

## Mechanism of Lithium Diisopropylamide-Mediated Substitution of 2,6-Difluoropyridine

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**Abstract:** Treatment of 2,6-difluoropyridine with lithium diisopropylamide in THF solution at  $-78\text{ }^{\circ}\text{C}$  effects ortholithiation quantitatively. Warming the solution to  $0\text{ }^{\circ}\text{C}$  converts the aryllithium to 2-fluoro-6-(diisopropylamino)pyridine. Rate studies reveal evidence of a reversal of the ortholithiation and a subsequent 1,2-addition via two monomer-based pathways of stoichiometries  $[\text{ArH}\cdot\text{t-Pr}_2\text{NLi}(\text{THF})]^{\ddagger}$  and  $[\text{ArH}\cdot\text{t-Pr}_2\text{NLi}(\text{THF})_3]^{\ddagger}$ . Computational studies fill in the structural details and provide evidence of a direct substitution without the intermediacy of a Meisenheimer complex.

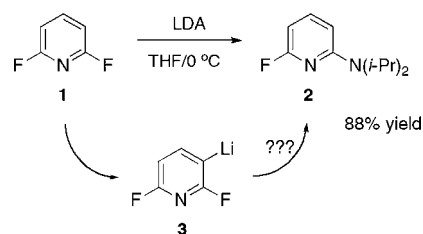
### Introduction

During mechanistic studies of lithium diisopropylamide (LDA)-mediated ortholithiations of 2-fluoropyridines we discovered the nucleophilic aromatic substitution depicted in Scheme 1. This substitution is similar to less hindered examples reported by Singaram and co-workers.<sup>1,2</sup> The yield is exceptional for such a hindered nucleophile, and heteroaromatic aminations are of great importance in the pharmaceutical industry.<sup>3,4</sup> Our interest, however, was piqued by the apparent intermediacy of 3-pyridyllithium<sup>5</sup> **3**, which forms rapidly and quantitatively at  $-78\text{ }^{\circ}\text{C}$ .

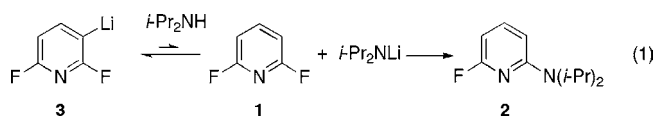
We considered the following mechanisms for the substitution in Scheme 1.

**Mechanism 1.** Reversal of the metalation<sup>5d,6</sup> is followed by a product-determining nucleophilic attack by LDA (eq 1). Although the LDA order would depend on the aggregation state of the nucleophilic form, a first-order dependence on the

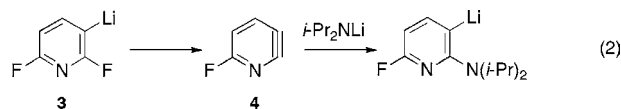
### Scheme 1



diisopropylamine concentration would be a hallmark of this mechanism.<sup>7</sup>



**Mechanism 2.** Rate-limiting elimination of LiF affords pyridyne **4**,<sup>8</sup> which undergoes a post-rate-limiting trap by LDA (eq 2).<sup>9</sup> In addition to the zeroth orders expected for LDA and diisopropylamine, an inverse dependence on THF concentration might be expected based on analogous LiF eliminations to form benzenes.<sup>10</sup>

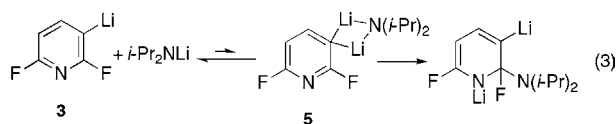


**Mechanism 3.** Direct substitution of the fluoro moiety of aryllithium **3** by a nucleophilic LDA fragment must be considered, although the electrophilicity of a heteroaryllithium

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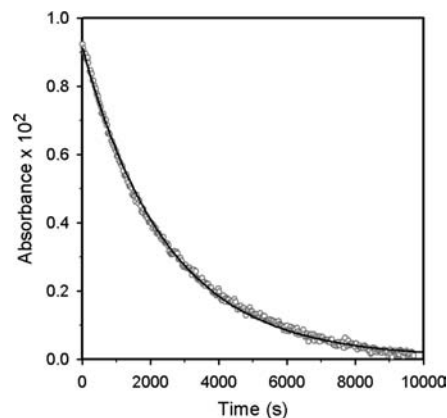
seems somewhat odd. A mixed dimer-based pathway involving the intraaggregate transfer depicted in eq 3 is one (admittedly somewhat fanciful) possibility.<sup>11</sup> Dependencies on both ArLi and LDA concentration would be characteristic.



