

Lithium Diisopropylamide-Mediated Ortholithiations:
Lithium Chloride Catalysis

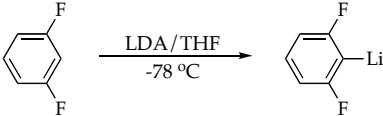
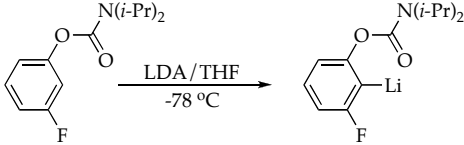
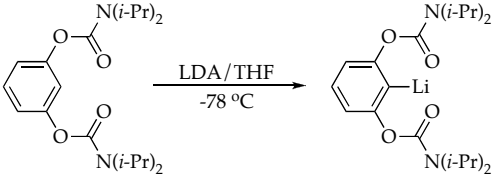
Lekha Gupta, Alexander C. Hoepker, Kanwal Jit Singh and David B. Collum*

Contribution from the Department of Chemistry and Chemical Biology

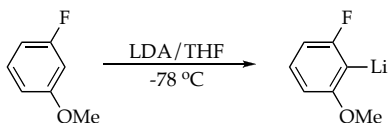
Baker Laboratory, Cornell University

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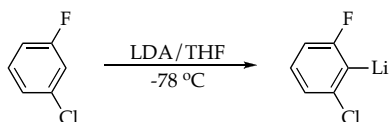
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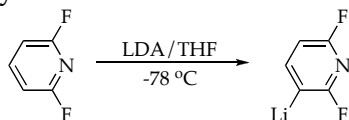
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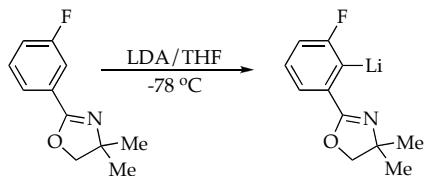
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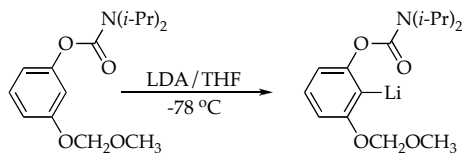
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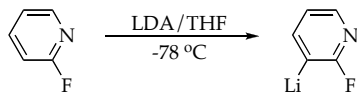
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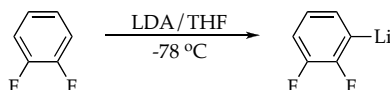
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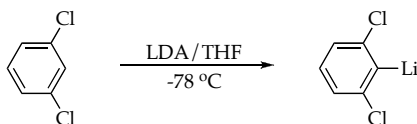
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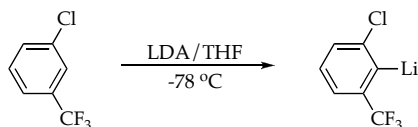
- XII** Plot of IR absorbances versus time for the ortholithiation of 1,2-difluorobenzene S17



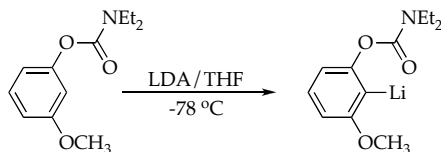
- XIII** Plot of IR absorbances versus time for the ortholithiation of 1,3-dichlorobenzene S18



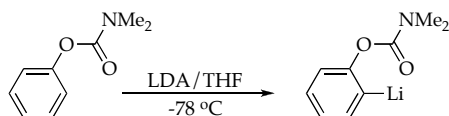
- XIV** Plot of IR absorbances versus time for the ortholithiation of 3-chlorobenzotrifluoride S19



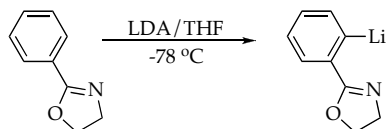
- XV** Plot of IR absorbances versus time for the ortholithiation of 3-methoxyphenyl-*N,N*-diethylcarbamate S20



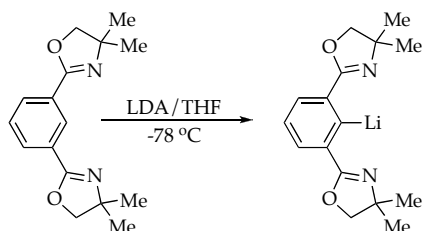
- XVI** Plot of IR absorbances versus time for the ortholithiation of phenyl-*N,N*-dimethylcarbamate S20



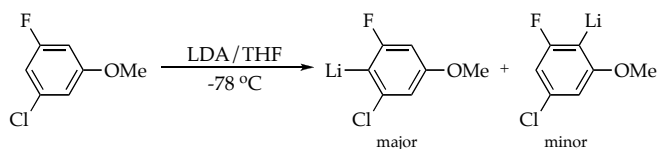
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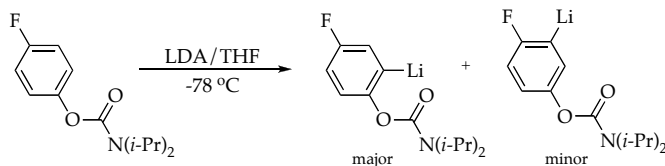


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Note:

- 1) All reported LiCl mol percentages are with respect to [LDA].
- 2) Rates corresponding to the plots from **XV** to **XVIII** were determined at temperatures other than -78°C .
- 3) Be aware of frequent changes in the scale on x-axis.

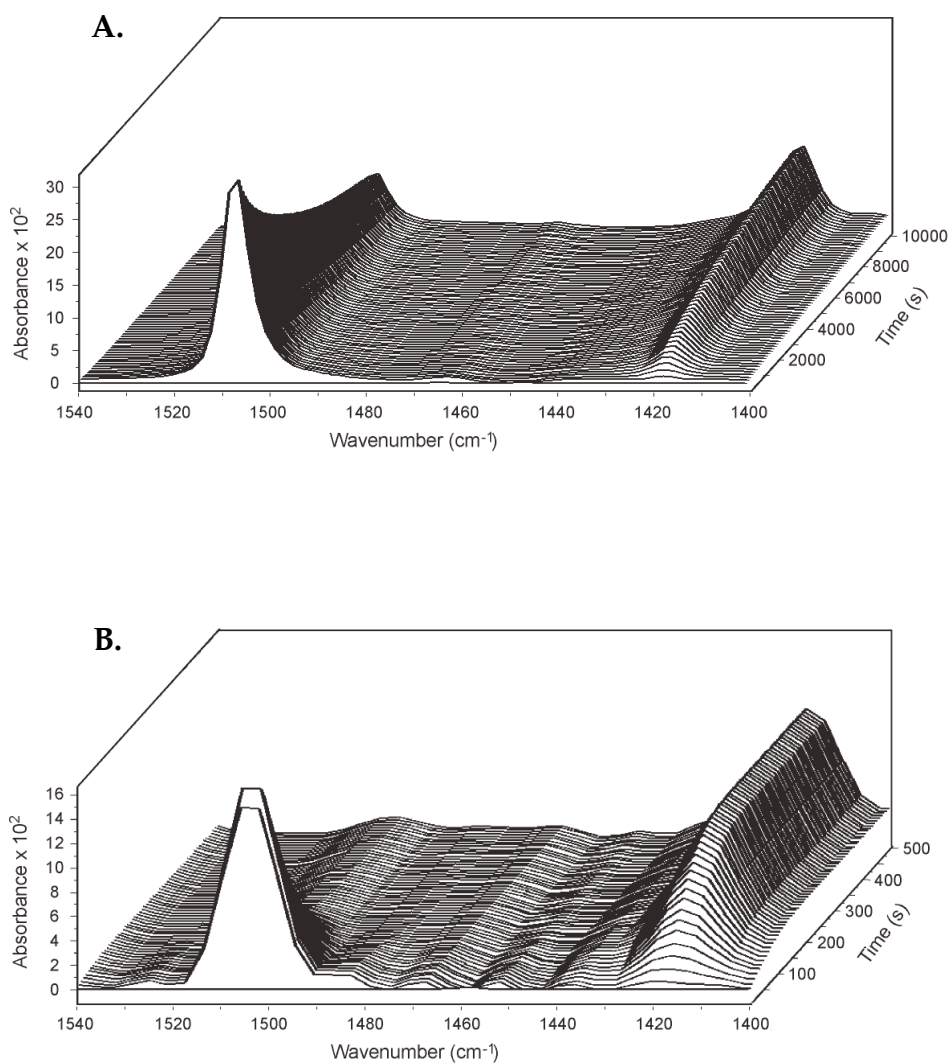
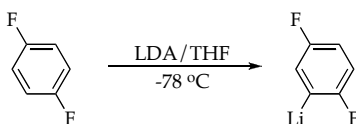
Experimental

