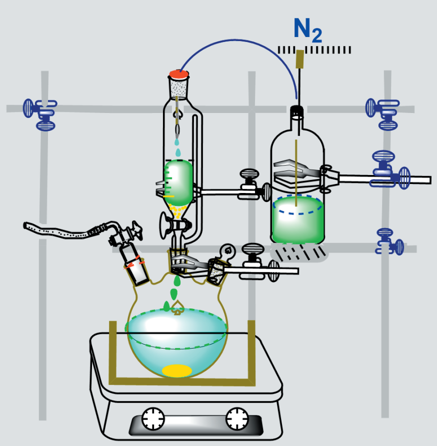
Lithiation Reaction

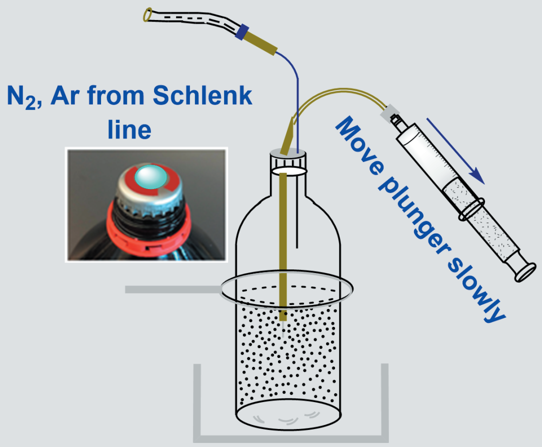
This Laboratory Reaction Safety Summary (LRSS) is a brief safety guide for laboratory chemists who plan to conduct a lithiation reaction using liquid reagents. Unlike a Laboratory Chemical Safety Summary (LCSS) or Safety Data Sheet (SDS), which are written specifically for laboratory chemicals, an LRSS is focused on reactions. This LRSS guides you through the RAMP process for managing chemical risks during lithiation reactions. RAMP is an acronym for recognize hazards, assess risks, minimize risks, and prepare for emergencies. Visit **What Is RAMP?** for more details. This LRSS will assist researchers in identifying and mitigating hazards and developing standard operating procedures (SOPs) for their specific substrates and reaction conditions.

Recognize Hazards

Alkyllithium compounds, such as *tert*-butyllithium, *sec*-butyllithium, and *n*-butyllithium, represent an important class of reagents, and their strong basic and reactive nature makes them both hazardous and useful in organic and inorganic syntheses.[1,2,3] These alkyllithium compounds pose a significant risk of fire. They, along with many organolithium compounds, are pyrophoric, meaning that they spontaneously ignite upon contact with air. They can also react with moisture in skin, resulting in the generation of alkaline hydroxide, which can cause severe caustic injuries or burns upon contact with skin, eyes, and mucous membranes. Fumes arising from the combustion of these compounds are mainly lithium oxide and lithium hydroxide, both of which are corrosive to eyes, skin, and the respiratory tract.



(Fig. 1: Cannula method)



(Fig. 2: Syringe method)

Assess Risks: What-If Analysis for Lithiation Reaction[4]

