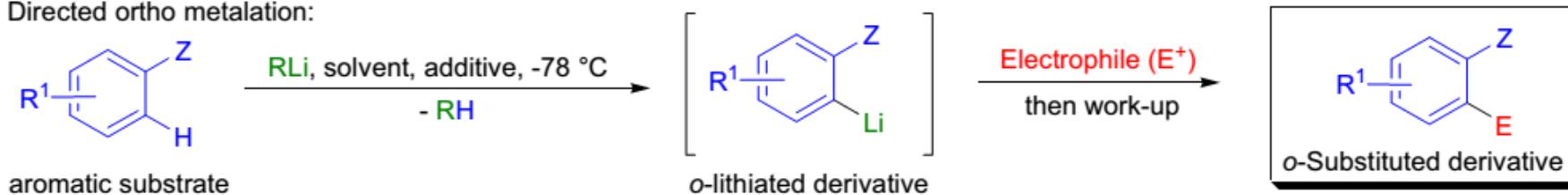


SNIECKUS DIRECTED ORTHO METALATION

Gillman and Wittig (1939 & 1940):

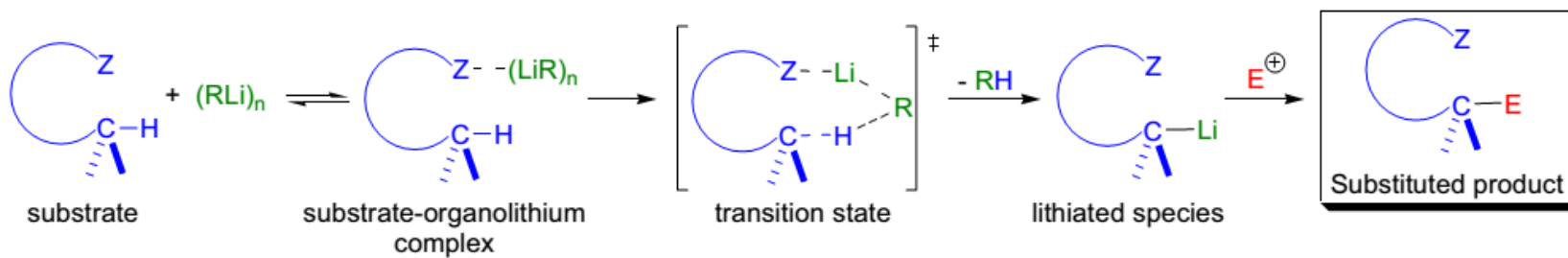


Directed ortho metalation:



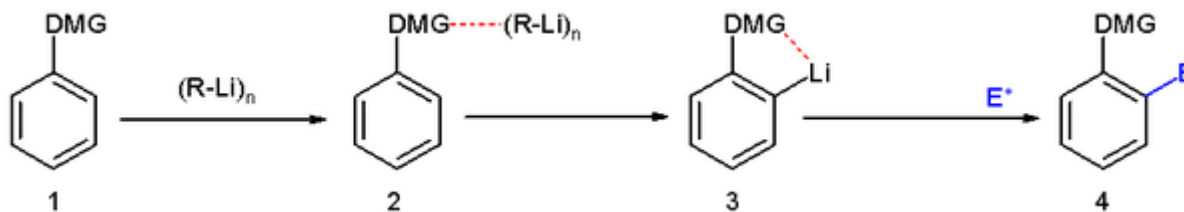
Z = directed metalation group = CONR₂, CONHR, CONH(Cumyl), CSNHR, 2-oxazolino, 2-imidazolino, CF₃, CH=NR, (CH₂)_nNR₂ where n=1 or 2, CH₂OH, NMe₂, NHCOR, NHCO₂R, OMe, OCH₂OMe, OCH(Me)OEt, OCONR₂, OSEM, OP(O)NR₂, SO₂NR₂, SO₂NHR, SO₂R; R = *n*-Bu, *sec*-Bu, *t*-Bu; solvent = THF, Et₂O, hexanes, benzene or combinations of these; additive: TMEDA

