

Preparation, Properties, and Safe Handling of Commercial Organolithiums: Alkylolithiums, Lithium *sec*-Organoamides, and Lithium Alkoxides

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S Supporting Information

ABSTRACT: This review includes the preparation and properties of various organolithiums, which are commercially available, up to manufacturing scale. The interdependent properties, such as pyrophoricity, solubility, stability, and aggregation, are tabulated and discussed. These properties have a direct bearing on their chemical reactivity and requirements for safe handling and storage. Extensive guidance for storage, use, analysis, and disposal of these organolithium solutions is also provided.

■ INTRODUCTION

In the not too distant past, the mention of using organolithiums (RLi) could have prompted the dialogue much like that illustrated by our famous nonchemist friend in Figure 1.¹

Indeed, pyrophoricity, the tendency to ignite spontaneously on exposure to air, is a property that all chemical handlers should know. Unfortunately, when their physicochemical properties and safe handling procedures are assumed to be known by all, instances can (and do) arise that cause serious consequences.² However, today much is known about the efficient chemical utilization³ of organolithium solutions and their safe handling protocols.^{4–6}

Organolithiums provide a diverse selection of uses (Scheme 1) such as nucleophiles in addition (1a) and substitution (1b) reactions, and as lithiating reagents in proton (1c) or halogen (1d) exchange reactions (Scheme 1). The "Substrates" range from monofunctional molecules to polyfunctional macromolecules, from monomers to polymers, and from other organometallics to their metal salts. An even greater diversity of applications of the end products results from these methodologies.

The purpose of this review is to serve as an organolithium resource for their preparation and pertinent physicochemical properties to foster their optimal usage and to provide safe and efficient handling information at any scale.⁷

In this review, the word "organolithium" (RLi) is much more encompassing than normally used. Most often a discussion about organolithiums involves those compounds that possess a lithium–carbon bond and then are compared to similar carbanionic type compounds, usually Grignard reagents, which possess a magnesium–carbon bond. However, we will discuss the three classes of organolithiums as defined by the elements carbon, nitrogen, and oxygen to which the lithium is formerly bonded and designated as CLi, NLi, and OLi, respectively. This approach should provide a broader understanding of organolithiums through the examination of the similarities and differences within each class and between each class. The respective organolithium classes are commonly called

alkylolithiums (CLi), which includes phenyllithium, *sec*-organoamides (NLi), and alkoxides (OLi). In contrast to similar organometallics of other first and second group metals, organolithiums generally possess better solubility and thermal stability in a wide range of solvents, especially and uniquely in hydrocarbon (HC) solvents. As for Lewis base solvents (LB) for CLi, there are only two main classes, ethers and tertiary amines; however, in several instances specific molar amounts of LB are only used. The Lewis base solvent types for *sec*-organoamides (NLi) and alkoxides (OLi) can be extended to include other Lewis bases, such as secondary amines and alcohols, respectively. Therefore, the three classes of organolithiums presented are also based on the types of solvents, hydrocarbon (HC) and Lewis base (LB):

1. Alkylolithiums (CLi) in HC and LB;
2. *sec*-Organoamides (NLi) in HC and LB;
3. Alkoxides (OLi) in HC and LB.

In addition to CLi's, these classes of organolithiums also represent the major categories of products that are commercially available⁷ and, as such, free the end user from the hazardous operation to prepare them from lithium metal.

■ DISCUSSION

Class 1: Alkylolithiums (CLi). For a discussion on commercially available CLi, there are two general types, those dissolved in hydrocarbon solvents (CLi/HC) (Table 1) and those which contain various amounts of Lewis base solvent (CLi/LB) (Table 2).

Preparation and Composition of Alkylolithiums. CLi/HC Availability. Since the early 1960s, hexanes have remained the favorite solvent for CLi because of its applicability to the polymer industry, which was the first large scale use of *n*-

Special Issue: Organometallic Carbanions in Practical Organic Synthesis

Received: May 21, 2014

Published: August 1, 2014

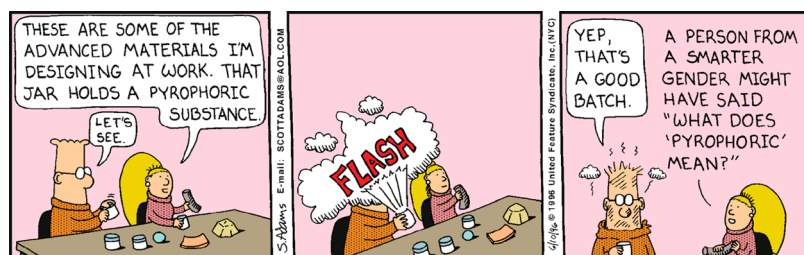


Figure 1. Better first understand the meaning of the words on the label! Reprinted from ref 1. Copyright 1996 UNIVERSAL UCLICK.

Scheme 1. Four primary uses of organolithiums

As a nucleophilic agent:

- a. Addition: $\text{RLi} + \text{Substrate} \rightarrow \text{R-Substrate-Li}$
- b. Substitution: $\text{RLi} + \text{Substrate-X} \rightarrow \text{R-Substrate} + \text{LiX}$

As a lithiating exchange reagent:

- c. proton-metal: $\text{RLi} + \text{H-Substrate} \rightarrow \text{Li-Substrate} + \text{R-H}$
- d. halogen-metal: $\text{RLi} + \text{X-Substrate} \rightarrow \text{Li-Substrate} + \text{R-X}$

Table 1. Typical commercial alkyllithiums (CLi) in hydrocarbon (HC) solvents⁷

CLi/HC	HC solvent	wt %	molarity
<i>n</i> -BuLi	hexanes	15	1.5
		23	2.5
		90	10.7
<i>i</i> -BuLi	heptanes	29	3.2
		20	2.3
		20	2.7
<i>s</i> -BuLi	cyclohexane ^a	12	1.4
<i>n</i> -HexLi ^b	hexanes	33	2.5
<i>t</i> -BuLi	pentanes	17	1.7
	heptanes	18	2

^aWith 5–10 wt % hexanes (or heptanes) added as an antifreeze.

^bNonpyrophoric according to UN testing procedure.⁸

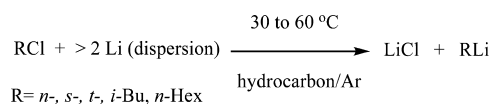
butyllithium. Today the organic synthesis⁹ and polymer industries equally share the annual usage of *n*-butyllithium, estimated at 2000–3000 t per year.¹⁰ Because of the similar boiling points of THF and hexanes, the synthetic industry often prefers to use heptanes as the solvent of choice for *n*-BuLi, especially if recovery of THF would be required. The polymer industry prefers cyclohexane as a solvent, especially for *sec*-butyllithium; however up to 10 wt % hexanes or heptanes are added to lower the freezing point of the solution. In addition to *n*-butyllithium, the isomeric alkyllithiums, *tert*-butyl- and isobutyllithium,¹¹ are also available.⁷ Butyllithium products are offered in several hydrocarbon solvents¹² and at different concentrations (Table 1).

CLi/HC Preparation. The various isomeric butyllithiums and *n*-hexyllithium (*n*-HexLi) are manufactured under argon atmosphere at various optimized temperatures in hydrocarbon solvent from the corresponding alkyl chlorides using a slight molar excess of lithium dispersion to ensure the complete reaction of the alkyl chloride.¹³ The reaction slurry is then filtered and diluted to the desired concentration.¹⁴

In contrast to the preparation of Grignard reagents, whereby the reactant mole ratio of metal to organohalide is 1, the alkyllithium preparation stoichiometry is 2. This mole ratio

comparison explains why alkyllithiums are considerably more costly on a mole basis than the corresponding Grignard reagents. Manufacturers of CLi/HC have continued to seek cost reductions by improvements in the manufacturing protocols. For instance, Na metal alloyed in Li metal is beneficial for initiation of this reaction. The maximum amount of Na metal alloyed into the lithium metal is 0.8 wt %. Additionally, the CLi manufacturers have also shown that less than 1 mol of sodium metal,¹⁵ which is less costly on a mole basis than lithium, may be substituted for some of the required moles of lithium metal (Scheme 2) to aid in cost reduction.

Scheme 2. Preparation of commercial alkyllithiums



However, this has its trade-offs, as lower yields proportionately result, and although less LiCl is present, the recycling of this byproduct becomes more problematic because of the contamination of NaCl.

***n*-Hexyllithium Use.** The alkyllithium manufacturers have added to their product line as new chemistry has emerged to find new uses for alkyllithiums.⁷ For instance, because of end-user safety issues, two improved products, *n*-HexLi and *t*-BuLi, were developed for large-scale manufacturing in the 1990s. The first CLi/HC product is *n*-hexyllithium (*n*-HexLi) at 33 wt % (2.5M) in hexane. There are two major advantages of using *n*-HexLi over *n*-BuLi:

1. *n*-HexLi, even at concentrations up to 85 wt %, in hexane is nonpyrophoric.⁸
2. *n*-HexLi generates *n*-hexane rather than butane in deprotonation reactions, a safer byproduct as it is not a gas and less flammable.

Although many companies are quite capable of handling in situ generated butane, those lacking these capabilities should have less issues handling the *n*-hexane byproduct instead. However, once a company becomes familiar with the handling of *n*-hexyllithium, it is not long until the switch to *n*-BuLi is made as a result of cost considerations. Therefore, a chemist whose desire is to incorporate CLi/HC chemistry into their company's toolbox may want to consider using nonpyrophoric 2.5 M *n*-HexLi as a starting point.

***t*-BuLi Preparation and Use.** The second CLi/HC modification that is notably easier to handle, especially in the lab, resulted from employing a hydrocarbon solvent that has a much lower vapor pressure at ambient temperatures. By changing from pentanes to heptanes solvent, *t*-butyllithium (*t*-BuLi), although still pyrophoric, becomes more manageable when used in laboratory and kilo lab settings since the volatility

Table 2. Commercial alkyllithiums (CLi) at typical concentrations in Lewis base (LB) solvent systems

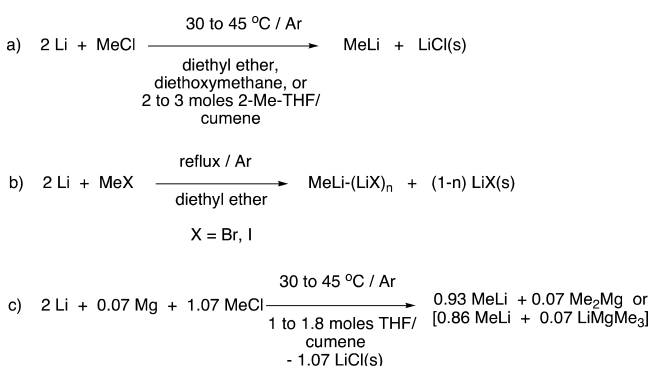
CLi/LB	additive (wt %)	solvent(s) LB/HC	wt % CLi	molarity CLi	LB/CLi ^a	stability data ^b (°C)	ref
MeLi		diethyl ether	5	1.6			7
	LiBr (13)	diethyl ether	3.0	1.1			7
	LiI (15)	diethyl ether	2.5	1.0			7
	Me ₂ Mg (0.5)	THF/cumene ^c	2.6	1.0	1–1.8	0.008 (15)	21
		THF/cumene	3.0	1.4	1.45	0.16 (24)	
		MeTHF/cumene	3.0	1.2	2–2.5	0.17 (40)	18
		diethoxymethane	8	3		0.02 (rt)	10, 19
EtLi		di- <i>n</i> -butyl ether	8	1.7		0.25(20)	25
PhLi		di- <i>n</i> -butyl ether ^c	20	1.9		0.22 (20)	24

^aMole ratio of Lewis base (LB) to MeLi (CLi). ^bAverage wt % loss/day after 30 days at (°C). ^cNonpyrophoric.⁸ Storage recommendation—except for MeLi in diethyl ether compositions, all should be stored between 2 and 8 °C for less than 30 days.

and flammability of the solvent was less of an issue. It should be noted that the trade-off in this solvent switch is that a lower yield is experienced in the preparation of *t*-BuLi in heptanes. The preparation in refluxing pentane (boiling point ~36 °C) always provided good and consistent yields. The yields of *t*-BuLi in heptane are apparently improved by running at reflux but under reduced pressure.¹⁶ Employment of trace amounts of Lewis bases for the preparation of *t*-BuLi in heptane does improve yields, but the resulting solutions tend to have poorer thermal stability.¹⁷

CLi/LB Preparation and Use. For alkyllithiums provided with Lewis bases (CLi/LB), the selection is limited. Methyllithium (MeLi) is the primary CLi in use and is offered in several LB compositions (Table 2). Methyllithium is prepared from methyl chloride and lithium metal in ether solvents such as diethyl ether, 2-MeTHF/cumene,¹⁸ and diethoxymethane (DEM),^{19,10} to produce essentially halide-free (of LiCl) solutions (Scheme 3a). If ethereal MeLi solutions

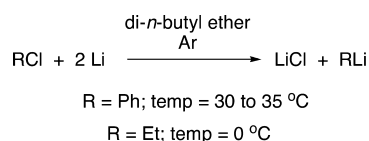
Scheme 3. Preparation of MeLi in various ether solvents (see Table 2 for compositions)



are prepared from methyl bromide or methyl iodide, the resulting solutions will contain the byproducts LiBr or LiI (Scheme 3b and Table 2). MeLi–LiBr in DEM can also be prepared by addition of LiBr to essentially halide-free MeLi solutions made from methyl chloride.²⁰ A composition of MeLi/dimethylmagnesium (Me₂Mg) in THF/cumene (Scheme 3c and Table 2) can be prepared by the reaction of methyl chloride with the required amounts of lithium and magnesium metal²¹ or magnesium halide.²² Because the molar concentration of MeLi is an order of magnitude higher than that of Me₂Mg, the formation of LiMgMe₃ may be possible (Scheme 3c); however, Ashby and Goel have reported that

LiMgMe₃ appears to only exist in an equilibrium mixture with MeLi and Me₂Mg in diethyl ether.²³

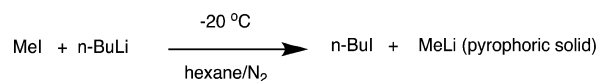
Similar to MeLi, phenyllithium (PhLi) and ethyllithium (EtLi) are prepared from Li metal and the corresponding organochlorides (Scheme 4). PhLi in diethyl ether (DEE) has

Scheme 4. Preparation of PhLi and EtLi in di-*n*-butyl ether

been offered both in the absence and presence of cyclohexane, but because of the volatility of DEE, these formulations are no longer available. However, PhLi in di-*n*-butyl ether²⁴ (DBE) has filled the need for such formulations (Table 2). Unfortunately, the problematic biphenyl impurity (<2 wt %) is still formed during the preparation and requires consideration by the user. Di-*n*-butyl ether has also been used in a formulation with ethyllithium (EtLi).²⁵

Preparation of MeLi Using *n*-BuLi.²⁶ Halogen–metal exchange to achieve lithiation (Scheme 1d) using CLi reagents and appropriate organobromides and iodides is extensively practiced at all preparative levels.²⁷ Because of the facile nature of the halogen-metal exchange reaction, it can also be adapted to continuous flow processes.²⁸ The first synthetic industrial application to use *n*-BuLi involved halogen-metal exchange to prepare a fungicide, fenarimol.²⁹ Typically this methodology is performed in the presence of a LB, but use is also possible in the absence or in the presence of limited LB content. For example, the exchange reaction was effective for the preparation of MeLi as a solid because of its poor solubility in aliphatic hydrocarbons (<0.01 M). Unsolvated MeLi solid, which is pyrophoric, can be prepared by the addition of *n*-BuLi to a hexane solution of methyl iodide at less than –20 °C (Scheme 5).^{21,30}

Please note that the hydrocarbon soluble byproduct, *n*-butyl iodide (*n*-BuI), must be washed out with dry hydrocarbon solvent from the finely divided methyllithium solids²⁶ before dissolution into the desired LB solvent system. Mixing of LB

Scheme 5. Preparation of unsolvated, pyrophoric methyllithium solid²⁶

solvent and unsolvated MeLi is exothermic and will require cooling.³¹ There is also potential inclusion of trace amounts of *n*-butyllithium or LiI in the precipitated methyllithium solids, which will depend on the mixing efficiency and temperature control in its preparation.