We describe herein mechanistic studies of the substitution in Scheme 1. Rate data support two competing variants of mechanism 1 that differ only in solvation number in the transition structures. Computational data fill in experimentally elusive details. The discussion includes a detailed description of how the rate law leads to the mechanistic hypothesis.

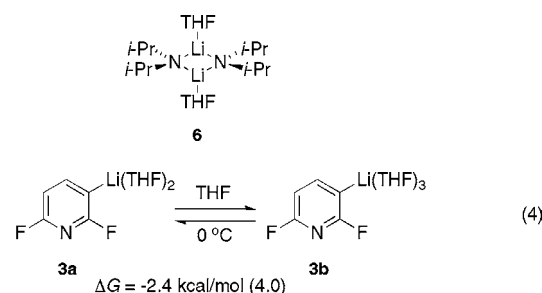
## Results

**Solution Structures.** Assessing the solution structures of LDA and ArLi is essential to interpret the rate data (vide infra). Previous studies of [<sup>6</sup>Li,<sup>15</sup>N]LDA using <sup>6</sup>Li and <sup>15</sup>N NMR spectroscopy revealed exclusively disolvated dimer **6**.<sup>12</sup> Aryllithium **3** is exclusively monomeric as evidenced by C-3 as a doublet of triplets (1:1:1 triplet) owing to <sup>13</sup>C–<sup>19</sup>F and <sup>13</sup>C–<sup>6</sup>Li coupling.<sup>13,14</sup> A solution containing [<sup>6</sup>Li,<sup>15</sup>N]LDA and aryllithium **3** shows no <sup>6</sup>Li–<sup>15</sup>N coupling in the <sup>6</sup>Li resonance of **3**. An especially large <sup>2</sup>J<sub>C–F</sub> of 122 Hz is emblematic of 2-fluoroaryllithiums.<sup>10,15,16</sup> (By comparison, the distal fluoro moiety displays <sup>2</sup>J<sub>C–F</sub> = 38 Hz.) Density functional theory (DFT) computations of **3** optimized at the B3LYP/6-31G(d) level<sup>17</sup> (Supporting Information) with single-point calculations at the MP2 level of theory indicate that trisolvated monomer **3b** is favored relative to disolvated monomer **3a** at 0 °C, consistent with previous studies of aryllithiums.<sup>10,18</sup> (The result without MP2 correction is shown in parentheses.) Moreover, alternative assignment of the monomer as disolvate **3a**, in



**Figure 1.** Plot of IR absorbance (1576 cm<sup>-1</sup>) vs time for the substitution of **3** (0.005 M) with LDA (0.10 M) in the presence of 0.10 M diisopropylamine in 2.5 M THF at 0 °C. The curve depicts an unweighted least-squares fit to  $y = ae^{-bx}$ .

conjunction with the rate studies, would force on us seemingly untenable mechanistic hypotheses (vide infra).



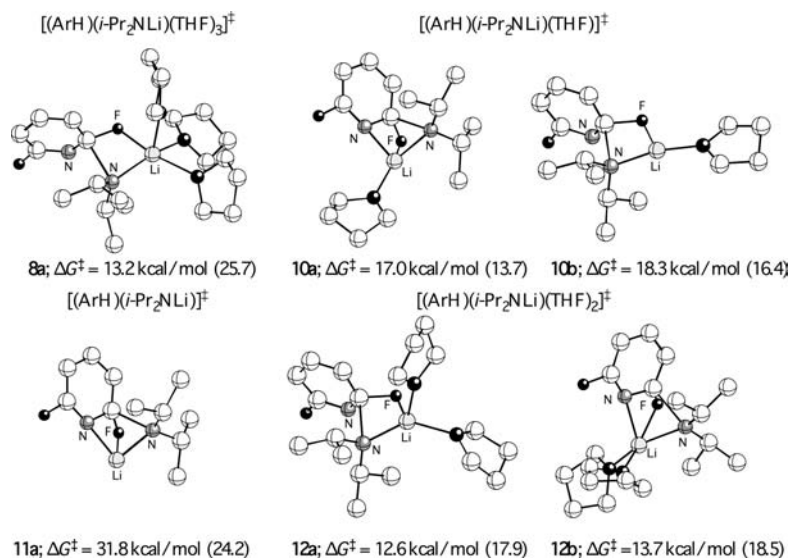
Pseudo-first-order conditions were established with LDA (recrystallized)<sup>12</sup> at normal concentrations (0.05–0.50 M) by restricting the substrate concentration to 0.005 M.<sup>19</sup> Diisopropylamine is maintained at 0.10 M unless stated otherwise. In situ IR spectroscopy showed that the disappearance of aryllithium **3** (1576 cm<sup>-1</sup>) and appearance of arene **2** (1617 cm<sup>-1</sup>) are first order (Figure 1). Analogous results were obtained by monitoring the <sup>19</sup>F resonances of **3** (–44.8 and –82.0 ppm) and **2** (–68.2 ppm). The resulting pseudo-first-order rate constants ( $k_{\text{obsd}}$ ) are independent of substrate concentration (0.004–0.04 M). Zeroing the IR baseline and monitoring a second injection of substrate afford no significant change in  $k_{\text{obsd}}$  (±10%), which shows that autocatalysis, autoinhibition, and other conversion-dependent effects are unimportant under pseudo-first-order conditions.

