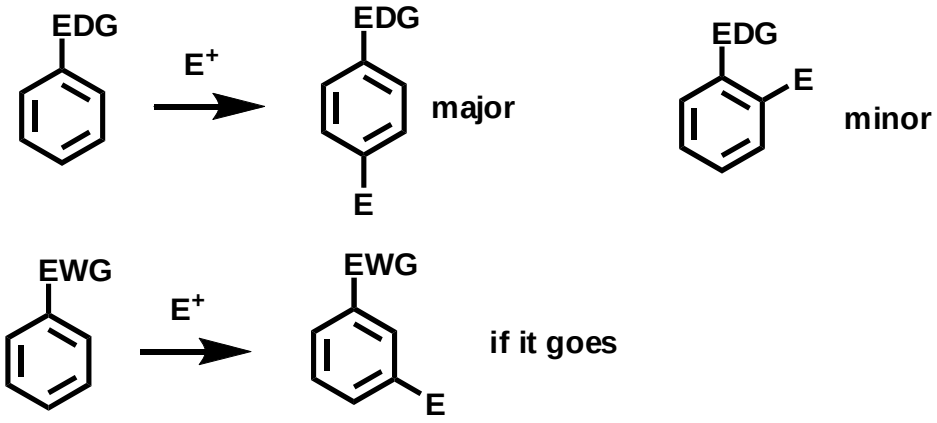
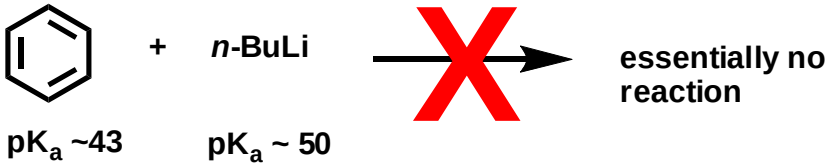
Progress in Aromatic Chemistry

Directed (ortho) Metallation

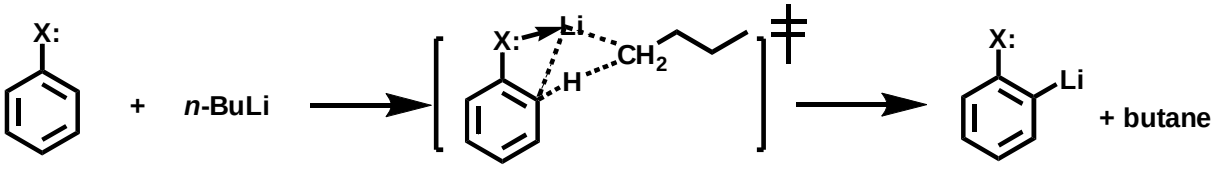
Aromatic substitution reactions are ruled historically by electrophilic aromatic substitution, which gives access to p- disubstituted compounds, some o- disubstituted ones (usually as minor products) and in a lesser nuber of cases, m- disubstituted products.



Perhaps the least obvious way of trying to add a functional group to a benzene is a deprotonate it. Nevertheless, strong based such as alkyllithiums do have a high enough pK_a associated with them to deprotonate a benzene. Unfortunately, butyllithium + benzene doesn't react at any appreciable rate; it is a kinetic problem, not a thermodynamic one.



This is not hopeless. If there is a group already on the benzene that is capable of coordination to a metal of an organometallic, a very strong base *will* deprotonate the ring. Since the coordination to the metal atom is critical in making the deprotonation occur at any kind of rate, the deprotonation is *ortho*.



So what are the practical requirements for this to occur? To go feature by feature

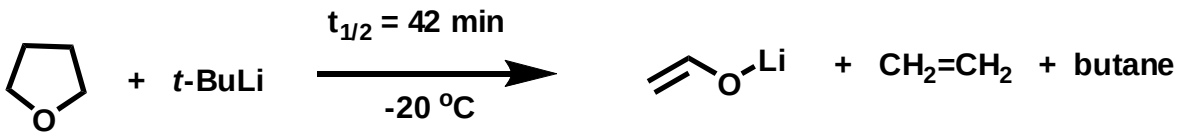
Bases – They must be very strong (basic) ones. If X is capable of undergoing nucleophilic attack, this must be suppressed somehow. Examples of the bases, ordered by basicity, are:

n-BuLi + KO*t*-Bu (Lickor superbases) > ***t*-BuLi > *s*-BuLi > *n*-BuLi (all pK_a ca. 50)** > LiTMP (37.1) > LDA (35.7)

The alkyllithium are the most commonly employed of them.

