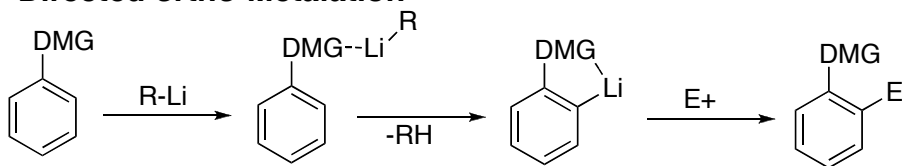


**Overview of topics to be discussed:**Directed *ortho*-Metalation, Heterocycle Metalation, Non-aromatic Metalations, Examples in Synthesis

**Relevant Reviews:** *Chem. Rev.* **1990**, 90, 879-933.; *Current Org. Chem.* **2006**, 10, 1817-1848.; *Acc. Chem. Res.* **1986**, 19, 356-363.; *Acc. Chem. Res.* **1982**, 15, 306-312.; *Angew. Chem. Int. Ed.* **2005**, 44, 376-393.; *Chem. Soc. Rev.*, **2007**, 36, 1069-1084.

**Directed *ortho*-Metalation**

The **direct metalation group (DMG)** is typically a Lewis basic moiety that interacts with the Lewis acidic lithium cation allowing for deprotonation by the alkyl-lithium species from the nearest *ortho*-position on the arene.

As long as deprotonation does not occur by the highly basic lithiated-aryl ring, it may react with various electrophiles at the lithiated position in an *ipso*-substitution.

*ortho*-Metalation followed by quench with an electrophile is favored over traditional electrophilic substitutions due to the regioselective preference for *ortho*-substitution as opposed to a mixture of *ortho*- and *para*-substitution

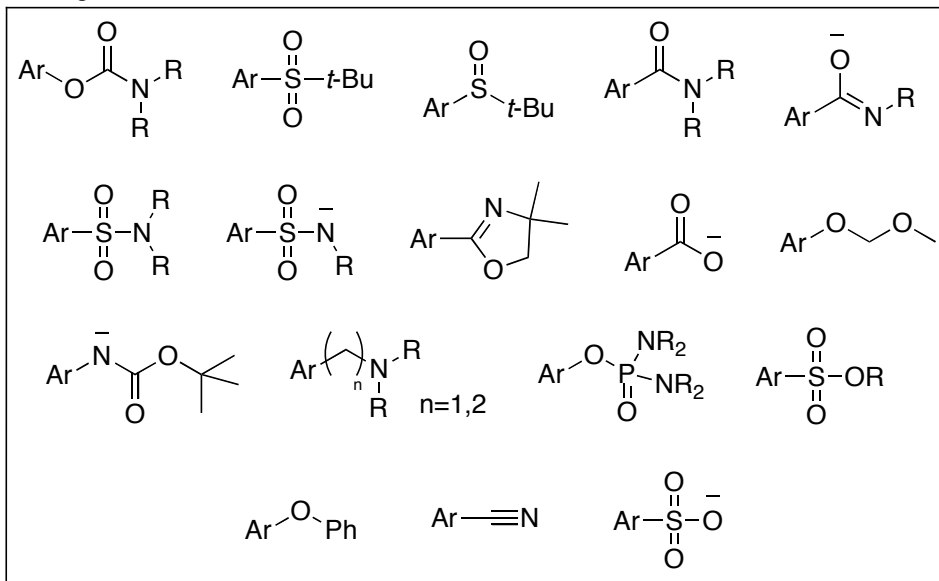
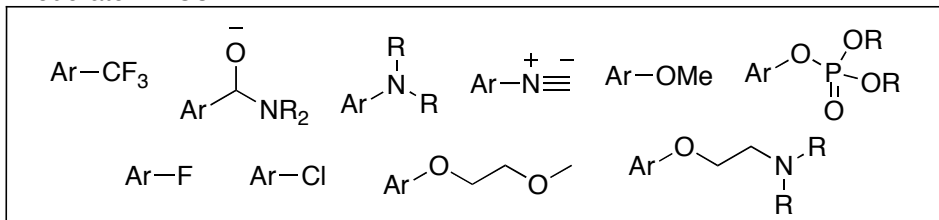
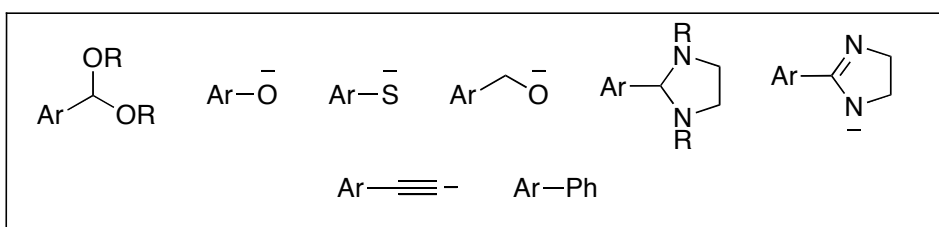
This reaction was first discovered independently by:

Henry Gilman (*JACS* **1939**, 61, 109-112.)  
Georg Wittig (*Chem. Ber.* **1940**, 73, 1197.)

**Nature of the DMG**

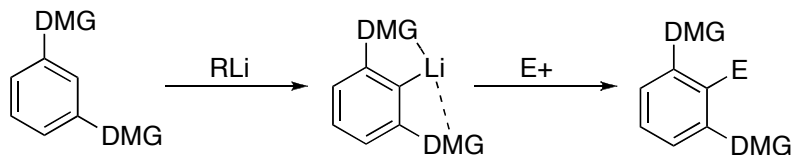
These groups should be able to effectively coordinate the alkyl-lithium species (making a hetero-atom a necessity) in order to establish a complex-induced proximity effect (CIPE) and at the same time be poorly electrophilic so as to not react via nucleophilic attack by the alkyl-lithium. Inductive effects may also play a role in some cases by lowering the pKa of the adjacent proton.

DMGs do not function alone in determining the site of metalation. Sterics and other functional groups on the arene also have a great deal of influence.

