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# Directed Metalation Reactions. 6.[1a] Competition of Substituents for Ortho Direction of Metalation in Substituted Anisoles

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Directed lithiation of benzenes containing the substituent groups $-NMe_2$, $-CH_2NMe_2$, $-CH_2CH_2NMe_2$, $-CONHMe$, $-OMe$, $-SO_2NMe_2$, $-SO_2NHMe$, $-CF_3$, and $-F$ are well known. This investigation summarizes metalation of a series of para-substituted anisoles whereby the competative directed metalation ability of the methoxy group vs. the eight other cited substituents was measured. Certain of the ortho and meta isomers of these compounds were also examined. In all instances a regiospecific metalation resulted such that the following ranking of directory substituents can be offered: $-SO_2NMe_2$, $-SO_2NHMe$, $-CONHMe$, $-CH_2NMe_2$ > $-OMe$ > $-CH_2CH_2NMe_2$, $-NME_2$, $-CF_3$, $-F$. In order to assess the effect of a para situated methoxy substituent upon benzyl proton acidity and benzoyl carbonyl electrophilicity, *p*-methoxy-*N,N*-dimethylbenzamide and the monomethyl derivative of *p*-methoxyphenylacetamide were treated with *n*-butyllithium. An ability of the methoxy substituent of some of these anisoles to cause exclusion of certain side reactions with *n*-butyllithium in these systems such as elimination of phenethylamines, nucleophilic substitution at the carbonyl in dimethylbenzamides, benzyne formation in fluorobenzenes, and benzylic hydrogen abstraction in phenylacetamide derivatives was discovered. Finally, an examination of the effect of tetramethylethylenediamine (TMEDA) upon the rate and orientation of metalation in the series of substituted anisoles was undertaken. Although this reagent had been found to be useful in controlling the rate and selectivity in a number of "random" metalations, its usefulness in "directed" metalation reactions had not previously been systematically explored.

The ability of certain substituents on aromatic systems to direct metalation at a position ortho to the substituent (ortho-directed metalation) has been observed[2] to be typical in a number of metalation reactions involving organolithium reagents. This phenomenon is of synthetic interest since such a procedure enables one to produce ortho disubstituted products virtually uncontaminated by meta or para isomers.

For the benzene aromatic system, the following substituent groups have been reported to direct the lithium atom to the ortho position upon metalation with *n*-butyllithium: $-NMe_2$,[3] $-CH_2NMe_2$,[4] $-CH_2CH_2NMe_2$,[5] $-OMe$,[6] $-CONHR$,[7] $-SO_2NHR$,[8] $-SO_2NR_2$,[9] $-CF_3$,[10,11] and $-F$.[12] Pertinent data concerning the metalation of these substituted benzenes[13] are presented in Table I. Since a number of biological compounds contain aromatic systems with a methoxy or hydroxy substituent along with various amine, carboxamide, and sulfonamide substituents,[14] a knowledge of the relative ortho-directing abilities of the various substituents toward metalation would be of great utility in planning the synthesis of such compounds.

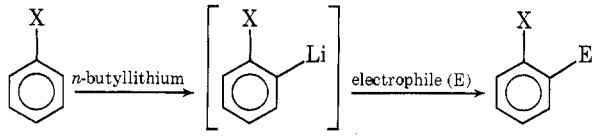
In three instances, data have appeared in the literature for para-substituted anisoles from which the relative directing ability of the methoxy group vs. a few other groups can be assessed. Klein and Hauser[15] found that metalation of *p*-methoxy-*N,N*-dimethylbenzylamine (**4**) gave exclusive 70% metalation ortho to the dimethylaminomethyl group based upon the yield of benzophenone adduct. Metalation of the corresponding meta-substituted isomer gave, exclusively, 75% metalation at the position ortho to both substituents, indicating that steric effects apparently were negligible in this case. Narasimhan and Bhide[16] later examined the metalation of *p*-, *m*-, and *o*-methoxy-*N,N*-dimethylbenzylamine (**4, 5,** and **6**) as a synthetic route to methoxy isoquinolines and found that, in agreement with the results of Hauser and co-workers, metalation of the para and meta isomers (**4** and **5**) occurred at the position ortho to the amine side chain, and at the position mutually ortho to both substituents, respectively. Metalation of the ortho isomer (**6**) led to the observation that "... the reaction took a complex course and no useful result was obtained".

Narasimhan and Bhide[16] also examined the metalation of the *o*-, *m*-, and *p*-methoxy-*N*-methylbenzamides as a possible route to methoxy isocoumarins and found that metalation of the para and meta isomers (**10** and **11**) occurred in good yields at the position ortho to the amide substituent, and at the position mutually ortho to both substituents, respectively. Once again, however, "... complications were encountered ..." with the ortho isomer.

Metalation of *p*-fluoroanisole with *n*-butyllithium[17] gave upon carbonation 2-methoxy-5-fluorobenzoic acid in 13% yield whereas metalation with methyllithium[18] gave a 17% yield of the same acid.

Although the relative directing ability of the methoxy group

Table I. Metalation of Monosubstituted Benzenes with *n*-Butyllithium




| Registry no. | X | E | *n*-BuLi/ substrate | Solvent | Metalation period, h | Temp, °C | % yield | Ref |
|---|---|---|---|---|---|---|---|---|
| 121-69-7 | $-NMe_2$ | $Ph_2CO$ | 1.0 | Hexane | 12 | 68 | 56 | 3 |
| 103-83-3 | $-CH_2NMe_2$ | $Ph_2CO$ | 2.0 | Ether/hexane | 18 | 25 | 84 | 4 |
| 1126-71-2 | $-CH_2CH_2NMe_2$ | $Ph_2CO$ | 1.2 | Ether/hexane | 11 | 25 | 7[a] | 5 |
| 100-66-3 | $-OMe$ | $CO_2$ | 1.0 | Ether/hexane | 21 | 35 | 65 | 6, 11 |
| 613-93-4 | $-CONHMe$ | $Ph_2CO$ | 2.5[b] | THF/hexane | 0.25 | 65 | 81 | 7 |
| 5183-78-8 | $-SO_2NHMe$ | $Ph_2CO$ | 2.5[b] | THF/hexane | 0.25 | 0 | 82 | 8 |
| 14417-01-7 | $-SO_2NMe_2$ | $Ph_2CO$ | 1.2 | THF/hexane | 0.25 | 0 | 82 | 9 |
| 98-08-8 | $-CF_3$ | $CO_2$ | 1.5 | Ether | 6 | 35 | 48[c] | 10 |
| 462-06-6 | $-F$ | $CO_2$ | 1.0 | THF | 7 | −50 | 60 | 12 |

[a] Apparently reaction proceeded to give mostly styrene via elimination. [b] A molar ratio of 2 butyllithium to 1 substrate needed owing to formation of dilithio intermediate. [c] Also gave approximately 8% of meta acid as product.

vs. three other directing substituents could be qualitatively determined from the literature in a limited number of cases, it appeared worthwhile to examine the entire series of eight substituents vs. the methoxy substituent and, to some extent, assess the relative importance of coordination and electronic effects on the directing ability of the various substituents. In addition, examination of the ortho and meta isomers was deemed of interest because of the potential utility of this method as a route to a series of relatively inaccessible 1,2,3-trisubstituted benzenes.

The addition of TMEDA to the reaction mixture has exerted a profound influence upon the rate of metalation of benzene[19] and toluene[20] substrates. The effect of TMEDA upon the rate and site of metalation in some systems involving a heteroatom has been noted in a preliminary communication.[21] Increased rates of ortho metalation were observed for dimethylbenzylamine, dimethylaniline, and anisole. In addition the site of metalation for *p*-methoxy-*N,N*-dimethylbenzylamine was altered from the usual site ortho to the amine side chain to the site ortho to the methoxy substituent by the addition of 1 equiv of TMEDA to the metalation reaction mixture.

A method for controlling the site of metalation at either the 2 or 8 position of 1-methoxynaphthalene by use of *n*-butyllithium/TMEDA has recently been described.[22] It was found that metalation of 1-methoxynaphthalene with *n*-butyllithium in ether/hexane gave upon carbonation a 28% yield of carboxylic acid products consisting of 73% 2 metalation and 27% 8 metalation. Under the same reaction conditions except that 1 equiv of TMEDA was present a product composition of 99.3% 2 metalation and 0.3% 8 metalation was obtained. The yield of 1-methoxy-2-naphthalenecarboxylic acid was increased to 60%. Similarly, increased rate as well as increased selectivity has been noted[23a] upon using *n*-butyllithium/TMEDA in the metalation of *o*- and *p*-*N,N*-dimethyltoluidines.

We would now like to report a comprehensive study of the ortho-directing ability of the methoxy substituent relative to other ortho-directing substituents in metalation reactions with *n*-butyllithium. Also discussed is the effect of TMEDA on the rate and course of the directed metalation reaction.

