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REGIOSELECTIVE METALLATIONS OF (METHOXYMETHOXY)ARENES

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Abstract—The methoxymethoxy substituent when attached to an aromatic ring functions as a moderately strong ortho-directing group in hydrogen–metal exchange reactions. In many cases the propensity of the methoxymethoxylated arene toward ring metallation is greatly enhanced with concomitant suppression of undesirable side reactions such as nucleophilic attack and addition of the metallating species. Unlike many other ortho-directing groups, the regio-direction of the methoxymethoxy substituent when in conjunction with other weaker directing groups is dependent upon the metalating medium. Thus, by changing the electron donating capacity of the metallating medium it is possible to selectively direct metallation to either of the positions ortho to the methoxymethoxy substituent.

Organolithium reagents prepared by metallation reactions are among the most useful and versatile reactive intermediates in synthetic organic chemistry. The generality of the metallation reaction has resulted in an almost explosive growth in activity in this area which has continued for several years and which has produced a remarkable variety of novel and useful metallated species.[1-3]

Metallation reactions, particularly the Li–H exchange, have been especially effective in the area of aromatic chemistry were substituents are capable of directing the introduction of the metal in a predictable manner.[4-11] Typically, the directing capability of aromatic substituents results in introduction of the metal regioselectively into the positions ortho to the substituent. A fairly large number of these ortho-directing groups have been investigated; for convenience their directing capability is often compared to the –OMe group which is usually considered to be of intermediate ortho-directing capacity.[12]

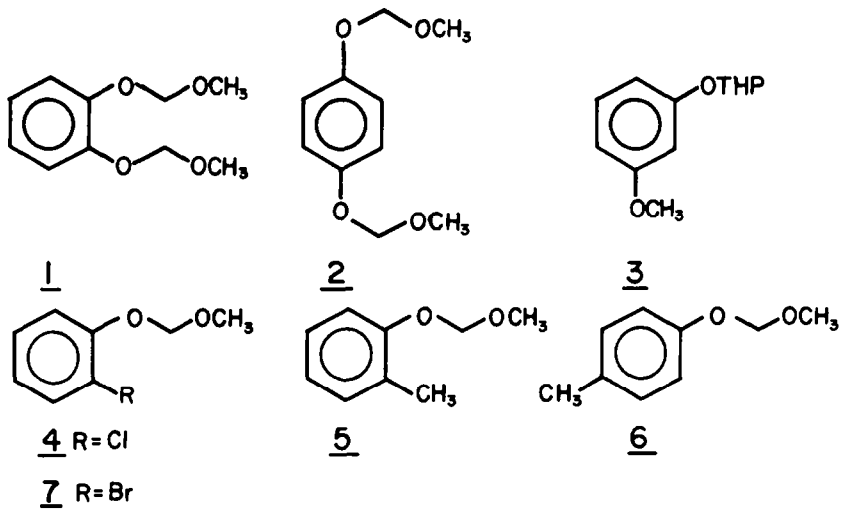
The ortho-directing capabilities of aromatic substituents appear to be derived from a combination of inductive and coordinative effects. Thus, it is not surprising that those substituents capable of exhibiting both effects are among the strongest ortho-directing groups. Strong directing groups are: $-SO_2NR_2$,[12] –SONHR,[12] $-CONR_2$,[13] –CONHR.[12] In the absence of strong inductive stabilization, the ortho-directing capacity depends upon strong coordinative effects. Usually these groups have either strongly basic electron donors, or have several weaker groups to bind the metal at more than one coordinative site. Some of these moderately strong groups are: $-CH_2-NR_2$,[12] $-OCH_2OMe$,[4,14,15] –NHCOR,[16] $-NHCO_2R$,[17] –CSNHR,[18] $-CH(OR)_2$,[19] oxazolines,[20,21] and imidazolines.[22] Weak ortho-directing groups include: $-NR_2$, $-CF_3$, –F,[12] $-CH_2-OH$,[23] O^-,[1,2] and –SR.[24] All of these groups direct regioselective ortho metallation; however, in many cases there is a lack of discrimination between nonequivalent ortho positions,[12,25] or between the ring positions and other acidic sites within the substrate.[16,18,22,26-28] In some cases the directing group itself or the aromatic nucleus may be subject to nucleophilic attack by the metallating reagent.[1,2,13,16,19] Despite these problems metallated aromatics are important synthetic reagents, and the metallation procedure affords a significant alternative to electrophilic reagents for aromatic substitution.[29]

Our work in the area of aromatic metallation chemistry has been centered around the use of the (methoxymethoxy) group in the regioselective metallation of unsymmetrically substituted phenolic derivatives.[4,30] While the –OMe group has had considerable use as a protecting group in the metallation of phenols, serious problems are encountered in releasing the free phenolic product subsequent to the metallation.[31] Our initial investigations using phenolic methoxymethyl ethers were prompted by the facile acidic cleavage of this formaldehyde acetal to afford the free phenolic compounds. In the course of these investigations we also found many desirable and unique properties of the (methoxymethoxy) group, properties that are especially useful in metallation reactions.[32]

The use of (alkoxyalkoxy) groups in metallation reactions has been known for several years. The earliest reports dealt with the metallation of tetrahydropyranyl ethers[33] which are a form of readily cleaved phenolic ethers. Polyphenolic compounds are more readily protected using the methoxymethyl ethers, and the monometallation of 1,2-di(methoxymethoxy)benzene **1** and 1,4-di(methoxymethoxy)benzene **2** has been reported.[34] Except for the report of Santucci and Gilman[33c] none of these earlier investigations deal with regiochemical aspects of the metallation other than to observe that metallation occurs *ortho* to the alkoxylalkoxy directing group. Santucci and Gilman reported that resorcinol mono-methyl mono-THP ether **3** metallated in the same sense as resorcinol dimethyl ether; the most reactive position is between the two ortho-directing groups.

Christensen was one of the first to report the enhanced selectivity toward metallation of methoxymethyl ethers.[14] Metallation of 2-chloro-(methoxymethoxy)benzene **4** occurred selectively at C-6 without competing halogen metal exchange. Similarly, the 2-methyl-(**5**) and 4-methyl(methoxymethoxy)benzene (**6**) afforded ortho metallated products which on treatment with dimethyl formamide resulted in aldehydes.

The selectivity for ring metallation in the case of 2-chloro ether **4** is in part due to the reduced reactivity of the chlorine in the competing halogen–metal exchange reaction. We investigated a similar metallation with the corresponding 2-bromo ether **7** and found that halogen–metal exchange proceeded to the

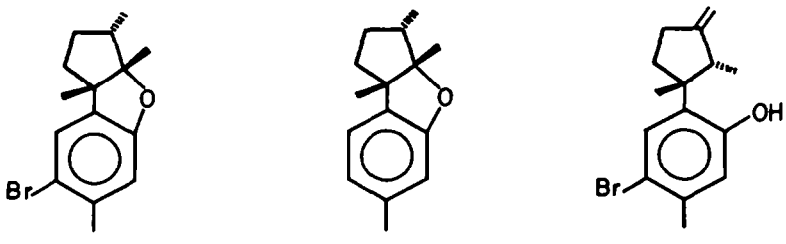


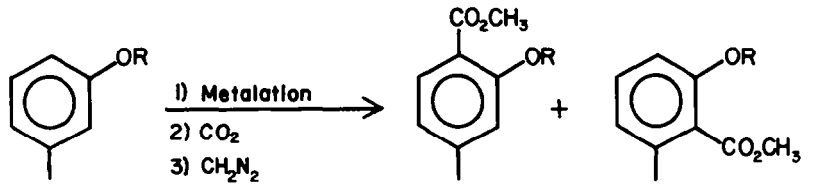
exclusion of metallation, even with phenyllithium or in the presence of TMEDA in the metallating medium. When the bromine is *para* to the methoxymethoxy group, these reagents afford excellent yields of ortho metallated products. In this case the activating effect of the methoxymethoxy substituent for metallation is apparent; using t-BuLi as a metallation/exchange reagent a 20% yield of ortho metallation is realized although the predominant reaction mode is the exchange reaction.[4]

The rapid halogen–metal exchange of a bromine ortho to an (alkoxyalkoxy) substituent can be used to advantage. We have applied this reaction in the syntheses of an optically active form of the marine sesquiterpenes (−)-apylsin **8** and (−)-debromoapylsin **9**.[35] By replacing the terminal methoxyl group of the methoxymethyl ether with a chiral alkoxyl group an optically active metallation reagent can be obtained. We have made the (menthyloxymethoxy)[36] and (isopinocampheyloxymethoxy)[35] substituents from readily available (−)-methol and (−)-isopinocampheol (obtained by hydroboration of (±)-pinene). These groups when substituted on aromatic rings function in metallation reaction similarly to the corresponding methoxymethoxy analogs except that the rates of metallation are significantly reduced apparently due to steric hindrance. For preparative purposes it can be advantageous to obtain the ortho metallated material by halogen metal exchange. For the sequiterpene syntheses we used the bromide **10** as our optically active reagent in condensation with the racemic enone **11** to produce a pair of diastereomeric chlorohydrins **12** and **13** which were readily separated[35] (Scheme 1). The requisite bromophenol precursor to **10** is most conveniently prepared by metallation, taking advantage of the high regioselectivity obtainable with the methoxymethoxy substituent, *vide infra*, of *m*-cresol methoxymethyl ether[4,32] **15** followed by bromination and exchange of the methoxymethyl group. The methoxymethyl ether **15** is a useful synthetic intermediate. We have also employed this in a synthesis of (±)-allolaurinterol **14**.[37]

One of the most interesting aspects of the metallation of (methoxymethoxy)arenes is the high degree of discrimination between non-equivalent ortho centers. For example, the lithiation of **15** with t-BuLi affords a >99.5% bias towards the less hindered position at C-6. That this selectivity is not due entirely to the bulky t-BuLi reagent can be seen in the comparisons of the lithiation of **15** with n-BuLi and the metallation of 3-methylanisole **16** with n-BuLi and t-BuLi[25,33,39] (Table 1). While in all cases there is a preference for metallation at C-6, the methoxymethoxy derivative clearly affords a greater bias in this direction.

