

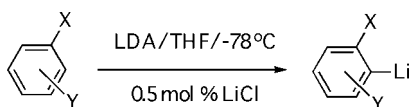
Lithium Diisopropylamide-Mediated Ortholithiations: Lithium Chloride Catalysis

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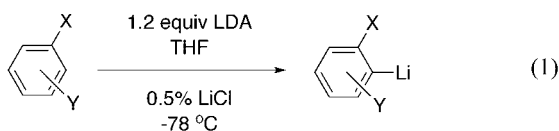
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Ortholithiations of a range of arenes mediated by lithium diisopropylamide (LDA) in THF at $-78\text{ }^{\circ}\text{C}$ reveal substantial accelerations by as little as 0.5 mol % of LiCl (relative to LDA). Substrate dependencies suggest a specific range of reactivity within which the LiCl catalysis is optimal. Standard protocols with unpurified commercial samples of *n*-butyllithium to prepare LDA or commercially available LDA show marked batch-dependent rates—up to 100-fold—that could prove significant to the unwary practitioner. Other lithium salts elicit more modest accelerations. The mechanism is not discussed.

We report herein lithium diisopropylamide (LDA)-mediated ortholithiations¹ that are markedly accelerated by LiCl (eq 1). Beneficial effects of LiCl on the chemistry of LDA and other organolithium reactions have been documented.^{2–4} Nevertheless, the magnitudes of these accelerations of ortholithiation are striking and the implications in synthesis are potentially significant.



We preface the results with several comments about protocol. Most investigators either purchase LDA as a THF solvate or prepare it in situ from commercially available *n*-BuLi.⁵ The implications of these procedures are discussed below. The LDA used in this study was prepared from recrystallized *n*-BuLi,⁶ further recrystallized from hexane,⁷ and shown to contain <0.02% LiCl by potentiometry⁸ and ion chromatography.⁹ The

added LiCl was generated in situ from recrystallized $\text{Et}_3\text{N}\cdot\text{HCl}$.¹⁰ The Et_3N byproduct is a poor ligand¹¹ that has no effect on the ortholithiations.

Ortholithiations were monitored using in situ IR spectroscopy¹² following both the disappearance of the arene and the formation of the resulting aryllithium.¹³ ^{19}F NMR spectroscopic analysis provided comparable results in a number of instances. Trapping experiments were consistent with lithiation but are unreliable measures of the rates because they generate catalytically active lithium salts. Trimethylchlorosilane, for example, generates LiCl ,^{3c} making LiCl-sensitive arene lithiations nearly instantaneous.

Although some metalations display normal (exponential) decays, autocatalysis¹⁴ arising from the aryllithiums was evident in the form of linear and sigmoidal decays for many substrates (Supporting Information). Consequently, the rates of uncatalyzed ortholithiations are simply reported as half-lives ($t_{1/2}$), and the LiCl-mediated accelerations as the ratios of $1/t_{1/2}$ values with and without added 0.5% LiCl (k_{LiCl}).¹⁵ The approximation is crude but adequate for our needs.

The results from LiCl-free and LiCl-catalyzed LDA-mediated metalations are illustrated in Table 1. The accelerations reflected by k_{LiCl} values derive from adding only 0.5 mol % of LiCl. Higher concentrations of LiCl produce greater accelerations (resulting in immeasurably high rates in many instances.) The substrates in Table 1 are ordered from the most reactive (small $t_{1/2}$) to the least reactive (large $t_{1/2}$), revealing an interesting

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TABLE 1. Rates of Lithium Diisopropylamide-Mediated Ortholithiations (Eq 1) Listed in Order of Decreasing Reactivity

entry	substrate	$t_{1/2}$ (in s) (-78 °C)	k_{LiCl}^a
1		80	2
2		170	2
3		190	2
4		240	5
5		450	9
6		1950	11
7		2800	10
8		2900	2
9		3600	45
10		4300	60
11		5600	55
12		7900	55
13		10^4	10
14		$>10^5$	1 (-65 °C)
15		$>10^5$	1 (-30 °C)
16		$>10^5$	1 (0 °C)
17		$>10^5$	1 (20 °C)

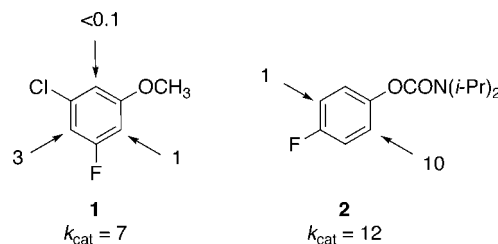
^a Measured at -78 °C unless otherwise noted.

pattern: Substrates of intermediate reactivity are most prone to catalysis. Both the fastest metalations ($t_{1/2} < 200$ s) and the

slowest ($t_{1/2} > 10^5$ s) metalations are relatively insensitive to external LiCl.