A plot of  $k_{\text{obsd}}$  versus THF concentration shows an inverse-second-order dependence at low THF concentrations and a zeroth-order dependence—a nonzero asymptote—dominating at high THF concentrations (Figure 2), consistent with two parallel pathways. Plots of  $k_{\text{obsd}}$  versus LDA concentration (Figure 3) and  $k_{\text{obsd}}$  versus diisopropylamine concentration (Figure 4) show

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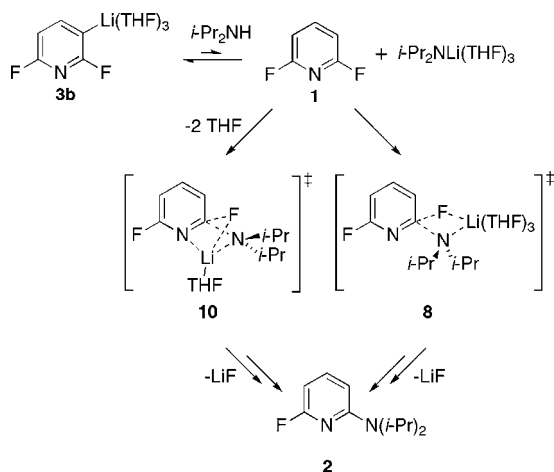
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Chart 1. Calculated Monomer-Based Transition Structures at 0 °C<sup>a</sup>

<sup>a</sup> Energies are calculated according to eq 10. Values in parentheses correspond to calculations without single-point MP2 corrections.

Scheme 2



We begin by stating a simple yet powerful maxim: *The rate law provides the stoichiometry of the rate-limiting transition structure(s) relative to the reactants.*<sup>7,22</sup> Assigning the reactant structures is critical to assessing the *absolute* stoichiometries of transition structures. LDA is a disolvated dimer **6**, and aryllithium **3** is shown spectroscopically to be a monomer and computationally to be trisolvate **3b**.

First orders in both ArLi and *i*-Pr<sub>2</sub>NH at low and high THF concentrations suggest  $[\text{ArH}\cdot i\text{-Pr}_2\text{NLi}]^\ddagger$ , implying a rate-limiting addition. A stoichiometrically equivalent formulation such as  $[\text{ArLi}\cdot i\text{-Pr}_2\text{NH}]^\ddagger$ , reflecting a rate-limiting proton transfer, is excluded by the reversibility of the proton transfer and an isotopically insensitive rate for *i*-Pr<sub>2</sub>ND. The affiliation of a zeroth-order LDA dependence with an LDA-monomer-based mechanism is a counterintuitive consequence of the resting state being ArLi/*i*-Pr<sub>2</sub>NH rather than ArH/LDA. We note in passing that, had an LDA-dimer-based transition structure been operative, a half-order dependence on LDA would have been observed.<sup>7</sup>

A plot of  $k_{\text{obsd}}$  versus THF concentration (Figure 2) provides key insights into the role of THF. An inverse second-order dependence—a marked acceleration with *decreasing* THF concentration—shows that *two* THFs are necessarily lost from the reactants en route to the rate-limiting transition structure, which we can now complete as  $[\text{ArH}\cdot i\text{-Pr}_2\text{NLi}(\text{THF})]^\ddagger$ . The approach to a nonzero asymptotic limit at high THF concentration points to a zeroth-order dependence, showing that THF is neither lost nor gained as part of a parallel mechanistic pathway en route to  $[\text{ArH}\cdot i\text{-Pr}_2\text{NLi}(\text{THF})_3]^\ddagger$ .