When a *meta* substituted (methoxymethoxy)arene has an additional ortho-directing group the interaction between the second directing group and the (methoxymethoxy) group can produce unusual and unique regio-directing effects. Ordinarily, the regioselectivity of most arene metallations is not influenced to any great extent by the metallating reagents or conditions.[1-3] Examination of the data in Table 1 supports this contention. There are, however, a few exceptions: 1-methoxynaphthalene metallates primarily at C-2 with n-BuLi/TMEDA in cyclohexane, and at C-8 with t-BuLi/cyclohexane–pentane;





15 R = CH_2OCH_3
16 R = CH_3

17 R = CH_2OCH_3 **18** R = $-CH_2OCH_3$
19 R = $-CH_3$ **20** R = $-CH_3$

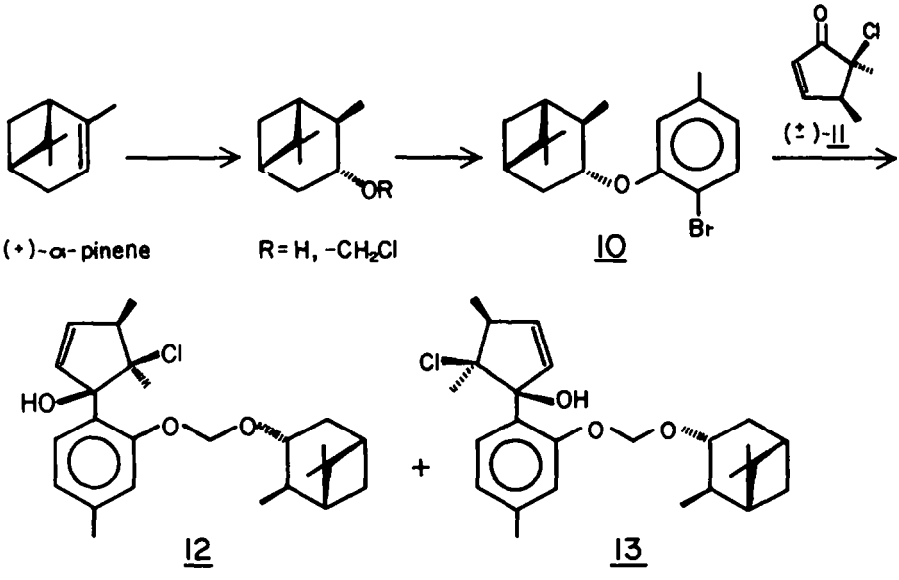
Table 1.

Substrate	Conditions	Ratio
15		**17:18**
	t-BuLi/Et_2O/0°	>200:1
	t-BuLi/hexane/0°	>200:1
	n-BuLi/hexane/25°	4:1
	n-BuLi/TMEDA/hexane/25°	4:1
16		**19:20**
	t-BuLi/C–C_6H_{12}/reflux	7:3
	n-BuLi/TMEDA/hexane/25°	6:4

and 4-methoxy-(*N*,*N*-dimethylaminomethyl)benzene metalates *ortho* to the amino group with n-BuLi, and *ortho* to the OMe group with n-BuLi/TMEDA.[12]

We have found that with certain relatively weak ortho-directing groups meta to a methoxymethoxy substituent it is possible to direct metallation selectively to either of the two non-equivalent positions *ortho* to the methoxymethoxy group by manipulating the metallating conditions. By far, the composition of the solvent system appears to have the most profound effect upon the regiochemical outcome of these metallations. In general, hindered metallating agents and strongly electron donating solvents tend to favor the *ortho* site farthest removed from the ortho-directing group (the distal position); whereas, in non-donating solvents with non-hindered metallating agents, the *ortho* position between the two directing groups is selected (the proximal position). As in the case of **3**,[33] when both groups are moderate to strong ortho-directors only proximal metallation is observed.

We investigated a series of *meta* substituted (methoxymethoxy)benzenes. To determine the ratios of the 1,2,4-isomer (distal metallation) to the 1,2,3-isomer (proximal metallation) the reaction mixtures were quenched with an ethylene iodochloride to produce the corresponding iodides. For the analysis of metallation mixtures, this iodinating agent was superior, affording nearly quantitative yields of aryl iodides with concomitant generation of ethylene and LiCl. Typically, the iodinating reagent was added as a solution in tetrahydrofuran. Since many of the metallated (methoxymethoxy)benzenes are insoluble in the hydrocarbon metallating medium the addition of tetrahydrofuran serves to dissolve the metallated arene and thereby promote rapid metallation. By a series of control experiments we have established that equilibration of the metallated (methoxymethoxy)arenes does not occur in tetrahydrofuran or other solvents in which they are soluble.[32]



Scheme 1.

The results of these metallation studies are summarized in Table 2.

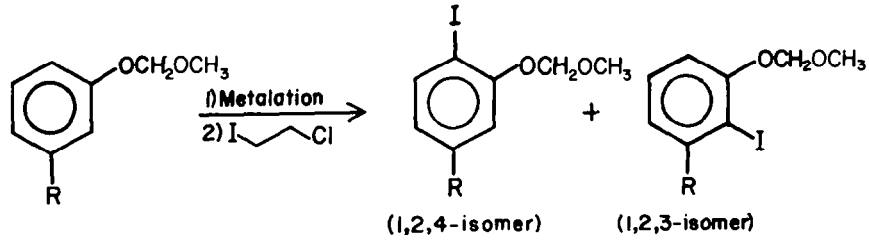
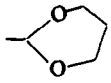


Table 2.

No.	R	Product (1, 2, 4), Conditions	(1, 2, 3-) Ratio	Yield%
15	–Me	t-BuLi/pentane/0°	**17,18** (200:1)	95
21	$-NMe_2$	2-BuLi/Et_2O/P°	**23,23** (99:1)	78
		n-BuLi/Et_2O/0°	(82:18)	44
		n-BuLi/hexane/25°	(2:98)	44
		t-BuLi/hexane/25°	(57:43)	
24	$-CH_2OH$	n-BuLi/benzene/25°	**25,26** (nil:100)	78
		n-BuLi/Et_2O/0°	(19:81)	79
		t-BuLi/benzene/0°	(40:60)	80
		t-BuLi/Et_2O/0°	(59:41)	72
		t-BuLi/TMEDA/Et_2O/−78°	(85:15)	68
27		n-BuLi/*c*-C_6H_{12}/0°	**28,29** (5:95)	71
		t-BuLi/*c*-C_6H_{12}/0°	(8:92)	78
		t-BuLi/Et_2O/0°	(1:1)	85
		n-BuLi/TMEDA/Et_2O/−78°	(1:1)	10
		t-BuLi/TMEDA/Et_2O/−78°	(90:10)	76
		t-BuLi/THF/−78°	(90:10)	10
30	$-OCH_3$	t-BuLi/hexane/0°	**31,32** (3:97)	78
		t-BuLi/Et_2O/0°	(41:59)	95
		t-BuLi/TMEDA/Et_2O/−78°	(5:95)	93
33	$-CONMe_2$	t-BuLi/Et_2O/hexane/−78°	**34,35** (nil:100)	35
36	$-CO_2H$	t-BuLi/THF/−78°	**37,38** (nil:100)	20

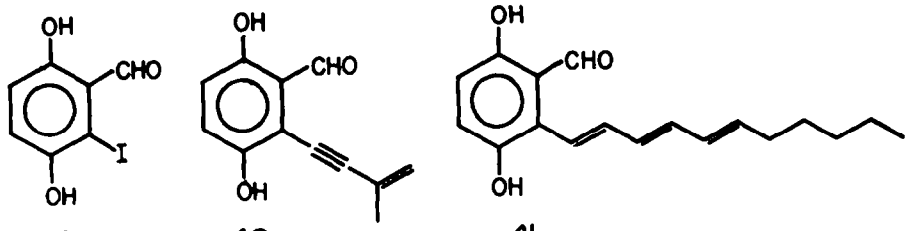
Yields are reported to isolated products obtained by either iodination with I–CH_2–CH_2–Cl or by carbonation.

