# Lithium Diisopropylamide-Mediated Ortholithiation of 2-Fluoropyridines: Rates, Mechanisms and the Role of Autocatalysis

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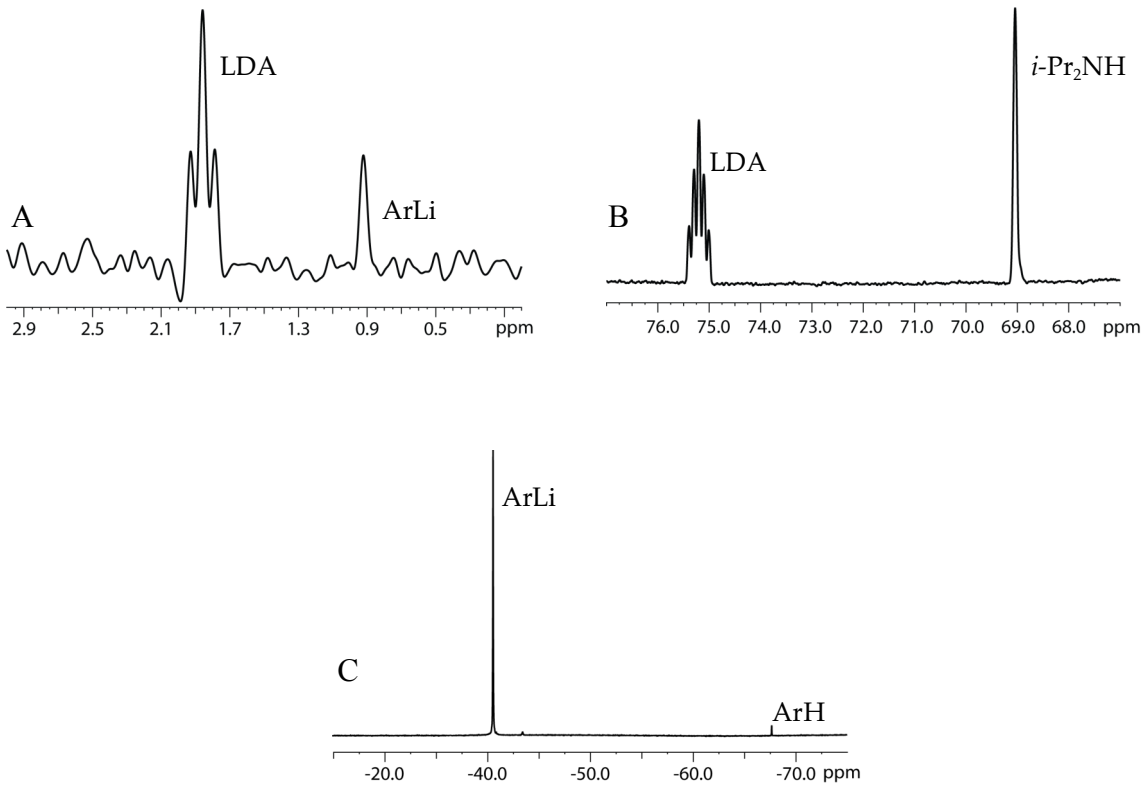
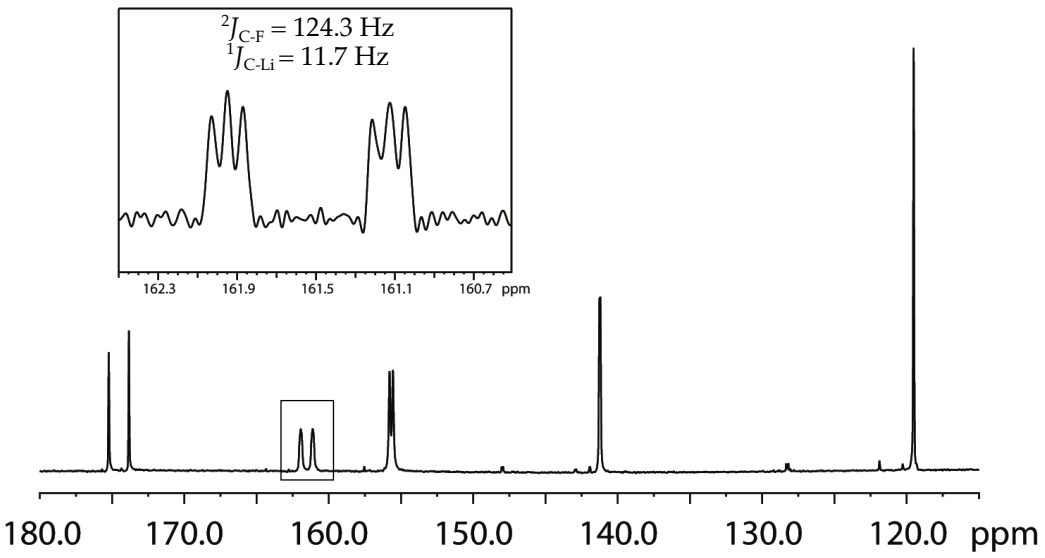
## Supporting Information

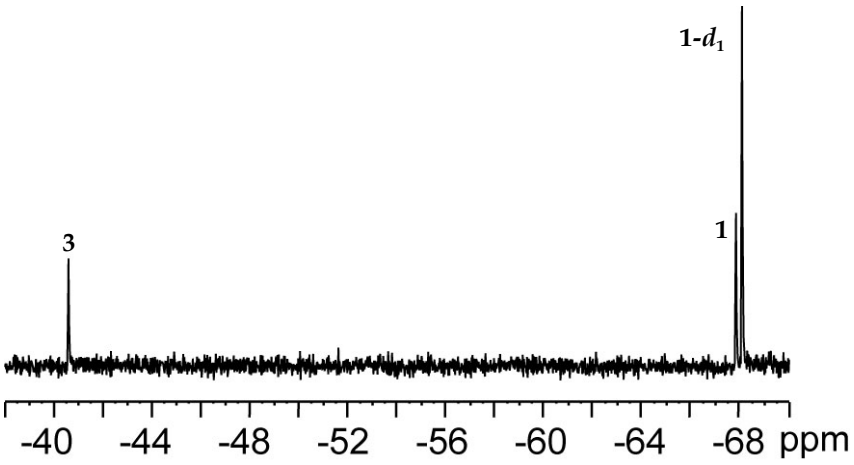
**Part 1: NMR Spectroscopic Studies**



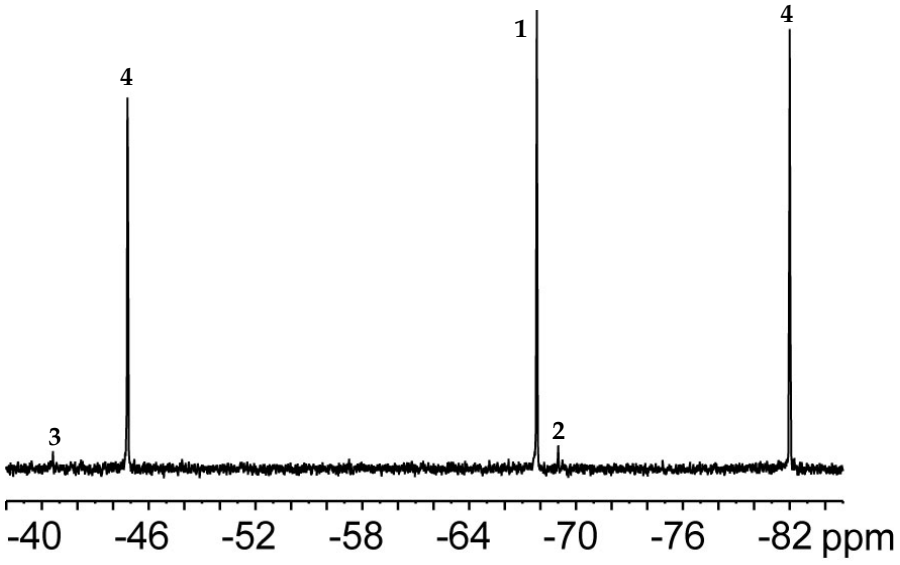

**I.** $^{6}$Li, $^{15}$N and $^{19}$F NMR spectra of 0.10 M [$^{6}$Li,$^{15}$N]LDA in neat THF recorded at -90 $^{o}$C in the presence of 0.025 M 2-fluoropyridine (**1**): (A) $^{6}$Li spectrum; (B) $^{15}$N spectrum; (C) $^{19}$F spectrum.




**II.** $^{13}C\{^{1}H\}$ NMR spectrum (150 MHz) of 0.050 M 2-fluoro-3-lithiopyridine (**3**) in neat THF at -100 °C: $\delta$ 175.54 (d, $^{1}J_{C\text{-}F}$ = 210.6 Hz), 161.54 (dt, $^{2}J_{C\text{-}F}$ = 124.3 Hz, $^{1}J_{C\text{-}Li}$ = 11.7 Hz), 155.68 (d, $^{3}J_{C\text{-}F}$ = 35.9 Hz), 141.24 (d, $^{3}J_{C\text{-}F}$ = 11.8 Hz), 119.52 (s). Inset shows the multiplet at $\delta$ 161.54 and includes lorentzian to gaussian transformation to enhance resolution.

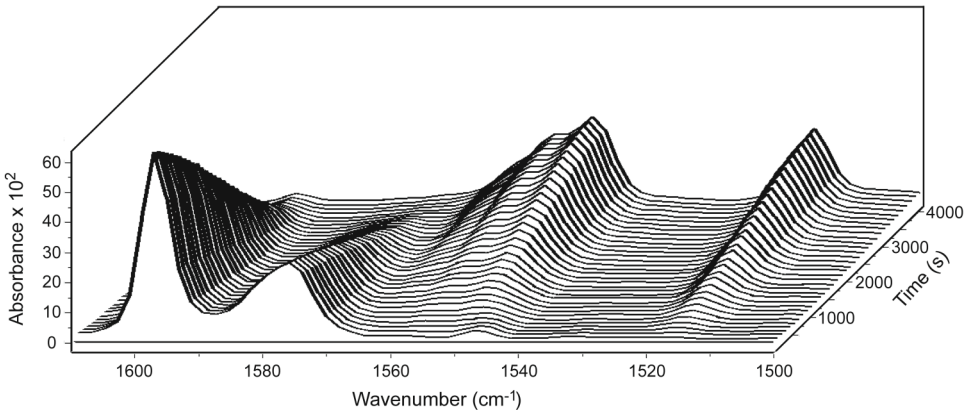



**III.** $^{19}$F NMR spectrum for the ortholithiation of a mixture of fluoropyridines **1** and **1-$d_1$** (0.002 M each) with LDA (0.10 M) in THF (12.20 M) at -78 °C.

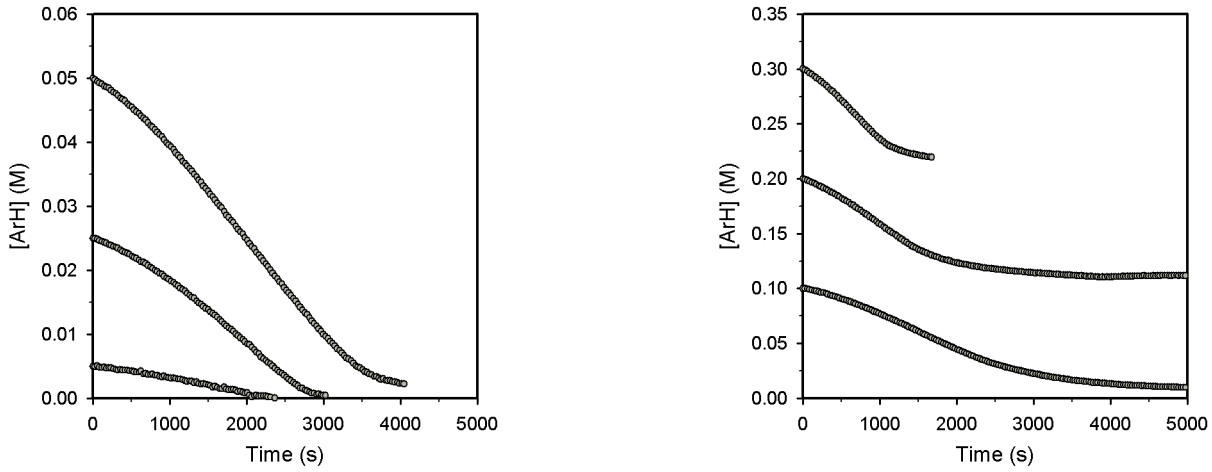



**IV.** $^{19}$F NMR spectrum for the ortholithiation of a mixture of fluoropyridines **1** and **2** (0.002 M each) with LDA (0.10 M) in THF (12.20 M) at -78 °C.

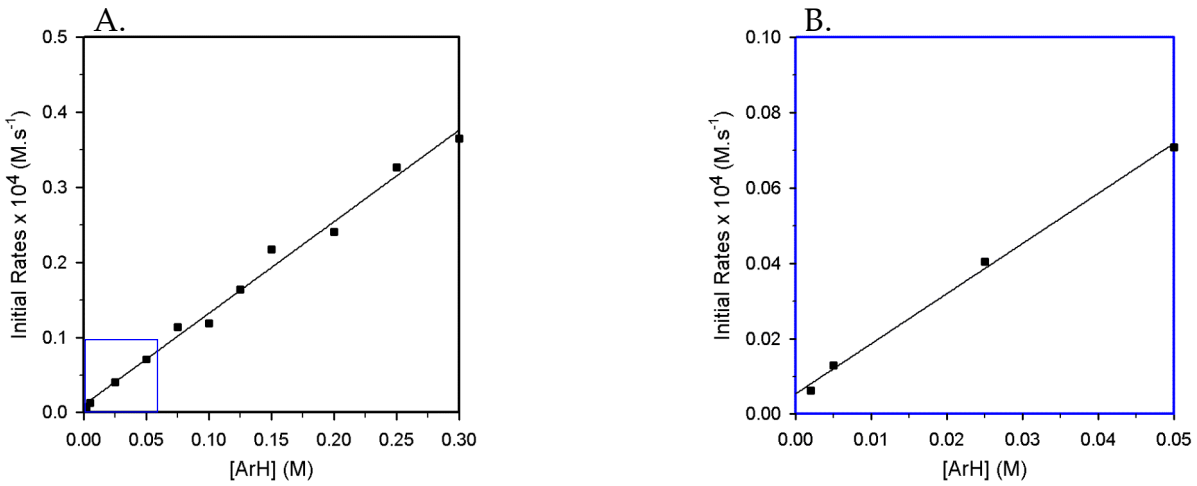
**Part 2: Rate Studies**




**XI.** Representative in situ IR spectroscopic analysis of the ortholithiation of **1** (0.05 M) by LDA (0.10 M) in THF at -78 °C. The IR absorbances at 1598 $cm^{-1}$ and 1576 $cm^{-1}$ correspond to **1**, whereas the absorbances at 1551 $cm^{-1}$ and 1517 $cm^{-1}$ correspond to its lithiated form **3**.

