1715, 1680, 1620; ^{1}H NMR 0.99 (t, J = 7.3, 3 H), 1.12 (t, J = 7.5, 3 H), 1.22 (t, J = 7.6, 3 H), 1.66 (sext, J = 7.4, 2 H), 2.40 (q, J = 7.4, 2 H), 2.43 (q, J = 7.5, 2 H), 2.72 (t, J = 7.3, 2 H), 3.75 (s, 2 H), 3.80 (s, 2 H); MS (m/e) (relative intensity) 235 (M^+, 22), 206 (100), 192 (32), 57 (16); HRMS (m/e) 235.1557, calcd for $C_{14}H_{21}NO_2$ 235.1572.

The stoichiometric reaction using **1i** (0.50 mmol), $Ni(COD)_2$ (0.50 mmol), and PEt_3 (1.00 mmol) under CO_2 pressure (initial pressure, 50 kg/cm^2) in pyridine (10 mL)–toluene (10 mL) at room temperature for 20 h produced **2i** in 22% yield as determined by GC. PLC (hexane:ether = 1:1 (v/v)) of the combined reaction products of the several reactions permitted isolation and identification of **2i**: IR (neat, cm^{-1}) 1720, 1635, 1535; ^{1}H NMR (quint, J = 3.4, 4 H), 2.46 (m, 2 H), 2.63 (m, 2 H), 6.07 (s, 1 H), 7.24 (s, 1 H); MS (m/e) (relative intensity) 150 (M^+, 100), 122 (81), 94 (33), 79 (38); HRMS (m/e) 150.0689, calcd for $C_9H_{10}O_2$ 150.0680.

Nickel(0)-Catalyzed Cycloaddition of 2,8-Decadiyne (1d) with Carbon Dioxide to the Bicyclic α-Pyrone 2d and the Dimerization Product 3. The reaction was carried out under nitrogen. In a 50-mL stainless steel autoclave were placed a THF solution (0.9 mL) of $Ni(COD)_2$ (0.050 mmol), tri-n-octylphosphine (0.046 mL, 0.10 mmol), and THF (4.1 mL). After the mixture was stirred for several minutes, **1d** (0.076 mL, 0.50 mmol) was added and then CO_2 gas was compressed up to 50 kg/cm^2 at room temperature. The reaction mixture was magnetically stirred for 5 h at 120 °C. The remaining CO_2 gas was purged off and then a THF solution (0.50 mL) of n-docosane (0.25 mmol) was added as a GC internal standard. GC analysis (a 1-m column of 20% silicone DC 550 on Celite 545) exhibited the formation of **2d** and **3** in 46% and 44% yields, respectively. PLC (hexane:ether = 7:1 (v/v)) of the combined reaction products of the several reactions permitted isolation and characterization of **3**: IR (neat, cm^{-1}) 1460, 1020; ^{1}H NMR 1.51–1.67 (m, 4 H), 1.73–1.82 (m, 4 H), 1.77 (t, J = 2.6, 3 H), 2.15 (s, 3 H), 2.18 (s, 3 H), 2.18–2.23 (m, 2 H), 2.25 (s, 3 H), 2.61–2.69 (m, 6 H); ^{13}C NMR 3.4, 15.0, 15.4, 16.0, 18.5, 23.3, 28.3, 28.4, 29.0, 29.4, 29.9, 75.7, 79.1, 131.5, 131.7, 132.5, 133.1, 133.2, 136.3; MS (m/e) (relative intensity) 268 (M^+, 100), 253 (25), 187 (69), 173 (16); HRMS (m/e) 268.2178, calcd for $C_{20}H_{28}$ 268.2191.

