

Safe handling of organolithium compounds in the laboratory

Organolithium compounds are extremely useful reagents in organic synthesis and as initiators in anionic polymerizations. These reagents are corrosive, flammable, and in certain cases, pyrophoric. Careful planning prior to execution of the experiment will minimize hazards to personnel and the physical plant. The proper personal protective equipment (PPE) for handling organolithium compounds will be identified. Procedures to minimize contact with air and moisture will be presented. Solutions of organolithium compounds can be safely transferred from the storage bottles to the reaction flask with either a syringe or a cannula. With the utilization of these basic techniques, organolithium compounds can be safely handled in the laboratory.

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INTRODUCTION

When properly handled, organolithiums provide unique properties that allow for more precise control and greater performance features. With proper care and attention, organolithiums can be safely and effectively utilized in both laboratory and physical plant environments, while being the effective choice for many synthesis applications. Organolithium compounds fall into four broad categories: alkyllithiums (exemplified by *n*-butyllithium), aryllithiums (such as phenyllithium), lithium amides (for example, lithium diisopropylamide and lithium hexamethyldisilazide) and lithium alk-

oxides (typified by lithium *t*-butoxide). These organolithium compounds have found wide utility as reagents for organic synthesis in a variety of applications. For example, they can be employed as strong bases (alkyllithiums, aryllithiums, lithium amides and lithium alkoxides), nucleophiles (alkyllithium and aryllithium compounds) and reagents for metal-halogen exchange (alkyllithium and aryllithium compounds).¹ Alkyllithium compounds have also found extensive application as initiators for anionic polymerization. The unique properties of the carbon-lithium bond in polymerization processes allow the precise control of the polymer's molecular architecture.²

CHARACTERISTICS OF ORGANOLITHIUM COMPOUNDS

Several characteristics of organolithium compounds have enhanced their utilization in the laboratory. First, organolithium compounds exhibit excellent solubility in organic solvents. As an example, *n*-butyllithium is available commercially as a solution in hexanes from 1.5 M (15 wt.%) to 10 M (85 wt.%). One caveat is that alkyllithium compounds do react with etheral solvents.³ Second, in contrast to alkylorganometallics derived from other alkali metals, alkyllithium compounds have enhanced stability.⁴ The alkyllithium compounds exhibit sufficient stability to be prepared, stored and transported. Third, a wide range of base strength is available from the

various classes of organolithium compounds, with pK_a from 15.2 (lithium methoxide) to 53 (*t*-butyllithium).⁵ Fourth, organolithium reagents demonstrate enhanced nucleophilicity compared to the corresponding organomagnesium compound. Finally, they are convenient, as a variety of organolithium compounds from all four categories are commercially available. Thus, the experimentalist can select and purchase the appropriate reagent needed for the desired transformation.

HAZARDS OF ORGANOLITHIUM COMPOUNDS

Organolithium compounds, which exhibit outstanding performance in a variety of applications, are highly reactive materials. There are three principal hazards associated with these compounds: corrosivity, flammability and, in certain instances, pyrophoricity. The inherent corrosive nature of all four classes of organolithiums can cause chemical and thermal burns upon operator exposure. The organolithium compounds themselves are flammable. Typically, they are supplied in an organic solvent, which exacerbates the flammability. Pyrophoricity⁶ is defined as the property of a material to spontaneously ignite on exposure to air, oxygen or moisture. In particular, all formulations of *n*-butyllithium, *s*-butyllithium and *t*-butyllithium are pyrophoric, as determined by the official Department of Transportation (DOT) protocol.⁷ Before any laboratory work with an organolithium is conducted,

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appropriate planning should be conducted to safeguard personnel and property against these hazards.