In a similar manner, solid PhLi may be initially prepared from bromobenzene and *n*-butyllithium using the same general procedure as that described above for solid MeLi; however, a small amount (<3 mol %) of methyl *t*-butyl ether (MTBE) appears to facilitate the exchange.¹⁷ Again, the same precautions mentioned for solid methyllithium apply for this unoptimized preparation of solid pyrophoric PhLi.³² These halogen–metal exchange procedures have only been practiced at laboratory bench scale, and once in solution, both PhLi and MeLi will cleave ethereal LB solvents as discussed in the Ether Cleavage and Solubility section and as indicated in Table 2.

Structure and Reactivity. CLi/HC. Focusing mainly on the commercially available alkylolithiums (CLi/HC), it is known that organolithiums exist as aggregates in hydrocarbon solvent (HC). The number of CLi molecules per aggregate is called the aggregation number; for instance a tetramer has an aggregation number of four and a hexamer has six (Figure 2). The nature of

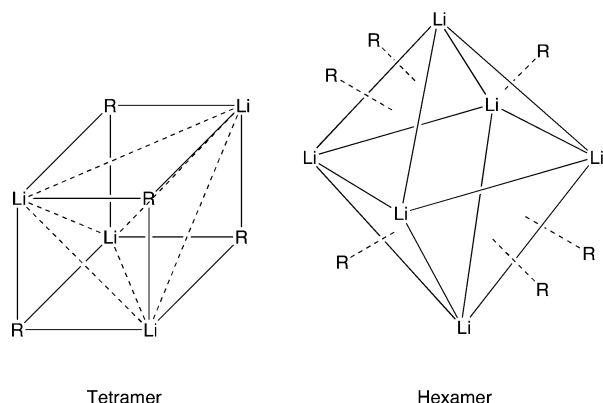


Figure 2. Idealized unsolvated alkylolithium aggregates.

the bonding of alkylolithiums is polar, meaning it is principally ionic with varying degrees of covalent character.³³ In each aggregate, the alkyl group occupies the surface of the polyhedron, being coordinated to three lithium atoms as a four-center two e-bond. For the tetramer, all faces of the tetrahedron are utilized; however, for the hexamer two parallel faces of the octahedron are unoccupied, and thus some distortion results as revealed by X-ray crystallographic analysis.³⁴ The aggregation numbers for the alkylolithiums soluble in hydrocarbons are listed in Table 3. In general, tetramers result from steric interactions of the CLi alkyl groups. In hydrocarbon solvent, *n*-BuLi³⁵ is a hexamer, while the bulkier CLi/HC species, such as *s*-BuLi^{35b,36} and *t*-BuLi,³⁷ are tetramers (Table 3). These aggregates are dynamic, meaning there is constant interchange of individual organolithium molecules between aggregates.³⁸

Historically, the determination of aggregation numbers was based on their colligative properties in solution, such as freezing point depression in benzene and cyclohexane; however, multinuclear NMR techniques bolstered by isotopic enrichment have proved to be useful for studying aggregation and dynamics.³⁹ More recently, the residual quadrupolar couplings technique using ⁷Li and ²H enabled the determination of the degree of association and other properties of CLi and NLi

Table 3. Aggregation numbers for selected organolithiums (CLi and NLi) in hydrocarbon (HC) and Lewis base (LB) solvents

RLi	solvent ^a	aggregation no.	ref
<i>n</i> -BuLi	cyclohexane	6	35a
	DEE	4	42
	THF	4/2	42, 43
<i>s</i> -BuLi	cyclopentane	4	36a
	THF	2/1	45
	TMEDA	4	46
<i>t</i> -BuLi	hexane	4	37a
	DEE	2	34, 44
	THF	1	45
MeLi	DEE	4	42a
	THF	4	42a, 48
	DEM ^b	4	10
LDA	THF	2	72
LHMDS	pentane	2/4	74
	THF	2/1	74
LTMP	pentane	3/4	76
	THF	2/1	77

^aDEE = diethyl ether; LHMDS = lithium hexamethyldisilazide; LTMP = lithium tetramethylpiperidide; DEM = diethoxymethane. ^bPolymeric aggregate, [(MeLi)₄(DEM)_{1.5}]_∞.

organolithiums.⁴⁰ While much has been learned by X-ray crystallography and solid state NMR techniques,¹⁰ there is no guarantee that the aggregation number in the solid state will be the same in solution. However, NMR techniques are closing the gap between solid and solution analyses as demonstrated for a common Li-substrate, 2-thienyllithium.⁴¹ In solution, the assigned aggregation number is an average number for the total population of aggregates. For instance CLi solutions at certain temperatures and concentrations may consist of mixtures of tetramers and dimers. These mixtures are more often observed when organolithiums are in the presence of Lewis bases.

CLi/LB. In the presence of Lewis bases, such as ethers and tertiary amines, the coordination sphere of the polarized Li atom is filled by the donor LB and thus extends the tetrameric and dimeric aggregate as shown in Figure 3. More noteworthy

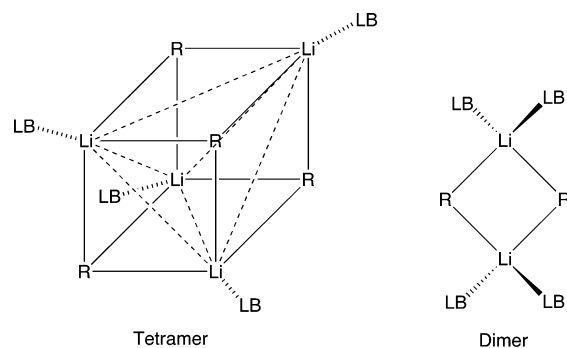


Figure 3. Lewis base (LB) solvated organolithium aggregates.

is that the aggregation numbers for the CLi/LB are usually lower than their corresponding CLi/HC (Table 3). For instance, hexameric *n*-BuLi in hydrocarbon becomes a tetramer in diethyl ether⁴² and a tetramer and dimer in THF,^{42,43} whereas *t*-butyllithium goes from a tetramer as a solid³⁴ and in hydrocarbon solvent³⁷ to a dimer in diethyl ether^{34,44} and a monomer in THF at < −100 °C,⁴⁵ showing the effect of

temperature. The most notable exception is found in MeLi. MeLi is basically insoluble in aliphatic hydrocarbon and as an unsolvated solid is a polymeric tetramer.⁴⁷ In the presence of ethers, such as THF,⁴⁸ MeLi becomes a tetramer in solution and as a solvated solid, (MeLi-THF)₄.⁴⁹

With regards to MeLi in DEM, a soluble microporous polymeric aggregate, $[(\text{MeLi})_4(\text{DEM})_{1.5}]_\infty$, results.¹⁰ Other bidentate donor solvents, such as TMEDA, form polymeric arrays with MeLi,⁵⁰ which, unlike $[(\text{MeLi})_4(\text{DEM})_{1.5}]_\infty$, lack solubility. Yet monodentate donors have also led to solids for certain organolithiums that were polymeric aggregates. For example, cooling a solution of monomeric benzylolithium^{42a} in THF/toluene produced a solid polymeric aggregate in which the backbone is comprised of alternating α -carbon and lithium atoms with the latter solvated by two THF molecules.⁵¹

Mixed Aggregates. Unlike Lewis bases which are located on the periphery of the aggregate, lithium compounds, often called modifiers, can be incorporated into the CLi aggregate itself. If so, they will displace an existing CLi entity to form a mixed aggregate. These modifiers can be compounds from the three classes of CLi, NLi, and OLi, as well as lithium halides, hydroxide, and even oxide. This exchange obviously decreases the aggregation number of the original CLi complex and may change the total number of alkylolithium species remaining in the aggregate. In this manner, the solubility of the lesser soluble lithium compound is enhanced by inclusion into the mixed aggregate, which provides avenues for interesting synthetic applications. For instance, in situ formed lithiated substrates, which are formed via the reaction between the strongly basic alkylolithiums and the conjugate acid of the substrate, are incorporated into a mixed aggregate as the lithiation reaction proceeds (Scheme 1c). This may also occur for addition reactions (Scheme 1a). Formation of mixed aggregates, often a consequence of the order of addition, can be either advantageous or detrimental and must be understood in order to optimize the chemical outcome of the desired reaction. Furthermore, the lithium byproducts of substitution reactions (Scheme 1b) may influence any subsequent reaction by their association into the reactant aggregate as well.

Reactivity of Organolithiums. As would be expected, especially for proton-metal exchange reactions, the reactivity of organolithiums is a function of their aggregate number and innate basicity of the anion itself which is a result of its inductive and electronegative effects. Generally lowering the aggregation number increases the reactivity, but the real goal is to modify the aggregate for the desired selectivity. It is important to keep in mind that the reduction of the aggregation number by a Lewis base solvent molecule increases the effective concentration of the organolithium as the number of aggregates per unit volume increased. Although quite helpful for selection of a strong base, relative basicity rankings⁵² of organolithiums, based on estimated pK_a 's of their conjugate acids, should be viewed only as a qualitative listing (Figure 4), because many factors will influence this property.

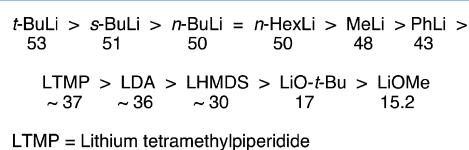


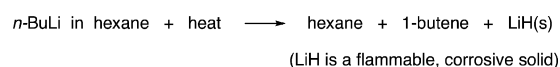
Figure 4. Basicity ranking based on pK_a 's of their corresponding conjugate acids.⁵²

In summary, the reactivity of organolithiums is not only a function of temperature, concentration, and the molecular structure of the individual organolithium molecule itself but also is influenced by the structure and composition of its aggregate that may include coordinating Lewis bases, other lithium compounds, or even other metal cations and their associated anions, such as for the Lochmann-Schlosser base.⁵³ As would be expected, these factors also influence the solubility and thermal stability of CLi and NLi reagents.

Solubility and Thermal Stability. CLi/HC. Alkylolithiums have excellent solubility in hydrocarbons, which is evidenced by the commercial availability of *n*-butyllithium in concentrations up to 90 wt % (10.7 M) (Table 1).⁵⁴

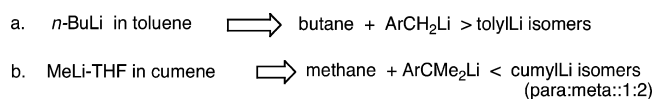
Thermal Stability. The major route of degradation of commercial alkylolithiums in HC is β -hydride elimination to form alkenes and LiH. Thus, the degradation products for *n*-BuLi are 1-butene, which is very soluble in the hydrocarbon solvent and produces very little increase in pressure, and LiH, which is insoluble and forms as a finely divided grayish powder. The LiH is usually the primary hazard of alkylolithium solution degradation as it is a flammable corrosive solid (Scheme 6).⁵⁵

Scheme 6. Thermal degradation products of *n*-butyllithium



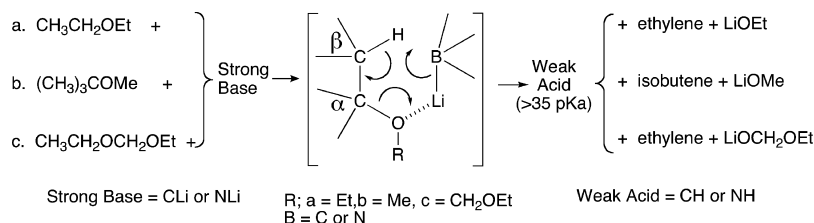
Specific decomposition data are provided in the Storage Requirements section and Table 8. As seen in Table 1, the only CLi/HC formulation to have further stability issues is *n*-butyllithium in toluene. In addition to elimination of LiH, *n*-BuLi slowly lithiates toluene to produce benzylolithium (ArCH_2Li) and minor amounts of tolylithium isomers (Scheme 7a). Exclusion of air is vital to prevent formation of LiO*t*Bu, which will increase LiH elimination as well as promote lithiation of the toluene.

Scheme 7. Metalation of aromatic solvents used for alkylolithiums



CLi/LB. For alkylolithiums such as MeLi, PhLi, and EtLi that are provided in ethereal solvents (CLi/LB) (Table 2), their viability is challenged by a different set of issues than those prepared in aliphatic hydrocarbon. The first issue is that these alkylolithiums possess insufficient solubility in aliphatic hydrocarbon solvent but are very soluble in ethers. This leads to the second issue that strongly basic alkylolithiums, i.e., pK_a greater than 35, will attack their Lewis base solvents. However, because of the variety of available ethers and knowledge of their association properties, several formulations have been developed over the years that overcome these problems.

MeLi in LB. Commercial MeLi solutions have evolved through a series of compositional changes (Table 2). Suppliers took an unexpected direction in that MeLi compositions began to incorporate the labile solvent THF but only in limited molar quantities (1.3–1.8 equiv).²¹ The MeLi-THF tetramer incorporates an equal molar amount of THF into its aggregate (Table 3). Thus, the additional 0.3 to 0.8 mol of THF must solubilize the aggregate itself and could be an indication of what

Scheme 8. Strong base cleavage of diethyl ether (a), methyl *t*-butyl ether (b), and diethoxymethane (c) via β -elimination

Collum has noted as the “secondary shell effect.”⁵⁶ Some compositions also include the use of an aromatic cosolvent such as cumene, which will be metalated (Scheme 7b) but at a slower rate when compared to toluene or ethylbenzene. A solubility trend for aromatic solvents is observed for the (MeLi-THF)₄ aggregate in that the solubility decreases rapidly as the size of the alkyl group on benzene increased. For instance, the solubility is maximized at 1.8 M in benzene and decreases to 1.1 M in cumene when these are used as cosolvents with THF. To show the dramatic effect of aromatics, when cyclohexane is used as the cosolvent instead of cumene, the solubility of the MeLi is 0.24 M even in the presence of additional THF. The MeLi/THF/cumene composition also includes 7 mol % of Me₂Mg, which significantly improved both the thermal stability and solubility of MeLi.