Mechanism

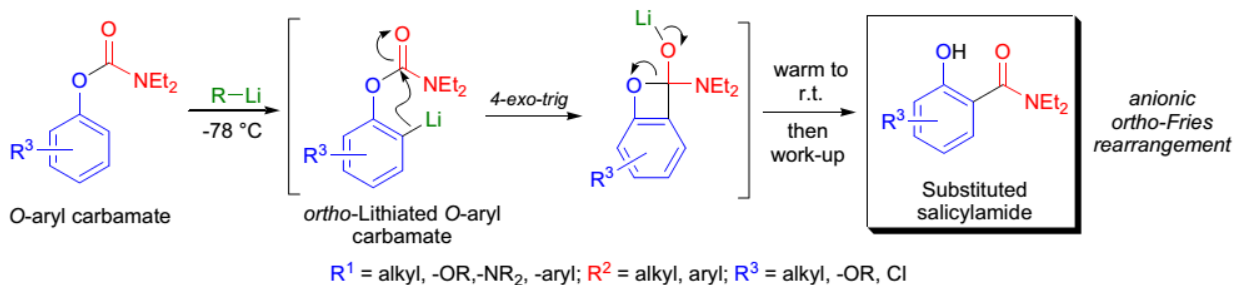


The directed ortho metalation is fundamentally a complex-induced proximity effect (CIPE) in which the formation of a pre-metalation complex brings reactive groups into proximity for directed deprotonation.

General Features



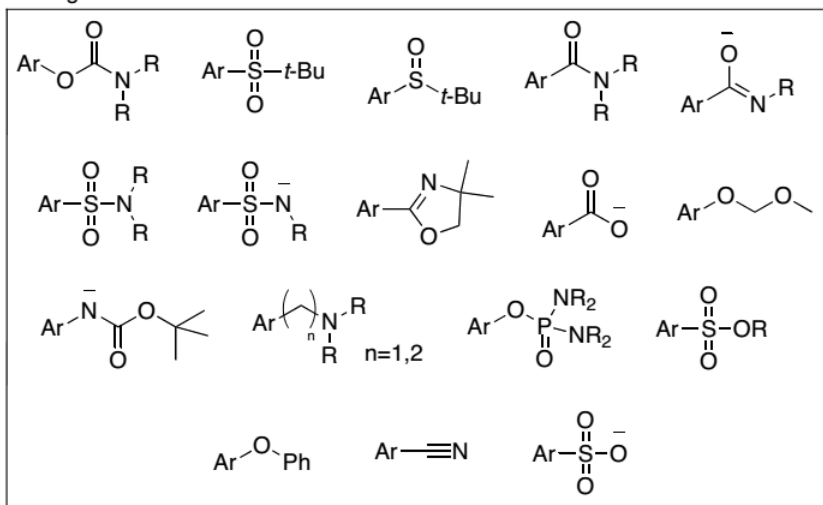
- The directed metalation group (Z group) must be resistant to nucleophilic attack by the metalating reagent, and it must contain at least one heteroatom, which can coordinate with the incipient ortho metal atom forming a 4-, 5-, or 6-membered intermediate.
- The formation of a 5-membered intermediate is the most favorable.
- The most popular DMG groups are tertiary amides and O-carbamates.
- The DMG groups can be ranked according to the strength of their directing effects (based on competition experiments), $SO_2t-Bu > CON(i-Pr)_2 > OCON(i-Pr)_2 > OMOM$ was the hierarchy of metalation when $n-BuLi/THF/-78^\circ C$ were used.
- Since alkyllithiums exist predominantly as aggregates in solvents, the addition of basic solvents such as ethers and tertiary amines or bidentate ligands (e.g., TMEDA) is necessary to break down the aggregates to monomers and dimers.
- when the Z group is a carbamate ($OCONR_2$), a facile 1,3-acyl shift occurs after the ortho lithiation is complete to afford a salicylamide.



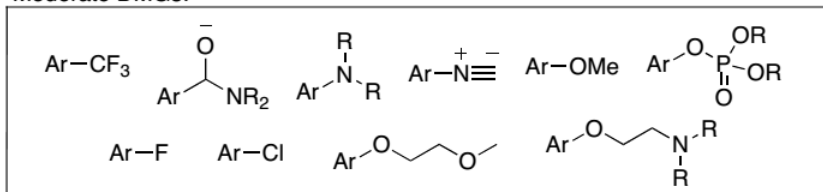
Relative Rates of Directed Metalation

Common DMGs and their relative strength in directing metalation:

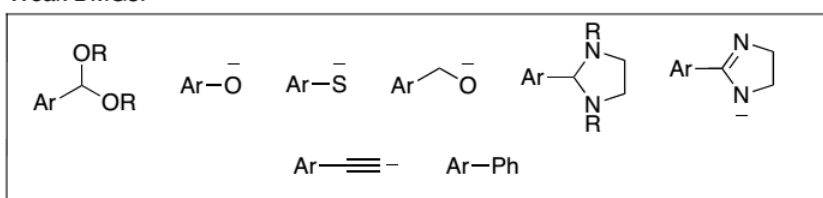
Strong DMGs:



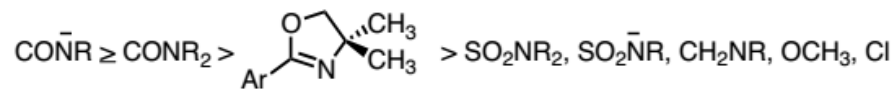
Moderate DMGs:



Weak DMGs:



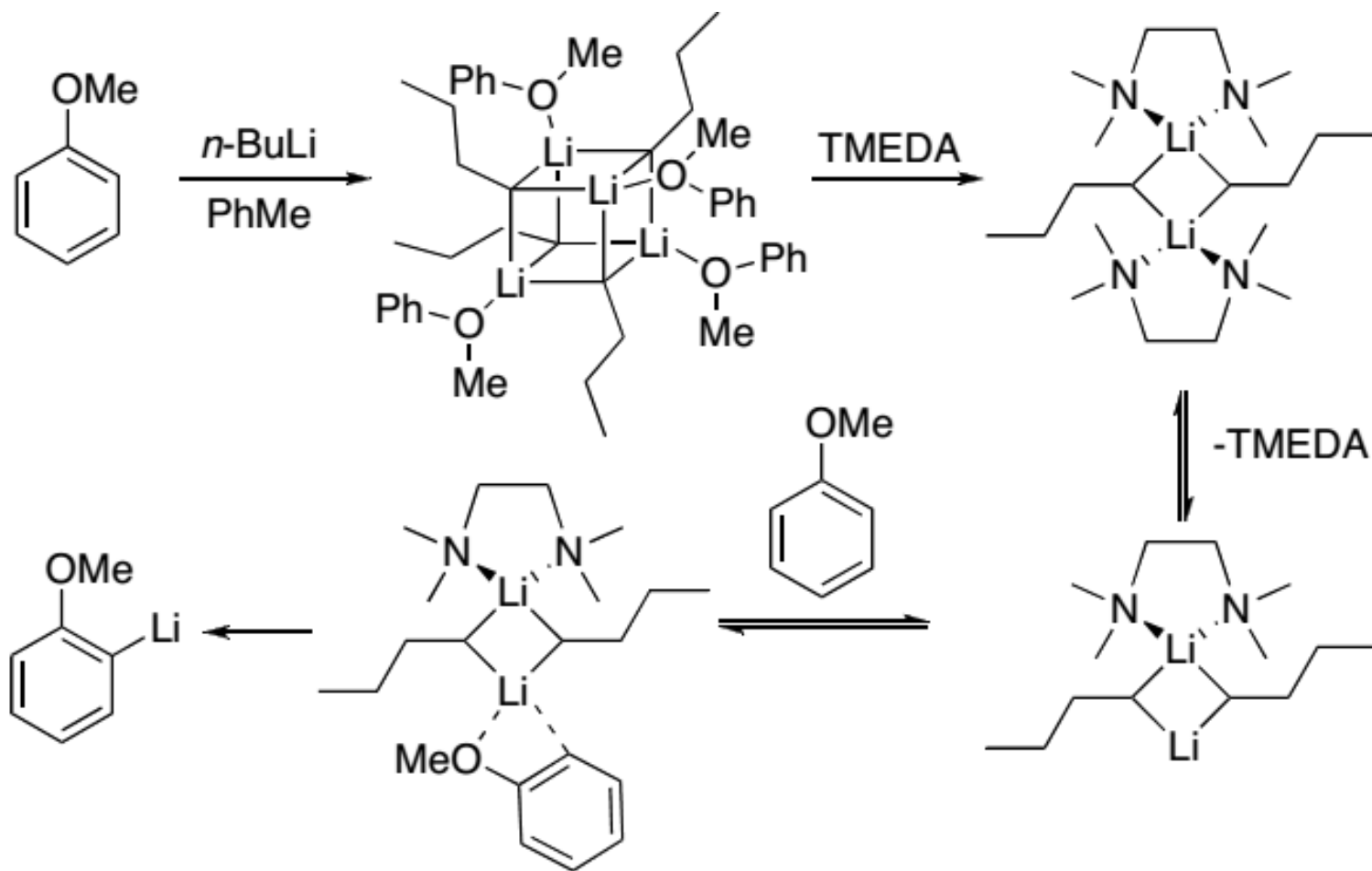
-Slocum, D. W.; Jennings, C. A. *J. Org. Chem.* **1976**, 41, 3653



-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.

