Abstract: Rate studies of the lithiation of benzene and related alkoxy-substituted aromatics by n-BuLi/TMEDA mixtures implicate similar mechanisms in which the proton transfers are rate limiting with transition structures of stoichiometry [(n-BuLi)2(TMEDA)]2(Ar−H)]n (Ar−H = benzene, C6H5OCH3, m-C6H4(OCH3)2, C6H5OCH2-OCH3, and C6H5(OCH2CH2)2Ni(CH3)2). Cooperative substituent effects and an apparent importance of inductive effects suggest a mechanism in which alkoxy−lithium interactions are minor or nonexistent in the rate-limiting transition structures. Supported by ab initio calculations, transition structures based upon triple ions of general structure [(n-BuLi)2Li]+/[Li(TMEDA)]2 are discussed.

Introduction

There are few reactions within organolithium chemistry that have captivated the attention of organic chemists more so than ortholithiation (eq 1). Exhaustive reviews by Gschwend in 19791 and Snieckus in 19902 illustrate the enormous collective effort of both academic and industrial chemists to exploit ortholithiations for the regiocontrolled synthesis of polysubstituted arenes.3 There has been a substantially smaller effort to investigate the mechanistic origins of the ortho selectivity.4−8 Early suggestions that substituents simply acidify ortho protons4 soon gave way to increasingly sophisticated models involving delivery of the organolithium via a discrete lithium−substituent interaction on so-called complex-induced proximity effect (CIPE).5 While the details of the lithium−substituent interactions have been the topic of considerable debate, the premise of a critical metal−substituent interaction is firmly entrenched as part of conventional wisdom. Only Schlosser and co-workers have vigilantly examined and supported the importance of inductive effects.12,14

The well-documented ortho selectivities appear to answer the title question at the outset: Ortholithiation is, by definition, “directed.” However, what is meant by “directed” is not so clear. Chart 1 depicts five arenes along with their relative rate constants for lithiation by n-BuLi/TMEDA.12,13 These examples underscore several key questions:

(1) Are there several mechanisms for ortholithiation? Contrasting reactivities of benzene (1) and anisole (2) could be construed as evidence that there are at least two mechanisms. Solvent-dependent changes in ortho selectivities in dissubstituted aromatics offer ample evidence of several viable mechanisms for ortholithiations.13,14,21 Meyers reported a particularly revealing

(20) A more extensive investigation of the relative reactivities of methoxy-substituted arenes by sec-BuLi/hexane was recently reported by Schlosser and Maggi.15 The values of kobs in Chart 1 are not statistically weighted compared with those of Schlosser.
ing example in which the high selectivity for lithiation ortho to an oxazoline could be redirected ortho to a methoxy moiety by adding the strongly coordinating hexamethylphosphoramide (HMPA).22

(2) Does the ortho selectivity for the lithiation of anisole stem from a discrete Li−OMe interaction (6)—the so-called complex-induced proximity effect (CIPE)?23 The high ortho selectivity for anisole and the nearly 1000-fold greater reactivity of anisole when compared with benzene are consistent with a discrete Li−OMe interaction central to most contemporary mechanistic discussions. Beak and Smith provided kinetic evidence that ortholithiations of aryl carboxamides occur by such a delivery mechanism.16 On the other hand, Schleyer has adamantly reiterated that it is not precomplexation that is important but the existence of a stabilizing metal−substituent interaction at the rate-limiting transition structure.7,19

(3) Does the cooperative influence of meta-disposed methoxy groups of resorcinol dimethylether (3) demand a third mechanism involving ligation by both methoxy moieties concurrently as shown in 79,23,24 If the ortho selectivity arises exclusively from a formal delivery-based mechanism via a single Li−OMe interaction, lithiation of 3 should afford a statistical 1:1 mixture25 of aryllithiums 8 and 9.