The selectivities observed can be rationalized as the result of competing solvation effects between the methoxymethoxy group, the meta substituent and solvent ligands. The effects in combination with steric interactions serve to direct the site of metallation to one of the two available positions ortho to the methoxymethoxy group. With strongly coordinating solvents the internal solvation becomes less important, steric interactions between the strongly coordinated metallating species and the weakly directing meta substituent direct the metallation to the distal position. In a weakly solvating medium the internal solvation with the coordinating meta substituent directs the metallation to the proximal position.

The bi-coordinate nature of the methoxymethoxy group is most likely the underlying basis for this unusual type of regiodirective control. While cooperative effects between substituent have been observed in many other systems, the increased coordination by the (methoxymethoxy) group results in a bulkier complex which increases the propensity towards distal metallation. With a methoxyl group as the primary director, the decreased coordination to the metallated species favors the proximal product in most cases. The metallation of *m*-anisidine, for example, produces only the 1,2,3-substituted product.[12] Clemura and Trost have reported the combined directive effects operating in a variety of *m*-methoxybenzyl alcohols.[8,41]

While the methoxymethoxy substituent exerts a considerable activating effect with respect to metallation, and in most cases it facilitates metallation with respect to that achieved with the more simple OMe analogs, the activating effect, however, is not of sufficient magnitude to suppress the addition to CO groups. The metallation of amide **33** and acid **36** are interesting, but addition of the organolithium metallating species is a serious side reaction. *N,N*-Dimethylamides are known to undergo fairly facile addition reactions; this problem has been solved by other investigators by using more hindered N,N-diethylamides or secondary amides which are rendered less reactive to addition by deprotonation.[13,42] Other CO substituents such as aldehydes, ketones, esters and nitriles suffer only addition by the metallating species.

The carboxaldehyde when protected as the 1,3-propandiol acetal (**27**) functions as a relatively



39 40 41

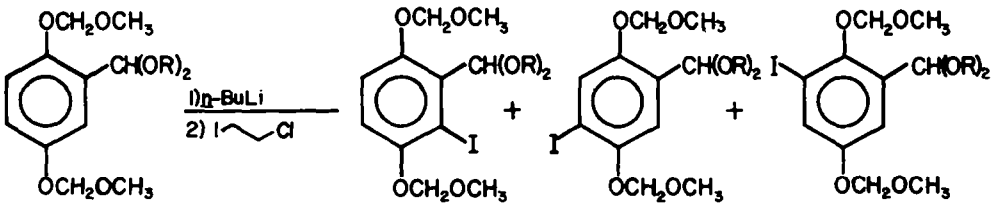
weak directing group, and thus permits an excellent degree of regiocontrol in the metallation reaction. The dioxane, in our hands, was superior to the dioxolane (ethylene glycol acetal) because the dioxolanes tend to undergo a fragmentation reaction from deprotonation of the benzal function that results in formation of the carboxylate anion and ethylene. In heterocyclic systems metallations of ethylene acetal containing substrates have been reported.[2] Acyclic acetals are also satisfactory in emthoxymethoxy metallations.

We have investigated the use of the carboxaldehyde acetals for the synthesis of the iodoaldehyde **39** which has been successfully employed in syntheses of the hydroquinone antibiotics frustulosin **40**[43] and aurocitrin **41**.[44] Lithiation of 1,4-*bis*(methoxymethoxy)-benzene **2** followed by transmetallation with magnesium bromide etherate affords upon treatment with orthoformates the aldehyde acetals **42a–c**. Based upon our experience with the propanediol acetal **27** we expected to be able to selectively metallate at C-3, however, we were unable to achieve the kind of selectivity in the metallation that would be synthetically useful (Table 2). The origin of the lack of selectivity may be due to the fact that the methoxymethoxy group *ortho* to the acetal may be either: involved in coordination of the metallating species in concert with acetal group; or it may be sterically interfering with the acetal so that conformations permitting coordination with the *meta* oriented methoxymethoxy group are disfavored. In metallation of 2,5-dimethoxybenzyl alcohol we have observed a similar lack of regioselectivity due to the coordination of lithium benzyloxide with the neighboring OMe group.[45]

When the activating group is flanked by benzylic hydrogens, metallation can be complicated by competing benzylic deprotonation;[16,18,26–28,46,47] although in the cases of **42** and **5**,[14,32] when the methoxymethoxy substituent was the directing group, benzylic interference was not a significant complication. Metallation of **5** with t-BuLi followed by quenching with ethylene iodochloride afforded an 87% yield of 3-iodo-2-(methoxymethoxy)toluene. Careful analysis by both GLC and TLC indicated no benzylic iodides or their products; thus, the metallation is highly selective (>99.5%) for the ring positions. In contrast, metallation of 2-methylanisole **46** afforded a 3:2 ratio of benzylic to ring metallation with t-BuLi. With a more potent metallating system, n-BuLi/TMEDA, the ratio was reversed to 1:3.[26,48] Other ortho tolyl compounds which afford benzyl metallated products are shown in Table 4.

Nucleophilic attack by the metallating species is a competing reaction in the metallation of certain arenes. Unsaturation in the directing group often renders them susceptible to nucleophilic addition reactions. The N,N-dimethylamido group[13] is one of the susceptible groups as are oxazolines.[21,49] In the amido case the more hindered N,N-diethylamido group, or the N-methylamido which is protected by deprotonation can be used in place of the more reactive functionality. In the oxazolinyl case, metallation at low temperature usually suffices to suppress addition. From the results in Table 2 it is seen that the activating effect of the methoxymethoxy group significantly reduces the amount of attack on the N,N-dimethylamido group.

The pyridine ring is especially prone to nucleophilic addition by most metallating reagents, and for this



42a-c 43a-c 44a-c 45a-c

No.	R	Ratio(43:44:45)	Yield%
42a	$-CH_3$	10:30:60	68
42b	$-CH_2CH_3$	17:26:57	53
42c	$-(CH_2)_3-$	26:24:50	59

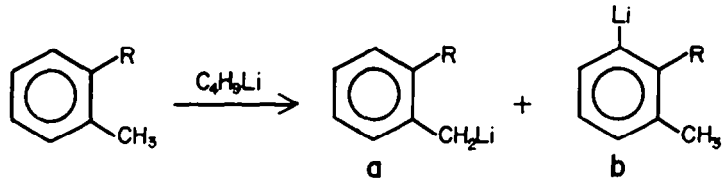


Table 3

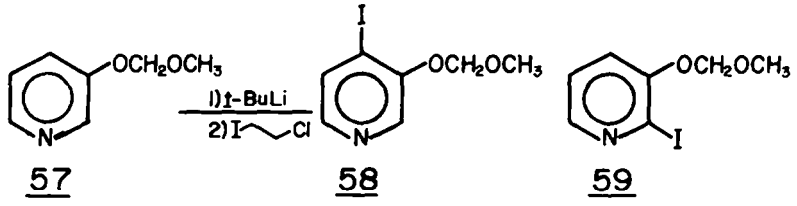
No.	R	Ratio (a:b)	Ref.
5	$-OCH_2OMe$	(1:200)[a,c]	14,32
46	-OMe	(2:1)[a]	
		(54:42)[b]	26,48
		(1:3)[c]	
47	$-NMe_2$	(3:1)[a]	
		(10:1)[c]	
48	$-CH_2NMe_2$	(>200:1)[d]	27
49	-NHCOtBu	(>200:1)[d]	16
50	$-CSNHCH_3$	(>200:1)[d]	18
51	-CONHMe	(>200:1)[d]	46
52	$-SO_2NHMe$	(>200:1)[d]	47
53	-oxazolinyl	(>200:1)[d]	49
54	-imidazolinyl	(>200:1)[d]	22
56	$-CO_2H$	(>200:1)[d]	50