What if...	Answer	Result	Consequence(s)	Recommendation(s)
...the glassware is not moisture-free?	Deactivation or hydrolysis of the reagent can occur.	Difficultly initiating the reaction is possible.	Loss of substrate/low yield of the product. Elevated risks during quenching and cleanup	Glassware should be flame-dried under vacuum or flowing dry inert gas. Alternatively, assemble immediately after removal from a drying oven and allow to cool to room temperature under vacuum or dry inert gas.
...the reaction flask is not large enough to hold the entire reaction volume?	Overflow of the reaction flask occurs.	Chemical spill	Fire and chemical exposure	As a rule, aim for a vessel that is no more than 50% full when all reaction contents have been added.
...the reaction setup is not adequate for effective stirring?	Poor mixing occurs.	Uncontrolled, localized heating results.	Chemical spill with the risk of a fire	Use a suitable oval-shaped magnetic stir bar or overhead mechanical stirrer to stir the mixture.
...the cooling bath is not adequate for effective cooling?	Excessive heat generation	Uncontrolled reaction occurs.	Chemical spill with the risk of a fire	Ensure that the cooling bath is large enough to accommodate a range of reaction flask depths for control of the cooling rate. Alternatively, use a suitable boiling-point solvent and reflux condenser for heat removal.
...there is uncontrolled addition of the reagent?	Excessive heat generation	Uncontrolled reaction occurs.	Chemical spill with the risk of a fire; substrate decomposition	Add reagent slowly using an addition funnel. Control the addition to avoid excessive heat generation. For larger scale, monitor the internal reaction temperature and adjust the addition rate as needed to maintain the target temperature.
...the reagent container is over-pressurized?	The container can rupture.	Possibility of reagent spill	Risk of a fire	Control the pressure of the inert gas using Schlenk line techniques or an oil bubbler.
...a syringe method is used for a large-scale reagent transfer?	Multiple transfers are required.	Possibility of reagent spill[3]	Risk of a fire	For a large-scale reagent transfer (>25 mL), always use a cannula transfer method.
...an insufficiently long needle is used to transfer the reagent from the bottle?	Difficulty in withdrawing the reagent, and the bottle is tilted to withdraw the reagent	Difficulty in withdrawing the reagent, and possibility of reagent spill	Chemical spill with the risk of a fire	Use a longer needle to withdraw the reagent, and eliminate the risk associated with tilting the bottle.
...the substrate is contaminated with unknown impurities?	There is a possibility of side-product formation.	Runaway reaction with energetic release of chemicals	Risk of chemical fire or explosion	Any substrate used for the lithiation should be purified.
...the addition funnel starts leaking during the alkyllithium addition?	There is a loss of reagent.	Chemical spill	Possibility of a fire; incomplete reaction	If using an addition funnel, thoroughly test it before use with pyrophoric reagents.
...the concentration of the alkyllithium reagent is not accurate?	The completeness of the reaction is unknown.	Incomplete reaction, or excess alkyllithium will remain	Incomplete reaction or fire hazard	Always titrate reagents before use.
...the reaction or quenching is incomplete?	An unanticipated hazard remains during cleanup.	The leftover reagent will react vigorously and unexpectantly.	Risk of fire or explosion hazard	Many accidents happen with pyrophoric chemicals during workup and cleanup. Have a plan prepared for these often-overlooked steps.

Minimize Risks

Before Beginning Work:

- Conduct a risk assessment, and use the results to develop a standard operating procedure (SOP).
- Ensure that another person familiar with these reagents is present in the laboratory.
- Don the proper personal protective equipment (PPE), including a flame-resistant lab coat, Nomex gloves, and chemical splash goggles or face shield (see more information below).
- Verify proper operation of the laboratory fume hood, and remove all unnecessary equipment, chemicals, and supplies, especially those that are flammable or combustible (e.g., solvent wash bottles, cork rings, paper towels).
- Inspect glassware and the reaction setup for any cracks in the flasks; replace any cracked glassware.
- Titrate alkyllithium reagents before use. Mark the bottle with the date when this was last done.

During Work:

- All pyrophoric chemical manipulations must be performed in a laboratory fume hood.[5]
- Use a cannula method for large-scale (>25 mL) reagent transfer (Fig. 1), and use a syringe method for small-scale (≤25 mL) transfer (Fig. 2). Never use a plastic syringe to make multiple transfers. The plunger tends to swell, making it hard to move.
- For precise reagent transfer by cannula, have the glass shop attach a 24/40 female ground-glass joint to a graduated cylinder. Transfer the reagent by cannula through a septum into the dried and nitrogen-purged graduated cylinder. Then transfer the required volume from the cylinder into the addition funnel.
- Use a long needle to reach the reagent level. Never invert the bottle, because such an action disturbs sediments that may clog the needle.[6]
- Use polypropylene syringes or gastight syringes with Luer locks that prevent needles from slipping off. Never use glass syringes with ground-glass plungers, because solvent evaporation and air infiltration along the plunger can cause the plunger to seize and/or at high pressures the solution can leak out the back and the plunger can easily fall out, resulting in a spill.
- Add pyrophoric reagents slowly to the substrate, using a cooling bath to control the reaction rate and heat dissipation. If possible, monitor the internal reaction temperature to alert you to rapid temperature increases before they become a problem.