Registry No. **1a**, 106449-82-5; **1b**, 61827-89-2; **1c**, 51566-74-6; **1d**, 4116-93-2; **1e**, 3779-15-5; **1f**, 114764-02-2; **1g**, 114764-03-3; **1h**, 114764-04-4; **1i**, 871-84-1; **2a**, 111395-95-0; **2b**, 111395-92-7; **2c**, 111395-96-1; **2d**, 111395-94-9; **2e**, 114764-05-5; **2f**, 114764-06-6; **2g**, 114764-07-7; **2h**, 114764-08-8; **2i**, 6249-20-3; **3**, 114764-09-9; $Ni(COD)_2$, 1295-35-8; PCy_3, 2622-14-2; P-*sec*-Bu_3, 17586-49-1; PEt_3, 554-70-1; P-n-Bu_3, 998-40-3; PPh_3, 603-35-0; PMe_3, 594-09-2; $P(n\text{-}C_6H_{13})_3$, 4168-73-4; $P(n\text{-}C_8H_{17})_3$, 4731-53-7; P-i-Bu_3, 4125-25-1; P-i-Pr_3, 6476-36-4; P-t-Bu_3, 13716-12-6; CO_2, 124-38-9; α,ω-bis(trimethylsilyl)-1,7-octadiyne, 63873-32-5.

Unexpected Regioselectivity in the Lithiation of Fluoroanisoles

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The regioselectivity of lithiation of a series of fluoroanisoles and fluoroveratroles has been studied by determining the ratio of isomeric aldehydes produced by dimethylformamide quenching. The position of lithiation is influenced by such factors as temperature and time of the reaction. Contrary to published reports, fluorine competes significantly with the methoxy group as an ortho director in lithiation reactions. Lithiation of dimethyl-*tert*-butylsilyl ethers of fluorophenols proceeds exclusively ortho to fluorine.

Electrophilic attack on aryllithium intermediates represents a versatile method for the functionalization of aromatic compounds.[1] Accordingly, factors controlling regioselectivity and efficiency of lithiation of aromatic substrates have been the subject of considerable research.[2] Of particular utility is the fact that certain functional groups on aromatic rings are effective in directing lithiation to the ortho position. The studies of Slocum[2b] and others[2] have resulted in a rank order in ortho-directing groups of $CONR_2 > SO_2NR_2 >$ 2-oxazoline $> CH_2NR_2 >$ OMe > F.

In the course of our research on fluorinated catecholamines we have used aryllithium intermediates extensively to prepare variously substituted fluorobenzaldehydes as convenient starting materials for side-chain elaboration. During this work we have noted unexpected behavior of fluorinated aromatic compounds. We have developed new procedures for regioselective introduction of electrophiles which exploit the ortho-directing influence of fluorine. These results are summarized in this report.

In an extensive investigation of aromatic lithiation, Slocum[2b] reported that lithiation of 4-fluoroanisole occurred exclusively ortho to the methoxyl group, while attempted lithiation of 2-fluoroanisole resulted in formation of a phenolic product, presumably through cleavage of the methyl ether, along with recovered starting material. On the other hand, Weinstock and Ladd[3] reported efficient lithiation of 3-fluoroanisole in the doubly activated 2-position under very mild conditions. In a later study, Adejare and Miller[4] cautioned that temperature-dependent benzyne formation can become a major competing pathway during lithiation of fluoroanisoles. Thus, at −35 °C benzyne formation is extensive during lithiation of 3-fluoroanisole, while at −78 °C benzyne-produced dimeric product can be minimized.

These previous studies were particularly relevant to our own work since we wished to use readily available fluoroanisoles and fluoroveratroles to prepare isomeric fluoroanisaldehydes and fluoroveratraldehydes by reaction of aryllithium intermediates with DMF. We also planned to introduce hydroxyl groups through oxidation of boronic

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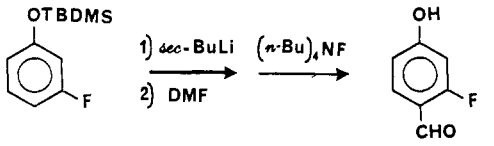
Table I. Aldehydic Products of Lithiated Fluoroanisoles

