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C–H Activation

A Study of BF_3-Promoted *ortho* Lithiation of Anilines and DFT Calculations on the Role of Fluorine–Lithium Interactions**

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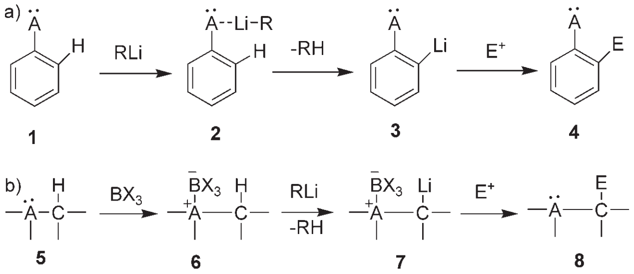
Synthetic and mechanistic aspects of heteroatom directed *ortho* metalation (DoM) of aryl substrates (**1**→**2**→**3**→**4**, Scheme 1) have fascinated organic chemists for more than six decades.[1] A hierarchy of DoM groups has been experimentally established and rationalized in terms of the inductive effect of the heteroatom and its ability to coordinate with the metal, which is usually the Li atom of the base that is used for deprotonation (complex induced proximity effect (CIPE)).[2] Since a nitrogen atom occupies a very low position in this established hierarchy, it was of interest to see if *ortho* metalation of anilines could be facilitated by Lewis acid complexation. This relatively recent methodology has been shown to be useful for lithiation of weakly acidic C–H centers α to the heteroatoms of many aliphatic tertiary amines and phosphines (**5**→**6**→**7**→**8**).[3] Lewis acid activation of alkyl lithium reactions with a variety of other heteroatom-containing substrates is also well documented;[4] for example, the 1,2-additions to imines, oximes, carbonyl compounds, and the cleavage of acetals, epoxides, and unstrained cyclic ethers. The effect of the Lewis acid is often evidenced by the improved reaction rates or changes in the chemo-, regio-, or stereoselectivities. However, not much is known about its mode of action, especially with respect to the role of CIPE.[3a–c,4] Since CIPE is considered to be particularly important in DoM reactions,[2,5] the effect of a Lewis acid on the metalation of anilines could offer some insight into this mechanism, which may also provide synthetic advantages. Apriori, coordination of the nitrogen atom lone pair with a Lewis acid should increase its inductive effect but may compromise its CIPE.



Scheme 1. a) Directed *ortho* metallation of aryl substrates. b) Lithiation of weakly acidic α-C–H centers. A = heteroatom; X = F, H.

In this work Lewis acid promoted lithiations were carried out by adding one equivalent of $BF_3{\cdot}Et_2O$ to a solution of *N*,*N*-dimethylanilines in THF prior to the addition of *s*BuLi (2 equiv) at −78 °C. The electrophile was introduced after 1 hour of stirring at −78 °C. Under these conditions, *ortho*-substituted products were obtained in 40–50 % yield (Table 1).[6a] The conditions were chosen so that product formation was not observed if BF_3 was omitted (Table 1, entries 1 and 8). Benzophenone was used as the electrophile

Table 1: Lithiation of Lewis acid complexed *N*,*N*-dimethylanilines with *s*BuLi.[a]

Entry	Substrate	Lewis acid	E^+	Product	Yield [%][b]
1	**9a**	None	Ph_2CO	None	–
2	**9a**	BF_3	Ph_2CO	**13a**, E = C(OH) Ph_2	41
3	**9a**	BF_3	PhCHO	**13a**, E = CH(OH)Ph	51
4	**9a**	BF_3	CH_3OD	**13a**, E = D	40[c]
5	**9a**	BF_3	Ph_2CO	**13a**, E = C(OH)Ph_2	60[d]
6	**9a**	BF_3	Ph_2CO	**13a**, E = C(OH)Ph_2	59[e]
7	**9a**	BH_3	Ph_2CO	None	–
8	**9b**	None	Ph_2CO	None	–
9	**9b**	BF_3	Ph_2CO	**13b**, E = C(OH)Ph_2	40[f,g]
10	**9c**	None	Ph_2CO	**14c**, E = C(OH) Ph_2	15
11	**9c**	BF_3	Ph_2CO	**13c**, E = C(OH) Ph_2	30[h]
12	**9a** + anisole	BF_3	Ph_2CO	**13a**, E = C(OH) Ph_2	25[i]

[a] Conditions: 2 equiv of *s*BuLi in THF at −78 °C. [b] Yields are for pure products isolated after chromatography/recrystallization. [c] Yield estimated from ^1H NMR spectrum of the crude product mixture. [d] With *t*BuLi as the base. [e] With Schlosser's base. [f] 24 % of **14b** was also formed. [g] No product formation with corresponding *o*,*m*-anisidines. [h] 3 % of **14c** was also formed. [i] Only one equivalent of base was used, no anisole substitution product detected. **a**: R = H; **b**: R = OMe; **c**: R = Cl.

