dd, J = 8.6, 1.8 Hz, 1 H), 7.17 (d, J = 1.8 Hz, 1 H), 7.70 (d, J = 8.6 Hz, 1 H); IR 2960, 2860, 1580, 1475, 1245, 1100, 1075, 1010, 975, 800, 765 cm^{-1}. Anal. Calcd for $C_{12}H_{15}IO_4$: C, 41.16; H, 4.32; I, 36.24. Found: C, 41.03; H, 4.47; I, 36.22.

(d) The distributions of products from metalation at 0 °C and −78 °C were compared. A sample of **18** (0.110 g, 0.49 mmol) was metalated with *t*-BuLi (0.26 mL, 1.9 M, 0.49 mmol) in ether (2.5 mL) at 0 °C. After 3 min the reaction was quenched with ethylene iodochloride in THF. Analysis by GC (220 °C) indicated that little (~15%) unreacted **18** remained and that the iodides **19** and **20** were present in a ratio of approximately 50:50.

A second metalation was performed by following the same procedure, except that the temperature was lowered to −78 °C. A sample of **18** (0.115 g, 0.51 mmol) in ether (2.5 mL) at −78 °C was metalated with *t*-BuLi (0.27 mL, 1.9 M, 0.51 mmol). After 2 h the ethylene iodochloride in THF was added, and the reaction mixture was warmed to ambient temperature. Analysis by GC (220 °C) indicated that the metalation was about 50% complete and that the ratio of iodides **19** and **20** was 49:51.

These parallel metalations indicate that the difference in temperature has little effect on the selectivity of the metalation of **18**.

Metalation of 3-Methoxy-1-(methoxymethoxy)benzene (21). (a) A sample of **21** (0.171 mg, 1.02 mmol) was metalated in hexane (5 mL) at 0 °C with *t*-BuLi (0.58 mL, 1.8 M, 1.0 mmol). After 25 min ethylene iodochloride (250 mg, 1.3 mmol) in THF (2 mL) was added. Gas chromatography (220 °C) of the crude product indicated that 2-iodo-5-methoxy-1-(methoxymethoxy)-benzene (**22**, retention time 3.6 min) and 2-iodo-3-methoxy-1-(methoxymethoxy)benzene (retention time 4.2 min) were present in a ratio of 3:97, respectively. The crude oily product was chromatographed on a silica gel plate developed with 30% ether–petroleum ether. This yielded 233 mg (78%) of a mixture of iodides **22** and **23**. Some starting material (17%) was also recovered. No method could be devised to completely separate **22** and **23** on a small scale. To obtain an analytical sample of **23**, we chromatographed the mixture on a silica gel plate with 10% ether–petroleum ether (developed twice). This produced one broad band which was divided in half. The bottom half produced a sample of pure **23** as a clear oil: bp 80–83 °C (0.10 mm); NMR (CCl_4) δ 3.54 (s, 3 H), 5.27 (s, 2 H), 6.51 (dd, J = 8.6, 1.5 Hz, 1 H), 6.76 (dd, J = 8.6, 1.5 Hz, 1 H), 7.25 (t, J = 8.6 Hz); IR 3070, 2940, 1580, 1460, 1240, 1150, 1090, 1060, 995, 915, 765, 700 cm^{-1}. Anal. Calcd for $C_9H_{11}IO_3$: C, 36.76; H, 3.77; I, 43.15. Found: C, 36.80; H, 3.74; I, 43.48.

(b) A sample of **21** (80.2 mg, 0.48 mmol) was metalated in ether (2.5 mL) at 0 °C with *t*-BuLi (0.25 mL, 1.9 M, 0.48 mmol). After iodination with ethylene iodochloride (150 mg, 0.77 mmol) in THF (1.0 mL) the GC (220 °C) showed unreacted **21** (5%) and the iodides **22** and **23** in a ratio of 41:59.