entry	substrate	method (time)	products[a]	yield, % (ratio)	mp, °C
1	4-[(dimethyl-*tert*-butylsilyl)oxy]fluorobenzene	B[b,c] (30 min)	2-formyl-4-hydroxyfluorobenzene	86	*b*
2	4-methoxyfluorobenzene	B (15 min)	3-formyl-4-methoxyfluorobenzene (**1**)	75 (3:1)	59–60
			2-formyl-4-methoxyfluorobenzene (**2**)		48–50
3	2-(trimethylsilyl)-3,4-dimethoxyfluorobenzene	B (15 min)	3,4-dimethoxy-5-fomrylfluorobenzene[c]	95 (1:1)	78–80
			3,4-dimethoxy-6-formylfluorobenzene[c]		*d*
4	2-methoxyfluorobenzene	B (10 min)	3-formyl-2-methoxyfluorobenzene (**5**)	64 (10:1)	47–48
			6-formyl-2-methoxyfluorobenzene (**6**)		oil
5	2-(trimethylsilyl)-4-methoxy-1,3-difluorobenzene	*n*-BuLi, −65 °C (1 h)	2-(trimethylsilyl)-4-methoxy-5-formyl-1,3-difluorobenzene	34 1.25:1)	oil
			2-(trimethylsilyl)-4-methoxy-6-formyl-1,3-difluorobenzene		oil
		n-BuLi, −78 °C (1 h)		24 (5:1)	
6	3-[(dimethyl-*tert*-butylsilyl)oxy]fluorobenzene	B[c] (30 min)	3-hydroxy-6-formylfluorobenzene	32	168–170[e]

[a] C, H analyses were within 0.4% of calculated values. [b] See ref 5. [c] Intermediate was desilylated by using the method described in ref 5. [d] See ref 8. [e] See ref 7.

esters prepared from aryllithium intermediates. Thus, using the report of Slocum as a precedent, and noting the advisability of using mild lithiation conditions, we attempted to prepare 4-fluoroguaiacol by lithiation of 4-fluoroanisole. After lithiation at −78 °C, reaction with $B(OCH)_3$ followed by peroxide oxidation produced a significant amount of the isomeric 5-fluoroguiacol in addition to the desired product.[5] This result suggested that, under appropriate conditions, ortho-lithiation of aryl fluorides can occur even at the expense of lithiation ortho to an ether function. Indeed, using the bulky *tert*-butyldimethylsilyl ether in place of the methyl ether, we were able to achieve lithiation exclusively ortho to fluorine. We have reported the application of this strategy in our synthesis of fluorinated phenylephrines.[5]

In an extension of this study, we have studied the lithiation of the corresponding silyl ether of 3-fluorophenol, this providing a more stringent test of the ability of the silyloxy function to direct lithiation away from its ortho position. Lithiation of 3-[(dimethyl-*tert*-butylsilyl)oxy]-fluorobenzene with *sec*-butyllithium in THF at −78 °C for 30 min followed by reaction with DMF gave, following fluoride ion desilylation, 2-fluoro-4-hydroxybenzaldehyde[6] as the only isolable benzaldehyde (eq 1). The yield (32%)



(1)

was substantially lower than that observed with the isomeric silylated fluorophenols reported previously.[5] Nonetheless, this result demonstrates that this blocking group is very effective in exerting regiocontrol in lithiations in a negative sense. Presumably steric factors predominate, although a decrease in coordination ability of oxygen could also be important, as has been reported with silyl ethers in other systems.[6]

Our initial results further suggest that lithiation conditions, not surprisingly, can effect regiocontrol, since our lithiation of 4-fluoroanisole at −78 °C gave results that are at variance with the results obtained by Slocum et al. under more vigorous reaction conditions. For this reason, we felt it important to reexamine the lithiation of fluoroanisoles under different conditions with respect to solvent, temperature, and alkyllithium reagent.

