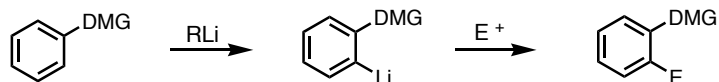


Review:

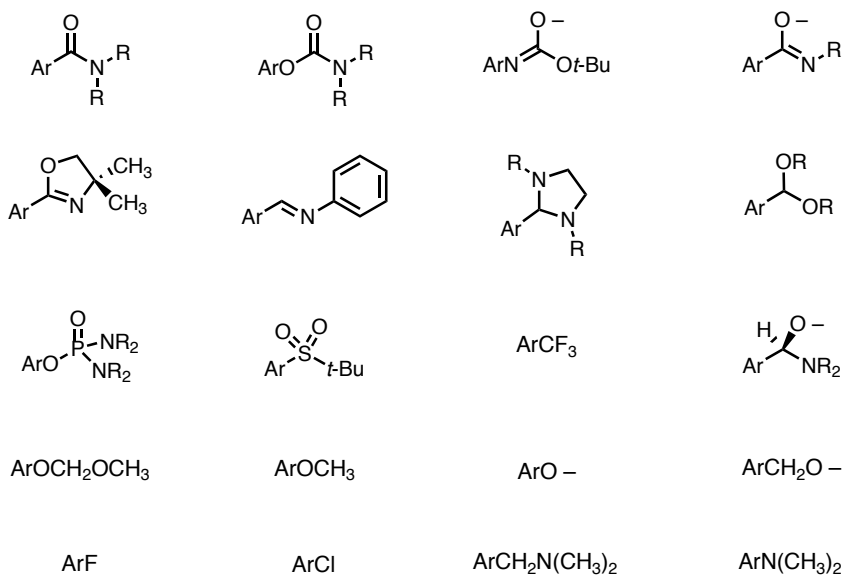
Snieckus, V. *Chem. Rev.* **1990**, 879.



Gilman, H.; Bebb, R. L. *J. Am. Chem. Soc.* **1939**, 61, 109.

Wittig, G.; Fuhrman, G. *Chem. Ber.* **1940**, 73, 1197.

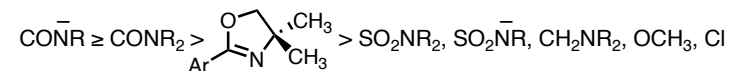
• Directed metalation of anisole with *n*-BuLi was discovered independently in 1939-1940 by Gilman and Wittig. This led to the discovery of more than 40 directing groups.



Relative Rates of Directed Metalation:



Slocum, D. W.; Jennings, C. A. *J. Org. Chem.* **1976**, 41, 3653.



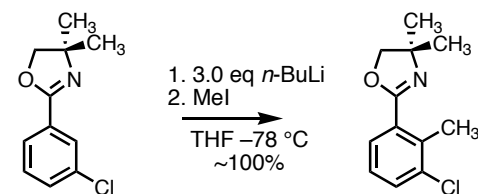
Beak, P.; Brown, R. A. *J. Org. Chem.* **1982**, 47, 34.

Beak, P.; Tse, A.; Hawkins, J.; Chen, C.; Mills, S. *Tetrahedron* **1983**, 39, 1983.

• Protective groups that also serve as strong directing groups are especially useful:

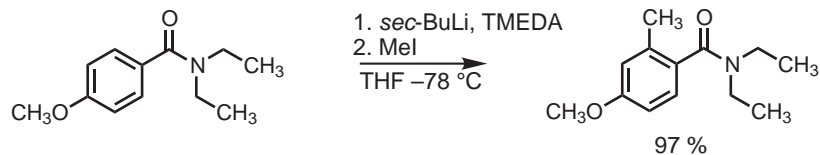


• Meta oriented directing groups almost always direct metalation to the position ortho to both groups.



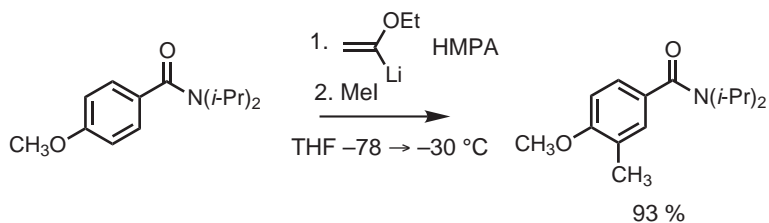
Pansegrau, P. D.; Rieker, W. F.; Meyers, A. I. *J. Am. Chem. Soc.* **1988**, 110, 7178.