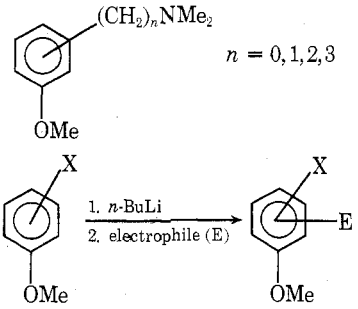
## Results and Discussion

Since there are eight ortho-directing groups besides the methoxy group ($-NMe_2$, $-CH_2NMe_2$, $-CH_2CH_2NMe_2$, $-CONHR$, $SO_2NHR$, $SO_2NR_2$, $-CF_3$, and $-F$) a simple calculation shows that 24 substituted anisoles exist if all para, meta, and ortho isomers are considered. However, certain of the meta and ortho compounds were accessible only through rather complicated synthetic routes and in most of these cases it was felt that examination of these compounds would lend little to the study. In all, 16 of the isomers including all the para isomers and representative meta and ortho compounds were prepared: *p*-, *m*-, and *o*-methoxy-*N,N*-dimethylaniline (**1, 2,** and **3,** respectively), *p*-, *m*-, and *o*-methoxy-*N,N*-dimethylbenzylamine (**4, 5,** and **6,** respectively), *p*- and *o*-methoxy-*N,N*-dimethylphenethylamine (**7** and **8,** respectively), *p*-, *m*-, and *o*-methoxy-*N*-methylbenzamide (**10, 11,** and **12,** respectively), *p*-methoxy-*N*-methylbenzenesulfonamide (**15**), *p*-methoxy-*N,N*-dimethylbenzenesulfonamide (**16**), *p*-methoxybenzotrifluoride (**17**), and *p*- and *o*-fluoroanisole (**18** and **19,** respectively). These compounds were obtained by either the synthetic procedure or from the commercial source given in the Experimental Section. In addition 3-(*p*-methoxyphenyl)-*N,N*-dimethylpropylamine (**9**), *p*-methoxy-*N,N*-dimethylbenzamide (**13**), and *p*-methoxyphenyl-*N*-methylacetamide (**14**) were prepared. All compounds were metalated with *n*-butyllithium using 1 equiv of *n*-butyllithium except for the methoxy-*N*-methylbenzamides (**10, 11, 12**), *p*-methoxy-*N*-methylbenzenesulfonamide (**15**), and phenylacetamide (**14**). In these systems 2 equiv of *n*-butyllithium was used, since the first equivalent was completely consumed in the abstraction of the amide proton. When conditions favoring metalation ortho to group one and those conditions favoring metalation ortho to group two of the disubstituted benzene were considerably different, the disubstituted benzene was metalated under both sets of conditions. However, as indicated in Tables II–IV, no appreciable change in orientation was brought about by this particular variance in the reaction conditions.

An examination of the effect of tetramethylethylenediamine upon the metalation reaction was accomplished by the addition of 1 equiv (with respect to the molar quantity of *n*-butyllithium or substrate) of this reagent to the reaction mixture. The *n*-butyllithium/TMEDA complex was first formed by dissolving TMEDA in the solvent and treating with *n*-butyllithium. Metalation was accomplished by adding the substrate to the *n*-butyllithium/TMEDA complex solution. In the equations which follow, yields in parentheses are those using TMEDA.[23b]

**Aminoanisoles [Substituents $(CH_2)_nNMe_2$, $n$ = 0, 1, 2, 3].** $-NMe_2$. Metalation of *N,N*-dimethyl-*p*-anisidine (1) with *n*-butyllithium indicated that metalation proceeded in 71% yield at the position ortho to the methoxy group, judging from the condensation product with benzophenone. The site of metalation was determined by NMR analysis of the $D_2O$ hydrolysis product. Although the NMR spectrum of anisidine 1 did not exhibit an AA'BB' spectrum for the aromatic pro-

Table II. Metalation Data for Aminoanisoles (1–9)



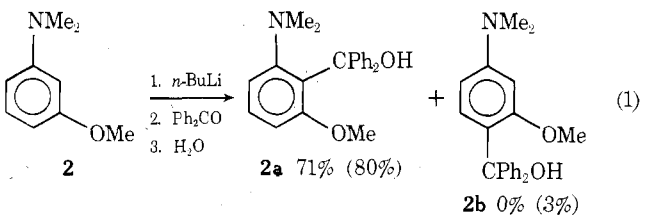

| Compd | X | Metalation conditions | | | Electrophile | % product ortho to | |
|---|---|---|---|---|---|---|---|
| | | Agent[a] | Time, h | Temp, °C | | Methoxy | X substituent |
| 1 | p-$NMe_2$ | A | 12 | 35 | $Ph_2CO$ | 71 | |
| 1 | p-$NMe_2$ | A | 12 | 35 | $D_2O$ | 85 | |
| 1 | p-$NMe_2$ | A | 21 | 35 | $D_2O$ | 85 | |
| 1 | p-$NMe_2$ | B | 0.25 | 35 | $D_2O$ | 22 | |
| 1 | p-$NMe_2$ | B | 5 | 35 | $D_2O$ | 45 | |
| 1 | p-$NMe_2$ | B | 12 | 35 | $D_2O$ | 78 | |
| 2 | m-$NMe_2$ | A | 12 | 35 | $Ph_2CO$ | 71[b] | |
| 2 | m-$NMe_2$ | B | 12 | 35 | $Ph_2CO$ | 80[b] | 3[c] |
| 3 | o-$NMe_2$ | A | 12 | 35 | $Ph_2CO$ | 56 | |
| 3 | o-$NMe_2$ | B | 12 | 35 | $Ph_2CO$ | 49 | |
| 4 | p-$CH_2NMe_2$ | A | 24 | 27 | $Ph_2CO$ | | 80 |
| 4 | p-$CH_2NMe_2$ | A | 24 | 27 | $D_2O$ | | 70 |
| 4 | p-$CH_2NMe_2$ | B | 2 | 27 | $Ph_2CO$ | 55 | 7 |
| 4 | p-$CH_2NMe_2$ | B | 5 | 27 | $D_2O$ | 48 | 18 |
| 4 | p-$CH_2NMe_2$ | B | 0.25 | 27 | $D_2O$ | 37 | 18 |
| 4 | p-$CH_2NMe_2$ | B | 24 | 27 | $D_2O$ | 16 | 5 |
| 5 | m-$CH_2NMe_2$ | A | 2 | 27 | $Ph_2CO$ | 79[b] | |
| 5 | m-$CH_2NMe_2$ | B | 0.5 | 27 | $Ph_2CO$ | 62[b] | |
| 5 | m-$CH_2NMe_2$ | B | 5 | 27 | $Ph_2CO$ | 54[b] | |
| 6 | o-$CH_2NMe_2$ | A | 24 | 27 | $Ph_2CO$ | 30–35 | 4–10[c] |
| 6 | o-$CH_2NMe_2$ | A | 2 | 27 | $Ph_2CO$ | 58 | <5[c] |
| 6 | o-$CH_2NMe_2$ | B | 5 | 27 | $Ph_2CO$ | 38 | 8[c] |
| 7 | p-$CH_2CH_2NMe_2$ | A | 32 | 27 | $Ph_2CO$ | 60 | |
| 7 | p-$CH_2CH_2NMe_2$ | A | 28 | 27 | $D_2O$ | 72 | |
| 7 | p-$CH_2CH_2NMe_2$ | B | 2 | 27 | $D_2O$ | 55 | |
| 7 | p-$CH_2CH_2NMe_2$ | B | 24 | 27 | $D_2O$ | 23 | |
| 8 | o-$CH_2CH_2NMe_2$ | A | 28 | 27 | $Ph_2CO$ | *d* | |
| 8 | o-$CH_2CH_2NMe_2$ | A | 2 | 27 | $Ph_2CO$ | *d* | |
| 8 | o-$CH_2CH_2NMe_2$ | B | 4 | 27 | $Ph_2CO$ | *d* | |
| 9 | p-$CH_2CH_2CH_2NMe_2$ | A | 24 | 27 | $Ph_2CO$ | 71 | |
| 9 | p-$CH_2CH_2CH_2NMe_2$ | A | 2 | 27 | $D_2O$ | 26 | |
| 9 | p-$CH_2CH_2CH_2NMe_2$ | A | 24 | 27 | $D_2O$ | 70 | |
| 9 | p-$CH_2CH_2CH_2NMe_2$ | B | 0.25 | 27 | $D_2O$ | 56 | |
| 9 | p-$CH_2CH_2CH_2NMe_2$ | B | 5 | 27 | $D_2O$ | 64 | |

[a] Metalation agents: A, 1.0 equiv *n*-BuLi/equiv substrate; ether–hexane solvent; B, 1.0 equiv *n*-BuLi + 1.0 equiv TMEDA/equiv substrate; ether–hexane solvent. [b] Metalation occurred at position between two substituents. [c] These yields determined by NMR data; product not isolated. [d] Compound **6** apparently underwent elimination to give *o*-methoxystyrene.

tons, the quaternary methiodide salt of *p*-anisidine showed such a spectrum in the $\tau$ 2.50 region. Hydrolysis of the lithio intermediate of *N,N*-dimethyl-*p*-anisidine (**1**) with $D_2O$ and subsequent treatment with methyl iodide gave a deuterated methiodide of compound **1** having 2.00 protons downfield and 1.15 protons in the upfield portion of the AA'BB' system. The downfield portion of the spectrum was assigned to the protons ortho to the quaternary amine substituent due to its deshielding effect. This result corresponded to an 85% yield of metalation at the position ortho to the methoxy substituent.

The addition of TMEDA to the metalation mixture had no effect upon the site of metalation and very little effect upon the yield of ortho metalation as yields of 22, 45, and 78% metalation ortho to the methoxy substituent were realized after metalation periods of 0.25, 5, and 12 h, respectively. These yields were determined by the extent of NMR signal attenuation after deuterolysis of the lithio intermediate as described above. Products resulting from metalation at the position ortho to the dimethylamine substituent were not detected in any of the experiments performed.

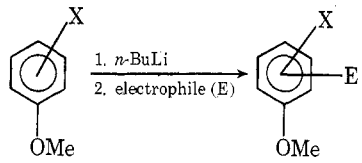
Metalation of *N,N*-dimethyl-*m*-anisidine (**2**) gave the anticipated result of metalation at the site mutually ortho to both substituents (eq 1). Condensation of the lithio intermediate of anisidine **2** with benzophenone gave as the sole product a 71% yield of 2-diphenylhydroxymethyl-*N,N*-dimethyl-*m*-anisidine (**2a**).



