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Selectivities in Reactions of Organolithium Reagents with Unprotected 2-Halobenzoic Acids

Frédéric Gohier, Anne-Sophie Castanet, and Jacques Mortier*

Université du Maine and CNRS, Unité de chimie organique moléculaire et
macromoléculaire (UMR 6011), Faculté des sciences, avenue Olivier Messiaen,
72085 Le Mans Cedex 9, France

jacques.mortier@univ-lemans.fr

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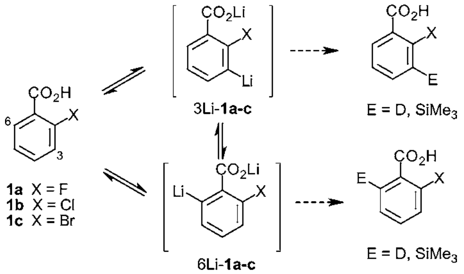
ABSTRACT



Exposing 2-fluorobenzoic acid (1a) to 2.2 equiv of LTMP at ca. –78 °C leads to deprotonation at the 3-position whereas 2-chloro/bromobenzoic acids (1b,c) are lithiated adjacent to the carboxylate. The resulting dianions 3Li-1a and 6Li-1b,c are trapped as such by chlorotrimethylsilane. In the absence of internal quench, 6Li-1b,c isomerize to the more stable 3Li-1b,c. The latter eliminate lithium halide and set free benzyne-3-carboxylate (2) that reacts regioselectively with LTMP to give 3-tetramethylpiperidinobenzoic acid (3).

Studies of selectivities of reactions of organolithium reagents with substrates bearing multiple sites for reaction can be useful for developing the understanding and use of these reagents. In the course of our investigation of the extension of the general ortho-lithiation of the lithium salts of unprotected benzoic acids,[1] we have shown recently that lithium 3-halo-2-lithiobenzoates (halo = F, Cl, Br), generated by the reaction of 3-halobenzoic acids and hindered lithium 2,2,6,6-tetramethylpiperidide (LTMP), react with a variety of electrophiles to give elaborated benzoic acids, most of which were unknown.[2]

We now describe our efforts in adding further to the synthetic utility of this approach by demonstrating a series of regioselective reactions derived from the competition of 2-fluoro/chloro/bromobenzoic acids (**1a**−**c**) with organolithiums. Results are listed in Table 1. Scheme 1 diagrams the manner in which the products are formed. The benzoic acid **1a**−**c** in THF was added to 2.2 equiv of base at the temperature *T* indicated in the table. The resulting reaction mixture was either stirred for the time *t* prior to addition of an excess (4−10 equiv) of deuterium oxide (D_2O) or immediately trapped by chlorotrimethylsilane (Me_3SiCl) (external quench (EQ) technique). The yields were estimated by an ^{1}H NMR analysis of the crude reaction mixtures, with pure sample being isolated and characterized. The isomer distribution was determined in each case to evaluate the orienting effect of the substituents on metalation.

Reaction of 2-fluorobenzoic acid (**1a**) with LTMP (2.2 equiv) at −50 °C followed by quench with a deuterium provided 3-tetramethylpiperidinobenzoic acid (**3**, 22%) plus a tiny yield of the d_3 isotopomer 2-fluoro-3-deuteriobenzoic acid (3D-**1a**, 5%, entry 1). Under these conditions, the acid **1a** is initially metalated ortho to the halogen. LiF is ejected from the resulting nucleophilic species 3Li-**1a** forming the now electrophilic, unsymmetrical lithium benzyne-3-carboxylate (**2**), which is readily attacked by LTMP furnishing the *cine* substitution product **3** as a single isomer after

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[1] (a) Mortier, J.; Moyroud, J.; Bennetau, B.; Cain, P. A. *J. Org. Chem.* **1994**, *59*, 4042. Reviews: (b) Mortier, J.; Vaultier, M. In *Recent Research Developments in Organic Chemistry*; Transworld Research Network: Trivandrum, India, 1998; Vol. 2, p 269. (c) Mortier, J.; Vaultier, M. *C. R. Acad. Sci. Ser. IIC* **1998**, *1*, 465.

[2] Gohier, F.; Mortier, J. *J. Org. Chem.* **2003**, *68*, 2030.