There are a number of factors that influence the pyrophoric nature of the alkyllithium compound. For the same concentration of alkyllithium, the pyrophoricity increases in the order *n*-butyllithium < *s*-butyllithium < *t*-butyllithium. For a given alkyllithium, the pyrophoricity also increases as the concentration of the alkyllithium increases in the formulation. The solvent in the formulation also influences pyrophoricity. The lower the flash point of the solvent the greater the pyrophoricity. Pyrophoricity is also impacted by environmental factors in the laboratory. Higher relative humidity and higher ambient temperature result in greater pyrophoricity.⁸

The stability of two classes of organolithium compounds must also be considered. Alkyllithium compounds undergo thermal decomposition *via* loss of lithium hydride, with formation of the corresponding alkene. The decomposition of *n*-butyllithium is illustrated in Figure 1.

Several factors influence the rate of this decomposition. The thermal stability of alkyllithiums increases in the series *s*-butyllithium < *n*-butyllithium < *t*-butyllithium, at the same concentration.⁹ For a given alkyllithium, the stability increases with decreasing concentration in the formulation.⁹ A lower storage temperature lowers the decomposition rate. The presence of alkoxide impurities, generated from admission of adventitious oxygen, accelerates the rate of decomposition.¹⁰ Lithium dialkylamides also undergo decomposition *via* loss of lithium hydride, to afford the corresponding imine. The decomposition of lithium diisopropylamide is illustrated in Figure 2. The rate of this decomposition is primarily impacted by the storage temperature. Higher temperature accelerates the decomposition. The lithium hydride that is produced in the decomposition of alkyllithium compounds and lithium dialkylamides precipitates from the

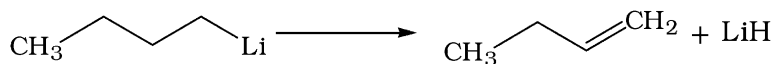


Figure 1. Thermal decomposition of *n*-butyllithium.

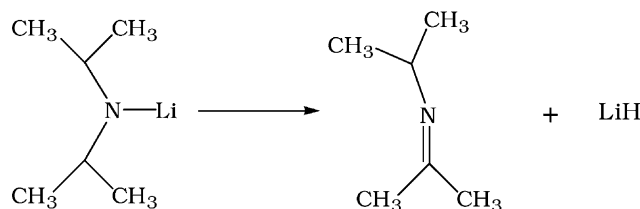


Figure 2. Thermal decomposition of lithium diisopropylamide.

solution as very fine particles. This finely divided lithium hydride is pyrophoric. To maximize the shelf-life of these materials, it is recommended that they be stored in an explosion-proof refrigerator at <10°C. Further, since the assay of these reagents can decline with storage, it is good practice to verify the assay prior to utilization in an experiment.¹¹

PLANNING THE EXPERIMENT

In spite of these hazards, the reactivity of organolithium compounds has been successfully harnessed. Indeed, with proper planning on the part of the experimenter, organolithium compounds can be safely handled in the laboratory. These same techniques can also be employed in large-scale applications, from kilo laboratory up to commercial-scale production. Proper precautions must be taken against the principle hazards of organolithium compounds: corrosivity, flammability and in certain instances, pyrophoricity. There are a number of circumstances that must be avoided in dealing with organolithium compounds in the laboratory: personnel exposure, air, oxygen, moisture, water, heat, clutter, source of ignition (spark) and fuel. Prior to the commencement of an experiment that utilizes an organolithium, it is strongly recommended to consult the Material Safety Data Sheet (MSDS) supplied by the vendor. The MSDS will contain recommendations for handling and storage of the specific organolithium compound of interest.

The first consideration in planning the experiment is location—where to conduct the experiment. To minimize personnel exposure, it is highly advi-

sable to conduct the experiment in an efficient fume hood. The fume hood should be free of clutter. The hood should not be used as a storage area for out of service equipment and supplies. Less clutter makes it easier to clean up a spill or extinguish a fire in the event of a release of an organolithium. The fume hood will also sweep fumes away more effectively with less clutter present. Combustible materials, such as solvents, flammable chemicals (reagents or samples), paper or cloth should be removed from the hood prior to the experiment. These are all potential fuel sources that can contribute to a fire in the event of spill of an organolithium. The fume hood must be equipped with a source of inert gas, such as nitrogen or argon. A delivery system to distribute the inert gas to the reactor, such as manifold or plastic lines, and a bubbler system are also required. The delivery system will be described in more detail in the next section. Equipment is also required to dry the glassware prior to the experiment.

