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Toward a Better Understanding on the Mechanism of Ortholithiation. Tuning of Selectivities in the Metalation of *meta*-Anisic Acid by an Appropriate Choice of Base

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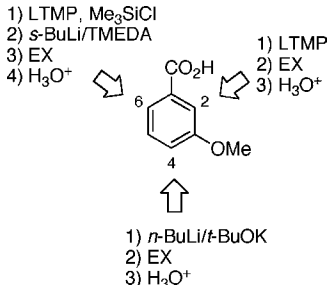
ABSTRACT



If employed in THF at 0 °C, LTMP metalates *meta*-anisic acid at the doubly activated position. In contrast, *n*-BuLi/*t*-BuOK deprotonates position C-4 preferentially at low temperature. Functionalization at C-6 requires protection of the C-2 site beforehand. As a result of these findings, a new mechanism is proposed for the heteroatom-directed ortholithiation of aromatic compounds.

There are a number of studies dealing with lithiations of arenes carrying 1,2- and 1,4-interrelated directed metalation groups (DMGs). The most dramatic effects are observed in cases where the selection of either of two ortho positions may be controlled by the metalating conditions.[1] Few examples of this kind of regioselective control for aromatic metalation are known. The best examples are perhaps the metalation of 2- and 4-fluoroanisole (**1** and **2**, respectively), which occurs primarily at the oxygen-adjacent position with *n*-BuLi and ortho to the fluorine with *n*-BuLi/*t*-BuOK or *n*-BuLi/*N*,*N*,*N*′,*N*″,*N*″-pentamethyldiethylenetriamine (PMDTA),[2] and the metalation of 4-fluoro- and 4-chlorobenzoic acids (**3**), which with *s*-BuLi, *s*-BuLi/ TMEDA, or *t*-BuLi results in exclusive reaction ortho to the carboxylate but with LTMP selects the C-3 positions.[3]

Literature furnishes much less information regarding lithiations of 1,3-interrelated systems, which offer selection of either of three possible ortho substitutions (C-2, C-4, and C-6). It is usually considered as a rule of thumb that the two DMGs function in concert to direct introduction of the metal between them. Even though this is true in most cases, there are a few exceptions. Thus, while *meta*-methoxy phenyl

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(1) Reviews: (a) Hartung, C. G.; Snieckus, V. *Modern Arene Chemistry*; Astruc, D., Ed.; Wiley-VCH: New York, 2002; p 330. (b) Schlosser, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 376.

(2) Maggi, R.; Schlosser, M. *J. Org. Chem.* **1996**, *61*, 5430.
(3) Gohier, F.; Castanet, A.-S.; Mortier, J. *J. Org. Chem.* **2005**, *70*, 1501.

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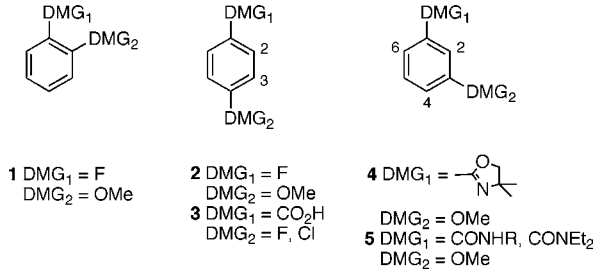
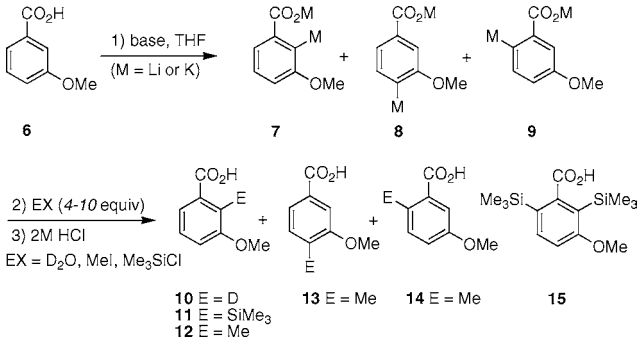
oxazoline (**4**) and secondary and tertiary benzamides (**5**) are deprotonated at the C-2 position by *n*-BuLi or *s*-BuLi/TMEDA,[4] Meyers has described the unusual behavior of α-ethoxyvinyllithium−HMPA at −83 °C, which metalates **4** and **5** exclusively at C-4.[5]



This letter discusses features of the CO_2H(Li) group that make it unique among ortho-directing groups.[6] We have been able to identify conditions that ensure good to excellent selectivities when CO_2H(Li) and MeO groups are located meta to one another. *meta*-Anisic acid (**6**) (Scheme 1) in THF

Scheme 1. Site-Selective Metalation of *meta*-Methoxybenzoic **6** by Strong Bases



was subjected to a series of strong bases under the conditions depicted in Table 1. All compounds obtained as the result of lithiation at the position C-2, ortho to both substituents, showed a characteristic triplet corresponding to the H-5 proton in the ^{1}H NMR spectra.[7] The products of lithiation ortho to the methoxy group and para to the carboxylate exhibited a doublet for the H-5 proton.