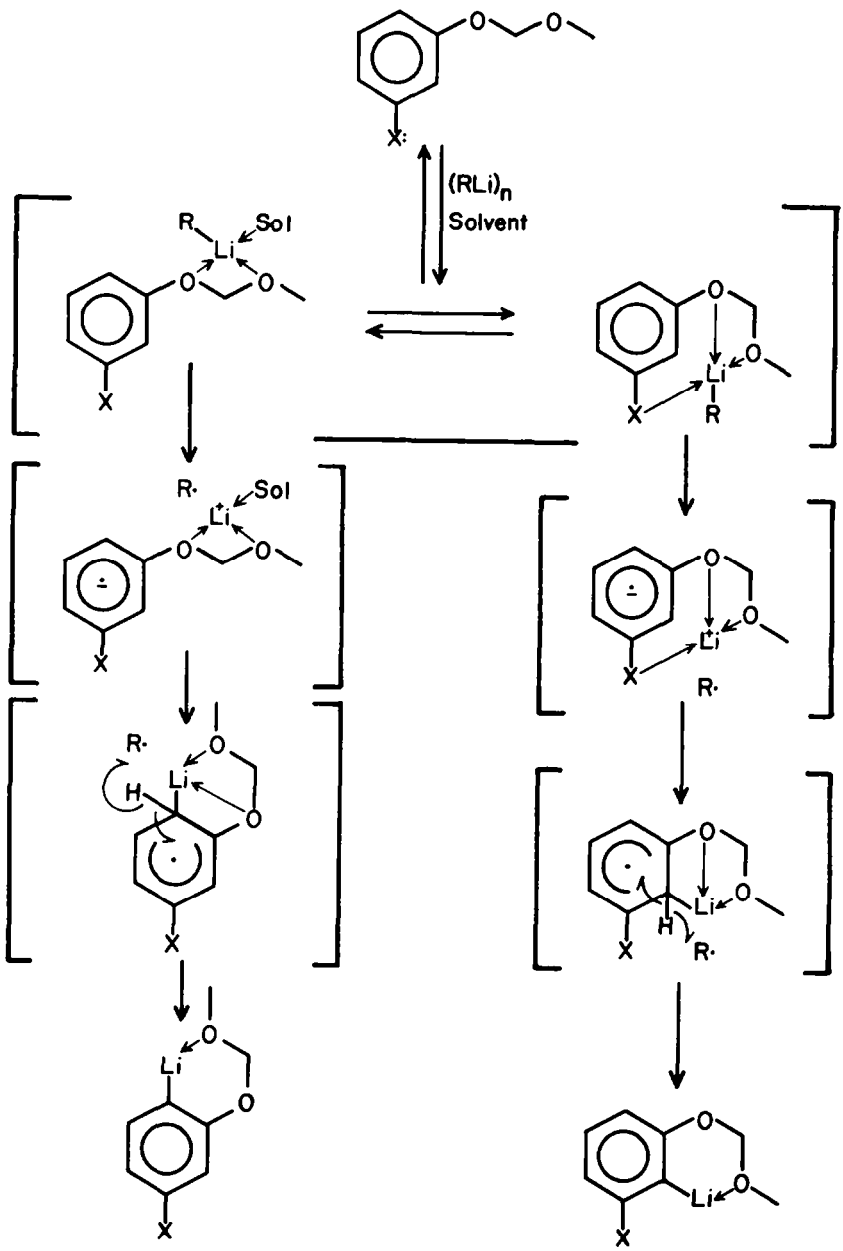
[a]nBuLi; [b]tBuLi; [c]NBuLi/TMEDA; [d]the authors report only the benzyl metallated products.

reason most lithiopyridines are prepared by halogen–metal exchanges.[1,2,51] Recently, there have been a few reports of the direct metallation of pyridines. Polychlorinated systems have for sometime been known to undergo metallation,[52] and systems with more than one ortho-directing and/or carbanion stabilizing groups also form lithiopyridines without undue competition from nucleophilic addition.[53] When only one ortho-directing group is present there are fewer examples of the direct metallation. The oxazolinyl group in the 4-position was reported by Meyers and Gabel to afford good yields of metallated products with methyllithium as a metallating agent.[54] With the more reactive butyllithiums, nucleophilic attack on the pyridine ring was the predominant mode of reaction. Recently, Katritzky *et al.* has reported that 2-aminocarbonylpyridines undergo lithiation at C-3 in good yields.[55]

We have investigated the metallation of 3-(methoxymethoxy)pyridine **57** principally to determine if the previously observed regiochemical effects could be duplicated in this heterocyclic system. The (methoxymethoxy) group produced substantial activation towards metallation, and nucleophilic attack on the pyridine was not a significant side reaction. With t-BuLi in ether the regioselectivity for the C-4 position **58** over the C-2 position **59** was quite high (32:1) and less than 4% of the crude product was derived from the addition of the metallating agent. While the metallation of **57** is highly regioselective the ratio of **58** to **59** is quite insensitive to changes in the metallating system.

It is intriguing to speculate upon the origin of the regioselectivities observed in the methoxymethoxy systems; particularly upon the very unusual regiodirective effects in the meta substituted cases. While these might be explainable in terms of a protophilic mechanism,[39] the insensitivity of these and also other oxy systems[25] to the nature of the metallating base is inconsistent with simple steric effects in the approach of the base resulting in the observed regioselectivities. The results of the methoxymethoxy system can be better accommodated by a modification of the radical anionic pathway proposed by Shirley *et al.*[25,38] in which the metallating agent is first coordinated to the methoxymethoxy group prior[56] to the electron transfer and hydrogen transfer steps (Scheme 2). The presence of strong solvent ligands would negate the coordinative contribution of weakly directing meta substituents; the meta substituents would be relegated to a steric function that would favor hydrogen abstraction from the distal position. In non-





Scheme 2.

coordinating solvents the solvating contribution from the weak meta substitutent would become relatively more important and the metallating agent would then be juxtaposed by chelation to abstract the proximal hydrogen. That the proximal selectivities reported in Table 2 for the non-coordinating solvent system are somewhat higher than the distal selectivities in strong donors is consistent with the model in which chelation is responsible for proximal direction while steric effects influence distal selection.

While the mechanistic proposal outlined in Scheme 2 accommodates the unusual regio-directive effects observed in the methoxymethoxy system, we have not observed any radical intermediates directly in this system. Electron spin resonance signals have been observed in the metallation of naphthalene with butyllithium–TMEDA;[38] and in the metallation of anisole with lithium in tetrahydrofuran and with lithium naphthalenide radical intermediates hve been proposed.[57] In these cases the increased stability of the napthalenide anion-radicals may account for these observatins.

By the means of control experiments we have established that while the ultimate metallated products frequently precipitate from the metallation mixture the ultimate distribution of metallated products is not the result of differential solubilities. Usually both metallated isomers are insoluble; however, even under conditions where they are soluble no isomerization has been observed. Isomerization has been shown to occur with some imine directing-groups,[58] but in general the absence of isomerization of ring positions is normal in aryllithium metallation chemistry.[59] In addition, we have observed constant ratios

of proximal and distal metallated isomers throughout the course of the metallations.

The methoxymethoxy substituent has many features that make it attractive for use in the synthesis of functionalized, polysubstituted phenolic compounds. In combination with other ortho-directing groups the regiodirective effects may be controlled in a predictable manner that is unique in the field of metallation chemistry. Furthermore, it is a convenient and stable phenolic protecting group that is easily introduced and readily removed under mild conditions. In many cases the rates of metallation are greatly enhanced over that achieved by ordinary ethers with a corresponding increase in the selectivity of metallation.

EXPERIMENTAL

General methods. M.p. determinations were made using a Thomas–Hoover Unimelt apparatus and are uncorrected. IR spectra were obtained on a Beckman Model IR 18A or on an Acculab 1 spectrophotometer. Spectra of liquid samples were obtained as films and solids as KBr pellets. NMR spectra were obtained on a Varian Associates Model EM 360 spectrophotometer using TMS as an internal standard. Gas chromatograms were obtained on a Packard–Becker Model 417 or a Varian Aerograph Series 1700 gas chromatographs using 3 mm × 2.6 m glass columns packed with 3% OV-17 on 80/100 chromosorb W HP. Analytical TLC were run on Merck precoated silica plates with 250 μm layers. Preparative TLC 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 laboatory.[45]

Preparation of (methoxymethoxy)arenes

(A) *From chloromethyl methyl ether.* A 500 mL 3-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 chloromethylmethyl 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 chloromethylmethyl ether. The reaction 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 with 10% NaOHaq, water, brine, dried with $MgSO_4$, and concentrated. The crude product was purified by distillation under vacuum.

(B) *From dimethoxymethane.* The method of Yardley and Fletcher[60] was employed. The phenol (0.04 mol), dimethoxymethane (16 mL, 0.18 mol), CH_2Cl_2 (90 mL), and *p*-toluenesulfonic acid monohydrate (40 mg) were placed in a 250 mL round-bottomed flask which was fitted with a Soxhlet containing 40 g of 4 Å molecular sieves. A $CaCl_2$ drying tube was attached to the condenser. The reaction was refluxed for 24 hr, cooled to room temp, and treated with 0.5 mL Et_3N. The reaction was washed twice with 10% NaOH, water and saturated brine, dried with $MgSO_4$, and concentrated. The crude product was distilled under vacuum.

Metallation 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 temp indicated. The metallating agent was added with a syringe. Usually the metallated product formed as a ppt. 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 insure rapid reaction.

The reaction mixture was then poured into water and extracted with ether (3 ×). The combined ethereal extract was washed with water (2 ×), once with brine, then dried with $MgSO_4$, and concentrated at reduced pressure to afford the crude reaction product.