2-Iodo-5-methoxy-1-(methoxymethoxy)benzene (22). Due to the difficulty of separating **22** from its isomer **23**, a pure sample of **22** was prepared by an independent method for purposes of identification. Iodination[48] of 3-methoxyphenol yielded 2-iodo-5-methoxyphenol, mp 71.5–72.5 °C (lit.[53] mp 72–73 °C). This phenol was then converted to the (methoxymethoxy)arene. Into a 25-mL round-bottomed flask flushed with nitrogen was placed NaH in oil (57% dispersion, 0.05 g, 1.2 mmol), which was then washed free of oil with petroleum ether. Ether (5 mL) and DMF (1 mL) were added. A solution of the iodophenol (0.153 g, 0.61 mmol) in ether (2 mL) was added dropwise. The reaction mixture was stirred for 4 min under nitrogen. Chloromethyl methyl ether (0.085 g, 1.1 mmol) was added. After 15 min the reaction was quenched with water (5 mL). The reaction mixture was diluted with ether and washed with water, with 10% aqueous Na_2CO_3, and with brine. The organic phase was dried ($MgSO_4$) and concentrated to a yellow oil. Chromatography on a silica gel plate developed with 30% ether–hexane yielded pure **22** as a clear oil: bp 86–87 °C (0.07 mm); NMR (CCl_4) δ 3.54 (s, 3 H), 3.80 (s, 3 H), 5.25 (s, 2 H), 6.39 (dd, J = 9.0, 3.5 Hz, 1 H), 6.72 (d, J = 3.5 Hz, 1 H), 7.67 (d, J = 9.0 Hz, 1 H); IR 3080, 2955, 1575, 1475, 1300, 1230, 1150, 1080, 1050, 990, 920, 835, 785 cm^{-1}. Anal. Calcd for $C_9H_{11}IO_3$: C, 36.76; H, 3.77; I, 43.15. Found: C, 37.02; H, 3.81; I, 42.97.

Metalation of *N*,*N*-Dimethyl-3-(methoxymethoxy)benzamide (24). The amide **24** (202 mg, 0.97 mmol) was metalated in a mixture of ether (5 mL) and hexane (2 mL) at −78 °C with *t*-BuLi (0.56 mL, 1.5 M, 0.98 mmol). After 10 min ethylene iodochloride (0.10 mL, 1.1 mmol) in THF (1 mL) was added, and the reaction mixture was warmed to room temperature. The reaction was quenched with water and the mixture analyzed by GC (240 °C). This showed two products (t_R = 1.7 and 8.0 min). The peak areas of the two products were roughly equal. The crude product was chromatographed on a silica gel preparative TLC plate developed with ether. The most polar band was unreacted **24** (20 mg). A second band yielded *N*,*N*-dimethyl-2-iodo-3-(methoxymethoxy)benzamide (**26**, 117 mg) as a colorless oil: NMR (CCl_4) δ 2.84 (s, 3 H), 3.06 (s, 3 H), 3.54 (s, 3 H), 5.25 (s, 2 H), 6.7–7.5 (m, 3 H) (splitting pattern of a 1,2,3-trisubstituted benzene). A third band afforded 87 mg of a ketone from the addition of *tert*-butyllithium: NMR (CCl_4) δ 1.35 (s, 9 H), 3.49 (s, 3 H), 5.21 (s, 2 H), 7.1–7.6 (m, 4 H).

Attempt to Metalate Methyl 3-(Methoxymethoxy)benzoate (27). Methyl 3-(methoxymethoxy)benzoate (**27**; 0.212 g, 1.11 mmol) was metalated in ether (4 mL) at −78 °C with *tert*-butyllithium (1.05 mL, 1.1 M, 1.2 mmol). After 1 h CO_2 was bubbled through the solution for about 3 min. The reaction mixture was added to water (15 mL), and 10% NaOH (2 mL) was added. The aqueous phase was washed with ether, acidified to pH 3, and immediately extracted four times with ether. The crude acid fraction was esterified with diazomethane. Thin-layer chromatography showed several products which were not identified.

