

# Organolithium reagent

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An **organolithium reagent** is an organometallic compound with a direct bond between a carbon and a lithium atom. As the electropositive nature of lithium puts most of the charge density of the bond on the carbon atom, effectively creating a carbanion, organolithium compounds are extremely powerful bases and nucleophiles.

## Production

Organolithium reagents are industrially prepared by the reaction of an halocarbon with lithium metal, i.e.  $R-X + 2 Li \rightarrow R-Li + LiX$ .<sup>[1]</sup> A side reaction of this synthesis, especially with alkyl iodides, is the Wurtz reaction, in which an R-Li species reacts with an R-X species forming an R-R coupled product. This side reaction can be almost completely avoided by using alkyl chlorides or bromides.

A second method is the reaction of an alkyl halide or aryl alkyl sulfide with a radical anion lithium salt, such as lithium naphthalide. These radical anions can be prepared by the reduction of an aromatic system such as naphthalene with metallic lithium. As the organic reduction of alkyl halides is much faster with radical anions than it is with direct reaction with lithium metal, this reaction enables a number of more exotic organolithium compounds to be prepared.

A third method involves the metal-halogen exchange between an organic halide compound (usually an iodide or bromide) and an organolithium species (usually n-BuLi, s-BuLi or t-BuLi). As this is an equilibrium reaction, the reaction is successful only if the formed lithium reagent has a more stable carbanion than the starting lithium reagent. This method is often used to prepare vinyl- aryl- and primary alkyl lithium reagents, and is especially valuable for the preparation of functionalized lithium reagents where the harsher conditions required for reaction with lithium metal may be precluded.

A fourth method is another exchange, this time between an organolithium compound and another organometallic compound. This is again an equilibrium reaction, where the most electropositive metal (lithium) will end up attached to the most electronegative organic group. An example is the synthesis of vinyl lithium out of tetravinyltin and phenyllithium. Vinyl lithium is very difficult to prepare with other methods.

A fifth method is the deprotonation of organic compound with an organolithium species, an acid-base reaction.

## Structure

Organolithium reagents can be aggregated, with lithium coordinating to more than one carbon atom and carbon coordinating to more than one lithium atom. Three general factors affect aggregation: the electrostatic interaction between opposite charges, the coordination sphere of lithium which can be either solvent molecules or Lewis base and the steric hindrance of the hydrocarbon part.<sup>[2]</sup> The lithium atoms tend to form triangles and higher aggregates.

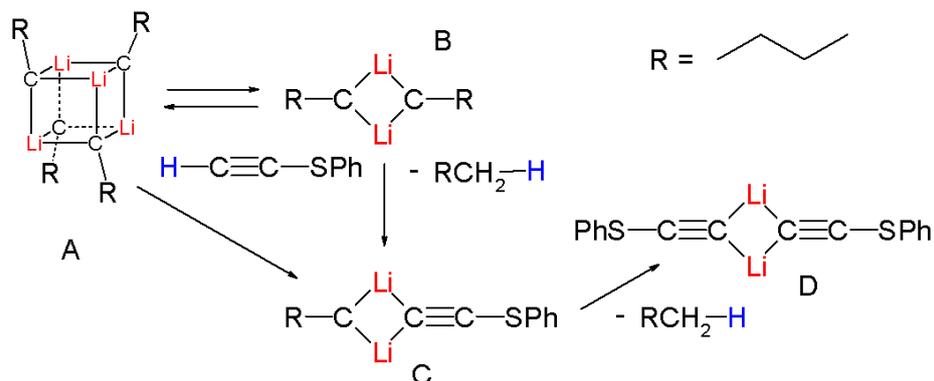
In the solid state of methyllithium, 4 lithium atoms form a tetrahedron with each face capped by a methyl group which bonds simultaneously to three Li atoms ( $\eta^3$  hapticity). Long-range interactions between  $(MeLi)_4$  units are based on  $\eta^3-Li-CH_3-\eta^1-Li$  bonding. Butyllithium forms a hexameric  $Li_6$  octahedron without any long-range interactions.

The addition of Lewis bases such as solvents diethyl ether or THF or nitrogen ligands TMEDA, PMDTA or sparteine tend to deaggregate organolithium compounds, making them more soluble and more reactive. The solid-state complex of MeLi with (-)-sparteine is a dimer. The complex of butyllithium with PMDTA is the closest thing to monomeric BuLi.

In solution, methyllithium in THF at 1M is a tetramer, n-butyllithium in benzene at 3M is a hexamer and in THF at 1M a tetramer. t-BuLi in THF is a dimer. Isopropyl lithium in cyclopentane is a mixture of hexamer, octamer and nonamer.