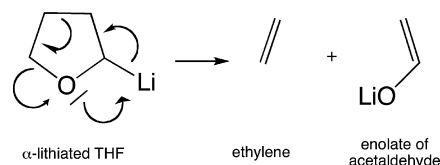
Expanding on the concept of limiting the percent of Lewis base in cumene, a more stable MeLi composition results when 2-methyltetrahydrofuran (MeTHF) is used instead of THF.¹⁸ For example, improved thermal stability is obtained when using 2–2.5 mol amounts of MeTHF per mole of MeLi, without the need for Me₂Mg as a stabilizer (Table 2). Further stabilization is most likely possible by the addition of LiBr to the same MeLi/MeTHF composition.

In the search for more stable Lewis base solvents, diethoxymethane (DEM) alone provides stable solutions of methylolithium and vastly increases the solubility as high as 3 M (8 wt %).¹⁹ Recently, a process to make MeLi–LiBr in DEM was reported.²⁰

PhLi and EtLi. The thermal stability data for PhLi²⁴ and EtLi²⁵ in di-*n*-butyl ether are listed in Table 2. With the noted thermal stability improvements of using LiBr and DEM in MeLi formulations, these modifiers may be useful for stabilizing PhLi and EtLi and other organometallics as well.

Ether Cleavage and Solubility. Alkylolithiums (CLi) and *sec*-organoamides (NLi) possess sufficient basicity to lithiate and thus cleave various ethers, especially at elevated temperatures. More importantly, the cleavage process is greatly accelerated when the molar amount of ethers exceed those prescribed in the commercial compositions.⁵⁷ Although an oversimplification, β -lithiation of LB solvents, such as DEE and MTBE, result in cleavage to form ethylene gas and lithium ethoxide (Scheme 8a) or isobutene and lithium methoxide (Scheme 8b), respectively. Presumably, DEM undergoes the same fate (Scheme 8c) because its thermal stability is recorded as 0.02 wt % loss of MeLi per day at room temperature (Table 2).

THF Cleavage. For THF solvent, this LB undergoes α -lithiation, which subsequently fragments via a concerted cycloreversion process to produce volatile ethylene and the enolate of acetaldehyde (Figure 5), but the mechanism is more complex than illustrated. In addition, adducts of *n*-BuLi and ethylene have been observed⁵⁸ and the kinetic studies of this fragmentation pathway revealed that the order with respect to THF was 2.5.⁵⁹ Interestingly, this reaction is a methodology to

Figure 5. Simplified fragmentation of α -lithiated THF.

make amine free enolates. For instance, the Bates group reported the conversion of several methyl substituted THF derivatives to their predicted enolates.⁶⁰ In this same study but using the ethers in excess, THF cleavage was ten times faster than MeTHF based on the observed half-lives at 35 °C. Thus, CLi's and NLi's, which cause α -lithiation of THF derivatives, would be anticipated to be more stable in MeTHF; however hydrocarbon cosolvents, preferably alkylaromatics, are still required to achieve a viable commercial composition.

MeTHF Cleavage. In addition to greater thermal stability, MeTHF may also provide an additional advantage for a MeLi/MeTHF/cumene compositions (Table 2). For instance, storage of MeLi/THF/cumene below 0 °C eventually forms (MeLi-THF)₄ crystals that can be easily redissolved with agitation and warming to room temperature.²¹ Similarly, crystallization during cold storage was also observed with benzylolithium in THF, but when MeTHF was used in place of THF, the appearance of benzylolithium–MeTHF solids was markedly decreased and the thermal stability notably increased.^{51a} In fact, even a 2:1 mixture of MeTHF:THF provided ample solubility and thermal stability for benzylolithium solutions. Apparently, the racemic solvent MeTHF provides enough spatially arranged variations of solvated aggregates, even if oligomeric, and thereby decreases the possibility for crystallization to occur. Thus, in addition to the other benefits of using MeTHF,⁶¹ this racemic solvent may provide an anticrystallization effect at low temperatures by providing an array of uniquely solvated aggregates in solution.

DEM Stability. The use of diethoxymethane (DEM) has been shown to vastly improve the thermal stability and solubility of MeLi (3M) (Table 2).^{10,19} Although the degradation products have not been reported for this composition, most likely DEM undergoes β -elimination as other ethers (Scheme 8c). An explanation for this enhanced stability may be that LiOCH₂OEt is less favorable as a leaving group as compared to the other alkoxides (Scheme 8a–b). However, the enhanced stability of MeLi in DEM may also be related to its unique aggregate structure, [(MeLi)₄(DEM)_{1.5}]_∞. Because of the proximity of the oxygen donor atoms of each DEM molecule, each oxygen coordinates with a Li atom of a different MeLi to create a microporous structure, which allows the resulting channels to be filled with solvent and thus provide solubility.¹⁰

Class 2: *sec*-Organoamides (NLi). For this class of organolithiums (NLi), those which lack steric bulk may be

Table 4. Commercial lithium *sec*-organoamides (NLI) in Lewis base/hydrocarbon (LB/HC) solvents

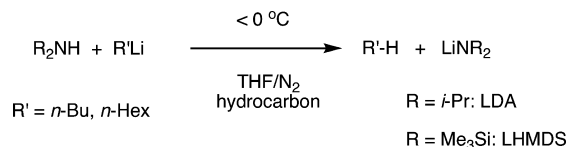
NLi	additive (wt %)	solvent(s) LB/HC	wt % NLi	molarity NLi	LB/NLi ^a	stability data ^b	ref
di-isopropyl-amide ^c (LDA)		THF/PhEt	26	2.0	0.8:1	0.2 (27)	66
	MDA (2.8)	THF/PhEt/heptane	26.5	2.0	1.5	0.05 (15)	67
		THF/PhEt/heptane	28	2.1	2.4:3	0.1 (23)	7
hexamethyl-disilazide ^c (LHMDS)		THF ^d					7
		none (solid)	>95				7

^aMole ratio of Lewis base (LB) to LDA. ^bAverage wt % loss/day after 30 days at (°C). The stability is very dependent on the amount of free di-isopropylamine. ^cNonpyrophoric. ^dByproduct, 2-methyl-2-butene, can be removed. MDA = magnesium bis(di-isopropylamide). Storage recommendation—LDA should be stored at less than 10 °C for less than 30 days. For more information see ref 7.

used as nucleophiles in useful addition reactions^{62a} (Scheme 1a) and substitution reactions⁶³ (Scheme 1b). In contrast, sterically hindered *sec*-organoamides are most often useful as strong bases to achieve lithiation of acidic sites (Scheme 1c). Mulvey and Robertson recently reviewed the properties and utility of the alkali (Li, Na, K) amides of di-isopropylamine (DIPA), hexamethyldisilazane (HMDS), and tetramethylpiperidine (TMP).⁶⁴ These lithium amides, in combination with other metal amides such as those of magnesium, zinc, or aluminum form “ate” complexes and provide a complementary class of metalating agents.⁶⁵

NLi/LB. There are only two commercial NLi/LB formulations available because the respective amines, DIPA and HMDS, are the most commonly used sterically hindered *sec*-amines (Table 4). Thus, the available NLi/LBs are lithium di-isopropylamide (LDA)^{66,67} and lithium hexamethyldisilazide (LHMDS).⁷

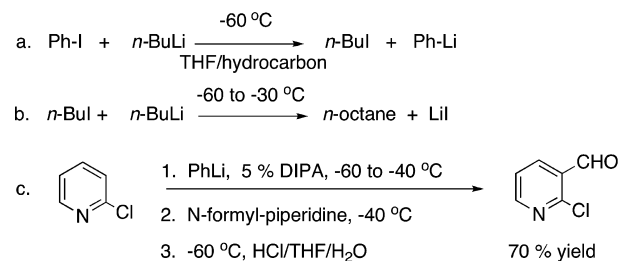
Preparation from *n*-BuLi. The most common NLi entity is lithium di-isopropylamide (LDA). This strongly basic and weakly nucleophilic NLi is conveniently prepared by the addition of *n*-butyllithium (*n*-BuLi/HC) to a slight molar excess of di-isopropylamine in an ethereal solvent, usually THF, at ≤0 °C (Scheme 9) and should be used immediately.⁶⁸ In practice,

Scheme 9. Convenient preparation of *sec*-organoamides from *n*-BuLi or *n*-HexLi

most often the H-substrate (Scheme 1c) is added to an LDA solution to form the Li-species, which is subsequently treated with an electrophile. Both of these steps often require identification of an optimum reaction temperature range, which could be different. This methodology has been practiced widely in academia since the 1960s but was not extensively used in industrial processes until the early 1980s.

Another procedure is to add a lithiation reagent, CLi, to an appropriately cooled solution of substrate, which contains less than one equivalent of di-isopropylamine. This methodology was apparently first reported using catalytic DIPA (5 mol %) and one equivalent of PhLi to achieve 3-lithiation of 2-chloropyridine (Scheme 10c).⁶⁹ The PhLi solution is first generated from iodobenzene and two equivalents of *n*-BuLi.⁷⁰ The resulting PhLi is then added to a solution of 2-chloropyridine containing a catalytic amount of DIPA. As the PhLi is added, LDA is rapidly formed and subsequently effects lithiation of 2-chloropyridine to produce the desired 3-lithiopyridine species.

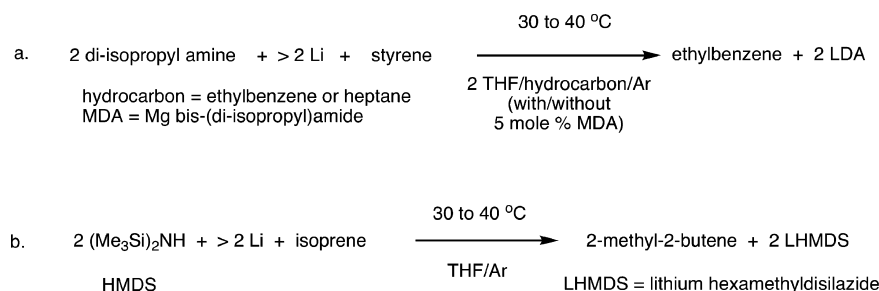
Scheme 10. 3-Lithiation of 2-chloro-pyridine using catalytic DIPA and in situ generated PhLi



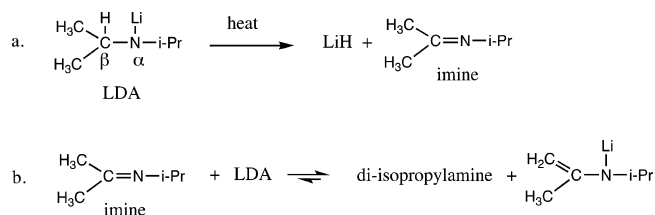
This procedure has the obvious problems of the generation of the byproducts benzene and lithium iodide. However, the formation of LDA using catalytic amounts of DIPA in the presence of substrate might be adapted to other processes that could use *n*-BuLi instead of the often problematic PhLi.

Preparation from Li Metal. Commercial NLi/LBs are prepared directly from lithium metal (two moles) and a “diene” (one mole), which is either styrene or isoprene (Scheme 11a-b). The “diene” is referred to as an electron carrier and is reduced by the Li metal and protons from the *sec*-amine (two moles) to give the *sec*-organoamide (two moles) and ethylbenzene or 2-methyl-2-butene, respectively. One of the reasons manufacturers of LDA and LHMDS use the metal route is because one mole of metal theoretically produces one mole of *sec*-organoamide whereas using *n*-BuLi to make the same *sec*-organoamide indirectly requires two moles of lithium metal or twice as much lithium metal (Scheme 2).

Although the lithium metal route, using conjugated dienes, has been known for some time,⁷¹ these methods produced solutions of LDA, which lacked sufficient thermal stability to be offered as a commercial product. However, by adjusting the preparative procedure^{66,67} so that the resulting molar THF:LDA ratio is approximately 1, a thermally stable and nonpyrophoric 2 M solution is achieved, presumably because the THF that is present is also an integral part of the (LDA-THF)₂ dimer⁷² (Table 3). Styrene is used to make LDA as the resulting ethylbenzene aids the solubility of this *sec*-organoamide, while isoprene has become the diene of choice for LHMDS because the resulting 2-methyl-2-butene can be removed by vacuum distillation. Additionally, because LHMDS is considerably more thermally stable than LDA, LHMDS solid is isolable from solution (Table 4). In fact, the exceptional stability of LHMDS was demonstrated by the preparation of all HMDS organoalkali's directly from the corresponding alkali metal at elevated temperatures in the presence of an iron catalyst without the need for a diene.⁷³ The stability of LHMDS, which has various aggregate states,⁷⁴ results from its lack of basicity to attack THF. In addition, this hindered base does not possess any β-hydrogens; thus the

Scheme 11. Preparation of *sec*-organoamides directly from lithium metal

elimination of LiH cannot occur, as is a problem for LDA (Scheme 12a). The imine degradation product of LDA also

Scheme 12. Thermal degradation of *sec*-organoamide, LDA

undergoes lithiation with LDA (Scheme 12b) especially when the THF/LDA mole ratio is less than 1.⁶⁷ As would be expected, a higher excess of di-isopropyl amine always improves the stability by suppression of the (THF + LDA) lithiation equilibrium, which forms α -lithio-THF that subsequently fragments via cycloreversion (Figure 5).⁶⁶

Stabilization. Analogous to the MeLi/Me₂Mg composition described earlier, in which the latter has been shown to significantly improve the thermal stability,²¹ the addition of 5 mol % magnesium bis(di-isopropylamide), MDA, was found to also improve the cold temperature (0–5 °C) solubility of LDA. Other more obvious methods of stabilizing an LDA solution have been investigated, such as adding LiBr^{67,75} or substituting MeTHF for THF. Finally, the variability of aggregate numbers for this class of organolithiums (NLi) is easily seen for LDA,⁷² LHMDs,⁷⁴ and LTMP,^{76,77} (Table 3). This variability emphasizes the need to pay close attention to the parameters

that affect aggregation states whether trying to stabilize an NLi species or to optimize a lithiation (Scheme 1c).

Reduction of Lewis Base. Interestingly, large-scale end users of organolithiums that employ ethereal solvents also try to limit the volume of these solvents, often driven by economic considerations. This encourages producers of commercial organolithiums containing ethereal solvents to do the same in order to produce a viable commercial reagent. Users of these two classes of commercial products (CLi/LB and NLi/LB) often use the delivered organolithium without further dilution, which often improves throughput. Also using lower molar amounts of ethereal solvents in chemical reactions involving highly basic organolithiums may permit higher reaction temperatures, which could lower the cost of cooling on commercial scale. The next section (NLi/HC) addresses the possibility of using NLi in the absence of ethereal solvent.