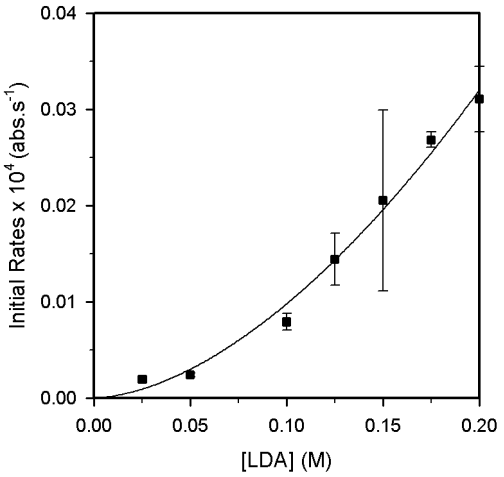



**XII.** Representative plots showing [ArH] vs time for the ortholithiation of 2-fluoropyridine (**1**) with LDA (0.1 M) in THF (12.20 M) at -78 °C.



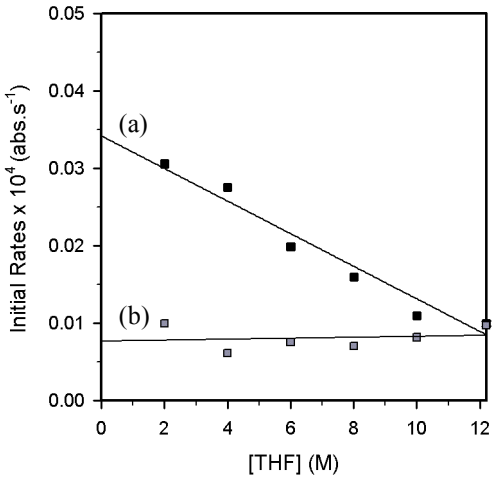

**XIII.** Plot of initial rates vs [ArH] for the ortholithiation of **1** with LDA (0.10 M) in THF (12.20 M) at -78 °C. The curve depicts an unweighted least-squares fit to y = $k$[ArH] + $k'$ ($k$ = (1.22 ± 0.04) x $10^{-4}$, $k'$ = (1.0 ± 0.6) x $10^{-6}$); (B) Magnified plot of the regime marked in blue square in (A). The curve depicts an unweighted least-squares fit to y = $k$[ArH] + $k'$ ($k$ = (1.32 ± 0.05) x $10^{-4}$, $k'$ = (5 ± 1) x $10^{-7}$)

| [ArH] (M) | $y_1$ x $10^4$ ($M.s^{-1}$) |
|---|---|
| 0.002 | 0.006 ± 2E-3 |
| 0.005 | 0.013 ± 2E-3 |
| 0.025 | 0.0405 ± 9E-4 |
| 0.050 | 0.0709 ± 7E-4 |
| 0.075 | 0.114 ± 2E-3 |
| 0.100 | 0.119 ± 2E-3 |
| 0.125 | 0.164 ± 2E-3 |
| 0.150 | 0.217 ± 6E-3 |
| 0.200 | 0.240 ± 5E-3 |
| 0.250 | 0.33 ± 2E-2 |
| 0.300 | 0.365 ± 8E-3 |




**XIV.** Plot of initial rates vs [LDA] in THF (11.5 M) using hexane as the cosolvent for the ortholithiation of **1** (0.002 M) at -78 °C. The curve depicts an unweighted least-squares fit to $y = k[\mathrm{LDA}]^n$ ($k = (5 \pm 2) \times 10^{-5}$, $n = 1.7 \pm 0.3$).

| [LDA] (M) | $y_1 \times 10^4$ (abs.s$^{-1}$) | $y_2 \times 10^4$ (abs.s$^{-1}$) | $y_3 \times 10^4$ (abs.s$^{-1}$) |
|---|---|---|---|
| 0.025 | 0.0018 ± 2E-4 | 0.0019 ± 2E-4 | — |
| 0.05 | 0.0022 ± 4E-4 | 0.0025 ± 4E-4 | — |
| 0.10 | 0.008 ± 1E-3 | 0.007 ± 2E-3 | — |
| 0.125 | 0.016 ± 4E-3 | 0.012 ± 3E-3 | — |
| 0.15 | 0.022 ± 4E-3 | 0.011 ± 4E-3 | 0.029 ± 6E-3 |
| 0.175 | 0.027 ± 7E-3 | 0.026 ± 4E-3 | — |
| 0.20 | 0.027 ± 3E-3 | 0.032 ± 1E-2 | 0.034 ± 9E-3 |



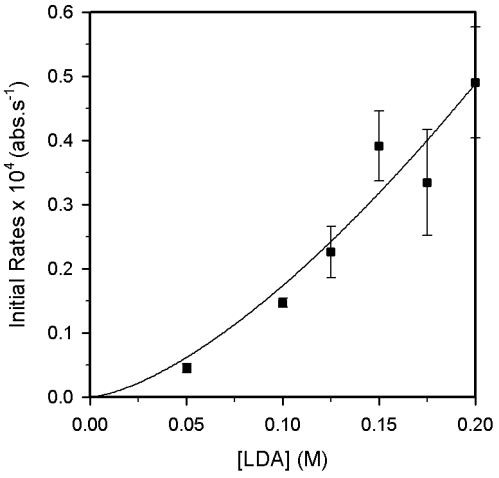

**XV.** Plot of initial rates vs [THF] for the ortholithiation of **1** (0.002 M) with LDA (0.10 M) at -78 °C in: (a) hexane cosolvent. The curve depicts an unweighted least-squares fit to $y = -k[THF] + k'$ ($k = (2.1 \pm 0.2) \times 10^{-7}$, $k' = (3.4 \pm 0.2) \times 10^{-6}$); (b) 2,5-dimethyltetrahydrofuran cosolvent. The curve depicts an unweighted least-squares fit to $y = -k[THF] + k'$ ($k = (6 \pm 19) \times 10^{-9}$, $k' = (8 \pm 1) \times 10^{-7}$).

(a) in hexane cosolvent:

| [THF] (M) | $y_1 \times 10^4$ (abs.s$^{-1}$) |
|---|---|
| 2.0 | 0.030 ± 1E-3 |
| 4.0 | 0.027 ± 1E-3 |
| 6.0 | 0.0199 ± 8E-4 |
| 8.0 | 0.0160 ± 3E-4 |
| 10.0 | 0.0109 ± 8E-4 |
| 12.20 | 0.009 ± 1E-3 |

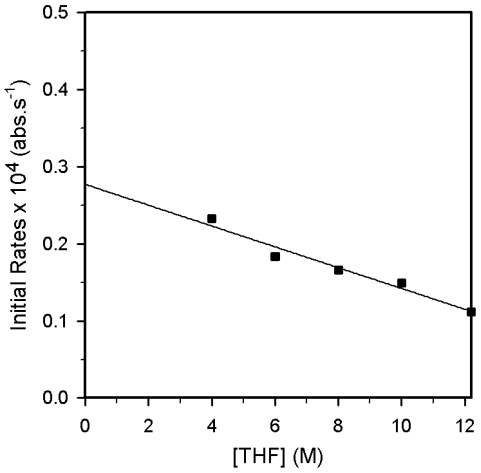
(b) in 2,5-$Me_2$THF cosolvent:

| [THF] (M) | $y_1 \times 10^4$ (abs.s$^{-1}$) |
|---|---|
| 2.0 | 0.010 ± 1E-3 |
| 4.0 | 0.006 ± 1E-3 |
| 6.0 | 0.0075 ± 6E-4 |
| 8.0 | 0.007 ± 3E-3 |
| 10.0 | 0.008 ± 2E-3 |
| 12.20 | 0.009 ± 1E-3 |



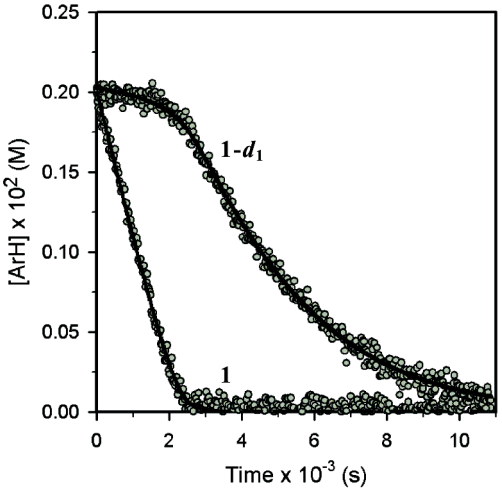

**XVI.** Plot of initial rates vs [LDA] in THF (11.5 M) using hexane as the cosolvent for the ortholithiation of **1** (0.20 M) at -78 °C. The curve depicts an unweighted least-squares fit to $y = k[LDA]^n$ ($k = (5 \pm 3) \times 10^{-4}$, $n = 1.5 \pm 0.3$).

| [LDA] (M) | $y_1 \times 10^4$ (abs.s$^{-1}$) | $y_2 \times 10^4$ (abs.s$^{-1}$) | $y_3 \times 10^4$ (abs.s$^{-1}$) |
|---|---|---|---|
| 0.050 | 0.050 ± 4E-3 | 0.040 ± 6E-3 | — |
| 0.100 | 0.15 ± 1E-2 | 0.142 ± 7E-3 | — |
| 0.125 | 0.25 ± 3E-2 | 0.19 ± 1E-2 | — |
| 0.150 | 0.42 ± 3E-2 | 0.33 ± 1E-2 | 0.43 ± 2E-2 |
| 0.175 | 0.39 ± 3E-2 | 0.27 ± 1E-2 | — |
| 0.200 | 0.40 ± 1E-2 | 0.49 ± 2E-2 | 0.58 ± 3E-2 |




**XVII.** Plot of initial rates vs [THF] in hexane cosolvent for the ortholithiation of **1** (0.20 M) with LDA (0.10 M) at -78 °C. The curve depicts an unweighted least-squares fit to $y = -k[THF] + k'$ ($k = (1.3 \pm 0.2) \times 10^{-6}$, $k' = (2.8 \pm 0.1) \times 10^{-5}$).

| [THF] (M) | $y_1 \times 10^4$ (abs.s$^{-1}$) |
|---|---|
| 4.0 | 0.23 ± 3E-2 |
| 6.0 | 0.18 ± 4E-2 |
| 8.0 | 0.2 ± 3E-1 |
| 10.0 | 0.15 ± 1E-2 |
| 12.20 | 0.11 ± 3E-2 |




**XVIII.** Parametric fit to the plot of [ArH] vs time for the ortholithiation of a mixture of fluoropyridines **1** and **1-*d*$_1$** (0.002 M each) with LDA (0.10 M) in THF (12.20 M) at -78 °C, monitored by $^{19}$F NMR spectroscopy. The functions result from best-fit numerical integration to the following model:

*Model*:

$$A_2 \underset{k_1}{\overset{k_{-1}}{\rightleftharpoons}} 2A$$

$$A + ArH \xrightarrow{k_H} ArLi$$

$$A + ArD \xrightarrow{k_D} ArLi$$

The model is described by the following differential equations:

$d[A_2]/dt = -k_1[A_2] + k_{-1}[A]^2$

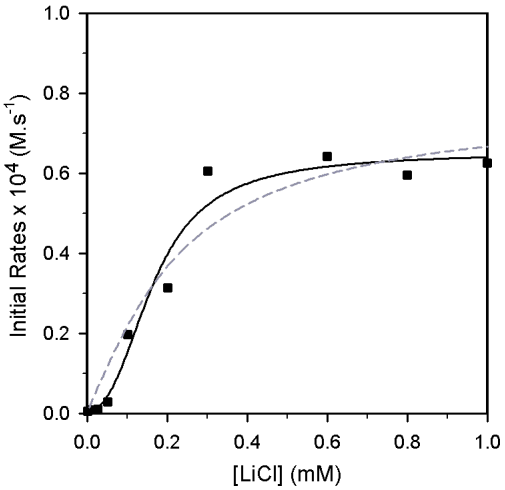
$d[A]/dt = 2k_1[A_2] - 2k_{-1}[A]^2 - k_H[ArH][A] - k_D[ArH][A]$

$d[ArH]/dt = -k_H[ArH][A]$

$d[ArD]/dt = -k_D[ArD][A]$

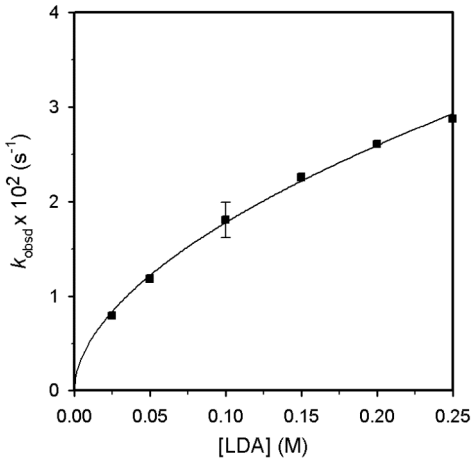
where, ArH = **1**, ArD = **1-*d*$_1$**, $A_2$ = **5**

$k_1$ = (9.87 $\pm$ 0.04) x $10^{-6}$
$k_{-1}$ = 2.31 $\pm$ 0.09
$k_2$ = 21.7 $\pm$ 0.8
$k_3$ = 0.89 $\pm$ 0.02



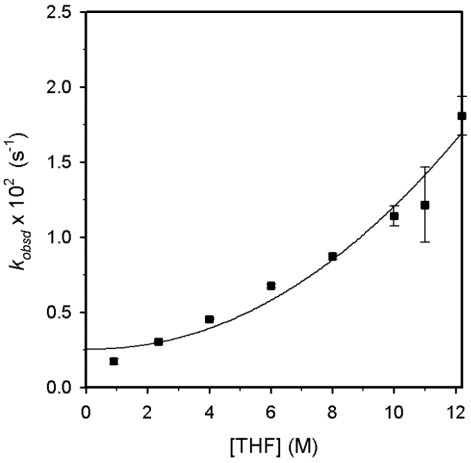

**XIX.** Plot of initial rates vs [LiCl] for the ortholithiation of **1** (0.004 M) with LDA (0.10 M) in THF (12.20 M) at -78 °C. The curve depicts an unweighted least-squares fit to $-d[\mathrm{ArH}]/dt = \{k_2[\mathrm{ArH}]/4k_{-1}[\mathrm{LiCl}]^n\}\ \{(k_2^2[\mathrm{ArH}]^2 + 16k_1k_{-1}[\mathrm{A_2S_2}]_0[\mathrm{LiCl}]^{2n})^{0.5} - k_2[\mathrm{ArH}]\} + c$. [ArH] = 0.004 M, $[\mathrm{A_2S_2}]_0 = 0.05$ M, $c = (5 \pm 1) \times 10^{-7}$, $n = 2$ and $k_1 = (1.6 \pm 0.1) \times 10^{-2}$, $k_{-1} = (1.03 \pm 0.03) \times 10^4$, $k_2 = (5.901 \pm 0.002) \times 10^1$. The dashed curve represents a fit to the data where $n = 1$ in the given equation.

| [LiCl] (mM) | $y_1 \times 10^4$ (M.s$^{-1}$) |
|---|---|
| 0.0 | 0.005 ± 1E-3 |
| 0.01 | 0.0084 ± 9E-4 |
| 0.025 | 0.010 ± 2E-3 |
| 0.05 | 0.028 ± 4E-3 |
| 0.10 | 0.20 ± 3E-2 |
| 0.20 | 0.31 ± 7E-2 |
| 0.30 | 0.61 ± 8E-2 |
| 0.60 | 0.64 ± 8E-2 |
| 0.80 | 0.6 ± 1E-1 |
| 1.0 | 0.6 ± 1E-1 |