- Lithiation occurs ortho to the stronger directing group in cases where two lithiation sites are possible.



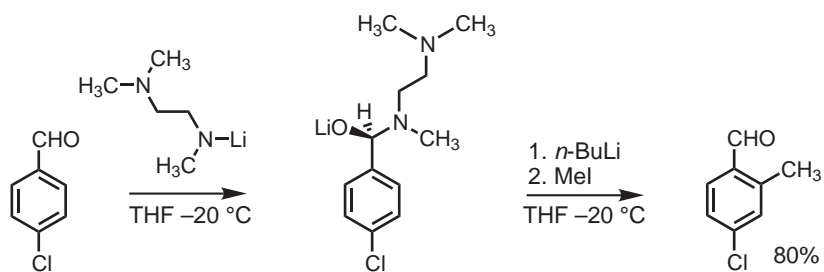
Mills, R. J.; Snieckus, V. *J. Org. Chem.* **1989**, *54*, 4386.

- Ethoxyvinyl lithium (EVL) with HMPA shows a reversal in selectivity; the proton ortho to the methoxyl group is removed.



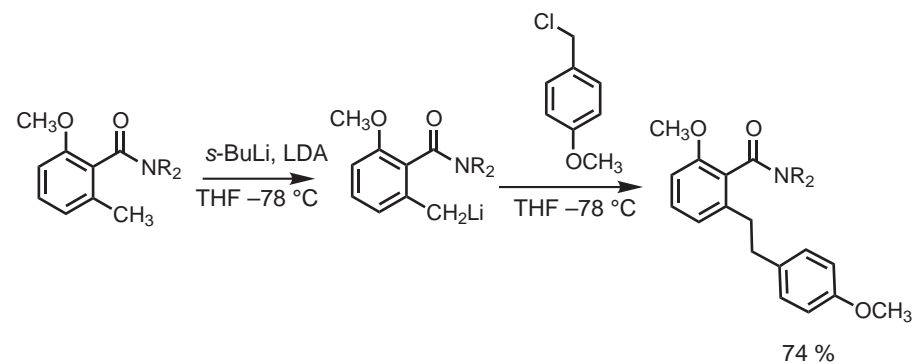
Shimano, M.; Meyers, A. I. *J. Am. Chem. Soc.* **1994**, *116*, 10815.

- Aldehydes can be transiently protected and, at the same time, transformed into a directing group by amide anion addition



Comins, D. L.; Brown, J. D. *J. Org. Chem.* **1984**, *49*, 1078.

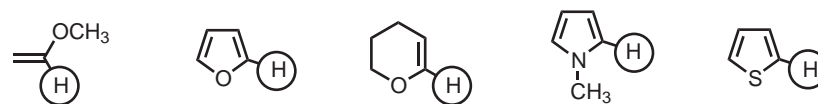
- Ortho tolyl anion formation is facile by directed metalation.



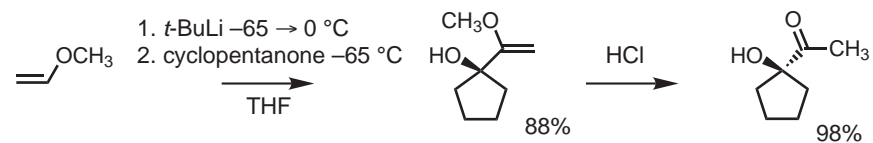
Reitz, D. B.; Massey, S. M. *J. Org. Chem.* **1990**, *55*, 1375.

Heterocycle and Vinyl Ether Metalation:

- Metalation of vinyl ethers and heterocycles occurs readily at the positions indicated.

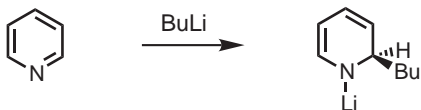


- Vinyl ether anions provide an acyl anion equivalent.