(1)

Determination of the orientation of substituents in benzophenone condensation products such as **2a** resulting from

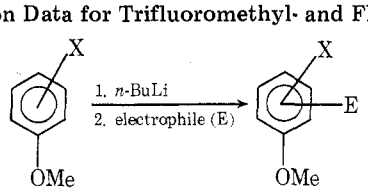
Table III. Metalation Data for Carboxamidoanisoles (10–14) and Sulfonamidoanisoles (15, 16)




| Compd | Substituent X | Metalation conditions | | | Electrophile | % product ortho to X substituent |
|---|---|---|---|---|---|---|
| | | Agent[a] | Time, h | Temp, °C | | |
| 10 | *p*-CONHMe | A | 0.25 | 65 | $Ph_2CO$ | 47 |
| 10 | *p*-CONHMe | A | 0.25 | 65 | $D_2O$ | 40 |
| 10 | *p*-CONHMe | A | 24 | 65 | $D_2O$ | 50 |
| 10 | *p*-CONHMe | B | 5 | 65 | $D_2O$ | 60 |
| 11 | *m*-CONHMe | A | 0.25 | 65 | $Ph_2CO$ | 48[b] |
| 11 | *m*-CONHMe | B | 1 | 65 | $Ph_2CO$ | 65[b] |
| 12 | *o*-CONHMe | A | 5 | 65 | $Ph_2CO$ | 46 |
| 12 | *o*-CONHMe | B | 0.25 | 65 | $Ph_2CO$ | 23 |
| 12 | *o*-CONHMe | B | 1 | 65 | $Ph_2CO$ | 53 |
| 13 | *p*-$CONMe_2$ | C | 0.25 | 35 | $Ph_2CO$ | *c* |
| 14 | *p*-$CH_2CONHMe$ | A | 0.5 | 27 | $D_2O$ | *d* |
| 14 | *p*-$CH_2CONHMe$ | A | 24 | 27 | $D_2O$ | *d* |
| 15 | *p*-$SO_2NHMe$ | A | 0.5 | 0–5 | $Ph_2CO$ | 77 |
| 15 | *p*-$SO_2NHMe$ | A | 0.5 | 0–5 | $D_2O$ | 80 |
| 15 | *p*-$SO_2NHMe$ | B[e] | 0.5 | 0–5 | $Ph_2CO$ | 50 |
| 15 | *p*-$SO_2NHMe$ | B[e] | 0.5 | 0–5 | $D_2O$ | 65 |
| 16 | *p*-$SO_2NMe_2$ | D | 0.5 | 0–5 | $Ph_2CO$ | 62 |
| 16 | *p*-$SO_2NMe_2$ | D | 0.5 | 0–5 | $D_2O$ | 74 |
| 16 | *p*-$SO_2NMe_2$ | E | 1.0 | 27 | $D_2O$ | *f* |

[a] Metalation agents: A, 2.0 equiv *n*-BuLi/equiv substrate, since first equivalent of base required to abstract amide proton; THF–hexane solvent; B, 2.0 equiv *n*-BuLi + 2.0 equiv TMEDA/equiv substrate; THF–hexane solvent; C, 1.0 equiv *n*-BuLi/equiv substrate; ether–hexane solvent; D, 1.0 equiv *n*-BuLi/equiv substrate; THF–hexane solvent; E, 1.0 equiv *n*-BuLi + 1.0 equiv TMEDA/equiv substrate; ether–hexane solvent. [b] Metalation occurred at position between two substituents and product isolated was the lactone which obviously arose from the appropriate ortho carbinolamide. [c] Compound 13 apparently underwent nucleophilic displacement of amide carbonyl to give 78% yield of *p*-methoxyvalerophenone. No ring metalation products were detected. [d] Compound 14 gave metalation exclusively at the benzyl and amide position. No ring metalation was detected. [e] Solvent employed for metalation using TMEDA was ether–hexane rather than THF–hexane. Metalations using TMEDA in THF–hexane gave no metalated products. [f] Under these conditions compound 16 apparently underwent nucleophilic attack at the sulfonamide linkage. No ring metalation products were detected.

Table IV. Metalation Data for Trifluoromethyl- and Fluoroanisoles (17–19)



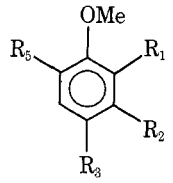

| Compd | Substituent X | Metalation conditions | | | Electrophile | % product ortho to methoxy |
|---|---|---|---|---|---|---|
| | | Agent[a] | Time, h | Temp, °C | | |
| 17 | *p*-$CF_3$ | A | 6 | 35 | $Ph_2CO$ | 79 |
| 17 | *p*-$CF_3$ | A | 6 | 35 | $D_2O$ | 92 |
| 17 | *p*-$CF_3$ | A | 21 | 35 | $D_2O$ | 90 |
| 17 | *p*-$CF_3$ | B | 4 | 35 | $D_2O$ | 90 |
| 18 | *p*-F | A | 7 | −50 | $CO_2$ | *b* |
| 18 | *p*-F | C | 5 | 27 | $CO_2$ | 32 |
| 18 | *p*-F | B | 5 | 27 | $CO_2$ | *c* |
| 19 | *o*-F | C | 5 | 27 | $CO_2$ | *d* |
| 19 | *o*-F | B | 2 | 27 | $CO_2$ | *e* |

[a] Metalation agents: A, 1.0 equiv *n*-BuLi/equiv substrate; ether–hexane solvent; B, 1.0 equiv *n*-BuLi + 1.0 equiv TMEDA/equiv substrate; ether–hexane solvent; C, 1.0 equiv *n*-BuLi/equiv substrate; THF–hexane solvent. [b] Only starting fluoroanisole was recovered. No metalation products were observed. [c] No metalation products were obtained. Reaction product carried phenolic odor. [d] Base-soluble material contained 36% yield of *o*-fluorophenol apparently via nucleophilic attack at the methoxy group. Starting fluoroanisole recovered in 32% yield. [e] Base-soluble material contained 27% yield of *o*-fluorophenol. Starting fluoroanisole recovered in 44% yield.

directed lithiation of the various anisoles was based largely on anisotropic effects exerted by the diphenylcarbinol substituent upon the protons of ortho-situated substituents.[24] An upfield shift of at least 10 Hz was deemed sufficient to identify the substituent(s) ortho to the diphenylcarbinol moiety (Table V).

Metalation of anisidine **2** using *n*-butyllithium/TMEDA followed by condensation with benzophenone produced a crude product which appeared to be a mixture of two isomers in a ratio of approximately 20:1. The NMR absorptions of the more abundant isomer were identical with those of the 1,2,3-oriented carbinolamine **2a**. Based on data recorded in

Table V. Proton Anisotropic Shifts (Relative to Monosubstituted Anisole) Due to Introduction of Diphenylcarbinol Substituent. Metalation Site Determination[a]



| Compd | Proton anisotropic shifts for –OMe | –$NMe_2$ | $CH_2NMe_2$[b] | Inferred position of $–CPh_2OH$ |
|---|---|---|---|---|
| 2a | +28.5 | +22.0 ($R_2$) | | $R_1$ |
| 2b | 0 | +35.0 ($R_2$) | | $R_5$ |
| 3a | +34.0 | +13.5 ($R_1$) | | $R_5$ |
| 4a | +8.5 | | +24.5 ($R_3$) | $R_2$ |
| 4b | +14.0 | | +7.5 ($R_3$) | $R_1$ |
| 6a | +39.0 | | +1.0 ($R_1$) | $R_5$ |
| 6b | +9.0 | | +14.5 ($R_1$) | $R_2$ |

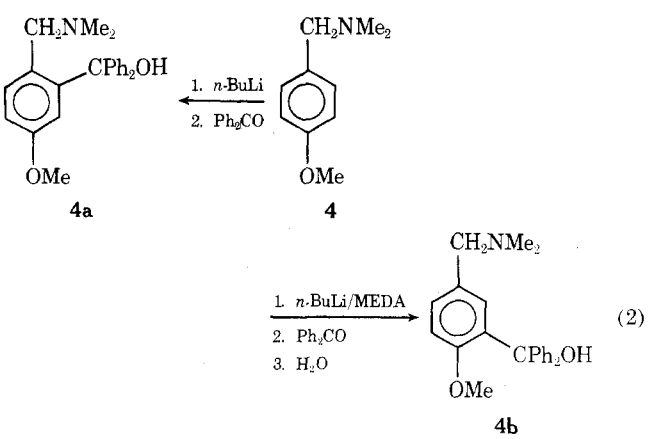
[a] All spectra obtained in $CDCl_3$; for a further explanation of this technique see ref 24. [b] Anisotropic shifts reported for methylene protons.

Table V isomer **2b** was identified as the 1,3,4 isomer. The products **2a** and **2b** were obtained in 80 and 3% yields, respectively.

Metalation of *N,N*-dimethyl-*o*-anisidine (**3**) with *n*-butyllithium followed by condensation with benzophenone gave a crude product which was shown by its NMR spectrum to contain only one of two possible isomers. The product, obtained in 56% yield, was identified as 3-diphenylhydroxymethyl-*N,N*-dimethyl-*o*-anisidine (**3a**) on the basis of its NMR data (Table V).

Metalation of anisidine **3** using *n*-butyllithium/TMEDA produced a crude product after condensation with benzophenone that was shown by NMR analysis to contain only isomer **3a.** The use of TMEDA did not appear to have any significant effect upon the yield of **3a** as 49% of this product was obtained.

**–$CH_2NMe_2$.** Results from the metalation of *p*-methoxy-*N,N*-dimethylbenzylamine (**4**) indicated agreement with previous work[15,16] in that good yields of metalation exclusively at the position ortho to the amine side chain were obtained. Condensation of the lithio intermediate with benzophenone afforded an 80% yield of the benzophenone adduct (**4a**) (eq 2). The site of metalation in compound **4** has been verified in this study by application of our anisotropy technique (Table V)[24] and by hydrolyzing the lithio intermediate with $D_2O$ followed by analysis of the NMR spectrum of the deuterated product. The NMR spectrum of amine **4** gave a well-resolved




AA′BB′ system in the $\tau$ 3.0 region for which the upfield proton signal was assigned to the protons ortho to the methoxy group. These assignments were based on a comparison with the NMR spectrum of *p*-methylanisole in which the upfield signal was assigned[25] to the protons ortho to the methoxy group. The deuterated product obtained via metalation of amine **4** followed by hydrolysis with $D_2O$ showed attenuation of the downfield proton signal and broadening of the upfield signal indicating deuterium incorporation ortho to the amine side chain. Integration of relative signal intensities indicated deuterium incorporation of about 70% of one deuterium.