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Different organolithium aggregation states are encountered in the simple deprotonation of the terminal alkyne (*phenylthio*)acetylene by *n*-butyllithium in THF at  $-135^{\circ}\text{C}$ , a process that can be followed by  $^7\text{Li}$  NMR spectroscopy.<sup>[3]</sup>



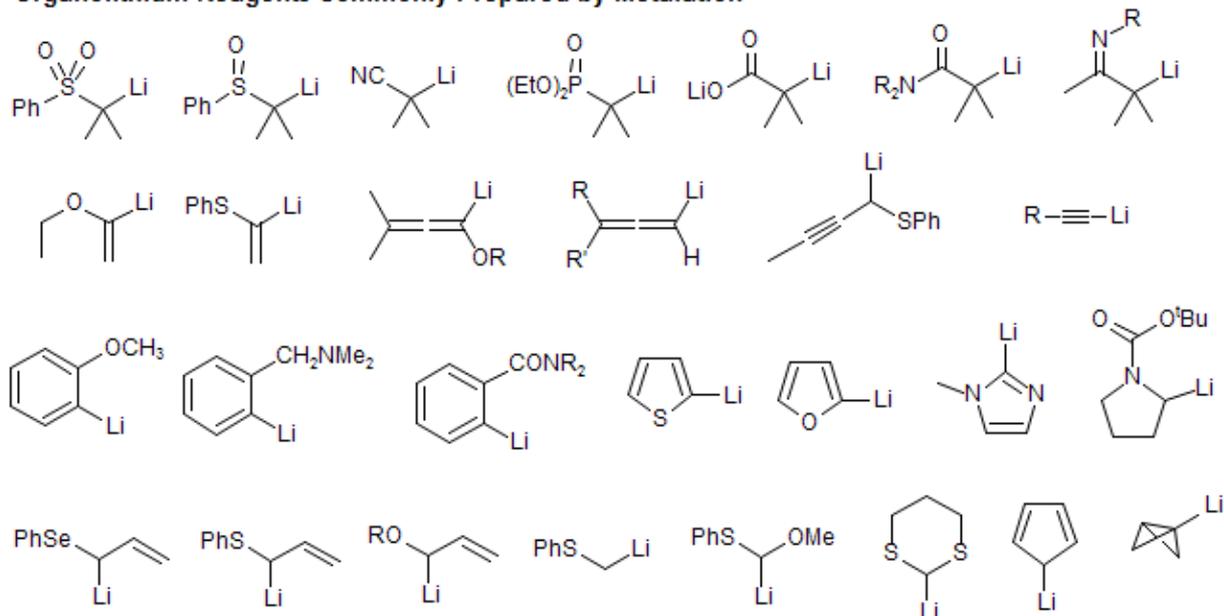
The cubane-like tetramer **A** is hardly reactive compared to the dimer **B** which forms first mixed-dimer species **C** and ultimately homodimer **D**. In fact the dimer is more reactive than the tetramer by a factor  $3.2 \times 10^8$ .

## Uses

Organolithium compounds are strongly polarised by the electropositive character of lithium. They are therefore highly reactive nucleophiles and react with almost all types of electrophiles. They are comparable to Grignard reagents, but are much more reactive. Due to this reactivity they are incompatible with water, oxygen ( $\text{O}_2$ ), and carbon dioxide, and must be handled under a protective atmosphere such as nitrogen or, preferably, argon.

A common use of simple commercially available organolithium compounds (like *n*-BuLi, *sec*-BuLi, *t*-BuLi, MeLi, PhLi) is as very strong bases. Organolithium compounds can deprotonate almost all hydrogen-containing compounds (the metalation or Li/H exchange reaction), with the exception of alkanes. In principle, a deprotonation can go to completion if the acidic compound is 2  $\text{pK}_\text{A}$  units stronger than the lithium species, although in practice a larger  $\text{pK}_\text{A}$  difference is required for useful rates of deprotonation of weakly acidic C-H acids. As alkyl groups are weakly electron donating, the basicity of the organolithium compound increases with the number of alkyl substituents on the charge-bearing carbon atom. This makes *tert*-butyllithium the single strongest base that is commercially available, with a  $\text{pK}_\text{a}$  greater than 53. The metalation reaction is an important synthetic method for the preparation of many organolithium compounds. Some examples are shown below:

### Organolithium Reagents Commonly Prepared by Metalation



Organolithium compounds are also commonly used for nucleophilic addition reactions to carbonyl compounds and other carbon electrophiles. Deprotonation can be a side reaction with enolizable carbonyl compounds, especially with hindered organolithium reagents such as *t*-butyllithium. Grignard reagents, although much less reactive, are an alternative in addition reactions, with less problems with deprotonation.