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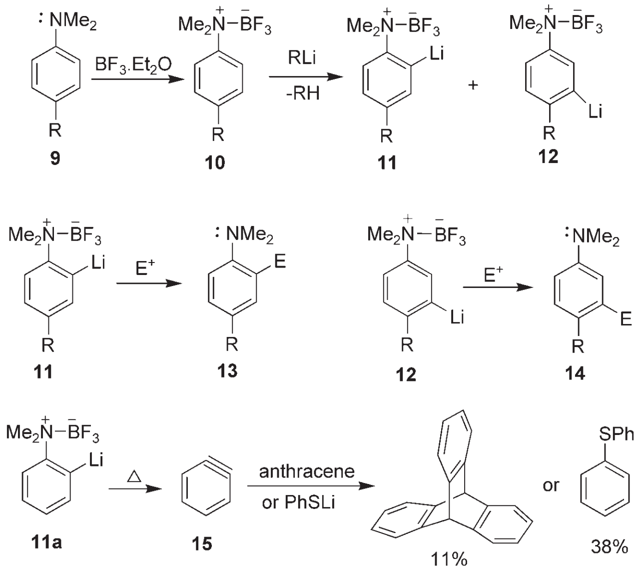
because of the ease in NMR characterization of the *ortho*-substitution products.

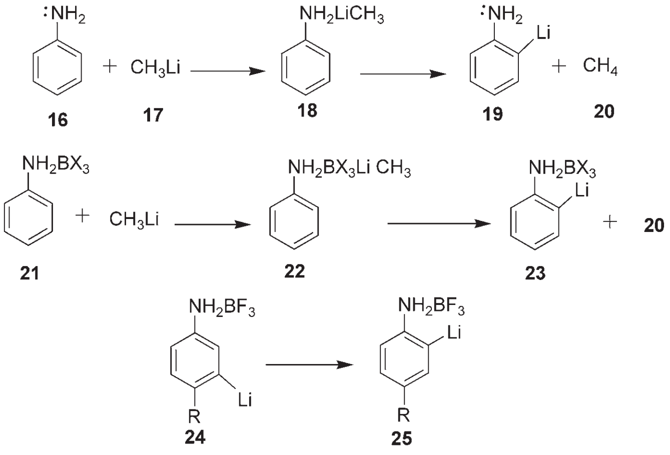
The yield could be improved to 60% by using *t*BuLi or Schlosser's base (*s*BuLi + *t*BuO$^-$K$^+$, Table 1, entries 5 and 6). Reactions using BH_3 or BCl_3 as the Lewis acid, or *n*BuLi, MeLi, or PhLi as the base were unsuccessful. In an effort to improve the yield, the time for the lithiation with *s*BuLi was increased to 6 hours at −78°, but product formation was not observed.[6a,b] Product formation was not detected at −78°C when lithium 2,2,6,6-tetramethylpiperidide (LTMP) was used as the base, but at 0°C fragmentation to benzyne was observed (**11a**→**15** + Me_2NBF_3Li) which was trapped with anthracene or PhSLi (Scheme 2).



Scheme 2. General reaction scheme: generation of the lithiated aryl ring (top), reaction of each of the lithiated regioisomers with an electrophile (middle), and trapping of the in situ generated benzyne species (bottom). E = electrophile. For structures: a) R = H, b) R = OMe, c) R = Cl.

Lithiation/substitution of *p*-*N*,*N*-dimethylaminoanisole (**9b**) is reported to occur exclusively at the position *ortho* to the methoxy substituent with *s*BuLi in ether at 35 °C.[5] At −78 °C in THF reaction was not observed with **9b** (Table 1, entry 8), however, upon the addition of one equivalent of $BF_3{\cdot}Et_2O$ prior to treatment with the base the metalation was accelerated and occurred to a greater extent at the position *ortho* to the amino group (Table 1, entry 9). The results with *p*-chloro-*N*,*N*-dimethylaniline were even more striking. In the absence of BF_3 some substitution at the *ortho* position to the chloro group was observed, but with prior BF_3 complexation substitution was almost exclusively at the position *ortho* to dimethylamino group (Table 1, entries 10 and 11). In an intermolecular competition experiment it was also found that in a 1:1 mixture of anisole and *N*,*N*-dimethylaniline, lithiation can be completely directed to the amine by prior addition of one equivalent of $BF_3{\cdot}Et_2O$ (Table 1, entry 12).