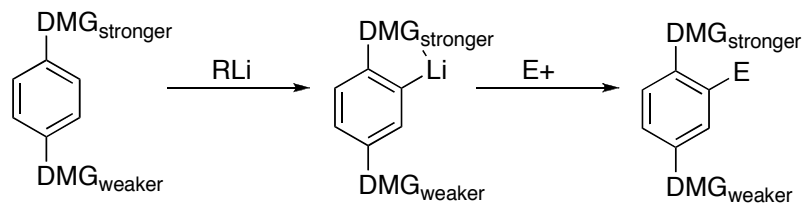
**Common DMGs and their relative strength in directing metalation:****Strong DMGs:****Moderate DMGs:****Weak DMGs:**

## Other Metalation Considerations

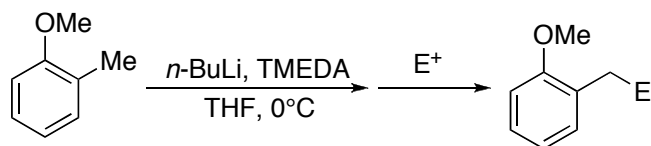
When two DMGs have a 1,3-disposition on the arene they will direct lithiation to the 2-position between them through a cooperative coordination of the alkyl-lithium:



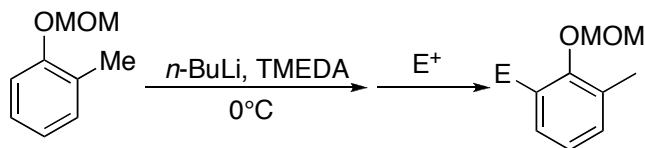
When two DMGs are 1,4-disposed on the arene the metalation will be directed ortho to the DMG that is a "stronger" DMG, if their strengths are similar a mixture may result:



Benzylic positions may be metalated more rapidly even in the presence of a DMG:

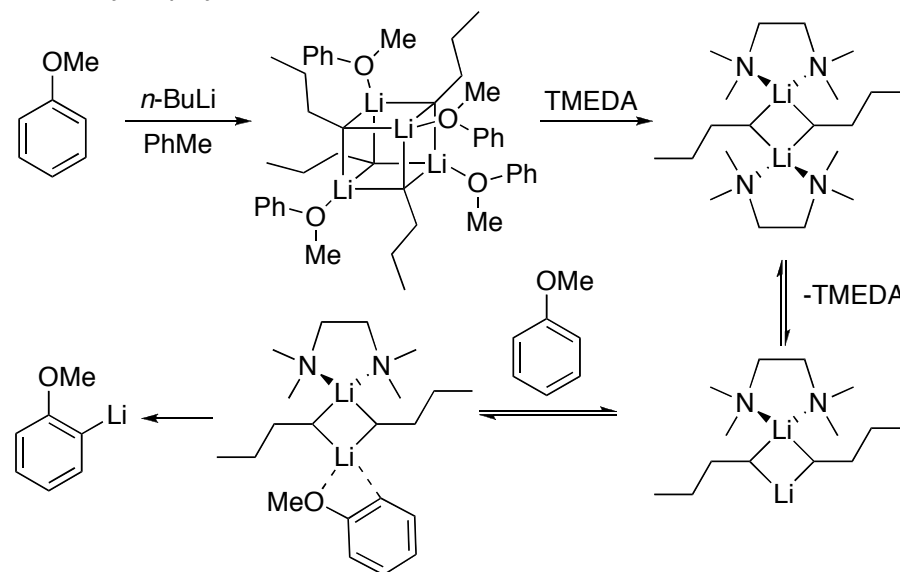


however:



## Nature of the Base and Solvent

Typically powerful alkyl-lithium bases are needed for these metalations. MeLi, *n*-BuLi, *sec*-BuLi and *t*-BuLi are the most common. These alkyl lithiums exist as various aggregates in solution and amine additives serve to break up these aggregates to allow accelerated reactivity due to increased basicity. TMEDA, a bidentate amine, is excellent as a ligand and is therefore more commonly employed.



## Reactivity of Metalated Arenes

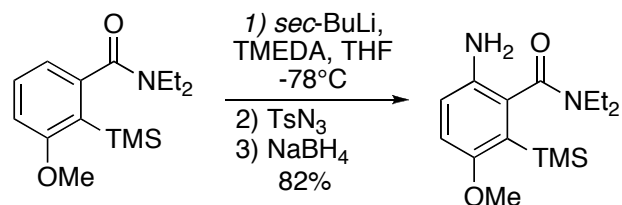
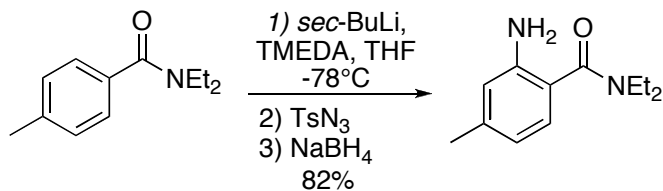
Many Electrophiles react with lithiated arenes. Common examples:

ArCHO, RCHO, D<sub>2</sub>O, RX, CO<sub>2</sub>, (RS)<sub>2</sub>, TMSCl, B(OR)<sub>3</sub>, DMF, Bu<sub>3</sub>SnCl, TsN<sub>3</sub>, BnX, HCO<sub>2</sub>Et, RCOCl, Ac<sub>2</sub>O, RNCO, RCN, X<sub>2</sub>, terminal epoxides, S<sub>8</sub>, Se, ZnCl<sub>2</sub>

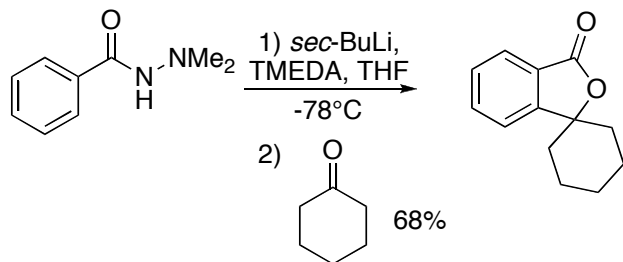
Transmetalation of lithiated arenes allows for transition metal catalyzed reactions.

Nucleophilic attack should be faster than deprotonation in the case where the electrophile has an acidic proton.

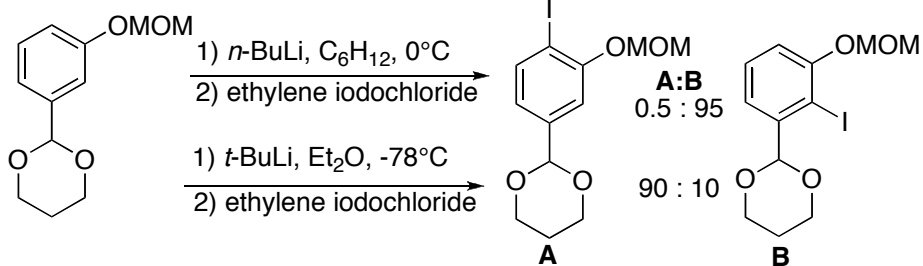
## Reactivity of Metalated Arenes-Examples



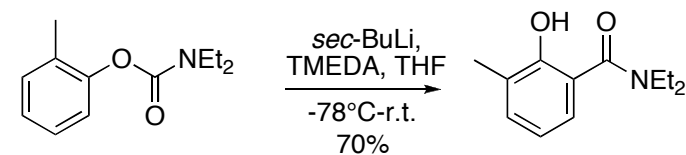
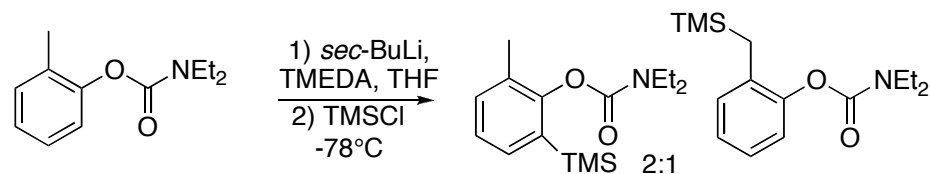
*Tet. Lett.* **1983**, 24, 3795-3798.