Solvents – They tend to be the polar aprotic ones: THF and Et_2O are more heavily used than all others, but benzene and alkane solvents are occasionally seen. This is due to the fact that alkyllithiums are not monomeric in solvents that are not coordinating, and the ability of THF (and to a lesser extent Et_2O) to deaggregate the organolithium concerned.

It is worth keeping in mind that bases these strong are not infinitely stable in ethereal solvents, due to ether cleavage reactions. The stability order is hydrocarbons > Et_2O > THF



Stannetty, P. et al *J. Org. Chem.* 1992, *57*, 6833.

for Et_2O at -20 °C, $t_{1/2}$ = 6 h

Additives – Deaggregation of *n*-BuLi and *s*-BuLi is further enabled by the addition of N,N,N',N'-tetramethylethylethylenediamine (TMEDA) **Me_2N-CH_2-CH_2-NMe_2**

The Nature of the Directed Metallation Group (the X) – Almost all contain a lone pair on the atom directly attached to the arene, or on the second atom removed from the arene. There are a substantial number of each of what would be considered electron withdrawing and electron donating groups. A list of many of them is included on the next page, but the most common are 2° and 3° amides (linked through C), 2° amides linked through N, carbamates (linked through each of O and N), OMOM ethers, oxazolines, and methoxy groups.

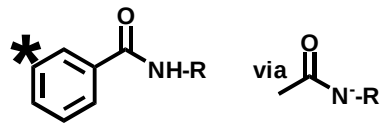
See Table

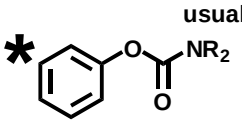
The ability to direct lithiation (their hierarchy) has been established through competition experiments; there is some discrepancy in the type of reaction, the O linked carbamate (-O-C(O)-NR_2) may be the strongest directed metallation group of all.

Directed Metallation Groups (DMG's)

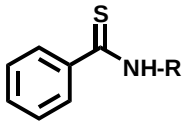
* - most commonly used

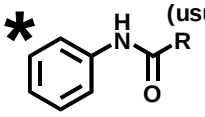
Strong



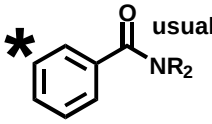


(37.2)

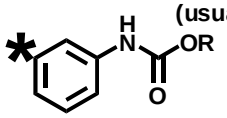


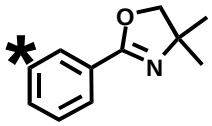


(40.5)

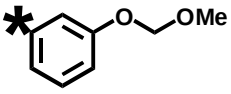


(pK_a 37.8)

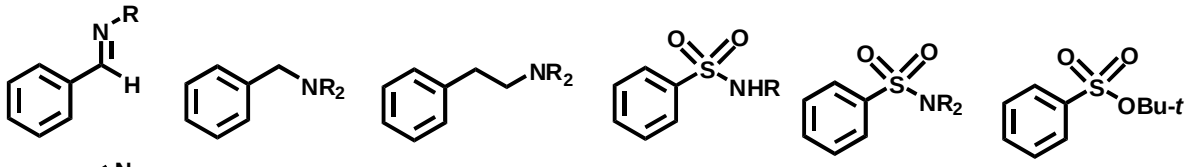


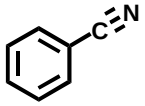


(38.1)



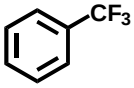
(OMOM)

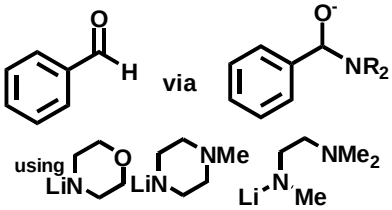


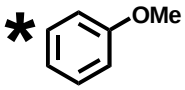


(38.1)

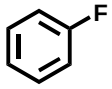
Moderate



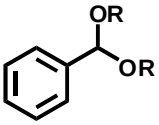


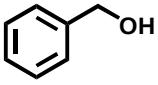


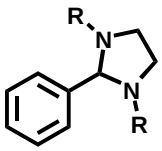
(39.0)