Metalation of 3-(Methoxymethoxy)benzoic Acid (28). The benzoic acid **28** (182 mg, 1.00 mmol) was metalated in THF (6 mL) at −78 °C with *t*-BuLi (1.95 mL, 1.1 M, 2.15 mmol). After 10 min carbon dioxide was bubbled through the solution. The reaction mixture was added to water, and 10% NaOH (3 mL) was added. The mixture was washed with ether, the pH of the aqueous solution was adjusted to pH 3, and the mixture was again extracted with ether. The crude acids were esterified with diazomethane. Chromatography on a silica gel preparative TLC plate developed with 60% ether–petroleum ether afforded mostly esterified starting material. A dicarboxylic acid, diester **29**, resulting from metalation, was also isolated: 44 mg; NMR (CCl_4) δ 3.57 (s, 3 H), 3.90 (s, 3 H, methyl ester), 3.94 (s, 3 H, methyl ester), 5.33 (s, 2 H), 7.7–8.1 (m, 3 H). The aromatic multiplet was consistent with a 1,2,3-substitution pattern.

Attempts to Metalate 3-(Methoxymethoxy)benzonitrile (30). The nitrile **30** (170 mg, 1.04 mmol) was metalated in ether (6 mL) at −78 °C with *t*-BuLi (0.99 mL, 1.1 M, 1.1 mmol). After 1 h D_2O was added. The crude product was chromatographed on a silica gel TLC plate developed with 50% ether–petroleum ether to afford a ketone (135 mg) apparently resulting from nucleophilic attack of the *tert*-butyllithium on the nitrile: NMR (CCl_4) δ 1.35 (s, 9 H), 3.49 (s, 3 H), 5.21 (s, 2 H), 7.1–7.6 (m, 4 H). Unreacted **30** (37 mg) was also recovered. NMR showed that no deuterium had been incorporated on the ring.

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Registry No. **1**, 57234-27-2; **2**, 58402-71-4; **3**, 58434-48-3; **4**, 100-84-5; **5**, 81245-24-1; **6**, 79383-44-1; **7**, 81245-25-2; **8**, 81245-26-3; **9**, 81245-27-4; **10**, 55359-65-4; **10a**, 578-58-5; **11**, 81245-28-5; **12**, 81245-29-6; **13**, 81245-30-9; **14**, 81245-31-0; **15**, 81245-32-1; **16**, 81245-33-2; **17**, 81245-34-3; **18**, 81245-35-4; **19**, 81245-36-5; **20**, 81245-37-6; **21**, 57234-28-3; **22**, 81245-38-7; **23**, 81245-39-8; **24**, 81245-40-1; **26**, 81245-41-2; **27**, 81245-42-3; **28**, 81245-43-4; **29**, 81245-44-5; **30**, 81245-45-6; 3-hydroxypyridine, 109-00-2; 3-(dimethylamino)phenol, 99-07-0; 3-hydroxybenzoic acid, 99-06-9; *N*,*N*-dimethyl-3-hydroxybenzamide, 15789-03-4; 3-hydroxybenzaldehyde, 100-83-4; 3-hydroxybenzoinitrile, 873-62-1; methyl 3-hydroxybenzoate, 19438-10-9; 3-acetoxybenzaldehyde, 34231-78-2; 1,3-propanediol, 504-63-2; 2-(3-hydroxyphenyl)-1,3-dioxane, 24393-13-3; 3-methoxyphenol, 150-19-6; 2-iodo-5-methoxyphenol, 41046-70-2; chloromethyl methyl ether, 107-30-2; dimethoxymethane, 109-87-5; 1-iodo-2-methoxytoluene, 25922-05-8; 2-(iodomethyl)anisole, 81245-46-7.

(53) Machzcek, V.; Sterba, V.; Valter, K. *Collect. Czech. Chem. Commun.* **1972**, *37*, 3073–3080.