Preparation of Highly Reactive Lithium Metal Dendrites for the Synthesis of Organolithium Reagents

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ABSTRACT

A long-standing problem in the area of organolithium chemistry has been the need for a highly reactive Li–metal source that mimics Li–powders but has the advantage of being freshly prepared from inexpensive and readily available Li–sources. Here we report a simple and convenient activation method using liquid ammonia that furnishes a new Li–metal source in the form of crystalline Li–dendrites. The Li–dendrites were shown to have ca 100 times greater surface area than conventional Li–sources created by prototypical mechanical activation methods. Concomitant with the surface area increase, the Li–dendrites are 19 times more reactive than Li–powders which are currently the industry standard for the preparation of organolithium compounds. These features were leveraged for the reproducible synthesis of organolithium reagents over a range of common laboratory scales.

1. INTRODUCTION

Lithium metal has revolutionized many scientific arenas from the development of active pharmaceuticals to Li–batteries (Figure 1A).[1,2] Perhaps unsurprisingly the physical form of the Li–metal greatly impacts its chemical properties and function as most processes take place at the Li–metal surface.[3] Fortunately, Li–metal is highly malleable and can be shaped into various workable forms such as pellets, rods, and foils. Although these physical forms of Li–metal find use in many real–life settings, the increased demand for faster electron transfer properties in several industrial applications has resulted in a great deal of investigation into Li–sources that vary in surface area and composition.[4,5] For instance, one of the most significant advances in the chemical sciences involved the development of Li–powders for the preparation of organolithium compounds which continue to provide solutions to many pressing synthetic challenges to this day.[6–12]

Beginning last year our group initiated a program of investigation that required the use of Li–metal to construct carbon–lithium bonds (Figure 1B). Unfortunately, commercial access to Li–powders or dispersions has become extremely limited, as lithium's broad impact and future potential in the energy and battery sector has shifted production lines of raw materials to other areas.[4,13,14] Moreover, the preparation of Li–powder requires onerous reaction conditions of dispersing molten Li–metal in mineral oil, making the overall process unsafe and impracticable in most academic settings (Figure 1C).[15] We report here a new technical advance in the form of a practical method to produce a highly reactive semicrystalline Li–metal source "Li–dendrites" which were plated and crystalized from liquid ammonia solutions (Figure 1D).[16] This innovative Li–dendrite material was found to be 19 times more reactive than common Li–powders and is easily accessible in most laboratories. Moreover, this new Li–source was found to be highly reactive toward oxidative addition reactions with organic halides allowing access to a wide variety of organolithium species that previously could only be prepared with Li-powders.

2. BACKGROUND

2.1. Preparation of Reactive Metal Powders. In the realm of organometallic chemistry, the transfer of electrons from a metal to an organic substrate is the quintessential process to form carbon–metal bonds (Figure 1B).[17] However, because the reactions are heterogenous, variabilities in the quality and area of the metal surface often renders these processes unpredictable and facetious in nature especially on routine laboratory scales.[18,19] Historically, reaction development in this field has relied on activating the metal by mechanically reducing the size of the metal particle and by the addition of chemical activators such as iodine to clean the metal surface.[20,21] In the 1970s, Rieke pioneered an elegant solution to these practical problems of efficiency and generality for several alkaline earth and transition metals such as magnesium, zinc, and copper by developing a method that allowed access to highly reactive metal powders *via* the reduction of metal salts with alkali metals (Figure 1C).[22,23] Beyond the obvious synthetic utility of preparing reactive metals freshly, Rieke's method was practical and straightforward making it an instant success amongst the chemistry community. Unfortunately, Li–metal bears the lowest reduction potential among the elements and therefore cannot be prepared using Rieke's method. As a departure from the current synthetic logic of mechanically pulverizing known Li–metal sources into reactive powders, we sought a new chemical approach which would allow for distinctive Li–metal sources to be practically prepared.