I. Measurement of chloride concentration:

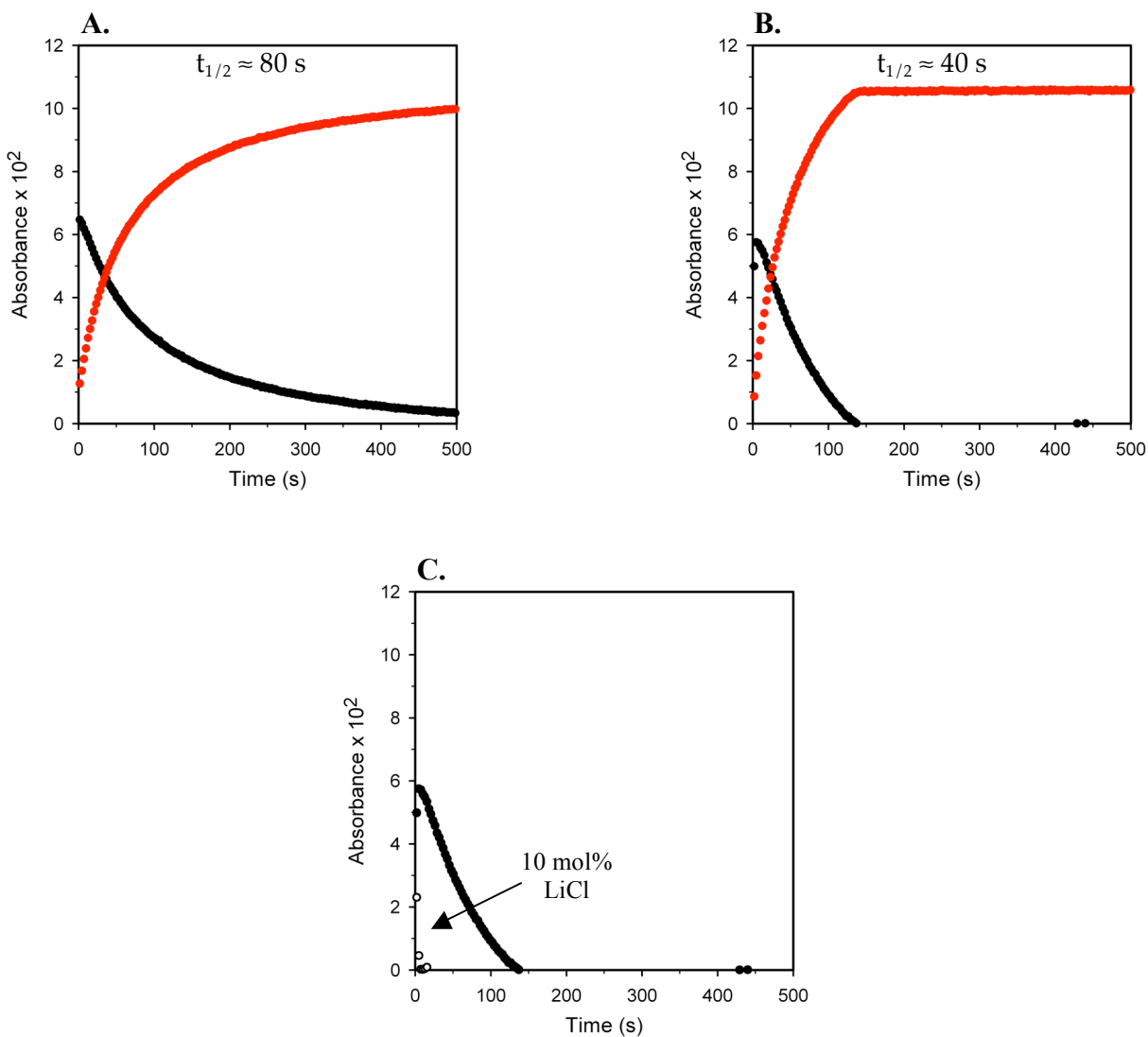
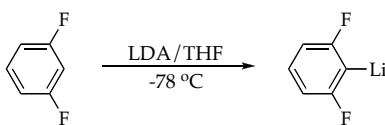
Potentiometry: The chloride concentration was determined potentiometrically by measuring the potential against a saturated potassium chloride solution. After calibrating with known concentrations of chloride, the concentration was calculated with the Nernst equation ($E = E^\circ - (RT/zF) \log_{10} Q$, where $Q = [\text{Cl}^-]$; RT/zF is determined via calibration and is ideally 59.1 mV). The potential was measured with a potentiostat of low impedance. Both reference and indicating electrodes are made of silver plated with silver chloride (Ag/AgCl). Samples were prepared by quenching 25 mg of LDA or 100 μl of 1.6 M *n*-BuLi with high-purity water (from Abruña group), evacuating to dryness and redissolving in water. Because the electrodes require a near neutral pH, the quenched base solutions needed to be neutralized with HNO_3 . The LiCl standards were accordingly enriched with NaNO_3 to ensure comparable activity. Both HNO_3 and NaNO_3 contained <0.5 ppm and <0.0003% Cl^- , respectively. The lower detection limit for Cl^- is approximately 0.5 ppm.

Ion Chromatography: Ion chromatography was performed on a Dionex ICS-2000 system (Sunnyvale, CA) with a Dionex Ionpac AG18 guard column and a Dionex Ionpac AS18 separation column. Samples and standards were run in the isocratic mode (1.0 ml/min) using 38 mM KOH as eluent. Elution time of chloride varied from 3.94 to 4.23 min. The suppression was achieved by a Dionex ASRS ULTRA II 4 mm self-regenerating suppressor. The column temperature was 30 °C and the working electric current was 100 mA. The eluent flow rate is 1.0 ml/min. The injection volume is 25 μl . Samples were prepared by quenching 25 mg of LDA or 100 μl of 1.6 M *n*-BuLi with high-purity water (from Abruña group), evacuating to dryness and redissolving in water. Aqueous samples of pH 12-13 were injected in duplicate into the chromatograph. The lower detection limit is approximately 10 ppb.

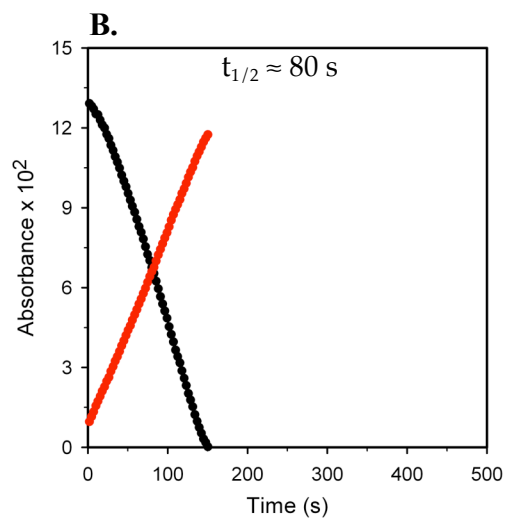
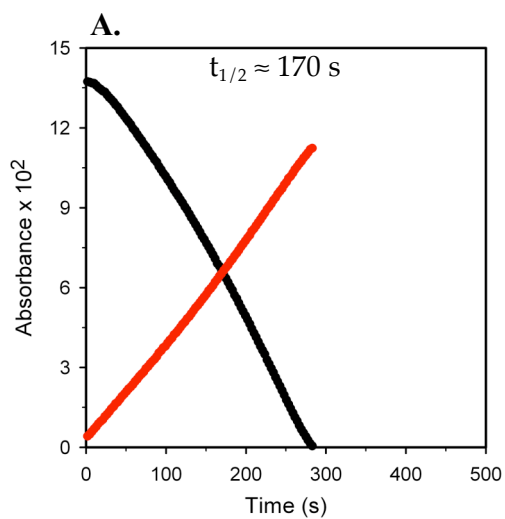
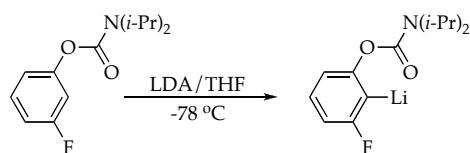
IR Rate Studies



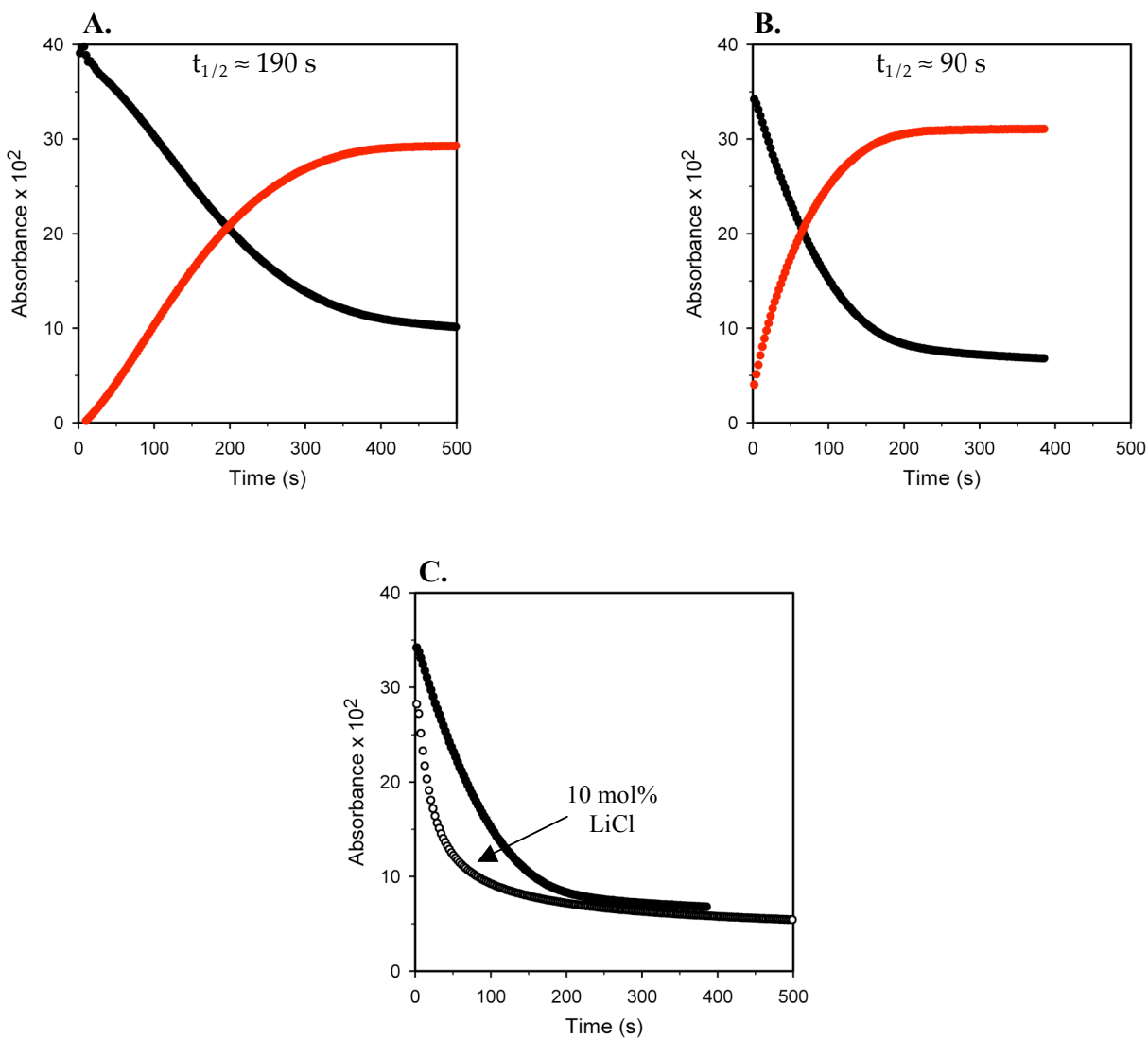
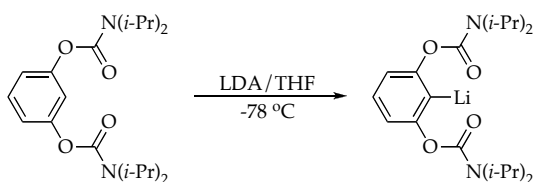
I. Representative in situ IR spectroscopic analysis of the ortholithiation of 1,4-difluorobenzene (0.1 M) with LDA (0.12 M) in neat THF at $-78\text{ }^{\circ}\text{C}$: (A) no added LiCl; (B) 0.5 mol % LiCl. The IR absorbance at 1507 cm^{-1} corresponds to 1,4-difluorobenzene, whereas the absorbance at 1418 cm^{-1} corresponds to its lithiated form.