10.1021/ol034491e CCC: $25.00

Table 1. Deprotonation of 2-Halobenzoic Acids by Strong Bases[a,b]

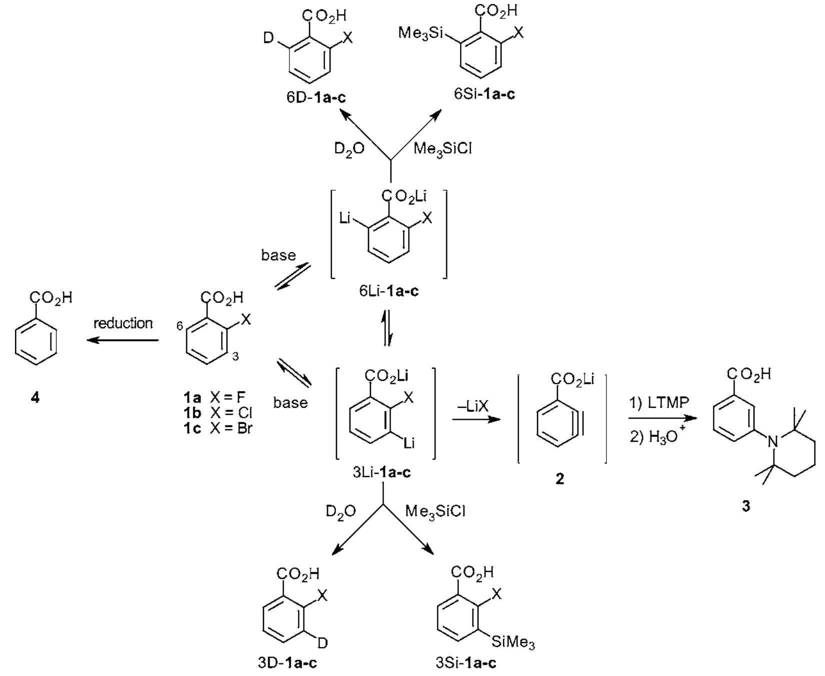
				D_2O[c]							Me_3SiCl[d]					
entry	acid	base[e]	*T* (°C)	*t* (h)	**1**[f]	6D-**1**	3D-**1**	**3**	**4**	others	**1**[f]	6Si-**1**	3Si-**1**	**3**	**4**	others
1	**1a**	LTMP	−50	1	41	0	5	22*	0	*g*	8	0	28	0	0	*g*
2	**1a**	LTMP	−78	1	48	0	21	9	0	0	0	0	62 (74*)	0	0	0
3	**1a**	LTMP	−90	1	79	0	21	0	0	0	0	0	57	0	0	0
4	**1a**	LTMP	−90	4	61	0	38	0	0	0						
5	**1a**	LTMP	−90	15	52	0	36	0	0	0						
6	**1a**	*s*-BuLi/TMEDA	−78	1	46	0	0	0	0	50 [**7**]	62	0	0	0	0	32 [**7**]
7	**1a**	*s*-BuLi	−78	0.5	50	0	0	0	0	29 [**7**]	53	0	0	0	0	30* [**7**], 11* [**9**]
8	**1a**	*n*-BuLi	−78	1	45	0	0	0	0	38 [**10**]	53	0	0	0	0	38* [**10**]
9	**1a**	*t*-BuLi	−78	2	9	0	0	0	0	63 [**8**]	15	0	0	0	0	51* [**8**], 10* [**11**]
10	**1b**	LTMP	−30	1	50	5	0	20	0	0	0	70	0	0	0	0
11	**1b**	LTMP	−50	1	75	4	0	8	0	0	0	78	0	0	0	0
12	**1b**	LTMP	−50	4	69	5	0	18	0	0						
13	**1b**	LTMP	−78	4	95	0	0	0	0	0	0	84 (74)	0	0	0	0
14	**1b**	*s*-BuLi/TMEDA	−78	0.5	5	85*	0	0	0	0	0	76*[h]	0	0	0	0
15	**1c**	LTMP	−50	1	3	0	0	6	86	0	0	(69)	0	0	7	0
16	**1c**	LTMP	−78	4	52	0	0	0	41	0	0	53 (74*)	0	0	7	0