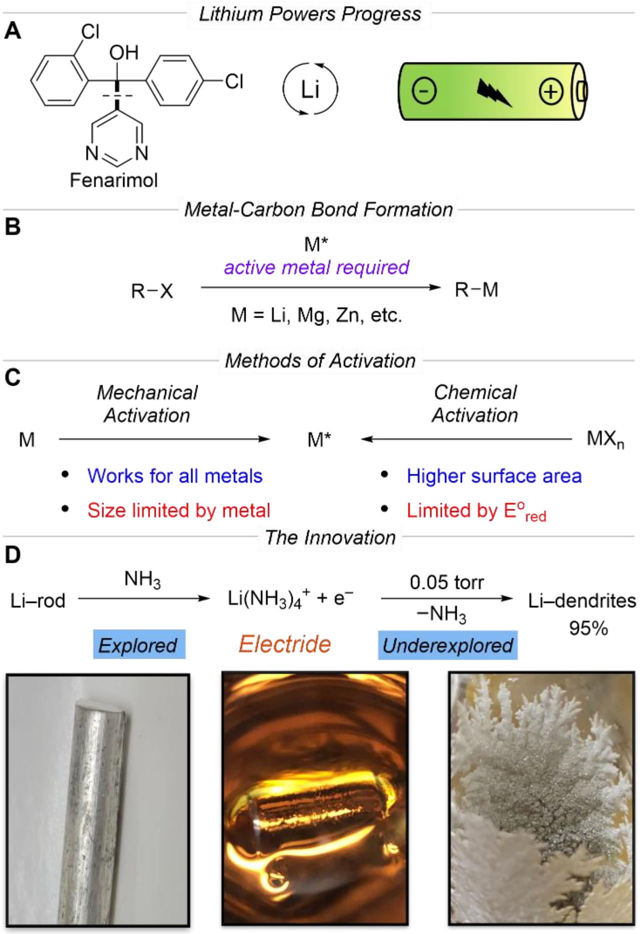


Figure 1. Uses of Lithium and Activation Methods. (**A**) Technologies underpinned by advances in lithium chemistry. (**B**) The primary method of generating metal-carbon bonds. (**C**) The methods for activation of metals for metal-carbon bond formation reactions. (**D**) This work – The formation of Li–dendrites from Li–ammonia solutions.

2.2. Formation of Lithium Electrides. Considering lithium's low reduction potential, we pondered if we could use this to our advantage by creating a chemical equilibrium which would allow for Li–metal to be briefly ionized to a Li–cation and electride followed by the microscopic reverse to reform the metal in a more reactive state. In fact, lithium's low reduction potential allows for it to be easily ionized in the presence of strongly Lewis basic ligands such as ammonia or alkylamines.[24,25] During this type of dissolution process the *s* electron from Li–metal is ionized into solution which leads to the characteristic blue hue of a solvated electron under relatively dilute conditions and a fiery bronze color at high concentrations (Figure 1D). Understanding the fundamental nature of the alkali metal electrides has been an ongoing topic of research for over a century.[26,27] More recent investigations of inorganic electrides have realized important applications in the production of ammonia and hydrogen storage.[28] Although the past few years have witnessed an upsurge of interest in understanding the physical properties and applications of these Li–

electride solutions in the energy sector, to our knowledge exploring the microscopic reverse of Li–metal formation and its capacity to influence the morphology of Li–metal appears to have reached an evolutionary dead–end.[29,30] With a need for a more reactive Li–metal source we theorized that Li–mirrors or crystals could be formed upon the removal of ammonia from Li–electride solutions.

3. RESULTS AND DISCUSSION

3.1 Synthesis and Structural Analysis of Li–Dendrites.

3.1.1. Preparation of Li-dendrites from bulk Li-metal and ammonia. Ammonia is manufactured annually on megaton scales making it an inexpensive and ideal solvent for both academic and industrial settings.[31] Although it is a gas at standard atmospheric temperatures and pressures, its enthalpy of vaporization (23.35 KJ/mol at rt) is high, making it simple to condense and easy to handle in liquid form.[32,33] Our studies began by investigating the solubility of Li–metal in anhydrous ammonia; where 0.5 g Li–metal/13 mL was found to dissolve at –78 °C affording a Li–bronze solution.[34] After warming to rt along with vigorous stirring the ammonia was slowly removed *in vacuo* at 0.05 torr where a metallic Li–mirror began to gradually deposit on the walls of the vessel.[35] Upon further evaporation (ca 10–15 min) of ammonia, metallic Li–dendrites began to grow affording a semicrystalline material (Figure 1D). After the removal of exogenous ammonia *via* vacuum for ca 0.5 h, the Li–dendrites could be used immediately or easily removed and stored under inert atmospheres without significant damage to the surface or morphology of the material. Moreover, this process was found to be reproducible and scalable up to at least 200 mmol where similar Li–dendrites were observed.