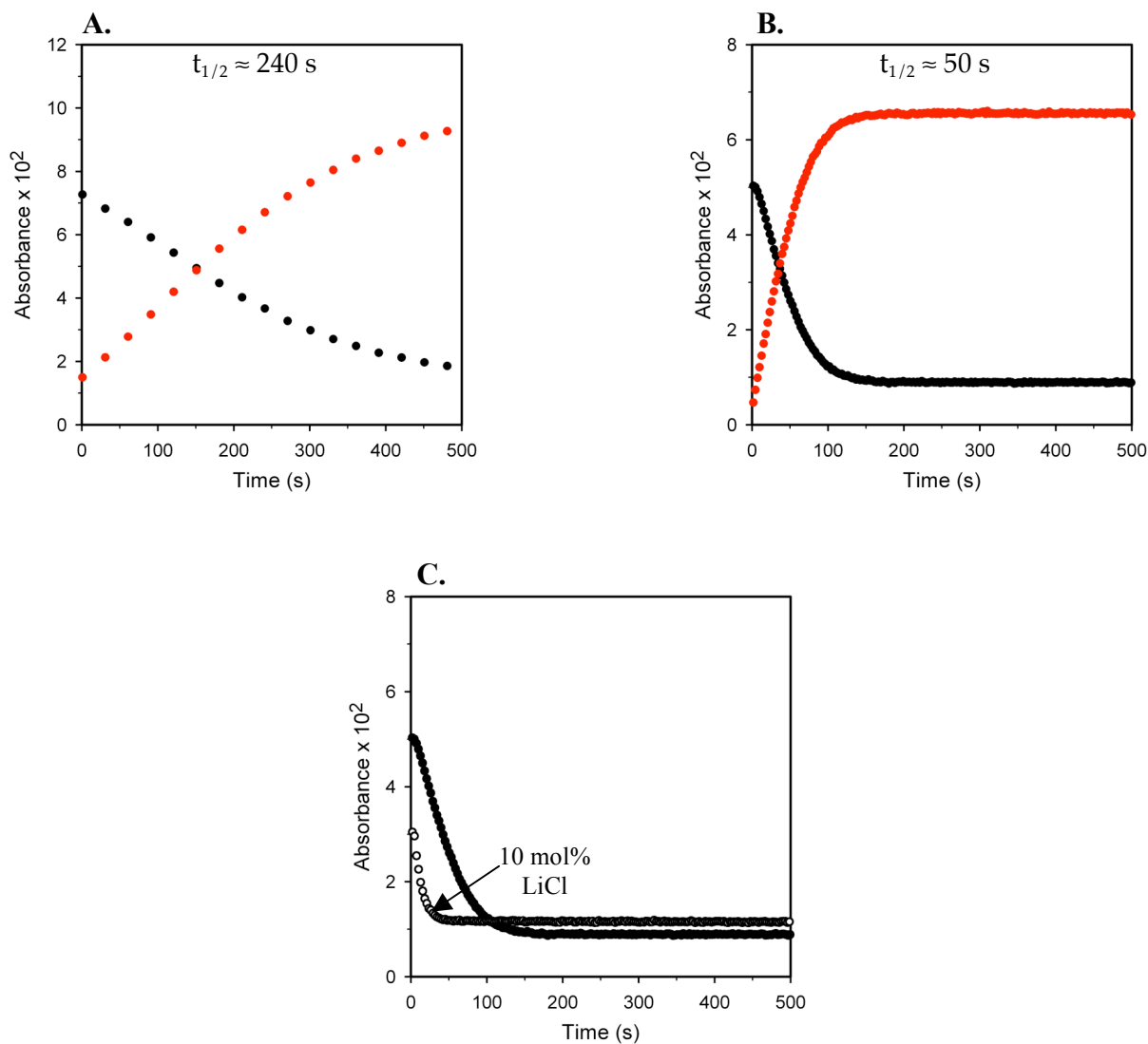
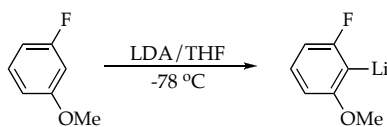
II. Plot of IR absorbances (black – 1606 cm⁻¹, red – 1406 cm⁻¹) versus time for the ortholithiation of 1,3-difluorobenzene (0.10 M) with LDA (0.12 M) in neat THF at -78 °C: (A) no added LiCl; (B) 0.5 mol% LiCl; (C) 0.5 and 10 mol% LiCl.



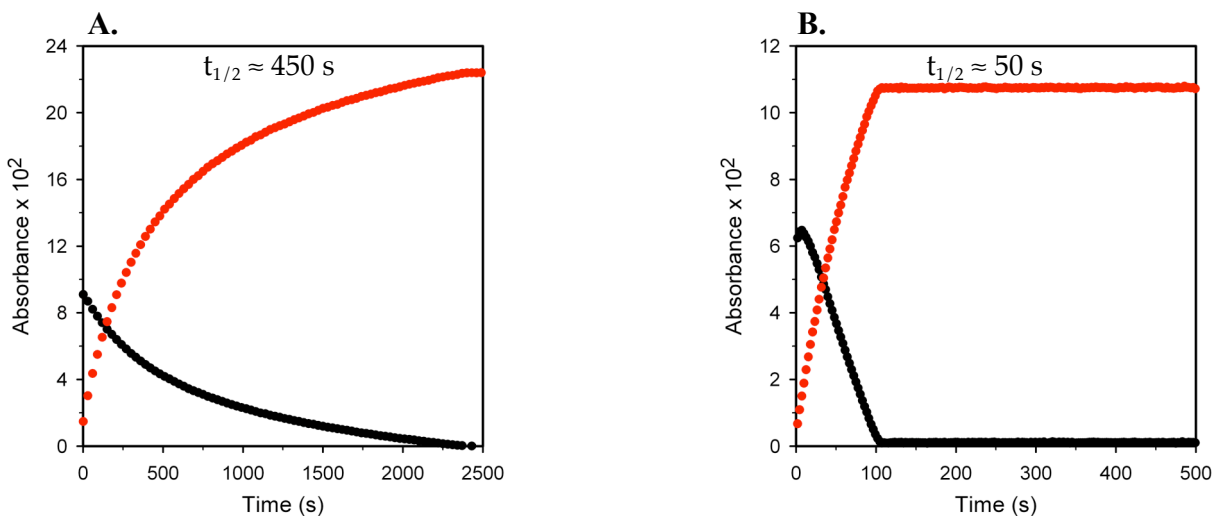
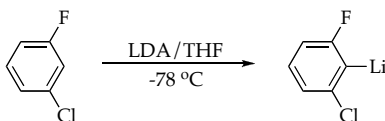
III. Plot of IR absorbances (black – 1715 cm^{-1} , red – 1657 cm^{-1}) versus time for the ortholithiation of 3-fluorophenyl-*N,N*-diisopropylcarbamate (0.10 M) with LDA (0.12 M) in neat THF at $-78\text{ }^{\circ}\text{C}$: (A) no added LiCl; (B) 0.5 mol% LiCl.



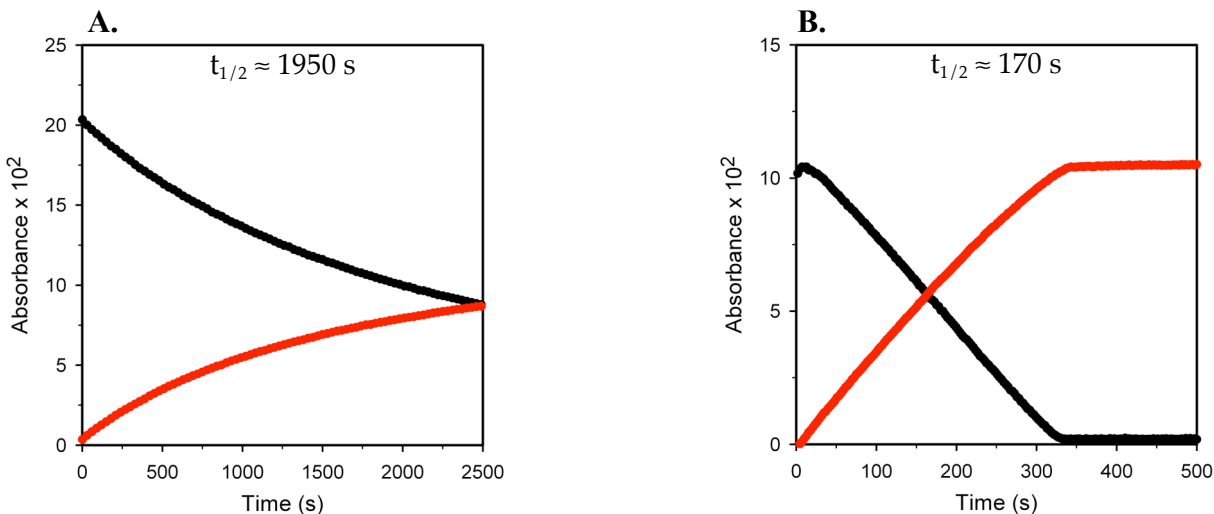
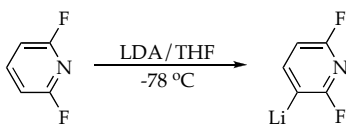
IV. Plot of IR absorbances (black – 1721 cm^{-1} , red – 1661 cm^{-1}) versus time for the ortholithiation of 1,3-bis(*N,N*-diisopropylcarbamoyl)benzene (0.10 M) with LDA (0.12 M) in neat THF at $-78\text{ }^{\circ}\text{C}$: (A) no added LiCl; (B) 0.5 mol% LiCl; (C) 0.5 and 10 mol% LiCl.