(4) Do the difunctional substituents in substrates 4 and 5 alter the rates and mechanisms through polydentate coordination to lithium9,23,26 The 14-fold rate increase for the lithiation of methoxymethoxy-substituted arene 4 (relative to anisole) is consistent with competition studies showing the methoxymethoxy moiety to be a superior ortho-directing group.24 Although the rate increase could support putative multidentate interactions with lithium (10), it is also well within reason for a model based largely upon inductive effects.12,14 The rates for the lithiation of 5 bearing a potentially chelating (2-dimethylamino)ethoxy moiety provide little evidence of a putative56,27 polydentate interaction (e.g., 11).

(5) Can we justify invoking as many as five distinctly different mechanisms to explain the ortholithiation rates illustrated in Chart 1? It seems unlikely.

(6) Are relative rate constants diagnostic of mechanistic homology (or lack thereof)?28–31 We have previously challenged the validity of relative rate constants (krel) as mechanistic probes.29,30 Two recent rate studies provide striking cases in point: (1) LDA-mediated ester enolizations in four different solvents proceed at nearly indistinguishable relative rates by four distinctly different mechanisms;31 (2) LiHMDS-mediated ketone enolizations in a range of monodentate solvents span a 3000-fold range of rates while proceeding via effectively the same mechanism.32 We maintain that fundamental mechanistic differences are best documented at the level of the rate equation.

As part of our effort to understand how TMEDA influences organolithium structures and reactivities,29,33 we have determined rate laws for the n-BuLi/TMEDA-mediated ortholithiations of the arenes shown in Chart 1. We will provide evidence that all proceed by a common mechanism entailing n-BuLi dimers. The rate studies support models based upon inductive effects12,14 but do not necessarily support models relying on the complex-induced proximity effects9 involving discrete lithium−substituent interactions. We explored a triple ion-based mechanism (Scheme 1) by ab initio computational studies. We hasten to add that the results described below do not conflict with Beak and Smith’s conclusion that carboxamides direct ortholithiation
Table 1. Summary of Rate Data for the n-BuLi/TMEDA-mediated Lithiation of Arenes 1–5

<table>
<thead>
<tr>
<th>Ar–H</th>
<th>temp (°C)</th>
<th>n-BuLi order</th>
<th>$k_f/k_D$</th>
<th>$k_{ad}(0 , ^\circ C)^{\text{a}}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0</td>
<td>0.96 ± 0.07</td>
<td>23 ± 4</td>
<td>0.0012</td>
</tr>
<tr>
<td>2</td>
<td>0</td>
<td>0.97 ± 0.06</td>
<td>20 ± 3</td>
<td>1.0</td>
</tr>
<tr>
<td>3</td>
<td>−35</td>
<td>0.93 ± 0.07</td>
<td>30 ± 4</td>
<td>60</td>
</tr>
<tr>
<td>4</td>
<td>−35</td>
<td>1.07 ± 0.04</td>
<td>34 ± 5</td>
<td>14</td>
</tr>
<tr>
<td>5</td>
<td>0</td>
<td>0.90 ± 0.03</td>
<td>a</td>
<td>1.3</td>
</tr>
</tbody>
</table>

Not measured. Chart 1.

via a discrete metal–ligand interaction and should not be extrapolated to other substrate–base combinations.

Results

General. n-BuLi was prepared and recrystallized as described previously. TMEDA was purified via recrystallization of the corresponding hydrochloride salt and sequentially dried over sodium-benzophenone and Na–Pb alloy prior to distillation. n-BuLi/TMEDA in hydrocarbons has been shown to be dimer with [n-BuLi] referring to the concentration of monomer subunit (normality). [TMEDA] refers to the molarity of the excess (uncoordinated) TMEDA.

The rate data and isotope effects are summarized in Table 1. For the lithiations of 2–5, pseudo-first-order conditions were established at normal n-BuLi concentrations (0.1–1.0 M) and TMEDA concentrations (0.5–4.5 M) by restricting the arene concentrations to 0.01 M. The lithiation rates were monitored by periodically quenching samples with HCl-free Me3SiCl/Et3N to concentration to 0.01 M. The lithiation rates were monitored by periodically quenching samples with HCl-free Me3SiCl/Et3N and following the loss of Ar–H and formation of ArSiMe3 by gas chromatography using decane as an internal standard.

