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The First Regioselective Metalation and Functionalization of Unprotected 4-Halobenzoic Acids

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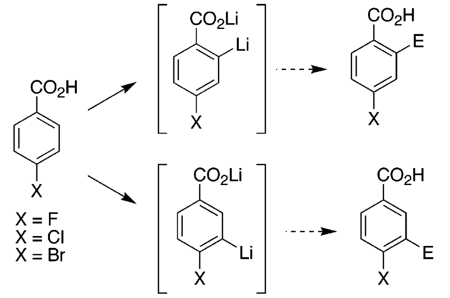
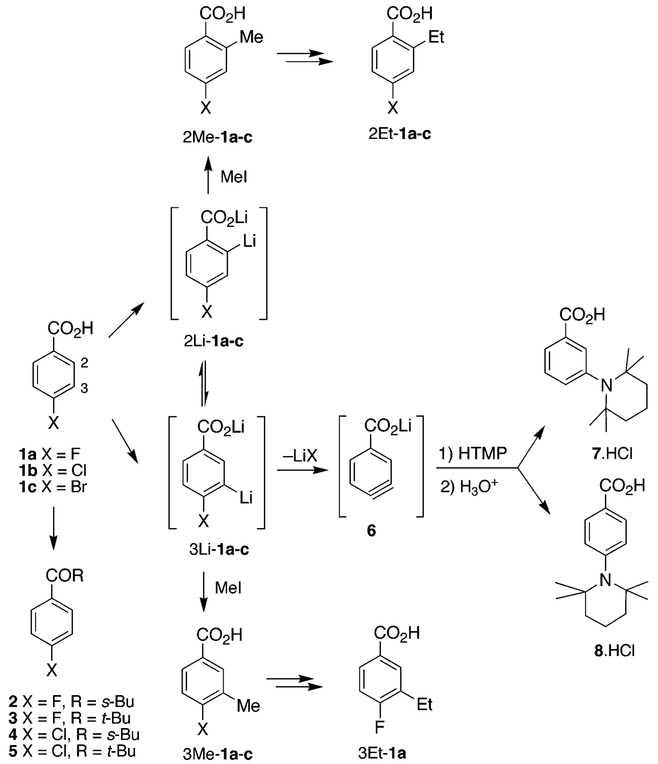


By treatment with *s*-BuLi, *s*-BuLi/TMEDA, or *t*-BuLi at ∼−78 °C, 4-fluoro- and 4-chlorobenzoic acids (**1a**,**b**) are metalated preferentially in the position adjacent to the carboxylate. A complete reversal in regioselectivity is observed for **1a** when treated with LTMP; a sequential process involving a rapid intraaggregate lithiation through a quasi dianion complex “QUADAC” is postulated to explain the unusual reactivity of Me_2S_2 and I_2.

Lithiation *ortho* to an unprotected carboxylic acid group in benzenoid systems is a powerful but still sparingly explored process which does not require protection and deprotection of the carboxylic acid group.[1] The presence of the carboxylate functionality makes benzoic acids more reactive and therefore more sensitive than their amide and oxazoline counterparts, thus requiring a gentler approach to lithiation. The carboxylate is susceptible to nucleophilic attack by alkyllithium bases such as *n*-butyllithium.[2] We have reported recently that lithium 3-chloro/bromo-2-lithiobenzoates can be generated upon treatment of 3-chloro/bromobenzoic acids with hindered lithium 2,2,6,6-tetramethylpiperidide (LTMP) at −50 °C.[3] 3-Fluorobenzoic acid also undergoes hydrogen/metal exchange at the position flanked by both substituents when treated with *s*-BuLi/TMEDA,[4] *n*-BuLi, or LDA.[5] These dianions can be trapped as such by electrophiles to afford a variety of simple 2-substituted-3-halobenzoic acids. On the other hand, addition of 2-fluorobenzoic acid to 2.2 equiv of LTMP at ∼−78 °C leads to deprotonation *ortho* to fluorine whereas lithiation of 2-chloro/bromobenzoic acids occurs *ortho* to the carboxylate functionality.[6]

SCHEME 1



We report here our first success in regioselective deprotonations of 4-halobenzoic acids **1a**−**c** (halo: F, Cl, Br) and describe the preparation of 3-substitued 4-fluorobenzoic acids. The most important question to be addressed was whether the protons of **1** in C-2 and C-3 positions possess sufficient difference in their acidities to allow regioselective deprotonations via appropriate bases. Toward this goal (Scheme 1 and Table 1), the acids **1a**−**c** in THF were submitted to a variety of bases in various (*n*) equivalents at the temperature *T* which was maintained for the time *t* prior to addition of an excess (4−10 equiv) of iodomethane (MeI) (normal addition). The yields were estimated by ^{1}H NMR analysis of the crude reaction mixtures, with pure sample being isolated and characterized.