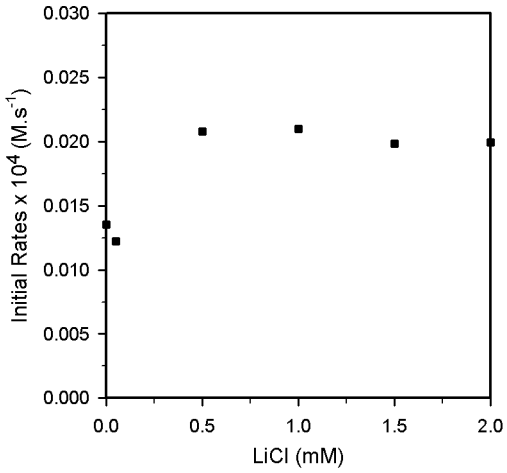

**XX.** Plot of $k_{obsd}$ vs [LDA] in THF (12.20 M) using hexane as the cosolvent for the ortholithiation of **1** (0.004 M) in the presence of 2 mol% LiCl at -78 °C. The curve depicts an unweighted least-squares fit to $k_{obsd} = k[\text{LDA}]^n$ ($k = (6.2 \pm 0.4) \times 10^{-2}$, $n = 0.54 \pm 0.03$).

| [LDA] (M) | $k_{obsd1}$ x $10^2$ ($s^{-1}$) | $k_{obsd2}$ x $10^2$ ($s^{-1}$) | $k_{obsd3}$ x $10^2$ ($s^{-1}$) |
|---|---|---|---|
| 0.025 | 0.79 ± 1E-2 | — | |
| 0.05 | 1.18 ± 2E-2 | — | |
| 0.10 | 1.94 ± 5E-2 | 1.67 ± 5E-2 | 1.80 ± 5E-2 |
| 0.15 | 2.26 ± 7E-2 | — | |
| 0.20 | 2.6 ± 1E-1 | — | |
| 0.25 | 2.9 ± 1E-1 | — | |



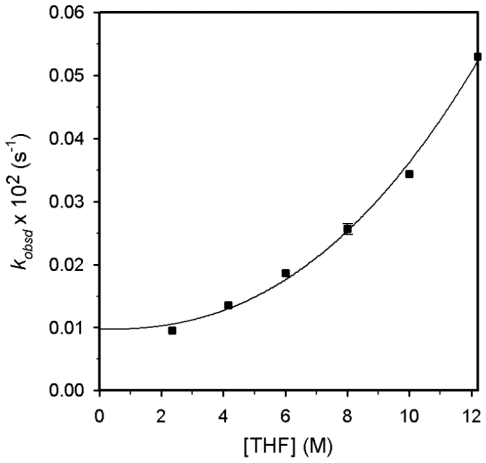

**XXI.** Plot of $k_{obsd}$ vs [THF] in hexane cosolvent for the ortholithiation of **1** (0.004 M) with LDA (0.10 M) in the presence of 2 mol% LiCl at -78 °C. The curve depicts an unweighted least-squares fit to $k_{obsd} = k[THF]^n + k'$ ($k = (8 \pm 7) \times 10^{-5}$, $n = (2.0 \pm 0.4)$, $k' = (2.5 \pm 0.7) \times 10^{-3}$).

| [THF] (M) | $k_{obsd1}$ x $10^2$ ($s^{-1}$) | $k_{obsd2}$ x $10^2$ ($s^{-1}$) | $k_{obsd3}$ x $10^2$ ($s^{-1}$) |
|---|---|---|---|
| 0.89 | 0.185 ± 4E-3 | 0.160 ± 5E-3 | — |
| 2.35 | 0.304 ± 5E-3 | 0.304 ± 4E-3 | — |
| 4.0 | 0.449 ± 8E-3 | 0.458 ± 9E-3 | — |
| 6.0 | 0.68 ± 1E-2 | 0.67 ± 1E-2 | — |
| 8.0 | 0.86 ± 2E-2 | 0.89 ± 2E-2 | — |
| 10.0 | 1.19 ± 5E-2 | 1.09 ± 3E-2 | — |
| 11.0 | 1.39 ± 6E-2 | 1.04 ± 4E-2 | — |
| 12.20 | 1.94 ± 5E-2 | 1.67 ± 5E-2 | 1.80 ± 5E-2 |



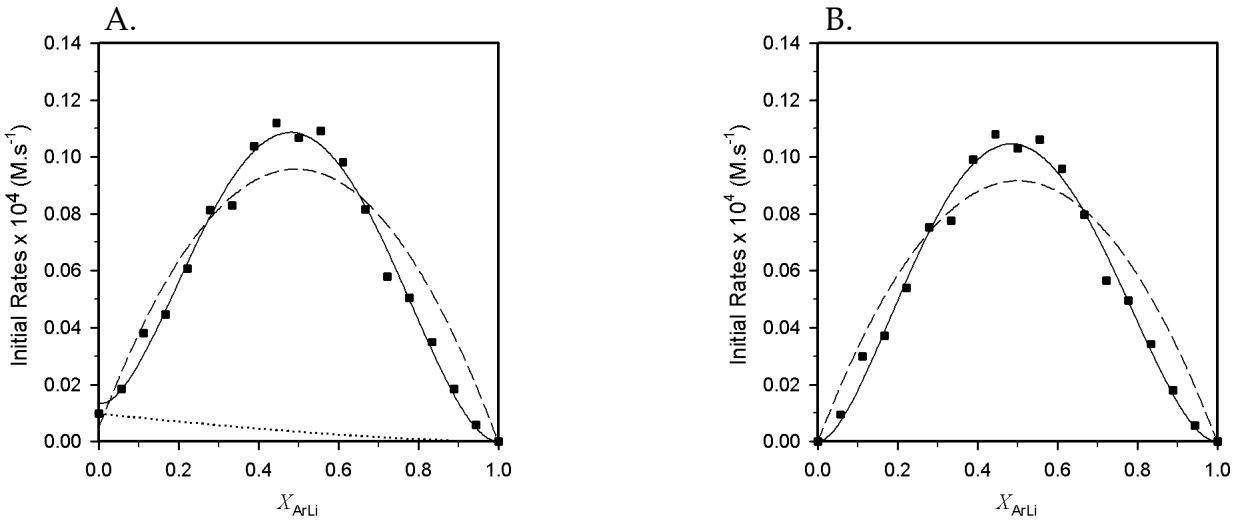

**XXII.** Plot of initial rates vs [LiCl] for the ortholithiation of **1-*d*$_1$** (0.004 M) with LDA (0.10 M) in THF (12.20 M) at -78 °C.

| [LiCl] (mM) | $y_1$ x $10^4$ ($M.s^{-1}$) |
|---|---|
| 0.0 | 0.0135 $\pm$ 2E-4 |
| 0.05 | 0.0122 $\pm$ 3E-4 |
| 0.5 | 0.0208 $\pm$ 3E-4 |
| 1.0 | 0.0209 $\pm$ 5E-4 |
| 1.5 | 0.0198 $\pm$ 5E-4 |
| 2.0 | 0.0199 $\pm$ 3E-4 |




**XXIII.** Plot of $k_{obsd}$ vs [THF] in hexane cosolvent for the ortholithiation of **1-$d_1$** (0.004 M) with LDA (0.10 M) in the presence of 2 mol% LiCl at -78 °C. The curve depicts an unweighted least-squares fit to $k_{obsd} = k[THF]^n + k'$ ($k = (1.1 \pm 0.6) \times 10^{-6}$, $n = (2.4 \pm 0.2)$, $k' = (10 \pm 1) \times 10^{-5}$).

| [THF] (M) | $k_{obsd1}$ x $10^2$ ($s^{-1}$) | $k_{obsd2}$ x $10^2$ ($s^{-1}$) |
|---|---|---|
| 2.35 | 0.00956 ± 8E-5 | — |
| 4.15 | 0.01355 ± 7E-5 | — |
| 6.0 | 0.0186 ± 3E-4 | — |
| 8.0 | 0.0262 ± 3E-4 | 0.0251 ± 5E-4 |
| 10.0 | 0.0344 ± 6E-4 | — |
| 12.20 | 0.0530 ± 7E-4 | — |




**XXIV.** Plot of initial rates versus mole fraction of 3-lithio-2-fluoropyridine ($X_{ArLi}$) for the serial injection of 0.0055 M aliquots of pyridine **1** to 0.10 M LDA in 12.20 M THF at -78 °C. The dotted line in figure A depicts the theoretical initial rates in the absence of autocatalysis, assuming an LDA order of 1.5. The solid line depicts an unweighted least-squares fit to $-d[\mathbf{1}]/dt = k(X_{ArLi})^n(1-X_{ArLi})^m + k'(1-X_{ArLi})^{1.5}$ ($n$ = 1.8 ± 0.1, $m$ = 1.9 ± 0.1, $k$ = (1.5 ± 0.3) x $10^{-4}$, $k'$ = (1.3 ± 0.4) x $10^{-6}$). The dashed curve represents a fit to the data where $n$ = 1 and $m$ = 1 in the given equation. In figure B, the contribution of the uncatalyzed pathway (dotted line in figure A) is subtracted.

| $X_{ArLi}$ | y x $10^4$ (M.s$^{-1}$) | $X_{ArLi}$ | y x $10^4$ (M.s$^{-1}$) |
|---|---|---|---|
| 0.0000 | 0.0098 ± 6E-4 | 0.5556 | 0.109 ± 7E-3 |
| 0.0556 | 0.018 ± 1E-3 | 0.6111 | 0.098 ± 8E-3 |
| 0.1111 | 0.038 ± 2E-3 | 0.6667 | 0.082 ± 5E-3 |
| 0.1667 | 0.045 ± 4E-3 | 0.7222 | 0.058 ± 3E-3 |
| 0.2222 | 0.061 ± 4E-3 | 0.7778 | 0.050 ± 3E-3 |
| 0.2778 | 0.081 ± 6E-3 | 0.8333 | 0.035 ± 2E-3 |
| 0.3333 | 0.083 ± 7E-3 | 0.8889 | 0.0184 ± 6E-4 |
| 0.3889 | 0.10 ± 1E-2 | 0.9444 | 0.0059 ± 5E-4 |
| 0.4444 | 0.112 ± 9E-3 | 1.0000 | 0.0 |
| 0.5000 | 0.107 ± 7E-3 | | |

**XXV.** Derivation of expression for fitting incremental addition curve (eq 19 in manuscript):

In a serial injection experiment, the amount of [ArH] injected remains constant, but the concentration of LDA and ArLi varies with each successive injection.

Hence, the rate of consumption of arene and its initial rate ($rate_{init}$) are defined as:

$$-d[\mathrm{ArH}]/d\mathrm{t} = k[\mathrm{ArLi}]^n[\mathrm{LDA}]^m \quad (1)$$

Writing the concentrations in terms of mole fractions:

$$-d[\mathrm{ArH}]/d\mathrm{t} = k[X_{\mathrm{ArLi}}]^n[X_{\mathrm{LDA}}]^m \quad (2)$$

where $X_{\mathrm{ArLi}} = \mathrm{N}_{\mathrm{ArLi}}/(\mathrm{N}_{\mathrm{ArLi}} + \mathrm{N}_{\mathrm{LDA}})$ (N stands for normality)

Also, $X_{\mathrm{LDA}} = 1 - X_{\mathrm{ArLi}}$ (3)

Substituting eq 3 into eq 2 gives:

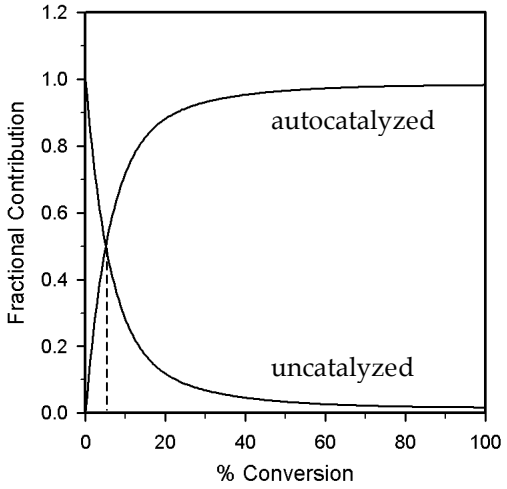
$$-d[\mathrm{ArH}]/d\mathrm{t} = k[X_{\mathrm{ArLi}}]^n[1 - X_{\mathrm{ArLi}}]^m \quad (4)$$

The initial rate in the absence of autocatalysis, assuming an LDA order of 1.5 is given by:

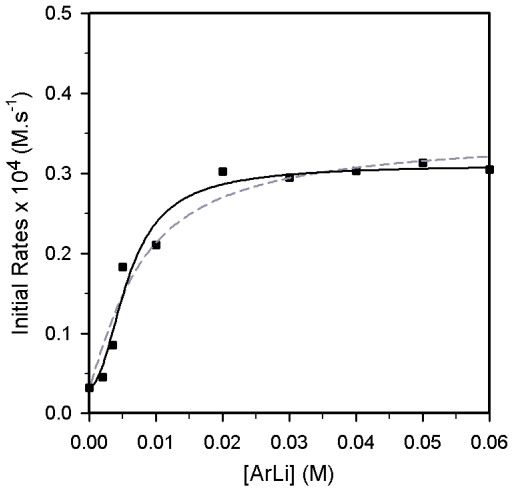
$$-d[\mathrm{ArH}]/d\mathrm{t} = k'[X_{\mathrm{LDA}}]^{1.5} \quad (5) \text{ or,}$$
$$-d[\mathrm{ArH}]/d\mathrm{t} = k'[1 - X_{\mathrm{ArLi}}]^{1.5} \quad (6)$$

To account for the rate in the absence of autocatalysis, we add eq 6 to eq 4. Hence, eq 4 becomes:

$$-d[\mathrm{ArH}]/d\mathrm{t} = k[X_{\mathrm{ArLi}}]^n[1 - X_{\mathrm{ArLi}}]^m + k'[1 - X_{\mathrm{ArLi}}]^{1.5} \quad (7)$$

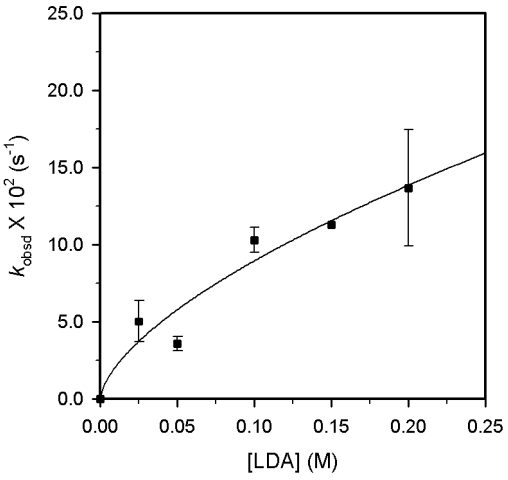



**XXVI.** Plot of fractional contribution of the autocatalyzed and uncatalyzed pathway to the total reaction rate versus percent conversion derived from the data in Figure XXIII. Equal contribution from the two pathways (dashed line) occurs at 6% conversion.