3.1.2. Surface area and BET analyses of Li-metal sources. Upon visual inspection of the Li–dendrites it was evident from their metallic state that the surface was clean along with a dramatic increase in area compared to lithium rods and foils (Figure 2A). Interestingly, BET surface area measurements of the Li–dendrites (115,000 cm^2/g) revealed that the material has, on average, ca 100 times higher surface area than the Li–powder (1,100 cm^2/g). To gain insight into the surface morphology of the Li–dendrites a sample for scanning electron microscopy (SEM) was randomly selected and carefully mounted under inert atmospheres. Although the bulk morphology was clearly agglomerated in a dendritic form, the SEM images revealed that the microstructure was comprised of non-porous crystals in the range of ca 20–100 μm in diameter (Figure 2B–D). The crystals exhibited significant amounts of screw and step dislocations which were likely the result of nucleation being disturbed during the ammonia removal process. To compare the microstructure of the Li–dendrites to Li–powder similar SEM pictures were collected and as expected the morphology of the powder was spherical with no significant crystalline features (Figure 2E).

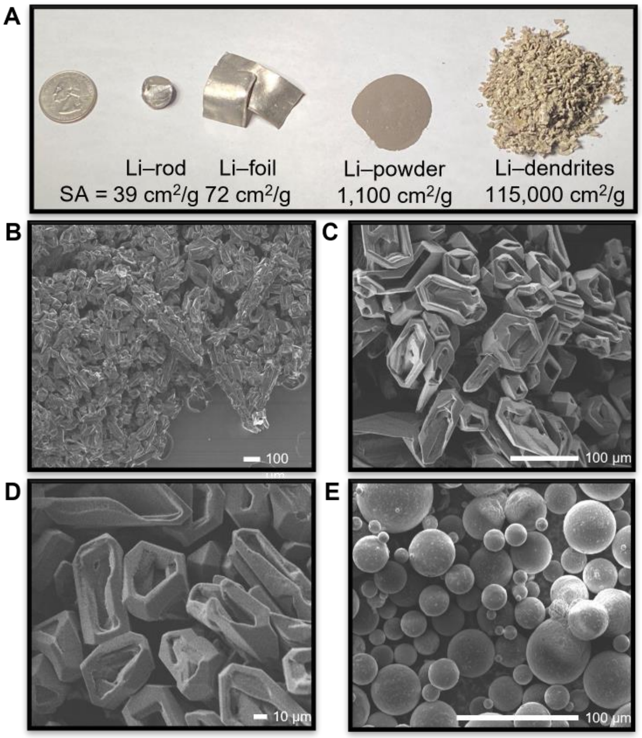
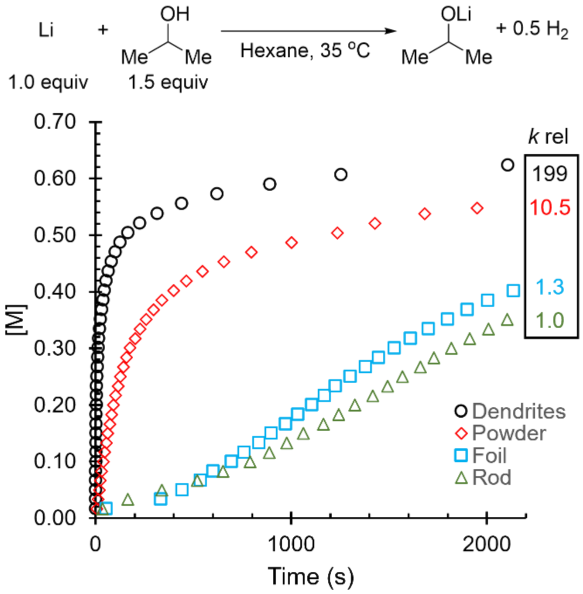


Figure 2. SEM Images of Li–materials. (**A**) Comparison image of different forms of Li–metal using 500 mg of each material. (**B**) SEM image of Li–dendrites, 60 x magnification. (**C**) SEM image of Li–dendrites, 250 x magnification. (**D**) SEM image of Li–dendrites, 500 x magnification. (**E**) SEM image of Li–powder, 1100 x magnification.