Metalation of 4-fluoro- and 4-chlorobenzoic acids (**1a**,**b**) with 2.2 equiv of *sec*-butyllithium (*s*-BuLi) at −78 °C in THF occurs preferentially *ortho* to the CO_2Li group

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TABLE 1. Reactivity of Unprotected 4-Halobenzoic Acids 1a−c toward Strong Bases[a,b]

entry	acid	base	*n* (equiv)	*T* (°C)	*t* (h)	2Me-**1a−c**	3Me-**1a−c**	**1a−c**	others[c]
1	**1a**	*s*-BuLi	2.2	−78	0.5	71	20	0	4 [**2**]
2	**1a**	*s*-BuLi	2.2	−100	0.5	56	22	20	1 [**2**]
3	**1a**	*s*-BuLi/ TMEDA	2.2	−78	0.5	65	12	13	6 [**2**]
4	**1a**	*t*-BuLi	2.2	−78	2	40	24	17	15 [**3**]
5	**1a**	*t*-BuLi	2.2	−90	2	32	2	54	3 [**3**]
6	**1a**	*t*-BuLi	5	−90	2	51	5	13	14 [**3**]
7	**1b**	*s*-BuLi	2.2	−78	0.5	69	8	9	8 [**4**]
8	**1b**	*s*-BuLi	2.2	−100	0.5	64	0	31	3 [**4**]
9	**1b**	*s*-BuLi/ TMEDA	2.2	−78	0.5	73	0	18	5 [**4**]
10	**1b**	*t*-BuLi	2.2	−90	2	52	0	37	6 [**5**]
11	**1a**	LTMP	2.2	−78	4	0	40	47	12 [3Et-**1a**]
12	**1a**	LTMP	2.2	−50	1	0	50	36	9 [3Et-**1a**]
13[d]	**1a**	**LTMP**	**6**	**−50**	**2**	**0**	**86**	**10**	**3 [3Et-1a]**
14	**1b**	LTMP	2.2	−78	4	7	9	63	21 [2Et-**1b**]
15	**1b**	LTMP	2.2	−50	4	0	3	62	6 [2Et-**1b**], 8 [**7**], 6 [**8**]
16	**1c**	LTMP	2.2	−78	4	12	0	57	22 [2Et-**1c**], 15 [**7**], 12 [**8**]

[a] The product ratio was determined by ^{1}H NMR after acidification and extraction of the crude reaction mixture with ether. [b] **General Procedure.** To a stirred solution of base (*n* equiv) in anhydrous THF (15 mL) at *T* °C was added dropwise under argon the recrystallized 4-halobenzoic acid (3.5 mmol) dissolved in dry THF (7 mL). After being stirred for *t* h at *T* °C, the mixture was treated with an excess of iodomethane (17.5 mmol, 1.1 mL). The resulting solution was allowed to warm to ambient temperature, and water (30 mL) was added. The aqueous layer was washed with ether (20 mL), shaken, and then acidified with HCl 4 M. The mixture was then diluted with ether, and the organic layer was separated and dried with $MgSO_4$. Filtration and concentration in vacuo gave the crude benzoic acids. [c] Purified yields (chromatography). [d] Reverse addition.

(entries 1 and 7). Conducting the reaction at −100 °C led unexpectedly to a loss of regioselectivity in the case of **1a** (71:20 → 56:22, entry 2) while the acid **1b** was exclusively converted to 2Me-**1b** (64%, entry 8). These experiments strongly suggest that 2Li-**1a,b** formation is the kinetically controlled process for both substrates. Undoubtedly, a strong interaction between the highly electron-rich π-system of the carboxylate and the reagent places *s*-BuLi in the proximity of the *ortho*-carbon (complex induced proximity effect (CIPE) process).[7] This interaction is capable of counterbalancing totally the acidifying effect of the chlorine. The acid **1a** displays lower regioselectivity that can be attributed to a stronger acidifying effect of the fluorine atom in its *ortho* position.[8] The use of alkyllithium bases does not allow for the presence of a bromine or iodine atom on the arene due to competing halogen−metal exchange.[9]