TMEDA

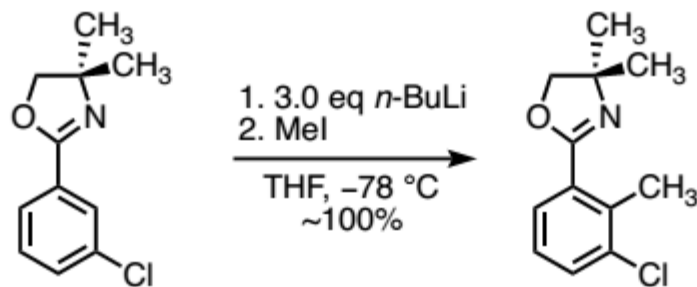


General Features

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

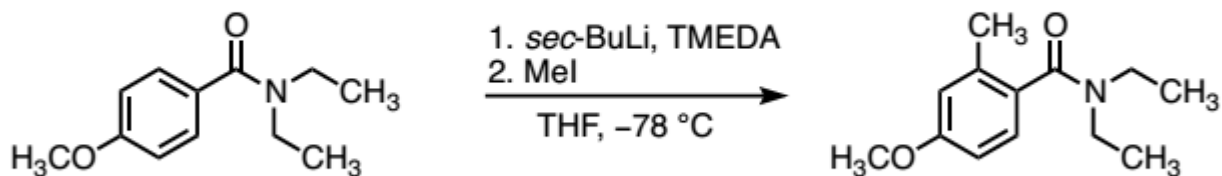


- Meta oriented directing groups almost always direct metalation to the position ortho to both groups.