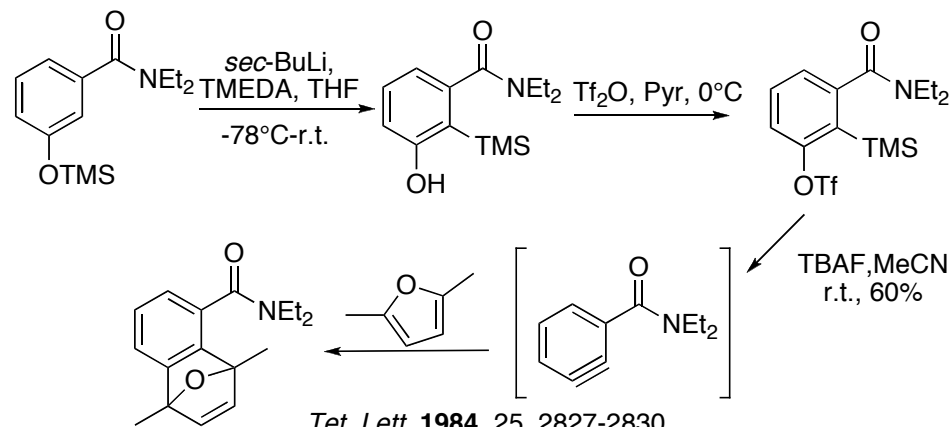
*Tet. Lett.* **2000**, 40, 3795-3798.



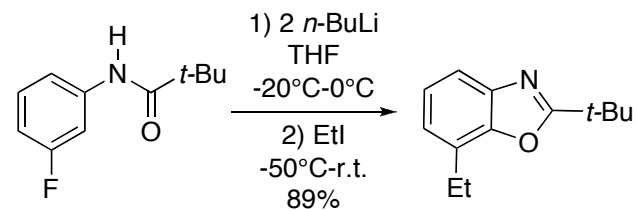
*J. Org. Chem.* **1982**, 47, 2101-2108.



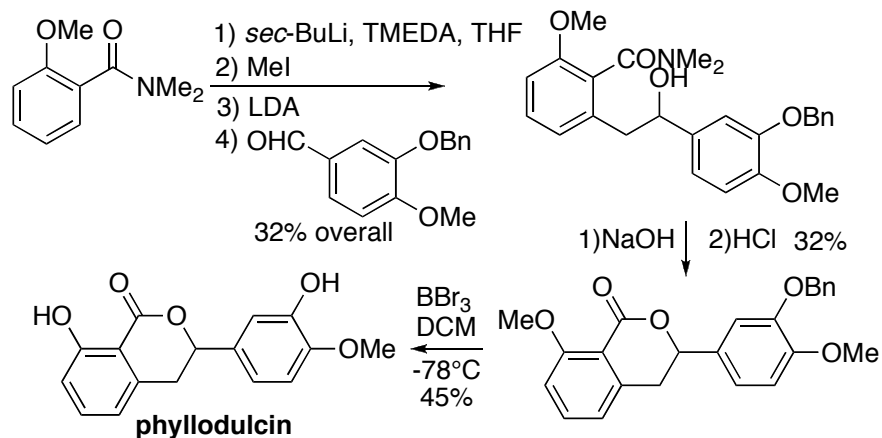
*J. Org. Chem.* **1983**, 48, 1935-1937.



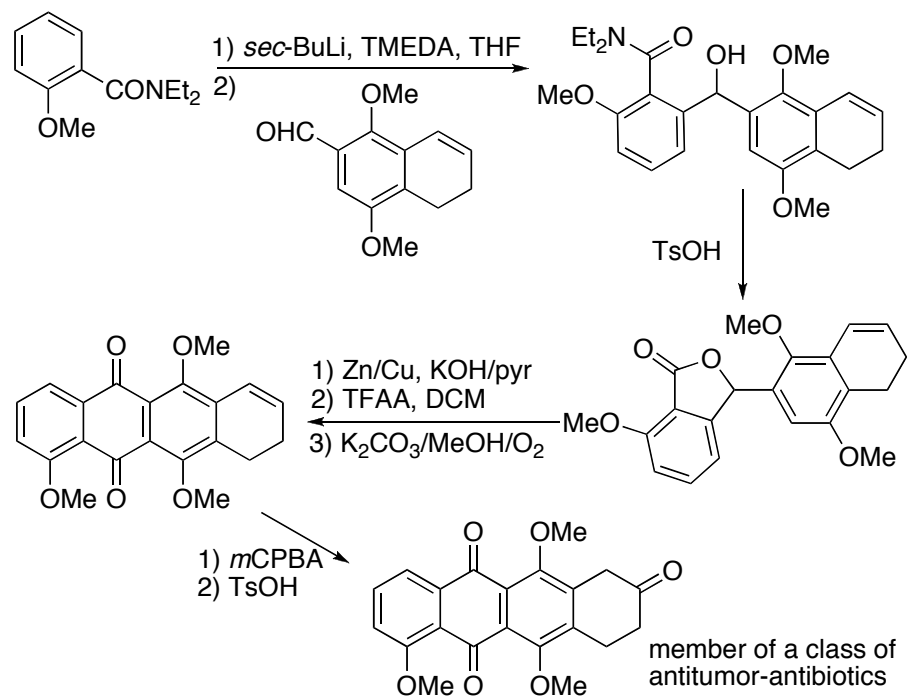
*Tet. Lett.* **1984**, 25, 2827-2830.



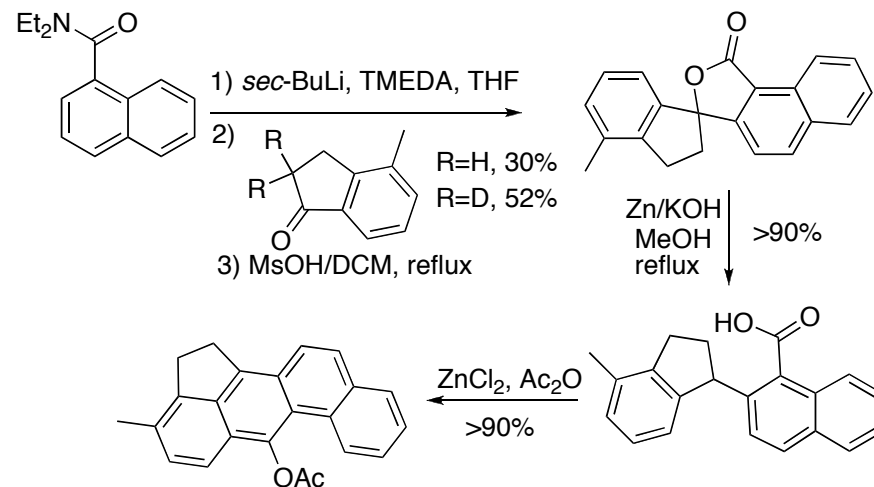
*J. Org. Chem.* **1982**, 47, 2804-2806.