Preparation of (methoxymethoxy)arenes

3-(*Methoxymethoxy*)*toluene* (**15**). By method A from *m*-cresol (21.6 g, 0.20 mol), NaH (9 g, 57% oil dispersion, 0.2 mol), chloromethyl methyl ether, ether (500 mL), and DMF (100 mL). The crude product was distilled b.p. 89–91° (13 mm)[4] to afford a 25.9 g (85%) yield. (Found: C, 70.69; H, 7.93. Calc for $C_9H_{12}O_2$: C, 71.02; H, 7.95.)

N,N-*Dimethyl*-3-(*methoxymethoxy*)*aniline* (**21**). By method A from 3-N,N-dimethylaminophenol (6.8 g, 0.05 mol). The crude material, a dark oil was distilled at reduced pressure, b.p. 144–145° (15 mm), to afford **21** as a clear liquid (4.62 g, 51%). NMR (CCl_4): δ 2.94 (s, 6H), 3.46 (s, 3H), 5.13 (S, 2H), 6.2–7.3 (m, 4H); IR: 3095, 2980, 2900, 1610, 1510, 1360, 1235, 1150, 1080, 1020, 920, 825, 755, 685 cm^{-1}. This material decomposed rapidly at room temp to a dark tarry mass.

Methyl 3-(*methoxymethoxy*)*benzoate.* By method B from methyl 3-(methoxymethoxy)benzoate (6.1 g, 0.04 mol). The crude material was distilled at reduced pressure, b.p. 161.5–162.5° (24 mm), to afford the ester, 5.2 g (66% yield). NMR (CCl_4): δ 3.45 (s, 3H), 3.91 (s, 3H), 5.26 (s, 2H), 7.1–7.9 (m, 4H); IR: 3035, 2940, 1720, 1585, 1445, 1270, 1145, 1100, 1060, 1010, 750 cm^{-1}. (Found: C, 61.18; H, 5.93. Calc for $C_{10}H_{12}O_4$: C, 61.22; H, 6.16.)

3-(*Methoxymethoxy*)*benzyl alcohol* (**24**). Methyl 3-(methoxymethoxy)benzoate (2.22 g, 0.011 mol) was reduced in ether (50 mL) with $LiAlH_4$ (0.22 g, 0.006 mol) to afford **24**, 1.83 g (96%), b.p. 88–90° (0.06 mm). NMR (CCl_4): δ 3.50 (s, 3H), δ 4.6 (s, 1H), 5.27 (s, 2H), 7.0–7.7 (m, 4H); IR: 3400, 2940, 2900, 1505, 1485, 1450, 1250, 1150, 1080, 1020, 920, 785, 735, 690. (Found: C, 64.02; H, 7.14. Calc for $C_9H_{12}O_3$: C, 64.27; H, 7.19.)

2 - [3 - (*Methoxymethoxy*)*phenyl*] - 1,3 - *dioxane* (**27**). 3-Hydroxybenzaldehyde (6.1 g, 0.05 mol) was acetylated to afford 3-acetoxybenzaldehyde, 7.8 g (95% yield) b.p. 65–66° (0.06 mm) [lit.[61] b.p. 100° (1.0 mm)]. The acetoxyaldehyde (7.4 g, 0.045 mol) was converted to the acetal with 1,3-propanediol (7 mL, 0.1 mol), benzene (50 mL) and toluenesulfonic acid (0.5 g), in a flask fitted with a Dean–Stark trap. After 2 hr the evolution of water ceased and excess 10% NaOHaq was added to remove the acetate. After 2 hr the mixture was neutralized to pH 8 and extracted with ether. The combined extracts were dried with $MgSO_4$ and concentrated. Color was removed from the crude material by passing through a short column (2.5 cm × 15 cm) of silica gel. Recrystallization from benzene afford 2-(3-hydroxyphenyl)a1,3-dioxane, m.p. 108–109° [lit.[62] m.p. 109–110°], in 60% from 3-hydroxybenzaldehyde.

2-[3-(*Methoxymethoxy*)*phenyl*]-1,3,-*dioxane* **27** was prepared by method A from 2-(3-hydroxyphenyl)-1,3-dioxane (4.5 g, 0.025 mol). Distillation of the crude material, b.p. 168–172° (4.0 mm) afforded 4.7 g (84% yield). NMR (CCl_4): δ 0.9–1.5 (m, 1H), 1.7–2.7 (m, 1H), 3.50 (s, 3H), 3.6–4.5 (m,

4H), 5.21 (s, 2H), 5.44 (s, 1H), 6.9–7.6 (m, 4H); IR: 3040, 2950, 2840, 1580, 1480, 1445, 1370, 1270, 1240, 1140, 1080, 1010, 790, 670 cm^{-1}. (Found: C, 60.30; H, 7.39. Calc for $C_{12}H_{16}O_4$: C, 64.27; H, 7.19.)

3-*Methoxy*-1-(*methoxymethoxy*)*benzene* (**30**). By method A from 3-methoxyphenol (6.2 g, 0.05 mol). The crude material was distilled at reduced pressure, b.p. 123–123.5° (17 mm), to afford **30**, 6.9 g (82% yield). NMR (CCl_4): δ 3.44 (s, 3H), 3.74 (s, 3H), 5.13 (s, 2H), 6.2–7.5 (m, 4H); IR: 3070, 2940, 1590, 1490, 1280, 1255, 1210, 1185, 1140, 1070, 1035, 1005, 915, 835, 740, 670 cm^{-1}. (Found: C, 64.57; H, 7.43. Calc for $C_9H_{12}O_3$: C, 64.24; H, 7.19.)

3-(*Methoxymethoxy*)*benzoic acid* (**36**). Methyl 3-(methoxymethoxy)benzoate (1.1 g, 5.7 mmol) was saponified with 10% NaOHaq (3 mL) in MeOH (5 mL) to afford **36**, m.p. 122–123°. NMR ($CDCl_3$): δ 3.62 (s, 3H), 5.38 (d, 2H), 7.3–81. (m, 4H); IR (Nujol): 2930, 1675, 1585, 1455, 1375, 1310, 1230, 1155, 1075, 1010, 990, 915, 760, 680 cm^{-1}.

N,N-*Dimethyl*-3-(*methoxymethoxy*)*benzamide* (**33**). Treatment of 3-hydroxybenzoic acid with DMF and P_2O_5 afforded N,N-dimethyl-3-hydroxybenzamide m.p. 127–128° (lit.[63] m.p. 128–130°). The hydroxy amide (8.3 g, 0.5 mmol) was methoxymethylated by method B. The conversion was not high. After 96 h, 5.3 g of hydroxyamide remained. This was extracted with 10% aqueous NaOH. The residue was chromatographed on silica gel eluted with 85% EtOAc-hexane. After decoloriation with charcoal (Nuchar C-190) afforded a colorless oil, 2.2 g (58% yield based on recovered starting material). NMR (CCl_4): δ 3.0 (s, 6H), 3.4 (s, 3H), 5.22 (s, 2H), 6.9–75 (m, 4H); IR (neat): 3070, 2930, 1625, 1575, 1480, 1265, 1180, 1150, 1010, 795, 750, 690 cm^{-1}.

3-(*Methoxymethoxy*)*pyridine* (**57**). By method A from 3-hydroxypyridine (4.7 g, 0.05 mol). The crude product was distilled under reduced pressure to afford **57**, b.p. 85–87° (15 mm), 2.4 g (32%). NMR (CCl_4): δ 3.51 (s, 3H), 5.23 (s, 2H), 7.0–7.6 (m, 4H); IR: 3040, 2910, 1570, 1480, 1425, 1230, 1200, 1155, 1085, 1045, 985, 805, 710 cm^{-1}. The bands at 805 cm^{-1} and 710 cm^{-1} are characteristic of 3-substituted pyridines.

2,5-Bis(*methoxymethoxy*)*benzaldehyde dimethylacetal* (**42a**). 1,4-*Bis*(methoxymethoxy)benzene **2** (1.01 g, 5.09 mmol) was metaliated with t-BuLi (4.4 mL, 1.2 M, 5.1 mmol) in petroleum ether (7 mL) at 0°. The lithio derivative precipitated and the supernatant was drawn off and replaced with trimethyl orthoformate (4 mL) and a solution of $MgBr_2$·etherate (10 mL, 1.0 M). The mixture was stirred at 40° for 42 hr. The crude product was chromatographed on a silica gel preparative plate developed with ether–petroleum ether (1:1) to afford **42a**, 315 mg (23%). NMR (CCl_4): δ 3.32 (s, 6H), 3.48 (s, 6H), 5.15 (s, 4H), 5.69 (s, 1H), 7.07 (m, 2H), 7.31 (m, 1H); IR (neat): 2930, 2820, 1585, 1485, 1395, 1360, 1270, 1210, 1185, 1150, 1070, 1010, 920, 880, 815, 705 cm^{-1}. Treatment of this material with acid afforded 2,5-dihydroxybenzaldehyde, m.p. 91–93°.