Metalation is influenced by additives[10] and by variation of metalating agent.[11] To explore the effect of additive, **1a** was treated with *s*-BuLi/TMEDA (1:1, 2.2 equiv/−78 °C/2 h) followed by MeI quench to afford 2Me-**1a** and 3Me-**1a** in a 65:12 ratio (entry 3). Under the same conditions, **1b** was metalated regiospecifically in the position adjacent to the carboxylate (73%, entry 9). The deprotonation regioselectivity for **1a−c** as a function of base was tested using *tert*-butyllithium (*t*-BuLi) and an amide base, lithium 2,2,6,6-tetramethylpiperidide (LTMP). When submitted to *t*-BuLi metalation−MeI quench conditions (entries 4−6), higher yields of the C-2 isomer 2Me-**1a** were reached when 5 equiv of the hindered base was used at low temperature (−90 °C); however, longer reaction times were required. *t*-BuLi deprotonates exclusively the C-2 position of **1b** (entry 10). In entries 1−10, small amounts of the undesired ketones **2−5** resulting from the nucleophilic addition of the alkyllithium to the carboxylate were formed.[2]

By dropwise addition of iodomethane to a solution containing 3Li-**1a** formed by treatment of **1a** with 2.2 equiv of LTMP in THF at −78 °C (normal addition), 4-fluoro-3-methylbenzoic acid (3Me-**1a**) was formed as a sole isomer (40%, entry 11) along with 3-ethyl-4-fluorobenzoic acid (3Et-**1a**) arising out of lateral metalation of 3Me-**1a** (12%).[12] Iodomethane in excess does not destroy the remaining LTMP, which can then further metalate 2Me-**1a** lithium salt, even in the presence of iodomethane, to give 3Et-**1a**.[13]

At higher temperature (−50 °C), 3Li-**1a** is stable and does not decompose to give the benzyne **6** (entry 12).[3,14] By slow addition of 3Li-**1a** (prepared by treatment of **1a** with 6 equiv of LTMP at −50 °C) to MeI in THF (reverse addition),[2c,15] 3Me-**1a** was produced in satisfactory yield (86%) and formation of 3Et-**1a** was reduced to 3% (entry 13). The initial interaction of LTMP with the carboxylate of **1a** in the preequibrium complex is presumably too weak to counterbalance the acidifying effect of the fluorine atom, and a complete reversal in regioselectivity is observed (thermodynamic control).[6,7] Lithiation via lithium amides occurs presumably by a single electron transfer (SET) to initially generate a radical anion.[16] While there is electron spin resonance (ESR) evidence for the SET theory, the overall mechanistic pathway is still being debated.[17]

The reaction of 4-chloro- and 4-bromobenzoic acid (**1b,c**) with LTMP was next studied (entries 14−16).

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(13) **3Et-1a−c** were prepared in higher yield (respectively 57%, 60%, and 51%) by treatment of **3Me-1a−c** with LTMP (3 equiv, −50 °C/THF) followed by trapping with iodomethane.

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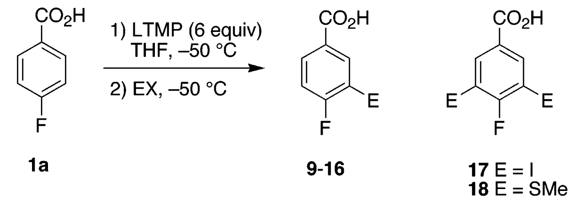
TABLE 2. Synthesis of 3-Substituted 4-Fluorobenzoic Acids[a,b]



entry	Add	EX/E	products (%)
1	N	I_2/I	39 [**9**], 47 (20*) [**17**]
2	R	I_2/I	83 (56*) [**9**], 13 [**17**]
3	N	Me_2S_2/MeS	41 [**10**], 42 (10*) [**18**]
4	R	Me_2S_2/MeS	89 (56*) [**10**], 8 [**18**]
5	N	D_2O/D[c]	86 [**11**]
6	N	CO_2/CO_2H	68* [**12**]
7	R	C_2Cl_6/Cl	80* [**13**]
8	R	$C_2Br_2Cl_4$/Br	65* [**14**]
9	R	PhCHO/PhCH(OH)	59* [**15**]
10	R	Me_3SiCl/Me_3Si[d]	25 (10*) [**16**]