After considerable experiment beforehand, we found that treatment of **6** with lithium 2,2,6,6-tetramethylpiperidide (LTMP, 5 equiv) in THF for 1.5−2 h at 0 °C provided quantitatively the dianion **7** (M = Li). Quenching with D_2O under external quench (EQ) conditions afforded a 92% yield of deuterated product **10** in which >95% of the deuterium was incorporated in the C-2 position (entry 1). Treatment of **6** with LTMP (3 equiv) and Me_3SiCl at −78 °C under in situ quench (ISQ) conditions,[8] followed by warming to room temperature provided a 75% yield of 2-trimethylsilyl-3-methoxybenzoic acid (**11**) after chromatography (entry 2). In addition, one other fraction was obtained in 7% yield. This was 3-methoxy-2,6-bis(trimethylsilyl)benzoic acid (**15**), resulting from the partial deprotonation of lithium salt of the primary product **11** by the excess of base at the carbon C-6.[9] The acid **15** was formed predominantly (63%, entry 3) when LTMP was used in large excess (5 equiv) at 0 °C (ISQ conditions). A sequential process involving a rapid intraaggregate lithiation through a quasi dianion complex "QUADAC" presumably proceeds during the formation of **15**.[3]

s-BuLi/TMEDA was found to be more reactive than LTMP. Although the selectivity obtained was not quite so favorable, the direction of the selectivity was maintained. After quenching with iodomethane at −78 °C, a mixture of three isomeric acids **12**−**14** was obtained in a 63:17:20 ratio with 70% overall yield (entry 4). The major C-2 isomer **12** was readily separated by fractional crystallization (31%). Whereas lithium 2-lithio-3-methoxybenzoate monomer (**7**) prepared by metalation with LTMP (according to entry 1 of Table 1) was found to be indefinitely stable in the interval of temperature 0−60 °C,[9] it degraded somewhat at 0 °C when generated from *s*-BuLi/TMEDA under the conditions reported in entry 5.[10]

When *meta*-anisic acid (**6**) was treated with *n*-BuLi/*t*-BuOK (1:1 ratio, 4 equiv) in THF (−78 → −50 °C) (entry 6), the dianion **8** arising from metalation in C-4 formed preferentially. Quenching with iodomethane followed by hydrolysis with dilute HCl resulted in a 84% yield of the

Table 1. Metalations of *meta*-Anisic Acid (**6**)

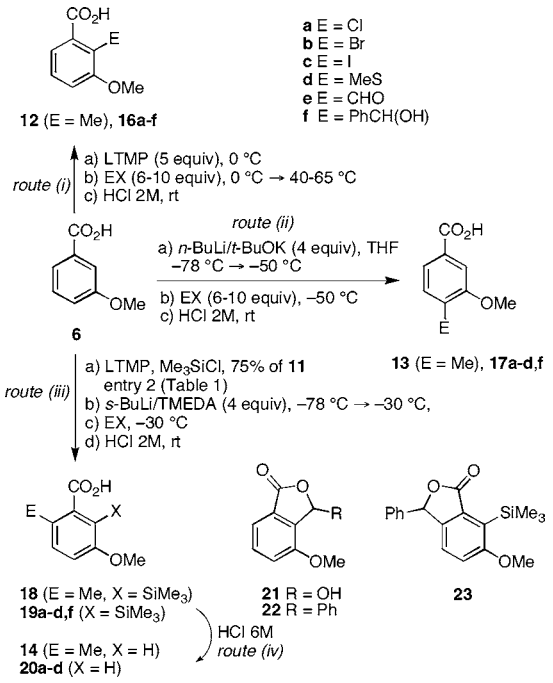
			regioselectivity (%)			
entry	conditions[a]	yield (%)[b]	C-2	C-4	C-6	other
1	(1) LTMP (5 equiv), 0 °C; (2) D_2O, 0 °C	92	100 [**10**]	0	0	
2	LTMP (3 equiv), Me_3SiCl, −78 °C → rt	90 (75* [**11**])	100 [**11**]	0	0	7* [**15**]
3	LTMP (5 equiv), Me_3SiCl, 0 °C	29	100 [**11**]	0	0	63 (51*) [**15**]
4	(1) *s*-BuLi/TMEDA (2.2 equiv), −78 °C; (2) MeI, −78 °C	70 (31* [**12**])	63 [**12**]	17 [**13**]	20 [**14**]	
5	(1) *s*-BuLi/TMEDA (2.2 equiv), −78 → 0 °C; (2) MeI, 0 °C	34	79 [**12**]	15 [**13**]	14 [**14**]	c
6	(1) *n*-BuLi/*t*-BuOK (4 equiv), −78 → −50 °C; (2) MeI, −50 °C	84 (59* [**13**])	9 [**12**]	80 [**13**]	11 [**14**]	