After Work:

- Never open any container or vessel with residual pyrophoric reagents to air; quenching of residual reagents is required using the standard procedure.
- Always store pyrophoric chemicals in an inert atmosphere. Procure the smallest volume of reagent needed for use. This also saves money, because these reagents tend to decompose over time.
- Store according to the manufacturer's recommended conditions. Note that many alkyllithiums are best stored in a refrigerator, not a freezer. In a freezer, the lithium reagent can crystalize out in some cases, and frost on the bottle can be a problem.

Recommended Controls and PPE:
Engineering Controls: Chemical fume hood.

Administrative Controls: Follow the precautions described above. Do not work alone when performing lithiation reactions. Develop and follow a standard operating procedure (SOP) specific to your reaction.

PPE: Splash goggles or face shield, a flame-resistant lab coat, and Nomex gloves. (Note: Fire-resistant Nomex gloves are recommended for working with pyrophoric compounds. Nomex flight gloves have been reported to provide improved dexterity compared with the conventional style.) Nitrile gloves offer better dexterity and some chemical protection but no fire protection.

Prepare for Emergencies

- Especially in small communities, make sure that local emergency responders and local trauma centers are aware of the chemicals used in your facility and that they are trained and equipped to respond to a spill, fire, and injuries.
- Double-check that the laboratory emergency call-out list is up to date.
- Before performing the actual experiment, conduct a dry-run rehearsal. Have colleagues who are experienced with lithiation reactions critique the procedure. Include various accidents in the rehearsal (e.g., spill, fire) to practice emergency procedures.
- Position a dry chemical (ABC) fire extinguisher nearby.
- During work with an alkyllithium reagent, keep a large beaker of dry ice in the hood. If the reaction needs to be aborted, lithium reagent in a syringe can be emptied into the beaker with the dry ice. The CO_2 subliming from the ice will retard the reaction with air.[7]

Note: For full legal considerations, refer to the **CCS Tipsheet page**. For more information and useful templates, visit **ACS Hazard Assessment Tools**. Laboratory Chemical Safety Summaries can be found at **PubChem**.

References

1. Wakefield, *B. J. Organolithium Methods*; Academic Press: London, **1988**.
2. Eisch, J. J.; Kaska, W. C. Chemistry of Alkali Metal-unsaturated Hydrocarbon Adducts: I. Metalations with Lithium Metal Adducts of Biphenyl Systems. *J. Org. Chem*. **1962**, 27, 3745–3752.
3. Kimsley, J. Learning from Mistakes. *Chem. Eng. News* **2009**, 87(8), 58.
4. ACS. Identifying and Evaluating Hazards in Research Laboratories; American Chemical Society: Washington, DC. **identifying-and-evaluating-hazards-in-research-laboratories.pdf** (acs.org)
5. Alnajjar, M.; Quigley, D.; Kuntamukkula, M.; Simmons, F.; Fraser, D.; Bigger, S. J. Methods for the Safe Storage, Handling, and Disposal of Pyrophoric Liquids and Solids in the Laboratory. *J. Chem. Health Saf.* **2011**, 18(1), 5–10.
6. Chandra, T.; Zebrowski, J. P.; Lenertz, L. Y. Safe Handling of Cannulas and Needles in Chemistry Laboratories. *J. Chem. Health Saf.* **2022**, 29(2), 175–183.
7. Gau, M. R.; Zdilla, M. J. A Protocol for Safe Lithiation Reactions Using Organolithium Reagents. *J. Vis. Exp.* **2016**, 117(Nov 12), 54705.