Nitrogen or argon can be employed as the inert gas in reactions that employ organolithium reagents. Typically, nitrogen is available in several grades from the supplier. Select the grade with the lowest moisture and oxygen content. Argon must be utilized in reactions where lithium metal is a reactant. Nitrogen reacts exothermically with lithium metal to afford lithium nitride (Li₃N). Further, this reaction is catalyzed by moisture.

The glassware employed in the reaction must be free of moisture and oxygen before introducing the organolithium compound. There are several techniques routinely employed to dry and inert a reaction apparatus. 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, isolate the vacuum, then refill the apparatus with the inert gas. This 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 the 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 pieces in an oven to dry. The glassware should remain in the oven for at least several hours at 120°C, assembled hot in the hood, and allowed to cool to room temperature in a stream of inert gas. Alternatively, the glassware can be removed from the oven, placed in a desiccator to cool to room temperature, assembled in the hood then purged with the inert gas.

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 of organolithium reagents (greater than 1 L) are employed. The flammability and pyrophoricity hazards are mitigated by the use of a flame-resistant lab coat or coveralls.¹² 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 of Viton[®] afford the best overall protection; however, they are expensive.¹³ Nitrile gloves offer a good compromise between chemical protection and affordability.¹⁴ Proper footwear, leather, closed-toe shoes, protect the feet from spills.

In the event of a spill, another important element to protection of personnel and equipment is a fire extinguisher. It is important to secure the appropriate fire extinguisher for organolithium reagents prior to initiation of the experiment. The recom-

mended fire extinguisher is a Class B fire extinguisher.¹⁵ It is imperative NOT to use fire extinguishers that contain water, carbon dioxide or halogenated hydrocarbons for organolithium fires. Alkylolithiums react violently with these three classes of extinguishing agents. The use of these improper extinguishers will exacerbate, rather than mitigate, the fire scenario.

LABORATORY SET-UP

A typical organolithium reaction apparatus, outfitted for cannula transfer, is illustrated schematically in Figure 3. The reactor is equipped with a mechanical stirrer, a pressure-equalizing addition funnel equipped with a septum, and a Claisen adapter fitted with a thermometer to measure 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 bubbler¹⁶ monitors the positive flow of inert gas through the system and prevents the inflow of air into the reactor in the event of partial vacuum. A second inert gas line is employed for the reagent bottle of organolithium. The mineral oil bubbler on this side has a clamp on the outlet to facilitate transfer *via* the cannula. The reaction vessel and the organolithium should each be placed

in a metal bowl. This serves as a catch pan for the organolithium solution in the event either breaks. In addition, the metal bowl surrounding the reaction vessel can be employed to hold the cooling medium for a cryogenic reaction. This cooling medium should be

There are two basic techniques for the transfer of organolithium solutions in the laboratory, the syringe technique and the cannula technique.

an inert hydrocarbon solvent, such as hexane or heptane, mixed with solid carbon dioxide, "dry ice." The more traditional cooling bath solvents, acetone or 2-propanol, react vigorously with organolithium solutions and should be avoided. Similarly, a water condenser should not be used, due to potential for leaks, which could enter the reaction vessel.