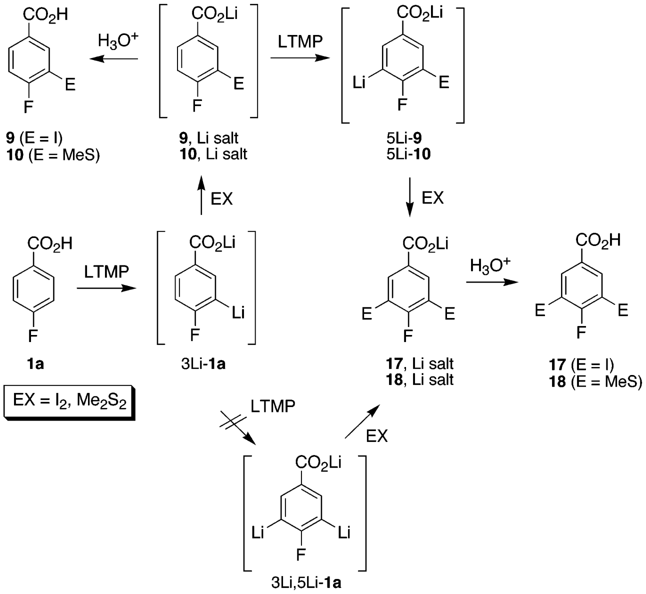
[a] Isolated yields (recrystallized or chromatographed) are followed by an asterisk (*). [b] Characterization was done by ^1H and ^{13}C NMR and IR spectroscopy and by matching melting points with those of authentic samples. See the Supporting Information. [c] The extent of deuteration was determined by ^1H NMR. [d] In situ quench technique. LTMP (2.2 equiv) and Me_3SiCl (3 equiv) were premixed prior to addition of 4-fluorobenzoic acid (**1a**).

Compared to **1a**, the acidity of the protons adjacent to chlorine and bromine is weaker. The deprotonation requires temperatures (~−50 °C) for which the dianions 3Li-**1b** and 3Li-**1c** are not stable.[18] LiX is rapidly ejected forming the transient lithium benzyne-4-carboxylate (**6**) which is readily attacked by tetramethylpiperidine (HTMP) both in the C-3 and C-4 position affording the anilinium chlorides **7** and **8**.[3] Compounds **7** and **8** were isolated from the aqueous layer by chromatography after acidic workup (HCl, 4 M) (entries 15 and 16). From the fact that both amino acids **7** and **8** arise from the dianions 3Li-**1b**,**c**, it can be deduced that the lithiation of **1b**,**c** is not site selective.

The established thermodynamic metalation conditions found in run 13 (Table 1) led to the development of a synthetically useful reaction. As summarized in Table 2, treatment of **1a** using 6 equiv of LTMP at −50 °C followed by addition of a variety of electrophiles provided a direct access to the acids **9**−**16**. Elemental iodine and dimethyl disulfide quenches (6 equiv) proceeded smoothly, leading, respectively, to 4-fluoro-3-(iodo/methylthio)benzoic acids **9** and **10** in 39% and 41% yield (entries 1 and 3), along with 4-fluoro-3,5-bis(iodo/methylthio)benzoic acids **17** (47%) and **18** (42%).

These results suggest the formation of 3Li-**1a** and 3Li,5Li-**1a** as intermediates (Scheme 2). Unlike aliphatic dimetalation which has been used extensively in organic synthesis,[19] dimetalation of aromatic compounds has remained relatively understudied and underutilized.[20] By changing the mode of deprotonation to addition of the mixture (formed by treatment of **1a** with LTMP at −50 °C) to a THF solution of the electrophile (reverse, R, addition, entries 2 and 4),[15] we hoped to minimize formation of the species **17** and **18**. Indeed, we discovered that their formation was reduced to 13% and 8%, respectively, under these conditions.

SCHEME 2



Next we attempted deuteration (D_2O) and carboxylation (CO_2) of **1a**. In the event, this resulted in the formation of only the d_3 isotopomer 3-deuterio-4-fluorobenzoic acid (**11**) and 4-fluorobenzene-1,3-dioic acid (**12**) with no detectable 3,5-bisdeutero-4-fluorobenzoic acid and 2-fluorobenzene-1,3,5-tricarboxylic acid (entries 5 and 6, normal addition). Likewise, reaction with hexachloroethane, dibromotetrachloroethane, and benzaldehyde afforded the monosubstituted products **13**−**15** exclusively in good recrystallized yields by reverse addition (entries 7−9). The in situ quench technique,[21] in which 4-fluorobenzoic acid (**1a**) was added to a solution containing LTMP (2.2 equiv) and chlorotrimethylsilane (3 equiv), gave 4-fluoro-3-(trimethylsilyl)benzoic acid (**16**) in low yield. The accompanying degradation products presumably arise from deprotonation of the trimethylsilyl group of **16** by LTMP.[22]

The seeming incompatibility of the results obtained can be resolved through a sequential mechanism involving, in the case of I_2 and Me_2S_2, the intermediate species **9** and **10**, Li salts (Scheme 2). The mechanism would require that (1) just prior to the addition of I_2/Me_2S_2, the reaction mixture contains 3Li-**1a** and four addition

