General References:

Organometallics in Organic Synthesis, Schlosser, M., Ed.; Wiley: New York, 1994.

Organolithium Methods, Wakefield, B. J.; Academic Press: London, 1988.

The Chemistry of Organolithium Compounds, Wakefield, B. J.; Pergamon, New York, 1974.

Industrial Production of Organolithium Reagents:

$$\mathrm{RCl} \quad + \quad \underset{\text{(dispersion, 0.5-2\% Na)}}{2\ \mathrm{Li}} \quad \longrightarrow \quad \mathrm{RLi} + \mathrm{LiCl} + \Delta$$

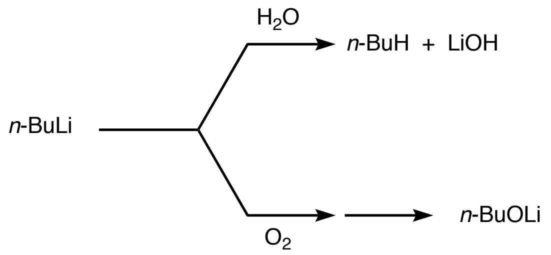
- Organolithium formation is carried out in hydrocarbon solvents. Afterwards, lithium chloride is removed and the solution is concentrated to as much as 90% w/w.
- Metalation occurs through a radical pathway. Sodium initiates and accelerates this highly exothermic reaction.

Availability (conc. in M):

n-butyllithium	1.6 M, 2.5 M, 11.0 M in hexane 2.7 M in heptane 2.2 M in cyclohexane 2.6 M in toluene
sec-butyllithium	1.3 M in cyclohexane/hexane (92/8) 1.4 M in cyclohexane
tert-butyllithium	1.9 M in pentane 2.0 M in heptane
methyllithium	1.6 M in ethyl ether 3.0 M in diethoxymethane 1.5 M in ethyl ether, complexed with LiBr 3% w/w in 2-MeTHF/cumene
ethyllithium	0.5 M in benzene/cyclohexane 1.7 M in dibutyl ether
phenyllithium	1.8 M in dibutyl ether
lithium acetylide	solid complex with ethylenediamine 25% w/w in toluene, complexed with ethylenediamine

Organometallics in Organic Synthesis, Schlosser, M., Ed., p. 170, Wiley: New York, 1994.

Handling of Organolithium Reagents:



- Contact with oxygen or water leads to stoichiometric loss of alkyllithium titre.

$$n\text{-BuLi} \xrightarrow[>\,50\ ^{o}\mathrm{C}]{\Delta} \mathrm{CH_2{=}CHCH_2CH_3} \quad + \quad \mathrm{LiH}$$

Ziegler, K.; Gellert, H. G. *Liebigs Ann. Chem.* **1950**, *567*, 179.

- Thermal decomposition of *n*-butyllithium produces butene and lithium hydride.

Decomposition Rates (% material lost per day)

Storage Temperature (^{o}C)	*n*-BuLi 15-20% in hexane	*n*-BuLi 90% in hexane	*sec*-BuLi 10-12% in isopentane
0	0.00001	0.0005	0.003
5	0.0002	0.0011	0.006
10	0.0004	0.0025	0.012
20	0.0018	0.013	0.047
35	0.017	0.11	0.32

Organometallics in Organic Synthesis, Schlosser, M., Ed., p. 171, Wiley: New York, 1994.

- These factors, along with solvent evaporation, can cause concentrations of alkyllithium reagents to fluctuate over time. For careful experimental work it is important to titrate alkyllithium reagents regularly.

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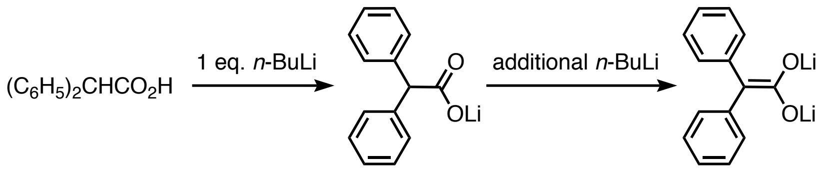
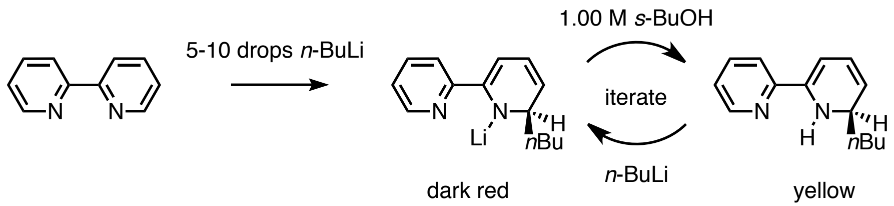
Titration:



colorless colorless bright yellow

Kofron, W. G.; Baclawski, L. M. *J. Org. Chem.* **1976**, *41*, 1879.

