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Fluorine as an ortho-Directing Group in Aromatic Metalation: Generality of the Reaction and the High Position of Fluorine in the Dir-Met Potency Scale

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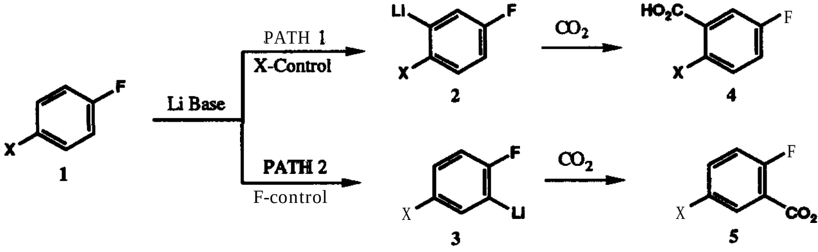
Abstract: *Many para-substituted fluorobenzenes can be lithiated ortho to fluorine in moderate to good yields, often with one of the dialkylamide bases. lithium diisopropylamide (LDA) or lithium 2,2,6,6-tetramethylpiperidide (LiTMP). Intramolecular competition experiments reveal that fluorine is one of the most potent Dir-Met activating groups under these conditions.*

In recent years, much of the advance in aromatic synthesis has come in the non-classical area of aromatic metalation.[1] A fluorine atom considerably acidifies the neighboring ortho hydrogen atom(s) of an aromatic ring.2 and should be a useful participant in this type of chemistry (Scheme 1, path 2). An *apparent* drawback in the use of this strategy is the perceived low position of fluorine on the directed-metalation (Dir-Met) potency scale.3 where most other ortho-directing functional groups are expected to control the metalation regiochemistry in preference to fluorine. This perception has come, in part, from early studies on the metalation of 4-fluoroanisole.4 where only the product of lithiation ortho to oxygen was observed.5 A recent preparation of quinolines[6] revealed that both the *t*-BOCamido and pivaloylamido groups both completely outcompete a para-fluorine atom in a Dir-Met reaction, rather confirming the view of fluorine as a poor ortho-directing group. Accordingly, the general opinion might be that, for many if not most useful metalations, path 1 (X-directed metalation) should dominate over path 2 (fluorine-dimcted metalation).



Scheme 1. Litbiatioa-Carboxylation of para-Fluorophenyl Derivatives

In this communication we wish to report that, in contrast to the low Dir-Met activity of fluorine implied by the literature, conditions can be readily found where a single fluorine atom can be one of the best ortho-directing substituents available. Furthermore, many aryl fluorides can be cleanly and rapidly metalated at low temperatures by lithium dialkylamide bases, and many useful functional groups are compatible with these metalating conditions. Carboxylation of the resulting aryllithiums 3 provides 2-fluorobenzoic acids 5 in useful

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synthetic yields. Similar results have also been obtained in our laboratory by trapping the intermediates 3 with other **electrophiles** (such as DMF, **TMSCl**, and **$ArSO_2SR$**).

We chose a standard protocol for all of our **metalations**,[7] using CO_2 as the electrophile.8 and varying only the base and reaction **times**.[9] In those cases, where we suspected that anion **instability** might be distorting our results, we used in ***situ*** chlorotrimethylsilanc as the electrophile. None of these reactions have been optimized, and we believe that many yields may be improved by examining other variables which we ignored (eg. solvent, concentration, stoichiometry, temperature).

Table 1 shows the results of our carboxylation experiments. Entries **1-4** demonstrate that the lithiation of fluorobenzene itself is not straightforward. n-Butyllithium proved inefficacious for metalation a**-78°C**, even in the presence of TMEDA, whereas **LiTMP** was quite effective, and s-butyllithium (Entry 3) was excellent. A wide variety of **para-substituents** are tolerated in these metalations, as can be seen in the remainder of Table 1. Although several substituents have been described in the literature as ortho directors for aromatic metalations **(-STHP,[10a] -CN,[10b] -CF_3,[10c] -OCH_3,[4,5])**, a fluorine atom is an overall superior ortho director under the conditions described. Furthermore, several entries (Entries **8-10, 12, 13**) demonstrate that even the most mildly

Table 1. Lithiation-Carboxylations of Aryl Fluorides (1)