[a] The structures of all products were confirmed by IR, MS, ^1H NMR, and ^{13}C NMR spectroscopy. [b] NMR yields (%). Isolated yields (recrystallized or chromatographed) are followed by an asterisk (*). See also footnote 9 and Supporting Information. [c] The base was allowed to react with **1a**−**c** at temperature *T* for *t* h *before* D_2O was added. [d] External quench (EQ) protocol. The benzoic acid **1a**−**c** was added to the base in THF at temperature *T*. The resulting reaction mixture was quenched immediately by Me_3SiCl. In parenthesis: in situ quench (ISQ) method. The base and Me_3SiCl were premixed prior to addition of the benzoic acid. [e] 2.2 equiv. [f] Recovered starting benzoic acid. [g] Degradation products. [h] *s*-BuLi/TMEDA and **1b** were stirred for 30 min at −78 °C prior to addition of Me_3SiCl.

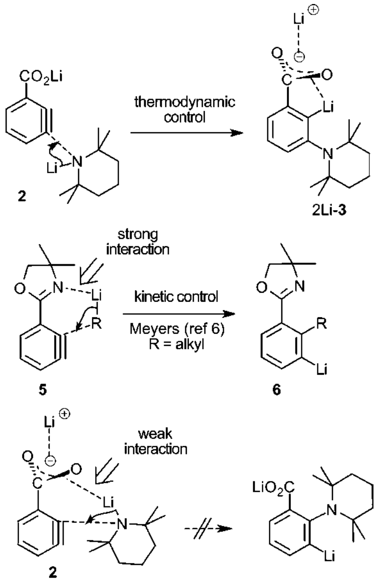
hydrolytic quenching. In agreement with other additions to benzynes containing an electron-withdrawing group,[3,4] the observed regioselectivity is due to a thermodynamic control in the addition of LTMP in a transition state that leads to the most stable (less basic) carbanion 2Li-**3** (chelation to the carboxylate) and hence the position of the lithium cation (Scheme 2).[5]

Meyers has shown[6] that *alkyllithium* addition to the 2,3-benzyne oxazolidines **5** gives preferentially the 3-lithio (kinetic) products **6** whose formation can be understood in terms of functional group−reagent preequilibrium complexation, which places the organolithium (RLi) in the proximity of the ortho carbon, prior to subsequent irreversible and necessarily intramolecular addition of the R group to the triple bond (Complex Induced Proximity Effect (CIPE) Process).[7] It seems reasonable to assume that the initial interaction of LTMP with the CO_2Li substituent of the aryne **2** is not strong enough to counterbalance the classical

Scheme 1



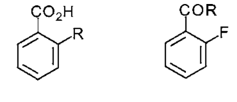
Scheme 2



resonance, stereoelectronic, inductive, and steric effects that would cause addition to occur meta to the carboxylate.

At −78 °C, the reaction of **1a** with LTMP followed by trapping with D_2O gave 3D-**1a** in 21% yield along with small amounts of the side product **3** (entry 2). The removal of the hydrogen H-3 has been shown to be rate determining in base-initiated aryne reactions.[8] Accordingly, although the dianion 3Li-**1a** is stable around −90 °C, the yield of 3D-**1a** decreases rapidly with the temperature (entries 1−3).[9] When quenched immediately thereafter with Me_3SiCl at −78 °C or below, 2-fluoro-3-trimethylsilylbenzoic acid (3Si-**1a**) was formed in 62% yield (EQ conditions). The deprotonation, which produces a small concentration of the trappable aryllithium 3Li-**1a**, is sufficiently rapid to make this process competitive in rate with the reaction of the hindered base with the in situ electrophile. The yield was enhanced when the base and Me_3SiCl were premixed prior to addition of the acid (in situ quench (ISQ) technique).[10] Chlorotrimethylsilane is known to react slowly with bulky bases such as lithium diisopropylamide (LDA) and LTMP, coexisting with them at low temperature over hours.[10,11] The same is the case with *tert*-butyllithium and *n*-butyllithium as recently shown by Schlosser.[12,13]

Whatever the nature of the electrophile, the reaction of **1a** with *sec*-butyllithium alone or chelated to 1 equiv of *N,N,N′,N′*-tetramethyl-1,2-ethylenediamine (TMEDA) did not afford the expected reaction products but the ipso product **7**, arising out of substitution of the fluorine atom by the alkyl group (entries 6 and 7). With Me_3SiCl, the ketone **9** was also detected (11%). In that case, the use of *s*-butyllithium does not suppress the reactivity of the carbonyl toward 1,2-addition.[1b,c,14] Nucleophilic addition of *n*-butyllithium to the CO_2Li functionality provided the butyrophenone **10** after aqueous workup (entry 8) whereas reaction of *tert*-butyllithium gave a mixture of 2-*tert*-butylbenzoic acid (**8**) and *tert*-butyl ketone **11** (entry 9).