To delineate the respective roles of the inductive and the CIPE effects in Lewis acid promoted metalations, DFT computations of the structures and the energies of the entities involved in the lithiation were carried out at the B3LYP level by using aniline and methyl lithium as model reactants (Scheme 3).[7a]



Scheme 3. General structures used for computational studies: lithiation of aniline (top), lithiation of aniline complexed to a boron atom (middle), and regioisomers of lithiated ring (bottom). For structures: **a**: R = H; **b**: R = OMe; **c**: R = Cl.

The computed energy values involved in the studied transformations are presented in Table 2. It can be seen that the heat of association of MeLi with aniline is about the same as that with BX_3-complexed aniline (Table 2, entries 1–3). The BX_3 coordination renders both ΔH and E_{act} more favorable for lithiation, and to a greater extent in the case of BF_3 (Table 2, entries 4–6; 9–11). Another interesting feature of the present DFT results is that in the cases where BF_3 is complexed with *p*-anisidine and *p*-chloroaniline, the intermediates with the Li atom *ortho* to the amino group (**25b** and **c**) are more stable than those with the Li atom *ortho* to the methoxy or chloro groups (**24b** and **c**, Table 2, entries 12, 13); this result is in qualitative agreement with the experimentally observed regioselectivity (Table 1, entries 9 and 11).

Table 2: Computed heats of reaction and activation energies.

Entry	Reaction	$\Delta H/E_{act}$ [kcal mol^{-1}]
1	**16** + **17**→**18**	$\Delta H = -16.56$
2	**21** + **17**→**22** (X = F)	$\Delta H = -16.12$
3	**21** + **17**→**22** (X = H)	$\Delta H = -16.03$
4	**16** + **17**→**19** + **20**	$\Delta H = -15.94$
5	**21** + **17**→**23** + **20** (X = F)	$\Delta H = -31.94$
6	**21** + **17**→**23** + **20** (X = H)	$\Delta H = -30.93$
7	**21** + **17**·2 Me_2O→**23**·2 Me_2O + **20** (X = F)	$\Delta H = -29.22$
8	**21** + **17**·2 Me_2O→**23**·2 Me_2O + **20** (X = H)	$\Delta H = -24.80$
9	**18**→**19** + **20**	$E_{act} = 22.60$
10	**22**→**23** + **20** (X = F)	$E_{act} = 11.20$
11	**22**→**23** + **20** (X = H)	$E_{act} = 14.20$
12	**24**→**25** (R = OMe)	$\Delta H = -10.67$
13	**24**→**25** (R = Cl)	$\Delta H = -13.01$

Absolute energy values calculated at B3LYP/6-31+G* level + ZPE scaled by 0.9806.