We must confess that we are uncomfortable using theory alone to explore the organolithium reaction mechanism—there are simply too many possibilities. Given the stoichiometric constraints imposed by the rate studies, however, we are positioned to consider the DFT computations described by Chart 1. We hasten to add that the quality of the calculations and the discussion were materially improved by the gentle prodding of a referee.

Monomer-based transition structures bearing one, two, and three coordinated THFs (eq 10, Chart 1) are all plausible within a liberal definition. Potentially stabilizing Li–F interactions are prominent, and Li–N interactions at the pyridyl nitrogen are prevalent at lower solvation numbers. The prominent Li–F interactions add to mounting evidence that Li–F contacts are key determinants of organolithium reaction mechanisms.<sup>10,23,24</sup> Li–N contacts are absent in the sterically congested trisolvate **8a**.

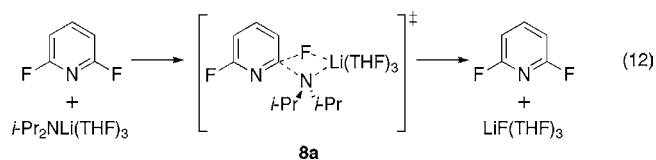
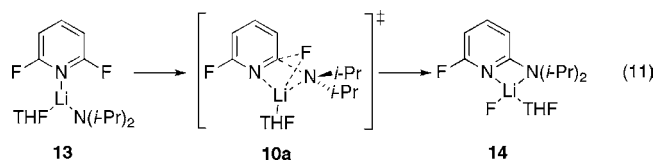
Transition structures **8a** and **10a** or **10b** computed at the B3LYP level of theory are fully compatible with the rate data and offer visually appealing, intimate details of the substitution. We must, however, underscore the quantitative disagreement of theory and experiment. Detecting trisolvated monomer-based transition structure **8a** appeared to be a pyrrhic victory. The

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rate studies indicate that **8a** and **10a** should be of roughly equal stability, whereas computations indicate **8a** is 12 kcal/mol less stable. Although the unprotected charge developing on the pyridyl nitrogen is likely to be the source of some computational problems,<sup>25</sup> 12 kcal/mol is a *large* discrepancy. Computations using diffuse orbitals (Supporting Information) generally increase all barriers by a few kcal/mol but preclude detecting trisolvate **8a** altogether. Single-point calculations adding MP2 corrections reversed the relative energies, rendering **8a** the preferred transition structure by a somewhat smaller (4 kcal/mol) margin.

IRC calculations proved very interesting. The stable minima preceding and following transition structure **10a** correspond to pyridine precomplex **13** and direct substitution product **14**, respectively (eq 11); the substitution proceeds directly without the intermediacy of a stable Meisenheimer complex. IRC calculations on the trisolvate reveal a direct substitution and the complete absence of substrate–lithium complexation prior to or following rate-limiting transition structure **8a** (eq 12). Those specializing in early transition metal chemistry would likely refer to these substitutions as  $\sigma$  bond metathesis.<sup>26</sup> We have always been baffled by the facility of nucleophilic substitutions of aryl fluorides;<sup>1</sup> these results seem to shed some light on why aryl fluorides are easily substituted.



## Conclusion

Mechanistic studies offer potentially practical insights for those interested in functionalizing pyridines.<sup>3</sup> The nucleophilic substitution of a 2-fluoropyridine by LDA is remarkably efficient given the exceptional steric demand. If one's goal is to achieve the substitution—if ortholithiation is an unwanted side equilibrium—then a low THF concentration and high diisopropylamine concentration are advised. (Donor solvent *concentration* is an often overlooked variable during optimizations.) If, by contrast, the goal is to achieve ortholithiation and the nucleophilic substitution is an unwanted side reaction—a problem likely to be observed with more electrophilic heteroaromatics than with **1**—then the opposite logic may hold true. In fact, scavenging

the free amine with an additional equivalent of *n*-BuLi<sup>27</sup> or using a more hindered lithium amide base should eliminate the unwanted addition altogether.