7 R = *s*-Bu
8 R = *t*-Bu

9 R = *s*-Bu
10 R = *n*-Bu
11 R = *t*-Bu

The action of LTMP on 2-chlorobenzoic acid (**1b**) was next studied. Since the relative stability of 2-halophenyllithiums toward elimination of LiX normally follows the order LiBr (−100 °C) < LiCl (−90 °C) < LiF (−60 °C),[2,15] it was expected that the carboxylate group would greatly affect the elimination temperature. Astonishingly, whereas D_2O quenching experiments between −50 and −30 °C provided 3-tetramethylpiperidinobenzoic acid (**3**) in low yield along with small quantities of 2-chloro-6-deuteriobenzoic acid (6D-**1b**, entries 10−12), trapping with Me_3SiCl at −78 °C led to 6Si-**1b** free of any isomers in 84% yield (entry 13)! Since the acidity of the proton in the position adjacent to the chlorine atom is normally weaker than that of the fluorine,[1b,c,16] deprotonation presumably proceeds initially ortho to the CO_2Li functionality leading to 6Li-**1b**. The latter isomerizes partly to the less basic dianion 3Li-**1b**, which reacts further to give **3** via the benzyne **2**. The reaction of

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(3) (a) Hoffmann, R. W. *Dehydrobenzene and Cycloalkynes*; Academic Press: New York, 1967. (b) Wickham, P. P.; Hazen, K. H.; Guo, H.; Jones, G.; Hardee Reuter, K.; Scott, W. J. *J. Org. Chem.* **1991**, *56*, 2045.

(4) Tripathy, S.; LeBlanc, R.; Durst, T. *Org. Lett.* **1999**, *1*, 1973.

(5) The reaction of sodamide and potassium amide in liquid ammonia on 2-chloro- and 2-bromobenzoic acids (**1b**,**c**) produced mixtures of 2- and 3-aminobenzoic acids: (a) Biehl, E. R.; Li, H.-M. *J. Org. Chem.* **1966**, *31*, 602. (b) Biehl, E. R.; Nieh, E.; Li, H.-M.; Hong, C.-I. *J. Org. Chem.* **1969**, *34*, 500.

(6) Pansegrau, P. D.; Rieker, W. F.; Meyers, A. I. *J. Am. Chem. Soc.* **1988**, *110*, 7178.

(7) (a) Beak, P.; Meyers, A. I. *Acc. Chem. Res.* **1986**, *19*, 356. (b) Klump, G. W. *Rec. Trav. Chim. Pays-Bas* **1986**, *105*, 1.

(8) Roberts, J. D.; Semonev, D. A.; Simmons, H. E.; Carlsmith, L. A. *J. Am. Chem. Soc.* **1956**, *22*, 601.

(9) 3D-**1a** was prepared in higher yield (50%) from 2-fluoro-3-bromobenzoic acid (preparation: Moyroud, J.; Guesnet, J.-L.; Bennetau, B.; Mortier, J. *Bull. Soc. Chim. Fr.* **1996**, *133*, 133) by treatment with *n*-butyllithium (2.2 equiv) in THF at −78 °C followed by quench with D_2O. See Supporting Information.

(10) (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. (c) Lipshutz, B. H.; Wood, M. R.; Lindsley, C. W. *Tetrahedron Lett.* **1995**, *36*, 4385.

(11) Dimethyldichlorosilane, trimethyl and triisopropyl borates, and hexafluorocetone are also effective as in situ traps with LTMP: (a) Krizan, T. D.; Martin, J. C. *J. Am. Chem. Soc.* **1983**, *105*, 6155. (b) Caron, S.; Hawkins, J. M. *J. Org. Chem.* **1998**, *63*, 2054. Dimethyl sulfate and *n*-butyllithium are mutually compatible in THF at −78 °C: (c) Nwokogu, G. C.; Hart, H. *Tetrahedron Lett.* **1983**, *24*, 5725.