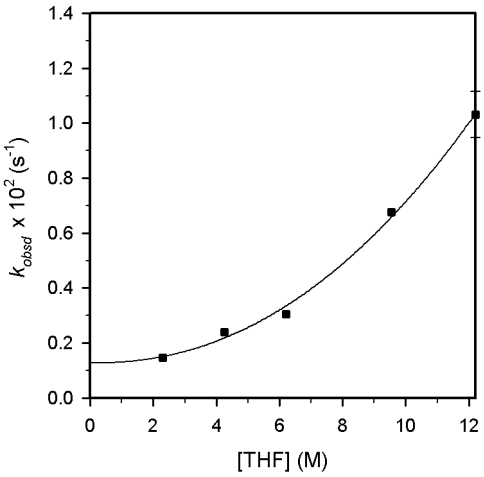

**XXVII.** Plot of initial rates vs [ArLi] for the ortholithiation of **1** (0.005 M) with LDA (0.10 M) in THF (12.20 M) at -78 °C. The curve depicts an unweighted least-squares fit to $-d[\mathrm{ArH}]/dt = \{k_2[\mathrm{ArH}]/4k_{-1}[\mathrm{ArLi}]^n\}\ \{(k_2^2[\mathrm{ArH}]^2 + 16k_1k_{-1}[\mathrm{A_2S_2}]_0[\mathrm{ArLi}]^{2n})^{0.5} - k_2[\mathrm{ArH}]\} + c$ (see XXX for derivation, substituting LiCl with ArLi). [ArH] = 0.005 M, $[\mathrm{A_2S_2}]_0$ = 0.05 M, c = (3.2 ± 0.5) x $10^{-6}$ and $n$ = 1.7 ± 0.4, $k_1$ = 1.2 ± 2.6, $k_{-1}$ = (1.6 ± 0.2) x $10^3$, $k_2$ = (9.2 ± 11.5) x $10^{-1}$. The dashed curve represents a fit to the data where $n$ = 1 in the given equation.

| [ArLi] (M) | $y_1$ x $10^4$ (M.s$^{-1}$) |
|---|---|
| 0.0 | 0.032 ± 5E-3 |
| 0.002 | 0.045 ± 5E-3 |
| 0.0035 | 0.085 ± 9E-3 |
| 0.005 | 0.18 ± 1E-2 |
| 0.01 | 0.21 ± 1E-2 |
| 0.02 | 0.30 ± 5E-2 |
| 0.03 | 0.29 ± 3E-2 |
| 0.04 | 0.30 ± 4E-2 |
| 0.05 | 0.31 ± 5E-2 |
| 0.06 | 0.30 ± 6E-2 |




**XXVIII.** Plot of $k_{obsd}$ vs [LDA] in THF (12.20 M) using hexane as the cosolvent for the ortholithiation of **1** (0.005 M) in the presence of 0.04 M ArLi at -78 °C. The curve depicts an unweighted least-squares fit to $k_{obsd} = k[\text{LDA}]^n$ ($k = (4 \pm 1) \times 10^{-2}$, $n = 0.6 \pm 0.1$).

| [LDA] (M) | $k_{obsd1} \times 10^2$ ($s^{-1}$) | $k_{obsd2} \times 10^2$ ($s^{-1}$) |
|---|---|---|
| 0.025 | 0.59 ± 1E-2 | 0.407 ± 6E-3 |
| 0.05 | 0.39 ± 1E-2 | 0.325 ± 7E-3 |
| 0.10 | 1.09 ± 2E-2 | 0.97 ± 2E-2 |
| 0.15 | 1.22 ± 3E-2 | — |
| 0.20 | 1.63 ± 4E-2 | 1.10 ± 2E-2 |




**XXIX.** Plot of $k_{obsd}$ vs [THF] in hexane cosolvent for the ortholithiation of **1** (0.005 M) with LDA (0.10 M) in the presence of 0.03 M ArLi at -78 °C. The curve depicts an unweighted least-squares fit to $k_{obsd} = k[THF]^n + k'$ ($k = (4 \pm 5) \times 10^{-5}$, $n = (2.1 \pm 0.5)$, $k' = (1.2 \pm 0.6) \times 10^{-3}$).

| [THF] (M) | $k_{obsd1}$ x $10^2$ ($s^{-1}$) | $k_{obsd2}$ x $10^2$ ($s^{-1}$) |
|---|---|---|
| 2.29 | 0.15 ± 1E-2 | — |
| 4.25 | 0.241 ± 3E-3 | — |
| 6.21 | 0.304 ± 6E-3 | — |
| 9.54 | 0.67 ± 1E-2 | — |
| 12.20 | 1.09 ± 2E-2 | 1.09 ± 2E-2 |

**XXX.** Derivation of expression for fitting LiCl saturation curve (eq 16 and eq 17 in manuscript):

$$A_2S_2 + 2m\text{THF} \underset{k_{-1}[\text{LiCl}]^n}{\overset{k_1[\text{LiCl}]^n}{\rightleftharpoons}} 2AS_{m+1}$$

$$AS_{m+1} + \text{ArH} \xrightarrow{k_2} \text{product}$$

The rate of consumption of arene and its initial rate ($\text{rate}_{\text{init}}$) are defined as:

$$-\frac{d[\text{ArH}]}{dt} = k_2[AS_{m+1}][\text{ArH}] \quad (1)$$

Applying the steady-state approximation to monomer $AS_{m+1}$,

$$\frac{d[AS_{m+1}]}{dt} = 2k_1[A_2S_2][\text{LiCl}]^n[\text{THF}]^{2m} - 2k_{-1}[AS_{m+1}]^2[\text{LiCl}]^n - k_2[AS_{m+1}][\text{ArH}] = 0 \quad (2)$$

solving for $[AS_{m+1}]$ using the quadratic equation,

$$[AS_{m+1}] = \frac{1}{4k_{-1}[\text{LiCl}]^n}\left(\sqrt{k_2^2[\text{ArH}]^2 + 16k_1k_{-1}[A_2S_2][\text{LiCl}]^{2n}[\text{THF}]^{2m}} - k_2[\text{ArH}]\right) \quad (3)$$

and substituting eq 3 into eq 1 gives:

$$-\frac{d[\text{ArH}]}{dt} = \frac{k_2[\text{ArH}]}{4k_{-1}[\text{LiCl}]^n}\left(\sqrt{k_2^2[\text{ArH}]^2 + 16k_1k_{-1}[A_2S_2][\text{LiCl}]^{2n}[\text{THF}]^{2m}} - k_2[\text{ArH}]\right) \quad (4)$$

where [ArH] and $[A_2S_2]$ are evaluated at $t$=0. To account for the LiCl-free pathway as outlined below:

$$A_2S_2 + 2m\text{THF} \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} 2AS_{m+1}$$

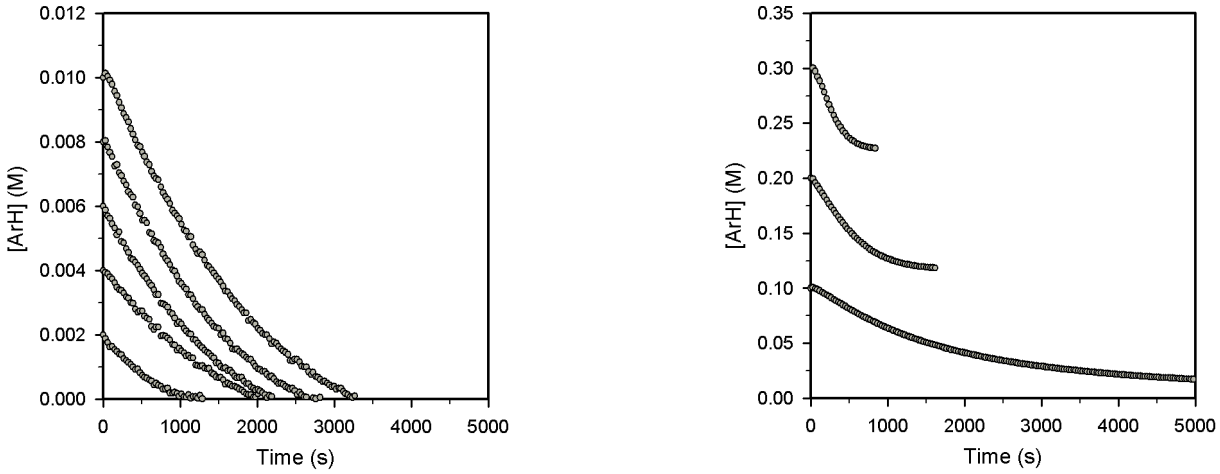
$$AS_{m+1} + \text{ArH} \xrightarrow{k_2} \text{product}$$

we add a constant c to eq 4 that reflects the initial rate without LiCl. The constant is determined experimentally rather than as an adjustable parameter.

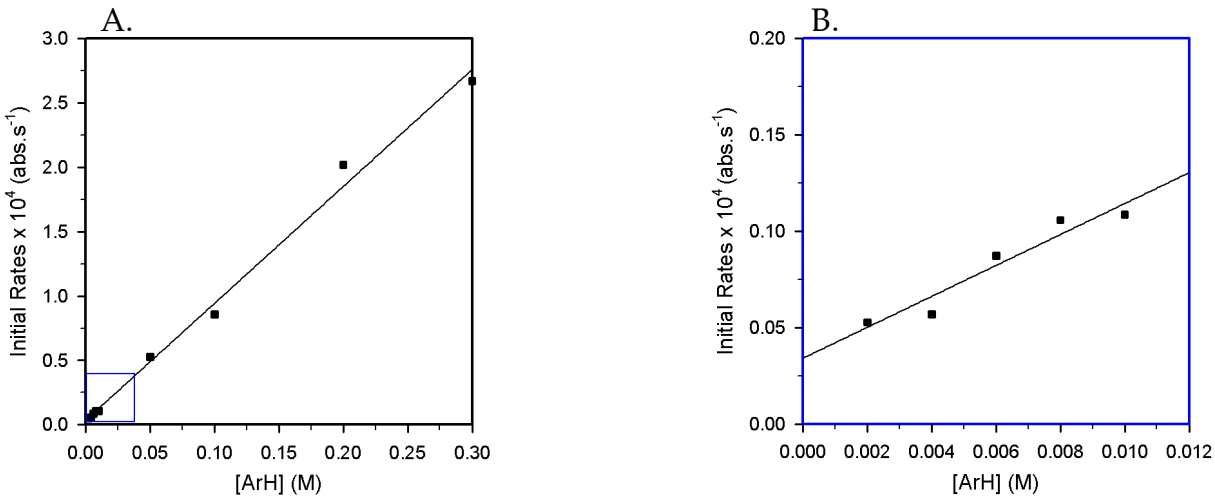
$$-\frac{d[\text{ArH}]}{dt} = \frac{k_2[\text{ArH}]}{4k_{-1}[\text{LiCl}]^n}\left(\sqrt{k_2^2[\text{ArH}]^2 + 16k_1k_{-1}[A_2S_2]_0[\text{LiCl}]^{2n}[\text{THF}]^{2m}} - k_2[\text{ArH}]\right) + c \quad (5)$$

In the limit of full saturation ($k_2 << k_{-1}[\text{LiCl}]^n$), eq 5 reduces to eq 6

$$-\frac{d[\text{ArH}]}{dt} = \frac{(k_1)^{1/2}k_2}{(k_{-1})^{1/2}}[\text{ArH}][\text{THF}]^m[\text{LDA}]^{0.5} \quad (6)$$

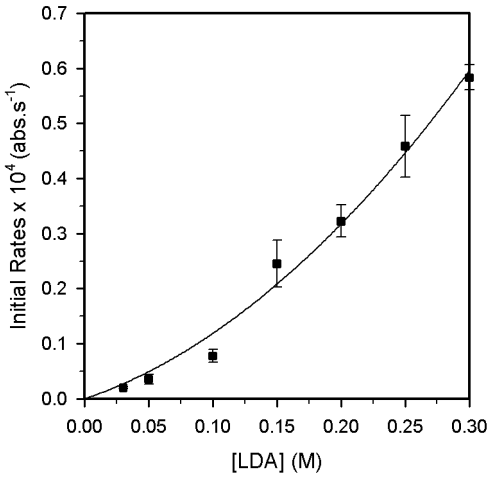



**XXXI.** Representative plots showing [ArH] vs time for the ortholithiation of 2,6-difluoropyridine (**2**) with LDA (0.1 M) in THF (12.20 M) at -78 °C.



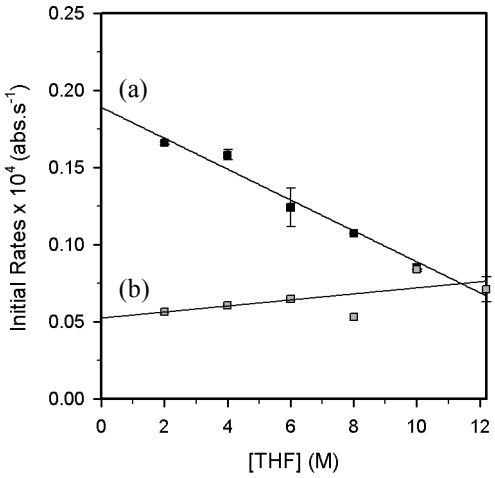

**XXXII.** Plot of initial rates vs [ArH] in THF (12.20 M) for the ortholithiation of **2** with LDA (0.10 M) at -78 °C. The curve depicts an unweighted least-squares fit to $y = k[\text{ArH}] + k'$ ($k = (9.1 \pm 0.3) \times 10^{-4}$, $k' = (3 \pm 3) \times 10^{-6}$); (B) Magnified plot of the pseudo-first-order regime marked in blue square in (A). The curve depicts an unweighted least-squares fit to $y = k[\text{ArH}] + k'$ ($k = (8 \pm 1) \times 10^{-4}$, $k' = (3.4 \pm 0.9) \times 10^{-6}$).

| [ArH] (M) | $y_1 \times 10^4$ (abs.s$^{-1}$) |
|---|---|
| 0.002 | 0.053 ± 1E-3 |
| 0.004 | 0.0569 ± 8E-4 |
| 0.006 | 0.087 ± 1E-3 |
| 0.008 | 0.106 ± 1E-3 |
| 0.010 | 0.109 ± 1E-3 |
| 0.050 | 0.528 ± 3E-3 |
| 0.100 | 0.858 ± 5E-3 |
| 0.200 | 2.02 ± 1E-2 |
| 0.300 | 2.67 ± 4E-2 |