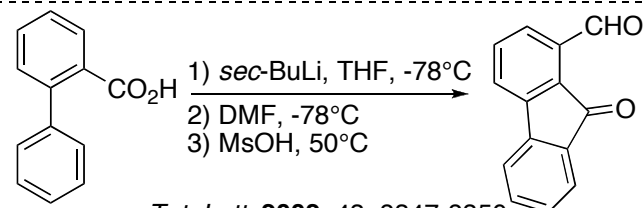
*J. Org. Chem.* **1984**, 49, 742-747.



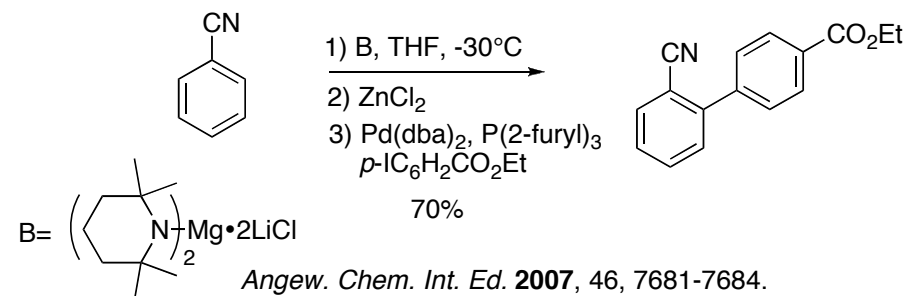
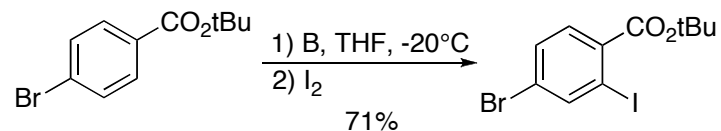
*Chem. Pharma. Bull. Jpn.* **1983**, 31, 2662.



*J. Org. Chem.* **1982**, 47, 2120-2125.



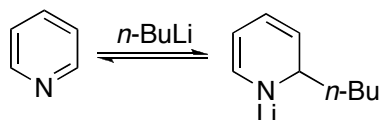
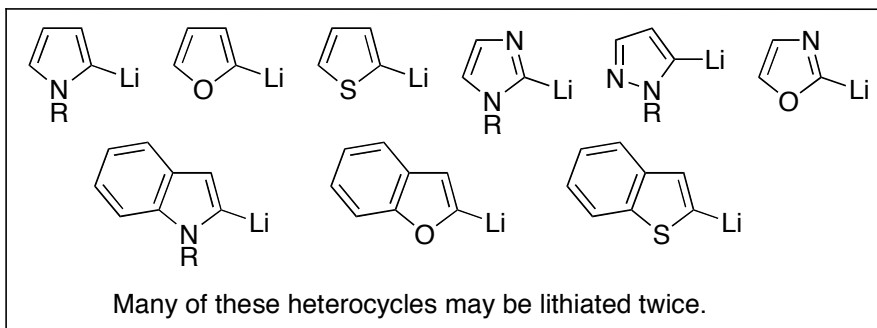
*Tet. Lett.* **2002**, 43, 8347-8350.



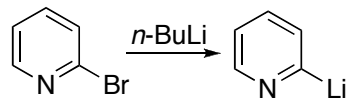
*Angew. Chem. Int. Ed.* **2007**, 46, 7681-7684.

## Metalation of Heterocycles

Position of lithiation:



Direct lithiation of pyridine is very useful since alkyl-lithiums may add into pyridine



However lithium-halogen exchange can provide the 2-lithiated pyridine

## Things to consider:

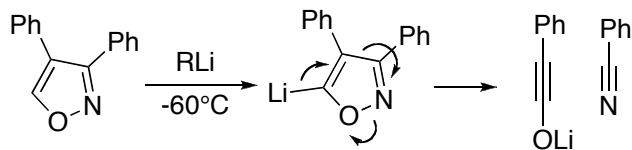
In addition to the heteroatom DMGs will influence the metalation site.

For heterocycles alkyl lithium bases are used as well as lithium amides.

Solvent choices for these lithiations are usually ether or THF.

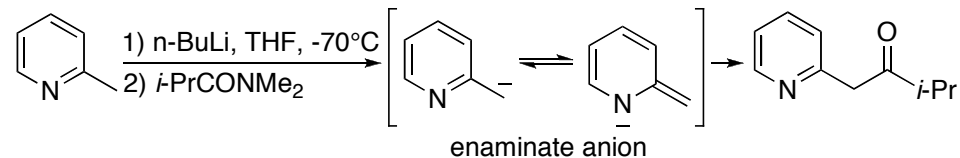
TMEDA or HMPA are often added as ligands to coordinate the metal cation.

Heterocycles can sometimes fragment:

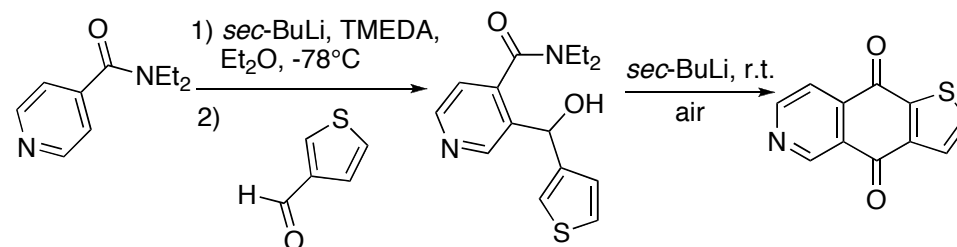


*Liebigs Ann. Chem.*, **1979**, 219.

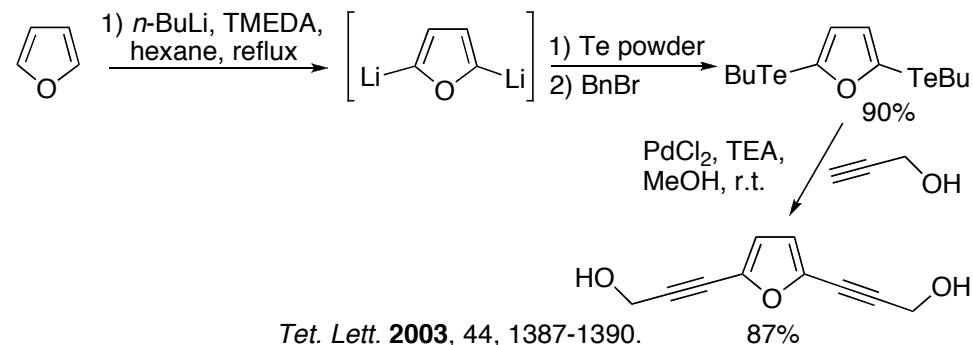
Side-chains may be metalated:



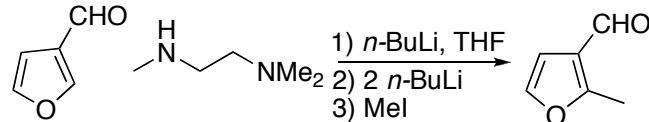
## Reactivity of Metalated Heterocycles-Examples



*J. Am. Chem. Soc.* **1980**, 102, 1457-1460.