In addition to the above results it was discovered that the site of ring metalation in *p*-methoxy-*N,N*-dimethylbenzylamine (**4**) can actually be reversed through the use of tetramethylethylenediamine (TMEDA). Metalation of amine **4** for 5 h with the addition of 1 equiv of TMEDA gave 55% metalation at the position ortho to the methoxy group based on NMR integration of the $D_2O$ hydrolysis product. A small amount of deuterium incorporation at the position ortho to the amine side chain was also indicated.

Metalation of amine **4** with the *n*-butyllithium/TMEDA complex for 2 h followed by condensation with benzophenone gave products **4b** and **4a** in 55 and 7% yields, respectively (eq 2). This preferential metalation ortho to the methoxy group in the presence of TMEDA may reflect some manifestation of lower order coordination in this system when compared to *n*-butyllithium/ether or it simply may reflect metalation at the most acidic site of the substrate.

Identification of isomer **4b** was based upon spectral and analytical data. The NMR data shown in Table XI (see paragraph at end of paper regarding supplementary material) indicated that the diphenylcarbinol substituent was situated at a ring position different than that of isomer **4a.** The relative integration of the $–OCH_3$ and $–CH_2–$ protons of **4a** and **4b** were identical, indicating that metalation had not occurred at these positions. The anisotropic data shown in Table V were consistent with a compound having the diphenylcarbinol substituent situated at the position ortho to the methoxy substituent.

Results obtained in the metalation of *m*-methoxy-*N,N*-dimethylbenzylamine (**5**) likewise indicated agreement with previous work[15,16] in that good yields of metalation exclusively at the position mutually ortho to both the methoxy and the amine side chain were obtained. Condensation of the lithio intermediate with benzophenone gave the corresponding, 1,2,3-trisubstituted benzene product (**5a**) in 79% yield. This result indicated that the transition state involved in stabilizing metalation at the position ortho to the dimethylaminomethyl side chain apparently was not sterically hindered by the presence of the methoxy group. In fact the methoxy group apparently contributed to the stability of the intermediate to some extent; otherwise metalation would have proceeded at the position ortho to the amine side chain but para to the methoxy group. This result was somewhat surprising in view of a previous examination of the steric and conformational aspects of alkyl aryl ether metalations[26] which had indicated that an increase in the steric bulk of the alkyl group resulted in a decrease in the overall rate of metalation.

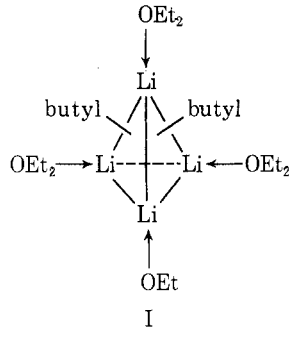
As recorded in Table II, metalation of amine **5** in the presence of TMEDA had no effect upon the site of metalation. Apparently the combined ortho-directing effects of 2 coordination by the dimethylaminomethyl substituent and inductive electron withdrawal by the methoxy substituent served to stabilize metalation at the position mutually ortho to both substituents to such an extent that an orientation reversal was not observed when the reaction was carried out in the presence of TMEDA.

Previous attempts to metalate *o*-methoxy-*N,N*-dimethylbenzylamine (**6**) were reported to be unsuccessful.[16]

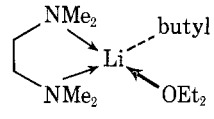
In this study amine **6** was observed to undergo metalation in good yield, primarily at the position ortho to the methoxy group, although small amounts of metalation were observed at the position ortho to the dimethylaminomethyl substituent (Table II).

Metalation of amine **6** for 24 h and condensation of the lithio intermediate with benzophenone gave a 30–35% yield of 3-diphenylhydroxymethyl-2-methoxy-*N,N*-dimethylbenzylamine (**6a**) and a 4–10% yield of another isomer, presumably the corresponding 6 isomer **6b**. Isomer **6b** was not separated and characterized but was noted in the NMR spectrum of the reaction product; its structure is inferred from the data in Table V. Metalation of amine **6** for a period of 2 h gave 58% of **6a** and 5% of **6b**.

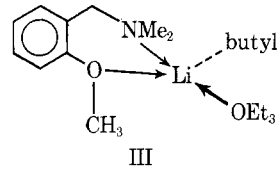
It is interesting to speculate as to the cause of domination of the methoxy group over the dimethylaminomethyl substituent in its ability to direct ortho metalation in amine **6**. It has been suggested that *n*-butyllithium in ether exists as a tetramer[27] as in structure I (*n*-butyl chains are also bonded




I




II




III

to the away faces of the pyramid). *n*-Butyllithium in an ether solution of TMEDA exists as a 1:1 complex that is monomeric,[2b] perhaps similar to structure II. Amine **6** is also capable of forming a 1:1 bidentate complex with *n*-butyllithium as illustrated in structure III. Models show that the O–N distance in amine **6** is essentially identical with the N–N distance in TMEDA. Para and meta amines **4** and **5** were incapable of such bidentate coordination; thus tetrameric *n*-butyllithium apparently effected metalation ortho to the dimethylaminomethyl substituent. Metalation of amines **4** and **5** by monomeric *n*-butyllithium generated in the presence of bidentate TMEDA occurred ortho to the methoxy group. In the case of methoxyamine **6** the possibility exists of the formation of monomeric *n*-butyllithium via complexation by the bidentate methoxyamine (III). As a result, metalation with or without TMEDA was observed to occur ortho to the methoxy group, the predicted site for metalation by monomeric *n*-butyllithium. This more basic, lower order coordinated metalating reagent may simply effect metalation at the most acidic site in the molecule, presumably in each case that ortho to the methoxy group.

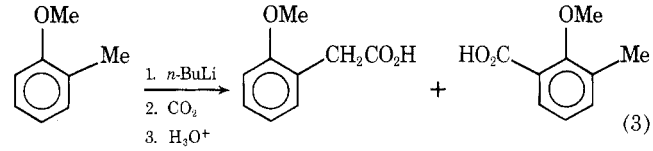
The identification of amine **6a** was determined from a number of observations. The benzophenone condensation product exhibited an NMR spectrum for which data shown in Table V are consistent with the situation of the diphenylcarbinol substituent ortho to the methoxy group. An ir spectrum of the benzophenone condensation product of the lithio intermediate of amine **6** exhibited a sharp O–H stretching frequency indicative of a "free" hydroxyl group experiencing little hydrogen bonding. If the diphenylcarbinol substituent had been situated ortho to the dimethylaminomethyl group an ideal intramolecular hydrogen bonding situation would exist and a broad hydroxyl absorption should have been observed.

The methiodide salt of carbinolamine **6a** was formed and subjected to a temperature of 200 °C. Under these conditions the methiodide salts of corresponding isomers **4a** and **5a** cyclized to give the cyclic ethers.[15] The methiodide salt of carbinolamine **6a** gave no detectable cyclic ether under these conditions suggesting metalation at a site other than that ortho to the dimethylaminomethyl group.

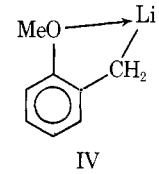
**$-CH_2CH_2NMe_2$.** The dimethylaminoethyl substituent has recently been demonstrated to be a good ortho-directing substituent as excellent yields of 2 metalation in *N,N*-dimethylaminoethylferrocene were obtained.[28] The benzene analogue, *N,N*-dimethyl-β-phenethylamine, has been shown[5] to give small amounts of ortho metalation but the primary course of reaction with *n*-butyllithium was the elimination of the elements of dimethylamine to give a styrene residue. Apparently the acidity of the benzyl proton was sufficiently greater than that of the ortho proton that metalation occurred at the benzyl site to give a lithio intermediate capable of facile elimination of the dimethylamide anion.

It was hypothesized that a methoxy group situated at the para position of *N,N*-dimethylphenethylamine might sufficiently decrease the acidity of the benzyl proton to permit ortho metalation to compete effectively with the elimination reaction. Metalation of *p*-methoxy-*N,N*-dimethylphenethylamine (**7**) with *n*-butyllithium in ether-hexane for 32 h gave 60% metalation exclusively ortho to the *methoxy* group, judging from the benzophenone condensation product. Hydrolysis of the metalation mixture with $D_2O$ gave recovered amine **7** having 1.28 protons remaining (72% metalation) at the position ortho to the methoxy substituent. The NMR spectrum of amine **7** gave a well-resolved AA'BB' system in the $\tau$ 3.1 region. In accord with the proton assignments of *p*-methylanisole,[25] which gives a similar AA'BB' system, the upfield proton resonance was assigned to the protons situated ortho to the methoxy substituent. This metalation result was of interest because it reflected the superior ability of the dimethylaminomethyl substituent over the dimethylaminoethyl substituent to direct metalation to the ortho position. No vinyl products were found, a situation which was also true for *N,N*-dimethylaminoethylferrocene.[28]

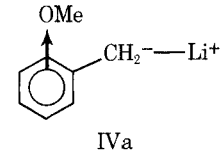
Earlier results had indicated that the methoxy substituent situated at the para position on a benzene ring played an important role in decreasing the acidity of benzyl protons to such an extent that ring metalation could be effected. Results from the metalation of *o*-methylanisole[29] indicated that an ortho-situated methoxy group may have an entirely different effect upon benzyl anion formation (eq 3). Metalation of *o*-methylanisole followed by carbonation reportedly gave equal amounts (although in low yield) of side-chain and ring metalated products. Although the authors did not elaborate upon the reasons for stabilization of the benzyl anion, it seemed plausible to consider stabilization via a five-membered coordinate ring as shown in structure IV. Stabilization simply by inductive electron withdrawal by oxygen (structure IVa) could also stabilize the benzyl anion.