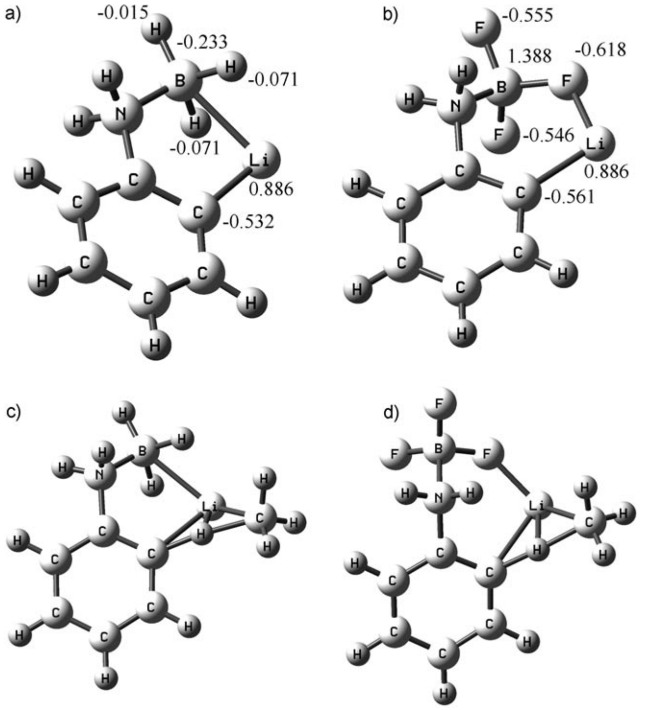


Figure 1. 3D-structures of the lithiated intermediates (**23**) and the transition states (**22 TS**) that lead to their formation. The important partial atomic charges are also shown. a) **23** (X = H): the Li atom is bonded to the B atom with a bond length of 2.21 Å, b) **23** (X = F): the Li atom is bonded to the F atom with a bond length of 1.80-Å, c) transition-state **22** (X = H): the Li–B bond length is 2.27 Å, and d) transition-state **22** (X = F): the Li–F bond length is 1.82 Å.

Calculations of the natural bond orbital (NBO)-based partial atomic charges,[8] show a negative charge of −0.54 on the lithiated carbon atom at the *ortho* position of aniline, and there is no significant change in this charge upon coordination of the nitrogen center with BH_3 or BF_3 (Figure 1).[7b] Even within the known limitations of the method,[8] this result is surprising, as well as contrary to apriori assumptions;[3] this suggests a more important role for dipole interactions and lithium chelation. In contrast, there is clear indication of a strong interaction between the fluorine and lithium atoms based on the computations of lithiated intermediate **23** (X = F). Although one may tend to consider the lithium–carbon bond as the primary bond, there is, in terms of an atoms in molecule (AIM) analysis,[9] a six-membered ring critical point in **23** and a remarkable similarity between the Li−F and Li−C bonds in terms of charge (C = −0.56, F = −0.62, Li = 0.90), bond length (C−Li = 2.01 Å, F−Li = 1.80 Å), ρ (C−Li = 0.039, F−Li = 0.036), $\nabla^2\rho$ (C−Li = 0.19, F−Li = 0.29), and ε (C−Li = 0.02, F−Li = 0.02). AIM computations on the solvate, **23**$\cdot 2\,Me_2O$, give essentially similar results, including a six-membered ring critical point with the expected decrease in electron density of the Li bonds to F and C (see the Supporting Information). In comparison, in the lithiated BH_3 complex of **23** (X = H) there is a five-membered ring critical point with Li···B distance of 2.21 Å (charge Li = 0.89, B = −0.23). Lithium is also in contact with two weakly charged hydrogen atoms ($\mathrm{Li{\cdots}H_1} = 1.92$ Å, $\mathrm{Li{\cdots}H_2} = 1.92$ Å), which results in high ellipticity of the Li−B bond ($\varepsilon = 2.74$).

From the NBO and AIM analyses described above, and the geometry shown in Figure 1, we infer that in case of BH_3 the primary electrostatic interaction of Li^+ is with the negatively charged boron atom, which brings two hydrogen atoms close to the Li center causing a greater spatial requirement for this bond. In contrast, with BF_3 even a single Li−F bond can, because of its strength, provide effective stabilization and this results in a six-membered chelation ring with less crowding around lithium (cf. X = F and X = H; Figure 1); this may also be additionally relevant for the solvated moieties. The dichotomy in BH_3 and BF_3 bonding to Li can not only help to explain the superior effectiveness of BF_3 in promoting lithiations, but also explain the gross variations in crystal structure of $LiBH_4$ (Li···B = 2.47-2.54 Å, Li···H = 1.98, 2.02, 2.15 Å) and $LiBF_4$ (F-Li = 1.85 Å).[10–12]

In conclusion we have shown that, in principle, BF_3 complexation methodology can be extended to directed *ortho* metalations and thereby improve the poor ability of the dimethyl amino group in DoM's to exceed the directing ability of even chloro and methoxy groups. The DFT computations are in line with the experimental findings on the comparative reactivity and regioselectivity of the reaction, and clearly indicate that chelation of lithium by BX_3 coordinated to a nitrogen center (CIPE) has an important role; an aspect largely ignored in earlier mechanistic considerations on BX_3 acceleration of alkyl lithium reactions.[3,4] Interestingly, in the lithiated intermediates complexed to BH_3, tridentate chelation of Li^+ is indicated, whereas a two-center F−Li bond, with characteristics remarkably similar to those of the C−Li bond, is seen in the corresponding BF_3 complexes. In view of the recent demonstration of the acceleration of metathesis by chelation of ruthenium to an aryl fluorine,[13] the effect of BF_3 on transition-metal-mediated reactions of heteroatom-containing substrates also needs to be explored, and if successful it can have an impact on the scope of this chemistry.[14]

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