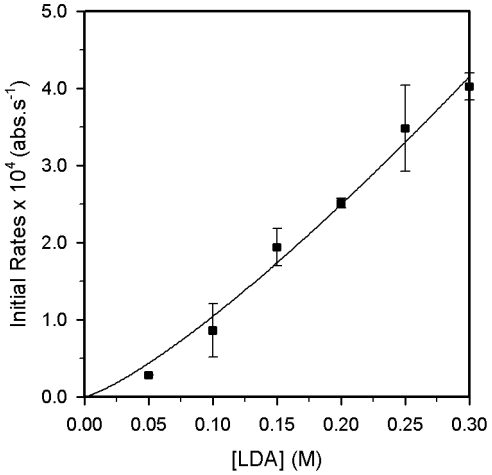

**XXXIII.** Plot of initial rates vs [LDA] in THF (12.20 M) for the ortholithiation of **2** (0.005 M) at -78 °C. The curve depicts an unweighted least-squares fit to $y = k[\mathrm{LDA}]^n$ ($k = (3.5 \pm 0.4) \times 10^{-5}$, $n = 1.48 \pm 0.09$).

| [LDA] (M) | $y_1 \times 10^4$ (abs.s$^{-1}$) | $y_2 \times 10^4$ (abs.s$^{-1}$) | $y_3 \times 10^4$ (abs.s$^{-1}$) |
|---|---|---|---|
| 0.03 | 0.0211 ± 3E-4 | 0.019 ± 1E-3 | 0.020 ± 1E-3 |
| 0.05 | 0.046 ± 1E-3 | 0.0283 ± 4E-4 | 0.0336 ± 4E-4 |
| 0.10 | 0.074 ± 2E-3 | 0.069 ± 2E-3 | 0.091 ± 2E-3 |
| 0.15 | 0.29 ± 1E-2 | 0.234 ± 8E-3 | 0.209 ± 7E-3 |
| 0.20 | 0.356 ± 7E-3 | 0.301 ± 8E-3 | 0.31 ± 1E-2 |
| 0.25 | 0.42 ± 1E-2 | 0.49 ± 2E-2 | — |
| 0.35 | 0.56 ± 2E-2 | 0.61 ± 3E-2 | 0.58 ± 1E-2 |



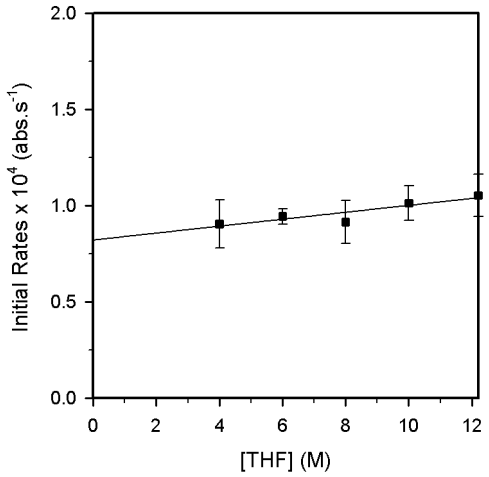

**XXXIV.** Plot of initial rates vs [THF] for the ortholithiation of **2** (0.005 M) with LDA (0.10 M) at -78 °C in: (a) hexane cosolvent. The curve depicts an unweighted least-squares fit to $y = -k[THF] + k'$ ($k = (1.00 \pm 0.06) \times 10^{-6}$, $k' = (1.89 \pm 0.05) \times 10^{-5}$); (b) 2,5-dimethyltetrahydrofuran cosolvent. The curve depicts an unweighted least-squares fit to $y = -k[THF] + k'$ ($k = (2 \pm 1) \times 10^{-7}$, $k' = (5.2 \pm 0.9) \times 10^{-6}$).

| [THF] (M) | $y_1 \times 10^4$ (abs.s$^{-1}$) | $y_2 \times 10^4$ (abs.s$^{-1}$) |
|---|---|---|
| 2.0 | 0.167 ± 4E-3 | 0.165 ± 4E-3 |
| 4.0 | 0.160 ± 3E-3 | 0.156 ± 4E-3 |
| 6.0 | 0.115 ± 2E-3 | 0.133 ± 2E-3 |
| 8.0 | 0.107 ± 1E-3 | 0.107 ± 1E-3 |
| 10.0 | 0.083 ± 1E-3 | 0.0867 ± 8E-4 |
| 12.20 | 0.0652 ± 8E-4 | 0.0767 ± 8E-4 |



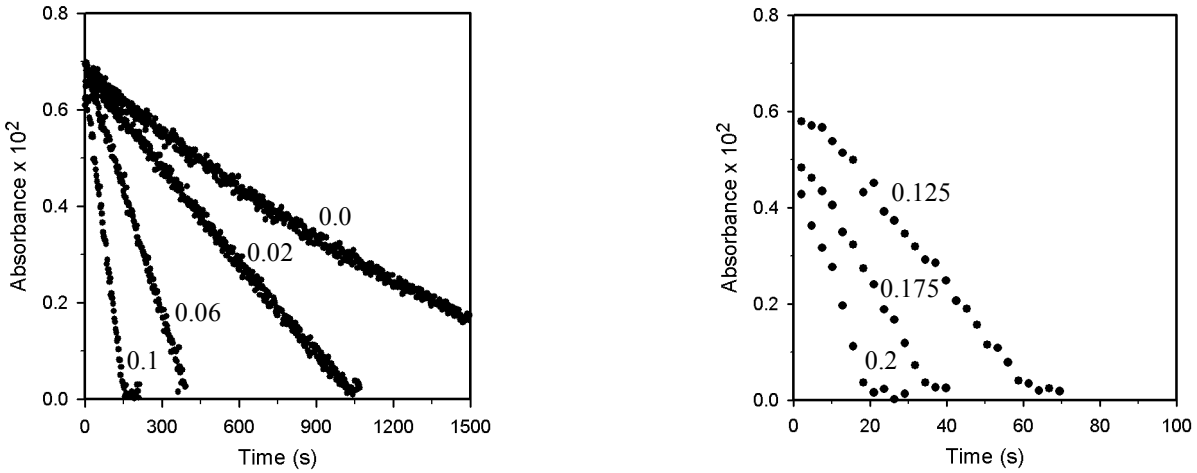

**XXXV.** Plot of initial rates vs [LDA] in THF (12.20 M) for the ortholithiation of **2** (0.10 M) at -78 °C. The curve depicts an unweighted least-squares fit to $y = k[\mathrm{LDA}]^n$ ($k = (1.8 \pm 0.2) \times 10^{-3}$, $n = 1.25 \pm 0.09$).

| [LDA] (M) | $y_1 \times 10^4$ (abs.s$^{-1}$) | $y_2 \times 10^4$ (abs.s$^{-1}$) | $y_3 \times 10^4$ (abs.s$^{-1}$) |
|---|---|---|---|
| 0.05 | 0.283 ± 1E-3 | 0.278 ± 1E-3 | 0.281 ± 1E-3 |
| 0.10 | 0.975 ± 4E-3 | 0.473 ± 2E-3 | 1.121 ± 9E-3 |
| 0.15 | 2.13 ± 2E-2 | 2.02 ± 2E-2 | 1.67 ± 1E-2 |
| 0.20 | 2.56 ± 3E-2 | 2.51 ± 3E-2 | 2.45 ± 3E-2 |
| 0.25 | 3.08 ± 4E-2 | 3.88 ± 6E-2 | — |
| 0.35 | 4.15 ± 6E-2 | 4.10 ± 7E-2 | 3.82 ± 6E-2 |

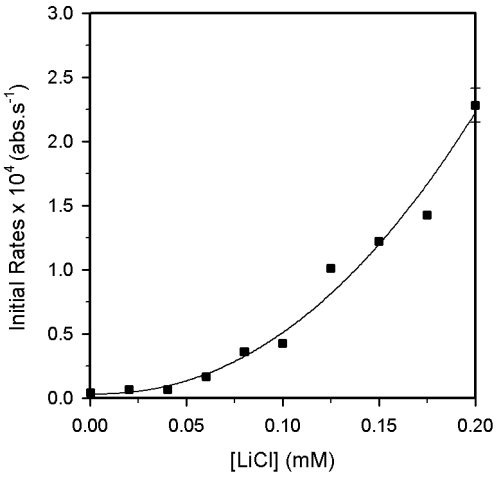



**XXXVI.** Plot of initial rates vs [THF] in hexane cosolvent for the ortholithiation of **2** (0.10 M) with LDA (0.10 M) at -78 °C. The curve depicts an unweighted least-squares fit to $y = -k[THF] + k'$ ($k = (1.8 \pm 0.9) \times 10^{-6}$, $k' = (8.2 \pm 0.8) \times 10^{-5}$).

| [THF] (M) | $y_1 \times 10^4$ (abs.s$^{-1}$) | $y_2 \times 10^4$ (abs.s$^{-1}$) |
|---|---|---|
| 4.0 | 0.99 ± 1E-2 | 0.81 ± 1E-2 |
| 6.0 | 0.97 ± 2E-2 | 0.91 ± 1E-2 |
| 8.0 | 0.90 ± 1E-2 | 0.83 ± 1E-2 |
| 10.0 | 0.95 ± 1E-2 | 1.08 ± 1E-2 |
| 12.20 | 0.975 ± 5E-3 | 1.131 ± 9E-3 |

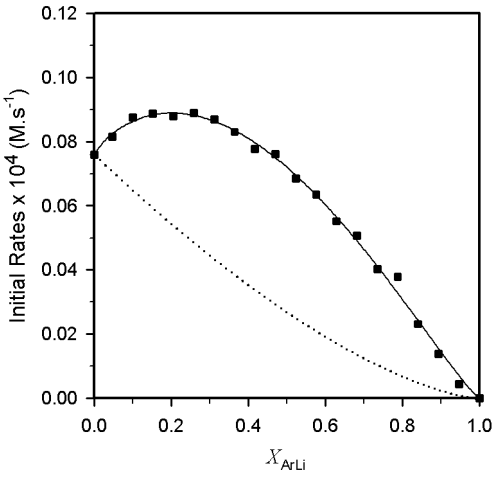



**XXXVII.** Plot of IR absorbances vs time for the ortholithiation of **2** (0.005 M) with LDA (0.10 M) in THF (12.20 M) at -78 °C in the presence of varying mol percentages of LiCl.



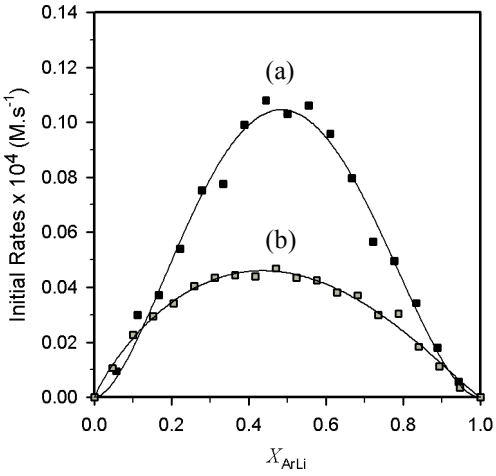

**XXXVIII.** Plot of initial rates vs [LiCl] for the ortholithiation of **2** (0.004 M) with LDA (0.10 M) in THF (12.20 M) at -78 °C. The curve depicts an unweighted least-squares fit to $y = k[\text{LiCl}]^n + k'$ ($k = (7 \pm 3) \times 10^{-3}$, $n = 2.2 \pm 0.3$, $k' = (3 \pm 7) \times 10^{-6}$).

| [LiCl] (mM) | $y_1 \times 10^4$ ($M.s^{-1}$) |
|---|---|
| 0.0 | 0.0399 ± 3E-4 |
| 0.02 | 0.0646 ± 2E-4 |
| 0.04 | 0.0662 ± 2E-4 |
| 0.06 | 0.1707 ± 8E-4 |
| 0.08 | 0.359 ± 3E-3 |
| 0.10 | 0.424 ± 5E-3 |
| 0.125 | 1.01 ± 2E-2 |
| 0.15 | 1.22 ± 3E-2 |
| 0.175 | 1.42 ± 3E-2 |
| 0.2 | 2.19 ± 9E-2 |



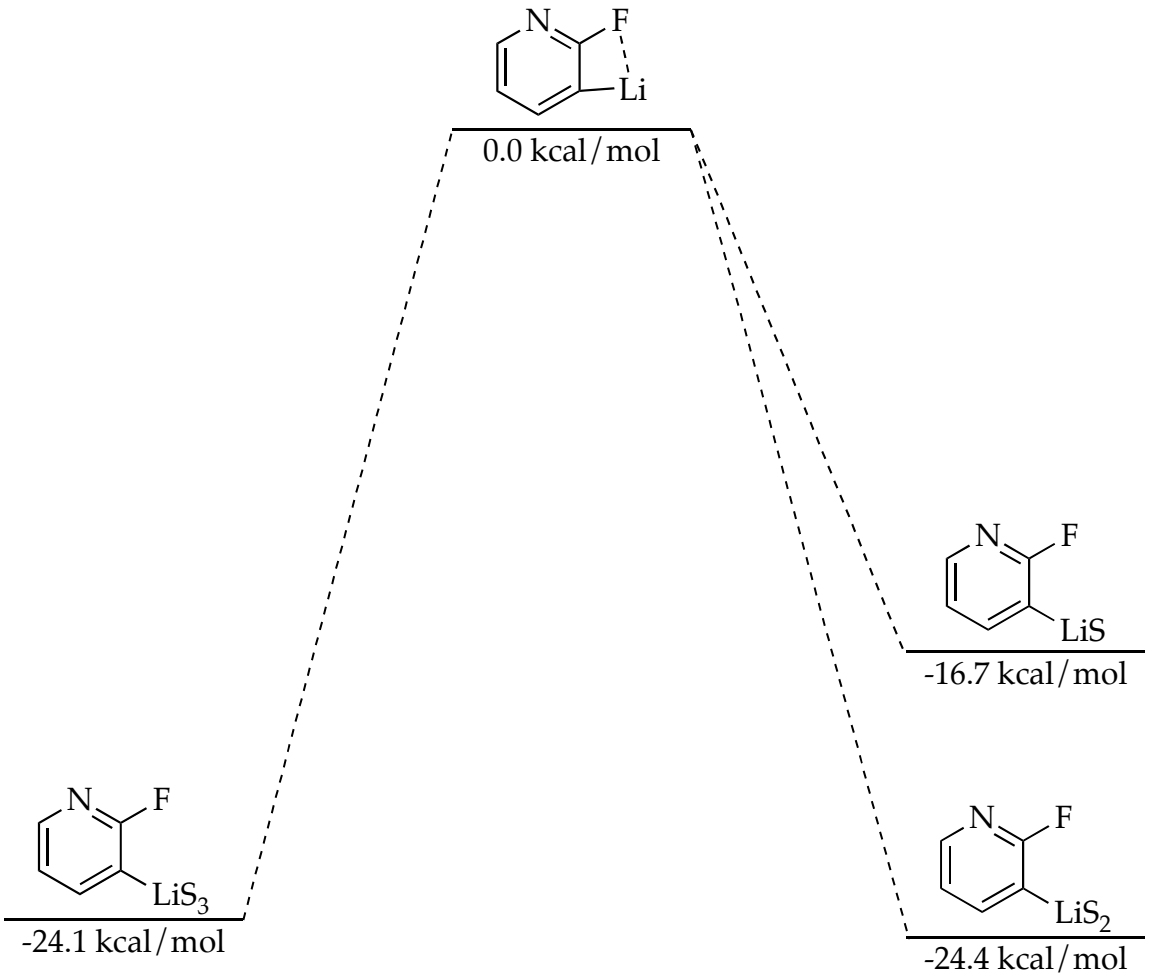

**XXXIX.** Plot of initial rates versus mole fraction of 3-lithio-2,6-difluoropyridine **4** ($X_{ArLi}$) for the serial injection of 0.0053 M aliquots of **2** to 0.10 M LDA in 12.20 M THF at -78 °C. The solid line depicts an unweighted least-squares fit to $-d[\mathbf{2}]/dt = k(X_{ArLi})^n(1-X_{ArLi})^m$ ($n = 0.87 \pm 0.04$, $m = 1.13 \pm 0.05$, $k = (1.8 \pm 0.1) \times 10^{-5}$).