2,5-Bis-(*methoxymethoxy*)*benzaldehyde diethyl acetal* (**42b**). With triethylorthoformate by the same method as for the dimethyl acetal, from **2** (0.985 g, 4.95 mmol). After chromatography on silica gel 560 mg (37% yield) of **42b** was obtained as a colorless oil. NMR (CCl_4): δ 1.21 (t, 6H), 3.53 (s, 6H), 3.63 (q, 4H), 5.21 (s, 4H), 5.83 (s, 1H), 7.12 (m, 2H), 7.38 (m, 1H). This material also produced 2,5-dihydroxybenzaldehyde upon acid treatment.

2,5-Bis-(*methoxymethoxy*)*benzaldehyde* 1,3-*propanediol acetal* (**42c**). With 2-methoxy-1,3-dioxane,[64] by the same method as for the dimethyl acetal, from **2** (0.991 g, 5.0 mmol). Chromatography on silica gel afforded 412 mg (29%) of **42c**, as heavy viscous oil. NMR (CCl_4) δ 1.2–2.2 (m, 2H), 3.3–4.5 (m, 4H), 3.53 (s, 6H), 5.18 (s, 4H), 5.79 (s, 1H), 7.07 (m, 2H), 7.33 (m, 1H); IR (neat): 2950, 1500, 1390, 1270, 1150, 1090, 1070, 1010, 920, 815, 785 cm^{-1}. Treatment of this material afforded 2,5-dihydroxybenzaldehyde.

Metallation of (methoxymethoxy) arenes

Metallation of 3-(*methoxymethoxy*)*toluene* (**15**). (a) **15** (152 mg, 1.0 mmol) was metallated in petroleum ether (1 mL) with t-BuLi (0.8 M in pentane, 1.5 mL, 1.2 mmol) at 0°. After 2.5 hr CO_2 was bubbled into the mixture until the Gilman test was negative. The mixture was partitioned into water to remove neutrals and acidified. The crude acids were esterified with diazomethane, then chromatographed on silica gel developed with 20% ether in petroleum ether to afford methyl 2-(methoxymethoxy)-4-methylbenzoate, as an oil, 200 mg (95%). (Found: C, 63.65; H, 6.62. Calc for: C, 62.84; H, 6.71.) The structure was confirmed by treatment with MeOH-toluenesulfonic acid to remove the methoxymethoxy group followed by saponification to the known 2-hydroxy-4-methylbenzoic acid m.p. 174–177° (lit.[65] m.p. 177°). Gas chromatographic analysis of the crude ester fraction (200°) showed that the distal isomer predominated (>99.5%).

(b) **15** (152 mg, 1.0 mmol) was metallated in petroleum ether (1.5 mL) with n-BuLi (2.2 M in hexane, 0.5 mL, 1.1 mmol) and TMEDA (120 μL) at 0°. After 1.2 hr the CO_2 was added and the mixture treated as in (a) above to afford 192 mg, (92% yield) of crude esters. Gas chromatography (200°) showed a 4:1 ratio of distal to proximal isomers that was confirmed by the isolation from column chromatography on silica gel of 133 mg of methyl 4-methyl-2-(methoxymethoxy)benzoate and 30 mg of methyl 2-methyl-6-(methoxymethoxy)benzoate. The structure of the proximal isomer was confirmed by conversion to 2-methyl-6-hydroxybenzoic acid, m.p. 170.5–171.5° (lit.[65] m.p. 173°).

Metallation of N,N-dimethyl-3-(*methoxymethoxy*)*aniline* (**21**)

(a) The aniline **21** (160 mg, 0.88 mmol) was metallated in ether (5 mL) at 0° with t-BuLi (0.51 mL, 1.9 M, 0.89 mmol). After 15 min the reaction was quenched with ethylene iodochloride (210 mg, 1.1 mmol) in THF (2 mL). GC (220°) of the iodination products N,N-dimethyl-4-iodo-3-(methoxymethoxy)analine (t_R 5.6 min) and N,N-dimethyl-2-iodo-3-(methoxymethoxy)-aniline (t_R 3.4 min) were present in a ratio of about 99:1).

The crude product was chromatographed on a silica gel plate developed with 70% CH_2Cl_2–hexane to afford 11 mg of recovered **21** and 210 mg (78%) of the 4-iodo isomer as a very light green oil which decomposed rapidly, b.p. 106–109° (0.05 mm). NMR (CCl_4): δ 2.96 [s, $N(CH_3)_2$], 3.55 (s, 3H), 5.23 (s, 2H), 6.17 (dd, J = 9.0, 3.5 Hz), 6.52 (d, J = 3.5 Hz, 1H), 7.56 (d, J = 9.0 Hz, 1H); IR: 3040, 2895, 1580, 1485, 1250, 1195, 1140, 1080, 1010, 990, 970, 920, 810, 780 cm^{-1}. Due to the rapid decomposition of this compound we were unable to obtain satisfactory analysis data.

(b) Metallation of **21** (194 mg, 1.07 mmol) with n-BuLi (0.47 mL, 2.3 M, 1.08 mmol) for 2 hr at 0° in ether (5 mL) afforded an 82:18 ratio of the 4-iodo and 2-iodo isomers, and demonstrated that changing the base had only a small effect on the selectivity of the metallation.

(c) Metallation of **21** (175 mg, 0.96 mmol) with n-BuLi (0.42 mL, 2.3 M, 0.97 mmol) in hexane (2 mL) at ambient temp for 2.5 hr resulted in about 50% conversion to the anion, which was reacted with ethylene iodochloride (230 mg, 1.2 mmol) in THF (2 mL). GC (220°) showed that the ratio of 4-iodo to 2-iodo isomers was less than 2:98.

The crude product (292 mg) was chromatographed as in (a) above to afford 72 mg (41%) of recovered **21** and 129 mg (44% yield) of the 2-iodoisomer as a clear liquid, b.p. 82–84° (0.05 mm); NMR (CCl_4): δ 2.78 [s, $N(CH_3)_2$], 3.53 (s, 3H), 5.26 (s, 2H), 6.7–7.0 (m, 2H), 7.25 (distorted triplet, J. 8.0 Hz, 1H). The aromatic resonances are typical of the ABC pattern of 1,2,3-trisubstituted benzene; IR: 3060, 2810, 1575, 1450, 1245, 1200, 1145, 1080, 1020, 965, 930, 850, 775, 710. (Found: C, 39.24;, H, 4.45; I, 40.98; N, 4.51. Calc for $C_{10}H_{14}INO_2$: C, 39.11; H, 4.59; I, 41.32; N, 4.56.)

Metallation of 3-(*methoxymethoxy*)*benzyl alcohol* (**24**)

(a) The alcohol **24** (164 mg, 0.97 mmol) was metallated in benzene (4 mL) at ambient temp with n-BuLi (0.89 mL, 2.4 M, 2.1 mmol). After 1 hr ethylene iodochloride (270 mg, 1.4 mmol) in THF (2.0 mL) was added. GC (195°) of the crude product showed only **24** (t_R 2.4 min) and 2-iodo-3-(methoxymethoxy)benzyl alcohol (t_R 11.0 min). The isomeric 4-iodo alcohol eas not present in detectable concentrations.

Chromatography on a silica gel perparative plate developed with 60% ether in petroleum ether afforded 32 mg of **24** and 222 mg (78% yield) of 2-iodo-3-(methoxymethoxy)benzyl alcohol, m.p. 88.5–91° (from CH_2Cl_2–hexane); NMR (CCl_4): δ 1.98 (broad s, OH), 3.55 (s, 3H), 4.68 (s, 2H), 5.30 (s, 2H), 6.9–7.4 (m, 3H, typical ABC pattern, of 1,2,3-trisubstituted benzene); IR: 3310–3100 (OH), 2900, 1590, 1565, 1445, 1250, 1155, 1085, 1010, 920, 765, 700 cm^{-1}. (Found: C, 35.80; H, 3.74; I, 43.48. Calc for $C_9H_{11}IO_3$: C, 36.76; H, 3.77; I, 43.15.)

(b) Metallation of **24** (91.5 mg, 0.55 mmol) with n-BuLi (0.64 mL, 1.8 M, 1.2 mmol) in ether (2.5 mL) at 0° for 24 hr afforded after treatment with ethylene iodochloride 128 mg (79% yield) of iodides. By GC (195°) the ratio of the 2-iodo- (t_R 11.0 min) to 4-iodoisomer (t_R 11.6 min) w > 81:19.

(c) Metallation of **24** (87.6 mg, 0.52 mmol) with t-BuLi (0.55 mL, 2.0 M, 1.1 mmol) in benzene at room temp for 10 min afforded after treatment with ethylene iodochloride 122 mg (80% yield) of iodides. By GC (195°) the ratio of the 2-iodo to 4-iodo isomer was 60:40.