NLi/HC. Although not commercially available, hydrocarbon soluble lithium *sec*-organoamides (and primary organoamides) have been reported (Table 5).^{78,79} These ether-free *sec*-NLi compositions offer the opportunity to investigate lithiation methodologies (Scheme 1c) in hydrocarbon solvents and thus exclude the effects derived from ethereal solvents. Because of the absence of labile ethers, higher temperatures of preparation are permitted (Scheme 13)

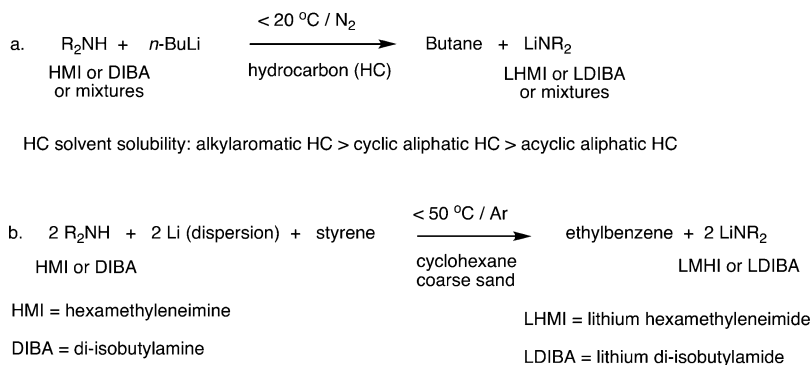
NLi/HC Preparation. Although only a few compositions are reported, these NLi/HC formulations may be prepared from *sec*-amines and hexamethylenimine (HMI), and *n*-butyllithium,^{78,79} or from Li metal and styrene⁸⁰ (Scheme 13a and b). For this discussion, N-lithiated HMI is named as lithium hexamethyleneimide (LHMI).

Table 5. Solubility of lithium *sec*-organoamides (NLi) in hydrocarbon solvents (HC) at 20 °C^a

NLi	<i>sec</i> -organoamide	NLi mol %	solvent	NLi molarity
LHMI	hexamethyleneimide ^b		toluene	>2.2
			cyclohexane	>1.6
			heptane	0.7
LDIBA	di-isobutylamide		toluene	1.44
			heptane	1.08
LDA	di-isopropylamide		toluene	0.49
			heptane	0.42
LDMAPA	dimethylaminopropylamide ^c		heptane	1.1
LDEAEA	diethylaminoethylamide ^c		toluene	>2.2
			heptane	>1.4
LHMI	hexamethyleneimide ^b and di-isopropylamide	20	cyclohexane	>1.6
LDA		80		
LHMI	hexamethyleneimide ^b and di-isobutylamide	20	heptane	>1.4
LDIBA		80		

^aSee refs 78 and 79. ^bPrepared from cyclic hexamethylenimine (CAS No. 111-49-9). ^cPrimary organoamide.

Scheme 13. Preparation of hydrocarbon soluble hexamethyleneimide and di-isobutylamide



Solubility. NLi/HC display a general solubility trend involving three types of hydrocarbon solvents: alkylaromatics (toluene is the best) > cyclic aliphatic hydrocarbons (cyclohexane) > acyclic aliphatic hydrocarbons (heptanes). Cyclic lithium hexamethyleneimide (LHMI) has a good solubility in toluene (2.2M), while the lithium pentamethyleneimides (piperidides) are considerably less soluble. For instance, the low hydrocarbon solubility for the 6-membered amide, tetramethylpiperidide (LTMP), was calculated to be 0.12 M in pentane/hexane at 0 °C.⁸¹ Of those reported, di-isobutylamide apparently has the best solubility of the dialkylorganoamides (1.44 M toluene; 1.08 M heptanes), while LDA's solubility in toluene and heptanes is reported at 0.49 and 0.42 M, respectively.⁷⁸ However, the results of a preparation from lithium and styrene indicated that LDA was more soluble in cyclohexane than ethylbenzene. Therefore, compared to toluene, the additional methylene (CH_2) group of ethylbenzene reduced the solubility of LDA. This same trend of lower solubility was observed for MeLi/THF in that changing from toluene to cumene decreased the solubility.^{21,22} Also, compared to MeLi, which is essentially insoluble in hexane or toluene (<0.01 M), LDA's low solubility in hydrocarbons may explain why only one equivalent of THF is sufficient for the solubilization of the $(\text{LDA-THF})_2$ dimer (Table 3 and Figure 3).

Another NLi/HC series involves primary organoamides having a terminal dialkylamino group.⁷⁹ The two most soluble dialkylaminoalkylamides reported are dimethylaminopropylamide (1.1 M in heptane) and diethylaminoethylamide (>1.4 M in heptane) (Table 5). The last four entries of Table 5 also demonstrate the tendency of NLi/HC to form mixed aggregates. For these two organoamide/imide mixtures, the more soluble organoamide or imide apparently enhances the solubility of the lesser soluble species by inclusion into a mixed aggregate.

Finally, although an NLi/LB example, there are two dialkylamides which have excellent solubility in its corresponding amine solvents but poor solubility in hydrocarbons. These are lithium dimethylamide in dimethylamine (3.27 M at -10°C) and lithium diethylamide in diethylamine (3.83 M at 25.5°C).⁸²

Uses. Although no thermal stability data are provided for any NLi/HC, the chemical utility of dimethylaminopropylamides in ethynylations has been amply demonstrated.⁷⁸ Also, a good example of using a primary lithium organoamide in hydrocarbon as a nucleophile has been reported.^{62b,c}

Class 3: Lithium Alkoxides (OLi). Compositions and Preparation. Three lithium alkoxides are currently commer-

cially available in solution or as solids (>99% purity). Typical product concentrations and solvents are as follows: lithium methoxide (10 wt % or 2.2M) in methanol, lithium isopropoxide, usually in heptane (less than 4M), and lithium *t*-butoxide (20 wt %, 2.2M) in THF (Table 6). Lithium

Table 6. Commercial lithium alkoxides (OLi) in solution or as a solid^a

OLi	solvent	wt %	molarity or solid	CAS No.
LiOMe	MeOH	10	2.2	865-34-9
		>99	solid	865-34-9
LiO- <i>i</i> -Pr ^b		>98	solid	2388-10-5
LiO- <i>t</i> -Bu	THF	20	2.2	1907-33-1
		>99	solid	1907-33-1

^aRockwood Lithium data sheets.⁷ ^bSolution available most likely in THF (<30 wt %) or heptanes (<38 wt %).

alkoxides are most often prepared from the corresponding alcohol using either lithium metal or, more conveniently, *n*-butyllithium. In either case, appropriate precautions must be taken during their preparation to handle the byproducts of hydrogen gas or butane, respectively. When using *n*-butyllithium, there is always a possibility of trace amounts of lithium *n*-butoxide being present.

Solubility Comparisons. A general knowledge of lithium alkoxide solubility is important when considering their use or even their methods of preparation. Lithium alkoxides show similar solubility trends as those of *sec*-organoamides. The most noteworthy similarity is that both methoxide and ethoxide exhibit greater than 2 M concentrations in their corresponding alcohols (Table 7) while dimethylamide and diethylamides possess greater than 3 M concentrations in their corresponding amines. In the limited comparison of "linear" or *n*-alkyl series, (methyl, ethyl, *n*-butyl-) the alkoxide solubility in their corresponding alcohol increases while the corresponding *sec*-organoamide concentrations decrease (Table 7).⁸² The solubility of the same *n*-alkoxides in ethers or aliphatic hydrocarbons is low. Although there is a slight increase in solubility as the chain length of the *n*-alkoxide increases, there is even less increase with temperature. Noteworthy is the inverse solubility of lithium methoxide in methanol as a function of temperature. This observation serves as a reminder of this occasional solubility reversal for lithium compounds.

Branched Alkoxides. On the other hand, branched lithium alkoxides, such as lithium isopropoxide, lithium *sec*-butoxide, and lithium *t*-butoxide, exhibit the reverse trend in that they are much less soluble in their own alcohol and very soluble in

Table 7. Solubility of lithium alkoxides (OLi) in various alcohols, ethers, and heptanes^a

OLi	alcohol	ether	heptanes	wt %	M	°C
LiOMe	methanol			12.7	2.90	0
	methanol			10.3	2.17	71
		DEE		0.04		25
			heptanes	0.00	0.00	26
LiOEt	ethanol				2.40	26
		DEE			0.035	25
			heptanes		0.05	26
LiO- <i>n</i> -Bu	<i>n</i> -butanol				5.14	26
			heptanes		0.25	25
LiO- <i>i</i> -Pr	isopropanol				0.05	41
	<i>t</i> -butanol				0.26	30
LiO- <i>i</i> -Bu			heptanes		3.78	23
	isobutanol				0.13	22
		DEE			2.11	23
		THF			2.30	27
			heptanes	45.3	4.33	23
LiO- <i>sec</i> -Bu	<i>sec</i> -butanol				0.28	20
			heptanes	81.0	7.98	25
LiO- <i>t</i> -Bu	<i>t</i> -butanol				0.15	23
		DEE			0.28	23
		THF		22.1	2.45	20
			heptanes	11.4	0.99	23

^aSee ref 82. DEE = diethyl ether.

hydrocarbon and ethers, of which THF was the best solvent of those examined. Perhaps the high solubility of lithium *sec*-butoxide (8 M in heptane) is the reason for using *sec*-butanol as the titrant in the Watson–Eastham analysis for alkyllithiums and various lithium organoamides.⁸³ In addition, the solubility of lithium isopropoxide makes isopropanol a good proton source for quenching highly basic organolithiums in hydrocarbon solution that have not undergone thermal degradation.

Aggregation. The aggregation states for lithium alkoxides are very dependent on temperature, concentration, and solvent type. The most studied alkoxide, lithium *t*-butoxide, can display several aggregation states. For instance, lithium *t*-butoxide (0.06–0.3 M) in cyclohexane (or hexane)⁸⁴ is a hexamer at 30 °C and a tetramer in THF under similar conditions.⁸⁵ Using more dilute and colder conditions, a less stable octamer of lithium *t*-butoxide was reproducibly prepared by a slow purge of dry air or O₂ into a hydrocarbon solution of *t*-BuLi.⁸⁶ Also association of lithium alkoxides with other lithium compounds was well demonstrated by Kamienski and Lewis⁸² by the addition of various amounts of *n*-butanol to different concentrations of *n*-butyllithium in *n*-heptane. As long as the lithium *n*-butoxide concentration, which alone in *n*-heptane has a maximum concentration of 2.8 wt % (0.25M) at 25 °C (Table 7), did not exceed the concentration of *n*-BuLi, the former stayed in solution. The highest determined concentration of lithium *n*-butoxide in a 1:1 molar ratio with *n*-BuLi was 9 wt %, but presumably higher concentrations could be achieved.

Uses. The use of lithium alkoxides as CLi modifiers for selective lithiations⁸⁷ and addition⁸⁸ reactions have been reported. Alkoxides, especially alkali metal methoxides, have been used frequently for the production of plastic additives.⁸⁹

Safe Handling of Organolithiums. Plan the Experiment. In spite of the hazards described so far, the reactivity of organolithium compounds can be handled safely. Indeed, with proper planning and appropriate equipment on the part of the

experimenter, organolithium compounds can be safely handled in the research and kilo laboratories, pilot plant, and commercial-scale production facilities. Proper precautions must be taken against the principal hazards of organolithium compounds: flammability, corrosivity, and in certain instances, pyrophoricity. There are a number of circumstances that must be avoided in dealing with organolithium compounds: contact with air, oxygen, moisture, water, heat, a source of ignition (spark) and fuel. It is prudent to always maintain a neat experimental area as well with a minimum of clutter.

To use them safely at any scale, the experimenter should obtain and carefully review a copy of the Material Safety Data Sheet (MSDS) supplied by the vendor of the organolithium compound to be used. The MSDS will contain the most up to date recommendations for handling and storage of the organolithium compound, particularly in view of the different properties that various solvents may introduce. Furthermore, the MSDS will contain additional recommendations on personal protective equipment (PPE) and firefighting equipment. Order the appropriate equipment prior to initiating any experimental protocol. The experimenter should have received proper laboratory safety training, including specific training regarding the safe handling of organolithium compounds.

Location. The first consideration in planning the experiment is location; where to conduct the experiment. In a research or kilo laboratory environment, it is highly advisable to conduct the experiment in an efficient fume hood to minimize personnel exposure. The hood should be free of clutter as this will render it easier to maneuver about the glassware and simplifies cleaning up a spill or extinguishing a fire in the event of an accident. The fume hood will also sweep away vapors more effectively in the absence of clutter. Combustible materials, such as extraneous solvents, flammable chemicals, and combustible materials should not be present. These are all potential fuel sources that can contribute to the intensity of a fire in the event of a spill of an organolithium. In a pilot plant or commercial scale facility, it is also important to minimize clutter and remove fuel from the vicinity of the reactor train that will be employed. The reasoning is the same: remove potential fuel sources and maximize access to permit fighting any fire.

The fume hood must be equipped with a source of inert gas. A delivery system to distribute the inert gas to the reactor, such as a manifold or plastic tubing, with a bubbler system is also required. Nitrogen or argon can be employed as the inert gas in reactions that employ organolithium compounds, and an in line bubbler will allow a slight pressure of gas on the reaction without the danger of overpressurization. Typically, nitrogen is available in several grades from the supplier, and it is advisable to purchase the tank with the lowest moisture and oxygen content. Argon must be utilized in reactions where lithium metal is a reactant as nitrogen reacts exothermically with lithium metal to form lithium nitride (Li₃N).⁹⁰ Furthermore, this reaction is catalyzed by moisture.

The equipment employed in the reaction must be free of moisture and oxygen prior to the introduction of the organolithium compound. Equipment, such as a drying oven or a heat gun, is required to dry the required glassware prior to the experiment. There are several techniques routinely employed to prepare an inert and moisture free apparatus for an organolithium reaction in the laboratory. One technique is to assemble the glassware in the hood, attach the inert gas line, evacuate the apparatus with a vacuum source, heat the apparatus with a heat gun for several minutes, close the inlet

Table 8. Average % active alkyllithium lost per day for commercial alkyllithiums in hydrocarbon solvent

storage temperature (°C)	<i>n</i> -butyllithium 23% in hexane	<i>n</i> -butyllithium 90% in hexane	<i>s</i> -butyllithium 12% in cyclohexane	<i>n</i> -hexyllithium 33% in hexane	<i>iso</i> -butyllithium 16% in heptane	<i>t</i> -butyllithium 16–18% in pentane
0	0.0001	0.0005	0.003	0.0001	0.02	
5	0.0002	0.0011	0.006			
10	0.0004	0.0025	0.012	0.0004		
20	0.0018	0.013	0.047	0.002		0.0005
23					0.1	
35	0.017	0.11	0.32		0.15	0.004

to the vacuum, and then refill the apparatus with the inert gas. The vacuum/inert gas cycle should be repeated several times. A popular alternative is to assemble the glassware in the hood, attach the inert gas line, start the flow of gas, heat the apparatus with a heat gun for several minutes and then let it cool to room temperature in a stream of the inert gas. One additional technique for glassware drying/inerting is to place the individual glassware components in an oven to dry. The glassware should remain in the oven for at least 4 h at 125 °C, then assembled hot in the fume hood, and allowed to cool to room temperature in a stream of inert gas. Alternatively, the dried glassware components can be removed from the oven, placed in a desiccator to cool to room temperature, assembled in the hood, and then purged with the inert gas. Open flames are no longer recommended for drying glassware.