- Treatment of non-hygroscopic diphenylacetic acid with one equivalent of *n*-BuLi results in the formation of the lithium carboxylate. Additional *n*-BuLi generates the corresponding enolate, producing a slight yellow color and indicating that one equivalent has been added.

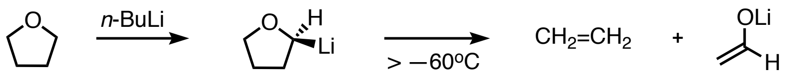


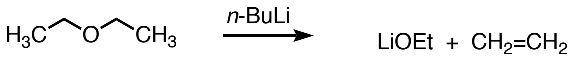
dark red yellow

Watson, S. C.; Eastham, J. F. *J. Organomet. Chem.* **1967**, *9*, 165.
Gaul, M.; House, H. O. *Org. Syn.* Collective Volume VI, 121.

- Double titration methods allow for multiple titrations in a single flask, and in this case only *n*-BuLi is measured.

Organolithium Reactions with Etheral Solvents:





- In general, the relative rates of reaction of alkyllithium reagents with ethers are DME (100 X) > THF (100 X) > diethyl ether

- The reaction of *n*-BuLi with THF produces the enolate of acetaldehyde, which is difficult to form cleanly by direct deprotonation of acetaldehyde.

Reaction of *n*-butyllithium with ethers

Ether	Temp (ºC)	$t_{1/2}$
ethyl ether	25	6 d
	35	31 h
isopropyl ether	25	18 d
DME	25	10 min
THF	0	23.5 h
	−30	5d

Organometallics in Organic Synthesis, Schlosser, M., Ed., p. 172, Wiley: New York, 1994.

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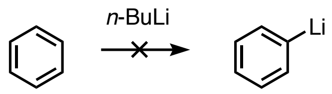
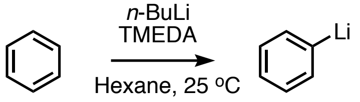
Additives:

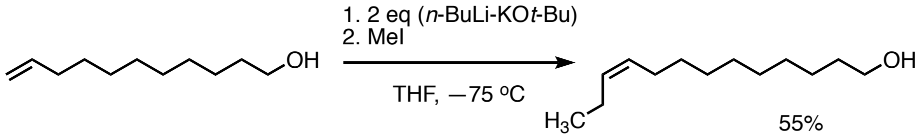
- Additives are often used to enhance the reactivity of alkyllithium reagents. Common additives are tetramethylethylenediamine (TMEDA), hexamethylphosphoramide (HMPA), and potassium *tert*-butoxide.

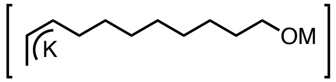




Chalk, A. J.; Hoogeboom, T. J. *J. Organomet. Chem.* **1968**, *11*, 615.

- Treatment of benzene with *n*-BuLi leads to little or no reaction, whereas addition of TMEDA leads to quantitative lithiation.



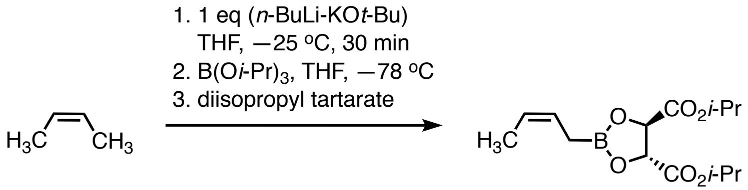


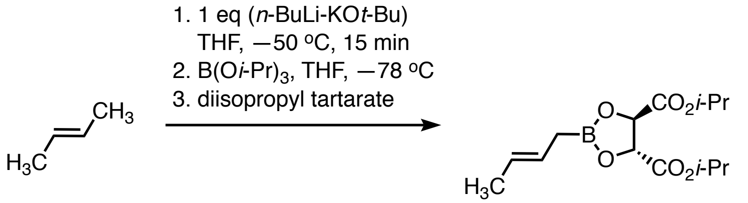
Z-η^3-allylpotassium intermediate

Schlosser, M. *Pure Appl. Chem.* **1988**, *11*, 1627.