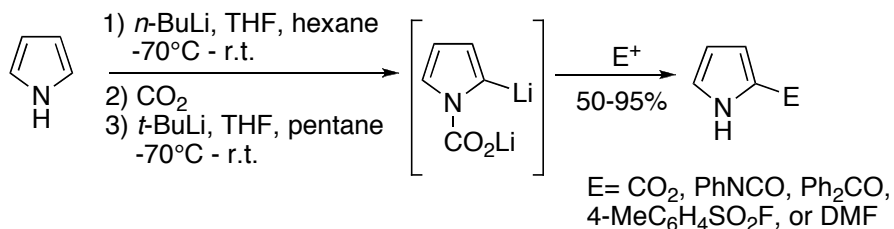


*Tet. Lett.* **2003**, 44, 1387-1390.

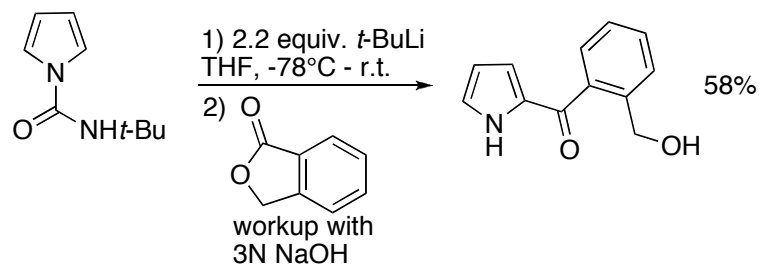


*J. Org. Chem.* **1987**, 52, 104-109.

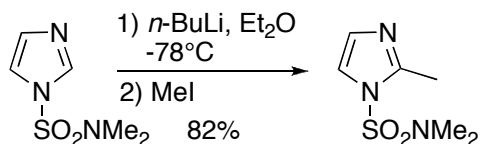
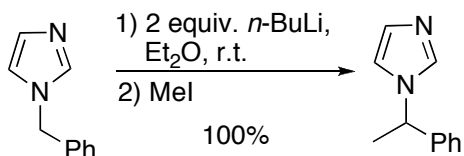
## Reactivity of Metalated Heterocycles-Examples



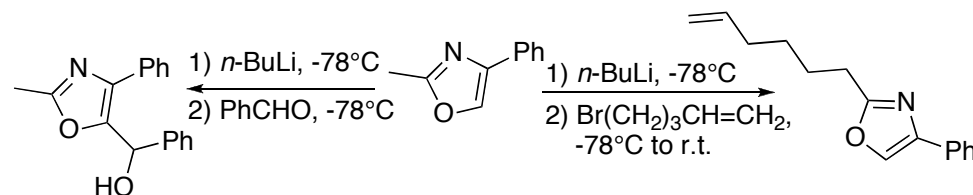
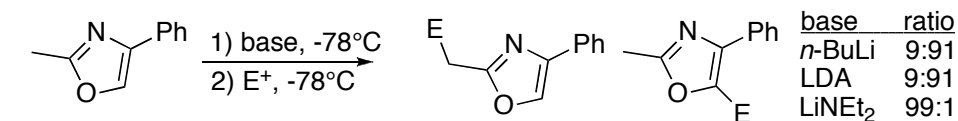
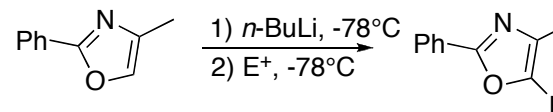
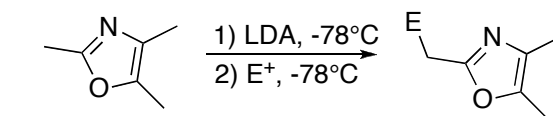
*Org. Pre. Proced. Int.* **1988**, 20, 585-590.



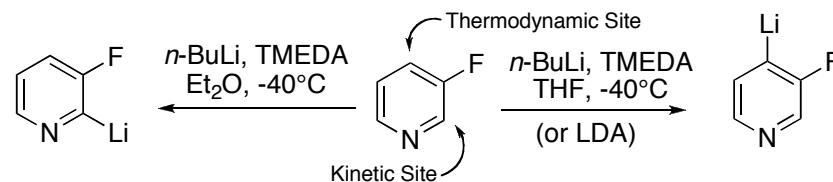
*Synthesis*, **1991**, 1079-1082.



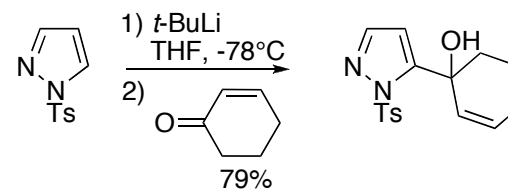
*J. Chem. Soc., Perkin Trans. 1*, **1984**, 481-486.



*Heterocycles*, **2002**, 57, 1211-1217.

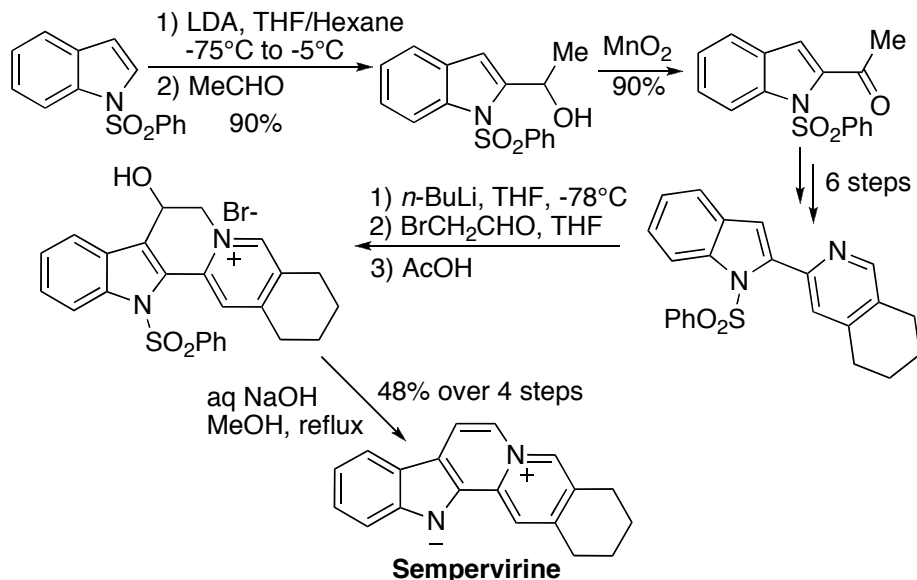


*Tetrahedron*, **1983**, 39, 2009-2021.  
*Tetrahedron*, **1994**, 50, 1129-1134.