Lithiation of 4-fluoroanisole with either *n*-butyl- or *sec*-butyllithium at room temperature followed by quenching with DMF (eq 2) gave only one product detectable by NMR and chromatographic (TLC, GC, and HPLC) analyses of the crude reaction mixture (see method A). This product was isolated and identified as 5-fluoro-2-methoxybenzaldehyde (**1**) by comparison of the BBr_3 demethylation product with authentic 5-fluoro-2-hydroxybenzaldehyde prepared previously. This result parallels the original observation of Slocum and Jennings. Thus, they reported that a similar lithiation procedure followed by reaction with CO_2 produced only 5-fluoro-2-methoxybenzoic acid. In contrast, lithiation of 4-fluoroanisole at −78 °C with *sec*-butyllithium, followed by quenching with DMF, gave **1** as well as an isomeric aldehyde, identified as 2-fluoro-5-methoxybenzaldehyde (**2**) by comparison of the corresponding phenol with authentic 2-hydroxy-5-fluorobenzaldehyde, as above (see method B). The ratio of isolated products (**1** and **2**) was approximately 3:1, respectively, after a 5-min reaction time. We attempted to increase the relative yield of **1** by replacing THF with hexane. We reasoned that coordination of lithium with THF could be decreasing the effective stabilizing influence of an *o*-methoxy group on the lithiated intermediate, thus increasing the influence of any acid-strengthening effects of fluorine. Although a change in polarity and coordination properties of solvent also could affect aggregation of any lithium species present, the absence of any change in isomer distribution caused by replacement of THF with hexanes suggests that solvent effects are minimal in determining product ratio. Although competing effects of aryllithium stabilization and aggregation effects cannot be ruled out, this matter was not pursued further.

We have examined the scope of lithiation products of fluoroaromatics and have found that the directive influence of fluorine is substantial in a number of substrates. A tabular listing is given in Table I.

Lithiation of 4-fluoroanisole at room temperature produced significant amounts of dimeric product, in addition to **1**, presumably as a result of benzyne formation. Of the two isomeric aryllithium intermediates **3** and **4** (eq 2), the precursor of aldehyde **2** could well be the less stable because of ready elimination of fluoride to produce benzyne. In parallel with the observations of Gilman et al.[2a] and

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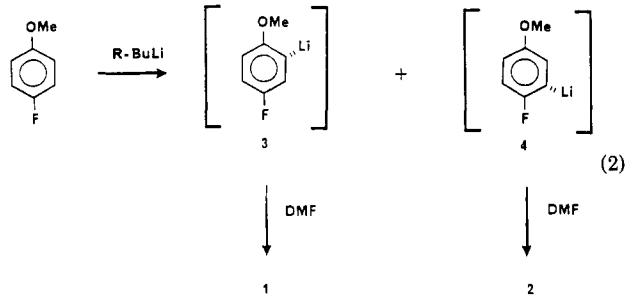
(8) Furlano, D. C.; Kirk, K. L. *J. Org. Chem.* **1986**, *51*, 4073.



(2)

Adejare et al.[4] this could explain why the room-temperature procedure produces only **1**. Accordingly, we studied the ratio of products **1** and **2** as a function of time under conditions (−78 °C) that give both products. Indeed, the ratio of **1** to **2** gradually increased (Table II), suggesting that the ratio of **3** to **4** also increases with time, presumably reflecting the greater stability of the former.

We have also reexamined the lithiation of 2-fluoroanisole at −78 °C and again have found significant differences from the original room-temperature results of Slocum.[2b] Lithiation with *sec*-butyllithium gave two aldehydic products, identified as 2-methoxy-3-fluorobenzaldehyde (**5**) and 3-methoxy-2-fluorobenzaldehyde (**6**) in an approximate ratio of 10:1. Structural assignments were based on comparison

5

6

with authentic samples prepared previously. Decomposition of the aryllithium intermediates at room temperature is a likely explanation for the previously reported failure of lithiation.

Regiocontrol in the lithiation of substituted anisoles is affected by several factors, including electron densities, kinetic acidities of susceptible protons, resonance and inductive effects, and coordinating properties of aryl substituents. Similar factors would affect regiochemistry in substituted aryl fluoride lithiations. Thus, analysis of our results requires interpretation of the combined influence of fluoro and methoxy substitution.

The precise mechanisms by which the methoxy group directs lithiation are still a matter of speculation.[9] Gilday[10] has studied the lithiation of chromium complexes of 2- and 4-fluoroanisole. In this work, he invoked increased kinetic acidity caused by the inductive influence of fluorine to explain lithiation ortho to fluorine. However, this clearly represents a special case in view of the added influence of the coordinated metal.