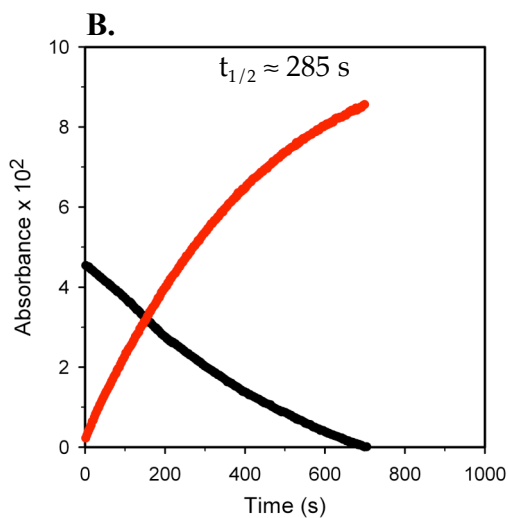
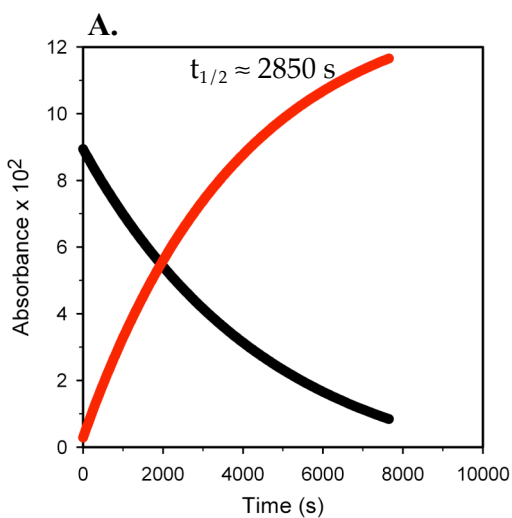
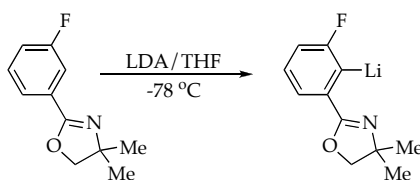
V. Plot of IR absorbances (black – 1617 cm^{-1} , red – 1412 cm^{-1}) versus time for the ortholithiation of 3-fluoroanisole (0.10 M) with LDA (0.12 M) in neat THF at -78°C : (A) no added LiCl; (B) 0.5 mol% LiCl (C) 0.5 and 10 mol% LiCl.



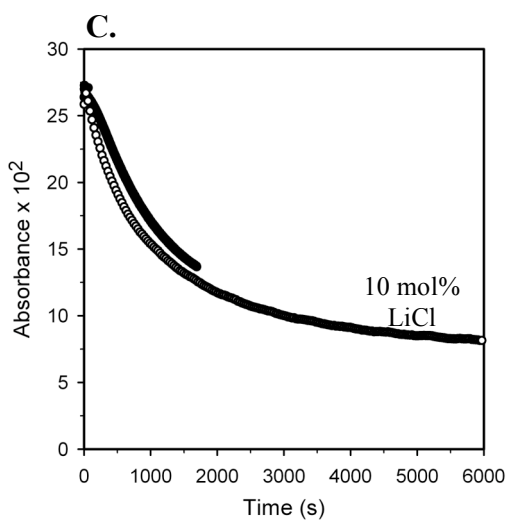
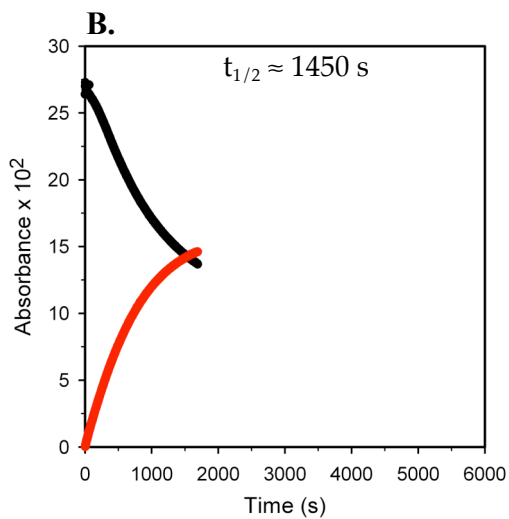
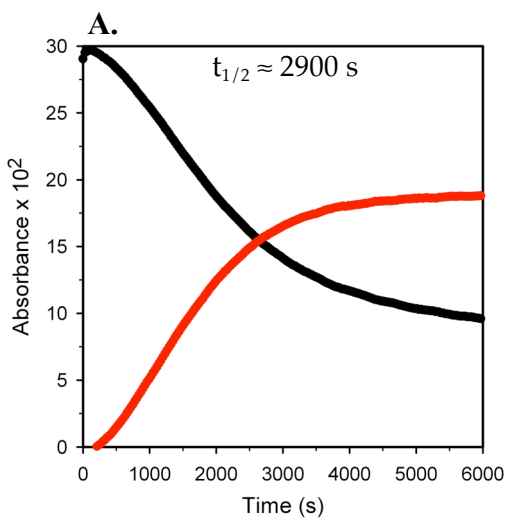
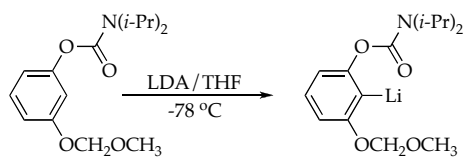
VI. Plot of IR absorbances (black – 1595 cm^{-1} , red – 1397 cm^{-1}) versus time for the ortholithiation of 1-chloro-3-fluorobenzene (0.10 M) with LDA (0.12 M) in neat THF at -78°C : (A) no added LiCl; (B) 0.5 mol% LiCl.



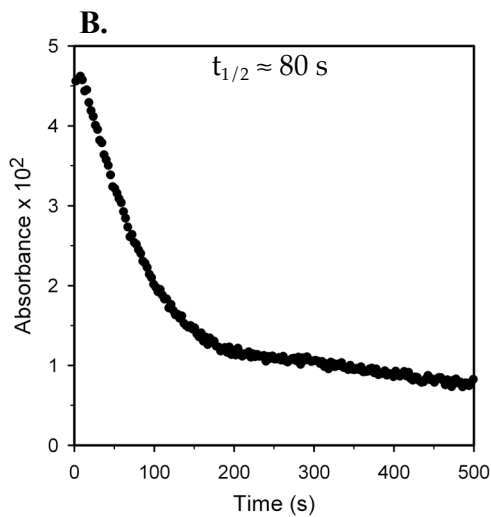
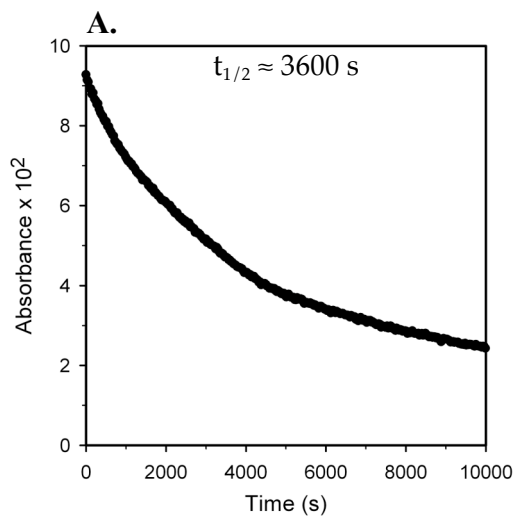
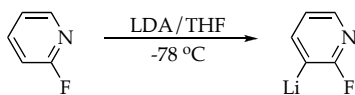
VII. Plot of IR absorbances (black – 1610 cm^{-1} , red – 1514 cm^{-1}) versus time for the ortholithiation of 2,6-difluoropyridine (0.10 M) with LDA (0.12 M) in neat THF at -78°C : (A) no added LiCl; (B) 0.5 mol% LiCl.



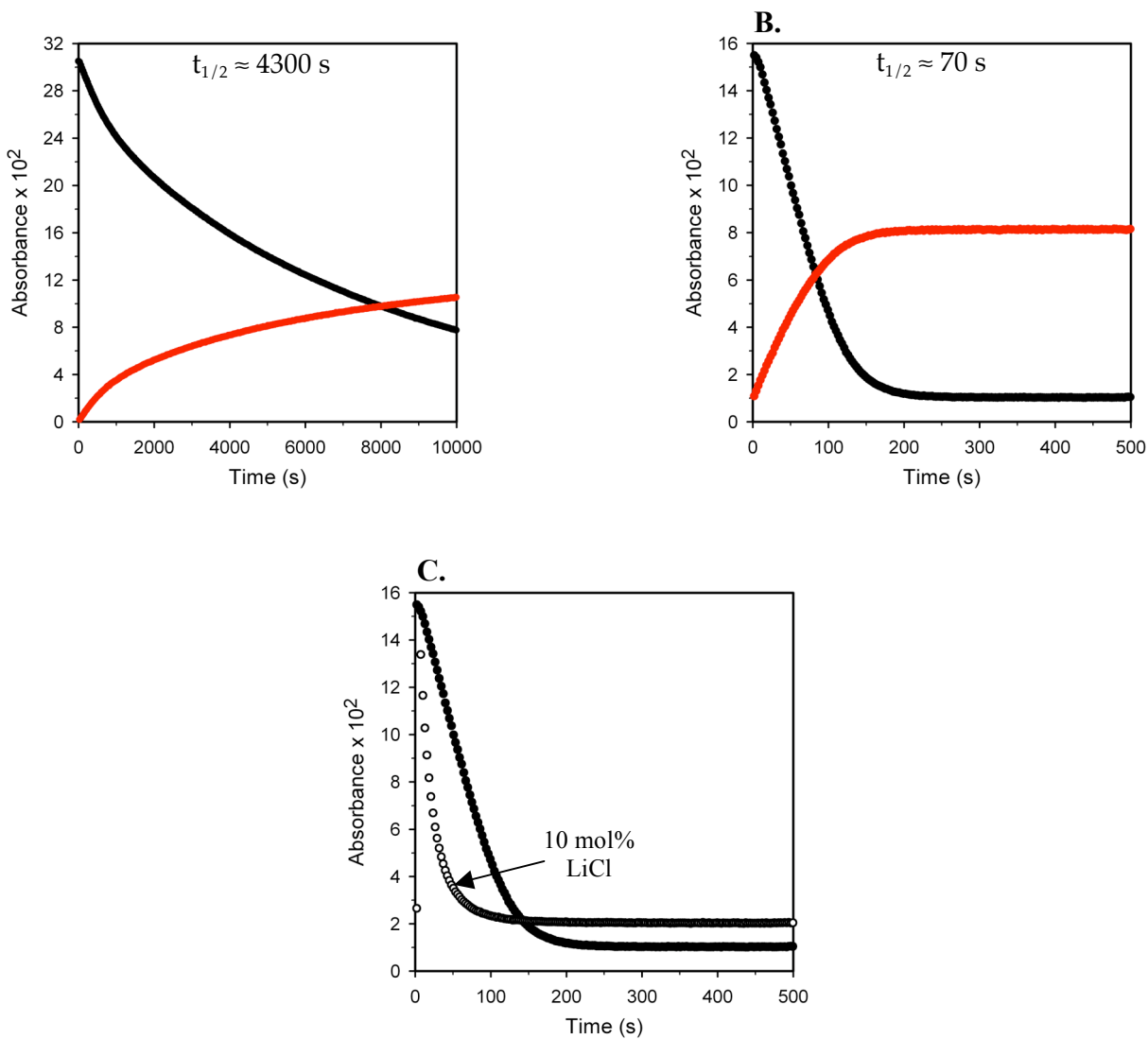
VIII. Plot of IR absorbances (black – 1653 cm^{-1} , red – 1622 cm^{-1}) versus time for the ortholithiation of 2-(3-fluorophenyl)-4,4-dimethyl-4,5-dihydro-1,3-oxazole (0.10 M) with LDA (0.12 M) in neat THF at $-78\text{ }^{\circ}\text{C}$: (A) no added LiCl; (B) 0.5 mol% LiCl.