[a] External quench (EQ) technique for D_2O and MeI. In situ quench (ISQ) method for Me_3SiCl. Hydrolysis was carried out at rt. [b] Overall yield (%). Isolated yields (recrystallized or chromatographed) are followed by an asterisk (*). [c] Degradation products.

acids **12**, **13**, and **14** in a ratio of 9:80:11, respectively.[11] The major C-4 isomer **13** was readily isolated by fractional crystallization in ethyl acetate (59%).

By employing the optimized conditions found, we were able to synthesize a variety of 2- (**12**, **16a**−**f**) and 4-substituted (**13**, **17a**−**d**,**f**) 3-methoxybenzoic acids (Scheme 2). The

Scheme 2



results with diverse electrophiles are summarized in Table 2. Although yields in this preliminary study are only moderate, they are, even at this stage, usable, since no protection and deprotection steps of the reactive carboxylic acid group are needed.

Table 2. Regioselective Preparation of 2-, 4-, and 6-Substituted 3-Methoxybenzoic Acids[a]

		route			
EX	E	i	ii	iii	iii + iv
MeI	Me	50	59	57	54
C_2Cl_6	Cl	47	39	57	55
$C_2Br_2Cl_4$	Br	60	65	66	63
I_2	I	53	20	53	50
Me_2S_2	MeS	46	51	61	61
DMF	CHO	27[b]			
PhCHO	PhCH(OH)	65[c]	54	20[c]	

[a] Isolated yields (recrystallized or chromatographed). For general procedures, see Supporting Information. [b] Product cyclized into hydroxyphthalide **21**. [c] Products cyclized into lactones **22** and **23**.

It does not seem feasible to direct metalation regioselectively at the C-6 carbon to give the dianion **9**. Then, to prepare 6-substituted 3-methoxybenzoic acids, one has to block the C-2 site by introducing a trimethylsilyl group to give **11** (see entry 2 of Table 1), lithiate again, deliver the electrophile, and remove the protective group.[12]

The C-6 position of **11** was lithiated regiospecifically by the *s*-BuLi/TMEDA complex (there was no trace of the C-4 isomer 3-methoxy-2,4-bis(trimethylsilyl)benzoic acid) and treated with electrophiles to give acids **18** and **19a**−**d**,**f** after careful hydrolysis with 2 M HCl. These acids were easily deprotected by 6 M HCl to afford **14** and **20a**−**d**. Condensation with DMF followed by acid-catalyzed cyclization gave the hydroxyphthalide **21** via the ortho formyl product **16e**. Clean hydroxy alkylation was achieved with benzaldehyde to give **16f** and **19f**, which were directly transformed into lactones **22** and **23**.

The mechanism of heteroatom-directed ortholithiation of aromatics still inspires very active debate and ongoing controversy in the scientific community. An early hypothesis, advanced by Beak and Meyers to account for regioselective lithiation of aromatic compounds bearing a Lewis basic heteroatom, is that the lithium coordinates with the lone pairs of the heteroatom of the directing group to form a prelithiation complex (CIPE effect).[13]

An alternative hypothesis claims that heteroatom-directed ortholithiation of aromatics should be strictly considered as a kinetically controlled reaction, i.e., a one-step reaction that Schleyer has named "kinetically enhanced metalation".[14] For this author, "*this is not precomplexation that is important but the existence of a stabilizing metal-substituent interaction at the rate-limiting transition structures*".[14] In this model, there is not an intermediate with a finite lifetime on the reaction pathway prior to proton transfer.

(4) (a) De Silva, S. O.; Reed, J. N.; Snieckus, V. *Tetrahedron Lett.* **1978**, *19*, 1823. (b) Beak, P.; Brown, R. A. *J. Org. Chem.* **1981**, *46*, 34.