The slow lithiations of benzene were carried out under non-pseudo-first-order conditions in which all species were maintained at high, yet adjustable, concentrations. The lithiation was monitored by following the appearance of PhSiMe3 at low conversion with careful calibration relative to an internal decane standard. Reaction orders were determined by plotting the initial rates ($\Delta C_6H4(TMS))/\Delta t$ versus the concentrations of n-BuLi, TMEDA, and benzene.

Isotope Effects. Isotope effects were determined by comparing the lithiations of arenes 1–4 with the lithiations of their analogues bearing perdeuterated aryl fragments. The KIEs are unusually large (Table 1), and they are consistent with rate-limiting steps involving C–H(D) bond cleavages. An apparent conflict between the large KIE for anisole measured by us and the small value measured by Stratakis remains unresolved. While it may be tempting to invoke “tunneling” effects, this would be out of convenience rather than insight or conviction. The mechanistic interpretation of these large KIEs is not obvious at this time.

Aren Concentration Dependencies. The time-dependent loss of all mono- and disubstituted arenes 2–5 fits clean first-order behaviors, affording rate constants that are independent of the initial arene concentrations. Figure 1 illustrates representative raw data.

The benzene lithiations were monitored using the initial rates over a considerable range of benzene concentrations (1.0–8.0 M). The results were quite confusing at first. Plots of the initial rates versus [benzene], in which the pentane cosolvent is incrementally replaced by benzene, afforded a second-order dependence (Figure 2) rather than the anticipated first-order dependence. We suspected that the superposition of a first-order dependence on the substrate (benzene) and a dependence on the percentage of the aromatic hydrocarbon solvent (also benzene) could afford such a second-order overall dependence. To eliminate contributions from “medium effects”, we exploited the large isotope effect by using benzene-decane (rather than pentane) as the cosolvent and obtained a more conventional first-order benzene dependence (Figure 3). Although the curve in Figure 3 includes corrections for the limited lithiation of the benzene, the first-order benzene dependence was clear even in the absence of such a minor correction. Odd aromatic hydrocarbon effects in organolithium chemistry may be related to the cation–arene interactions discussed extensively by Dougherty.

The benzene concentrations listed in Table 1 were fitted clean first-order (20) reactions. The rate constants are independent of the arene concentration. The rate constants are independent of the arene concentration.

Figure 1. Representative plot of $[m-C_6H_4(OCH_3)_2]/[\text{decane}]$ versus time for the lithiation of $m$-C6H4(OCH3)2 (3; 0.01 M) by n-BuLi (0.7 M) in TMEDA (1.2 M) and pentane cosolvent at −35 °C. The curve depicts the result of an unweighted least-squares fit to the following expression: $a = 0.80 ± 0.01$, $b = (1.94 ± 0.04) × 10^{-7}$.

Figure 2. Chart 1. Chart 2.

Figure 3. Chart 3.
Since \( n\)-BuLi\(\cdot\)TMEDA exists as dimer \( \text{12} \), all metalations are suggested to proceed via dimer-based transition structures. 43

**TMEDA Concentration Dependencies.** All lithiations are essentially independent of the TMEDA concentrations. Plots of \( k_{\text{obsd}} \) versus \([\text{TMEDA}]\) show limited positive or negative [TMEDA] dependencies, as illustrated in Figure 5. However, these deviations fall well within generalized medium effects noted previously. 44 The effective zeroth-order dependencies are consistent with mechanisms requiring no net change in the per-lithium solvation number upon proceeding from dimer \( \text{12} \) to the rate-limiting transition structures.