(d) Metallation of **24** (175 mg, 1.04 mmol) with t-BuLi (1.1 mL, 1.9 M, 2.1 mmol) in ether (5 mL) at 0° for 20 min afforded 220 mg (72% yield) of iodides upon treatment with ethylene iodochloride. By GC (195°) the ratio of the 2-iodo to 4-iodo isomer was 41:59.

(e) Metallation of **24** (152 mg, 0.90 mmol) with t-BuLi (10 mL, 2.0 M, 2.0 mmol) and TMEDA (0.35 mL, 2.3 mmol) in ether (3 mL) at −78° for 1 hr afforded a ratio of the 2-iodo to 4-iodo isomer of 15:85 by GC (195°) after treatment with ethylene iodochloride (0.09 mL, 1.0 mmol) in THF (2.0 mL).

Chromatography of the crude product on a silica gel preparative plate developed with 60% ether in petroleum ether afforded 36 mg of **24**, 27 mg of the 2-iodo isomer, and 153 mg of 4-iodo-3-(methoxymethoxy)benzyl alcohol, b.p. 99–101° (0.01 mm) (kugelrohr); NMR (CCl_4): δ 3.00 (s, OH), 3.52 (s, 3H), 4.53 (s, 2H), 5.24 (s, 2H), 6.74 (d, J = 8.6 Hz, 1H), 7.06 (s, 1H), 7.81 (d, J = 8.6 Hz, 1H); IR: 3400 (OH), 2940, 2900, 1585, 1485, 1450, 1250, 1150, 1080, 1020, 920, 785, 735, 690. (Found: C, 36.96; H, 3.90; I, 43.06. Calc for $C_9H_{11}IO_3$: C, 36.76; H, 3.77; I, 43.15.)

Metallation of 2-[3-(*methoxymethoxy*)*phenyl*]-1,3-*dioxane* (**27**)

(a) The acetal **27** (234 mg, 1.04 mmol) was metalated in cyclohexane (4.0 mL) containing hexane (0.5 mL) at 0° with n-BuLi (0.64 mL, 1.9 M, 1.2 mmol). After 30 min ethylene iodochloride (0.14 mL, 1.5 mmol) in THF (1 mL) was added. GC (220°) of the crude material indicated that very little unreacted **27** remained and that the ratio of 2-[2-iodo-3-(methoxymethoxy)phenyl]-1,3-dioxane to 2-[4-iodo-3-(methoxymethoxy)phenyl]-1,3-dioxane was 95:5.

Chromatography of the crude product of a silica gel preparative plate developed with 1:1 ether–hexane afforded two bands: the minor band, 52 mg of a mixture of **27** and the 4-iodo isomer; and the major band, 242 mg of 2-[2-iodo-3-(methoxymethoxy)phenyl]-1,3-dioxane, m.p. 83.5–84.5° (from cyclohexane–CH_2Cl_2); NMR (CCl_4): δ 1.1–1.6 (m, 1H), 1.8–2.4 (s, 1H), 3.54 (s, 3H), 3.7–4.5 (m, 4H), 5.3 (s, 2H), 5.63 (s, 1H), 7.1–7.5 (m, 3H); IR: 3070, 2915, 2850, 1565, 1455, 1430, 1370, 1250, 1145, 1100, 1080, 1035, 995, 785, 770, 705 cm^{-1}. (Found: C, 41.07; H, 4.59; I, 36.41. Calc for $C_{12}H_{12}IO_4$: C, 41.16; H, 4.32; I, 36.24.)

(b) Metallation of **27** (244 mg, 1.09 mmol) in cyclohexane (4 mL) with t-BuLi (0.64, 1.9 M, 1.2 mmol) at 0° for 10 min afforded 298 mg (28%) of crude iodides upon treatment with ethylene iodochloride (0.15 mL, 1.7 mmol) in THF (2 mL). By GC (220°) the ratio of the 2-iodo to the 4-iodo isomer was 92:8.

(c) Metallation of **27** (110 mg, 0.49 mmol) in ether (2.5 mL) with t-BuLi (0.26 mL, 1.9 M, 0.49 mmol) at 0° for 3 min afforded 146 mg (85% yield) of crude iodides upon treatment with ethylene iodochloride. By GC (220°) the ratio of the 2-iodo to the 4-iodo isomer was 1:1.

(d) Metallation of **27** (241 mg, 1.08 mmol) in ether (10 mL) with n-BuLi (0.59 mL, 1.9 M, 1.1 mmol) and TMEDA (0.20 mL, 1.3 mmol) at −78° for 1.5 hr produced a turbid mixture. This was treated with iodine (0.40 g, 1.6 mmol) in THF (5 mL). GC (220°) of the crude product showed that about 10% of **27** had been converted to the iodides in the ratio of 1:1.

(e) Metallation of **27** (229 mg, 1.02 mmol) with t-BuLi (0.65 mL, 1.9 M, 1.2 mmol) and TMEDA (0.19 mL, 1.3 mmol) in ether (3.5 mL) and hexane (1.5 mL) at −78° for 20 min afforded 273 mg (76% yield) of crude iodides upon treatment with ethylene iodochloride (0.13 mL, 1.4 mmol) in THF (3 mL). By GC (220°) the ratio of the 2-iodo to the 4-iodo isomer was 10:90.

Recrystallization from hexane–CH_2Cl_2 afforded 2-[4-iodo-3-(methoxymethoxy)phenyl]-1,3-dioxane, m.p. 58–59.5°; NMR (CCl_4): δ 1.1–1.6 (m, 1H), 1.8–2.4 (m, 1H), 3.55 (s, 3H), 3.6–4.5 (m, 4H), 5.29 (s, 2H), 5.39 (s, 1H), 6.87 (dd, J = 8.6, 1.8 Hz, 1H), 7.17 (d, J = 1.8 Hz, 1H), 7.70 (d, J = 8.6 Hz, 1H); IR (KBr): 2960, 2860, 1580, 1475, 1375, 1245, 1100, 1075, 1010, 975, 800, 765 cm^{-1}. (Found: C, 41.13; H, 4.47; I, 36.22. Calc for $C_{12}H_{13}IO_4$: C, 41.16; H, 4.32; I, 36.24.)

(f) Metallation of **27** (233 mg, 1.04 mmol) with t-BuLi (0.65 mL, 1.6 M, 1.04 mmol) in THF (5 mL) at −78° for 1 hr afforded less than 10% conversion to the iodides in a 1:1 ratio.

Metallation of 3-*methoxy*-1-(*methoxymethoxy*)*benzene* (**30**)

(a) Metallation of **30** (171 mg, 1.02 mmol) with t-BuLi (0.58 mL, 1.8 M, 1.0 mmol) in hexane (5 mL) at 0° for 25 min afforded upon treatment with ethylene iodochloride 233 mg (78% yield) of a mixture of iodides. GC (220°) showed that the ratio of 2-iodo-3-methoxy-1-(methoxymethoxy)benzene (t_R 4.2 min) (the 2-isomer), and 2-iodo-5-methoxy-1-(methoxymethoxy)-benzene (t_R 3.6 min) (the 4-isomer) was 97:3.

Separation of the two isomers by chromatography on silica gel was at best marginal. An analytical sample of 2-iodo-3-methoxy-1-methoxymethoxy)benzene was obtained by removing the lower half of band produced over preparative silica gel plate developed twice with 10% ether–petroleum ether. The 2-iodide had, b.p. 80–83° (0.10 mm); NMR (CCl_4): δ 3.54 (s, 3H), 5.27 (s, 2H), 5.61 (dd, J = 8.6, 1.5 Hz, 1H), 6.76 (dd, J = 8.6, 1.5 Hz, H), 7.25 (t, J = 8.6 Hz, 1H); IR: 3070, 2940, 1580, 1460, 1240, 1150, 1090, 1060, 995, 915, 765, 700 cm^{-1}. (Found: C, 36.80; H, 3.74; I, 43.48. Calc for $C_9H_{11}IO_3$: C, 36.76; H, 3.77; I, 43.15.)

(b) Metallation of **30** (80.2 mg, 0.48 mmol) with t-BuLi (0.25 mL, 1.9 M, 0.48 mmol) in ether (2.5 mL) at 0° for 30 min followed by treatment with ethylene iodochloride (150 mg, 0.77 mmol) in THF (1 mL) afforded 134 mg (95% yield) of iodides. Analysis by GC (220°C) showed the ratio of the 2-iodo to the 4-iodo isomer was 59:41.

(c) Metallation of **30** (89.0 mg, 0.53 mmol) with t-BuLi (0.32 mL, 2.0 M, 0.64 mmol) and TMEDA (0.10 mL, 0.63 mmol) in ether (2.5 mL) at −78° for 30 min followed by treatment with ethylene iodochloride (0.06 mL, 0.7 mmol) in THF (0.5 mL) afforded 145 mg (93% yield) of iodides. Analysis by GC (220°C) indicated that the ratio of the 2-iodo to the 4-iodo isomer was 95:5.