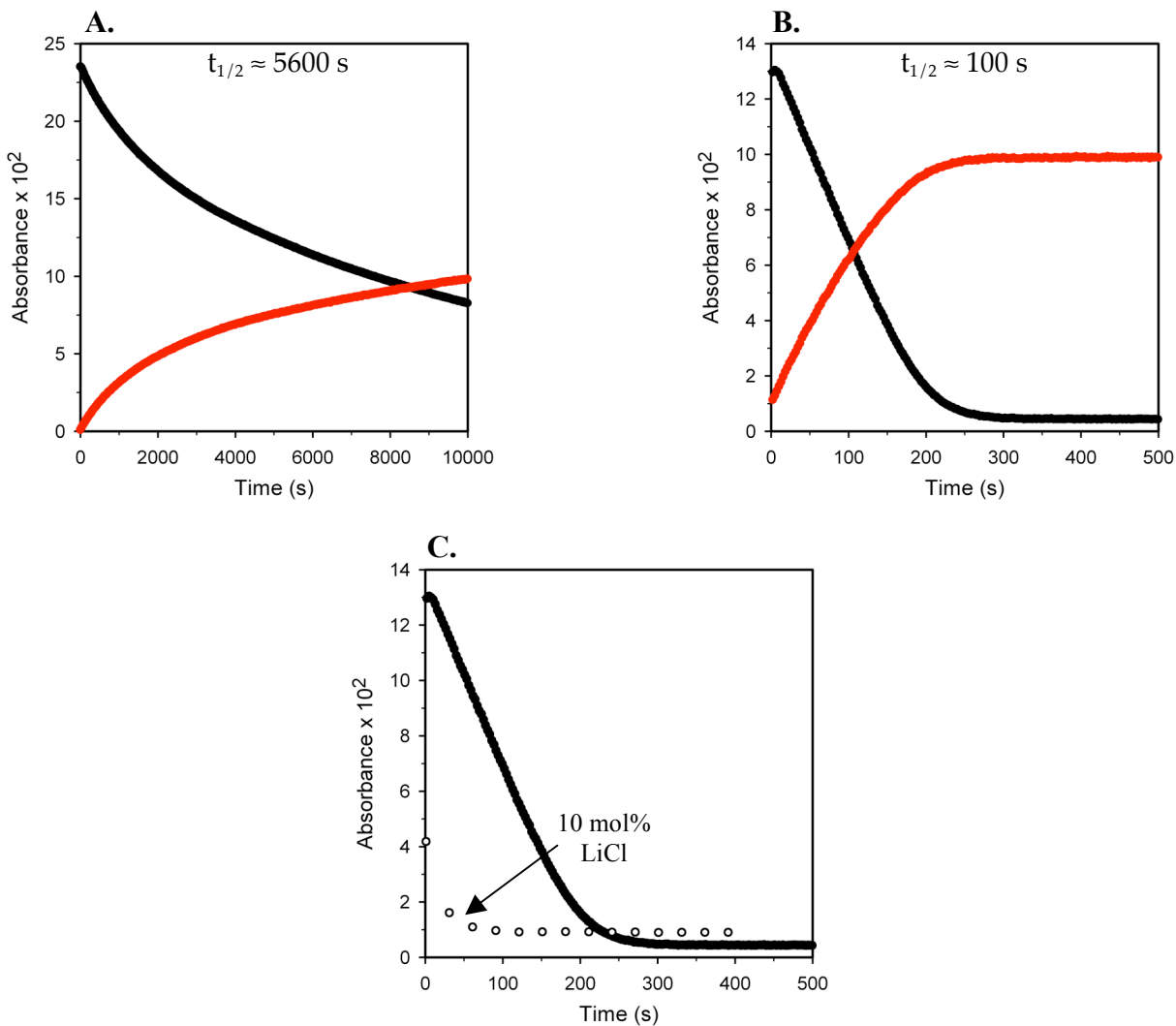
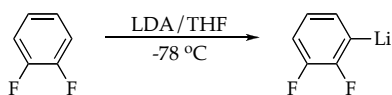
IX. Plot of IR absorbances (black – 1719 cm^{-1} , red – 1659 cm^{-1}) versus time for the ortholithiation of 3-methoxymethoxyphenyl-*N,N*-diisopropylcarbamate (0.10 M) with LDA (0.12 M) in neat THF at $-78\text{ }^{\circ}\text{C}$: (A) no added LiCl; (B) 0.5 mol% LiCl; (C) 0.5 and 10 mol% LiCl.



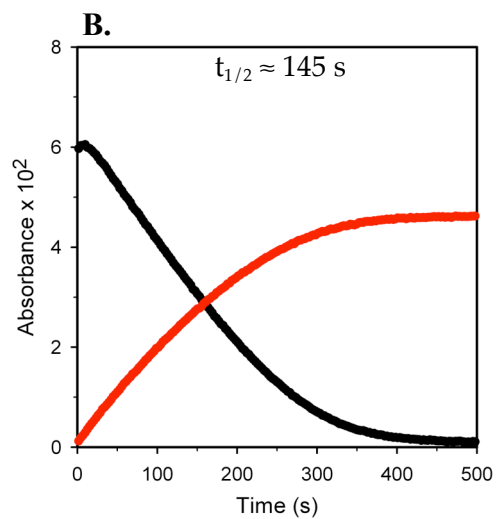
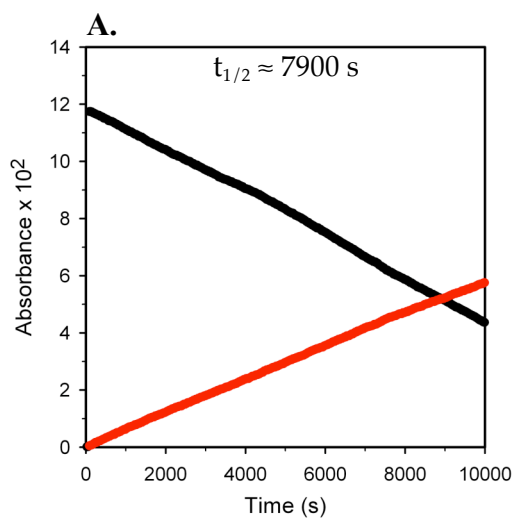
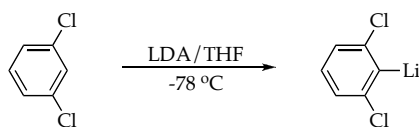
X. Plot of IR absorbances (black – 1597 cm⁻¹) versus time for the ortholithiation of 2-fluoropyridine (0.10 M) with LDA (0.12 M) in neat THF at -78 °C: (A) no added LiCl; (B) 0.5 mol% LiCl.



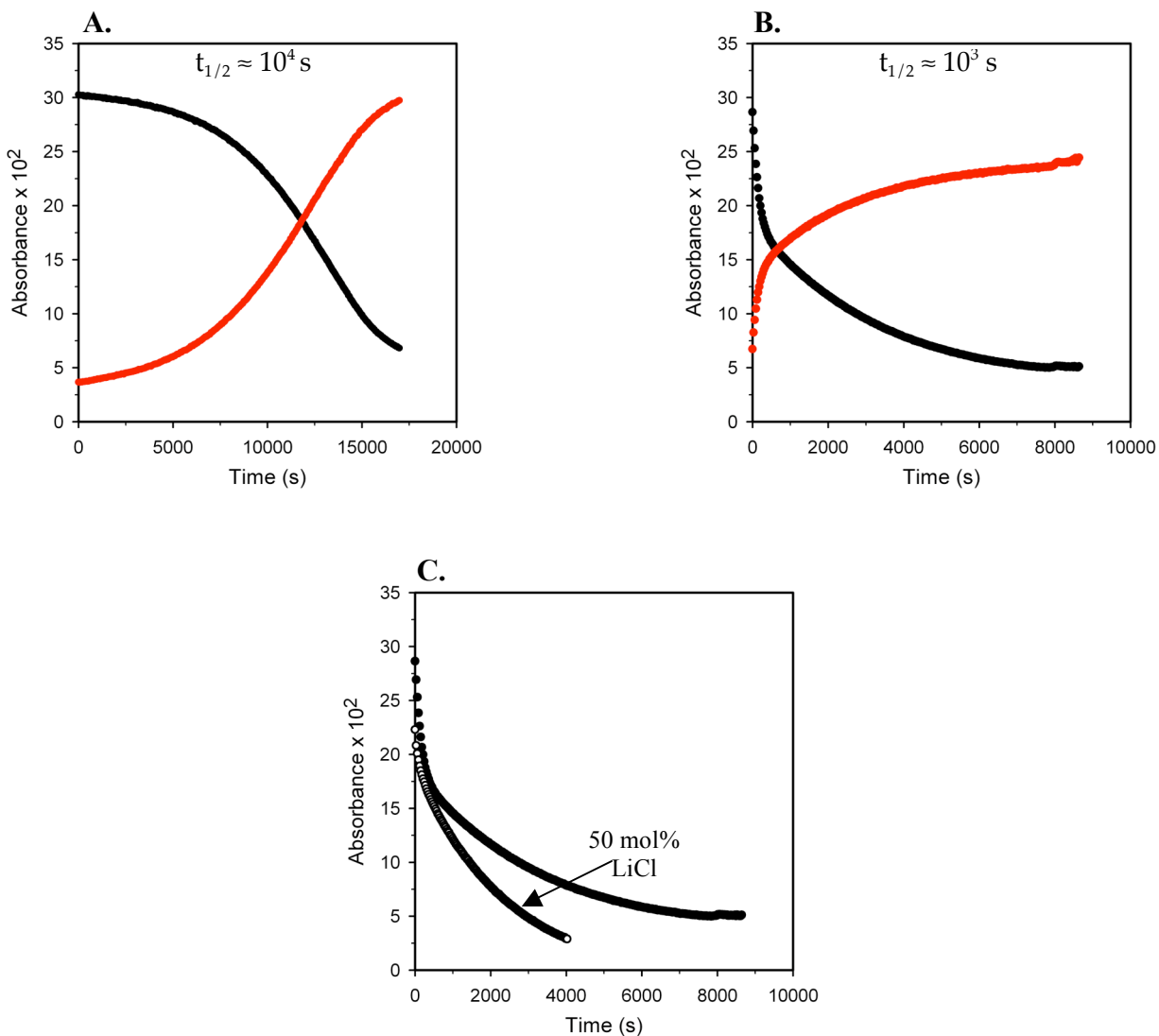
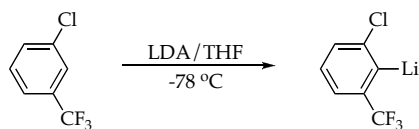
XI. Plot of IR absorbances (black – 1507 cm^{-1} , red – 1418 cm^{-1}) versus time for the ortholithiation of 1,4-difluorobenzene (0.10 M) with LDA (0.12 M) in neat THF at $-78\text{ }^\circ\text{C}$: (A) no added LiCl; (B) 0.5 mol% LiCl; (C) 0.5 and 10 mol% LiCl.



