**Abstract:** Treatment of 2,6-difluoropyridine with lithium diisopropylamide in THF solution at −78 °C effects ortholithiation quantitatively. Warming the solution to 0 °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 [ArH•+Pr2NLi(THF)] and [ArH•+Pr2NLi(THF)]. 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. The yield is exceptional for such a hindered nucleophile, and heteroaromatic aminations are of great importance in the pharmaceutical industry. Our interest, however, was piqued by the apparent intermediacy of 3-pyridyllithium, which forms rapidly and quantitatively at −78 °C.

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

**Mechanism 1.** Reversal of the metalation 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 diisopropylamine concentration would be a hallmark of this mechanism.

**Mechanism 2.** Rate-limiting elimination of LiF affords a post-rate-limiting trap by LDA (eq 2). In addition to the zeroth orders expected for LDA and diisopropylamide concentration, an inverse dependence on THF concentration might be expected based on analogous LiF eliminations to form benzenes.

**Mechanism 3.** Direct substitution of the fluoro moiety of aryllithium by a nucleophilic LDA fragment must be considered, although the electrophilicity of a heteroaryllithium...
seems somewhat odd. A mixed dimer-based pathway involving the intraaggregate transfer depicted in eq 3 is one (admittedly somewhat fanciful) possibility.\textsuperscript{11} Dependencies on both ArLi and LDA concentration would be characteristic.

![image](52x414)

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 $[^6\text{Li},^{15}\text{N}]$LDA using $^6\text{Li}$ and $^{15}\text{N}$ NMR spectroscopy revealed exclusively disolvated dimer 6.\textsuperscript{12} Aryllithium 3 is exclusively monomeric as evidenced by C-3 as a doublet of triplets (1:1:1 triplet) owing to $^1\text{H}$-$^3\text{C}$-$^13\text{C}$-$^19\text{F}$ and $^1\text{H}$-$^3\text{C}$-$^13\text{C}$-$^6\text{Li}$ coupling.\textsuperscript{13,14} A solution containing $[^6\text{Li},^{15}\text{N}]$LDA and aryllithium 3 shows no $^6\text{Li}$-$^{15}\text{N}$ coupling in the $^6\text{Li}$ resonance of 3. An especially large $^2\text{J}_{\text{C-F}}$ of 122 Hz is emblematic of 2-fluoroarylolithiums.\textsuperscript{10,18} (The result without MP2 correction is shown in parentheses.) Moreover, alternative assignment of the monomer as disolvate 3a, in conjunction with the rate studies, would force on us seemingly untenable mechanistic hypotheses (vide infra).

Pseudo-first-order conditions were established with LDA (recrystallized)\textsuperscript{12} at normal concentrations (0.05–0.50 M) by restricting the substrate concentration to 0.005 M.\textsuperscript{19} Diisopropyl ether is maintained at 0.10 M unless stated otherwise. In situ IR spectroscopy showed that the disappearance of aryllithium 3 (1576 cm$^{-1}$) and appearance of arene 2 (1617 cm$^{-1}$) are first order (Figure 1). Analogous results were obtained by monitoring the $^{19}\text{F}$ 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 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 that the concentration of the monomer unit (normality). The concentration of THF is expressed as total concentration of free (uncoordinated) ligand.
nearly zeroth- and first-order dependencies, respectively. These orders persist at low and high THF concentrations.

The resulting two-term rate law described by eq 5 is consistent with two monomer-based reaction pathways differing in the number of coordinated THFs (eqs 6–9) representing variants of mechanism 1 (eq 1). One pathway (labeled pathway 1 in eq 5) manifests a zeroth-order dependence on THF concentration. Pathway 2 is distinguished by an inverse-second-order dependence on THF concentration. (The solvation number of 9 is not meant to imply the resting state of LDA monomer but simply reflects the eventual loss of two THFs.) Comparing the rates using \( i\text{-Pr}_2\text{NH} \) versus \( i\text{-Pr}_2\text{ND}_2 \) affords \( k_H/k_D = 1.2 \), confirming the reversibility of the proton transfer.6

The results from DFT calculations of monomer-based transition structures bearing 0 to 3 THF ligands are summarized in Chart 1. Free energies include single-point MP2 calculations. The values without the single-point energy corrections are shown in parentheses. Detailed analysis is deferred to the Discussion section.