Metallation of N,N - *dimethyl* - 3 - (*methoxymethoxy*) - *benzamide* (**33**)

The amide **24** (202 mg, 0.97 mmol) was metallated with t-BuLi (0.65 mL, 1.5 M, 0.98 mmol) in a mixture of ether

(5 mL) and hexane (2 mL) at −78°. After 10 min ethylene iodochloride (0.10 mL, 1.1 mmol) in THF (1 mL) was added and the mixture allowed to warm to ambient temp.

Chromatography of the crude product on a silica gel preparative plate developed with ether afforded N,N - dimethyl - 2 - iodo - 3 - (methoxymethoxy)benzamide (117 mg, 35% yield); NMR (CCl_4: δ 2.84 (s, 3H), 3.06 (s, 3H), 3.54 (s, 3H), 5.25 (s, 2H), 6.7–7.5 (m, 3H). A second band afforded 87 mg of a ketone from the addition of t-BuLi; NMR (CCl_4: δ 1.35 (s, 9H), 3.49 (s, 3H), 5.21 (s, 2H), 7.1–7.6 (m, 4H).

Metallation of 3-(*methoxymethoxy*)*benzoic acid* (**36**)

The acid **36** (182 mg, 1.00 mmol) was metallated with t-BuLi (1.95 mL, 1.1 M, 2.15 mmol) in THF (6 mL) at −78°. After 10 min CO_2 was bubbled into the mixture.

The acid fraction was esterified with CH_2N_2 and the crude esters chromatographed on a silica gel preparative plate developed with 60% ether in petroleum ether. The major band afforded, methyl 3-(methoxymethoxy)benzoate. A more polar band was a dicarboxylic acid diester (44 mg, 20% yield); NMR (CCl_4): δ 3.57 (s, 3H), 3.90 (s, 3H, methyl ester), 3.94 (s, 3H, methyl ester), 5.33 (s, 2H), 7.7–8.1 (m, 3H). The aromatic multiplet was consistent with a 1,2,3-trisubstituted benzene.

Metallation of 2,5-*bis*-(*methoxymethoxy*)*benzaldehyde dimethyl acetal* **42a**

The dimethyl acetal **42a** (208 mg, 0.76 mmol) was metallated with n-BuLi (0.37 mL, 2.3 M, 0.86 mmol) in cyclohexane (4 ml) at room temp. After 15 min ethylene iodochloride (0.13 mL, 1.4 mmol) in THF (1.5 mL) was added.

Chromatography of the crude product on a silica gel preparative plate developed with 50% ether in petroleum ether produced three bands. The most polar band, 15 mg of **43a**; NMR (CCl_4): δ 3.44 (s, 6H), 3.51 (s, 3H), 3.54 (s, 3H), 5.12 (s, 2H), 5.20 (s, 2H), 5.83 (s, 1H), 7.11 (m, 2H). The middle band, 115 mg of a 2:1 mixture of starting material (**42a**) and **44a**. The NMR spectrum of this mixture had two singlets at δ 7.16 and 7.47 indicating that the iodinated product was 4-iodo-2,5-*bis*-(methoxymethoxy)-benzaldehyde dimethylacetal. The least polar band afforded 90 mg of **45a**; NMR (CCl_4): δ 3.31 (s, 6H), 3.46 (s, 3H), 3.64 (s, 3H), 5.00 (s, 2H), 5.13 (s, 2H), 5.57 (s, 1H), 7.18 (d, J = 32. Hz, 1H), 7.46 (d, J = 3.2 Hz, 1H). Acid hydrolysis afforded the known iododihydroxybenzaldehydes.[44]

Metallation of 2,5-bis-(*methoxymethoxy*)*benzaldehyde diethyl acetal* **42b**

The diethylacetal **42b** (287 mg, 0.93 mmol) was metallated with n-BuLi (0.42 mL, 2.3 M, 0.97 mmol) in petroleum ether (5 mL) at 0°. After 30 min ethylene iodochloride (0.10 mL, 1.1 mmol) in THF (2 ml) was added.

Chromatography on a silica gel preparative plate developed with 40% ether–petroleum ether afforded three bands. The most polar, 36 mg of **43b**; NMR (CCl_4): δ 1.24 (t, 6H), 3.56 (s, 3H), 3.58 (s, 3H), 3.63 (q, 4H), 5.17 (s, 2H), 5.27 (s, 2H), 5.95 (s, 1H), 7.17 (m, 2H). The intermediate band, 55 mg of **44b**; NMR (CCl_4): δ 1.21 (t, 6H), 3.56 (s, 3H), 3.60 (s, 3H), 3.61 (q, 4H), 5.20 (s, 2H), 5.29 (s, 2H), 5.73 (s, 1H), 7.37 (s, 1H), 7.62 (s, 1H). The least polar band, 120 mg of **45b**; NMR (CCl_4): δ 1.21 (t, 6H), 3.55 (s, 3H), 3.62 (q, 4H), 3.73 (s, 3H), 5.07 (s, 2H), 5.18 (s, 2H), 5.75 (s, 1H), 7.31 (d, J = 3.2 Hz, 1H), 7.55 (d, J = 3.2 Hz, 1H). Acid hydrolysis afforded the known dihydroxyiodobenzaldehydes.[44]

Metallation of 2,5-bis-(*methoxymethoxy*)*benzaldehyde* 1,3-*propanediol acetal* (**42c**)

The acetal **42c** (197 mg, 0.69 mmol) was metallated with n-BuLi (0.30 mL, 2.3 M, 0.69 mmol) in cyclohexane (6 mL) at 0°. After 20 min the mixture was treated with ethylene iodochloride (0.15 mL, 1.7 mmol) in the THF (2 mL).

Chromatography of the crude material on a silica gel preparative plate developed with 50% ether produced three bands. The most polar afforded recovered **42c** (46 mg). The intermediate band, 33 mg of **43c**; NMR: δ 1.0–1.5 (m, 1H), 1.9–2.6 (m, 1H), 3.56 (s, 6H), 3.8–4.5 (m, 4H), 5.17 (s, 2H), 5.25 (s, 2H), 6.15 (s, 1H), 7.17 (m, 2H). The least polar band produced 96 mg of a 1:2 mixture of **44c** and **45c**. The NMR spectrum of this mixture shows two acetal resonances at δ 5.78 and 5.82 with relative areas 1:2. The aromatic region has singlets at δ 7.36 and 7.63 from **44c** and doublets at δ 7.40 and 7.60 (J = 4.0 Hz) from **45c**.

Metallation of 2-(*methoxymethoxy*)*toluene* (**5**)

Metallation of **5** (162 mg, 1.07 mmol) with t-BuLi (0.71 mL, 1.5 M, 1.07 mmol) in hexane (3 mL) at 0°. After 1 hr the mixture was treated with ethylene iodochloride (0.11 mL, 1.2 mmol) in THF (1 mL). GC (170°) of the crude reaction product had only two peaks, the starting material (**5**) (t_R 1.3 min) and 3-iodo-2-(methoxymethoxy)toluene (t_R 5.2 min). These compounds were not separable on silica gel. Chromatography on an alumina preparative plate developed with 4% ether in hexane afforded a broad band from the lower half of which an analytical sample of 3-iodo-2-(methoxymethoxy)toluene, b.p. 59–60° (0.25 mm); NMR (CCl_4): δ 2.37 (s, 3H), 3.65 (s, 3H), 5.08 (s, 2H), 6.80 (t, J = 8.0 Hz, 1H), 7.25 (d, J = 8.0 Hz, 1H), 7.71 (d, J = 8.0 Hz, 1H); IR (neat): 3060, 2940, 1560, 1455, 1395, 1260, 1230, 1200, 1160, 1075, 960, 840, 770 cm^{-1}. (Found: C, 38.97; H, 3.97. Calc for $C_9H_{11}IO_2$: C, 38.87; H, 3.99.)

Metallation of 3-(*methoxymethoxy*)*pryidine* (**57**)

The pyridine **57** (166 mg, 1.2 mmol) was metallated with t-BuLi (0.95 mL, 1.1 M, 1.05 mmol) in ether (5 mL) at −78°. After 0.5 hr the mixture was treated 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 5% petroleum ether in ether. The major band (284 mg, 90%) and two more mobile bands (8 mg and 7 mg) were removed. The major band was identified as **58**, the minor bands as the products of addition of t-BuLi and **59**, respectively.

An analytical sample of **58** was prepared by sublimation at 48–50° (0.25 mm), m.p. 62.5–65°; NMR: δ 3.58 (s, 3H), 5.36 (s, 2H), 7.78 (distorted doublet, 1H), 8.00 (broad multiplet, 1H), 8.44 (broad multiplet, 1H); IR: 3080, 2900, 1550, 1475, 1410, 1390, 1295, 1150, 1090, 970, 915, 825 cm^{-1}. (Found: C, 31.58; H, 3.00; I, 48.15; N, 5.24. Calc for $C_7H_6INO_2$: C, 31.72; H, 3.04; I, 47.88, N, 5.29%).

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