(5) Shimano, M.; Meyers, A. I. *J. Am. Chem. Soc.* **1994**, *116*, 10815.

(6) For recent work on ortholithiation reactions of unprotected benzoic acid derivatives, see: (a) Gohier, F.; Castanet, A.-S.; Mortier, J. *Org. Lett.* **2003**, *5*, 1919. (b) Gohier, F.; Mortier, J. *J. Org. Chem.* **2003**, *68*, 2030. (c) Tilly, D.; Samanta, S. S.; De, A.; Castanet, A.-S.; Mortier, J. *Org. Lett.* **2005**, *7*, 827. (d) Tilly, D.; Castanet, A.-S.; Mortier, J. *Chem. Lett.* **2005**, *34*, 446.

(7) The term "the H-5 proton" used refers to the 5-position of the aromatic ring of the starting anisic acid and to the meta position with respect to both the methoxy and the carboxylate groups in the obtained products.

(8) (a) Marsais, F.; Laperdrix, B.; Güngör, T.; Mallet, M.; Quéguiner, G. *J. Chem. Res., Miniprint* **1982**, 2863. (b) Krizan, T. D.; Martin, J. C. *J. Am. Chem. Soc.* **1983**, *105*, 6155.

(9) By comparison, lithium ortho-lithio benzoate 2-Li$C_6H_4CO_2$Li condenses instantaneously with itself as the temperature is increased to −20 °C to give benzophenone derivatives. See: Bennetau, B.; Mortier, J.; Moyroud, J.; Guesnet, J.-L. *J. Chem. Soc., Perkin Trans. 1* **1995**, 1265.

(10) Since an excess (5 equiv) of base was required for optimal conversion with LTMP using EQ conditions, the stability of **7**:LTMP might be due to steric effects created by a large cluster of yet undetermined stoichiometry involving both the reactive monomer and LTMP. Attempts of crystallization for X-ray structure determination in ether or THF failed. ^{1}H NMR spectrum of the residue in THF-d_8 displayed broad signals with poor resolution in the aromatic region, which are probably due to the presence of aggregates that prevent a simple structural elucidation.

(11) Minor isomers **12** and **14** were not detected by other investigators: Sinha, S.; Mandal, B.; Chandrasekaran, S. *Tetrahedron Lett.* **2000**, *41*, 3157.

(12) Mills, R. J.; Taylor, N. J.; Snieckus, V. *J. Org. Chem.* **1987**, *52*, 448.

(13) (a) Beak, P.; Meyers, A. I. *Acc. Chem. Res.* **1986**, *19*, 356. (b) Whisler, M. N.; MacNeil, S.; Snieckus, V.; Beak, P. *Angew. Chem., Int. Ed.* **2004**, *43*, 2206.

(14) Van Eikema Hommes, N. J. R.; Schleyer, P. v. R. *Tetrahedron* **1994**, *50*, 5903.

In our opinion, both theories furnish a complete picture if adequately put together. Since there is abundant evidence in the literature for coordination of lithium to heteroatoms in ground states,[15] it is very probable that the alkyllithium (i.e., the 1:1 *s*-BuLi/TMEDA complex in this work) approaches the benzoate **6** in the initial step by strong coordination with the highly electron-rich π-system of the carboxylate and the p-electrons of the methoxy group, leading to a prelithiation complex **PLC1** (kinetic control) (Figure 1).

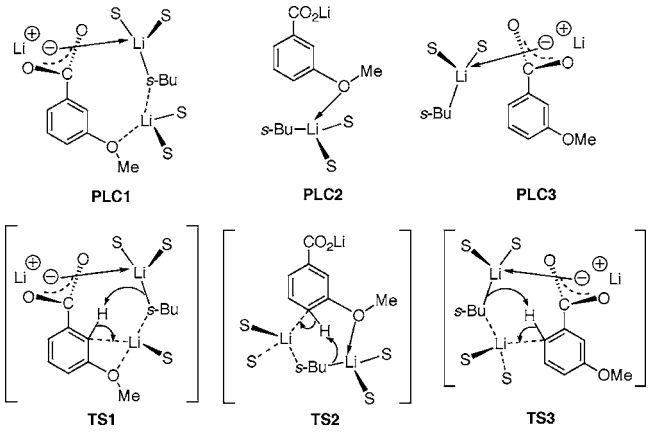


Figure 1. Prelithiation complexes **PLC1**−**3** and transition states **TS1**−**3** (S: solvent, TMEDA, or RLi aggregate).