3.2. Kinetic Analysis of Li–Metal in Various Physical Forms.

Given the ability to reproducibly synthesize Li–dendrites we set out to quantify and compare the reactivity of our system to Li–metal in other physical forms. To establish the kinetic behavior, isopropanol was added separately to hexane suspensions of lithium rod, foil, powder, and dendrites such that the evolution of hydrogen gas could be visually monitored by video recording using a burette (Figure 3).[36] This analysis revealed sigmoidal concentration vs time curves for the rod, foil and dendrites which is characteristic of an induction period and consistent with literature reports (Figures. S33-35 and S39-44).[37] To allow for a straightforward comparison, the rate of hydrogen formation was measured through the linear region of each curve and first with Li–rod (2.08 $\pm$ 0.05) x 10^{-4} M/s so that the rates could be normalized. While lithium rod and foil both resulted in near identical reaction rates, Li–powder was 10.5 times faster than the Li–rod. Interestingly, the Li–dendrites were 199 times more reactive than the rod and 19 times faster than the Li–powder – demonstrating that the Li–dendrites provided a superior reaction surface over the other Li–metal sources. Not only was the overall reaction faster with the Li–dendrites but the induction period was significantly reduced over the Li–rod and foil. We suspect that the drastic rate increase is due to the combination of clean and increased surface areas as well as the high densities of dislocations and imperfections which are all known to accelerate rates of electron transfer.[38]



Li-Dendrite Video

Li-Powder Video

Figure 3. Kinetic measurements of various Li-sources. Kinetic measurements carried out by rapidly injecting a hexane solution of isopropanol (3.0 mmol) into Li–metal (2.0 mmol) suspensions in hexanes. Full videos of kinetic experiments are available by following the QR codes pictured, full links available in the supporting information.

3.3. Synthesis of Organolithium Reagents with Li-Dendrites.

3.3.1. Optimization of organolithium synthesis. The discovery of a new Li–source exhibiting enhanced reactivities inspired us to explore its preparative significance by developing a simple protocol for the preparation of organolithium reagents. To test the feasibility of the outlined reductive metalation, *s*–BuCl was selected as the model substrate because its rate of Li–metal insertion is known to be in between that of *n*–BuCl and *t*–BuCl making it ideal for reaction optimization.[39] After an extensive survey of the reaction conditions, we found that *s*–BuLi could be produced in 87% yield employing 4.0 equiv of Li–dendrites along with 1 mol% of sodium on a 2.5 mmol scale (Figure 4).[40] Our observations support previous findings that the addition of sodium (~1 mol%) as well as the employment of multiple equivalents of Li–metal was vital for reasonable rates of Li–insertion to be achieved and prevent deleterious elimination and or dimerization pathways.[41]

3.3.2. Reliability and scalability of organolithium formation with Li-dendrites. The next phase of our investigations focused on evaluating the reliability of our optimized protocol over a range of reaction scales that are common practice in the synthetic laboratory: 0.1, 2.5, 10 and 50 mmol scales.[42,43] As can be seen by inspection of Figure 4, each of these reaction scales resulted in similar yields. Of note, the volume of the Li–dendrites allows for minute amounts of Li-metal to be reliably and accurately weighed affording reproducible results even on small scales, which is often challenging for Li-insertion reactions.[44]