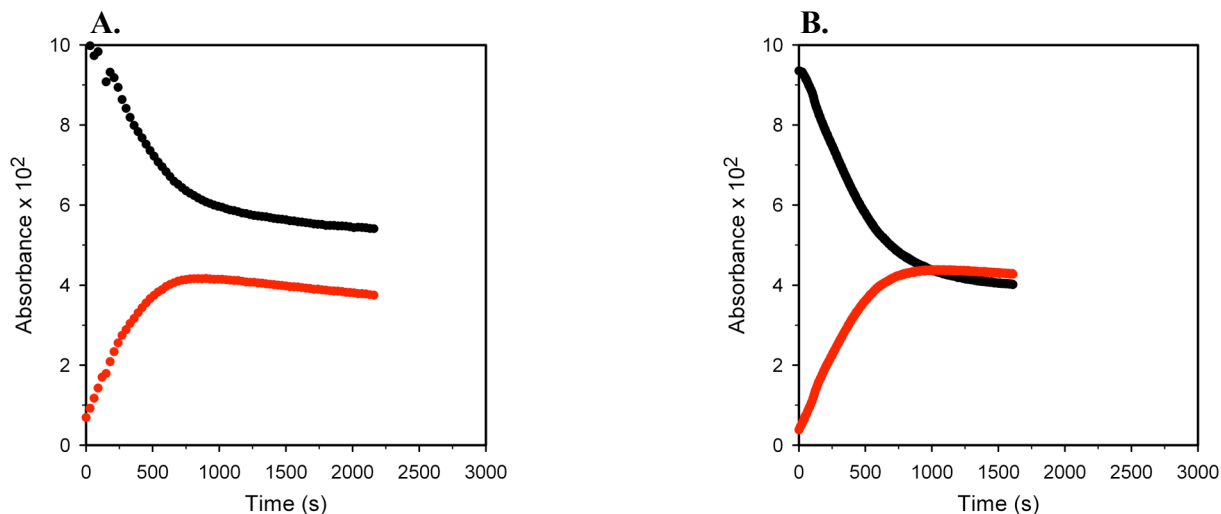
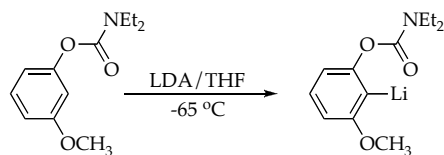
XII. Plot of IR absorbances (black – 1509 cm^{-1} , red – 1391 cm^{-1}) versus time for the ortholithiation of 1,2-difluorobenzene (0.10 M) with LDA (0.12 M) in neat THF at $-78\text{ }^{\circ}\text{C}$: (A) no added LiCl; (B) 0.5 mol% LiCl; (C) 0.5 and 10 mol% LiCl.



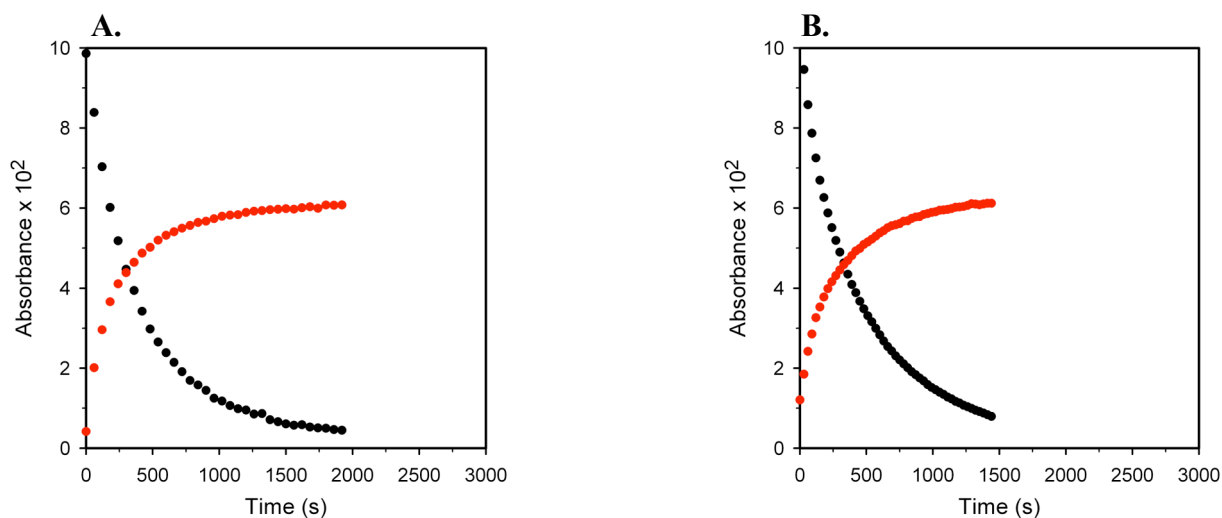
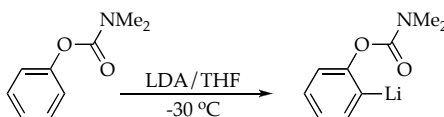
XIII. Plot of IR absorbances (black – 1576 cm^{-1} , red – 1534 cm^{-1}) versus time for the ortholithiation of 1,3-dichlorobenzene (0.10 M) with LDA (0.12 M) in neat THF at $-78\text{ }^{\circ}\text{C}$: (A) no added LiCl; (B) 0.5 mol% LiCl.



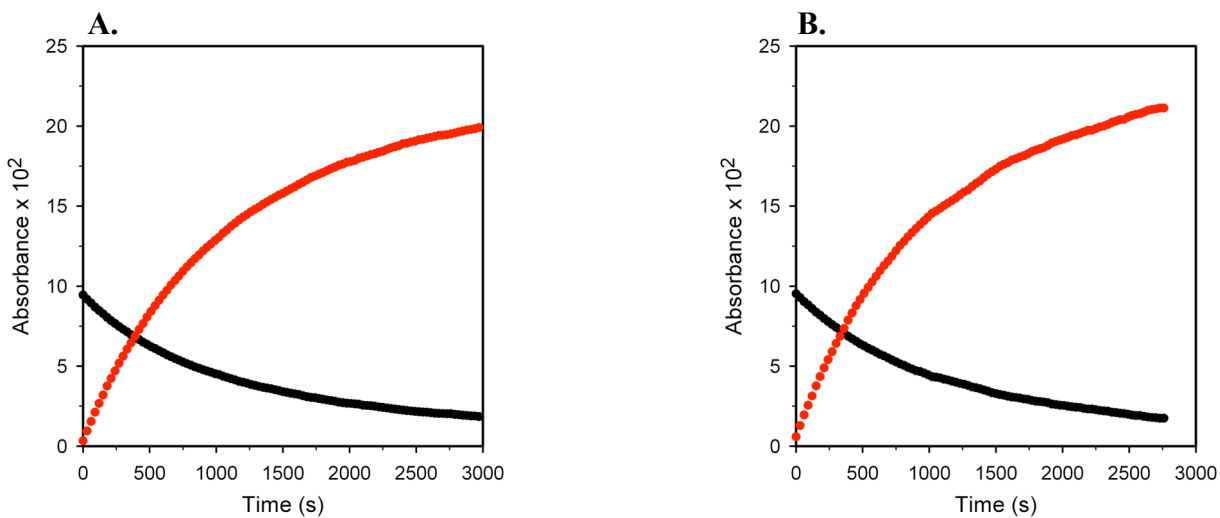
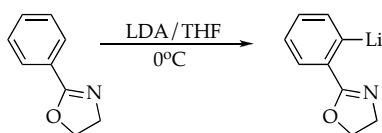
XIV. Plot of IR absorbances (black – 1326 cm^{-1} , red – 1306 cm^{-1}) versus time for the ortholithiation of 3-chlorobenzotrifluoride (0.10 M) with LDA (0.12 M) in neat THF at -78°C : (A) no added LiCl; (B) 0.5 mol% LiCl; (C) 0.5 and 50 mol% LiCl.