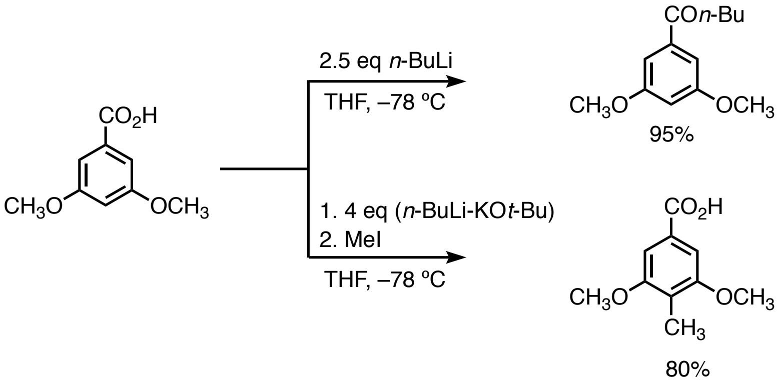
- Alkyllithium reagents combined with potassium alcoholates ("LICKOR" reagents) provide highly activated and yet selective organometallic reagent. The reaction depicted above provides an η^3-allylpotassium reagent. The Z isomer is favored (ratio 20:1 Z:E at −50 °C). Alkylation of allylpotassium reagents usually occurs at the unsubstituted terminus.

- The LICKOR base system allows for the stereospecific preparation of synthetically important crotylboronate reagents from butene





Roush, W. R.; Ando, K; Powers, D. B.; Hlaterman, R. L.; Palkowitz, A. D. *Tetrahedron Lett.* **1988**, *29*, 5579.



Sinha, S.; Mandal, B.; Chandrasekaran, S. *Tetrahedron Lett.* **2000**, *41*, 3157.

- The LICKOR base system metalates the arene ring while *n*-BuLi alone attacks the carboxylate to provide the corresponding ketone.

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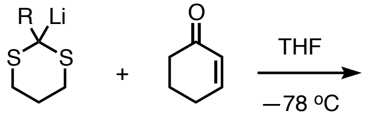
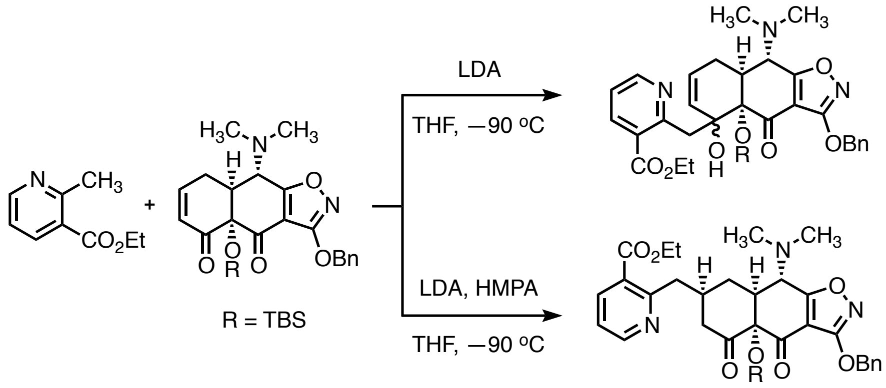
- HMPA (1-2 equiv) can sometimes change the regioselectivity from 1,2- to 1,4- in the addition of stabilized organolithium reagents to α,β–unsaturated carbonyl compounds.



	1,2 addition	1,4 addition
no additive:	>99	0
HMPA:	<5	>95

Sikorski, W. H., Reich, H. J.; *J. Am. Chem. Soc.* **2001**, *123*, 6527.



Brubaker, J. D. A Practical Synthetic Route to Structurally Diverse Tetracycline Antibiotics. Ph.D. Dissertation, Harvard University, Cambridge, MA 2007.

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