Entry	X	Base	Time	T (°C)	Yield % 4	Yield % 5	Ratio[a] 5/4
1	H	*n*-BuLi	2 h	-78	--	4	--
2	H	*n*-BuLi/TMEDA	2 h	-78	--	10	--
3	H	*s*-BuLi	2 h	-78	--	81	--
4	H	LiTMP	2 h	-78	--	50	--
5	CH_3	LiTMP	2 h	-78	0	45	--
6	CH_3	*s*-BuLi/TMEDA	2 h	-78	0	77	--
7	Ph	*s*-BuLi/TMEDA	2 h	-78	0	79	--
8	Cl	LDA	30 min	-78	1	57	57
9	Br	LDA	30 min	-78	0.4	72	180
10	I	LDA	30 min	-78	0	70	--
11	STHP	*s*-BuLi/TMEDA	2 h	-78	0	80	--
12	CN	LDA	2 h	-78	0	49	--
13	CF_3	LDA	2 h	-78	0	76	--
14	$CH(OCH_2)_2$	*n*-BuLi/TMEDA	4 h	-78	0	49[b]	--
15	OCH_3	LiTMP	12 h	-78	0.3	53	177
16	OCH_3	*n*-BuLi	2 h	-78	8	9	1.1
17	OCH_3	*n*-BuLi/TMEDA	2 h	-78	10	28	2.8
18	OCH_3	*s*-BuLi/TMEDA	2 h	-78	41	38	0.9
19	OCH_3	*t*-BuLi	2 h	-78	48	15	0.3
20	$OCONEt_2$	*s*-BuLi/TMEDA	2 h	-78	80	0	<0.01
21	$OCONEt_2$	LiTMP	2 h	-78	10	47	0.21
22	2-OCH_3[c]	*s*-BuLi/TMEDA	2 h	-78	3.7[d]	81[e]	22

[a] **Ratios determined** by **nmr.** [b] **Acid** unstable to workup, yield quoted for **aldehyde from** DMF quench. [c] **2-Fluoroanisole** used. [d] **3-Fluoro-2-methoxybenzoic** acid. [e] **2-Fluoro-3-methoxybenzoic** acid.

acidifying substituent shows additivity with fluorine in acidification of its ortho proton, making high yield metalations by LDA possible at **-78°C.** This allows for the very reactive but versatile iodo (or **bromo)** group to be tolerated during lithiition (Entries 9 and **10),** without the problems of competing halogen-metal exchange reactions associated with the use of alkyl **lithiums.** Even **4-fluorotoluene** can be metalated in moderate yield with **LiTMP,** although the yield is considerably improved using ***s*-BuLi/TMEDA** (Entries 5 and **6).**[8,11] No products of benzylic metalation were isolated in these reactions. The lithiation of **4-fluorobenzonitrile** (Entry 12) is not only completely tegiospecific, but produces an anion which is reasonably stable at **-78°C,** in sharp contrast to simple ortho lithiated **benzonitriles.**[10b] Additionally, in contrast to an older literature **report,**[4] the metalation regiochemistry of **4-fluoroanisole** can be completely controlled by fluorine when LiTMP is used as the base (Entry 15). Recently, this complete reversal of regiochemistry has also been reported using ***n*-BuLi/KOBu^t.**[5b] In contrast to these earlier reports. under our conditions, we ***found no bases which metalated exclusively ortho to methoxy*** (Entries 16-19). and ***n*-BuLi** was again surprisingly inefficacious. However, when **4-fluorophenyl** carbamate was metalated (Entries 20 and **21),** no ortho to fluorine metalation was seen with ***s*-BuLi/TMEDA,** and less than 20% with LiTMP. As Entry 22 shows, the directing effect of fluorine versus methoxy was enhanced when the two groups were ortho rather than **para.**