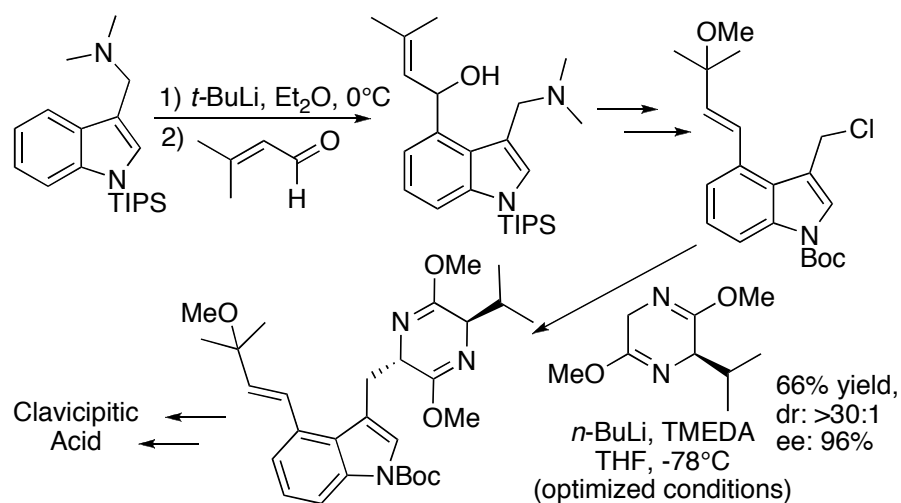


*Synlett*, **1992**, 327-328.

## Reactivity of Metalated Heterocycles-Examples

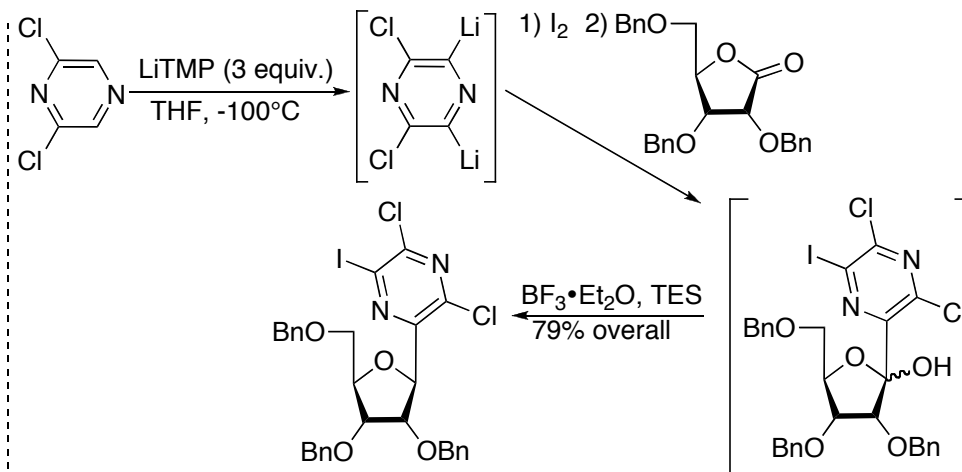


*Tetrahedron*, **1988**, 44, 3195-3202.



*Tetrahedron*, **1999**, 55, 10989-11000.

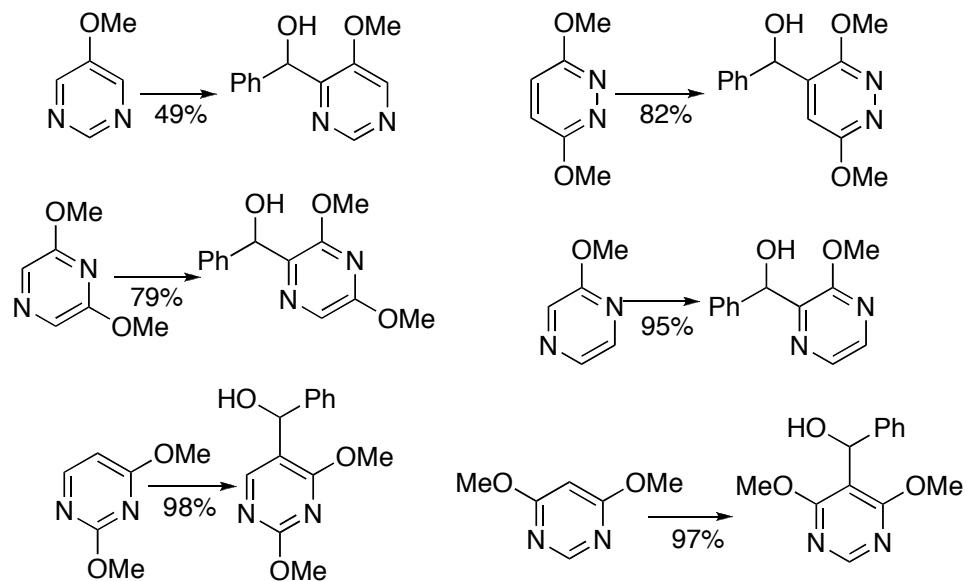
see also: *Heterocycles*, **1993**, 36, 29-33. (first study of C-4 lithiation)



*J. Org. Chem.* **2001**, 66, 4783-4786.

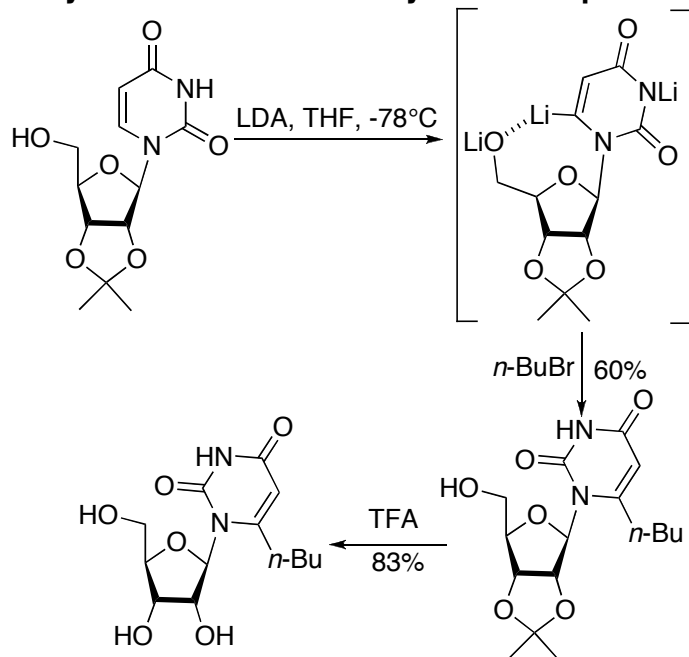
Reaction Conditions:

1) LiTMP, THF, -78°C  
2) PhCHO, -78°C-r.t.