TRANSFER TECHNIQUES

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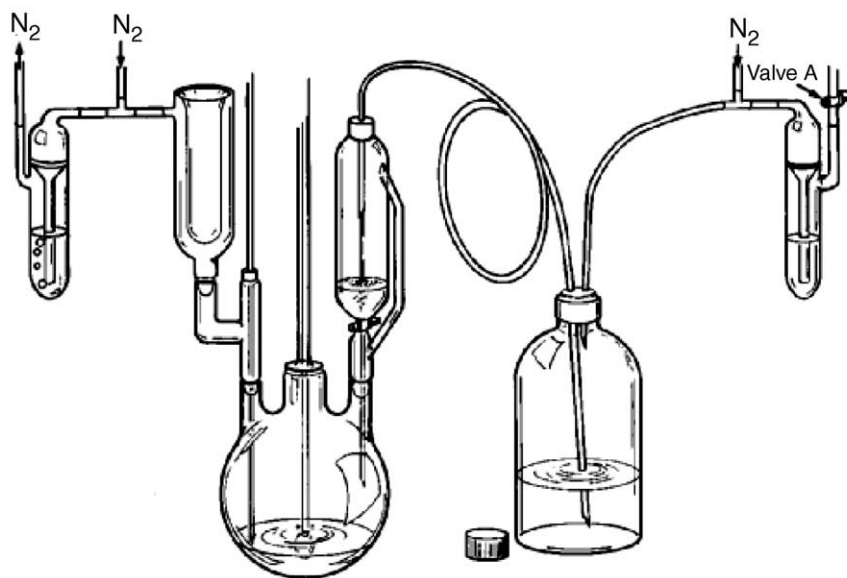


Figure 3. Laboratory apparatus for cannula transfer.

and the cannula technique. The two techniques are very similar. The syringe technique is preferred when relatively small volumes of organolithium solutions are required (less than 50 mL). The transfer of larger volumes is most easily accomplished with the cannula technique. The laboratory apparatus for a cannula transfer is illustrated in Figure 3.¹⁷

Syringe Technique

Clutter and combustibles are removed from the hood where the reaction will be conducted. The reaction apparatus is dried, purged with an inert gas and assembled in the hood using one of the techniques detailed previously. The reaction flask is placed in a metal bowl. The bottle of the organolithium compound is removed from the refrigerator and is clamped in the hood in a metal bowl. This minimizes the chance of a spill if the bottle is accidentally bumped during the transfer. It is recommended that the syringe be at least twice the volume of the organolithium to be dispensed. The syringe that will be employed in transfer must also be dried before it is employed. The syringe should be dried in an oven for at least 2 hr at 120°C, placed in a desiccator to cool to ambient temperature, then purged with a stream of inert gas. Don all the recommended PPE. 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 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 from the sample bottle. Care must be taken not to withdraw the organolithium solution faster than the inert gas flow can refill the void. This would allow air to enter the inert gas line and possibly contaminate the organolithium solution. The tip of the syringe needle is then inserted into the septum of the addition funnel. The organolithium solution is then dispensed into the funnel by pushing

down on the syringe plunger. The solid cap is replaced on the sample bottle and it is returned to the refrigerator. The amount of the organolithium dispensed can be calculated by noting the final volume in the addition funnel. A more accurate technique for determining the amount of organolithium transferred is by weight. This is accomplished by weighing the sample bottle before and after the reagent has been dispensed. It is advisable to clean the syringe soon after the transfer is complete, to minimize the chance of the plunger sticking and “freezing” in the barrel. 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 then be quenched by slowly mixing with an equal volume of cold water.

Cannula Technique

Clutter and combustibles are removed from the hood where the reaction will be conducted. The reaction apparatus is dried, purged with an inert gas and assembled in the hood using one of the techniques detailed previously. The reaction flask is placed in a metal bowl. The bottle of the organolithium compound is removed from the refrigerator and is clamped in the hood in a metal bowl. This minimizes the chance of a spill if the bottle is accidentally bumped during the transfer. The cannula is a long syringe needle with a sharpened tip at each end. The cannula that will be employed in transfer must also be dried before it is employed. The cannula should be dried in an oven for at least 2 hr at 120°C, placed in a desiccator to cool to ambient temperature, then purged with a stream of inert gas. Don all the recommended PPE. 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 sample bottle. Observe the inert gas flow at the bubbler and adjust the flow accordingly. One tip of the cannula is then inserted into the septum of the reagent