**Idealized Rate Laws.** The rate studies afford a remarkably substrate-independent mechanistic picture, as represented by the idealized rate law and generalized mechanism described by eqs 43.

\[
\begin{align*}
\text{ArH} + (n\text{-BuLi})_2(\text{TMEDA})_2 & \rightarrow \nonumber \\
[(n\text{-BuLi})_2(\text{TMEDA})_2(\text{ArH})]^+ & \nonumber \\
\end{align*}
\]

4) Since \( n\)-BuLi\(\cdot\)TMEDA exists as dimer \( \text{12} \), all metalations are suggested to proceed via dimer-based transition structures. 43

**Ab Initio Calculations.** The rate studies implicating transition structures with stoichiometry \( [(n\text{-BuLi})_2(\text{TMEDA})_2(\text{ArH})]^+ \) suggest a commonality of mechanism despite the diversity of substituents. We will invoke lithiations via TMEDA-solvated triple ion \( \text{13} \), illustrated generically in eqs 4 and 5 (and elaborated in Scheme 1 in the Discussion section). We investigated the reaction coordinate computationally to understand the substituent-dependent rates and the efficacy of the triple ion-based model. Unfortunately, MNDO calculations are inadequate for severely congested systems. 45 Moreover, pre-

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(43) Lithiation of PhOCH\(2\text{CH}_2\text{OCH}_3\) afforded seemingly contradictory results in which the relative rate constant was indistinguishable from that of amino ether 5 yet afforded a fractional (0.55 \( \pm \) 0.06) \( n\)-BuLi order. Unfortunately, the reaction was atypically messy, as noted previously. 27 We tentatively dismiss the rate studies as spurious.

liminary calculated transition structures for the lithiation step (eq 5 or 6) suggested that a more sophisticated treatment of electron correlation would be required.46

\[(n\text{-BuLi})_2(\text{TMEDA})_2 \leftrightarrow (n\text{-Bu})_2\text{Li}^{+/+}\text{Li(}\text{TMEDA})_2\]  \hspace{1cm} (4)

\[(n\text{-Bu})_2\text{Li}^{+/+}\text{Li(}\text{TMEDA})_2 \leftrightarrow \text{ArH}^-\]  \hspace{1cm} (13)

\[
\left[\left(n\text{-Bu}\right)_2\text{Li}\cdot\text{Ar}^-\text{H}^-\right]/\text{Li(}\text{TMEDA})_2\right]^+  \hspace{1cm} (5)

\[
(n\text{-Bu})_2\text{Li}^{+/+}\text{Li(}\text{TMEDA})_2 \leftrightarrow \text{ArH}^-\]  \hspace{1cm} (14)

\[
\left[\left(Me\right)_2\text{Li}\cdot\text{Ar}^-\text{H}^-\right]^+  \hspace{1cm} (6)

Ab initio calculations were performed with the Gaussian 98 package at the B3LYP level of density functional theory using the 6-31G* basis set.47 MeLi was employed as a model for \(n\text{-BuLi}\) according to eq 6. Since the pairing energies in triple ion 13 and transition structure 14 should largely cancel,48 omitting the \(+\text{Li(}\text{TMEDA})_2\) in eq 6 would have minimal impact on the relative activation enthalpies. Fully optimized structures were obtained for the linear triple ion fragment 15, substrates 1–3, and transition structures 23–28 (Chart 2). Although the ortholithiations of arenes 17–22 were not investigated kinetically, we calculated transition structures 29–36 to explore the nuances of the triple-ion-based model. The relative activation enthalpies (\(\Delta H^f\)) calculated from the ab initio energies (\(E_{\text{elec}}\)) at 298.15 K and 1.0 atm are shown under the structures. Total enthalpies with zero-point energy corrections49 are listed in the Supporting Information. The transition structures were initially optimized by fixing the critical fractional bonds of the C–2H–Li four-centered ring using the optimized benzene transition

\[(\text{Me})_2\text{Li} \leftrightarrow \text{F}^-\text{Ar}^-\text{H}^-\text{Li(}\text{TMEDA})_2\]  \hspace{1cm} (16)
structure as a template. Reoptimization without constraints afforded fully valid transition structures, as shown by the existence of a single imaginary frequency. Special care was taken to sample a range of initial geometries to locate critical saddle points (especially for the methoxy substituents). Anisole derivatives afforded transition structures and enthalpies for both syn and anti forms, as defined by 37 and 38. Similarly, resorcinol dimethylether afforded structures defined as syn,anti (39), syn-syn (40), and anti,anti (41).