(12) Schlosser, M.; Guio, L.; Leroux, F. *J. Am. Chem. Soc.* **2001**, *123*, 3822.

(13) Nevertheless, Me_3SiCl does not survive in the presence of *s*-BuLi or *s*-BuLi: TMEDA at −85 °C in THF. See Supporting Information.

(14) Depending on the nature of the base and the reaction conditions, treatment of a lithium benzoate with an additional equivalent of an organolithium reagent can lead to addition rather than metalation, providing useful ketone syntheses: (a) Jorgenson, M. J. *Org. React.* **1970**, *18*, 1. (b) Ahn, T.; Cohen, T. *Tetrahedron Lett.* **1994**, *35*, 203. See also: (c) Plunian, B.; Mortier, J.; Vaultier, M.; Toupet, L. *J. Org. Chem.* **1996**, *61*, 5206.

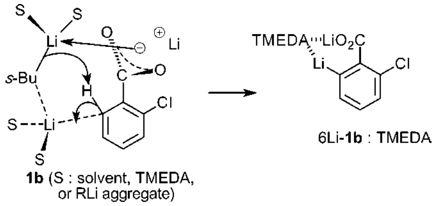
(15) Caster, K. C.; Keck, C. G.; Walls, R. D. *J. Org. Chem.* **2001**, *66*, 2932.

(16) (a) Mongin, F.; Schlosser, M. *Tetrahedron Lett.* **1997**, *38*, 1559. (b) Moyroud, J.; Guesnet, J.-L.; Bennetau, B.; Mortier, J. *Tetrahedron Lett.* **1995**, *36*, 881.

6Li-**1b** with Me$_3$SiCl is comparatively faster and the system balances to form 6Si-**1b** exclusively.[17]

Treatment of **1b** with 2.2 equiv of a 1:1 *s*-BuLi/TMEDA complex at -78 °C in THF provided 6D-**1b** (85%) and 6Si-**1b** (76%) (entry 14). The regiochemistry observed can be explained in terms of a CIPE process in which kinetic domination over the resonance and inductive effects is operative (Scheme 3).[7] Thus, the organolithium approaches the benzoate **1b** by chelation with the highly electron-rich π-system in the carboxylate, and this complex forces the deprotonation to occur into the ortho position of the benzoate leading to 6Li-**1b** and ultimately the products 6D-**1b** and 6Si-**1b**. Since 6Li-**1b** isomerizes to 3Li-**1b** when LTMP is the base (vide supra), it is conceivable that the interaction between 6Li-**1b** and the TMEDA molecule stabilizes the chelate 6Li-**1b**:TMEDA.

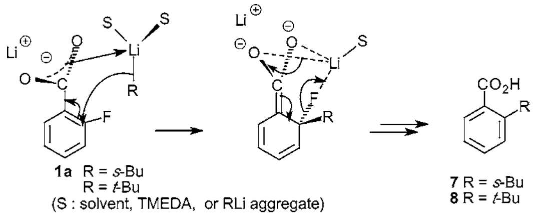
Scheme 3



The behavior of 2-bromobenzoic acid (**1c**) is of particular interest. Some rare examples of the literature indicate that the ortho-acidifying capacity of bromine is comparable with that of chlorine.[16,18] When treated successively with LTMP (-50 °C) and D$_2$O, **1c** gave the parent benzoic acid (**4**), and traces of **3** resulting from the decomposition of 3Li-**1c**.[19] Since the LTMP molecule does not have hydrogen atoms connected to the β-carbons, and is not capable of hydride donation, the formation of **4** is thought to proceed via a single electron-transfer process (SET). Me$_3$SiCl trapping makes it possible to reduce dramatically the formation of **4**. Compound 6Si-**1c** was prepared in satisfying yield under these conditions (53%, EQ protocol).[20,21] The yield of 6Si-**1c** was enhanced (up to 74%) when the base and Me$_3$SiCl were premixed prior to addition of **1c** (ISQ conditions).