In larger pilot plant or production equipment, the equipment can be dried and inerted by applying heat to the jacket of the reactor and vacuum to the equipment itself, isolation of the vacuum, and releasing the vacuum to the vessel with an inert gas. The vacuum/inert gas cycle should be repeated several times. The jacket may then be cooled to allow processing. An alternative is to apply heat to the jacket of the reactor and purge the vessel with an inert gas. It is also possible to dry a reactor train by boiling a water absorbing solvent, such as THF in the reactor under an inert gas. The solvent is then drained from the reactor, along with the water. The water content of the solvent can be determined analytically, for instance via Karl Fischer titration, to determine the efficiency of water removal.⁹¹ If the detected water value is higher than the background, the solvent boil up process can be repeated. Sometimes it is more cost-efficient to simply charge sufficient excess organolithium solution to account for the water content although all chemistry will not allow this shortcut.

Another hazard consideration for larger scale equipment is that the heat transfer fluid must be nonreactive with organolithium compounds. If there is a leak in the jacket or condenser and the heat transfer fluid comes in contact with the organolithium solution, the result can be catastrophic. Clearly this is not a risk worth taking on large scale although large-scale equipment rarely leaks into the vessel. Water, glycol, and brine solutions are examples of reactive heat transfer fluids that should not be employed as heat transfer fluids in this service.

PPE. The proper personal protective equipment (PPE) for handling organolithium compounds should also be secured prior to experimentation. To protect the eyes from the corrosivity of organolithium compounds, eye protection in the form of safety glasses or goggles should always be worn. Additional eye protection, provided by a face shield, is recommended in experiments where higher volumes (greater than one liter) of organolithium reagents are employed and particularly if organolithium solutions are pressurized, for instance in order to transfer them via tubing. The flammability

and pyrophoricity hazards to personnel are mitigated by the use of a flame-resistant lab coat or coveralls.⁹² Proper glove selection will provide protection for hands potentially exposed to the corrosive nature of the organolithium compounds and the organic solvents in which they are formulated. Gloves made from Viton afford the best overall chemical protection; however, they are expensive.⁹³ Nitrile gloves offer a good compromise between chemical protection and affordability.⁹⁴ Commercially available extended sleeve/gauntlets provide protection from the hand to the shoulder. Proper footwear, leather, closed-toe shoes, protect the feet from spills. Bottles of organolithium solutions should be transported in appropriately sized bottle tote safety carriers, to minimize the potential for breakage and spills.⁹⁵

In the event of a spill, another important element for protection of personnel and equipment is a fire extinguisher. It is important to secure the appropriate fire extinguisher for organolithium compounds prior to the initiation of the experiment. The recommended fire extinguisher for this application is a dry chemical, Class B, fire extinguisher.⁹⁶ It is imperative NOT to use fire extinguishers that contain water, carbon dioxide or halogenated hydrocarbons (Halon) for organolithium fires. Alkyllithiums react violently with these three classes of extinguishing agents. The use of these improper extinguishers will exacerbate, rather than mitigate, the fire scenario. It is a prudent precaution to remove such extinguishers from the proximate areas where work is to be done as researchers will react precipitously in the event of a fire.

Right Size Order. A final consideration in planning the experiment is to consider the total volume of organolithium compound required. Is the experiment a single, small scale preparation, or is it the first of a long campaign? It is recommended to only order the amount of organolithium compound required for the planned experiment(s). This strategy assures that the organolithium solution will be fresh, will have undergone minimal decomposition and was not contaminated by improper handling in a prior unsupervised experiment. Minimizing the quantity of organolithium storage also reduces the severity of any accident that may occur in the storage room. The higher cost per mole of the smaller package size will more than be offset by lower analytical and waste disposal charges. Furthermore, the organolithium producers offer the option of custom packaging, particularly for larger quantities of material. Ideally, the quantity of organolithium contained in a single unit is equal to the amount required for one reaction. This option should be explored particularly as the scale of the project increases.

Storage Requirements. The decomposition rate of alkyllithiums is highly dependent on the chemical structure, the concentration, the storage temperature, and the presence of lithium alkoxides. The major products of thermal degradation of *n*-BuLi are 1-butene and solid LiH (Scheme 6). The average

decomposition rates per day for some commercially important organolithium compounds are presented in Table 8.⁹⁷

The thermal stability of alkylolithiums increase in the series: *s*-butyllithium \leq *iso*-butyllithium $<$ *n*-butyllithium \approx *n*-hexyllithium $<$ *t*-butyllithium.⁹⁸ The thermal stability rises with decreasing concentration in the formulation for a given alkylolithium.⁹⁸ The stability also increases with a decrease in the storage temperature (Table 8).⁹⁹ Although the products of decomposition are clearly known, to explain the relative thermal stabilities will not be attempted because of the numerous variables and the extent to which they influence the degradation; however, the presence of alkoxide impurities, generated from adventitious oxygen, accelerates the rate of decomposition. Therefore, to maximize the shelf life of these organolithium solutions, it is recommended that they be stored in an explosion proof refrigerator or cold room at <10 °C. Further, the organolithium solutions should be stored in tightly closed containers, to minimize ingress of oxygen or moisture.

Analysis and Standardization of Organolithium Compounds. The weight percent concentration of the organolithium solution is often a critical parameter in the design of an experimental procedure. This is particularly the case when a reaction requires an exact number of equivalents of the organolithium compound. The potential for decomposition of the organolithium during storage, particularly for alkylolithiums as noted in the previous section, exacerbates the issue, as the titer can drop. Alternatively, the titer can potentially rise if solvent evaporates without organolithium degradation. Therefore, it is highly recommended to analyze the organolithium solution prior to the start of the experiment, particularly if the solution has not been used recently. There are a variety of analytical methods available for establishing organolithium species concentration. Contact the vendor to obtain the analytical methods that the vendor employed to generate the values on the Certificate of Analysis (CoA). In the end, analysis of the organolithium solution prior to the experiment will save time and ensure the most meaningful experimental results.

One of the classic techniques for the analysis of organolithium solutions, particularly solutions of alkylolithium species, is the Gilman double titration method.¹⁰⁰ This method served as the standard for the industry for many years. The double titration technique differentiates between the lithium bound to carbon from that of basic entities arising from decomposition, such as the corresponding lithium alkoxide or lithium carbonate. However, this method is capricious, particularly regarding the quality of benzyl chloride used for the titration method. Therefore, a plethora of alternative reagents have been advanced to overcome this limitation.

The Watson–Eastham titration method is particularly useful for the analysis of secondary lithium organoamides.⁸³ It involves only a single titration and is quite straightforward. The analysis of solutions of lithium alkoxides are typically performed by a total base titration.¹⁰¹ Nondestructive instrumental analysis techniques have also been developed for the rapid analysis of organolithium solutions.

An FT-IR analytical technique was recently described which provides excellent correlation with the results from the Gilman double titration method for *n*-butyllithium.¹⁰² Also, if the ¹H NMR absorptions for the solvent and organolithium, especially the protons of the carbon bearing lithium, can be distinguished, integration of the corresponding spectrum will provide an accurate concentration value.¹⁰³ ¹H NMR spectroscopy was used extensively in the determination of several MeLi

compositions.^{18–22} Due to the variety of analytical techniques available,¹⁰⁴ it is strongly recommended to contact the vendor to secure the latest methods available.

Laboratory Set-Up. A typical organolithium reaction apparatus, outfitted for cannula transfer, is illustrated schematically in Figure 6.⁵ The reactor is equipped with a mechanical

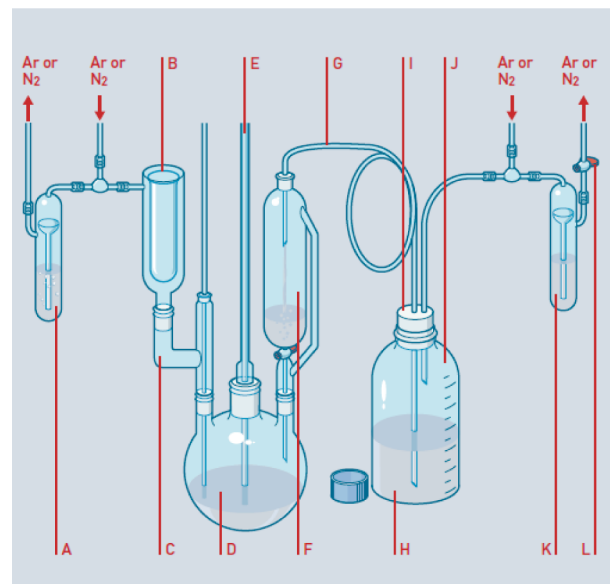


Figure 6. Laboratory apparatus for cannula transfer. Reprinted with permission from ref 5. Copyright 2005 FMC Corporation. Key: A, mineral oil bubbler (outlet); B, dry ice condenser; C, Claisen adapter; D, three-neck round bottom flask; E, mechanical stir shaft; F, addition funnel; G, cannula; H, organolithium sample; I, septum; J, glass bottle; K, mineral oil bubbler (inlet); L, valve.

stirrer, a pressure-equalizing addition funnel fitted with a septum, and a Claisen adapter fitted with a thermocouple to measure the internal temperature, and a dry ice condenser. The inert gas line is attached to the outlet of the condenser, which is connected via a “T” fitting to a bubbler filled with mineral oil. This bubbler (outlet)¹⁰⁵ monitors the positive flow of inert gas through the system and prevents the influx of air into the reactor in the event of a partial vacuum, which may occur upon cooling if there is insufficient inert gas pressure. A second inert gas line is employed for the reagent bottle of the organolithium reagent (inlet). The mineral oil bubbler on the inlet side has a clamp or valve on the outlet to facilitate transfer via the cannula.

The reaction vessel and the organolithium reagent bottle should each be placed in a metal bowl to act as a catch pan for the organolithium solution in the event either vessel breaks. In addition, the bowl can be employed to hold the cooling medium for the reactor if a cryogenic reaction. In that case, the cooling medium should be an inert, hydrocarbon solvent, such as hexane or heptane, mixed with solid carbon dioxide, “dry ice”. The traditional cooling mediums, such as acetone or isopropanol, react vigorously with organolithium solutions and should be avoided. Similarly, a water condenser should not be used, due to the potential for leaks, which could enter the reaction vessel. Many of the concepts regarding planning the experiment, the laboratory glassware setup, and transfer of organolithium compounds on laboratory scale are illustrated in videos available free of charge on the Internet.⁶ A checklist which details the various aspects of the planning and execution

of a laboratory scale reaction involving organolithium solutions is available in the Supporting Information.

Laboratory Transfer Techniques. There are two basic techniques for the transfer of organolithium solutions in the laboratory, the syringe technique and the cannula technique. The syringe technique is preferred when relatively small volumes of organolithium solutions are required (less than 50 mL) for the reaction, while transfer of larger volumes is most easily accomplished with the cannula technique.

Syringe Techniques. The experimental area is cleaned and prepared as was outlined before. The bottle of the organolithium compound is removed from the explosion proof refrigerator, transported to the hood in a safe carrier, and clamped in the hood inside a metal bowl. This minimizes the probability of a spill if the bottle is accidentally bumped during the transfer. The transfer of the organolithium solution should take place promptly after the bottle is clamped in place. This is particularly the case for pentane solutions of organolithium, as the heat transferred from the hand to the bottle is sufficient to cause expansion of the solution in the syringe. This will force the organolithium out of the syringe, a potentially hazardous situation. A Luer lock syringe valve may be a good idea in this case. Gloves, in addition to providing personal protection, also provide some mitigation of this phenomenon. It is recommended that the syringe be at least twice the volume of the organolithium to be dispensed. The syringe that will be employed for the transfer must also be dried prior to the transfer. Verify that the syringe needle is long enough to reach the liquid level in the organolithium bottle. The syringe should be dried in an oven at 125 °C for at least 4 h, placed in a desiccator to cool to ambient temperature, and then purged with a stream of inert gas.

Don all the PPE recommended by the supplier of the organolithium compound. The hood sash should be closed as much as possible during the transfer operation and reaction, to provide an additional level of personnel protection. If the reagent bottle for the organolithium compound was shipped with a solid cap from the supplier, it should be replaced with a cap with a septum. The inert gas flow is started on the reagent line. A standard syringe needle is inserted into the end of the inert gas line. The tip of this needle is then inserted into the septum on the reagent bottle. Observe the inert gas flow at the bubbler and adjust the flow accordingly. The syringe is then employed to withdraw the required amount of organolithium solution from the reagent bottle. Care must be taken not to withdraw the organolithium solution faster than the inert gas flow can refill the resultant void. This would allow air to enter the inert gas line and possibly contaminate the organolithium solution. The transfer syringe needle is withdrawn and capped with a rubber stopper. The tip of the transfer syringe needle is then inserted into the septum of the pressure-equalizing addition funnel and then dispensed into the addition funnel. The solid cap is replaced on the sample bottle, and it is returned to the refrigerator.

The amount of the organolithium solution dispensed can be calculated by noting the final volume in the pressure-equalizing addition funnel. A more accurate technique for the measurement of the amount of organolithium dispensed is via the difference in weight between the full syringe and the syringe after the transfer. It is advisable to clean the syringe soon after the transfer is completed, to minimize the chance of the plunger sticking and "freezing" in the barrel of the syringe. For pyrophoric solutions, any residue in the syringe should be

diluted to less than 5 wt % with an inert solvent, such as heptane. This rinse solution can be quenched by slowly mixing with an equal volume of 2 M solution of isopropanol in heptanes.

Cannula Techniques. The experimental area is cleaned and prepared as was outlined before, and the bottle is brought to the hood as outlined above. A cannula (G in Figure 6) will be used. The cannula is a long syringe needle with a sharpened tip at each end. The cannula that will be employed in the transfer must also be dried prior to the transfer. The cannula should be dried in the same manner as the oven techniques previously outlined.