Table 1 does not include the strong ortho directors **diethylcarboxamido,**[12a] **2-oxazolidino,**[12b] and **pivaloylamido**[12c,6] as the **para-substituent** in competition with fluorine. The **lithiation/carboxylation** of these substrates was examined, and gave very low yields of carboxylic acids and surprisingly poor material balances. For example, ***N,N*-diethyl 4-fluorobenzamide** did show exclusive ortho to fluorine metalation in 26% yield **(LiTMP, -78°C,** 2 h), but under other conditions three different acids were obtained in even lower yields, none of which could be unequivocally identified. The **lithiation/carboxylation** of the other two aryl fluorides was even less promising. In order to obtain a relative potency order against fluorine for these three groups, the anions generated by LiTMP **(-78°C)** were trapped ***in situ*** by **chlorotrimethylsilane,** with the results shown in Table 2. Under these conditions, diethylcarboxamide (Entry 23) appears approximately equal in **directing** ability when compared to fluorine. However, fluorine was a much stronger ortho director than oxaxoline (Entry **24),** and no trace of metalation ortho to the pivaloylamido group was observed (Entry 25). This last result is in contrast to the **results** of Muchowski and coworkers6 who reported exclusive ortho to nitrogen lithiation with ***n*-BuLi** (2.5 equiv base, **THF, 0°C).** Apparently, the N- (or 0-) lithioamide produced with ***n*-BuLi** is a much stronger ortho director than the (presumed) 0-silylimidate produced under our conditions. A possible explanation for the difference between our silylations and carboxylations is that ortho-lithio aryl fluorides were always **predominantly** generated in the latter reactions, and that these ***meta*-amido** lithium species do not share the same protection from self-condensation (in the absence of a trapping agent) that the ***ortho*-amido** analogues possess.

Table 2. *In Situ* **Trapping with Chlorotrimethylsilane**

Entry	**X**	LiTMP **TMSCl 1:1** **THF -78°C 2h to -20°C**	**% 1** recovered	**% 2-Si** **α to X**	% 3-Si α to F	**% 3,5-** di-Si	% 2,5- di-Si	a-F/ **α-X**[a]
23	**CONEt$_2$**	1.0 **equiv**	34	24	15	3	9.5	0.54-1.2
24	**2-oxazolidino**	1.0 equiv	15	0	39	22	6	**10->100**
25	***t*-BuCONH**	2.0 **equiv**	19	0	54	23	0	**>100**

[a] Ratio varies, depending on where **2,5-disubstituted** compound is assumed to have silylated first.

In summary, we have demonstrated that most para-substituted fluorobenzenes can be lithiated ortho to **fluorine** in good yields and with high mgioselectivity.[13] From our internal competition results it is clear that a fluorine atom can be one of the most potent ortho directing groups for aromatic metalation, given that the appropriate base (often LDA) is used in conjunction with a low reaction temperature.* In addition, many useful functional groups can be tolerated in these lithiations, especially if LDA is the metalating agent, and substitution of other electrophiles for CO_2 should allow for the preparation of a wide variety of highly functionalized aromatics.

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8. A typical experimental **(Entry** 6) is as follows: ***sec*-Butyllithium** (1.06 M in cyclohexane, 1.88 **mL,** 2.0 mmol) was added **dropwise** over 5 min to a **-78°C** solution of 4-fluorotoluene (220.4 mg. 2.0 mmol) and **TMEDA** (231.5 mg, 2.0 mmol) in THF (5 **mL),** stirred under N_2. After 2 h, the slurry was blown rapidly through a catheter onto solid CO_2 in ether (50 **mL).** When the reaction **mixture** warmed up to **0°C,** it was quenched with dilute **HCl** (1 M, 10 **mL).** The phases **were** separated, the organic phase was washed with water (10 **mL),** and extracted with dilute **NaOH** solution (0.2 M, 2x10 **mL).** The combined base extracts were washed with ether (10 **mL),** acidified with dilute **HCl** (1 M, 10 **mL),** and extracted with ether (3x10 **mL).** The combined ether extracts were washed with water **(2x10mL),** saturated brine (10 **mL),** and dried **($MgSO_4$).** After filtration, the solvent was removed under reduced pressure to give **2-fluoro-5-**methylbenzoic acid (238.7 mg 77%) as white needles, mp **159-60°C**: ^{1}H NMR **(DMSO-d_6)** 12.9 **(1H,** br s), 7.65 **(1H,** sl br dd, J = 1.9, 7.3 Hz), 7.41 **(1H,** sl br ddd, J = 1.9, 4.2, 8.3 Hz), 7.18 **(1H,** dd, J = 8.3, 11.0 Hz), 2.31 **(3H,** s).
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