**Discussion**

**Rate Studies.** We investigated the ortholithiation of arenes 1–5, obtaining both relative lithiation rates (Chart 1) and rate laws (see eq 2 and Table 1). The highly substituent-dependent rates mirror previous studies showing the widely varying laws (see eq 2 and Table 1). The highly substituent-dependent-

![Image](https://example.com/image.png)

**Mechanism: Triple Ion Intermediates.** Implication of a dimer-based mechanism is especially interesting in light of recent discussions of open dimers (e.g., 42)\(^{51}\) and triple ions (e.g., 13)\(^{48}\) as possible reactive intermediates. If one subscribes to the notion that precomplexation is important,\(^{5,7,8}\) there are a number of mechanisms involving either Li–O or (C=C)Li (7) interactions (43 and 44, respectively). Our interpretation of the rate data is dominated by three key considerations: (1) The substrate-independent rate laws strongly implicate a common mechanism. (2) The \(n\)-BuLi cyclic dimer 12 (or open dimer 42; see below) has, at best, a highly limited capacity to accept coordination by the aren. (3) Schlosser has shown that ortho selectivities correlate with \(pK_a\)s attributable to inductive effects (although such a correlation is extremely complex).\(^{52–55}\) Accordingly, we posed the title question and then formulated the mechanism based upon triple ions shown in Scheme 1.

**Triple ions were first described by Fuoss in 1933\(^{55}\) and may prove to be the most underappreciated reactive intermediates in organolithium chemistry.\(^{56}\) Analogous to other main group “ate” complexes,\(^{56}\) triple ions should show high basicities and nucleophilicities, as suggested by Wittig in 1951,\(^ {57}\) yet have received limited subsequent attention.\(^ {48}\) Although triple ion 13 is not spectroscopically observable, it seems plausible in light of spectroscopic studies of the HMPA-solvated PhLi triple ion as well as crystallographic\(^ {58}\) and computational studies\(^ {59}\) showing the stability of the \(Li^{+}(TMEDA)\) cation.

**Computational Studies: Complexation versus Induction.** We turned to ab initio studies using the (Me\(_2\))\(^{2+}\) Li\(^-\) fragment (eq 6) to explore the implications of the proposed triple-ion-based ortholithiations. The spatial relationships within transition structures 23–36 (Chart 2), the relative activation enthalpies (\(\Delta H^\ddagger\); Chart 2), and the experimentally observed lithiation rates (Chart 1) paint an intriguing picture. In the following discussion, syn and anti orientations of methoxy groups are defined by structures 37–41. The existence of a lithium–substrate

\(^{(50)}\) A triple ion analogous to 13 was invoked as a possible key intermediate by Shirley; however, it was in the context of a mechanism involving electrophilic aromatic substitution first proposed by Gilman\(^ {7}\) that has gone out of favor. Shirley, D. A.; Hendrix, J. P. J. Organomet. Chem. 1968, 11, 217.


\(^{(52)}\) As noted by Schlosser,\(^ {12,14}\) comparison of ortholithiation rates with experimentally measured “acidities” will depend upon whether the acidities stem from (1) solution-phase equilibria or heats of reaction,\(^ {56}\) which reflect the stabilities of widely varying and complex aggregate structures of little relationship to transition structures,\(^ {59}\) (2) solution-phase kinetic acidities (relative rate constants) for other reactions, which will depend strongly on the choice of solvent, rate, and mechanism, (3) gas-phase kinetic acidities,\(^ {14}\) which should reflect at least some dependence on the reference base, or (4) experimental gas-phase thermodynamic acidities, which should show no dependence on the reference base.


\(^{(58)}\) The \(\text{Li}(\text{TMEDA})\) is quite stable, as evidenced by a number of metal ions in the crystallographic literature. Of particular interest are triple ions of general structure \([\text{X}](\text{Li})^{+}/\text{Li}^{+}(\text{TMEDA})\); Hosmane, N. S.; Yang, J.; Zhang, H.; Maguire, J. A. J. Am. Chem. Soc. 1996, 118, 5150. Eaborn, C.; Lu, Z.-R.; Hitchcock, P. B.; Smith, J. D. Organometallics 1996, 15, 1651.