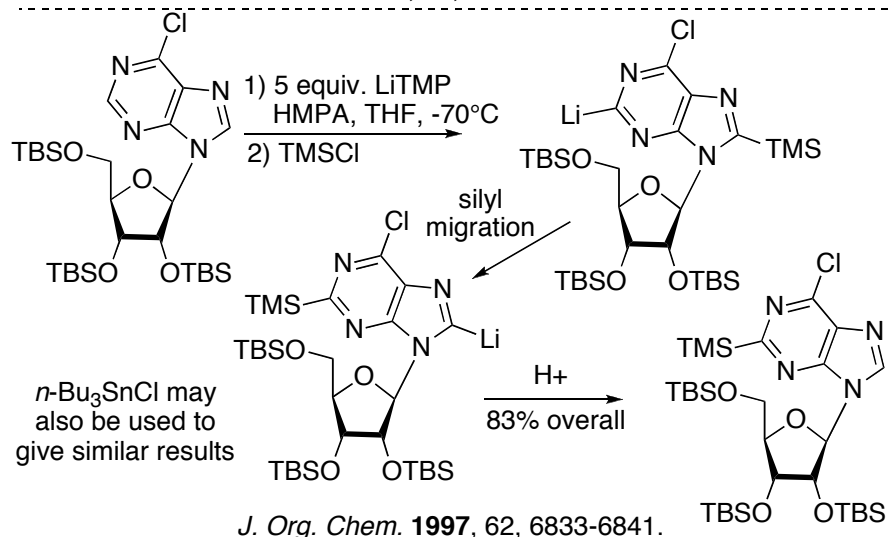


*J. Org. Chem.* **1990**, 55, 3410-3412.

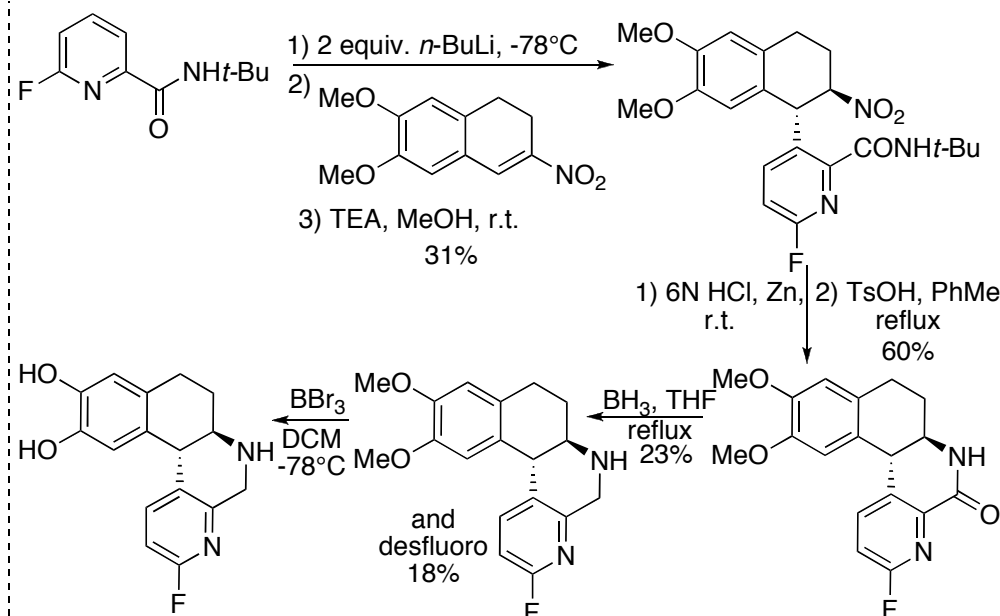
## Reactivity of Metalated Heterocycles-Examples



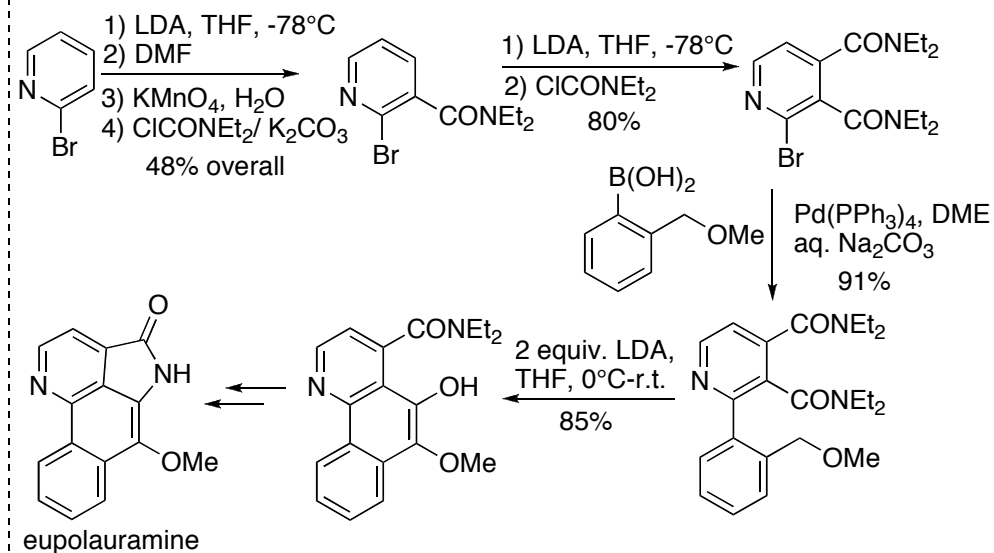
*Tet. Lett.* **1979**, 19, 4755-4758.



*J. Org. Chem.* **1997**, 62, 6833-6841.



*Bioorg. Med. Chem. Lett.* **1999**, 9, 1341-1346.

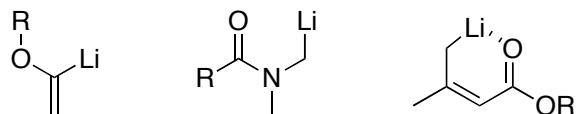


*Tet. Lett.* **1991**, 32, 4883-4884.



## Non-aromatic Metalations

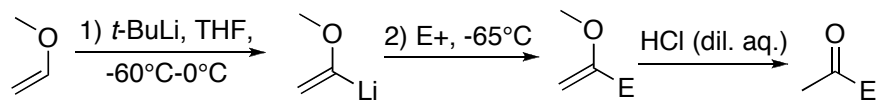
A few general examples:



These metalations are possible due to directing groups present in the substrate and are moderated by combination of factors such as: resonance, stereoelectronic, inductive, steric and the complex-induced proximity effect (CIPE).