(3)



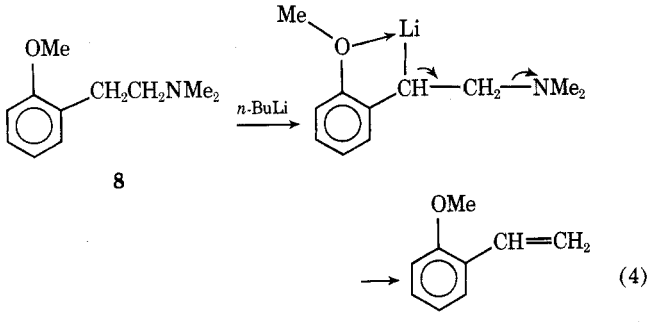

IV




IVa

Attempts to metalate *o*-methoxy-*N,N*-dimethylphenethylamine (**8**) gave no detectable ortho-metalation product. Compound **8** apparently underwent elimination to give a methoxystyrene residue as evidenced by ir data (band at 6.2

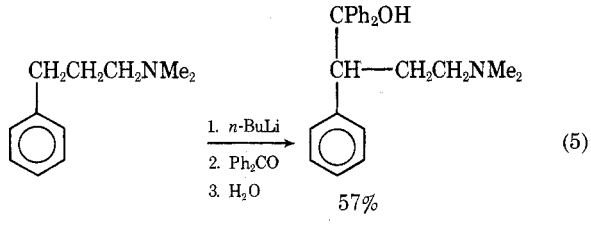
$\mu$) and NMR data (absence of $-NMe_2$ methyls and presence of vinyl proton absorptions). Presumably the *o*-methoxy substituent facilitated formation of the benzyl anion intermediate which could easily collapse to olefin with elimination of the dimethylamide anion (eq 4). Metalation of amine **8** with



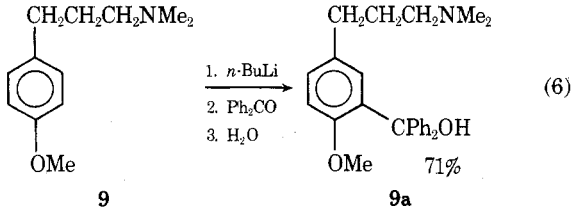

**8** (4)

*n*-butyllithium/TMEDA likewise gave no ortho metalation, judging from the absence of any diphenylcarbinol product after treatment of the reaction mixture with benzophenone.

**$-CH_2CH_2CH_2NMe$.** The role of the methoxy group in decreasing the acidity of benzyl protons was further illustrated in the case of 3-(*p*-methoxyphenyl)-*N,N*-dimethylpropylamine. Metalation of 3-phenyl-*N,N*-dimethylpropylamine and condensation of the lithio intermediate with benzophenone has been reported to give the metalation product resulting from metalation exclusively at the benzyl position[30] (eq 5).




(5)

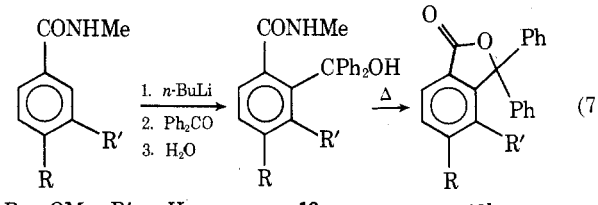



**9** **9a** (6)

Metalation of 3-(*p*-methoxyphenyl)-*N,N*-dimethylpropylamine (**9**) followed by condensation with benzophenone gave a 71% yield of carbinolamine **9a** having the diphenylcarbinol substituent situated on the ring ortho to the methoxy group (eq 6). No other isomeric products were detected. Proof of structure for the benzophenone condensation product **9a** was based on NMR and analytical data recorded in Tables X and XI (see paragraph at end of paper regarding supplementary material). The site of metalation was determined by hydrolysis of the metalation mixture with $D_2O$ and analysis of the AA'BB' system as was done previously for amines **4** and **7**.

The use of TMEDA appeared to have no effect upon the orientation of metalation for phenethylamine **7** and phenylpropylamine **9**. As shown in Table II a significant increase in the rate of metalation of these amines was observed although extended metalation periods using TMEDA actually tended to decrease the yield of metalation of amine **1**. Optimum periods for metalation of amines of this type with TMEDA appeared to be 2–4 h.

**Amide Anisoles (Substituents $-CONHMe$, $-CONMe_2$, $-CH_2CONHMe$). $-CONHMe$.** Results from the metalation of *p*-methoxy-*N*-methylbenzamide (**10**) indicated partial agreement with previous work,[16] in that metalation was found to proceed in good yield exclusively at the position ortho to the carboxamide substituent. Under the experimental conditions employed (*n*-butyllithium in refluxing ether followed by condensation with benzophenone at room temperature) the carbinolamide **10a** (mp 198 °C dec to expel a basic gas) was isolated as the sole product in 47% yield. Earlier reports[16] identified the corresponding lactone **10b** as the reaction product. However, upon heating carbinolamide **10a** near 200 °C essentially quantitative conversion to the lactone **10b** was observed (eq 7).




**10**, R = OMe; R′ = H **10a** **10b** (7)
**11**, R = H; R′ = OMe **11a** **11b**

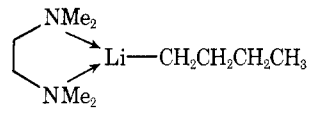
The ring proton NMR spectrum of amide **10** exhibited a well-resolved AA'BB' spectrum in which the upfield resonance was assigned to the protons ortho to the methoxy group. The data for $D_2O$ incorporation listed in Table III were obtained from the NMR integration of the $D_2O$ hydrolysis products. Metalation of amide **10** using *n*-butyllithium/TMEDA produced a slight increase in the amount of metalation ortho to the carboxamide substituent (60% metalation after 5 h).

Reexamination of the metalation of *m*-methoxy-*N*-methylbenzamide (**11**) indicated agreement with a previous study[16] in that a good yield of metalation exclusively at the position mutually ortho to both substituents was observed. Condensation of the lithio intermediate of amide **11** with benzophenone afforded the corresponding lactone **11b** (48% yield) which, in view of the result for amide **10**, certainly arose from the corresponding carbinolamide **11a**. None of the isomeric carbinolamide resulting from metalation at either of the other two possible metalation sites was observed.

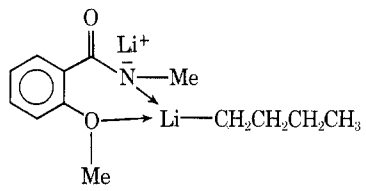
It is interesting to note that although identical conditions were employed for both amides **10** and **11**, amide **10** gave the carbinolamide product **10a** while amide **11** gave the lactone product (**11b**). The difference in product appears to be another manifestation of the effect of a para-situated methoxy group. Apparently, the resonance effects of the methoxy group situated para to the carboxamide substituent decreased the electrophilicity of the carbonyl group and therefore discouraged cyclization which would have involved nucleophilic substitution at the carbonyl. The methoxy substituent situated meta to the carbonyl could not donate deactivating negative charge to the carbonyl and therefore cyclization via nucleophilic substitution occurred at room temperature.

Metalation of amide **11** with *n*-butyllithium/TMEDA resulted in a substantial increase in yield of metalation as a 65% yield of lactone **11b** was obtained. No isomeric products resulting from metalation at either of the two possible metalation sites were observed.

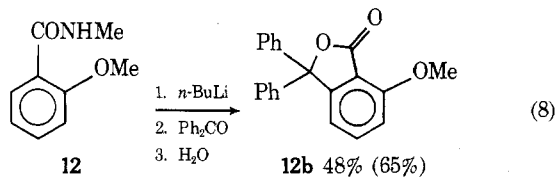
It was reported in an earlier study[16] that metalation of *o*-methoxy-*N*-methylbenzamide (**12**) gave extremely poor yields of metalation ortho to the carboxamide substituent. Although the authors did not indicate the solvent employed for this experiment, it was presumed that THF was used since the metalation of *N*-methylbenzamide was carried out in THF. Our attempts to metalate amide **12** in THF met with no success. However, attempts to metalate amide **12** in ether gave a fair yield (46% lactone **12b**) which certainly arose via metalation ortho to the carboxamide substituent (eq 8). Metalation of amide **12** using *n*-butyllithium/TMEDA gave a slight increase in yield (53%) of the lactone product **12b**.



V



VI



12 12b 48% (65%) (8)

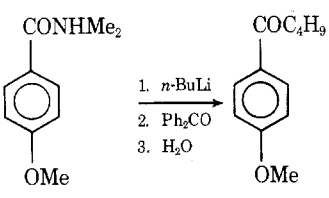
The fact that metalation of amide **12** proceeded only in ether solvent, whereas that of isomeric amides **10** and **11** proceeded in both ether and THF, would prompt one to speculate that the ortho situation of the methoxy and carboxamide substituents may have been responsible for this phenomenon. In the case of *o*-methoxy-*N,N*-dimethylbenzylamine (**6**) it was proposed that a complex could be formed with *n*-butyllithium in a manner similar to that with TMEDA and therefore monomeric *n*-butyllithium was responsible for the observed metalation ortho to the methoxy substituent.

Rausch and Ciappenelli have shown[31] that attempts to effect metalation using TMEDA in THF have been unsuccessful. Although THF often enhances the yield of metalation as compared to ether solvent, certain organolithium reagents are reportedly[32] relatively unstable in the presence of THF.

Perhaps complexation of the type shown by structure VI is responsible for generation of monomeric butyllithium in these solvent systems, as is the case when *n*-butyllithium is complexed with TMEDA (structure V). Since metalation in THF by monomeric butyllithium complexed with TMEDA is known to be unsuccessful, failure of metalation attempts in THF using monomeric butyllithium generated by complexation with amide **12** might be anticipated.

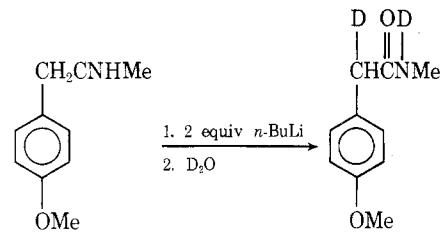
**–CONMe$_2$ and –CH$_2$CONHMe.** The electron-donating effects of the methoxy substituent situated at the para position of certain substituted benzenes was shown earlier in this study to decrease the acidity of benzyl protons and decrease the electrophilicity of the carbonyl group. These results prompted an examination of the metalation of *p*-methoxy-*N,N*-dimethylbenzamide (**13**) and *p*-methoxyphenyl-*N*-methylacetamide (**14**).