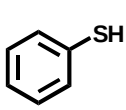


Weak

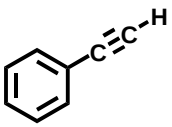




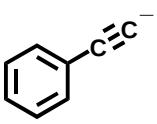




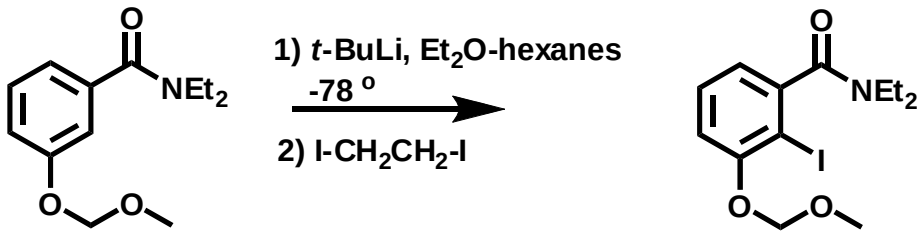
via S^-



via

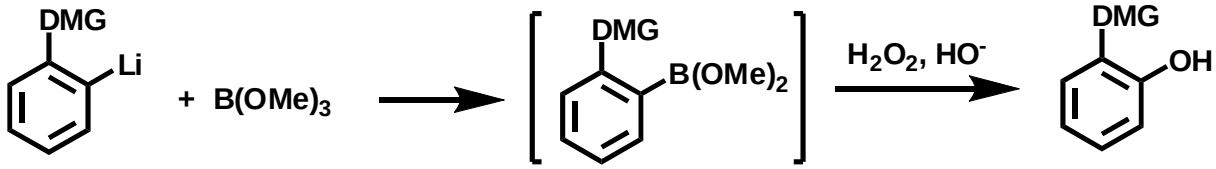


Additivity of DMG groups – As might be expected, the effect of two DMG's is generally additive, although it is sometimes necessary to go to less polar/coordinating solvents THF → Et_2O → hexanes to observe this unilaterally.



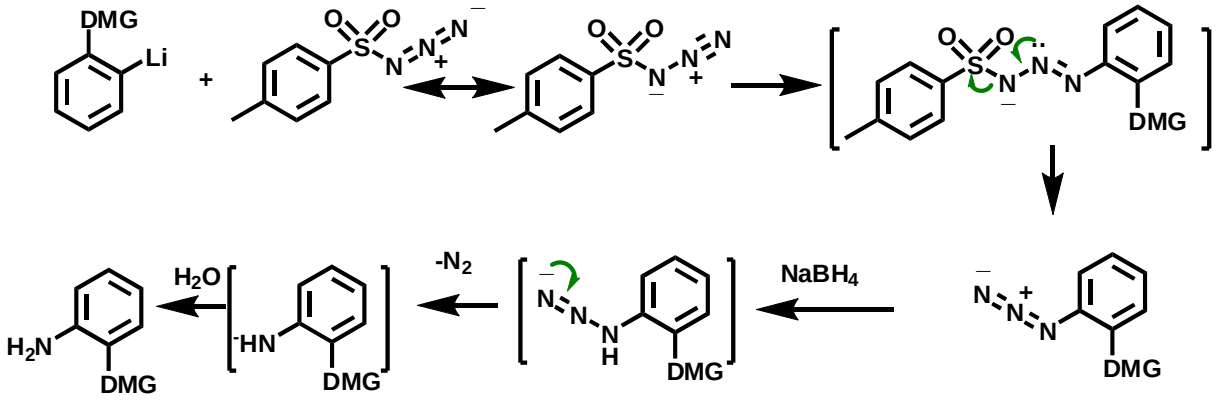
Electrophiles – Many very expected electrophiles can be incorporated, alkyl halides (sometimes with converting to organomagnesium), aldehydes/ketones, DMF (H-C(O)-NMe_2, incorporates aldehyde), Br_2 (or Br-CH_2CH_2-Br), Cl-PPh_2, Cl-$SiMe_3$. Some unexpected nucleophiles ("HO^+", "H_2N^+") can be incorporated by special 'tricks'.

For example, to incorporate OH, $B(OMe)_3$ followed by basic hydrogen peroxide works well.