Don all the PPE recommended by the supplier of the organolithium compound except also don a face shield since pressurized organolithium solutions will be manipulated. The hood sash should be closed as much as possible during the transfer operation. If the reagent bottle for the organolithium compound was shipped with a solid cap from the supplier, it should be replaced with a cap with a septum. The inert gas flow is started on the reagent line. A standard syringe needle is inserted into the end of the inert gas line. The tip of this needle is then inserted into the septum of the organolithium sample bottle. Observe the inert gas flow at the bubbler and adjust the gas flow accordingly. One tip of the dried cannula is inserted into the septum of the organolithium sample bottle. The other tip of the cannula is then inserted into the septum in the pressure-equalizing addition funnel. The tip of the cannula in the sample bottle is then lowered into the liquid of the organolithium solution. The valve on the exit of the mineral oil bubbler attached to the organolithium sample bottle is slowly closed or restricted. This causes pressure to build up in the reagent bottle, and the organolithium solution will be transferred by pressure to the addition funnel. The inert gas pressure should never exceed 5 psi (0.3 bar). When the desired volume of organolithium solution has been transferred, the valve on the bubbler is opened, and the tip of the cannula is raised above the liquid level in the bottle. This latter action will prevent siphoning of the organolithium solution. Any excess organolithium solution is allowed to drain back into the reagent bottle by gravity.

The cannula is removed from the reagent bottle and then from the pressure-equalizing addition funnel. The septum on the pressure-equalizing addition funnel is replaced with a solid stopper, and the bottle is returned to the refrigerator. The amount of the organolithium solution dispensed can be calculated by noting the final volume in the pressure-equalizing addition funnel. A more accurate technique for measurement of the amount of organolithium dispensed is by weight lost from the reagent bottle. It is advisable to clean the cannula soon after the transfer is complete, to minimize the chance for cannula plugging. For pyrophoric solutions, any residue in the cannula should be diluted to less than 5 wt % with an inert solvent, such as heptane. The rinse solution can then be quenched by mixing with an equal volume of 2 M solution of isopropanol in heptanes.

Large-Scale Transfer of Organolithium Solutions. Kilo laboratory, pilot plant, and commercial scale transfers of organolithium solutions all utilize a transfer technique very similar to the laboratory cannula technique. Ideally, a kilo laboratory reactor is located in a suitable, walk-in hood. Similar experimental site preparations are conducted as outlined above. The reactor is dried and purged with an inert gas using one of the previously described techniques. The organolithium

transfer line is T-shaped, with fittings at each end to connect to the organolithium solution container, a container which contains the same solvent as the organolithium, and the reactor addition port. Depending on the reaction to be performed, the organolithium solution can be added directly into the reactor or into a separate charge vessel attached to the reactor. Typically, larger volumes (>1 L) of organolithium solutions are supplied in cylinders, ranging in size from 20 L to 35 000 L. While the cylinders of organolithium solutions are different in size, shape, valve location, and valve configuration, the transfer technique is essentially the same for each.

The cylinders have two valves—an inert gas inlet valve and an organolithium solution discharge valve. The organolithium solution discharge valve is left-hand thread, to minimize the opportunity for cross contamination. The organolithium solution discharge valve is connected to a dip tube in the cylinder which reaches almost to the bottom of the cylinder. Both valves are also fitted with plugs to minimize leaking during transportation and staging. The suppliers of the organolithium solutions can provide detailed engineering drawings of the cylinder, which lists the size of the ports on the cylinder and the type of connection required for the organolithium solution discharge port and the inert gas addition port. The transfer line should be constructed of material that is compatible with the organolithium solution, such as polytetrafluoroethylene (PTFE) or stainless steel. It is also important that any gasket material is compatible with the organolithium solution and the solvent. Use of steel/graphite gaskets, which retain their efficacy in the event of a fire, are recommended.¹⁰⁶

Furthermore, the transfer line should have a manual shut off valve near the end of each segment, to permit the isolation of the transfer line. The transfer line should be purged with an inert gas and then connected to the various ports. The cylinder should be grounded, to prevent static electrical discharge when transferring a hydrocarbon solution. The cylinder can be placed on a scale, so the weight of organolithium solution actually transferred can be accurately determined. The inert gas inlet on the cylinder is connected to a source of inert gas to facilitate the transfer. The inert gas line should include a valve to allow the pressure to be released at the conclusion of the transfer.

Prior to transfer of organolithium solution, pressure test the fully assembled apparatus with an inert gas for leaks. Typically the system is pressurized to 10–15 psig. Watch for a pressure drop over 15–20 min. If there is less than 1 psig change in that time, then one can be certain there are no leaks.

To begin transfer of the organolithium solution, the inert gas valve on the cylinder is opened and the pressure is slowly increased to ~5 psi (maximum recommended pressure for transfer is 60 psi \approx 4 bar).¹⁰⁷ The valve on organolithium solution transfer line is opened at the reactor. The last valve to be opened is the discharge valve on the cylinder. The transfer is monitored by personnel in appropriate PPE to make sure there are no spills. Once the desired amount of organolithium solution has been discharged from the cylinder, the organolithium discharge valve on the cylinder is closed. This is followed by closure of the corresponding valve on the transfer line. The pressure is partially released on the cylinder by opening the valve on the inert gas line, down to a ~2–3 psi, followed by closure of the cylinder inert gas valve. The solvent cylinder is then pressurized to ~5 psi with an inert gas. The valve on the inert solvent container and the corresponding valve on the transfer lines are opened. A sufficient volume of inert solvent is flushed through the transfer line, to ensure that

all of the organolithium solution is indeed transferred to the reactor. The valve on the solvent cylinder and the corresponding valve on the transfer line are closed. The pressure is released on the solvent container by opening the valve on the inert gas line. It is important not to purge the transfer line dry with an inert gas, as this will leave a concentrated residue of the organolithium on the wall of the transfer line. Finally, the transfer line valve at the reactor is closed. The transfer line can then be disconnected from the organolithium solution cylinder, the solvent container and the reactor. The inert gas line can be removed from the cylinder. The plugs should be replaced on the organolithium solution discharge valve and the inert gas valve on the cylinder.

Disposal of Organolithium Compounds. Small residues of organolithium compounds can be safely quenched in a laboratory fume hood. Pyrophoric materials should be diluted to less than 5 wt % with an inert solvent, such as heptanes. The organolithium solution should then be added slowly, via an addition funnel, to a well-stirred 2 M solution of isopropanol in heptanes. The temperature of this quench solution should be monitored with a thermocouple. The temperature is maintained at 50 °C or below by controlling the feed rate of the organolithium solution or by application of an external cooling bath of dry ice/heptanes. The resultant solution of lithium isopropoxide in heptane can then be disposed of as flammable, hazardous waste, in accordance with local environmental regulations or further quenched.

The decomposition of organolithiums, particularly *s*-BuLi, and LDA during storage will generate highly reactive LiH solids (Scheme 6). Containers of organolithium solutions that have developed significant quantities of solids should be sent out for disposal as a lab pack by a licensed waste disposal company. Larger volumes of organolithium reagents that are no longer needed should also be sent out for disposal as a lab pack. The lab pack of these organolithium solutions minimizes laboratory personnel exposure to the hazards of quenching large volumes of organolithium solutions and their decomposition products. Empty cylinders of organolithium solutions can be returned to the original supplier.

Reactions of Organolithiums – Pyrophoricity. All solutions of organolithium compounds are classified as flammable and corrosive. Further, certain organolithium solutions are also pyrophoric.⁸ Check the MSDS supplied by the manufacturer to ascertain the classification of the specific organolithium solution of interest. Several factors which affect the pyrophoricity include:

- Nature of the organolithium (pK_a , aggregation state)
- Concentration
- Solvent (flash point, solvation ability)
- Humidity
- Temperature
- Combustible materials

Hydrocarbon solutions which contain lower molecular weight (4 carbons or less) alkylolithiums are generally pyrophoric, which includes *n*-BuLi, *s*-BuLi, and *t*-BuLi. More concentrated solutions have a higher probability of immediate ignition. For hydrocarbon solutions of *n*-BuLi, concentrations in the range of 50–80% are considered the most hazardous, as they will ignite immediately upon exposure to air. Curiously, at concentrations above 80%, the pyrophoricity of *n*-BuLi in hydrocarbon solution decreases slightly due to the decreased amount of solvent that is considered a supportive “flammable

fuel". The relationship between pyrophoricity and concentration of *n*-BuLi in hydrocarbon solution is shown schematically in Figure 7. Volatile hydrocarbon solvents will evaporate

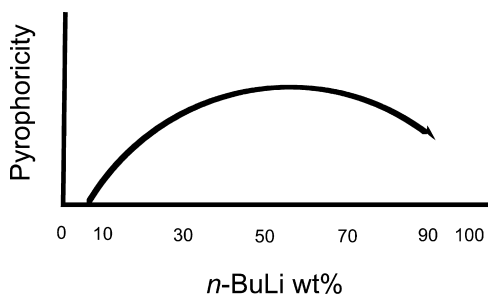


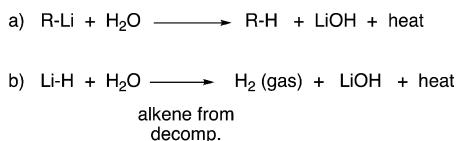
Figure 7. Pyrophoricity of *n*-BuLi in hydrocarbon solution as a function of concentration.

quickly in the event of a spill, which will increase the relative concentration of the alkyl lithium and, thus, the pyrophoricity. Alkyl lithiums formulated in hydrocarbon solvents with higher flash points, for instance *n*-heptane or toluene, have a lower probability to spontaneously ignite. The presence of Lewis bases in the formulation, which coordinate with the alkyl lithium, will also lessen the probability of spontaneous ignition. Higher relative humidity, higher temperature, and combustible material in the area of a release of an alkyl lithium solution all increase the probability of spontaneous ignition.¹⁰⁸

With proper attention to the safe handling techniques previously presented and thoughtful experimental planning, organolithium solutions can be safely and effectively utilized as reagents in the research laboratory, kilo lab, and production environments.

Reactions of Organolithiums: Water. All alkyl lithiums react exothermically (heat of hydrolysis for *n*-BuLi = -226 kJ/mol)¹⁰⁹ with water to produce lithium hydroxide, and the corresponding alkane (Scheme 14a). For alkyl lithiums which have undergone degradation to form LiH and an alkene, this hydrolysis obviously will evolve hydrogen gas (Scheme 14b).

Scheme 14. Hydrolysis of alkyl lithiums (a) and degraded alkyl lithiums (a and b)



The obvious differences in their hydrolyses are the various respective conjugate acids that are produced and therein lies the problem. In Scheme 14a, where R = methyl through pentyl, low molecular weight hydrocarbons are generated and can be volatilized by the heat generated by hydrolysis. Thus, different precautions must be taken depending on whether the system is unvented, as it would be for storage, or if the system is being purged by an inert gas, as is the case when the organolithium is being used in a reaction. For a closed or container system, this increased pressure will obviously have to be reduced, either by cooling the container or slowly venting the container through the inert gas manifold. However, for a purged inert gas system, the increase in flammable organics in the vapor phase will require increased dilution with an inert gas purge whether

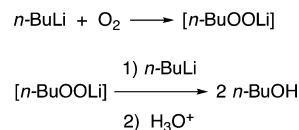
vented to the atmosphere or first sent through a thermal oxidizer, in accordance with local regulations.

The reaction of phenyllithium with water is another special case, in that the hydrocarbon coproduct is benzene. Any process streams potentially exposed to benzene have to be segregated and disposed of according to local environmental regulations. During laboratory usage of organolithiums, one is normally not too concerned about release of hydrocarbons as the volumes are small and easily diluted in the hood exhaust. But on a larger scale, one needs to be aware of the potential release of these compounds at any time, especially during workup procedures for both safety reasons and air quality regulations. A review of incidents reported in the literature reveals that most accidents occur during this time, which includes handling of waste streams and cleanup steps.

Additionally, with the off gassing of the volatiles in place, a quench of unused organolithium solutions can be carried out only after prior dilution with less volatile hydrocarbons to render the organolithium solution less than 5 wt % organolithium. The dilution step is recommended for any scale. However, again this assumes that no degradation during storage and/transport has occurred that would produce finely divided solids of highly reactive lithium hydride, LiH (Scheme 6). The best approach for avoidance of the need to quench unused organolithium solutions is to ensure that they are stored at temperatures which limit degradation to LiH and order cylinders which contain no more than the amount required for the batch process.

Reactions of Organolithiums: Oxygen. With dry air, the reaction of organolithiums with molecular oxygen to produce the corresponding alkoxide has been used sparingly in synthesis to produce alcohols.¹¹⁰ However, with commercial alkyl lithiums, this reaction readily occurs if oxygen is present. Exposure of these alkyl lithiums in hydrocarbon solution to even the smallest amount of oxygen will produce the stoichiometric amount of the corresponding alkoxide. This reaction presumably goes through a transient intermediate peroxide, which is quickly attacked by a second molecule of RLi to yield two molecules of the corresponding lithium alkoxide. The specific reaction of *n*-BuLi with oxygen is shown in Scheme 15.

Scheme 15. Reaction of *n*-butyllithium with molecular oxygen



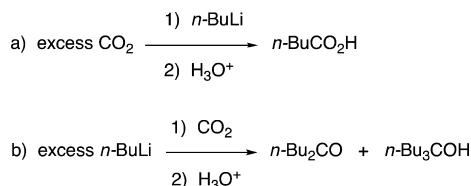
Although the precise mechanism for alkoxide formation is unknown, it is not too difficult to imagine the reaction of molecular oxygen taking place within the hexameric, *n*-butyllithium aggregate. The fact that the initially formed lithium *n*-butoxide, which is sparingly soluble in hydrocarbon alone, remains in solution even at cold temperatures is most likely due to being incorporated into the *n*-butyllithium hydrocarbon soluble aggregate.

Finally, when concentrated *n*-BuLi is stored at cold temperatures for an extended amount of time and solids form, the difference between the weight percent of lithium bound to carbon (CLi) and the total base decreases. Although the original total base has decreased, this observation appears to indicate that the concurrent formation of solids must contain

more *n*-butoxide (and other basic sources) than *n*-BuLi; however, it is possible the solids also contain LiH.

Reactions of Organolithiums: Carbon Dioxide. Alkyl- and aryl-lithium reagents readily react with carbon dioxide as an electrophile as a useful method of carboxylation in organic synthesis.¹¹¹ (Scheme 16a). The derived lithium carboxylate

Scheme 16. *n*-BuLi and excess CO₂ (a) and CO₂ and excess *n*-BuLi (b)



can be quenched with mild acid to afford the corresponding one-carbon homologated carboxylic acid. However, in the presence of excess of any alkyl- or aryl-lithium, the resulting lithium carboxylate intermediate will further react to give rise to ketones and tert-alcohols after an aqueous acid quench. This constitutes a useful method for the preparation of ketones.¹¹² (Scheme 16b).

These reactions illustrate one of the reasons that carbon dioxide fire extinguishers should never be used to extinguish a fire involving these reagents.