*N,N*-Dimethylbenzamide had been shown[7] to undergo substitution with *n*-butyllithium to form valerophenone. It was anticipated that the *p*-methoxy substituent would decrease the electrophilicity of the carbonyl sufficiently to allow the directed ring metalation as an alternative course of reaction. However, excellent yields of *p*-methoxyvalerophenone were obtained upon treatment of amide **13** with *n*-butyllithium (eq 9). Apparently the electron-donating effect of the para-situated methoxy substituent is not sufficient to discourage substitution at the amide carbonyl. No products resulting from ring metalation were observed.



13 (9)

In order to more accurately assess the effect of the para methoxy group upon benzyl proton acidity, the metalation of *p*-methoxyphenyl-*N*-methylacetamide (**14**) was examined. As might be expected, metalation of *N*-methylphenylacetamide with 2 equiv of *n*-butyllithium gave essentially quantitative metalation at the benzyl and amide proton sites. It was anticipated that the *p*-methoxy substituent would sufficiently decrease the benzyl proton acidity to allow ring metalation either ortho to the amide or methoxy substituent in amide **14**. However, the effect of the para-situated methoxy substituent was not sufficient to effect this result as near-quantitative metalation at the benzyl and amide protons of amide **14** was observed judging from NMR integration of the D$_2$O hydrolysis products (eq 10).



14 (10)

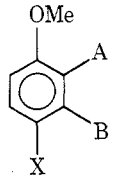
Although the results obtained for *p*-methoxy-*N,N*-dimethylphenethylamine (**7**), 3-(*p*-methoxy)-*N,N*-dimethylpropylamine (**9**), and methoxy-*N*-methylbenzamides **10**, **11**, and **12** indicated that the para-situated methoxy substituent is capable of altering the usual course of metalation in certain cases, apparently such influence is not sufficient to allow the predominance of ring metalation over alternate reaction routes for compounds **13** and **14**.

**Sulfonamide Anisoles (Substituents –SO$_2$NHMe, –SO$_2$NMe$_2$). –SO$_2$NHMe.** As shown in Table III, metalation of *p*-methoxy-*N*-methylbenzenesulfonamide (**15**) with *n*-butyllithium indicated that the methylsulfonamide group predominated over the methoxy substituent in ortho-directing ability to afford good yields of 4-methoxy-2-diphenylhydroxymethyl-*N*-methylbenzenesulfonamide (**15a**). Carbinolsulfonamide **15a** was not cyclized; rather identification of the site of metalation was based on hydrolysis of the lithio intermediate of sulfonamide **15** with D$_2$O and subsequent NMR integration of the deuterated product. Sulfonamide **15** exhibited an NMR spectrum having a well-resolved AA'BB' pattern representing the aromatic protons in the $\tau$ 2.64 region. Based on the spectra of known compounds, the downfield resonance was assigned to the protons ortho to the sulfonamide substituent. Hydrolysis of the lithio intermediate of sulfonamide **15** gave a deuterated product having 1.20 protons downfield and 2.00 protons upfield in the AA'BB' system.

Metalation of amide **15** using *n*-butyllithium/TMEDA brought about no change of orientation of metalation, although a slightly lower yield of carbinolsulfonamide **15a** was realized, possibly the result of the use of ether as solvent rather than THF.

**–SO$_2$NMe$_2$.** As shown in Table III, metalation of *p*-methoxy-*N,N*-dimethylbenzenesulfonamide (**16**) with *n*-butyllithium indicated that the dimethylsulfonamide substituent was a better ortho-directing substituent than the methoxy substituent. Proof of the site of metalation was based on NMR integration of the deuterated product obtained from hydrolysis of the lithio intermediate of sulfonamide **16** with D$_2$O. Sulfonamide **16** exhibited an NMR spectrum having a well-resolved AA'BB' pattern in the $\tau$ 2.68 region representing the aromatic protons assignments for which were analogous to those of sulfonamide **15**.

Table VI. Competitive Metalation of Para-Substituted Anisoles



| X | % metalation[a] Position A | Position B |
|---|---|---|
| $-CH_2NMe_2$ | 0 (55) | 80 (7) |
| $-CONHMe$ | 0 (0) | 50 (60) |
| $-SO_2NHMe$ | 0 (0) | 80 (65) |
| $-SO_2NMe_2$ | 0 (0) | 74 (0) |
| $-CH_2CH_2NMe_2$ | 72 (55) | 0 (0) |
| $-CF_3$ | 92 (90) | 0 (0) |
| $-NMe_2$ | 85 (78) | 0 (0) |
| $-F$ | 32 (0) | 0 (0) |

[a] Yields for metalation using TMEDA are given in parentheses. Maximum yields from $D_2O$ hydrolysis or benzophenone condensation are cited.

Attempts to metalate sulfonamide **16** with *n*-butyllithium/TMEDA were unsuccessful. Spectroscopic examination indicated that the *n*-butyl anion may have effected substitution at the sulfonamide linkage to give a sulfone derivative as evidenced by the presence of a nine-proton multiplet in the alkyl region of the NMR spectrum. This result was consistent with the observation that *N,N*-dimethylbenzamide was more susceptible to nucleophilic substitution at the carbonyl than was *N*-methylbenzamide.[7]

**Fluorinated Anisoles (Substituents $-CF_3$, $-F$). $-CF_3$.** Results obtained in the metalation of *p*-methoxybenzotrifluoride (**17**) indicated that the methoxy substituent was a better ortho director than was the trifluoromethyl substituent. The site of metalation was determined by NMR analysis of the deuterated product obtained by hydrolysis of the lithiointermediate of *p*-methoxybenzotrifluoride (**17**) with $D_2O$. Compound **17** exhibited a well-resolved AA'BB' spectrum in the $\tau$ 2.80 region representing the aromatic protons for which the downfield resonance was assigned to the protons ortho to the trifluoromethyl substituent. Judging from the data (Table IV), TMEDA apparently had little effect upon the course of metalation for compound **17**.

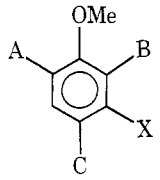
**$-F$.** Metalation of *p*-fluoroanisole (**18**) with *n*-butyllithium in THF at ambient temperature afforded 5-fluoro-2-methoxybenzoic acid (32%) upon carbonation with dry ice. *p*-Fluoroanisole was recovered in 42% yield and the crude product possessed a slight phenolic odor indicative of a small amount of decomposition to a phenolic product, perhaps *p*-fluorophenol. A previous study[17] had reported a 13% yield of 5-fluoro-2-methoxybenzoic acid via metalation with *n*-butyllithium.

It is interesting to note that the metalation of fluorobenzene itself was carried out at low temperatures (−50 °C) since benzyne formation to yield triphenylene occurs at room temperature.[17] However, attempts to metalate *p*-fluoroanisole at −50 °C were unsuccessful and only starting material was recovered.

Metalation of *p*-fluoroanisole using *n*-butyllithium/TMEDA followed by carbonation with dry ice gave no acid product except valeric acid. It is suggested that decomposition of the *p*-fluoroanisole to the corresponding phenol may account for a portion of the loss of starting material. Although this product was not isolated, the reaction product carried a strong phenolic odor.

Metalation of *o*-fluoroanisole (**19**) with *n*-butyllithium gave no ring metalation under the conditions employed. This result was not surprising since our argument of bidentate chelation of certain ortho-substituted anisoles with *n*-butyllithium to form the monomeric complex could be extended to *o*-fluoroanisole (structure VII). Earlier it was noted that attempts to metalate *p*-fluoroanisole with *n*-butyllithium/TMEDA gave no ring metalation but instead some phenolic product was formed.

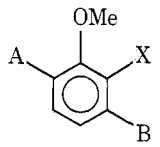
Table VII. Competitive Metalation of Meta-Substituted Anisoles



| X | % metalation[a] Position B | Position C |
|---|---|---|
| $-CH_2NMe_2$ | 79 (62) | |
| $-CONHMe$ | 48 (65) | |
| $-NMe_2$ | 71 (80) | 0 (3) |

[a] Yields for metalation using TMEDA are given in parentheses. Maximum yields from $D_2O$ hydrolysis or benzophenone condensation are cited.

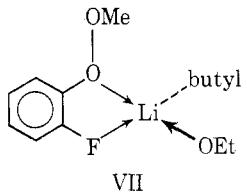
Table VIII. Competitive Metalation of Ortho-Substituted Anisoles



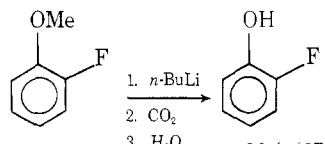
| X | % metalation[a] Position A | Position B |
|---|---|---|
| $-CH_2NMe_2$ | 58 (38) | 5 (8) |
| $-CH_2CH_2NMe_2$ | | |
| $-CONHMe$ | | 46 (53) |
| $-NMe_2$ | 56 (49) | |
| $-F$ | | |

[a] Yields for metalation using TMEDA are given in parentheses. Maximum yields from $D_2O$ hydrolysis or benzophenone condensation are cited.

Metalation of *o*-fluoroanisole gave a product identified by ir spectroscopy as *o*-fluorophenol in 36% yield along with 33% recovery of *o*-fluoroanisole (eq 11). Attempted metalation of



VII



**19** **19a** 36% (27%) (11)

*o*-fluoroanisole with *n*-butyllithium/TMEDA gave a 27% yield of *o*-fluorophenol along with 44% recovery of starting material. No ring metalation products were detected in any of the experiments performed.