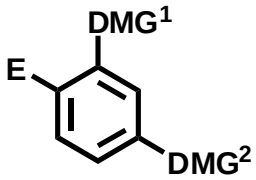
MoOPh has been known to work, on occasion.

For incorporation of NH_2, tosyl azide, followed by reduction, works.

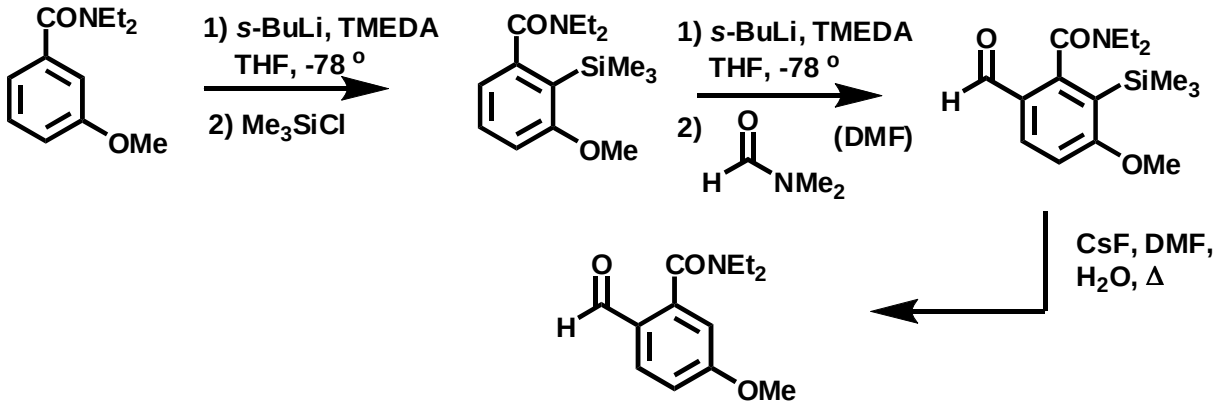


Blocking Groups (i.e., $SiMe_3$)

There will be many situations where one would want a compound that corresponds to directed lithiation at the *second* most preferred site, such as in



The can be done readily by blocking (or protecting) the most preferred site using a group that can be removed readily later; $SiMe_3$ is the best group for this. Silicon has a tremendous affinity for fluoride ion, so reagents such as CsF will remove an aryl TMS group when heated with water present.

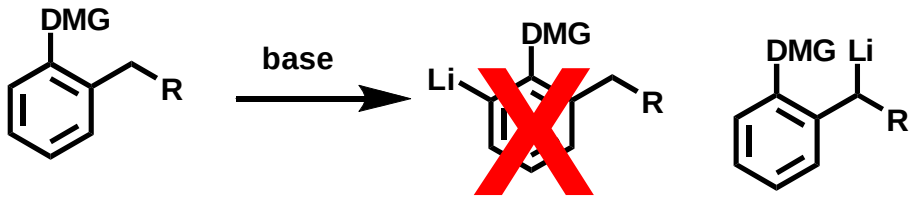


Aside: There are other things that can be done with Ar-$SiMe_3$ as well (F^- + E^+; Br_2 susbt)

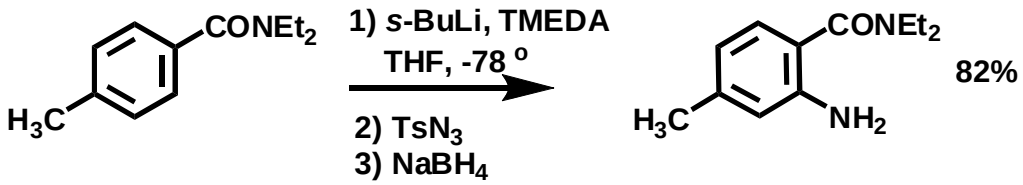
Side/Competing Reactions

Benzylic Lithiation – The benzylic site (unactivated pK_a ~ 41) is normally a little bit more acidic than the ring site (pK_a ~ 43), but is subject to the same kinetic issues as the benzene ring protons; (i.e., toluene is very hard to lithiate).

Kinetically, lithiation of these site are also enhanced by the presence of a strong directing group.