From the fact that 2-chloro- and 2-bromobenzoic acids (**1b**,**c**) do not lead to the ipso substitution products **7** and **8** when treated with either *s*-BuLi or *t*-BuLi whereas 3Li-**1b**,**c** are expected to be less stable than the corresponding fluoro derivative 3Li-**1a** toward LiX-elimination, we deduce that the formation of **7** and **8** arises from an addition−elimination sequence (S$_N$Ar mechanism) rather than from a reaction proceeding through an aryne intermediate. While *n*-butyllithium displays a strong nucleophilic character and a low complexing ability toward the carboxylate (entry 8),[2] a critical transition-state geometry must be achieved between *s*-BuLi/*t*-BuLi, and the substrate in a preequilibrium complex for *direct*, rate-determining nucleophilic addition of RLi followed by nucleofugal elimination of the fluoride enhanced by strong chelation of the lithium cation (Scheme 4).[22] Most striking, the reactivity of the alkyllithiums follows the order *n*-Bu < *s*-Bu < *t*-Bu hence there are virtually no steric effects of the alkyl group to inhibit fluorine displacement. The mode of entry of the alkyllithium would be relatively free of nonbonded interactions thus allowing bulky alkyl groups easy access to the sp^2 carbon at the ortho position.[23] Further studies of this interesting phenomenon are currently in progress and will be reported soon.

Scheme 4



In conclusion, intramolecular competitive lithiations between the unprotected carboxylic acid and fluorine, chlorine, and bromine atoms in ortho-disubstituted benzenes under the prescribed conditions follow the order (Cl, Br) < CO$_2$H < F. Development of this metalative approach for synthesis of contiguously substituted benzoic acids,[24] as well as studies of the underlying structure−stability relationships of other lithium benzoates, are currently in progress in our laboratories.

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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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[17] See also: Graneto, M. J.; Phillips, W. G.; Van Sant, K. A.; Walker, D. M.; Wong, S. C. European Patent 538231, 1992.

[18] Wang, A.; Maguire, J. A.; Biehl, E. *J. Org. Chem.* **1998**, *63*, 2451.

[19] Reduction of aryl halides with lithium amides was observed shortly after lithium amides were developed as a new class of compounds: (a) Ziegler, K.; Ohlinger, H. *Justus Liebigs Ann. Chem.* **1932**, *495*, 84. Review: (b) Majewski, M.; Gleave, D. M. *J. Organomet. Chem.* **1994**, *470*, 1. See also: (c) Creary, X. *J. Org. Chem.* **1980**, *45*, 2419.

[20] The position of the silicon atom in 6Si-**1c** was confirmed after subsequent bromination in carbon tetrachloride, which afforded 2,6-dibromobenzoic acid exclusively (23%). See Supporting Information.

[21] Gilman reported in 1947 the formation and the stability at -78 °C of lithium 2-lithiobenzoate derived from 2-bromobenzoic acid and *n*-butyllithium in diethyl ether: (a) Gilman, H.; Arntzen, C. E. *J. Am. Chem. Soc.* **1947**, *69*, 1537. (b) Parham, W. E.; Bradcher, C. K. *Acc. Chem. Res.* **1982**, *15*, 300.

[22] Only a few examples of fluorine displacement reactions have been explained in terms of a CIPE process: (a) Meyers, A. I.; Reuman, M.; Gabel, R. A. *J. Org. Chem.* **1981**, *46*, 783. (b) Meyers, A. I.; Gabel, R. A. *J. Org. Chem.* **1977**, *42*, 2653. See also: (c) Strekowski, L.; Janda, L.; Patterson, S. E.; Nguyen, J. *Tetrahedron* **1996**, *52*, 3273. (d) Field, L. D.; Pierens, G. K. *Tetrahedron* **1990**, *46*, 7059. (e) Inukai, Y.; Takuma, K.; Toritani, K.; Sonoda, T.; Kobayashi, H. *Bull. Chem. Soc. Jpn.* **1984**, *57*, 225.

[23] There also exists the possibility that these displacements are proceeding via an electron-transfer process.

[24] The reactivity of I$_2$, MeI, PhCHO, C$_2$Br$_2$Cl$_4$, and CO$_2$ as electrophiles is similar to that observed with D$_2$O. When treated with *s*-BuLi/TMEDA, 2-chlorobenzoic acid (**1b**) gives the expected *ortho*-substituted benzoic acids in good yield.