| $X_{ArLi}$ | y x $10^4$ ($M.s^{-1}$) | $X_{ArLi}$ | y x $10^4$ ($M.s^{-1}$) |
|---|---|---|---|
| 0.0000 | 0.0759 ± 6E-4 | 0.5556 | 0.0685 ± 7E-4 |
| 0.0556 | 0.0815 ± 9E-4 | 0.6111 | 0.0635 ± 9E-4 |
| 0.1111 | 0.087 ± 1E-3 | 0.6667 | 0.0552 ± 6E-4 |
| 0.1667 | 0.089 ± 1E-3 | 0.7222 | 0.0507 ± 9E-4 |
| 0.2222 | 0.088 ± 1E-3 | 0.7778 | 0.0403 ± 6E-4 |
| 0.2778 | 0.081 ± 6E-3 | 0.8333 | 0.0378 ± 9E-4 |
| 0.3333 | 0.087 ± 1E-3 | 0.8889 | 0.0232 ± 3E-4 |
| 0.3889 | 0.0830 ± 8E-4 | 0.9444 | 0.0138 ± 3E-4 |
| 0.4444 | 0.0777 ± 8E-4 | 1.0000 | 0.0045 ± 1E |
| 0.5000 | 0.0762 ± 9E-4 | | |

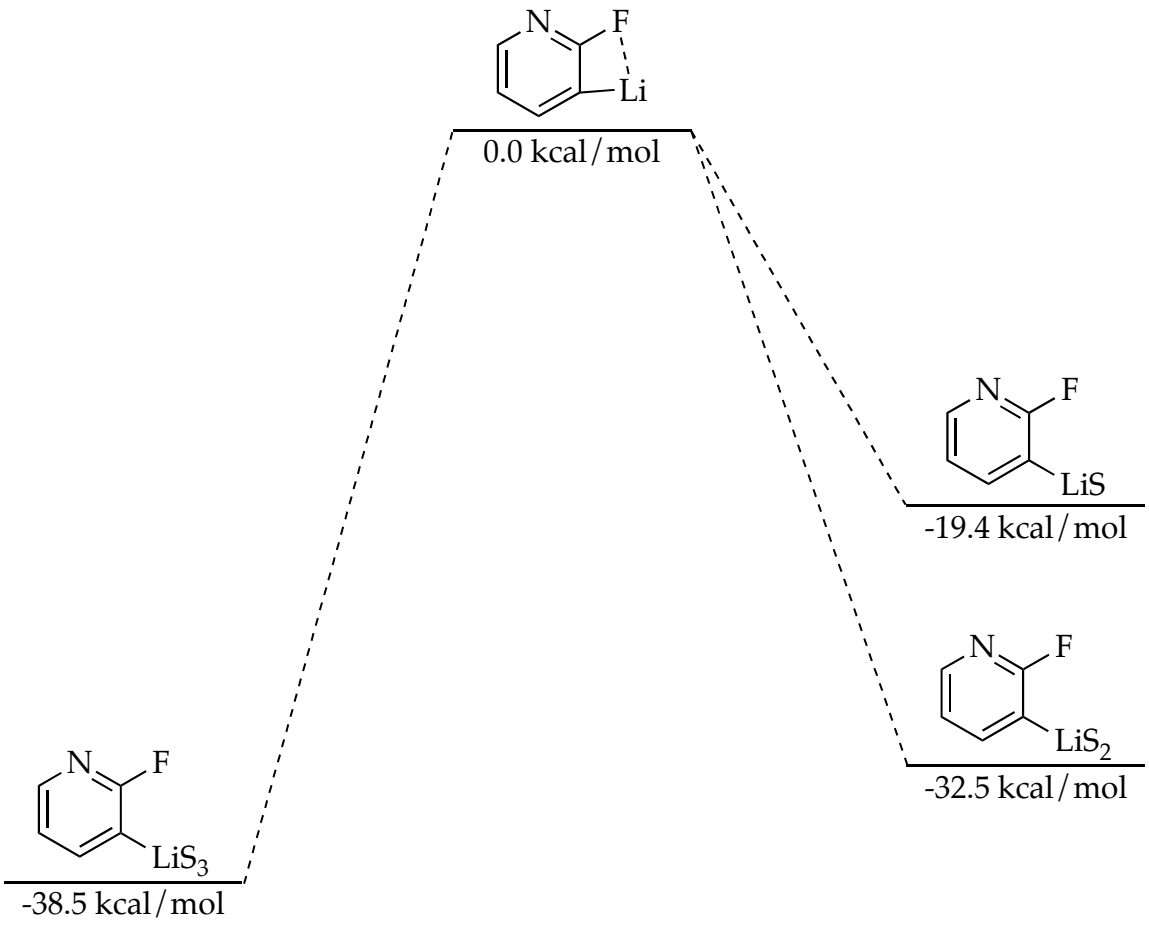



**XXXX.** Comparison of the plots of initial rates versus mole fractions of 3-lithio-fluoropyridines **3** and **4** ($X_{ArLi}$) for the serial injection of 0.005 M aliquots of pyridines **1** and **2** to 0.10 M LDA in 12.20 M THF at -78 °C: (a) pyridine **1**. The solid line depicts an unweighted least-squares fit to $-d[\mathbf{1}]/dt = k(X_{ArLi})^n(1-X_{ArLi})^m$ ($n = 1.8 \pm 0.1$, $m = 1.9 \pm 0.1$, $k = (1.3 \pm 0.2) \times 10^{-5}$); (b) pyridine **2**. The solid line depicts an unweighted least-squares fit to $-d[\mathbf{2}]/dt = k(X_{ArLi})^n(1-X_{ArLi})^m$ ($n = 0.87 \pm 0.04$, $m = 1.13 \pm 0.05$, $k = (1.8 \pm 0.1) \times 10^{-5}$). The contribution of the uncatalyzed pathway (assuming an LDA order of 1.5) is subtracted from both the plots.

**Part 3: DFT Computational Studies**

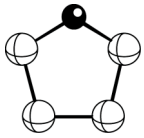



**XXXXI.** Relative free energies for the solvation (Δ*G*, kcal/mol) of 2-fluoro-3-lithiopyridine (**3**) at -78 °C (S = THF) calculated using B3LYP level of theory with 6-31G(d) basis set.



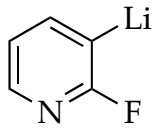

**XXXXII.** Relative free energies for the solvation (Δ*G*, kcal/mol) of **3** at -78 °C (S = THF) calculated using single point MP2 corrections to B3LYP/6-31G(d) optimized structures.

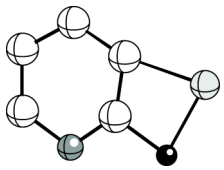
**Table I.** Optimized geometries at B3LYP level of theory with 6-31G(d) basis set for the serial solvation of 2-fluoro-3-lithiopyridine (**3**) at -78 °C with free energies (Hartrees) and cartesian coordinates (X, Y, Z). (Note: $G_{MP2}$ includes single point MP2 corrections to B3LYP/6-31G(d) optimized structures)

$G$ = -232.349202
$G_{MP2}$ = -231.569352

| Atom | X | Y | Z |
|---|---|---|---|
| C | -0.77676 | 0.78926 | -0.12614 |
| C | -1.13241 | -0.69941 | 0.08086 |
| O | -0.00028 | -1.43271 | -0.37154 |
| C | 1.13192 | -0.69999 | 0.08156 |
| C | 0.77743 | 0.78860 | -0.12707 |
| H | -1.99954 | -1.03544 | -0.49441 |
| H | -1.32099 | -0.90818 | 1.14790 |
| H | 1.99943 | -1.03711 | -0.49250 |
| H | 1.31917 | -0.90803 | 1.14900 |
| H | 1.16400 | 1.14893 | -1.08517 |
| H | 1.20108 | 1.42138 | 0.65905 |
| H | -1.16426 | 1.15158 | -1.08311 |
| H | -1.19880 | 1.42112 | 0.66158 |

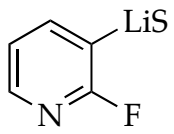


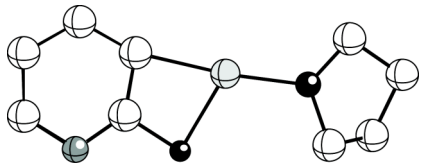



$G$ = -354.394923
$G_{MP2}$ = -353.331677

| Atom | X | Y | Z |
|---|---|---|---|
| C | 0.86201 | 0.97288 | -0.00006 |
| C | 1.14630 | -0.38236 | -0.00012 |
| Li | 2.83029 | 1.20280 | -0.00015 |
| F | 2.58112 | -0.65448 | 0.00014 |
| N | 0.42332 | -1.46768 | -0.00007 |
| C | -0.90225 | -1.21871 | -0.00002 |
| C | -1.41854 | 0.07596 | 0.00005 |
| C | -0.53093 | 1.16338 | 0.00005 |
| H | -0.94421 | 2.17226 | 0.00008 |
| H | -2.49487 | 0.22687 | 0.00010 |
| H | -1.55223 | -2.09092 | 0.00001 |

**Table I (Continued).**

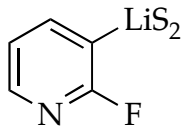


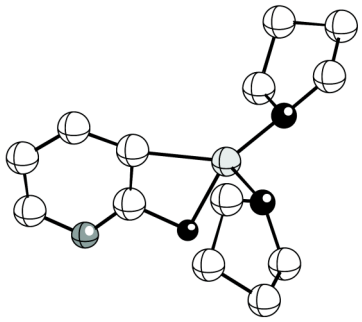



$G$ = -586.770686
$G_{MP2}$ = -584.9319088
S = THF

| Atom | X | Y | Z |
|---|---|---|---|
| C | -2.50499 | 1.17711 | -0.24166 |
| O | -1.54999 | 0.14705 | -0.61792 |
| C | -2.09542 | -1.17105 | -0.33443 |
| C | -3.21235 | -0.92142 | 0.67415 |
| C | -3.76863 | 0.43181 | 0.20174 |
| Li | 0.32708 | 0.33538 | -0.70371 |
| F | 1.25006 | -1.38176 | -0.53787 |
| C | 2.45357 | -0.63118 | -0.26527 |
| C | 2.26029 | 0.74138 | -0.31003 |
| C | 3.47387 | 1.39778 | -0.03913 |
| C | 4.65480 | 0.68598 | 0.22681 |
| C | 4.61691 | -0.70636 | 0.22228 |
| N | 3.48701 | -1.39756 | -0.03019 |
| H | -4.31203 | 0.97174 | 0.98209 |
| H | -4.44709 | 0.28896 | -0.64680 |
| H | -3.96072 | -1.71886 | 0.67231 |
| H | -2.80029 | -0.83941 | 1.68640 |
| H | -1.27700 | -1.79302 | 0.03530 |
| H | -2.47775 | -1.59937 | -1.26932 |
| H | 5.50599 | -1.30065 | 0.42391 |
| H | 5.58997 | 1.20021 | 0.43479 |
| H | 3.51499 | 2.48794 | -0.03171 |
| H | -2.66371 | 1.83101 | -1.10404 |
| H | -2.06457 | 1.76430 | 0.57232 |

**Table I (Continued).**

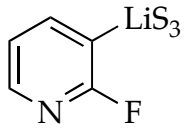


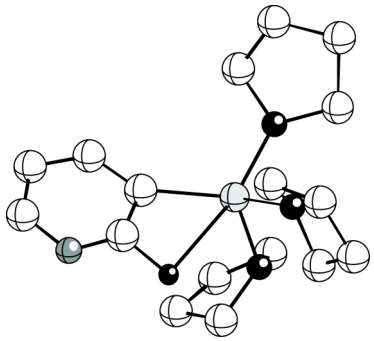



$G$ = -819.132244
$G_{MP2}$ = -816.522168
S = THF

| Atom | X | Y | Z | Atom | X | Y | Z |
|---|---|---|---|---|---|---|---|
| C | 1.40459 | 2.07056 | 1.21795 | H | 3.23764 | 1.57287 | 0.18733 |
| O | 0.45881 | 1.89993 | 0.13075 | H | 2.94610 | 3.37960 | -1.45434 |
| C | 0.94235 | 2.58396 | -1.05842 | H | 1.99303 | 4.33584 | -0.30633 |
| C | 2.22195 | 3.31593 | -0.63711 | H | 1.13873 | 1.82428 | -1.82202 |
| C | 2.71589 | 2.46717 | 0.54568 | H | 0.15456 | 3.25583 | -1.41338 |
| Li | -0.16396 | 0.05942 | -0.12065 | H | 1.32843 | -2.60428 | 2.36280 |
| C | 1.00190 | -1.53788 | 0.50199 | H | 3.05159 | -4.14427 | 1.45065 |
| C | 1.51990 | -1.61548 | -0.78548 | H | 3.71685 | -3.94505 | -0.95438 |
| F | 0.95433 | -0.66227 | -1.69046 | H | -1.72780 | -2.09112 | -0.58226 |
| N | 2.42166 | -2.37850 | -1.35508 | H | -2.80322 | -1.45403 | -1.85996 |
| C | 2.96315 | -3.28931 | -0.52186 | H | -4.47504 | -2.31546 | -0.30523 |
| C | 2.58837 | -3.39309 | 0.81496 | H | -3.46442 | -1.91551 | 1.09745 |
| C | 1.61164 | -2.51390 | 1.31197 | H | -4.99031 | 0.01605 | 1.02136 |
| O | -2.06466 | -0.05639 | -0.51137 | H | -4.91755 | 0.06087 | -0.74952 |
| C | -3.07181 | 0.69648 | 0.20431 | H | -3.17904 | 1.67235 | -0.27836 |
| C | -4.34189 | -0.15747 | 0.15753 | H | -2.72630 | 0.84980 | 1.23494 |
| C | -3.77018 | -1.58290 | 0.09877 | H | 1.45105 | 1.12178 | 1.75826 |
| C | -2.54530 | -1.39778 | -0.79506 | H | 1.03411 | 2.85992 | 1.88606 |
| H | 3.38482 | 3.01204 | 1.21851 | | | | |

