

Formation of Benzenes from 2,6-Dihaloaryllithiums: Mechanistic Basis of the Regioselectivity

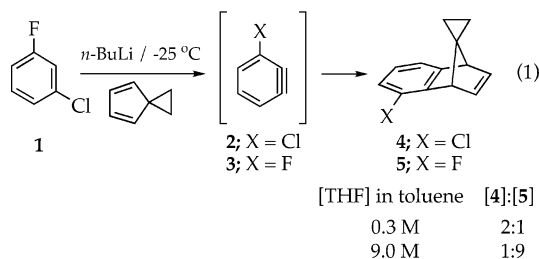
Antonio Ramírez,[†] John Candler,[‡] Crystal G. Bashore,[‡] Michael C. Wirtz,[‡] Jotham W. Coe,^{*,‡} and David B. Collum^{*,†}

Baker Laboratory, Department of Chemistry and Chemical Biology, Cornell University, Ithaca, New York 14853-1301, and Pfizer Global Research and Development, Groton Laboratories, Pfizer, Inc., Groton, Connecticut 06340

Received August 24, 2004; E-mail: coejw@groton.pfizer.com; dbc6@cornell.edu

Benzyne was first discussed over a century ago by Stoermer and Kahlert.¹ Fifty years later, Roberts and co-workers reported their landmark isotopic labeling studies on the KNH₂-mediated reaction of chlorobenzene that left little doubt about the existence of benzyne as a highly reactive intermediate.² Since then, the generation, structure, and reactivity of benzenes have been studied by synthetic organic and physical organic chemists.³ Although ortholithiated haloarenes are often used to generate benzenes,⁴ the understanding of coordinating solvents in the key elimination step is based largely on empirical observations.⁵ Moreover, evidence supporting or refuting a central importance of aggregation is nonexistent.⁶

As part of a program to identify nicotinic receptor agonists as potential aids for smoking cessation and other neurochemically mediated conditions,⁷ we observed that the reaction of 1-chloro-3-fluorobenzene (**1**) with *n*-BuLi affords intermediate benzenes **2** and **3** (eq 1) that can be trapped to form bicycloadducts **4** and **5**.⁸ Unexpectedly, the key elimination step displays a pronounced solvent-dependent regioselectivity.⁹ A combination of structural and rate studies described herein provides the first detailed view of how the mechanism influences the rates and regioselectivity of the key elimination step.



⁶Li and ¹³C NMR spectra recorded on [⁶Li]2-chloro-6-fluorophenyllithium (**6**) prepared from **1** and recrystallized [⁶Li]*n*-BuLi at -100 °C¹⁰ show a single species in both neat THF and THF/toluene mixtures (Figure 1). The ⁶Li-¹³C, ⁶Li-¹⁹F, and ¹⁹F-¹³C couplings and multiplicities¹¹ are consistent with aryllithium monomer **6**. The ²J_{F-C(ipso)} coupling constant of 130.3 Hz is substantially larger than the analogous 19.8 Hz coupling in 1,3-dihaloarene **1**.¹² On a practical note, the ¹⁹F in the arene serves as an excellent surrogate for an inaccessible ¹³C label at the ⁶Li-bearing (ipso) carbon. Although we do not have a spectroscopic measure of solvation number, DFT calculations (B3LYP/6-31G*) show that serial solvation of the monomer is exothermic up to the trisolvate.¹³ Assignment of the monomer as the trisolvate **6** is also consistent with conventional views of lithium as preferring four coordination.¹⁴ The exclusive formation of monomer **6** presumably stems from a

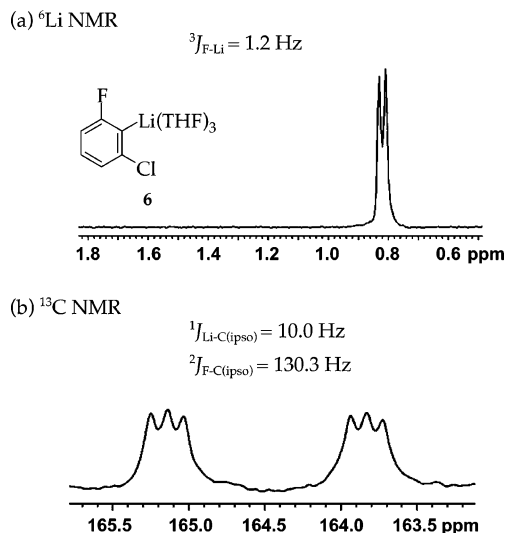


Figure 1. (a) ⁶Li NMR spectrum of 0.2 M [⁶Li]2-chloro-6-fluorophenyllithium (**6**) in THF (10.3 M) with toluene cosolvent at -100 °C. (b) ¹³C NMR spectrum of 0.4 M [⁶Li]-**6** in neat THF at -100 °C.

combination of inductive stabilization of the charge and steric inhibition of aggregation.^{15,16}

Rate studies were carried out by treating THF/toluene solutions of **1** and spiro[2.4]hepta-4,6-diene with *n*-BuLi at -25 °C. Under these conditions, aryllithium **6** is generated instantaneously. The initial rates¹⁷ for the formation of intermediate benzenes **2** and **3** are monitored by following the loss of **1** and formation of bicycloadducts **4** and **5** via GC analysis. Arene **1** was maintained in 0.2 M excess to aryllithium concentrations. The initial rates were independent of the concentration of spiro[2.4]hepta-4,6-diene (maintained at >20% molar excess), indicating that the halide elimination is irreversible.^{3a} There was no evidence of downward curvature that would indicate autocatalysis by the lithium halide. The rate constant for the loss of **6** (*k*_{obsd(6)}) corresponds to the sum of the rate constants for formation of benzenes **2** and **3** (*k*_{obsd(2)} + *k*_{obsd(3)}), which, in turn, were determined by monitoring the ratio of cycloadducts **4** and **5** (*k*_{obsd(4)}/*k*_{obsd(5)}).