## Conclusions

Tables VI–VIII provide a summary of metalation results

Table IX. Preparation of Substituted Anisoles[a]

| Compd | X | % yield | Mp or bp, °C (mm) | Lit. mp or bp, °C (mm) | Ref |
|---|---|---|---|---|---|
| 1 | p-($NMe_2$) | 29 | mp 45–47 | mp 48–49 | 33, 40 |
| 2 | m-($NMe_2$) | 20 | bp 119–123 (17) | bp 237 (760) | 33, 44 |
| 3 | o-($NMe_2$) | 22 | bp 86–90 (16) | bp 113 (18) | 33 |
| 4 | p-($CH_2NMe_2$) | 74 | bp 88–90 (3.5) | bp 73–77 (2.0) | 34, 36 |
| 5 | m-($CH_2NMe_2$) | 80 | bp 76–78 (3) | bp 101–102 (9.5) | 35, 41 |
| 6 | o-($CH_2NMe_2$) | 70 | bp 82–84 (4) | bp 113 (20) | 35, 42 |
| 7 | p-($CH_2CH_2NMe_2$) | 75 | bp 50–52 (1.0) | bp 108 (11) | 34 |
| 8 | o-($CH_2CH_2NMe_2$) | 40 | bp 101–105 (3) | | 36 |
| 9 | p-($CH_2CH_2CH_2NMe_2$) | 80 | bp 115–117 (4) | | 30 |
| 10 | p-(CONHMe) | 95 | mp 117–119 | mp 116 | 37 |
| 11 | m-(CONHMe) | 78 | mp 66–68 | mp 67–68 | 37, 38 |
| 12 | o-(CONHMe) | 84 | bp 100–105 (0.3) | bp 175 (14) | 38 |
| 13 | p-(CONHMe) | 68 | mp 41–42 | mp 42 | 45 |
| 14 | p-($CH_2$CONHMe) | 80 | mp 96–97 | | 38 |
| 15 | p-($SO_2$NHMe) | 83 | mp 96–98.5 | | 39 |
| 16 | p-($SO_2NMe_2$) | 90 | mp 72–74 | mp 71–72 | 39 |
| 17 | p-($CF_3$) | 53 | bp 166–168 (760) | bp 168.6 (760) | 43 |

[a] NMR and ir data confirmed the structures of these substituted anisole derivatives.

for the para-, meta-, and ortho-substituted anisoles examined in this study. On the basis of the para-substituted anisole results it was found that the substituents having stronger ortho-directing ability than the methoxy group were the following: $-CH_2NMe_2$, -CONHMe, $-SO_2NHMe$, and $-SO_2NMe_2$. Substituents which were inferior ortho directors relative to the methoxy group were the following: $-CH_2CH_2NMe_2$, $-CF_3$, $-NMe_2$, and -F.

The ortho-directing ability of the methoxy, dimethylamino, and fluoro substituents apparently involved both coordination and inductive effects. If coordination effects alone were considered the relative order of directing would be $-NMe_2 > -OCH_3 > -F$. Inductive and resonance effects would predict $-F > -OCH_3 > -NMe_2$. However, the observation that $-OCH_3 > -NMe_2$, -F suggests that both effects may be operative in these cases.

The para-situated methoxy group was found to have a significant effect upon (1) benzyl proton acidities of compounds **7** and **9** and (2) the carbonyl electrophilicity of amide **10**.

TMEDA has been found to be effective in increasing the rate of certain ortho-directed metalation reactions and was shown in certain cases to alter the site of metalation.

## Experimental Section

**General.** *n*-Butyllithium (1.6 M in hexane) used in the following reactions was purchased from the Foote Mineral Co. *N,N,N′,N′*-Tetramethylethylenediamine (TMEDA) (bp 120–122 °C) was obtained from Aldrich Chemical Co. and was redistilled with the fraction bp 120.5–121.0 °C being collected. The redistilled TMEDA was stored over Linde 4A molecular sieves under an atmosphere of argon. The ether used as a reaction solvent was Matheson Coleman and Bell "absolute" grade and was stored over Linde 4A molecular sieves. Tetrahydrofuran (THF) used as solvent was filtered through activated alumina immediately before use.

Elemental analyses were performed by Galbraith Laboratories, Knoxville, Tenn., Alfred Bernhardt Laboratories, Mulheim, West Germany, and Joseph Nemeth Laboratory, Urbana, Ill. Melting points were determined on a Hoover melting point apparatus and are corrected. Column chromatographies were performed on Matheson Coleman and Bell activated alumina using redistilled solvents. Thin layer chromatographies were performed on E. Merck silica gel G using ethyl acetate as solvent.

All ir spectra were obtained on a Perkin-Elmer Model 137 Infracord using the 6.246-$\mu$ band of polystyrene as a reference. All NMR spectra were obtained on a Varian A-56/60 spectrometer using $Me_4Si$ as an internal standard. Integrations used to report deuterium incorporation were accurate to ±0.04 proton, judging from the accuracy obtained for the integration of protons in known pure compounds.

All yields are expressed as percent conversion, i.e., no effort was made to assess the amount of recovered starting materials.

**Preparation of Substituted Anisole Derivatives, 1–19. Aminoanisoles.** *N,N*-Dimethylanisidines **1–3** were obtained in fair yield by treatment of the corresponding anisidine with dimethyl sulfate.[33] *p*-Methoxy-*N,N*-dimethylbenzylamine (**4**) was prepared from the corresponding primary amine via the Eschweiler–Clark methylation reaction.[34] The meta and ortho isomers, amines **5** and **6**, were prepared by a procedure involving formation of the *N,N*-dimethylanisamides from the anisic acids and reduction of the amides[35] to the corresponding benzylamines. *p*-Methoxy-*N,N*-dimethylphenethylamine (**7**) was prepared via the Eschweiler–Clark methylation[34] of the corresponding primary amine. The ortho isomer **8** was obtained via a synthetic procedure involving metalation of anisole and condensation of the 2-lithio intermediate with ethylene oxide to give 2-(*o*-methoxyphenyl)ethanol conversion of the ethanol derivative to the bromide using $PBr_3$ and conversion of the bromide to amine **8** using dimethylamine.[36] Treatment of 3-(*p*-methoxyphenyl)propanol (Aldrich Chemical Co.) with $PBr_3$ and subsequent treatment of the intermediate bromide with dimethylamine in ethanol[36] gave 3-(*p*-methoxyphenyl)-*N,N*-dimethylpropylamine (**9**).

**Amide Anisoles.** *N,N*-Dimethylbenzamides **10–12** were prepared[37,38] from the corresponding anisic acid using thionyl chloride to form the corresponding acid chloride and reaction of the acid chloride with methylamine. Amides **13** and **14** were prepared by usual procedures[37] via *p*-anisyl chloride and 4-methoxyphenylacetyl chloride, respectively.

**Sulfonamide Anisoles.** Sulfonamides **15** and **16** were prepared[39] by reaction of *p*-methoxybenzenesulfonyl chloride with methylamine and dimethylamine, respectively.

**Fluorinated Anisoles.** *p*-Methoxybenzotrifluoride (**17**) was prepared by treatment of *p*-chlorobenzotrifluoride with sodium methoxide under pressure at 160 °. Fluoroanisoles **18** and **19** were purchased from Aldrich Chemical Co.

A complete summary of physical properties of the substituted anisole derivatives is presented in Table IX.

**General Metalation Procedure—Benzophenone Condensation and $D_2O$ Hydrolysis. Aminoanisoles (1–9).** The amine was dissolved in dry ether (2 ml ether/mmol substrate) at room temperature under argon and 1 equiv of 1.6 M *n*-butyllithium in hexane was slowly added. After stirring for the period designated in Table II, a mixture of benzophenone (1.25 equiv) in dry ether was added at a rate sufficient to produce only slight reflux. The reaction solution was stirred for 4 h and then hydrolyzed with water. The ether layer and ether extracts of the aqueous layer were combined and extracted with 10% HCl. The acid layer was separated and neutralized with solid NaOH. Ether extracts of the neutralized portion were dried over $MgSO_4$. After the ether had been removed under vacuum, unreacted starting amine (and TMEDA, where appropriate) was removed by vacuum distillation. The benzophenone condensation product was then purified by the appropriate procedure as designated in Table X.

The $D_2O$ hydrolysis products were formed by adding excess $D_2O$ to the lithiation mixture, extracting with ether, and redistilling the recovered amine. The methiodide salt of the deuterated amine (**1**) was formed by stirring with an ether solution of excess methyl iodide for 12 h. The white precipitate, mp 255 °C dec, was collected and recrystallized from methanol.

When TMEDA was employed in the metalation reaction, the TMEDA/*n*-butyllithium complex was first formed by treating TMEDA in ether with 1 equiv of 1.6 M *n*-butyllithium in hexane.

Table X. Physical Data[c]

| Compd | % yield | Mp, °C | Purification[a] |
|---|---|---|---|
| 1a | 71 | 145–146 | A (100% ethanol) |
| 2a | 71 | 142–143 | A (95% ethanol) |
| 3a | 56 | 101–102 | A (100% ethanol) |
| 4a | 80 | 128–130 | A (100% ethanol) |
| 4b | 55 | 88–89 | B[b] |
| 5a | 79 | 104–104.5 | A (100% ethanol) |
| 6a | 58 | bp 180–190 (2.0) C | |
| 7a | 60 | 99–101 | A (100% ethanol) |
| 9a | 71 | Oil | |
| 10a | 47 | 198 dec at 200 | A (tetrahydrofuran) |
| 11b | 65 | 222–224 | A (100% ethanol) |
| 12b | 53 | 168–170 | D (50:50 benzene ligroin) |
| 15a | 77 | 165–167 | A (100% ethanol) |
| 16a | 62 | 150–151 | A (100% ethanol) |
| 17a | 79 | 104–105 | A (hexane) |

[a] Purification procedures used: A recrystallization; B, thin layer chromatography; C, vacuum distillation; D, column chromatography (alumina with 6% $H_2O$). [b] TLC on silica gel G gave two bands upon development with ethyl acetate: band 1 ($R_f$ 0.63), **4a**; band 2 $R_f$ 0.39), **4b**. [c] Satisfactory analytical data (± 0.3% for C, H, N, F, and S) were obtained and were submitted for review.

After stirring for 1 h an ether solution of the amine was added and the reaction continued as previously described.