CIPE is a non-classical way of describing the pre-lithiation complex that forms between a Lewis basic heteroatom on the directing group and the alkyl-lithium. By the establishment of this complex the lithiating species is brought in close proximity to the relatively acidic proton of the substrate and thus accounting for the observed regioselectivity

## Non-aromatic Metalations-Examples

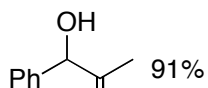
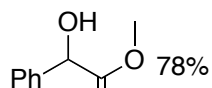


E+:

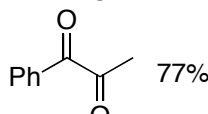
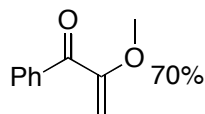
Vinyl Ether Product:

Hydrolysis Product:

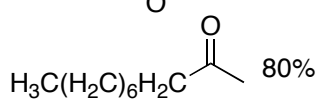
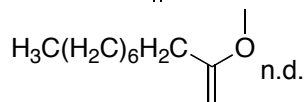
Ph-CHO



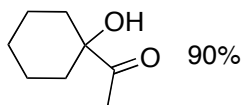
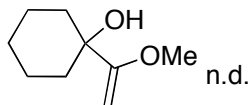
Ph-CN



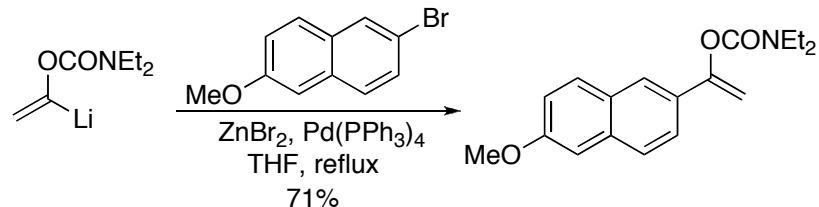
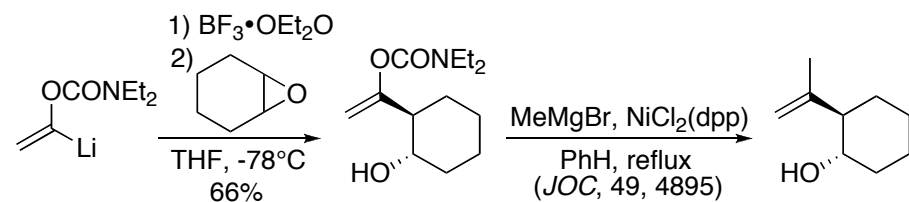
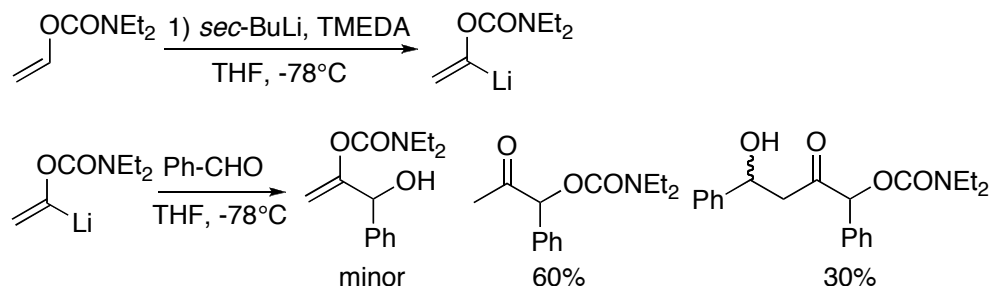
CH<sub>3</sub>(CH<sub>2</sub>)<sub>6</sub>CH<sub>2</sub>I



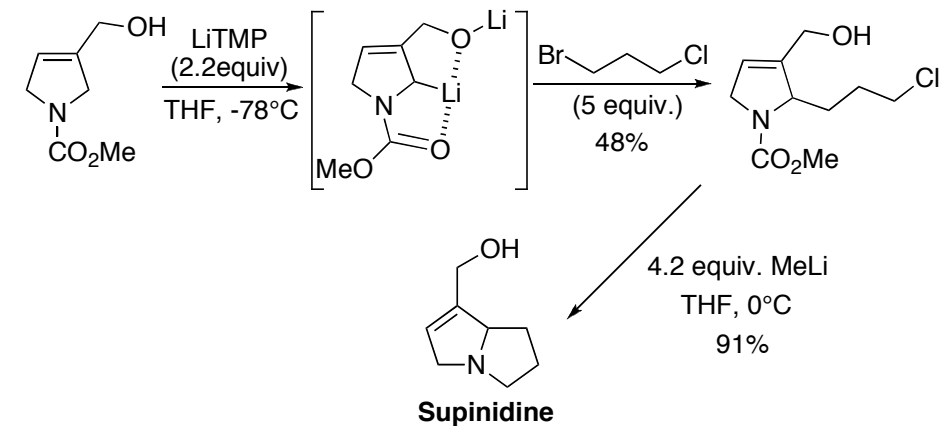
cyclohexanone



*J. Am. Chem. Soc.* **1974**, *96*, 7125-7127.



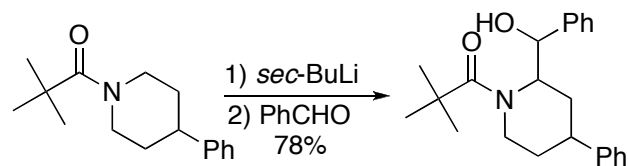
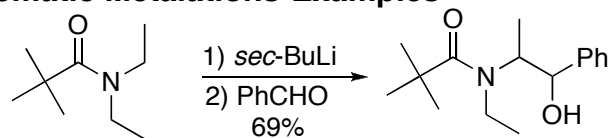
*J. Org. Chem.* **1990**, *55*, 5680-5683.



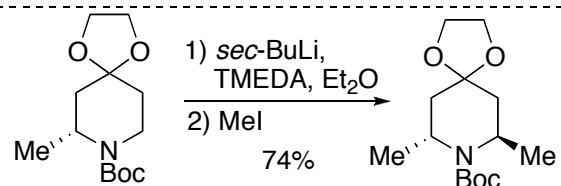
Supinidine

*J. Org. Chem.* **1983**, *48*, 1129-1131.

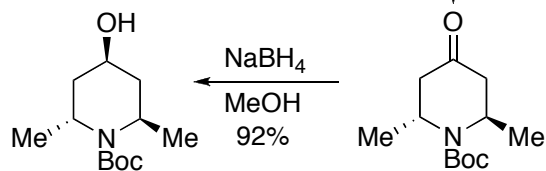
## Non-aromatic Metalations-Examples



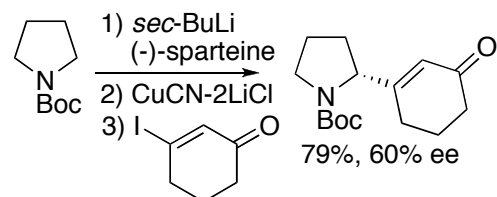
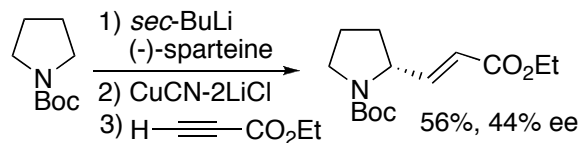
*J. Am. Chem. Soc.* **1984**, 106, 1010-1018.



5% TFA/DCM | 92%



*J. Org. Chem.* **1990**, 55, 2578-2580., *J. Org. Chem.* **1993**, 58, 1109-1117.



*J. Org. Chem.* **2004**, 69, 3076-3086.