An important use of organolithium reagents is in the preparation of other organometallic compounds, usually by reaction with metal halides. Especially important in synthetic organic chemistry is the formation of organocopper reagents (including Gilman reagents) by reaction of RLi with CuI or CuBr, and the preparation of organozinc reagents by reaction with ZnCl<sub>2</sub>. Even Grignard reagents are sometimes prepared by reaction of RLi with MgBr<sub>2</sub>, in situations where the lithium reagent (but not the Grignard) can be easily prepared by a metalation reaction. Organotin, organosilicon, organoboron, organophosphorus, and organosulfur compounds are also frequently prepared by reaction of RLi with appropriate electrophiles.

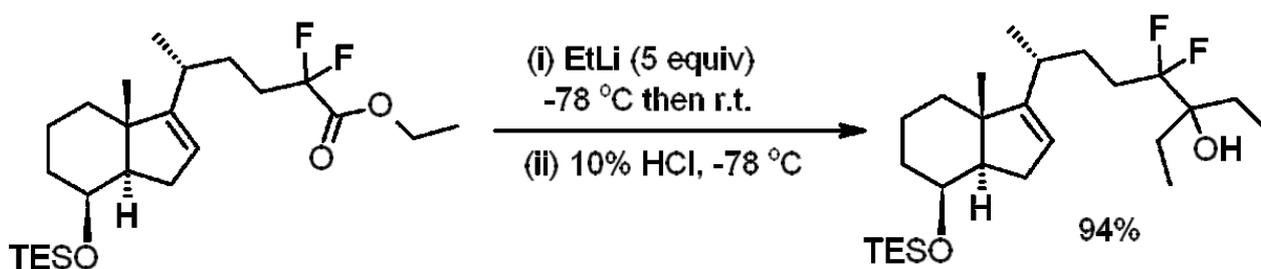
A recent review of process chemistry indicates that the following are the most commonly used organolithium reagents: butyllithium, hexyllithium, *sec*-butyllithium, and phenyllithium.<sup>[4]</sup> Methylithium is also commonly used. Two very commonly used strong bases prepared using butyllithium are lithium diisopropylamide (LDA), and lithium hexamethyldisilazide (LiHMDS).

Aryllithium derivatives are intermediates in directed ortho metalation such as Me<sub>2</sub>NCH<sub>2</sub>C<sub>6</sub>H<sub>4</sub>-2-Li obtained from dimethylbenzylamine and butyllithium.

## Reactivity

Some general reactions of organolithium compounds are:

- Protonation in reaction with any compound containing acidic protons
- Reaction with ketones and aldehydes to alcohols.<sup>[5]</sup>
- Reaction with epoxides to alcohols.
- Reaction with carboxylic acid salts and acid chlorides to the corresponding ketone.<sup>[6]</sup>
- Reaction with carboxylic esters to give tertiary alcohols. In the example shown, ethyllithium was shown to be very effective, but ethylmagnesium bromide gave mainly reduction products.<sup>[7]</sup>



- Reaction with oximes to the corresponding amines.<sup>[5]</sup>
- Reaction with isonitriles to the corresponding lithium aldimine. Subsequent hydrolysis effectively converts the organolithium compound to its aldehyde.<sup>[8]</sup>
- Reaction with certain epoxides to the corresponding alkenes.<sup>[9]</sup>

Organolithium reagents also react with the ether solvents that are used for most reactions. The table below lists approximate half-lives of several of the more common lithium reagents in typical solvents.<sup>[10]</sup>

Solvent/Temp	n-BuLi	s-BuLi	t-BuLi	MeLi	CH <sub>2</sub> =C(OEt)-Li	CH <sub>2</sub> =C(SiMe <sub>3</sub> )-Li
THF/-20 °C			40 min, 360 min			
THF/20 °C					>15 hr	17 hr
THF/35 °C	10 min					
THF/TMEDA/-20 °C	55 hr					
THF/TMEDA/ 0 °C	340 min					
THF/TMEDA/20 °C	40 min					
Ether/-20 °C			480 min			
Ether/0 °C			61 min			
Ether/20 °C	153 hr		<30 min			17 days
Ether/35 °C	31 hr					
Ether/TMEDA/ 20 °C	603 min					
DME/-70 °C		120 min	11 min			
DME/-20 °C	110 min	2 min	<<2 min			
DME/0 °C	6 min					

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