Since we have checked that bromine−lithium exchange of 2-bromo-3-methoxybenzoic acid (**16b**) (preparation vide supra) with *s*-BuLi (2 equiv) alone or chelated to TMEDA in ether (−78 °C → rt) followed by trapping with iodomethane provides 3-methoxy-2-methylbenzoic acid (**12**) as a *single* regioisomer, it is reasonable to assume that *s*-BuLi/TMEDA metalates **6** randomly at the C-2, C-4, and C-6 sites and that there is no interconversion of the resulting organometallic species **7**−**9**. Consequently, equilibration occurs between the prelithiation complex **PLC1** and the less stabilized forms **PLC2** and **PLC3** coordinated by only one substituent.

The probable reaction pathway for the conversion of **6** to the dianions **7**−**9** is illustrated by the qualitative energy diagram in Figure 2. The directed lithiation is suggested to proceed by a two-step mechanism in which initial complexation is reversible, whereas the second step is rate determining.[16] Not only must the reactants be brought together by chelation of *s*-BuLi by the substituents (to form the prelithiation complexes **PCL1**−**3**) but they also have to be held in exactly the right orientation relative to each other in the transition states **TS1**−**3** (represented in Figure 1) to ensure that deprotonation can occur. Both of these factors raise the free energy of the system by lowering the entropy. Some energy also must be invested to begin breaking the C−H bond so that the C−Li bond can form.

(15) See, inter alia: (a) Streitwieser, A. Jr.; Williams, J. E.; Alexandralos, S.; McKelveg, J. M. *J. Am. Chem. Soc.* **1987**, *111*, 4778. (b) Hay, D. R.; Gallagher, D. J.; Du, H.; Long, S. A.; Beak, P. *J. Am. Chem. Soc.* **1996**, *118*, 11391.

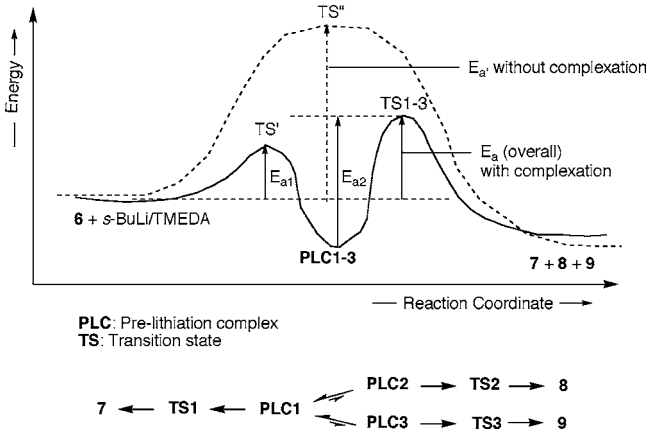


Figure 2. Directed metalation reaction. Qualitative energy diagram.

The directing and accelerating effect of substituents is due to the stabilization of both the initial complex and the transition structure. *The metal is involved in partial bonds, and coordination by the substituent becomes stronger in the transition state than in the initial complex*. As a result, *complexation increases the rate of reaction by providing a new mechanism that has a smaller activation energy* (E_a).[17] The geometries of the precursor complex and the transition structure could be radically different.

The results obtained with LTMP (entry 1 of Table 1) firmly suggest that the regiochemistry of the lithiation of **6** is truly thermodynamically controlled. Resonance and inductive effects favor removal of the H-2 proton.

The major product **13** obtained (entry 6 of Table 1) arises from a noncoordinating−deprotonation mechanism at what would appear to be the least activated of the methoxy ortho centers. Superbases are not significantly influenced by ortho-directing groups and preferentially attack the inductively activated aromatic position next to the most electronegative heteroatom and/or the most acidic position available.[18]

Extensions of the manipulation of carboxylic functional group are ongoing in our laboratories and will be reported upon in due course.

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Note Added after ASAP Publication. Errors were detected in Scheme 2 and Table 2 in the version published ASAP May 17, 2005; the revised version was published ASAP May 18, 2005.

Supporting Information Available: Details of compound characterization. This material is available free of charge via the Internet at http://pubs.acs.org.

OL050761C

(16) Anderson, D. R.; Faibish, N. C.; Beak, P. *J. Am. Chem. Soc.* **1999**, *121*, 7553.

(17) There are two transition states, each with its own activation energy (E_{a1} and E_{a2}). The overall activation energy is the difference in energy between the reactant state and the highest energy transition state (E_a).

(18) See: (a) Bauer, W.; Lochmann, L. *J. Am. Chem. Soc.* **1992**, *114*, 7482. (b) Shi, G.; Takagishi, S.; Schlosser, M. *Tetrahedron* **1994**, *50*, 129.