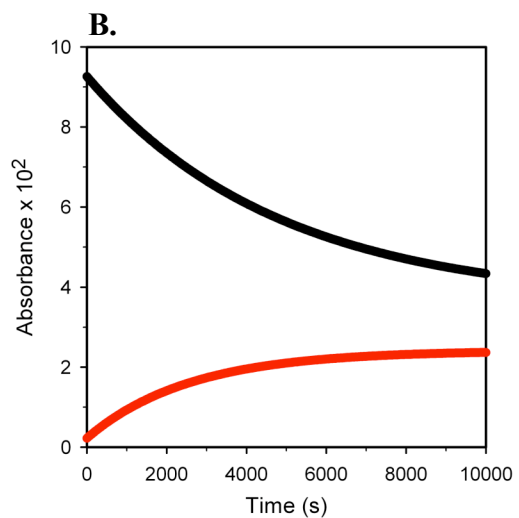
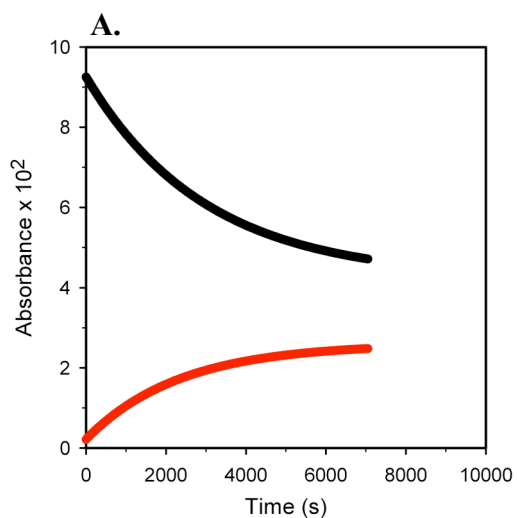
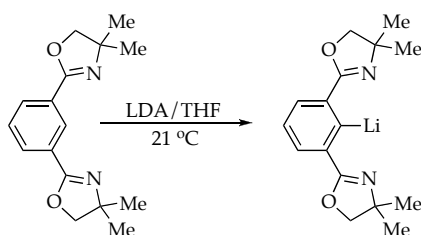
XV. Plot of IR absorbances (black – 1725 cm^{-1} , red – 1675 cm^{-1}) versus time for the ortholithiation of 3-methoxyphenyl-*N,N*-diethylcarbamate (0.10 M) with LDA (0.12 M) in neat THF at $-65\text{ }^{\circ}\text{C}$: (A) no added LiCl; (B) 0.5 mol% LiCl.



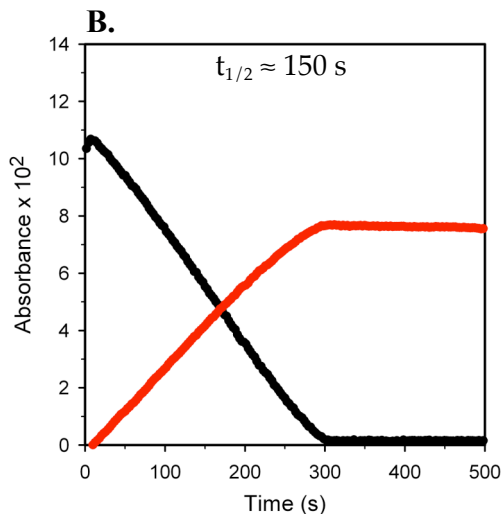
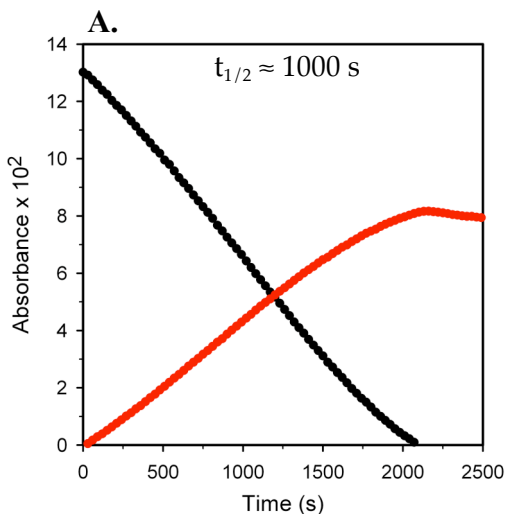
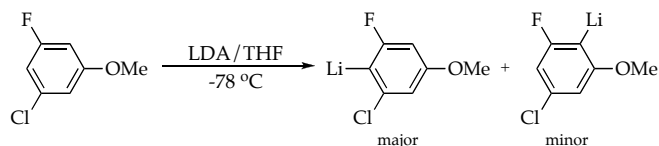
XVI. Plot of IR absorbances (black – 1725 cm^{-1} , red – 1675 cm^{-1}) versus time for the ortholithiation of phenyl-*N,N*-dimethylcarbamate (0.10 M) with LDA (0.12 M) in neat THF at $-30\text{ }^{\circ}\text{C}$: (A) no added LiCl; (B) 0.5 mol% LiCl.



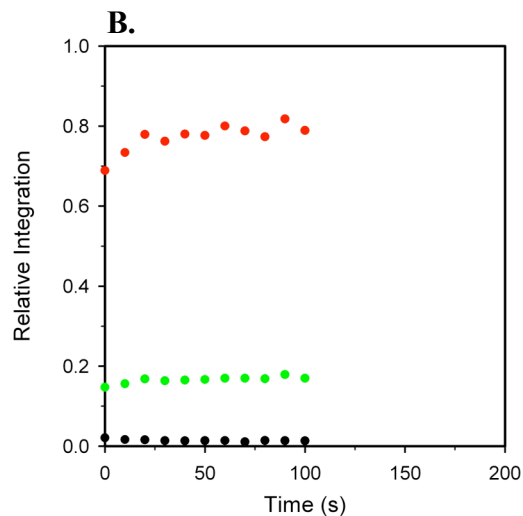
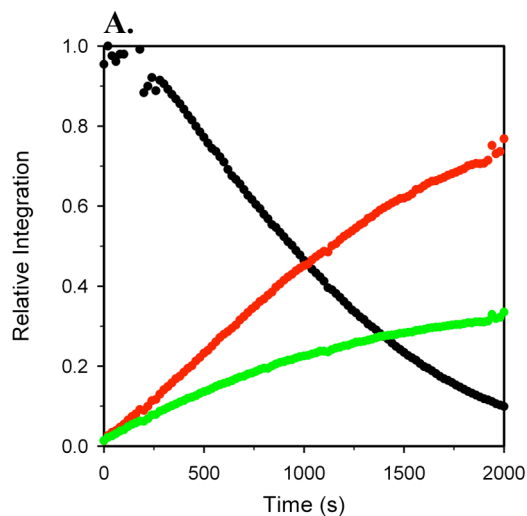
XVII. Plot of IR absorbances (black – 1652 cm⁻¹, red – 1526 cm⁻¹) versus time for the ortholithiation of 2-phenyl-2-oxazoline (0.10 M) with LDA (0.12 M) in neat THF at 0 °C: (A) no added LiCl; (B) 0.5 mol% LiCl.



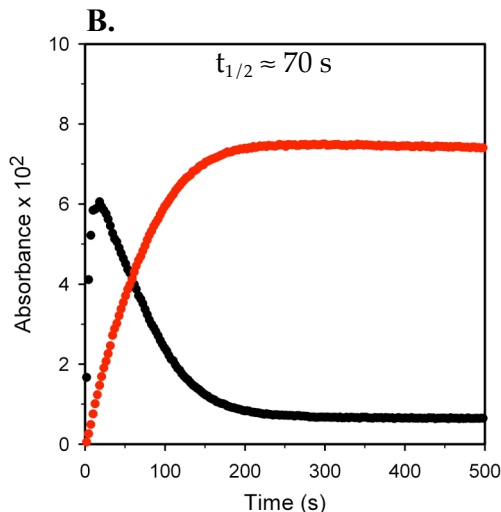
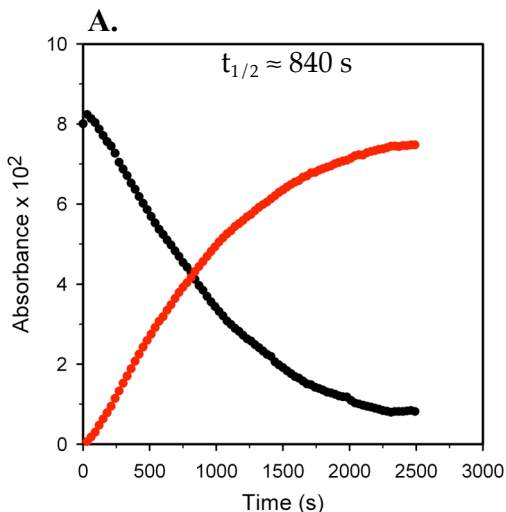
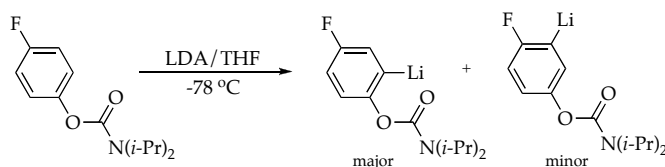
XVIII. Plot of IR absorbances (black – 1654 cm^{-1} , red – 1520 cm^{-1}) versus time for the ortholithiation of 1,3-bis(4',4'-dimethyl-2'-oxazoliny)benzene (0.10 M) with LDA (0.12 M) in neat THF at 21 °C: (A) no added LiCl; (B) 0.5 mol% LiCl.



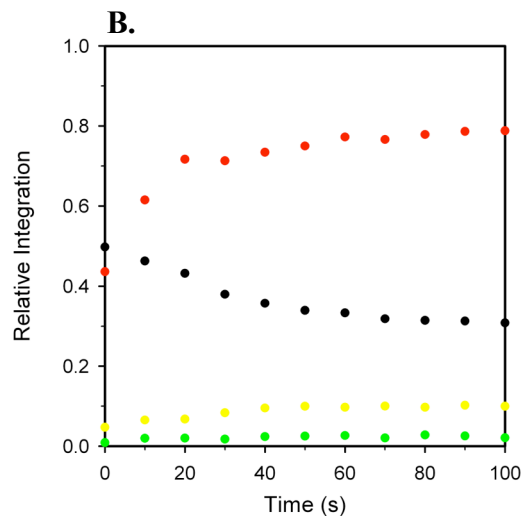
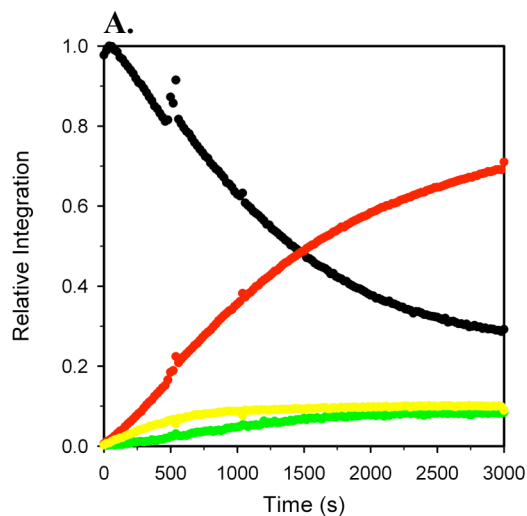
XIX. Plot of IR absorbances (black – 1611 cm^{-1} , red – 1553 cm^{-1}) versus time for the ortholithiation of 3-chloro-5-fluoroanisole (0.10 M) with LDA (0.12 M) in neat THF at -78°C : (A) no added LiCl; (B) 0.5 mol% LiCl.