## Experimental Section

**Reagents and Solvents.** THF and hexanes were distilled from blue or purple solutions containing sodium benzophenone ketyl. The hexane contained 1% tetraglyme to dissolve the ketyl. Both LDA<sup>12</sup> and *n*-BuLi<sup>28</sup> used to prepare LDA were recrystallized. Solutions of LDA were titrated using a literature method.<sup>29</sup>

**1,2-Addition: Preparative Scale.** A 1.6 M solution of *n*-butyllithium (6.9 mL, 11.0 mmol) in hexanes was added via syringe to a solution of dry diisopropylamine (5.0 mL, 3.61 g, 35.6 mmol) in dry hexanes at 0 °C under Ar. After the solution was stirred for 10 min, 2,6-difluoropyridine (500  $\mu$ L, 634 mg, 5.5 mmol) was added to the LDA solution. After being stirred at 0 °C for 2 h, the reaction was quenched with wet THF. The organic layer was washed with aqueous NaCl (3  $\times$  10 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and evaporated to dryness under reduced pressure. Flash chromatography (50% ethyl acetate/hexanes) afforded 2-fluoro-6-(diisopropylamino)pyridine (**2**) as a brown liquid (949 mg, 4.84 mmol) in 88% yield: <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$  7.39 (q, *J* = 8.4 Hz, 1H), 6.30 (dd, *J* = 8.3 Hz, 2.9 Hz, 1H), 5.99 (dd, *J* = 7.6 Hz, 3.2 Hz, 1H), 4.17 (sept, *J* = 6.8 Hz, 2H), 1.29 (d, *J* = 6.5 Hz, 12H); <sup>13</sup>C NMR (CDCl<sub>3</sub>)  $\delta$  162.6 (d, *J* = 232.5 Hz), 157.0 (d, *J* = 16.7 Hz), 140.8 (d, *J* = 8.5 Hz), 104.4 (d, *J* = 4.0 Hz), 93.5 (d, *J* = 38.4 Hz), 46.1 (s), 20.6 (s); <sup>19</sup>F NMR (THF-*d*<sub>8</sub>)  $\delta$  -68.2; HRMS [C<sub>11</sub>H<sub>17</sub>N<sub>2</sub>F] requires *m/z* 196.1376, found 196.1368.

**IR Spectroscopic Analyses.** IR spectra were recorded using an in situ IR spectrometer fitted with a 30-bounce, silicon-tipped probe.<sup>30</sup> The spectra were acquired in 16 scans at a gain of 1 and a resolution of 4 cm<sup>-1</sup>. A representative reaction was carried out as follows: The IR probe was inserted through a nylon adapter and an O-ring seal into an oven-dried, cylindrical flask fitted with a magnetic stir bar and a T-joint. The T-joint was capped by a septum for injections and a nitrogen line. After evacuation under full vacuum, heating, and flushing with nitrogen, the flask was cooled to 0 °C and charged with LDA (108 mg, 1.01 mmol) and the quantities of THF and *i*-Pr<sub>2</sub>NH required to achieve the final molarities. After recording a background spectrum, arene **1** was added (0.050 mmol) as a 0.50 M solution in THF, affording **3** instantaneously. The disappearance of aryllithium **3** was monitored via the absorbance at 1576 cm<sup>-1</sup>.

**NMR Spectroscopic Analyses.** All samples were prepared using stock solutions and sealed under partial vacuum. Standard <sup>6</sup>Li, <sup>13</sup>C, <sup>15</sup>N, and <sup>19</sup>F NMR spectra were recorded on a 500 MHz spectrometer at 73.57, 125.79, 50.66, and 470.35 MHz (respectively). The <sup>6</sup>Li, <sup>13</sup>C, <sup>15</sup>N, and <sup>19</sup>F resonances are referenced to 0.30 M [<sup>6</sup>Li]LiCl/MeOH at -90 °C (0.0 ppm), the CH<sub>2</sub>O resonance of THF at -90 °C (67.57 ppm), neat Me<sub>2</sub>NEt at -90 °C (25.7 ppm), and C<sub>6</sub>H<sub>5</sub>F in neat THF at -78 °C (-113.15 ppm), respectively.

**Acknowledgment.** We thank the National Institutes of Health (GM39764) for direct support of this work and Pfizer and Sanofi-Aventis for indirect support.

**Supporting Information Available:** Spectroscopic data, rate data, and a complete list of authors for refs 5c and 17. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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