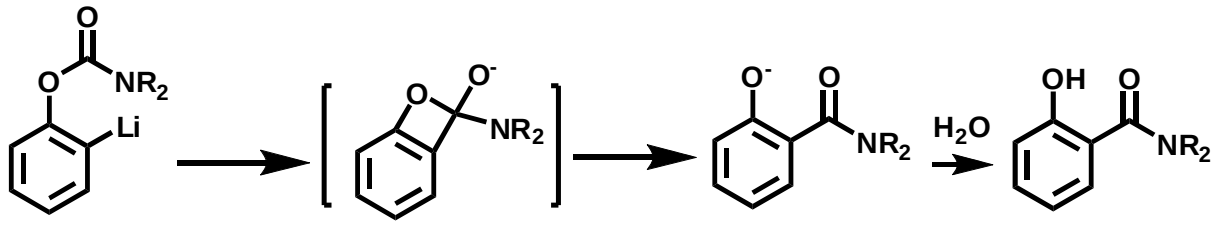


If there is not a DMG ortho to the alkyl group, one can usually get lithiation of the arene ring with alkyllithium bases. Benzylic lithiation is usually done by switching to a lithium amide base. This can be used to advantage in many cases.



The Anionic Fries Rearrangement (Snieckus Rearrangement?)

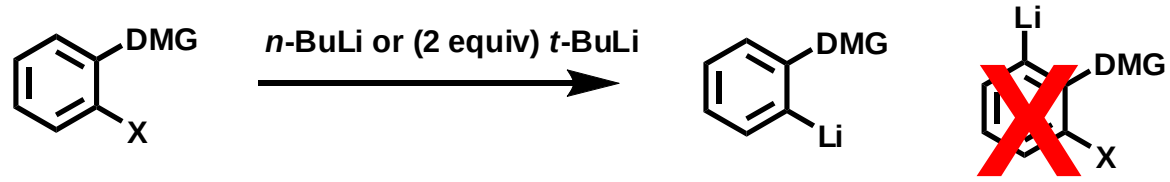
Ortho lithiated carbamates are not infinitely stable. The diethyl carbamates are stable at -78 °, but rearrange at RT; the diethyl carbmates rearrange even at -78 °. The products, which amides with an ortho hydroxyl (or an ortho carbamoyl phenol), are themselves very useful. This is called an anionic-Fries rearrangement, or sometimes a Snieckus rearrangement. These are the most important groups to do this, but O-aryl esters and O-aryl phosphinate esters are known to act similarly.



R = Et, stable @ -78 °
rearr @ RT
R = Me, rearr @ -78 °

Metal-Halogen Exchange

If the arene has a halogen, there is a competitive reaction where the alkyllithium and aryl halide switch organic units, to make an aryllithium at a different position. For bromides, iodides, and trialkyltins (yes, this is not a halide) this process is faster than directed lithiation. For chlorides and fluorides, this is much harder and directed lithiation occurs. Although presented as a 'problem', this feature can often be used to advantage.

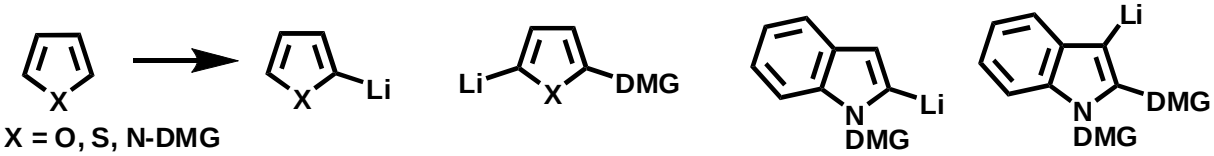


X = Br, I, SnR_3

Lithium Link, Winter 2003

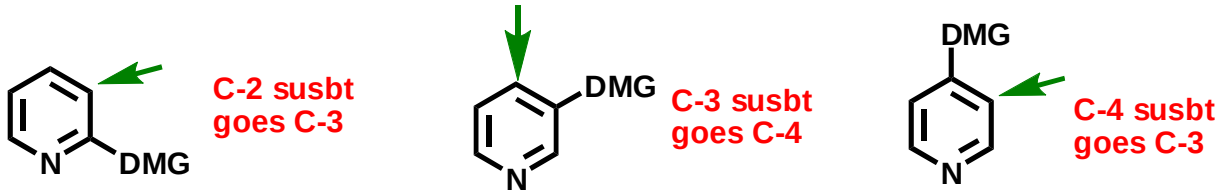
Lithiation of Heterocycles

We will look at heterocycles in more detail later, but a quick discussion of the preferred site of common heterocycles is appropriate here. For π- excessive heterocycles (furan, thiophene, and N- protected pyrroles and indole) C-2 lithiation is highly dominant, to the point where even directing groups on the ring have trouble overriding this.