CONCLUDING REMARKS

Commercial organolithium compositions utilize several types of hydrocarbon and an expanding number of Lewis base solvents. The compositions and methods of preparation are defined by their physicochemical properties. These properties, namely, structure, solubility, thermal stability, and reactivity are a composite manifestation of the aggregates present in solution. These solutions contain different types of aggregates, solvated or unsolvated and mixed, in a wide range of concentrations. Some aggregates result from purposeful addition of modifiers, which can range from a stronger donor LB, lithium halide, organolithium, or other organometallics, while others may contain trace impurities. A remarkable amount of knowledge^{39,64} has been learned about aggregation of organolithiums via the complementary methods of X-ray crystallography and advancing NMR spectroscopy techniques; however, the associated conditions are often not representative of the practical parameters, namely, temperature and concentration, that are desirable for an optimized synthetic process. This aggregation information still provides a knowledgeable starting point on which to develop a process that successfully scales up from microwave into the plant. Most importantly, all process development at whatever scale must be carried out in a safe and efficient manner. May this review be a simple reminder to thoughtfully plan these activities as well.

ASSOCIATED CONTENT

Supporting Information

Internet links for commercial producers of organolithium products and a laboratory scale checklist for working with organolithium solutions. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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Author Contributions

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Notes

The authors declare no competing financial interest.

Biographies



Terry Lee Rathman was born in Providence, R.I. on November 10, 1944. Although his undergraduate studies in chemistry included an important side step of serving four years in the U.S. Army Security Agency/NSA, his degree was completed in 1971 at Kutztown University. Under the guidance of Professor James F. Wolfe at Virginia Tech, he earned in 1976 his Ph.D. in Organic Chemistry, which involved carbanionic methodologies. After a post-doc at Hershey Medical School of Penn State and research associate position at NASA, in 1979 he continued his organolithium journey with Lithium Corporation of America, which became FMC Lithium in 1985. In 1989, he switched from Director of Organometallic Research to become the Organic Technical Development Manager, which involved visiting and speaking at many conferences and fine chemical and pharmaceutical companies around the world. In 2000, he started his own consultancy, t-Links, which specializes in process optimization involving alkali and alkaline earth organometallics.



James Schwindeman was born in Cincinnati, OH on October 30, 1955. He earned his B.S. degree in Chemistry at Miami University in 1977. His Ph.D. in Organic Chemistry was earned at the Ohio State University in 1981, under the tutelage of Professor Philip Magnus. He began his industrial career as a discovery chemist in the Agrochemical Business for PPG Industries. He then worked for over 12 years at FMC Lithium, where he developed the synthesis of various

organometallic compounds and explored their applications in organic synthesis. He is the inventor of over 75 US patents and numerous publications related to the utilization of organometallic chemistry in synthetic methodology. Currently, he is Executive Vice President for Rohner Inc., a Swiss pharmaceutical fine chemical company, where he is responsible for business development activities in North America.

■ ACKNOWLEDGMENTS

We thank the editorial board of this journal and specifically Jaan Pesti for his encouragement and advice as well as the reviewers for their helpful comments and suggestions. Initially, we had hoped to include other cometalas as well but quickly realized that we should focus mainly on the commercial organolithiums, although we did venture beyond those borders briefly to gain a better view of this organolithium landscape. Of course, with that narrower focus in mind, we could never have provided the information in this review without the help of the manufacturers of these products: Rockwood Lithium and FMC Corporation.

■ REFERENCES

- (1) DILBERT. Copyright 1996, Scott Adams. Used with permission of UNIVERSAL UCLICK. All rights reserved.
- (2) (a) Kemsley, J. Researcher Dies After Lab Fire. *Chem. Eng. News* [Online] 2009, <http://cen.acs.org/articles/87/web/2009/01/Researcher-Dies-Lab-Fire.html> (accessed May 15, 2014). (b) <http://www.chemistry-blog.com/2009/01/20/tert-butyllithium-claims-fellow-chemist-at-ucla/> (accessed June 30, 2014).
- (3) (a) Wakefield, B. J. *Organolithium Methods*; Academic Press: London, 1988. (b) Brandsma, L.; Verkruijsse, H. D. *Preparative Polar Organometallic Chemistry Vol. 1*; Springer-Verlag: New York, 1987. (c) Brandsma, L. *Preparative Polar Organometallic Chemistry Vol. 2*; Springer-Verlag: New York, 1990. (d) Schlosser, M., Ed. Chapter 1: Organoalkali Chemistry. In *Organometallics in Synthesis – A Manual*, 2nd ed.; John Wiley & Sons Ltd.: New York, 2002; pp 1–352. (e) Rathman, T. L.; Bailey, W. F. *Org. Process Res. Dev.* **2009**, *13*, 144. (f) Clayden, J. In *Organolithiums: Selectivity for Synthesis*, Vol. 23; Baldwin, J. E., Williams, R. M., Eds.; Elsevier: Oxford, 2002. (g) The chemistry of organolithium compounds. In *The Chemistry of Organolithium Compounds*; Rappoport, Z., Marek, I., Eds.; John Wiley & Sons: New York, 2004. (h) *Lithium Compounds in Organic Synthesis: From Fundamentals to Applications*; Luisi, R., Capriati, V., Eds.; Wiley-VCH: Weinheim, 2014.
- (4) *Butyllithium*. Brochure available at no charge from Rockwood Lithium, April 2012; <http://www.rockwoodlithium.com/products/butyllithium/>.
- (5) *Butyllithium Safe Handling Guide*. Brochure available at no charge from FMC Corporation, May 2005; <http://www.fmclithium.com/>. Permission was granted to use drawing in Figure 6, Laboratory apparatus for cannula transfer.
- (6) (a) One such video is available from Yale University Environmental Health and Safety Department at the following link: <http://ehs.yale.edu/training/organolithium-compounds-training> (accessed May 16, 2014). (b) Dartmouth University also has a video available, which emphasizes the cannula transfer technique: http://www.youtube.com/watch?v=gi_ODNJCbqY (accessed May 16, 2014). (c) Undergraduate safety orientation video series for Schlenk techniques: http://www.stalke.chemie.uni-goettingen.de/virtuelles_labor/advanced/de.html (accessed June 12, 2014).
- (7) Contact manufacturers for product inquiries and large scale handling advice. See the Supporting Information.
- (8) *Recommendations on the Transport of Dangerous Goods, Manual of Tests and Criteria*, 5th revised ed.; United Nations: New York and Geneva, 2009; p 363.
- (9) Wu, G.; Huang, M. *Chem. Rev.* **2006**, *106*, 2596.
- (10) Walfort, B.; Lameyer, L.; Weiss, W.; Herbst-Irmer, R.; Bertermann, R.; Rocha, J.; Stalke, D. *Chem.—Eur. J.* **2001**, *7*, 1417.
- (11) Schwindt, M. A.; Belmont, D. T.; Carlson, M.; Franklin, L. C.; Hendrickson, V. S.; Karrick, G. L.; Poe, R. W.; Sobieray, D. M.; Van De Vusse, J. J. *Org. Chem.* **1996**, *61*, 9564.
- (12) Various grades of hexanes and heptanes are used.
- (13) Weiss, W.; Dawidowski, D.; Pleyer, V.; Kruckel, F. Method for Producing Alkyl Lithium Compounds and Aryl Lithium Compounds by Monitoring the Reaction by Means of IR-Spectroscopy (Inventors). U.S. Patent Appl. 2007/0152354, July 5, 2007.
- (14) Orbison, D. R.; Hardwick, P. J.; Birch, J. S. Method and Apparatus for the Controlled Dilution of Organometallic Compounds (Inventors). U.S. Patent Appl. 2003/0199649, Oct. 23, 2003.
- (15) Nakousi, C. F.; Currin, T. R., Jr. Process for the Preparation of Alkylolithium Compounds (SQM Lithium Specialties Limited Partnership, LLP). U.S. Patent 7,005,083, February 28, 2006.
- (16) Weiss, W.; Dolling, E.; Schneider, B. Method for the Production of Alkyl Lithium Compounds by Using Reduced Pressure (Chemetall GmbH). U.S. Patent 7,175,784, February 13, 2007.
- (17) Morrison, R. C.; Hall, R. W.; Schwindeman, J. A.; Kamienski, C. W.; Engel, J. F. Catalyzed Hydrocarbyllithium Process (FMC Corporation). U.S. Patent 5,340,507, August 23, 1994.
- (18) Hintze, M. J.; Wen, J. Q. Process for Preparing Methyllithium (Chemetall Foote Corporation). U.S. Patent 6,861,011, March 1, 2005.
- (19) Emmel, U.; Rittmeyer, P.; Weiss, W. Dissolved Methyllithium-Containing Composition for Use in Synthesis Reactions (Metallgesellschaft AG). U.S. Patent 5,677,543, October 14, 1997.
- (20) Emmel, U.; Rittmeyer, P.; Wietelmann, U.; Aul, R. Synthesis Agent Containing Methyllithium/Lithium Bromide, and Process for the Preparation Thereof (Chemetall GmbH). U.S. Patent 7,501,075, March 10, 2009.
- (21) Morrison, R. C.; Rathman, T. L. Preparation of Organometallic and Organobimetallic Compounds (Lithium Corp. of America). U.S. Patent 4,976,886, December 11, 1990.
- (22) Mehta, V. C.; Morrison, R. C.; Kamienski, C. W. Synthesis of Organometallic/Bimetallic Compositions (FMC Corporation). U.S. Patent 5,171,467, December 15, 1992.
- (23) Ashby, E. C.; Goel, A. B. *Inorg. Chem.* **1978**, *17*, 322.
- (24) Morrison, R. C.; Schwindeman, J. A.; Stryker, S. S.; Sutton, D. E. Aryllithium Products and Processes (FMC Corporation). U.S. Patent 5,626,798, May 6, 1997.
- (25) Weiss, W.; Aul, R. A.; Emmel, U.; Rittmeyer, P. Ethyllithium in Dibutyl Ether (Chemetall GmbH). U.S. Patent 6,495,064, December 17, 2002.
- (26) Although conducted under an inert atmosphere, experience in handling pyrophoric solids is required. This procedure was only used at the laboratory bench scale.²¹
- (27) Bailey, W. F.; Rathman, T. L. In *Process Chemistry in the Pharmaceutical Industry: Challenges in an Ever Changing Climate*; Gadamasetti, K.; Braish, T., Eds.; CRC Press: Boca Raton, FL, 2008; Vol. 2, pp 205–216.
- (28) Newby, J. A.; Huck, L.; Blaylock, D. W.; Witt, P. M.; Ley, S. V.; Browne, D. L. *Chem.—Eur. J.* **2014**, *20*, 263.
- (29) (a) Taylor, H. M.; Davenport, J. D.; Hackler, R. E. Alpha,Alpha-Disubstituted-5-Pyrimidinemethanes Used as Fungicides (Eli Lilly and Company). U.S. Patent 3,887,708, June 3, 1975. (b) Taylor, H. M.; Davenport, J. D.; Hackler, R. E. Synthesis of 5-Pyrimidinecarbinols (Eli Lilly and Company). U.S. Patent 3,869,456, March 4, 1975. (c) Taylor, H. M.; Davenport, J. D.; Hackler, R. E. Plant Growth Regulation (Eli Lilly and Company). U.S. Patent 3,868,244, February 25, 1975. (d) Taylor, H. M.; Davenport, J. D.; Hackler, R. E. Alpha,Alpha-Disubstituted-5-Pyrimidinemethanes (Eli Lilly and Company). U.S. Patent 3,818,009, June 18, 1974.
- (30) The use of 2 equiv of *n*-BuLi to prepare the MeLi·LiI complex was not explored, nor was the use of methyl bromide instead of methyl iodide investigated.
- (31) Quirk, R. P.; Kester, D. E. *J. Organomet. Chem.* **1977**, *127*, 111.
- (32) Unpublished results, Rick Ross, Far Research.