Unequivocal mechanistic interpretations are not possible at this time. Any intrepretation must take into account a combination of factors, including electron densities, differences in effectiveness of methoxy coordination of intermediate anions, and/or inductive influences of fluorine.[11] Additional research is underway which we hope will produce a clearer understanding of this process. From a practical standpoint, we have demonstrated that reaction conditions are critical in lithiation of fluroanisoles and that fluorine can be quite effective in directing ortho-lithiation. In particular, the reversal of regioselectivity in the fluorinated silyloxy derivatives is very advantageous. Thus, fluorophenols can now be used as precursors for either of two regioisomers by appropriate ether formation followed by lithiation. We are using this procedure extensively in our own work involving syntheses of ring-fluorinated analogues of phenolic biomolecules.

Table II. Time Dependency of Isomeric Ratio (2:1)[a]

time (min)	isomeric ratio, % (2:1)	time (min)	isomeric ratio, % (2:1)
5	42	30	<5
10	38	40	<5
20	15	180	<5

[a] Determined by gas chromatographic analyses.

Experimental Section

Gas chromatography was performed on a DB-1 silicone column (J+W Scientific, Folsom, CA) and a Hewlitt-Packard 5890 GC instrument. Column chromatography using Merck silica gel, 230–400-mesh, is referred to as silica gel chromatography. NMR spectra were obtained on a Bruker 220- or 300-MHz instrument. *n*-Butyllithium and *sec*-butyllithium were obtained from Aldrich. All lithiation procedures were performed under an argon atmosphere.

Typical Lithiation Procedures. Method A. A solution of 4-fluoroanisole (1 g, 0.008 M) in THF (10 mL) was treated with *n*-butyllithium (5 mL of 1.6 M solution), while being cooled in an ice bath (reaction is exothermic). The ice bath was removed after addition, and the mixture was stirred for 12 h at room temperature. The brown solution was treated with dry DMF (5 mL) in anhydrous THF (10 mL). The solution was stirred for an additional 20 min, then 20 mL of 10% HCl was added. Ether was added, and the organic layer was washed with water and brine and then dried over $MgSO_4$.

Method B. A solution of 4-fluoroanisole (1 g, 0.008 M) in anhydrous THF (25 mL) was treated dropwise with *sec*-butyllithium (6.7 mL of a 1.3 M solution) while maintaining the reaction temperature below 70 °C. Stirring was continued for the appropriate time at this temperature. DMF (5 mL) in THF (10 mL) was added dropwise. A solution of 10% HCl was added carefully, and the products were extracted into ether. The resulting aldehydes were separated by low pressure column chromatography (EtOAc/hexane).

Registry No. **1**, 19415-51-1; **2**, 105728-90-3; **5**, 74266-68-5; **6**, 103438-88-6; (*t*-Bu)(Me)$_2$SiO-*p*-C_6H_4-F, 113984-68-2; MeO-*p*-C_6H_4-F, 459-60-9; MeO-*o*-C_6H_4-F, 456-49-5; (*t*-Bu)(Me)$_2$SiO-*m*-C_6H_4-F, 114635-97-1; 2-formyl-4-hydroxyfluorobenzene, 103438-84-2; 3,4-dimethoxy-5-formylfluorobenzene, 114635-98-2; 3,4-dimethoxy-6-formylfluorobenzene, 71924-62-4; 2-(trimethylsilyl)-4-methoxy-5-formyl-1,3-difluorobenzene, 114635-99-3; 2-(trimethylsilyl)-4-methoxy-6-formyl-1,3-difluorobenzene, 114636-00-9; 3-hydroxy-6-formylfluorobenzene, 348-27-6; 2-(trimethylsilyl)-3,4-dimethoxyfluorobenzene, 114636-01-0; 2-(trimethylsilyl)-4-methoxy-1,3-difluorobenzene, 114636-02-1.

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(11) **Note added in proof**: A referee noted that Slocum's method of preparation of alkyllithium reagent might lead to the formation of certain lithium salts which could affect the regioselectivity of the metalation reaction.