\(^{(59)}\) MNDO calculations of the equilibrium of 4THF + \(\text{Li}(\text{TMEDA})\) = 2TMEDA + \(\text{Li}(\text{THF})\) are endothermic by 12.9 kcal/mol. However, given the high sensitivity of MNDO to steric effects, we were surprised to find a minimum for \(\text{Li}(\text{TMEDA})\).
interaction, whether highly stabilizing or not, is inferred from the orientation of the C₃H₆Li plane involved in the proton transfer relative to the plane defined by the aren ring. For example, transition structure 24 for the lithiation of anisole bearing a syn-oriented methoxy group shows the C₃H₆Li and aren planes to be orthogonal while the corresponding transition structure 25 bearing an anti-oriented methoxy group shows the two planes to be nearly coplanar with an accompanying close Li–OMe contact.

Important insight can be gleaned by considering the influence of substituents on the calculated activation enthalpies as follows:

1. **Syn-oriented methoxy moieties** bearing no capacity to coordinate to lithium at the transition structure reduce ΔH° by 3–5 kcal/mol (cf. 23/24, 25/26, and 29/31). The activation must stem from induction rather than Li–OMe complexation. A notable exception is transition structure 27, bearing two syn-oriented methoxy moieties. Whereas anisole-derived transition structure 24, bearing a syn-oriented methoxy group, shows a distinct canting of the C₃H₆Li plane in response to steric interactions, the two potentially stabilizing syn-oriented methoxy moieties of 27 cause buttingress with a consequent destabilization (cf. 23/24/27).

2. **Anti-oriented methoxy moieties** showing evidence of discrete Li–OMe interactions at the transition structures also reduce ΔH° by 3–5 kcal/mol (cf. 23/25 and 24/26). While 3–5 kcal/mol constitutes considerable activation of the orthon lithiation, such complex-induced proximity effects are indistinguishable from the purely inductive effects noted in point 1.

3. **Anti-oriented methoxy moieties** that do not form discrete Li–OMe interactions at the transition structures have almost no effect whatsoever on ΔH° (cf. 25/28 and 29/32). We believe that significant activation offered by induction is largely offset by considerable electron repulsion of the lone pairs with the electron rich C₃H₆Li portion.60

4. Fluorinated arenes displaying discrete Li–F interactions in the transition structures show a 6–7 kcal/mol decrease in ΔH° (cf. 23/29 and 24/31), consistent with the high reactivities observed experimentally.14,61,62 However, a fluoro substituent showing no such Li–F interaction reduces ΔH° by 5–6 kcal/mol (cf. 25/33). Therefore, the Li–F interactions, while visually conspicuous, may not be significantly stabilizing when compared with the substantial inductive effects. For example, when given a choice of an Li–F interaction or an Li–OMe (anti-OMe) interaction (cf. 32/33), the Li–OMe interaction is strongly preferred. Interestingly, transition structure 31, containing an Li–F interaction and a noncoordinating syn-oriented methoxy moiety, is the most stable.

(5) Extremely slow lithiations of N,N-dimethylaniline (20) are expected from the limited inductive effects. Transition structure 34 shows no Li–NMe₂ interaction and a considerable relative activation enthalpy. Similarly, 1,3-benzodioxole (21) and 2,3-dihydrobenzofuran (22) appear to be ideally suited for orthon lithiations by a mechanism relying upon a CIPE, yet are found to react sluggishly.64 The calculated activation enthalpies associated with transition structures 35 and 36 are not exceptional when compared with those of the anisole-derived counterparts; however, there is no evidence of Li–O interactions. To the extent that 21 and 22 are structural analogues of anti-oriented anisoles with no stabilizing interaction (see point 3), the experimentally observed low reactivities are logical in retrospect.