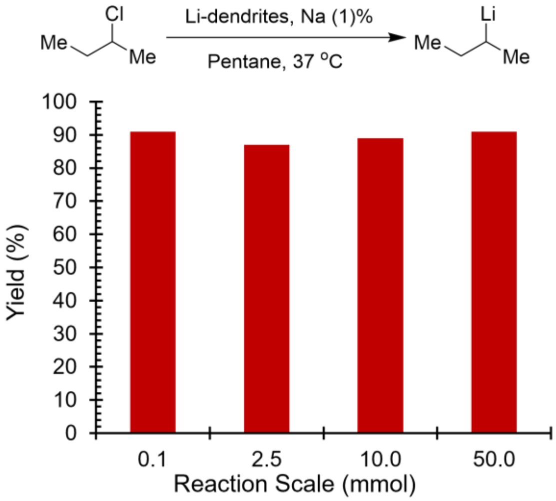


Figure 4. Scalability of lithium reagent synthesis from the Li–dendrites. Experiments were conducted over a range of reaction scales under identical conditions.

3.3.3. Preparative formation of organolithium reagents with Li-dendrites. The ability to prepare Li–dendrites exhibiting high reactivity patterns towards organic halides provided us the unique opportunity to explore the generality of the organic halide scope (Figure 5). Beginning with *n*–BuCl an 86% yield was observed indicating that primary alkyl chlorides were as reactive as the secondary alkyl chlorides as described above. Furthermore, *n*–BuLi could be readily prepared in comparable yields in a safer non–flammable poly(α–olefin) SpectraSyn^{TM}2, further highlighting the robustness of our protocol.[45] Moreover, methyl chloride **2,** neopentyl chloride **3**, and trimethylsilylmethyl chloride **4** all resulted in high yields (86–94%). Although primary alkyl bromides **5** and **6** were found to give the desired insertion reaction in excellent yields (>91%); the secondary alkyl bromide substrate **8** resulted in slightly lower yield (63%) emphasizing that secondary bromide leaving groups offer avenues for nonproductive E2–elimination pathways to become competitive. Next, a set of halocarbocycles (**9**–**12**) were surveyed. In all cases, the reaction proceeded smoothly with the corresponding Li–carbocycle being formed in moderate to good yields (65–86%). A slight modification was needed for the 5– and 6–membered halocarbocycles whereby tert-butyl methyl ether (TBME) was identified as a sacrificial additive to prevent unproductive consumption of the organic halide.[46] This method was further applied to the synthesis of tertiary alkyl lithium reagents, which are difficult to access using previously reported Li–insertion reactions on laboratory scales. Like the 5– and 6– membered ring systems, *t*–BuCl **13** benefited greatly from the addition of TBME (77% vs. 45% without). Norbornyl chloride **14** on the other hand displayed moderate yields (72%) and showed no improvement with TBME, consistent with TBME's role in the suppression of E2–elimination.[47]

To broaden the utility of the Li–dendrite system, a series of vinyl and aryl chlorides were surveyed. After a solvent change to diethyl ether, 1-chlorocyclohexene **15** resulted in good yields of the vinyl lithium reagent. Furthermore, chlorobenzene **16**, 4–chlorotoluene **17**, 4–chloroanisole **18**, and 4–chlorodimethylaminobenzene **19** all resulted in excellent yields (91–96%).[48] Moreover, aryl bromide **20**, a substrate known to undergo facile side reactions from lithium halogen exchange, was found to afford its corresponding aryl lithium in excellent yields (92%).[49] By investigating the aryl halide substrate scope, we also noticed some limitations, as strongly electron deficient arenes such 4-chlorobenzotrifluoride **21** were completely unreactive under our described conditions.[50]

To further establish the versatility of our methodology we turned our attention to the preparation of organolithium compounds that bear functional groups that are often incompatible with alkyl lithium reagents such as *t*–BuLi, which is often the only viable option for complementary Li–halogen exchange processes.[51] Notably, ethers are often susceptible to facile deprotonation reactions with strong organolithium bases and this limits their applications in synthesis.[52] Accordingly, chloroarene **22** bearing both alkylether and tetrahydrofuran functional groups underwent Li–insertion cleanly and efficiently. Importantly, primary alkyl chloride **23** incorporating an alkylether subunit underwent smooth conversion into its organolithium, highlighting the robustness of our Li–source to create disconnections that have been employed in the synthesis of biologically relevant compounds.[53]