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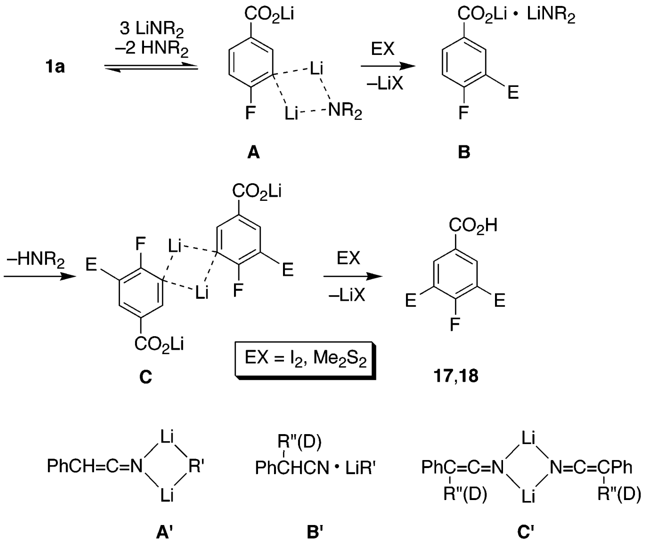
SCHEME 3



equivalents of LTMP; (2) 3Li-**1a** is quenched by some of the added electrophile to give **9** and **10**, Li salts; (3) contrary to the other electrophiles, I_2 and Me_2S_2 do not destroy the remaining LTMP, which can then further metalate **9/10**, Li salts even in the presence of electrophile, to give 5Li-**9** and 5Li-**10**; (4) 5Li-**9** and 5Li-**10**, like 3Li-**1a**, are captured by the electrophile to give **17** and **18**, Li salts, before they eliminate lithium fluoride to form arynes; and (5) Due to steric hindrance of attack by the third electrophile or to steric inhibition of the third lithiation, **17** and **18**, Li salts are not further metalated under the reaction conditions, so that no 4-fluoro-2,3,5-triiodo/trimethylthiobenzoic acid is formed. It is worthy of note that the second lithiation occurs at C-5 and not at the C-2 position.[23]

A sequential process involving a rapid intraaggregate lithiation through a transient QUAsi DiAnion Complex "QUADAC" **A** is postulated to explain the unusual reactivity of Me_2S_2 and I_2 in these transformations (Scheme 3). QUADACs have been sought in order to explain the fact that, while (supposed) dilithiation of $PhCH_2CN$[24] or other products[25] by a base R′Li followed by treatment with electrophiles R″X or D_2O often leads successfully to disubstituted products, the envisaged dilithium species $PhCLi_2CN$ (if it exists) has proved difficult to isolate. The existence of QUADAC **A′**,[24b] RCN·LiR′ complex of the type **B′**[26] and the dimeric "anion" **C′**[27] was demonstrated by means of X-ray crystal determinations. By analogy, in this work, QUADAC **A**, which could be apparented to a "preequilibrium complex" of the CIPE theory,[7] might be selectively substituted to give the $ArCO_2Li{\cdot}LiNR_2$ complex **B**, which in turn could be converted by an intramolecular proton shift (Me_2S_2 or I_2 compete with the complexed carboxylate for the base $LiNR_2$) to the possibly dimeric mono "anion" **C**; a further alkylation of the latter then would give **17**,**18**.[28,29]

The results reported in this paper corroborate the recent concept of how to achieve regiocontrol in hydrogen/metal exchange processes through mechanism-based matching of substituents and reagents.[30] Although the CO_2Li group does activate neighboring positions toward metalation, its effect remains fairly weak. This enables regioflexibility as most other electronegative substituents outperform a competing carboxylate group by their superior *ortho*-directing power.

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

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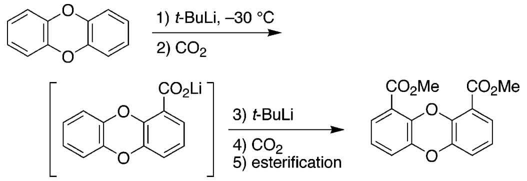
[28] While **1a** is not dilithiated when CO_2 is the electrophile (entry 6 of Table 2), reaction of dibenzodioxin with 2 molar equiv of *t*-BuLi at −30 °C followed by quench with CO_2 and esterification affords a symmetrical 1,9-diester. The initially formed 1-carboxylate is able to direct a second deprotonation of the 9-position during the quench. The intermediacy of a Quadac is clearly dependent on the nature of the electrophile and the substrate to be metalated. See: Palmer, B. D.; Boyd, M.; Denny, W. A. *J. Org. Chem.* **1990**, *55*, 438.



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