Loss of aryllithium **6** is first order in **6** in both 0.3 and 6.8 M THF (*k*_{obsd(6)} ∝ [**6**]⁰), which, in conjunction with NMR spectroscopic studies, indicates a monomer-based mechanism.⁶ Moreover, the independence of the [4]:[5] ratio on the initial concentration of **6** confirms that elimination of LiF and LiCl (*k*_{obsd(2)} and *k*_{obsd(3)}, respectively) both proceed via transition structures of equivalent (monomeric) aggregation state.

The THF-concentration-dependent rates are particularly revealing (Figure 2). The overall rate at which aryllithium **6** eliminates lithium

[†] Cornell University.
[‡] Pfizer, Inc.

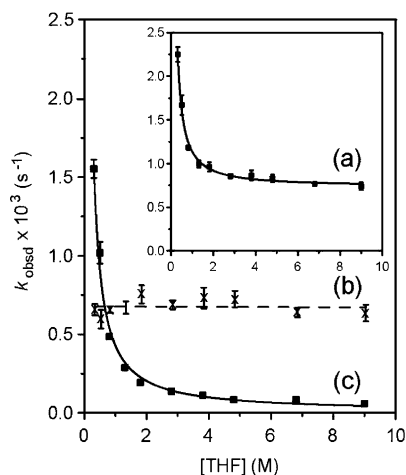
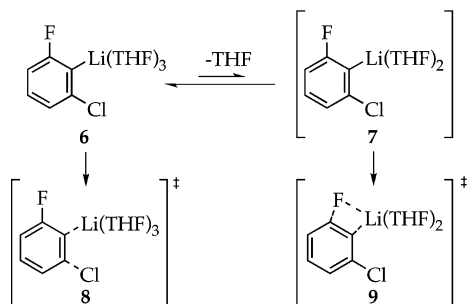


Figure 2. (a) Plot of $k_{\text{obsd}(6)}$ vs [THF] in toluene cosolvent for the formation of benzynes **2** and **3** from **6** (0.2 M) at $-25\text{ }^{\circ}\text{C}$. The curve depicts the result of an unweighted least-squares fit to $k_{\text{obsd}(6)} = k[\text{THF}]^n + k'$ ($k = (4 \pm 0.4) \times 10^{-5}$, $n = -1.12 \pm 0.09$, $k' = (7.3 \pm 0.3) \times 10^{-4}$). (b) Plot of $k_{\text{obsd}(3)}$ vs [THF]. $k_{\text{obsd}(3)} = k[\text{THF}] + k'$ ($k = -(1 \pm 9) \times 10^{-6}$, $k' = (7.1 \pm 0.2) \times 10^{-4}$). (c) Plot of $k_{\text{obsd}(2)}$ vs [THF]. $k_{\text{obsd}(2)} = k[\text{THF}]^n + k'$ ($k = (4.2 \pm 0.6) \times 10^{-4}$, $n = -1.1 \pm 0.1$, $k' = (1 \pm 4) \times 10^{-5}$).

Scheme 1



halide ($k_{\text{obsd}(6)}$, curve a) displays a profile that derives from the superposition of a [THF]-independent elimination of chloride ($k_{\text{obsd}(3)} \propto [\text{THF}]^0$, curve b) and inverse-first-order dependence on fluoride elimination ($k_{\text{obsd}(2)} \propto 1/[\text{THF}]^{1.1 \pm 0.1}$, curve c).

The structural and rate data are fully consistent with the mechanism outlined in Scheme 1. The solvent-dependent regioselectivity clearly derives from the LiF elimination requiring THF dissociation. Presumably, the lower solvation number enhances a highly stabilizing Li–F interaction,^{14b,19} as implied in transition structure **9**. It has been suggested that the propensity of halogens to eliminate follows the order $\text{I} > \text{Br} > \text{Cl} > \text{F}$.^{18,20} However, based on these results, the capacity of the halide ions to function as leaving groups clearly depends on the reaction conditions and mechanism.²¹ In our opinion, caution should be exercised when using categorical rules about halide reactivities in a more general sense.

We are currently studying other 1,3-dihaloaryl lithiums both experimentally and computationally. These investigations will be described in due course.

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for indirect support. We also acknowledge the National Science Foundation Instrumentation Program (CHE 7904825 and PCM 8018643), the National Institutes of Health (RR02002), and IBM for support of the Cornell Nuclear Magnetic Resonance Facility.

Supporting Information Available: Spectral data, rate data, and experimental procedures. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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