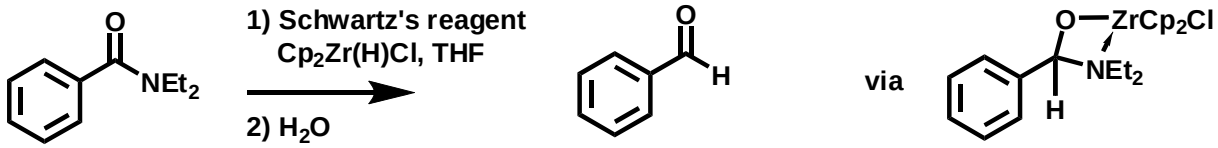
X = O, S, N-DMG

For the most important π-deficient heterocycle, pyridine, a DMG is required, and nucleophilic attack on the pyridine can compete. As a result, LDA and LiTMP are often used. Given these caveats,tThe general rule is that ortho lithiation can be done, and under normal situations the system will do anything *but* C-2 lithiation.



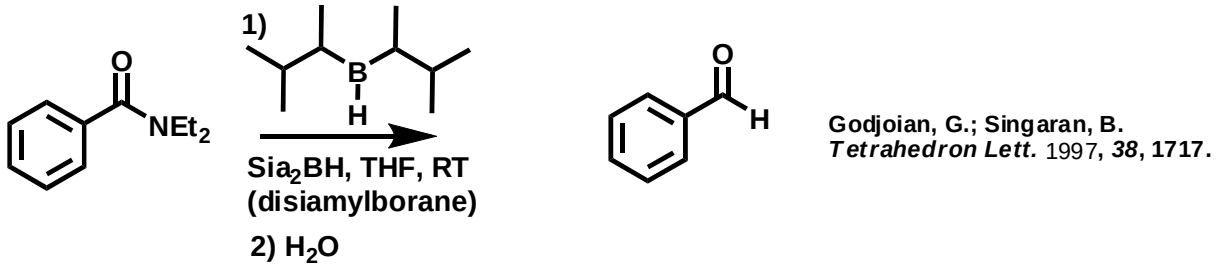
How do we get DMG groups to something more useful?

One of the often unstated issues with directed lithiation is that some of the best DMG's (esp. 3° amides) are the most difficult to convert to other, more useable functional groups. 3° Amides are buggers to hydrolyze, but there are recent protocols developed that have been able to convert 3° benzamides to aldehydes. It works well in many cases, although not so well with ortho, ortho' disubstituted benzamides.



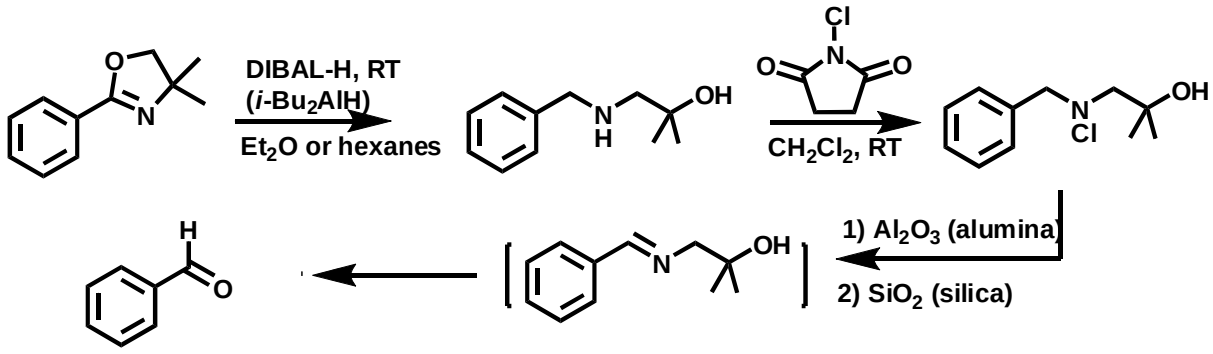
$Cp_2Zr(H)Cl$ is commercially available, or can be generated *in situ* with Cp_2ZrCl_2 + $LiAlH(Ot\text{-}Bu)_3$
-tolerates pyridines, acetates, cyano groups, and nitro groups
Spletstoser, J. T.; White, J. M.; Tunoori, A. R.; George, G. I. *J. Am. Chem. Soc.* 2007, *129*, 3408.