**Table I (Continued).**

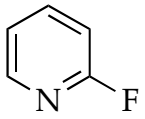


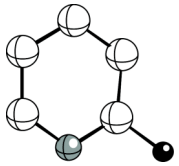



$G$ = -1051.480867
$G_{MP2}$ = -1048.101158
S = THF

| Atom | X | Y | Z | Atom | X | Y | Z |
|---|---|---|---|---|---|---|---|
| Li | 0.06194 | -0.11884 | -0.08758 | H | 1.85625 | -3.66780 | -1.27766 |
| O | 0.40437 | -0.97447 | -1.90448 | H | 1.76400 | -3.60893 | -3.03959 |
| C | 1.65876 | -0.63887 | -2.53298 | H | 3.43541 | -1.89452 | -2.82226 |
| C | 2.59143 | -1.78179 | -2.13499 | H | 2.98149 | -1.58909 | -1.13169 |
| C | 1.65161 | -3.01205 | -2.12864 | H | 1.51372 | -0.59012 | -3.62335 |
| C | 0.23159 | -2.39808 | -2.05292 | H | 1.95753 | 0.33921 | -2.15642 |
| C | 1.78887 | 0.23325 | 1.07632 | H | 2.10639 | -1.19343 | 2.68239 |
| C | 2.48387 | 1.33542 | 0.57308 | H | 4.23710 | -0.21336 | 3.47798 |
| F | 1.90354 | 1.97237 | -0.53432 | H | 5.15925 | 1.80190 | 2.30626 |
| N | 3.61148 | 1.91286 | 0.93498 | H | -0.07697 | 2.92002 | 0.47066 |
| C | 4.22553 | 1.34049 | 1.98706 | H | -1.45238 | 2.22488 | 1.36771 |
| C | 3.70829 | 0.22440 | 2.63412 | H | -3.02704 | 3.62642 | 0.19223 |
| C | 2.49748 | -0.31223 | 2.16556 | H | -1.61936 | 4.65746 | -0.07539 |
| O | -1.16585 | 1.46243 | -0.51721 | H | -1.71624 | 4.07773 | -2.39669 |
| C | -1.13506 | 2.04370 | -1.83312 | H | -3.07898 | 3.00812 | -2.05186 |
| C | -2.06105 | 3.26876 | -1.74603 | H | -0.10428 | 2.33686 | -2.06812 |
| C | -2.02227 | 3.65398 | -0.24028 | H | -1.46053 | 1.27642 | -2.53807 |
| C | -1.11500 | 2.58129 | 0.39184 | H | -0.18778 | -1.29280 | 2.43579 |
| O | -1.31639 | -1.38221 | 0.72964 | H | -1.03532 | -2.84808 | 2.18674 |
| C | -2.73373 | -1.28198 | 0.44690 | H | -2.54814 | -1.75260 | 3.78038 |
| C | -3.46379 | -1.51690 | 1.78194 | H | -2.27605 | -0.17042 | 3.02440 |
| C | -2.36886 | -1.24498 | 2.82778 | H | -4.33741 | -0.86795 | 1.89437 |
| C | -1.12148 | -1.75407 | 2.11105 | H | -3.80792 | -2.55478 | 1.85627 |
| H | -0.35287 | -2.73463 | -1.19464 | H | -2.99829 | -2.02674 | -0.31282 |
| H | -0.33775 | -2.59331 | -2.97232 | H | -2.90910 | -0.28297 | 0.03795 |

**Table II.** Optimized geometries of reactants and monomer-based transition structures at B3LYP level of theory with 6-31G(d) basis set for the ortholithiation of **1** at -78 °C with free energies (Hartrees), and cartesian coordinates (X,Y,Z). (Note: $G_{MP2}$ includes single point MP2 corrections to B3LYP/6-31G(d) optimized structures)

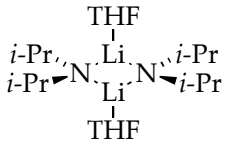


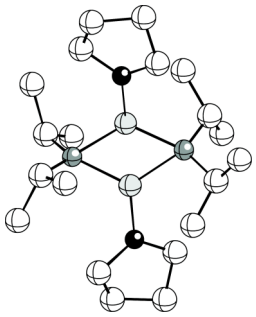



**1**
$G$ = -347.462128
$G_{MP2}$ = -346.4450685

| Atom | X | Y | Z |
|---|---|---|---|
| C | -0.75185 | 1.04361 | -0.00000 |
| C | 0.63880 | 1.01860 | 0.00000 |
| C | 1.29814 | -0.21475 | 0.00000 |
| C | 0.52570 | -1.37331 | 0.00000 |
| N | -0.81720 | -1.36891 | -0.00000 |
| C | -1.40228 | -0.19110 | -0.00001 |
| F | -2.74537 | -0.19710 | 0.00001 |
| H | 1.20092 | 1.94828 | 0.00000 |
| H | 2.38156 | -0.27571 | 0.00000 |
| H | 0.99462 | -2.35470 | 0.00000 |
| H | -1.32306 | 1.96509 | 0.00000 |

**Table II (Continued).**

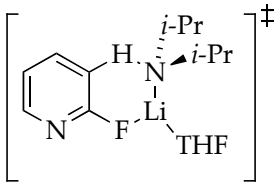


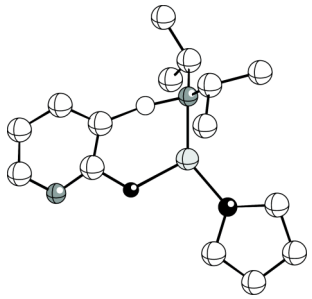



**5**
$G$ = -1063.135543
$G_{MP2}$ = -1059.34387
S = THF

| Atom | X | Y | Z | Atom | X | Y | Z |
|---|---|---|---|---|---|---|---|
| Li | -1.19464 | -0.00774 | 0.01421 | H | 1.83816 | -3.21720 | 1.36630 |
| O | -3.18299 | 0.01572 | -0.13583 | H | -2.15959 | -1.60468 | 1.84082 |
| C | -3.98409 | -1.09503 | -0.60154 | H | -1.26327 | -2.26497 | 3.22164 |
| C | -5.41144 | -0.77445 | -0.16155 | H | -0.80287 | -0.70251 | 2.54173 |
| C | -5.43839 | 0.75767 | -0.27769 | H | -0.65863 | -3.39245 | 1.09537 |
| C | -4.03238 | 1.14387 | 0.19102 | H | -1.65573 | -2.60864 | -2.05785 |
| N | -0.01403 | -1.64369 | 0.06875 | H | -0.68498 | -4.07367 | -2.32132 |
| C | -0.19692 | -2.41025 | 1.31036 | H | -1.50052 | -3.82045 | -0.77116 |
| C | -1.16039 | -1.70758 | 2.28179 | H | 1.87669 | -1.33857 | -1.92728 |
| C | 1.13099 | -2.71953 | 2.04026 | H | 1.14764 | -2.49745 | -3.05209 |
| Li | 1.19465 | 0.00783 | 0.01436 | H | 0.26500 | -1.03245 | -2.60504 |
| N | 0.01400 | 1.64376 | 0.06872 | H | 1.00263 | -3.33501 | -0.73003 |
| C | 0.19652 | 2.41040 | 1.31033 | H | 3.90323 | 1.15737 | -1.69393 |
| C | 1.15952 | 1.70771 | 2.28220 | H | 3.57283 | 2.00952 | -0.16815 |
| C | -1.13164 | 2.71990 | 2.03968 | H | 6.16235 | 1.26993 | -0.78433 |
| C | -0.27768 | 2.55391 | -1.04433 | H | 5.57076 | 1.08298 | 0.87817 |
| C | -0.93195 | 1.81412 | -2.22127 | H | 5.59112 | -1.05745 | -1.32156 |
| C | 0.96199 | 3.31164 | -1.57823 | H | 6.21990 | -1.22706 | 0.32667 |
| O | 3.18302 | -0.01557 | -0.13517 | H | 3.99129 | -1.30081 | 1.27554 |
| C | 4.03229 | -1.14374 | 0.19184 | H | 3.63030 | -2.03115 | -0.30431 |
| C | 5.43806 | -0.75816 | -0.27799 | H | -1.87605 | 1.33861 | -1.92791 |
| C | 5.41178 | 0.77396 | -0.16178 | H | -1.14658 | 2.49738 | -3.05257 |
| C | 3.98424 | 1.09517 | -0.60075 | H | -0.26417 | 1.03236 | -2.60515 |
| C | 0.27810 | -2.55390 | -1.04412 | H | 1.65649 | 2.60840 | -2.05742 |
| C | 0.93270 | -1.81416 | -2.22091 | H | 0.68595 | 4.07349 | -2.32131 |
| C | -0.96133 | -3.31179 | -1.57838 | H | 1.50097 | 3.82031 | -0.77087 |
| H | 2.15887 | 1.60463 | 1.84163 | H | -1.00225 | 3.33509 | -0.73054 |
| H | 1.26211 | 2.26520 | 3.22203 | H | -3.99064 | 1.30159 | 1.27458 |
| H | 0.80177 | 0.70272 | 2.54212 | H | -3.63100 | 2.03110 | -0.30596 |
| H | -1.59922 | 1.79146 | 2.39591 | H | -6.21992 | 1.22625 | 0.32760 |
| H | -0.98370 | 3.37716 | 2.90874 | H | -5.59242 | 1.05690 | -1.32113 |
| H | -1.83853 | 3.21752 | 1.36538 | H | -5.56953 | -1.08360 | 0.87850 |
| H | 0.65842 | 3.39254 | 1.09542 | H | -6.16225 | -1.27067 | -0.78359 |
| H | 1.59838 | -1.79101 | 2.39653 | H | -3.90377 | -1.15665 | -1.69482 |
| H | 0.98277 | -3.37667 | 2.90936 | H | -3.57208 | -2.00943 | -0.16966 |

**Table II (Continued).**

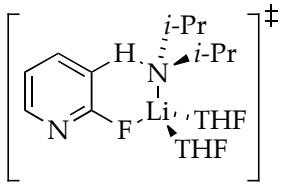


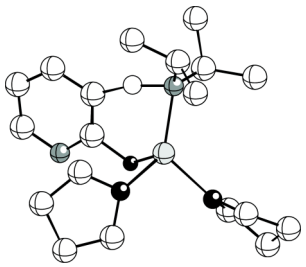



**38**
$G$ = -879.003664
$G_{MP2}$ = -876.0900414
S = THF
$\Delta G^{‡}$ = 16.5 kcal/mol
$\Delta G_{MP2}{}^{‡}$ = 16.9 kcal/mol

| Atom | X | Y | Z | Atom | X | Y | Z |
|---|---|---|---|---|---|---|---|
| C | -2.70101 | -2.39998 | 0.43881 | H | 1.49653 | 0.32213 | 2.44204 |
| O | -2.30634 | -1.00305 | 0.40443 | H | 1.00356 | 1.73846 | 3.38547 |
| C | -3.46316 | -0.16106 | 0.15594 | H | -0.22666 | 0.74136 | 2.59959 |
| C | -4.67147 | -1.10415 | 0.14037 | H | 0.13297 | 2.82603 | 1.32382 |
| C | -4.04512 | -2.44289 | -0.28206 | H | -0.35698 | 3.82471 | -0.54298 |
| Li | -0.48372 | -0.42637 | 0.32530 | H | -0.65573 | 3.47306 | -2.24793 |
| F | 0.43357 | -2.06971 | 0.38427 | H | -1.57094 | 2.61377 | -0.98870 |
| C | 1.83831 | -2.08227 | 0.08968 | H | -0.81749 | 0.43525 | -2.19966 |
| C | 2.40807 | -0.84408 | -0.14640 | H | 0.17784 | 1.36319 | -3.33115 |
| C | 3.77891 | -0.97360 | -0.41976 | H | 0.91978 | 0.08245 | -2.35276 |
| C | 4.40933 | -2.22667 | -0.43253 | H | 1.44191 | 2.38124 | -1.49598 |
| C | 3.64561 | -3.36040 | -0.16777 | H | 4.08525 | -4.35554 | -0.16670 |
| N | 2.32697 | -3.29537 | 0.10089 | H | 5.47099 | -2.32514 | -0.64395 |
| N | 0.57301 | 1.19096 | 0.04556 | H | 4.37488 | -0.08404 | -0.62797 |
| C | 0.47680 | 1.90674 | -1.23413 | H | -3.89485 | -2.47483 | -1.36744 |
| C | 0.17656 | 0.88651 | -2.34370 | H | -4.64584 | -3.31030 | 0.00611 |
| C | -0.58444 | 3.02058 | -1.25063 | H | -5.10681 | -1.18776 | 1.14265 |
| C | 0.88453 | 2.02577 | 1.21871 | H | -5.45480 | -0.75827 | -0.53996 |
| C | 0.78540 | 1.15599 | 2.48253 | H | -3.51296 | 0.59994 | 0.94016 |
| C | 2.26773 | 2.70726 | 1.15620 | H | -3.31668 | 0.33734 | -0.80896 |
| H | 2.35824 | 3.35759 | 0.27920 | H | -1.90709 | -2.97940 | -0.03556 |
| H | 2.43947 | 3.32779 | 2.04492 | H | -2.79284 | -2.71371 | 1.48655 |
| H | 3.06686 | 1.95850 | 1.10339 | H | 1.54186 | 0.30198 | -0.06989 |

**Table II (Continued).**

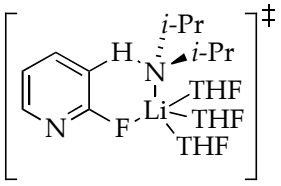


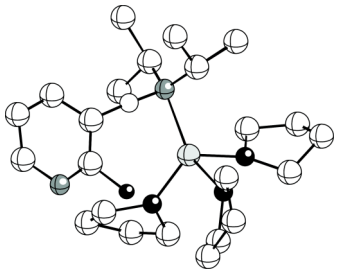



**39**
$G$ = -1111.354111
$G_{MP2}$ = -1107.674425
S = THF
$\Delta G^{‡}$ = 15.7 kcal/mol
$\Delta G_{MP2}{}^{‡}$ = 7.5 kcal/mol

| Atom | X | Y | Z | Atom | X | Y | Z |
|---|---|---|---|---|---|---|---|
| C | 0.57461 | 2.43920 | -0.86232 | H | 1.73554 | -1.86654 | -2.48853 |
| N | 0.02440 | 1.65041 | 0.25363 | H | 2.44763 | -0.23580 | -2.46219 |
| C | 0.05268 | 2.32047 | 1.56380 | H | -2.04946 | -0.70887 | 1.64108 |
| C | 0.97333 | 1.58871 | 2.56060 | H | -1.33811 | -1.65757 | 2.97723 |
| C | -1.35747 | 2.47348 | 2.16677 | H | -3.14313 | -3.15192 | 2.30465 |
| Li | 0.35400 | -0.31242 | -0.01467 | H | -2.98161 | -2.67724 | 0.60070 |
| F | -0.67052 | -0.84928 | -1.66168 | H | -1.69130 | -4.76785 | 0.64737 |
| C | -2.02195 | -0.42762 | -1.61812 | H | -1.00811 | -4.36825 | 2.23457 |
| C | -2.27793 | 0.69480 | -0.84596 | H | 0.76996 | -3.50032 | 0.85132 |
| C | -3.63987 | 1.02658 | -0.86584 | H | -0.35724 | -3.08265 | -0.46532 |
| C | -4.56700 | 0.26956 | -1.59832 | H | -1.19035 | 1.29422 | -0.19113 |
| C | -4.10911 | -0.83764 | -2.30712 | H | -3.99396 | 1.89011 | -0.30078 |
| N | -2.81248 | -1.20520 | -2.31915 | H | -5.62262 | 0.52834 | -1.61787 |
| O | 2.09269 | -1.09498 | -0.60424 | H | -4.78741 | -1.46154 | -2.88573 |
| C | 3.25151 | -1.23114 | 0.24983 | H | 1.99531 | 1.52985 | 2.16786 |
| C | 4.46286 | -1.20284 | -0.68563 | H | 1.01189 | 2.09656 | 3.53451 |
| C | 3.88778 | -1.80742 | -1.97641 | H | 0.61980 | 0.56289 | 2.73254 |
| C | 2.47287 | -1.22849 | -1.99585 | H | -1.82931 | 1.49461 | 2.31784 |
| O | -0.35605 | -1.78496 | 1.14937 | H | -1.32297 | 2.97861 | 3.14089 |
| C | -1.58608 | -1.66085 | 1.90765 | H | -2.00556 | 3.05511 | 1.50230 |
| C | -2.42726 | -2.87727 | 1.52419 | H | 0.45679 | 3.34013 | 1.46352 |
| C | -1.34969 | -3.94515 | 1.28232 | H | 2.62703 | 1.72877 | -0.66251 |
| C | -0.23420 | -3.13144 | 0.62174 | H | 2.47539 | 3.20033 | -1.65161 |
| C | -0.16557 | 3.76873 | -1.13200 | H | 2.34283 | 3.29865 | 0.10934 |
| C | 2.09286 | 2.68099 | -0.76248 | H | -0.04649 | 4.47923 | -0.30486 |
| H | 3.23772 | -0.41504 | 0.97777 | H | 0.21929 | 4.25610 | -2.03737 |
| H | 3.17678 | -2.18522 | 0.78795 | H | -1.23605 | 3.58673 | -1.27298 |
| H | 4.78707 | -0.17046 | -0.85983 | H | 0.41046 | 1.81816 | -1.75927 |
| H | 5.31234 | -1.76307 | -0.28402 | H | -3.96159 | -1.72769 | -0.47756 |
| H | 3.85468 | -2.90121 | -1.90686 | H | -2.89614 | -1.09771 | -1.76135 |
| H | 4.45875 | -1.54107 | -2.87066 | | | | |