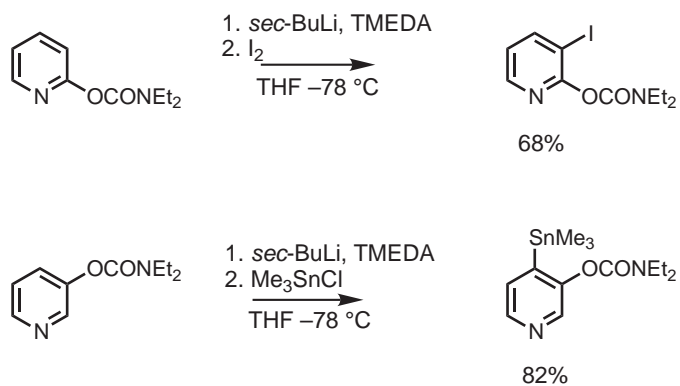


Baldwin, J. E.; Hofle, G. A.; Lever, O. W., Jr. *J. Am. Chem. Soc.* **1974**, *96*, 7125.

- Metalation of pyridine is complicated by 1,2-addition of the organometallic into the pyridine ring.

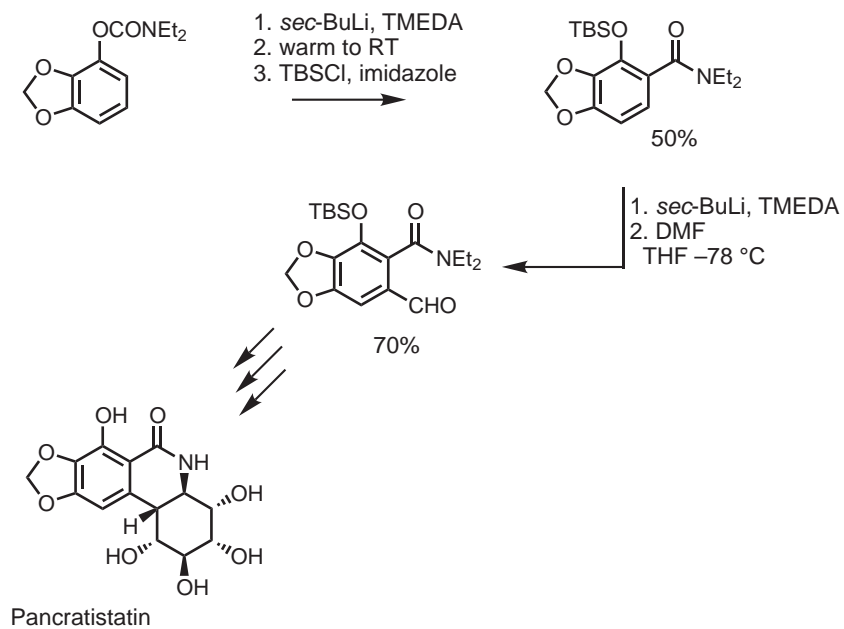


- With appropriate directing groups, lithiation of the pyridine ring can be efficient.



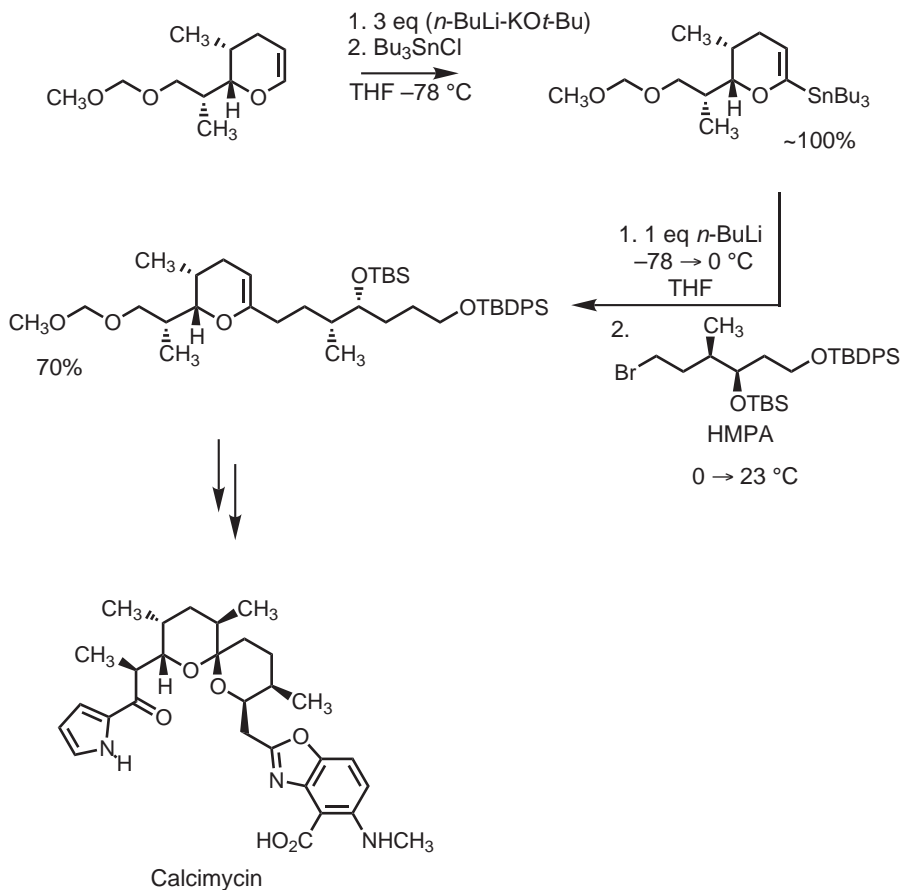
Examples of Directed Ortho Metalation in Synthesis:

- Carbamate directing groups can rearrange upon warming after lithiation. The resulting amide can be used for a second metalation reaction.



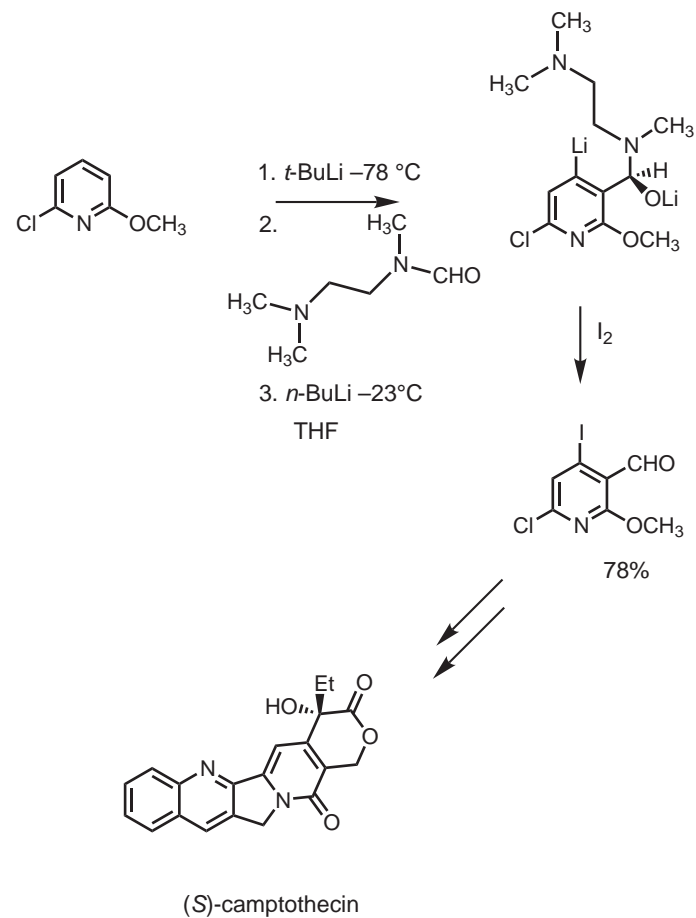
Danishefsky, S.; Lee, J. Y. *J. Am. Chem. Soc.* **1989**, *111*, 4829.

Miah, M. A.; Snieckus, V. *J. Org. Chem.* **1985**, *50*, 5436.



- Note that treatment with *t*-BuLi alone failed to provide the desired anion. Trapping the anion under LICKOR conditions with tin provided a substrate that could be readily converted to the corresponding organolithium reagent.

Boeckman, R. K., Jr.; Charette, A. B.; Asberom, T.; Johnston, B. H. *J. Am. Chem. Soc.* **1987**, *109*, 7553.



- Lithiation adjacent to the methoxy group followed by trapping with the formamide shown provides an α -amino alkoxide to direct a second metalation reaction.

Comins, D. L.; Baevsky, M. F.; Hong, H. *J. Am. Chem. Soc.* **1992**, *114*, 10971.