**Discussion**

LDA quantitatively ortholithiates 2,6-difluoropyridine (1) in THF at \(-78^\circ C\) to form aryllithium 3. Warming the solution to 0 °C affords aminopyridine 2 (Scheme 1). At the outset, we considered three mechanisms for the conversion of aryllithium 3 to adduct 2: (1) Reversible lithiation with nucleophilic attack by LDA on unlithiated pyridine 1 (eq 1); (2) LiF elimination to form 2-pyridyne 4 with subsequent trapping by LDA (eq 2); and (3) direct nucleophilic attack of LDA on aryllithium 3, possibly via a mixed aggregate (eq 3). The rate data described herein support the reversible lithiation described by eq 1. As is often the case, however, a more complex picture emerges (Scheme 2).

A first-order dependence on diisopropylamine distinguishes the mechanism in eq 1 from the other two. Orders in THF and LDA fill in the details. Recognizing, however, that the nonspecialist may find this example somewhat baffling because of the resting state as aryllithium, we take this opportunity to walk through the process of how one extracts mechanistic insights from the rate law described by eq 5.

(20) The most stable form of LDA monomer is calculated to be a trisolvate.

(21) (a) A solution of diisopropylamine (50 mL, 0.35 mol) in 100 mL of methylene chloride was washed with deuterium oxide (10 × 10 mL) containing NaCl. The organic layer was dried over Na2SO4 and distilled to give N-deuterated diisopropylamine (30 mL, 0.21 mol). The absence of N–H resonance in a 1H NMR spectrum confirmed the quantitative deuteration of the sample. (b) Newcomb, M.; Reeder, R. A. J. Org. Chem. 1980, 45, 1489.
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. Assigning the reactant structures is critical to assessing the absolute stoichiometries of transition structures. LDA is a disolvated dimer, and aryllithium is shown spectroscopically to be a monomer and computationally to be trisolvate. 

First orders in both ArLi and i-Pr₂NH at low and high THF concentrations suggest [ArH•i-Pr₂NLi(THF)]‡, implying a rate-limiting addition. A stoichiometrically equivalent formulation such as [ArLi•i-Pr₂NH(THF)]‡, reflecting a rate-limiting proton transfer, is excluded by the reversibility of the proton transfer and an isotopically insensitive rate for i-Pr₂ND. 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-Pr₂NH 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.

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 [ArH•i-Pr₂NLi(THF)]‡. 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 [ArH•i-Pr₂NLi(THF)]‡.

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. Li–N contacts are absent in the sterically congested trisolvate.

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 unproctected charge developing on the pyridyl nitrogen is likely to be the source of some computational problems, 12 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 intermediary 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 σ bond metathesis. 14 We have always been baffled by the facility of nucleophilic substitutions of aryfluorides: 1 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. 3 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 disopropylamine 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 27 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 benzenophenone ketyl. The hexane contained 1% tetraglyme to dissolve the ketyl. Both LDA 12 and n-BuLi 28 used to prepare LDA were recrystallized. Solutions of LDA were titrated using a literature method. 29

1,2-Addition: Preparative Scale. A 1.6 M solution of n-butylthiophene (6.9 mL, 11.0 mmol) in hexanes was added via syringe to a solution of dry disopropylamine (5.0 mL, 36.1 g, 35.6 mmol) in dry hexanes at 0 °C under Ar. After the solution was stirred for 10 min, 2,6-difluoropyridine (500 µL, 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 × 10 mL), dried over Na2SO4, filtered, and evaporated to dryness under reduced pressure. Flash chromatography (50% ethyl acetate/hexanes) afforded 2-fluoro-6-(disopropylamino)pyridine (2) as a brown liquid (949 mg, 4.84 mmol) in 88% yield: 1H NMR (CDCl3) δ 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); 13C NMR (CDCl3) δ 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); 19F NMR (THF-d8) δ −68.2; HRMS [C11H17N2F] 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. 30 The spectra were acquired in 16 scans at a gain of 1 and a resolution of 4 cm−1. 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-Pr2NH required to achieve the final molarities. After recording a background spectrum, arena 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−1.

NMR Spectroscopic Analyses. All samples were prepared using stock solutions and sealed under partial vacuum. Standard 1H, 13C, and 19F NMR spectra were recorded on a 500 MHz spectrometer at 73.57, 125.79, 50.66, and 470.35 MHz (respectively). The 1H, 13C, and 19F resonances are referenced to 0.30 M [1H]LiCl/MeOH at −90 °C (0.0 ppm), the CH2O resonance of THF at −90 °C (67.57 ppm), near Me2NEt at −90 °C (25.7 ppm), and C6H6F in neat THF at −78 °C (−113.15 ppm), respectively.

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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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