3.3.4. Preparation of isotopically labeled n-Bu^{6}Li with Li-dendrites. The ability to achieve high yields from Li–insertion reactions on small scales with short reaction times is of great synthetic importance. A particularly useful application of this methodology is the synthesis of ^{6}Li isotopically labeled organolithium reagents which are often used to obtain detailed aggregate structural information by ^{6}Li NMR investigations.[54,55] Using our standard protocol, both high yields and concentrations were obtained for *n*–Bu^{6}Li **24**, a ubiquitous base used to prepare other organolithium congeners through Li–halogen exchange reactions (Figure 5).[56] Several contemporary protocols for the synthesis of **24** require either the reduction of toxic diorganomercury compounds with ^{6}Li–rod or costly syntheses on scales of >100 mmol for high yields and purities to be achieved.[57,58]

3.4. Synthetic Usage of Freshly Prepared Organolithium Reagents

Taken together the examples illustrated above they clearly demonstrate the practical and synthetic advantages of Li–dendrites over other Li–sources in the synthesis of various organolithium compounds; however, for our lithium reagents to be deemed truly useful they needed to be successfully employed in various synthetic settings. To showcase the robustness of our freshly prepared organolithium reagents several highly utilized synthetic transformations were chosen and explored (Figure 5).[59] Prototypical carbon–carbon bond forming processes such as nitrile addition performed well. Furthermore, the alkylation of 4–phenyl–1–bromobutane **6** was found to be simple, clean, and high yielding (93%) employing the freshly prepared cyano–Gilman reagent **28**. Finally, potassium trifluoroborate **32** which is a common reagent employed in Suzuki–Miyaura cross–coupling reactions was also isolated in good yields through trapping vinyllitihum **30** with trimethyl borate **31**.[60]