bottle. The other tip of the cannula is inserted into the septum in the addition funnel. The tip of the cannula is lowered into the liquid of the organolithium solution. The clamp on the exit of the mineral oil bubbler attached to the reagent bottle is slowly closed. This causes pressure to build in the reagent bottle and the organolithium solution will transfer to the addition funnel. Inert gas pressure should never exceed 5 psi (0.3 bar). When the desired volume has been transferred, the clamp on the bubbler is released 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. Let any excess organolithium solution drain back into the reagent bottle by gravity. The cannula is removed from the reagent bottle and then from the addition funnel. The solid cap is replaced on the sample bottle and it is returned to the refrigerator. The amount of the organolithium dispensed can be calculated by noting the final volume in the addition funnel. A more accurate technique for determining the amount of organolithium transferred is by weight. This is accomplished by weighing the sample bottle before and after the reagent has been dispensed. It is advisable to clean the cannula soon after the transfer is complete, to minimize the chance of 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. This rinse solution can then be quenched by slowly mixing with an equal volume of cold water.

DISPOSAL OF ORGANOLITHIUM COMPOUNDS

Small residues of organolithium compounds can be safely quenched in a hood. Pyrophoric materials should be diluted to less than 5 wt.% with an inert solvent, such as heptane. This solution should then be added slowly (*via* an addition funnel) to well-stirred solution 2 M of 2-propanol in heptane. Monitor the temperature of this quench solution with an internal thermometer. Maintain the temperature 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/heptane. The resultant solution of lithium isopropoxide in heptane can then be disposed of as flammable, hazardous waste. Containers of organolithium reagents that have developed significant quantities of solids should be discarded. These larger volumes of organolithium reagents that are no longer needed should be sent out for disposal as a lab pack. This minimizes laboratory personnel exposure to the hazards of quenching large volumes of organolithium compounds and their decomposition products.

NEW DEVELOPMENTS

Several innovative organolithium compounds and formulations have recently been commercialized. These innovations have improved safety characteristics over the older, more traditional organolithium reagents. The first is 33 wt.% *n*-hexyllithium in hexanes. This 2.5 M solution of *n*-hexyllithium has similar reactivity to the analogous

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concentration of *n*-butyllithium in typical applications. Furthermore, it exhibits two significant safety advantages over *n*-butyllithium. First, this formulation of *n*-hexyllithium in hexanes tested as non-pyrophoric, even at concentrations up to 85 wt.%.⁷ The second advantage is that in deprotonation experiments, the co-product is *n*-hex-

ane, a liquid with a boiling point of 67°C. A similar reaction with *n*-butyllithium would afford butane (boiling point = -0.5°C) as the co-product. *n*-Hexane is much easier to contain than butane, particularly on an industrial scale. Another innovation is the commercial availability of preformed solutions of lithium diisopropylamide (LDA). These formulations of LDA are non-pyrophoric.⁷ In addition, when the preformed solution of LDA is employed, the experimenter does not have to handle pyrophoric *n*-butyllithium traditionally employed. A further advantage of the preformed LDA formulation is that again, the experimenter does not have to deal with the emission of the co-product butane. A third innovation is the newly commercialized formulation of *t*-butyllithium in heptane.¹⁸ While this new formulation is still pyrophoric, it is much safer to handle than the traditional pentane formulation of *t*-butyllithium.¹⁹ This is due to the much higher flash point of heptane (Fp = -1°C) versus pentane (Fp = -49°C).