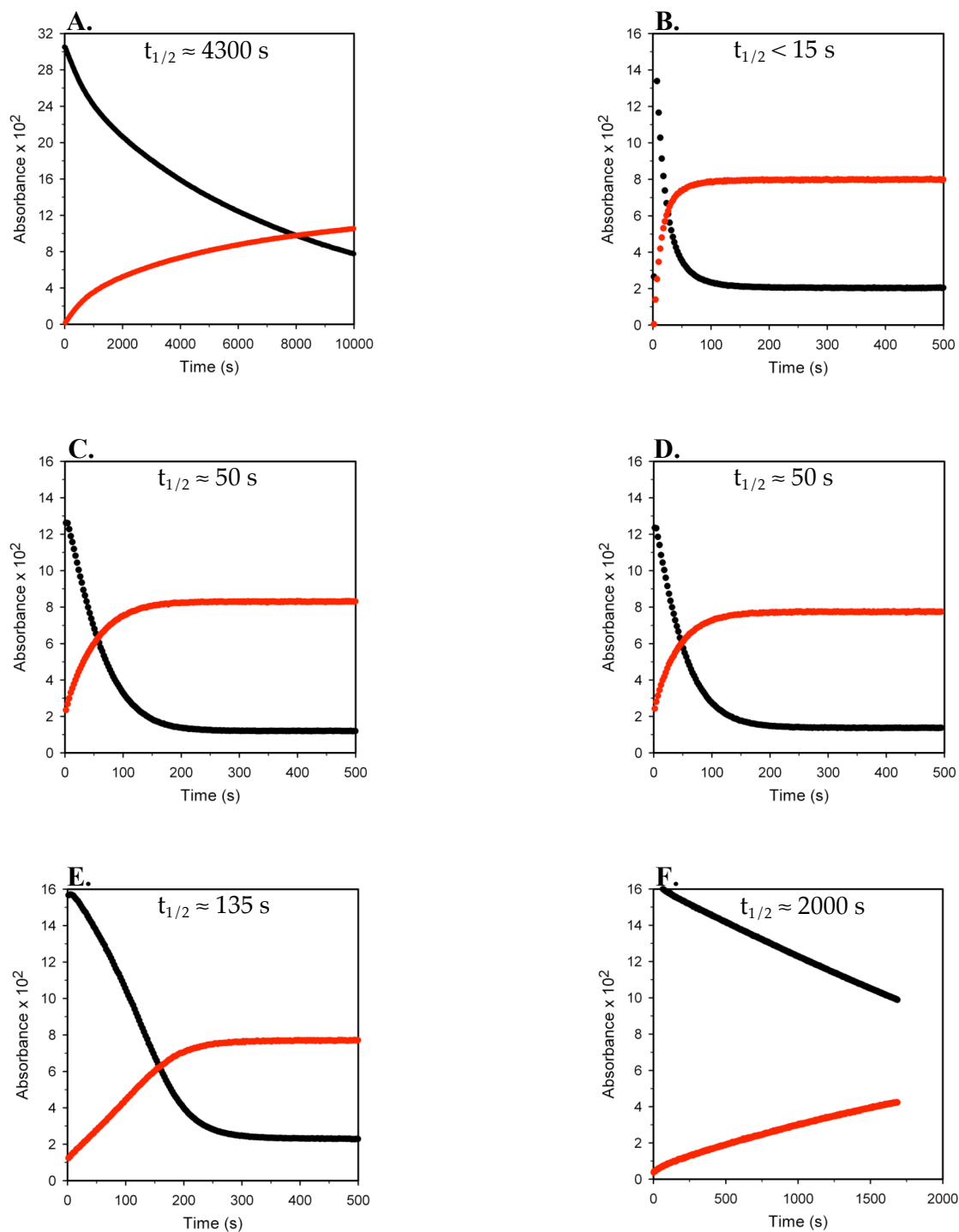
XX. Plot of ^{19}F NMR peak integrations (black: $\delta -110.1$, red: $\delta -77.8$, green: $\delta -76.6$) versus time for the ortholithiation of 3-chloro-5-fluoroanisole (0.05 M) with LDA (0.20 M) in neat THF at -78°C : (A) no added LiCl; (B) 10 mol% LiCl.



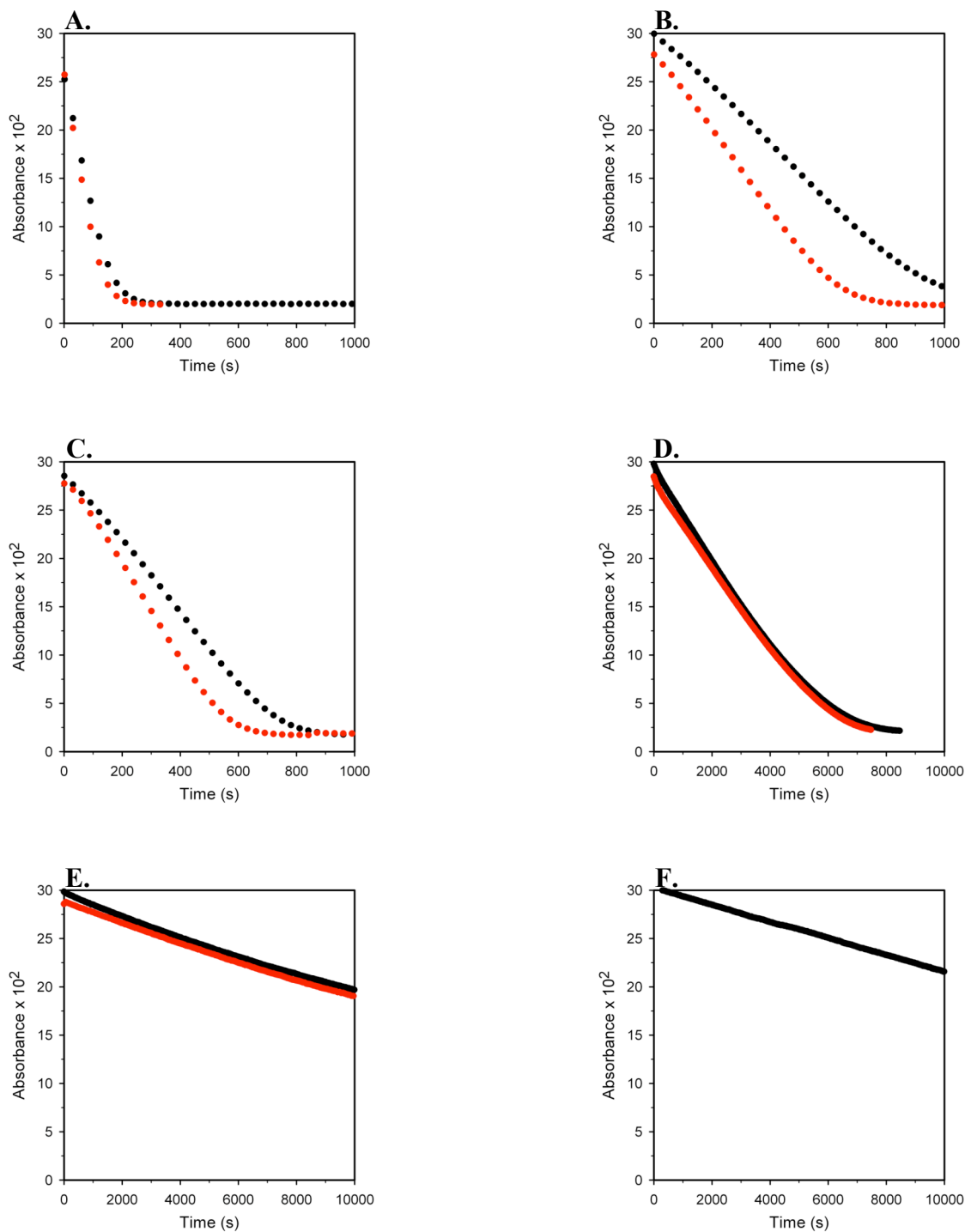
XXI. Plot of IR absorbances (black – 1717 cm⁻¹, red – 1657 cm⁻¹) versus time for the ortholithiation of 4-fluorophenyl-*N,N*-diisopropylcarbamate (0.025 M) with LDA (0.12 M) in neat THF at -78 °C: (A) no added LiCl; (B) 0.5 mol% LiCl.



XXII. Plot of ¹⁹F NMR peak integrations (black: δ -118.8, red: δ -123.7, green: δ 85.5, yellow: δ -124.1) versus time for the ortholithiation of 4-fluorophenyl-*N,N*-diisopropylcarbamate (0.05 M) with LDA (0.20 M) in neat THF at -78 °C: (A) no added LiCl; (B) 10 mol% LiCl.



XXIII. Plot of IR absorbances (black – 1507 cm^{-1} , red – 1418 cm^{-1}) versus time for the ortholithiation of 1,4-difluorobenzene (0.10 M) with LDA (0.12 M) in neat THF at $-78\text{ }^{\circ}\text{C}$: (A) no additive; (B) 10 mol% LiCl; (C) 10 mol% LiBr; (D) 10 mol% PhCCl₂; (E) 10 mol% PhCOOLi; (F) 10 mol% PhOLi.



XXIV. Plot of IR absorbances (black/red – duplicated rates) versus time for the ortholithiation of 1,4-difluorobenzene (0.10 M) with LDA (0.12 M) in 10.0 M THF/hexane at -78 °C using: (A) Acros *n*-BuLi – batch1; (B) Acros *n*-BuLi – batch2; (C) Aldrich *n*-BuLi – batch1; (D) Aldrich *n*-BuLi – batch2; (E) Acros LDA; (F) Aldrich LDA