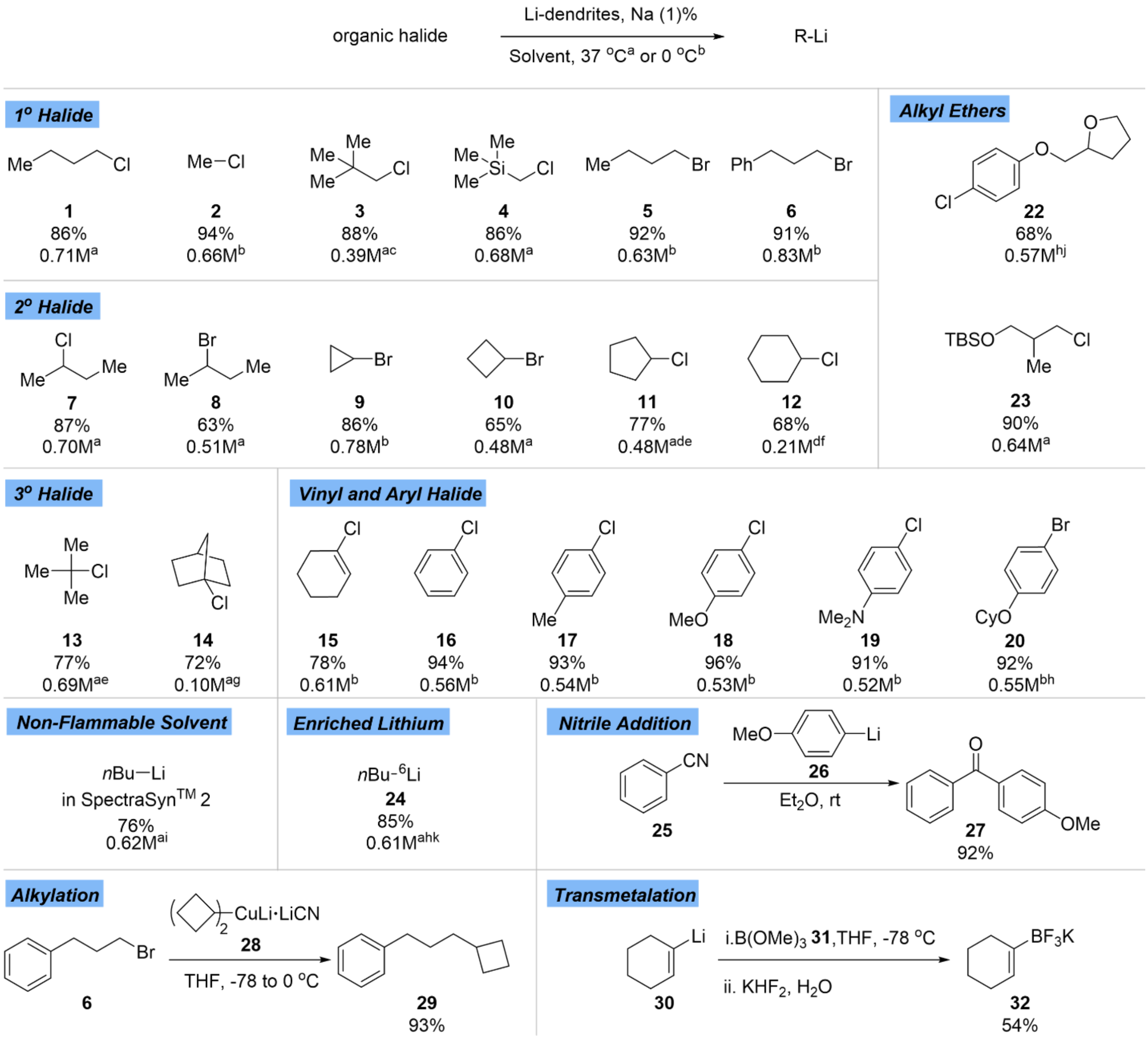


Figure. 5. Preparation of Organolithium Reagents and Use in Further Transformations. [a]Standard reaction conditions employed the organic halide (2.5 mmol) and Li-dendrites (10.0 mmol, 1 wt% sodium) in pentane (2.5 mL). Yields are an average of two runs. [b]Diethyl ether (2.5 mL) employed as the solvent. [c]5.0 mL of pentane employed in the reaction. [d]2.0 mol% of MTBE added to the halide stock solution before addition. [e]Cyclohexane (2.5 mL) employed as the solvent. [f]Toluene (5.0 mL) employed as the solvent at 50 °C. [g]12.5 mL of pentane employed in the reaction. [h]Single run experiment. [i]Spectrasyn™ 2 (2.5 mL) employed as the solvent. [j]THF (2.5 mL) employed as the solvent at 0 °C. [k]95% enriched ^{6}Li–chunk used in place of natural abundance Li–rod.

4. CONCLUSION

In summary, we have developed the first practical synthesis of a new crystalline Li–metal source which is 19 times more reactive than the current industry standard Li-powders. The protocol to activate the Li–metal is simple and can be performed over a range of reaction scales allowing for fresh batches of activated Li–metal to be prepared. This reactivity enhancement has important ramifications not only in a temporal sense but also as an avenue improve the scalability and reproducibility of Li–metal reactions. While this manuscript only focuses on applying this new Li–dendrite material to the synthesis of organolithiums we foresee this material finding utility in many settings that require highly reactive Li–metal surfaces.

ASSOCIATED CONTENT

Supporting Information

Full experimental procedures, characterization, and kinetic data and videos can be found in the supporting information.

NOTES: Authors declare that they have filed a provisional patent application for the preparation of the lithium dendrites.

ACKNOWLEDGMENTS

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(35) For video of the ammonia removal process, see the link provided in the supporting information on page S87.

(36) For hydrogen evolution videos please see links provided in the supporting information on page S87.

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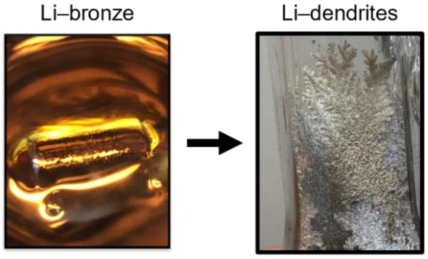

- 19x reactivity of Li–powder
- Simple synthesis
- >20 lithium reagents made