The considerable stabilizations imparted by noncoordinating ortho substituents (point 1) and the highly additive influence of meta-disposed substituents lacking the capacity to coordinate concurrently argue that inductive effects are critical, while direct lithium-substituent interactions are of relatively minor importance. If, for the sake of discussion, one accepts a model in which lithium–substituent interactions are important (which we do not), the computational results underscore the concern expressed by Schleyer and co-workers that the importance of precomplexation may be overestimated: we were unable to computationally detect stable precomplexes of general structure [(CH₃)₂Li–X]⁻ (X = OMe or F). Thus, the triple-ion-based model suggests that Li–OMe and Li–F interactions are found only at the transition structures.

Ab initio calculations probed the triple-ion-based model with considerable success. Nevertheless, other models might mirror the relative activation enthalpies, while revealing a substantially greater contribution from lithium–substituent interactions. For example, lithiation of anisole by MeLi monomer is highly favorable via the anti transition structure 47, displaying a discrete Li–OMe interaction when compared with the corresponding benzene-derived transition structure 46 or syn-oriented transition structure 48. However, to ascribe significance to a
strong interaction with naked MeLi monomer would be foolish. Such gross simplifications will often produce highly spurious results. Can the same criticism be levied against the calculations employing \((\text{Me}_2\text{Li})^-\)? Curiously, the answer may be no. Considerable evidence suggests that the internal lithiums of related \([\text{R}−\text{Li}−\text{R}]^-\) fragments remain unsolvated.\(^{35,48}\) Moreover, the pairing energies of \(13\) and \(45\) are likely to be nearly equivalent,\(^{35}\) justifying the omission of the \(^+\text{Li}(\text{TMEDA})_2\) counterion to calculate relative activation enthalpies.

Summary and Conclusion

The rate studies of the \(n\)-BuLi/TMEDA-mediated lithiations of five arenes (Chart 1) reveal a high mechanistic homology, suggesting that the lithiations do not necessarily rely significantly on the complex-induced proximity effect. To account for the substituent-dependent rates and substituent-independent mechanisms, we proposed a triple-ion-based model (Scheme 1) that depends largely upon inductive effects espoused by Schlosser and co-workers.\(^{12,14}\) While the proposed model is speculative and certainly not the only dimer-based model, ab initio calculations afforded surprisingly strong theory–experiment correlations. The calculations suggest that orienting the oxygen lone pairs of the alkoxy moiety toward the lithium is marginally stabilizing at best and may be destabilizing. Discrete Li–F interactions appear prominently in the calculations, yet there is no evidence that they offer significant stabilization beyond the substantial inductive effects. As usual, we must conclude with the disclaimer that extrapolating the results to other classes of ortholithiation should be done cautiously, especially when strongly coordinating substituents such as carboxamides are involved.\(^{16}\)

**Experimental Section**

**General Reagents and Solvents.** Anisole was vacuum transferred from a purple solution containing sodium benzophenone ketyl. Anisole-\(d_8\) (Aldrich) was used without purification. Resorcinol dimethylether (3) was stored over molecular sieves and used without further purification. Substrates \(3-d_3, 4-d_3, 4-d_5, 5-d_5\) and \(5\) were prepared by literature procedures. \(n\)-BuLi was multiply recrystallized from pentane, as described previously.\(^{17,33,34}\) Pentane, benzene, and benzene-\(d_6\) were distilled from blue solutions containing sodium benzophenone ketyl with approximately 1% tetraglyme to dissolve the ketyl. Chlorotrimethylsilane (TMSCl) was freshly distilled from calcium hydride under nitrogen. Triethylamine (NEt\(_3\)) was vacuum transferred from a blue solution of sodium benzophenone ketyl. TMEDA was purchased from Aldrich and purified by recrystallization of its hydrochloride salt as described previously.\(^{17}\)

**Kinetics.** The rate studies were carried out as described previously and are described in detail in the Supporting Information. Methods for determining the relative rate constants and isotope effects are also included in the Supporting Information.

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**Supporting Information Available:** Tabular and graphical presentation of rate data, general experimental methods, and calculated heats of formation (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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