- (33) (a) McKeever, L. D.; Waack, R.; Doran, M. A.; Baker, E. B. *J. Am. Chem. Soc.* **1968**, *90*, 3244. (b) Lambert, C.; Schleyer, P. v. R. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 1129.
- (34) Kottke, T.; Stalke, D. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 580.
- (35) (a) Margerison, D.; Pont, J. D. *Trans. Faraday Soc.* **1971**, *67*, 353. (b) Thomas, R. D.; Jensen, R. M.; Young, T. C. *Organometallics* **1987**, *6*, 565.
- (36) (a) Fraenkel, G.; Henrichs, M.; Hewitt, J. M.; Su, B. M. *J. Am. Chem. Soc.* **1984**, *106*, 255. (b) Bywater, S.; Worsfold, D. J. *J. Organomet. Chem.* **1967**, *10*, 1.
- (37) (a) Weiner, M.; Vogel, G.; West, R. *Inorg. Chem.* **1962**, *1*, 654. (b) Thomas, R. D.; Clarke, M. T.; Jensen, R. M.; Young, T. C. *Organometallics* **1986**, *5*, 1851.
- (38) (a) Fraenkel, G.; Fraenkel, A. M.; Geckle, M. J.; Schloss, F. J. *Am. Chem. Soc.* **1979**, *101*, 4745. (b) Pöppler, A.-C.; Meinholz, M. M.; Faßhuber, H.; Lange, A.; John, M.; Stalke, D. *Organometallics* **2012**, *31*, 42.
- (39) Reich, H. J. *Chem. Rev.* **2013**, *113*, 7130.
- (40) (a) Pöppler, A.-C.; Keil, H.; Stalke, D.; John, M. *Angew. Chem.* **2012**, *124*, 7963; *Angew. Chem., Int. Ed.* **2012**, *51*, 7843. (b) Pöppler, A.-C.; Frischkorn, S.; Stalke, D.; John, M. *ChemPhysChem* **2013**, *14*, 3103.
- (41) Granitzka, M.; Pöppler, A.-C.; Schwarze, E. K.; Stern, D.; Schulz, T.; John, M.; Herbst-Irmer, R.; Pandey, S. K.; Stalke, D. *J. Am. Chem. Soc.* **2012**, *134*, 1344.
- (42) (a) West, P.; Waack, R. *J. Am. Chem. Soc.* **1967**, *89*, 4395. (b) Lewis, H. L.; Brown, T. L. *J. Am. Chem. Soc.* **1970**, *92*, 4664.
- (43) (a) Bauer, W.; Seebach, D. *Helv. Chim. Acta* **1984**, *67*, 1972. (b) Seebach, D.; Hässig, R.; Gabriel, J. *Helv. Chim. Acta* **1983**, *66*, 308. (c) McGarrity, J. F.; Ogle, C. A. *J. Am. Chem. Soc.* **1985**, *107*, 1805.
- (44) (a) Bates, T. F.; Clarke, M. T.; Thomas, R. D. *J. Am. Chem. Soc.* **1988**, *110*, 5109. (b) Bergander, K.; He, R.; Chandrakumar, N.; Eppers, O.; Günther, H. *Tetrahedron* **1994**, *50*, 5861.
- (45) Bauer, W.; Winchester, W. R.; Schleyer, P. v. R. *Organometallics* **1987**, *6*, 2371.
- (46) Hay, D. R.; Song, Z.; Smith, S. G.; Beak, P. J. *Am. Chem. Soc.* **1988**, *110*, 8145.
- (47) (a) Weiss, E.; Lucken, E. A. C. *Organometal. Chem.* **1964**, *2*, 197. (b) Weiss, E.; Lambertsen, T.; Schubert, B.; Cockcroft, J. K.; Wiedenmann, A. *Chem. Ber.* **1990**, *123*, 79.
- (48) Fox, T.; Hausmann, H.; Günther, H. *Magn. Reson. Chem.* **2004**, *42*, 788.
- (49) Ogle, C. A.; Huckabee, B. K.; Johnson, H. C., IV; Sims, P. F.; Winslow, S. D.; Pinkerton, A. A. *Organometallics* **1993**, *12*, 1960.
- (50) Köster, H.; Thoenes, D.; Weiss, E. *J. Organomet. Chem.* **1978**, *160*, 1.
- (51) (a) Hage, M.; Ogle, C. A.; Rathman, T. L.; Hubbard, J. L. *Main Group Met. Chem.* **1998**, *21*, 777. (b) Tatic, T.; Hermann, S.; John, M.; Loquet, A.; Lange, A.; Stalke, D. *Angew. Chem., Int. Ed.* **2011**, *50*, 6666.
- (52) (a) Smith, M. B.; March, J. *March's Advanced Organic Chemistry: Reactions, Mechanisms, and Structure*, 5th ed.; John Wiley & Sons, Inc.: New York, 2001; pp 330–331. (b) Reich, H. J. *Lithium Amide Bases – A Primer*; 2002, A-7; <http://www.chem.wisc.edu/areas/reich/handouts/lireagents/amidebases.pdf> (accessed May 16, 2014).
- (53) Boche, G.; Etzrodt, H. *Tetrahedron Lett.* **1983**, *24*, 5477.
- (54) Viscosity data at low temperatures: Butyllithium in hexane (90 wt %) Product Data Sheet, Rockwood Lithium, September, 2012.
- (55) *Lithium Hydride Product Data Sheet*. Rockwood Lithium, September 2012; <http://www.rockwoodlithium.com/products/hydrides/>.
- (56) Sun, X.; Collum, D. B. *J. Am. Chem. Soc.* **2000**, *122*, 2452.
- (57) (a) Stanetty, P.; Mihovilovic, M. D. *J. Org. Chem.* **1997**, *62*, 1514. (b) Schlosser, M., Ed. Chapter 1: Organoalkali Chemistry. In *Organometallics in Synthesis – A Manual*, 2nd ed.; John Wiley & Sons Ltd.: New York, 2002; pp 290–293.
- (58) Kottke, T.; Lagow, R. J.; Hoffmann, D.; Thomas, R. D. *Organometallics* **1997**, *16*, 789.
- (59) Honeycutt, S. C. *J. Organomet. Chem.* **1971**, *29*, 1.
- (60) Bates, R. B.; Kroposki, L. M.; Potter, D. E. *J. Org. Chem.* **1972**, *37*, 560.
- (61) Aycock, D. F. *Org. Process. Res. Dev.* **2007**, *11*, 156.
- (62) (a) Comins, D. L.; Nolan, J. M.; Bori, I. D. *Tetrahedron Lett.* **2005**, *46*, 6697. (b) Lipton, M. F.; Mauragis, M. A.; Velely, M. F.; Bundy, G. L.; Bannitt, L. S.; Doberwolski, P. J.; Palmer, J. R.; Schwartz, T. M.; Zimmerman, D. C. *From Bench to Pilot Plant, Process Research in the Pharmaceutical Industry*; ACS Symposium Series; ACS: Washington, DC, 2001; p 101. (c) Bundy, G. L.; Bannitt, L. S.; Dobrowolski, P. J.; Palmer, J. R.; Schwartz, T. M.; Zimmerman, D. C.; Lipton, M. F.; Mauragis, M. A.; Velely, M. F.; Appell, R. B.; Clouse, R.; Daus, E. D. *Org. Process Res. Dev.* **2001**, *5*, 144.
- (63) (a) Bradley, D. C.; Thomas, I. M. *J. Chem. Soc.* **1960**, 3857. (b) Reetz, M. T.; Urz, R.; Schuster, T. *Synthesis* **1983**, 540.
- (64) Mulvey, R. E.; Robertson, S. D. *Angew. Chem., Int. Ed.* **2013**, *52*, 11470.
- (65) Mulvey, R. E.; Mongin, F.; Uchiyama, M.; Yoshinori, K. *Angew. Chem., Int. Ed.* **2007**, *46*, 3802.
- (66) Morrison, R. C.; Hall, R. W.; Rathman, T. L. Stable Lithium Diisopropylamide and Method of Preparation (FMC Corporation). U.S. Patent 4,595,779, June 17, 1986.
- (67) Mehta, V. C.; Rathman, T. L.; Kamienski, C. W.; Morrison, R. C.; Hall, R. W. Preparation of Organometallic Amide Compositions (FMC Corporation). U.S. Patent 5,320,774, June 14, 1994.
- (68) Butane evolution is most often experienced during the higher temperatures of the workup procedures.
- (69) Mallet, M. *J. Organomet. Chem.* **1991**, *406*, 49.
- (70) A second equivalent of *n*-BuLi (Scheme 10b) is required to decompose *n*-butyl iodide byproduct generated in the first step (Scheme 10a). Also, butene and butane are possible decomposition products but were not reported.
- (71) (a) Ziegler, K.; Jakob, L.; Wollthian, H.; Wenz, A. *Justus Liebigs Ann. Chem.* **1934**, *64*, 511. (b) Reetz, M. T.; Maier, W. F. *Liebigs Ann. Chem.* **1980**, *10*, 1471.
- (72) (a) Remenar, J. F.; Lucht, B. L.; Collum, D. B. *J. Am. Chem. Soc.* **1997**, *119*, 5567. (b) Gilchrist, J. H.; Collum, D. B. *J. Am. Chem. Soc.* **1992**, *114*, 794.
- (73) (a) Barendt, J. M.; Chiu, K.-W.; Ellenberger, D. H. Preparation of Alkali-Metal Hexamethyldisilazanes (Mine Safety Appliances Company). U.S. Patent 5,420,322, May 30, 1995. (b) Hall, R. W.; Kamienski, C. W.; McElroy, B. J.; Morrison, R. C.; Rathman, T. L.; Schwindeman, J. A. Contaminant Free Organometallic Amide Compositions and Processes for Making Same (FMC Corporation). U.S. Patent 6,060,617, May 9, 2000.
- (74) Lucht, B. L.; Collum, D. B. *Acc. Chem. Res.* **1999**, *32*, 1035.
- (75) Hintze, M. J.; Wen, J. Q. Lithium Diisopropylamide (Cyprus Foote Mineral Company). U.S. Patent 5,679,850, October 21, 1997.
- (76) (a) Hevia, E.; Kennedy, A. R.; Mulvey, R. E.; Ramsay, D. L.; Robertson, S. D. *Chem.—Eur. J.* **2013**, *19*, 14069. (b) Lucht, B. L.; Collum, D. B. *J. Am. Chem. Soc.* **1994**, *116*, 7949.
- (77) Hall, P. L.; Gilchrist, J. H.; Harrison, A. T.; Fuller, D. J.; Collum, D. B. *J. Am. Chem. Soc.* **1991**, *113*, 9575.
- (78) Louer, C.; Smith, W. N., Jr. Stable Lithium Cycloalkylimides (Cyprus Foote Mineral Company). U.S. Patent 5,173,209, December 22, 1992.
- (79) Smith, W. N., Jr. Preparation of Mixed Lithium Amide Reagents (Cyprus Foote Mineral Company). U.S. Patent 5,196,138, March 23, 1993.
- (80) Engel, J. F.; Hall, R. W.; Kamienski, C. W.; Schwindeman, J. A. Lithium Dialkylamide and Lithium Alkylencycloimide Formulations and Methods of Preparation (FMC Corporation). U.S. Patent 5,923,044, July 13, 1999.
- (81) Hodgson, D. M.; Humphreys, P. G.; Fleming, M. J.; checked by Morimoto, H.; Mihara, H.; Shibasaki, M. *Org. Synth.* **2008**, *85*, 1.
- (82) Kamienski, C. W.; Lewis, D. H. *J. Org. Chem.* **1965**, *30*, 3498.
- (83) Watson, S. C.; Eastham, J. F. *J. Organomet. Chem.* **1967**, *9*, 165.
- (84) Hartwell, G. E.; Brown, T. L. *Inorg. Chem.* **1966**, *5*, 1257.
- (85) Halaska, V.; Lochmann, L.; Lim, D. *Collect. Czech. Chem. Commun.* **1968**, *33*, 3245.

- (86) Allan, J. F.; Nassar, R.; Specht, E.; Beatty, A.; Calin, N.; Henderson, K. W. *J. Am. Chem. Soc.* **2004**, *126*, 484.
- (87) (a) Gros, P.; Fort, Y.; Caubere, P. *J. Chem. Soc., Perkin Trans.* **1997**, *1*, 3071. (b) Gros, P.; Fort, Y.; Caubere, P. *J. Chem. Soc., Perkin Trans.* **1997**, *1*, 3597. (c) Choppin, S.; Gros, P.; Fort, Y. *Org. Lett.* **2000**, *2*, 803. (d) Gros, P.; Viney, C.; Fort, Y. *Synlett* **2002**, *4*, 628.
- (88) (a) Ye, M.; Logaraj, S.; Jackman, L. M.; Hillegass, K.; Hirsh, K.; Bollinger, A. M.; Grosz, A. L.; Mani, V. *Tetrahedron* **1994**, *50*, 6109. (b) Thompson, A.; Corley, E. G.; Huntington, M. F.; Grabowski, E. J. J.; Remenar, J. F.; Collum, D. B. *J. Am. Chem. Soc.* **1998**, *120*, 2028. (c) Xu, F.; Reamer, R. A.; Tillyer, R.; Cummins, J. M.; Grabowski, E. J. J.; Reider, P. J.; Collum, D. B.; Huffman, J. C. *J. Am. Chem. Soc.* **2000**, *122*, 11212. (d) Grabowski, E. J. *J. Chirality* **2005**, *17*, S249. (e) Parsons, R. L., Jr. Synthesis of Cyclopropylacetylene (DuPont Pharmaceuticals Co.). U.S. Patent 6,028,237, February 22, 2000.
- (89) Malz, H.; Flug, T.; Rybicki, S. Esterification, Transesterification, Transamidation, and/or Amidation (BASF Aktiengesellschaft). U.S. Patent 7,625,849, Dec. 1, 2009.
- (90) McHale, J. M.; Navrotsky, A.; Kowach, G. R.; Balbarin, V. E.; DiSalvo, F. J. *Chem. Mater.* **1997**, *9*, 1538.
- (91) (a) Washington State University Vancouver ASTM Digital Library. <http://libguides.vancouver.wsu.edu/content.php?pid=222162&sid=1889000> (accessed May 24, 2014). (b) Jayawardhana, D. A.; Woods, R. M.; Ying, Z.; Wang, C.; Armstrong, D. W. *LC-GC North America* **2012**, *30*, 142. (c) Rapid, Efficient Quantification of Water in Solvents and Solvents in Water Using an Ionic Liquid-based GC Column. <http://www.chromatographyonline.com/lcgc/article/articleDetail.jsp?id=747879> (accessed May 24, 2014).
- (92) One brand of flame-resistant fabric is Nomex. A variety of Nomex clothing styles, including lab coats, coveralls, shirts, and pants, is commercially available. Flame-resistant clothing is available from a number of laboratory supply vendors, including Fisher Scientific, Sigma-Aldrich, and VWR.
- (93) One pair of Viton gloves, size 9, is listed in the VWR catalog for \$236.54. https://us.vwr.com/store/catalog/product.jsp?catalog_number=89236-764 (accessed May 16, 2014).
- (94) One pair of Nitrile gloves, size 9, is listed in the VWR catalog for \$31.40. https://us.vwr.com/store/catalog/product.jsp?catalog_number=57100-100 (accessed May 16, 2014).
- (95) A variety of bottle tote safety carriers are commercially available from laboratory supply houses, in multiple sizes. One set of such carriers can be found at: https://www.spectrumchemical.com/OA_HTML/lab-supplies-products_Bottle-Tote-Safety-Carrier_301205.jsp?section=12095 (accessed May 16, 2014).
- (96) Ansul Purple-K is one popular brand of dry chemical fire extinguisher. Other dry chemical extinguishers effective for organolithium fires include Plus Fifty B and Monnex.
- (97) (a) iso-Butyllithium Data Sheet, Rockwood Lithium, September, 2012; <http://www.rockwoodlithium.com/products/butyllithium/>. (b) tert-Butyllithium in Pentane Data Sheet, Rockwood Lithium, September, 2012; <http://www.rockwoodlithium.com/products/butyllithium/>.
- (98) Totter, F.; Rittmeyer, P. *Organometallics in Synthesis: A Manual*; Schlosser, M., Ed.; Wiley: Chichester, 1994; pp 171–2.
- (99) Kamienski, C. W.; McDonald, D. P.; Stark, M. W. *Kirk-Othmer Encyclopedia of Chemical Technology*, 4th ed; Kroschwitz, J. I., Ed.; Wiley: New York, NY, 1995; Vol. 15, pp 453–454.
- (100) Gilman, H.; Haubein, A. H. *J. Am. Chem. Soc.* **1944**, *66*, 1515.
- (101) *Butyllithium*, op. cit., p 33.
- (102) Hardwick, P. *PharmaChem* **2002**, *1* (6), 11.
- (103) Hoyer, T. R.; Eklov, B. M.; Voloshin, M. *Org. Lett.* **2004**, *6*, 2567.
- (104) Schlosser, M. Chapter 1: Organoalkali Chemistry. In *Organometallics in Synthesis – A Manual*, 2nd ed.; John Wiley & Sons Ltd.: New York, 2002; pp 293–297.
- (105) A variety of bubbler designs are commercially available from laboratory glassware suppliers. A versatile bubbler design is Chemglass catalog number AF-0513-20. http://www.chemglass.com/product_view.asp?pnr=AF-0513 (accessed May 16, 2014).
- (106) *Butyllithium Safe Handling Guide*, op. cit., p 33.
- (107) *Ibid.*, p 69.
- (108) (a) Wakefield, B. J. *Organolithium Methods*; Academic Press: London, 1988; p 12. (b) Schwindeman, J.; Woltermann, C.; Letchford, R. *Chemical Health & Safety*, May/June **2002**, *9*, No. 3, p 6.
- (109) *Butyllithium*, op. cit., p 7.
- (110) Wakefield, B. J. *Organolithium Methods*; Academic Press: London, 1988; p 129.
- (111) Brandsma, L.; Verkruijsse, H. D. *Preparative Polar Organometallic Chemistry Vol. 1*; Springer-Verlag: New York, p 33.
- (112) Jorgenson, M. J. Preparation of Ketones from the Reaction of Organolithium Reagents with Carboxylic Acids. *Organic Reactions*; John Wiley & Sons Ltd.: New York, 1970; Vol. 18, pp 1–98.