**Table II (Continued).**

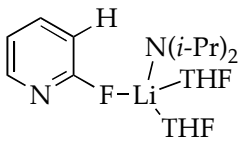


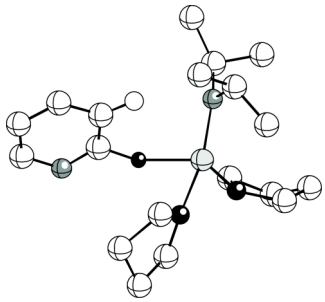



**40**
*G* = -1343.686183
$G_{MP2}$ = -1339.237299
S = THF
$\Delta G^{‡}$ = 26.4 kcal/mol
$\Delta G_{MP2}{}^{‡}$ = 11.5 kcal/mol

| Atom | X | Y | Z | Atom | X | Y | Z |
|---|---|---|---|---|---|---|---|
| Li | -0.48170 | -0.31703 | -0.04953 | H | -0.25633 | -3.15937 | -0.19657 |
| N | 0.37396 | 1.56629 | -0.22056 | H | -1.47875 | -3.53375 | -1.44261 |
| C | 0.18519 | 1.98853 | -1.62856 | H | 6.36400 | -1.27536 | 0.12002 |
| C | -1.11042 | 2.77854 | -1.88929 | H | 6.29222 | 1.20118 | 0.48111 |
| C | 1.38587 | 2.70434 | -2.29752 | H | 4.08517 | 2.36122 | 0.41368 |
| C | 0.12398 | 2.58789 | 0.81024 | H | -1.20510 | -3.28941 | 2.15424 |
| C | 0.26531 | 1.94090 | 2.19773 | H | -2.27191 | -1.86814 | 1.99368 |
| C | 1.01637 | 3.85162 | 0.76635 | H | -1.57579 | -1.01267 | 4.15564 |
| C | 2.93689 | 0.56884 | 0.03547 | H | -1.37696 | -2.73610 | 4.49595 |
| C | 3.18986 | -0.78750 | -0.14033 | H | 1.00778 | -2.48870 | 4.44696 |
| F | 2.07927 | -1.59879 | -0.36468 | H | 0.73044 | -0.74684 | 4.39748 |
| N | 4.31738 | -1.46885 | -0.12160 | H | 1.59373 | -0.85142 | 2.15759 |
| C | 5.42080 | -0.73127 | 0.10250 | H | 1.39120 | -2.61545 | 2.11922 |
| C | 5.37512 | 0.64476 | 0.30257 | H | 1.29471 | 1.60008 | 2.35826 |
| C | 4.12447 | 1.27992 | 0.26397 | H | 0.01987 | 2.65804 | 2.99095 |
| O | -0.50226 | -1.71321 | -1.64896 | H | -0.39672 | 1.07471 | 2.30143 |
| C | 0.26472 | -1.53318 | -2.86910 | H | 0.83248 | 4.45573 | -0.12628 |
| C | 0.50203 | -2.93791 | -3.42442 | H | 0.81799 | 4.49034 | 1.63760 |
| C | 0.58053 | -3.77636 | -2.14041 | H | 2.07864 | 3.58200 | 0.77884 |
| C | -0.48010 | -3.11049 | -1.26341 | H | -0.91763 | 2.95300 | 0.73513 |
| O | -2.60074 | -0.24678 | 0.07638 | H | -1.08423 | 3.77601 | -1.43528 |
| C | -3.30028 | 0.75872 | 0.84991 | H | -1.26377 | 2.91665 | -2.96724 |
| C | -4.71485 | 0.86544 | 0.25249 | H | -1.98204 | 2.24875 | -1.48728 |
| C | -4.54404 | 0.26068 | -1.15155 | H | 2.31303 | 2.15402 | -2.11462 |
| C | -3.49791 | -0.82054 | -0.89501 | H | 1.23084 | 2.76137 | -3.38407 |
| O | -0.29170 | -1.48818 | 1.66374 | H | 1.52427 | 3.72715 | -1.93398 |
| C | 0.92458 | -1.66933 | 2.42037 | H | 0.07586 | 1.05079 | -2.19467 |
| C | 0.49241 | -1.69203 | 3.90218 | H | 1.60259 | 1.12465 | -0.08465 |
| C | -1.04306 | -1.91861 | 3.84973 | H | -2.73551 | 1.69035 | 0.76286 |
| C | -1.30716 | -2.21321 | 2.36746 | H | -3.31126 | 0.45453 | 1.90303 |
| H | -0.31266 | -0.88990 | -3.53979 | H | -5.42687 | 0.27098 | 0.83651 |
| H | 1.20554 | -1.03853 | -2.61313 | H | -5.07749 | 1.89720 | 0.23488 |
| H | -0.34373 | -3.25777 | -4.04558 | H | -4.15082 | 1.00729 | -1.85041 |
| H | 1.41062 | -2.99218 | -4.03111 | H | -5.47519 | -0.14026 | -1.56353 |
| H | 1.56573 | -3.66816 | -1.67863 | H | -3.96159 | -1.72769 | -0.47756 |
| H | 0.37928 | -4.83975 | -2.30289 | H | -2.89614 | -1.09771 | -1.76135 |

**Table III.** Optimized geometries at B3LYP level of theory with 6-31G(d) basis set for the IRC calculations on disolvated monomeric transition structure (**39**) for the ortholithiation of **1** at -78 °C with free energies (Hartrees), and cartesian coordinates (X,Y,Z).

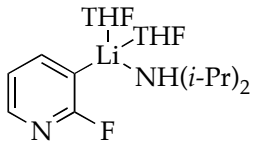


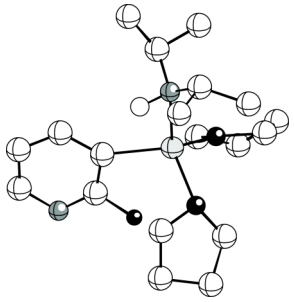



**41**
*G* = -1111.365230
S = THF

| Atom | X | Y | Z | Atom | X | Y | Z |
|---|---|---|---|---|---|---|---|
| C | 1.13362 | 2.19613 | -0.91468 | H | 3.96840 | -2.14491 | -3.02789 |
| N | 0.63915 | 1.51690 | 0.27990 | H | 1.25176 | -2.29265 | -2.55887 |
| C | 0.84694 | 2.24930 | 1.52331 | H | 2.07939 | -0.71825 | -2.45259 |
| C | -0.44589 | 2.90694 | 2.06764 | H | -1.95872 | -0.12897 | 1.97016 |
| C | 1.44235 | 1.33883 | 2.61736 | H | -1.30007 | -1.26523 | 3.17271 |
| Li | 0.38032 | -0.35930 | 0.08669 | H | -3.53236 | -2.21069 | 2.86050 |
| F | -0.93889 | -0.73772 | -1.67126 | H | -3.52912 | -1.79652 | 1.13359 |
| C | -2.20044 | -0.19966 | -1.65629 | H | -2.81976 | -4.15005 | 1.06873 |
| C | -2.36933 | 1.01378 | -0.99691 | H | -1.82416 | -3.93821 | 2.51919 |
| C | -3.66603 | 1.52159 | -1.00832 | H | -0.10059 | -3.54612 | 0.88531 |
| C | -4.68113 | 0.80856 | -1.65774 | H | -1.26101 | -2.91588 | -0.30635 |
| C | -4.35736 | -0.39985 | -2.26817 | H | -3.88112 | 2.46565 | -0.51488 |
| N | -3.11327 | -0.91358 | -2.26766 | H | -5.70071 | 1.17985 | -1.68762 |
| O | 1.71950 | -1.67968 | -0.64406 | H | -5.11401 | -0.99109 | -2.77903 |
| C | 2.91221 | -1.88236 | 0.15377 | H | 2.42935 | 0.97028 | 2.31232 |
| C | 4.08306 | -1.90383 | -0.83339 | H | 1.55139 | 1.85461 | 3.58217 |
| C | 3.41716 | -2.41273 | -2.12157 | H | 0.79518 | 0.46516 | 2.78091 |
| C | 2.04686 | -1.73946 | -2.05258 | H | -1.19944 | 2.13724 | 2.28696 |
| O | -0.73709 | -1.59583 | 1.19690 | H | -0.26993 | 3.47593 | 2.99299 |
| C | -1.72623 | -1.17825 | 2.16412 | H | -0.87677 | 3.58989 | 1.32765 |
| C | -2.90331 | -2.13161 | 1.96881 | H | 1.57325 | 3.07324 | 1.39332 |
| C | -2.18534 | -3.44244 | 1.61045 | H | 3.11148 | 1.26639 | -0.93974 |
| C | -1.00936 | -2.95082 | 0.75854 | H | 3.01660 | 2.72649 | -1.95525 |
| C | 0.54911 | 3.60749 | -1.18265 | H | 3.10184 | 2.86960 | -0.19245 |
| C | 2.68087 | 2.27252 | -1.01130 | H | 0.84568 | 4.31825 | -0.40154 |
| H | 2.97487 | -1.07171 | 0.88547 | H | 0.89849 | 4.01266 | -2.14253 |
| H | 2.80906 | -2.83723 | 0.68510 | H | -0.54652 | 3.57860 | -1.20801 |
| H | 4.47391 | -0.89112 | -0.98254 | H | 0.81277 | 1.57732 | -1.77410 |
| H | 4.90499 | -2.53852 | -0.48893 | H | -1.51204 | 1.47491 | -0.48963 |
| H | 3.31043 | -3.50382 | -2.09602 | | | | |

**Table III (Continued).**



**42**
*G* = -1111.363605
S = THF

| Atom | X | Y | Z | Atom | X | Y | Z |
|---|---|---|---|---|---|---|---|
| C | -2.10275 | -1.59267 | -1.06251 | H | 0.91858 | 3.36318 | -3.87527 |
| N | -1.59419 | -1.16472 | 0.26961 | H | 1.76954 | 1.34705 | -2.16953 |
| C | -2.60255 | -0.96808 | 1.34773 | H | 0.33064 | 1.10254 | -3.19398 |
| C | -2.80054 | 0.52535 | 1.63816 | H | 1.71502 | -1.10127 | 2.00786 |
| C | -2.17456 | -1.71889 | 2.61373 | H | 1.11056 | -0.36139 | 3.52360 |
| Li | 0.23436 | 0.01903 | -0.02895 | H | 3.48426 | 0.16702 | 3.70513 |
| C | 1.58727 | -1.46626 | -0.74097 | H | 3.62716 | 0.36329 | 1.94106 |
| C | 1.59477 | -2.82449 | -1.11765 | H | 3.37121 | 2.69389 | 2.67051 |
| C | 2.76011 | -3.50057 | -1.51552 | H | 2.16290 | 2.23354 | 3.88452 |
| C | 3.95515 | -2.79103 | -1.53629 | H | 0.65599 | 2.79430 | 2.09152 |
| N | 4.02810 | -1.49173 | -1.19269 | H | 1.83787 | 2.30509 | 0.84561 |
| C | 2.88166 | -0.95008 | -0.83429 | H | 0.66179 | -3.39602 | -1.11012 |
| F | 3.02840 | 0.40071 | -0.49029 | H | 2.74138 | -4.54986 | -1.80181 |
| O | -0.03740 | 1.63578 | -1.21826 | H | 4.89122 | -3.26099 | -1.83540 |
| C | -0.79380 | 2.84987 | -1.03190 | H | -3.11927 | 1.06271 | 0.73930 |
| C | -0.63912 | 3.64421 | -2.33110 | H | -3.56600 | 0.67501 | 2.40985 |
| C | 0.75700 | 3.21041 | -2.80413 | H | -1.86045 | 0.96694 | 1.98672 |
| C | 0.78104 | 1.73225 | -2.41692 | H | -1.19757 | -1.36310 | 2.96323 |
| O | 0.84388 | 0.75408 | 1.78850 | H | -2.89560 | -1.56169 | 3.42344 |
| C | 1.63567 | -0.17178 | 2.57669 | H | -2.10180 | -2.79781 | 2.43163 |
| C | 2.97582 | 0.52388 | 2.80436 | H | -3.56835 | -1.38428 | 1.02752 |
| C | 2.55447 | 1.99891 | 2.88724 | H | -2.47782 | 0.43335 | -1.74883 |
| C | 1.44066 | 2.07289 | 1.83865 | H | -3.27865 | -0.82453 | -2.71084 |
| C | -3.00151 | -0.52568 | -1.69364 | H | -3.93158 | -0.38506 | -1.12972 |
| C | -2.78280 | -2.97341 | -1.05463 | H | -3.71178 | -2.97547 | -0.47145 |
| H | -1.82957 | 2.58197 | -0.80300 | H | -3.03655 | -3.27978 | -2.07630 |
| H | -0.37924 | 3.39822 | -0.17582 | H | -2.11651 | -3.73694 | -0.63536 |
| H | -1.40047 | 3.34012 | -3.05926 | H | -1.19913 | -1.67307 | -1.67897 |
| H | -0.73257 | 4.72297 | -2.17353 | H | -0.93834 | -1.88939 | 0.56383 |
| H | 1.53398 | 3.76154 | -2.26109 | | | | |