The benzophenone condensation product mixture of amine **6** (1.0 g, 0.003 mol) was treated with excess methyl iodide for 14 h at room temperature. The crystalline product was recrystallized from methanol to give yellow crystals, mp ~250 °C with decomposition. The methiodide was placed in a flask filled with argon and heated at 200–210 °C for 20 min. Boiling ether extracts of the reaction residue gave no cyclic ether, the product to be expected if the predominant isomer were the 6 isomer, **6b**.

**Carboxamide Anisoles (10–14).** The same procedure was followed as for the amines above except that THF was used as solvent and the reaction temperature was that of the refluxing solvent, i.e., approximately 65 °C. Two equivalents of *n*-butyllithium was required to effect metalation for all compounds of this series except compound **13** since the first equivalent would have been initially consumed in the abstraction of the amide proton. Metalation of **13** was attempted using only 1 equiv of *n*-butyllithium. Metalations using TMEDA were run in refluxing ether since all attempts to effect metalation using TMEDA in THF were unsuccessful.

*p*-Methoxy-*N,N*-dimethylbenzamide (**13**, 7.16 g, 0.04 mol) was dissolved in 80 ml of dry ether and treated with 1.6 M *n*-butyllithium (25 ml, 0.04 mol) at reflux under argon for 0.25 h. Benzophenone (7.28 g, 0.04 mol) in 40 ml of dry ether was added to the cooled mixture and stirred for 4 h. A basic gas was expelled throughout the course of the reaction. The metalation mixture was hydrolyzed with $H_2O$ and extracted with ether. The ether extracts were dried over $MgSO_4$ and stripped to give an oil shown to be a mixture of benzophenone and *p*-methoxyvalerophenone. A comparison of relative proton integrations indicated that 55% of the 10.8 g of total product mixture was *p*-methoxyvalerophenone. This corresponded to 5.95 g (78% yield) of *p*-methoxyvalerophenone. No metalation products were detected.

Repetition of the above metalation procedure for carboxamide **14** followed by $D_2O$ hydrolysis and NMR analysis of the deuterated product indicated 1.00 atom deuterium incorporation at the benzyl position and 0.70 atom deuterium incorporation at the –NH site.

Repetition of the above experiment except for a metalation time of 24 h gave 1.00 atom deuterium incorporation at the benzyl and –NH sites, judging from NMR integration of the deuterated product.

**Sulfonamide Anisoles (15, 16).** The same procedure as for the amides above was followed except that the metalation was performed at 0–5 °C. Upon condensation with benzophenone the reaction mixture was allowed to warm to room temperature. Sulfonamide **16** required the use of only 1 equiv of *n*-butyllithium.

**Fluorinated Anisoles (17–19).** The same procedure as for the amines above was followed except that the reaction mixture was refluxed in ether during the metalation step and cooled to room temperature during the benzophenone condensation step.

Using conditions favoring metalation of fluorobenzene,[12] *p*-fluoroanisole (**18**, 6.30 g, 0.05 mol) was dissolved in 100 ml of dry ether and cooled to −63 °C using a $CHCl_3$/liquid $N_2$ slush. To the cooled solution was added 31.2 ml (0.05 mol) of 1.6 M *n*-butyllithium in hexane. The mixture was stirred at −63 °C for 7 h and then poured in portions into a dry ice/ether slurry under argon. After standing for 12 h the mixture was extracted with ether. The ether layer was extracted with 3 N NaOH and the basic layer separated and neutralized with 6 N HCl. Ether extracts of the neutralized layer were dried over $MgSO_4$ and stripped to yield 2.8 g (55% yield) of valeric acid. *p*-Fluoroanisole (5.5 g, 84% recovery) was isolated from the base-insoluble portion.

Using conditions favoring metalation of anisole,[6,11] *p*-fluoroanisole (3.15 g, 0.025 mol) was dissolved in 59 ml of dry THF under argon. To this solution was added 15.6 ml (0.025 mol) of 1.6 M *n*-butyllithium in hexane and the mixture stirred at room temperature for 5 h. The mixture was poured into a dry ice/ether slurry under argon. After the mixture had stood for 12 h, 30 ml of $H_2O$ was added and the mixture extracted with ether. Basic extraction of the ether layer gave 1.35 g (32% yield) of pale yellow crystals of 5-fluoro-2-methoxybenzoic acid, mp 82–85 °C (lit.[46] mp 87 °C). None of the isomeric product was observed. *p*-Fluoroanisole was recovered in 42% yield along with a small amount of material having a phenolic odor. After metalation using *n*-butyllithium/TMEDA in ether, a basic extraction of the ether layer produced some valeric acid but none of the fluoromethoxybenzoic acid products. Almost quantitative recovery of *p*-fluoroanisole along with a small amount of material having phenolic odor was obtained.

*o*-Fluoroanisole (**19**, 3.78 g, 0.03 mol) was dissolved in 60 ml of dry THF and treated with 1.6 M *n*-butyllithium (18.7 ml, 0.03 mol) in hexane for 5 h at room temperature under argon. The metalation mixture was poured into a dry ice/ether slurry and left to stand for 12 h. A basic extraction of the ether layer produced a small amount of valeric acid along with 1.2 g (36% yield) of *o*-fluorophenol [bp 180–185 °C (750 mm), lit.[47] bp 46 °C (10 mm)]. No fluoromethoxybenzoic acid products were obtained and only 1.15 g (30%) of the *o*-fluoroanisole was recovered. After metalation using *n*-butyllithium/TMEDA in ether, a basic extraction of the ether layer produced some valeric acid along with 0.6 g (27% yield) of *o*-fluorophenol. Approximately 1.1 g (44%) of *o*-fluoroanisole was recovered from the organic layer. No fluoromethoxybenzoic acid products were detected in the product mixture.

**Acknowledgments** are made to the donors of the Petroleum Research Fund, administered by the American Chemical Society, for support of this research. Thanks are also due Art Langer, Exxon Research and Engineering Co., Linden, N.J., for salient advice on the interpretation of the metalations using TMEDA/*n*-butyllithium reagent.

**Registry No.**—**1**, 701-56-4; **1a**, 59907-30-1; **2**, 15799-79-8; **2a**, 35339-88-9; **2b**, 59907-31-2; **3**, 700-75-4; **3a**, 35339-89-0; **4**, 15175-54-9; **4a**, 10126-23-5; **4b**, 35339-84-5; **5**, 15184-99-3; **5a**, 10126-27-9; **6**, 58774-83-7; **6a**, 35339-85-6; **6b**, 59907-32-3; **7**, 775-33-7; **7a**, 35339-86-7; **8**, 59907-33-4; **9**, 59907-34-5; **9a**, 59907-35-6; **10**, 3400-22-4; **10a**, 35339-90-3; **11**, 35129-32-9; **11b**, 20144-53-0; **12**, 3400-35-9; **12b**, 20144-51-8; **13**, 7291-00-1; **14**, 59907-36-7; **15**, 7010-86-8; **15a**, 35339-91-4; **16**, 59907-37-8; **16a**, 59907-38-9; **17**, 402-52-8; **17a**, 59907-39-0; **18**, 459-60-9; **19**, 321-28-8.

**Supplementary Material Available.** Table XI, ir and NMR spectral data of substituted benzenes (2 pages). Ordering information is given on any current masthead page.

## References and Notes

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# Directed Metalation Reactions. 7.[1] Directed Metalation of Methoxymethylferrocene: 2- and 1′-Metalated Ferrocene Intermediates

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A unique regiospecific metalation of a substituted ferrocene has been observed in the lithiation of methoxymethylferrocene (MMF, 1). Approximately equal amounts of 2- and 1′-monometalated intermediates were produced as judged by derivatization experiments. Among the most interesting of the new compounds isolated were 2- and 1′-chloromercurimethoxymethylferrocene (2-ClHg-MMF) and (1′-ClHg-MMF). 1′-ClHg-MMF underwent a transmetalation reaction with *n*-butyllithium to produce a unique ferrocenyllithium derivative, namely, 1′-lithiomethoxymethylferrocene (1′-Li-MMF). Also found to undergo 2 lithiation were ethyoxymethylferrocene (EMF, 5) and α-methoxyethylferrocene (MEF, 6). These results are interpreted in terms of coordination of oxygen with a lithium ion in the metalated intermediate.

The displacement of a hydrogen atom from a carbon–hydrogen bond by an alkali metal to give an organometallic intermediate, i.e., metalation, has become of increasing interest to organic chemists. In recent years, the ability of certain groups on aromatic systems to direct lithiation at a position "ortho" to the substituent has been demonstrated to be of synthetic utility, since such a procedure enables a chemist to produce "ortho" disubstituted products virtually uncontaminated by other isomers.[3] More recently, ortho metalation of aromatic systems by various transition metal derivatives has also received attention.[4]

Although many of the early reports focused on the directing ability of amines, several articles dealing with directed metalation of aromatic ethers also appeared. Notable among these were the early studies of Gilman and co-workers on the directed lithiation of dibenzofuran, anisole, and related ethers.[3a] Subsequent papers by other workers have contained suggested mechanism(s)[5a,b,6] and caveats[5c] for the observed ortho lithiation of aryl ethers and these contain estimates of contributions of coordination by oxygen to the overall transition state. In the preceding paper,[1] the methoxy group was found to be intermediate in directing ability among the group of nine directing substituents studied. Moreover, the methoxy group has also been found to direct metalation in other systems, namely, ferrocene[7] and naphthalene.[8] Some evidence for the importance of coordination in the mechanism of directed lithiation by the methoxy group has been inferred from the observed significant decrease in the extent of lithiation of the anisole nucleus by the presence of an ortho *tert*-butyl group.[9]

In our opinion, no unequivocal demonstration of a coordinating direction of lithiation by oxygen has ever been accomplished. Such an example is provided herein, namely, the formation of 2-Li-MMF and 1′-Li-MMF upon metalation of MMF with *n*-butyllithium. Both the regiospecificity of the metalation (no 3 metalation) as well as the observation that the rate is much faster and the extent greater than metalation of ferrocene itself under these conditions[10] dictate a decided