There is an earlier report of disiamylborane working for this transformation, but there hasn't been a lot of subsequent investigation to determine its scope.



Godjoian, G.; Singaran, B.
Tetrahedron Lett. 1997, ***38*, 1717.**

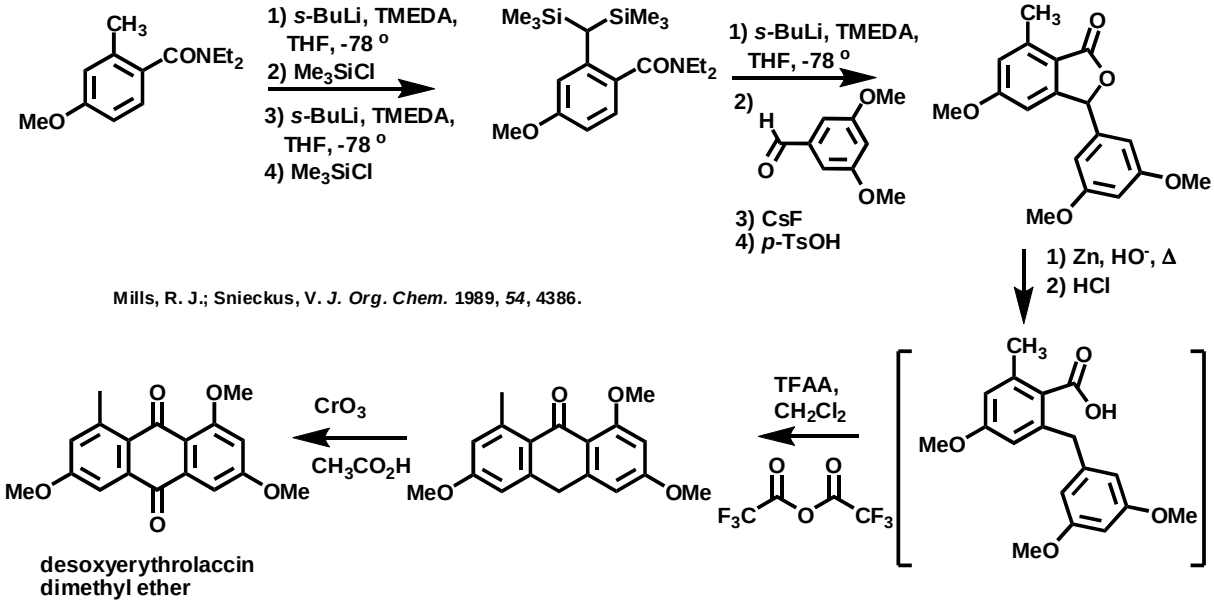
The Meyers oxazolines also have a well- worked out protocol for conversion to an aldehyde. Although it is multistep, it is known to work well.



Meyers, A. I.; Himmelsbach, R. J.; Reuman, M.
***J. Org. Chem.* 1983, *48*, 4053.**

Applications

Directed lithiation has been used innumable times in synthesis. The following is simply one example, chosen because it demonstrates many of the features discussed:



Mills, R. J.; Snieckus, V. *J. Org. Chem.* 1989, *54*, 4386.

desoxyerythrolaccin dimethyl ether

Some Reviews:

Snieckus, V. *Chem. Rev.* **1990**, *90*, 879.
Gray, M.; Tinkl, M.; Snieckus, V. *Comprehensive Organometallic Chemistry II*, Vol. 11, Ch. 1
Gschwend, H. W.; Rodriguez, H. R. *Org. React.* **1979**, *26*, 1.
Beak, P.; Snieckus, V. *Acc. Chem. Res.* **1982**
Whisler, M. C.; MacNeil, S.; *Snieckus*, V.; Beak, P. *Angew. Chem. Int. Ed.* **2004,** *43*, 2206.
FMC Lithium Link, Spring 1992; Spring 1993.
Hartung, C. G.; Snieckus, V. *Modern Arene Chemistry*, 2002, 330 (Ch 10).