CONCLUSIONS

Organolithium compounds are extremely useful reagents in organic synth-

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corrosive, flammable and in certain cases, pyrophoric. However, these hazards can be minimized. The experiment should be carefully planned prior to its execution to minimize hazards to personnel and the physical plant. Proper PPE to mitigate the hazards of organolithium compounds should be secured and worn at all times. All equipment that is employed for the experiment must be free of moisture. An inert atmosphere of nitrogen or argon is also critical in minimizing the hazards of organolithium compounds. Solutions of organolithium compounds can be safely transferred from the storage bottles to the reaction flask with either a syringe or a cannula. With the utilization of these basic techniques, organolithium compounds can be safely handled in the laboratory. When properly handled, organolithiums provide unique properties that allow for precise control of a molecular architecture, while also demonstrating enhanced nucleophilicity, stability, and excellent solubility in organic solvents. With proper care and attention, organolithiums can be safely and effectively utilized in both laboratory and physical plant environments.

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References

1. Wakefield, B. J. *The Chemistry of Organolithium Compounds*; Pergamon: Oxford, 1974; Wakefield, B. J. *Organolithium Methods*, Academic Press: London, 1988; Brandsma, L.; Verkruijssse, H. *Preparative Polar Organometallic Chemistry I*; Springer-Verlag: Berlin, 1987; Brandsma, L. *Preparative Polar Organometallic Chemistry II*; Springer-Verlag: Berlin, 1990; Stowell, J. C. *Carbanions in Organic Synthesis*; Wiley: New York, NY, 1979. (For the application of organolithium reagents in organic synthesis.)
2. Hsieh, H. L.; Quirk, R. P. *Anionic Polymerization*; Marcel Dekker: New York, NY, 1996. (For an excellent overview of anionic polymerization.)

3. Stanetty, P.; Mihovilovic, M. D. *J. Org. Chem.*, **1997**, *62*, 1514. (For example, the half-life of *n*-butyllithium in THF at 20°C is 1.78 hr. The half-lives of various alkyllithiums in ethereal solvents as a function of temperature.)
4. Malpass, D. B.; Fannin, L. W.; Ligi, J. J. *Kirk-Othmer Encyclopedia of Chemical Technology*, 3rd ed.; Grayson, M., Ed.; Wiley: New York, NY, 1981, Vol. 16, pp. 557–8.
5. March, J. *Advanced Organic Chemistry*, 5th ed.; Wiley: New York, NY, 2001, p. 330.
6. Pyrophoric is derived from the Greek word *pyrophoros*, which is a combination of *pyr* (fire) and *pherein* (to bear), in *Webster's New World Dictionary of American English*, 3rd College ed.; Prentice Hall: New York, NY, 1994, p. 1096.
7. The official test for pyrophoricity is detailed in the Department of Transportation (DOT) regulations (49 CFR 173, Appendix E).
8. Wakefield, B. J. *Organolithium Methods*; Academic Press: London, 1988, p. 12.
9. Totter, F.; Rittmeyer, P. *Organometallics in Synthesis: A Manual*; Schlosser, M., Ed.; Wiley: Chichester, 1994, pp. 171–2.
10. 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. 453–4.
11. Kamienski, C. W. *Lithium Link*, **1994** (Winter). (For an excellent review of the various methods of analysis of organolithium compounds.)
12. One brand of flame resistant fabric is Nomex[®]. A variety of 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 Aldrich, Fisher and VWR.
13. One pair of Viton[®] gloves, size 9, is listed in the 2000–2001 Aldrich catalog for \$57.60.
14. One pair of nitrile gloves, size L, is listed in the 2000–2001 Aldrich catalog for \$7.20.
15. Ansul[®] Purple K is one popular choice for a Class B fire extinguisher.
16. A number of bubbler designs are commercially available from laboratory glassware suppliers. A versatile bubbler design is Chemglass catalog number AF-0513-20.
17. *Butyllithium: Guidelines for Safe Handling*, a brochure available at no charge from FMC Lithium. (For a more extensive discussion of these transfer techniques.)
18. Commercially available from FMC Lithium, 449 N. Cox Road, Gastonia, NC 28054.
19. Bailey, B.; Longstaff, S. *Lithium Link*, **2000** (Fall). (For an excellent review of *t*-butyllithium chemistry.)