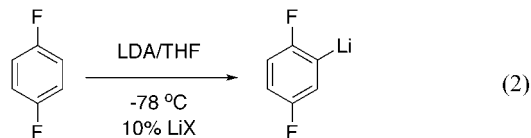
We draw the readers attention to entry 8, which does not follow the pattern. Notably, increasing the LiCl concentration to 10 mol % has no effect. In short, a k_{LiCl} of 2 appears to be within the experimental error of unity. But why is entry 8 aberrant? Curiously, the LiCl-sensitive ortholithiations involve substrates containing halogen-based directing groups (F, Cl, or CF₃). Similarly, the ortholithiation in entry 3 shows only a marginal increase in k_{LiCl} with larger aliquots of LiCl. This result may foreshadow conclusions from ongoing mechanistic studies.

It would be especially provocative if the accelerations elicited significant changes in regioselectivity. Schlosser, for example, noted advantageous regiochemical effects of a brew containing both *i*-Pr₂NCOOLi and catalytic LiBr.⁴ Metalations of **1** and **2**, however, reveal strong LiCl catalysis, but the regioselectivities (indicated by the arrows) remain unchanged, as expected for reversible metalations.^{4,16,17}



Using standard protocols in which the LDA is unpurified, we observed $>10^2$ -fold swings in the reaction rate depending on the commercial source of the *n*-BuLi or LDA. These variations were not supplier dependent per se, but rather batch dependent. A statistically marginal sampling suggests that commercially available LDA may have a lower LiCl titer and be less prone to inadvertent accelerations compared to LDA generated from commercial *n*-BuLi. Lloyd-Jones noted batch dependencies of aryl triflate metalations that appeared to stem from lithium halides.^{3d} Nonetheless, the variations were enormous, inspiring us to repeat a timeless maxim: buyer beware.

Cursory investigation of the influence of other lithium salts (10 mol %) revealed the accelerations illustrated in eq 2. Clearly, LiCl is the most efficient catalyst.



LiX	k_{cat} (10%)
LiCl	>300
LiBr	90
PhCClLi	90
PhCOOLi	30
PhOLi	2

We have explicitly deferred mechanistic speculation. The dramatic LiCl-mediated accelerations do, however, appear to correlate with arene metalations that are also prone to autocatalysis.¹⁴

In conclusion, LDA/THF/-78 °C-mediated ortholithiations are anomalous in many respects,¹⁴ including a marked penchant for LiCl catalysis. The catalysis is observed in a narrow but potentially consequential window. Unsuspecting academic

chemists may have detected irregularities—batch dependencies—that proved a source of annoyance. The results suggest opportunities to optimize protocols. We believe, however, that industrial chemists should be especially wary of these results. Rate variations that go undetected on small scales could give way to unexpected and potentially costly variations on process and plant scales. Our advice to both communities is the same: try adding a few mole percent of $\text{Et}_3\text{N}\cdot\text{HCl}$ to LDA at the outset.

Experimental Section

Reagents and Solvents. THF and hexane were distilled from blue or purple solutions containing sodium benzophenone ketyl. The hexane contained 1% tetraglyme to dissolve the ketyl. Both *n*-BuLi and LDA were recrystallized.^{6,7} Solutions of *n*-BuLi and LDA were titrated using a literature method.¹⁸ Arenes were either commercially available or prepared via literature protocols.¹⁹ $\text{Et}_3\text{N}\cdot\text{HCl}$ was recrystallized from THF/2-propanol.

IR Spectroscopic Analyses. Spectra were recorded using an in situ IR spectrometer fitted with a 30-bounce, silicon-tipped probe. 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 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 charged with LDA (129 mg, 1.20 mmol) in THF and cooled in a dry ice–acetone bath prepared from fresh acetone. LiCl (0.5 mol % relative to LDA) was added as a stock solution (0.50 mL) containing $\text{Et}_3\text{N}\cdot\text{HCl}$ (8.3 mg, 0.06 mmol) and LDA (13.5 mg, 0.12 mmol) in 5 mL of THF. After recording a background spectrum, we added an arene (1.0 mmol) with stirring. IR spectra were recorded over the course of the reaction. Absorbances corresponding to the arene moieties ($1350\text{--}1650\text{ cm}^{-1}$) were monitored in most cases. Spectra were recorded every 3 s.

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

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