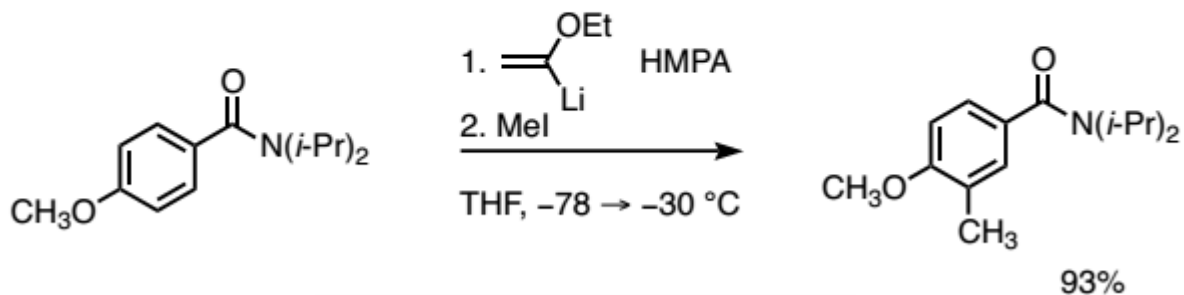


General Features

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



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

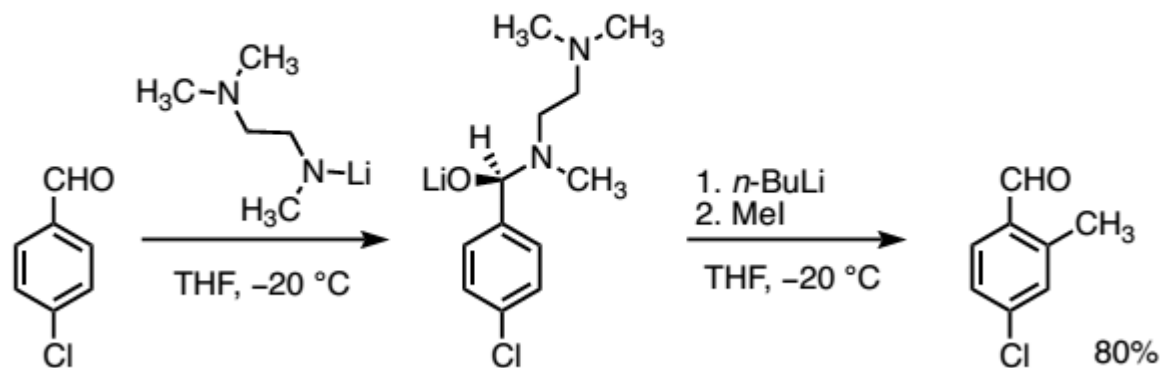


Ethoxyvinyl lithium–HMPA. Surprising Regiochemistry in Aromatic Metalation

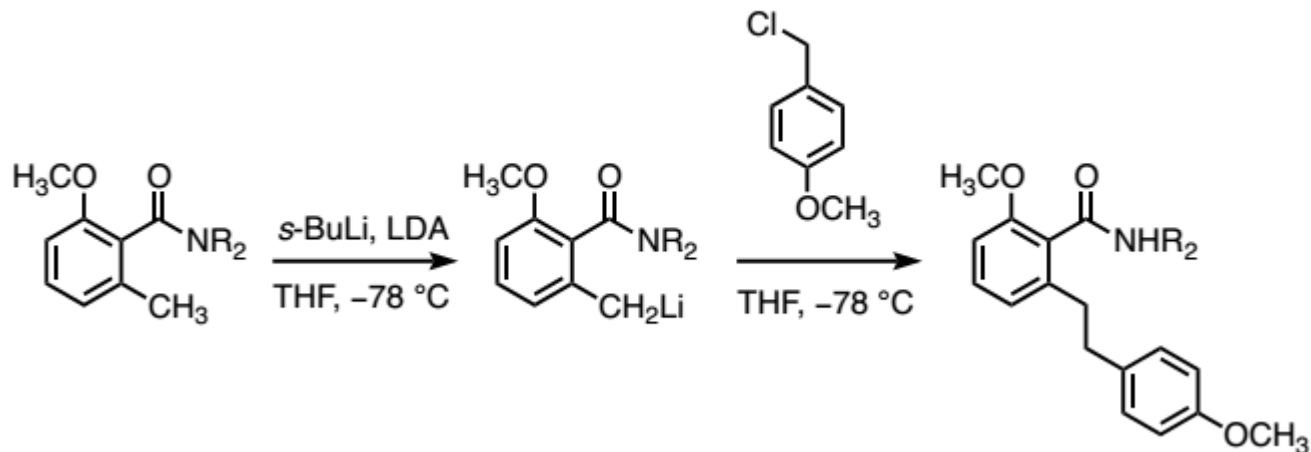
Masanao Shimano and A. I. Meyers*

General Features

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

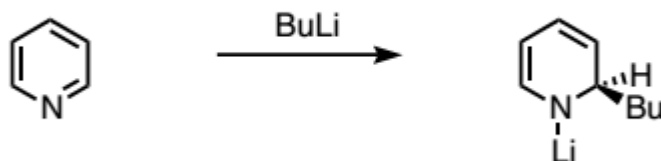


- Ortho tolyl anion formation is facile by directed metalation.

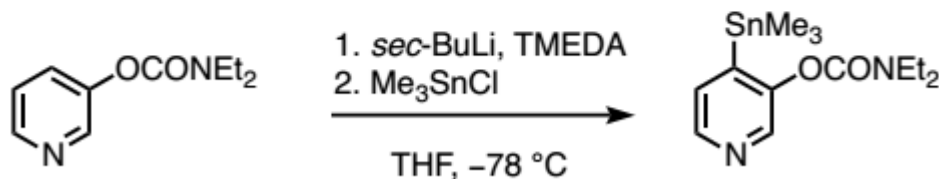
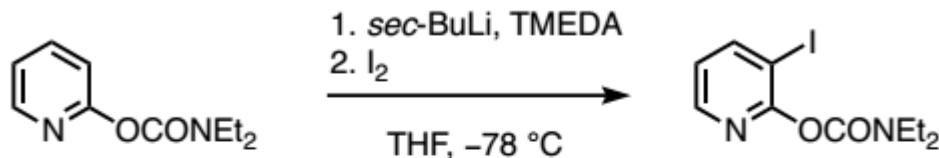


General Features

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

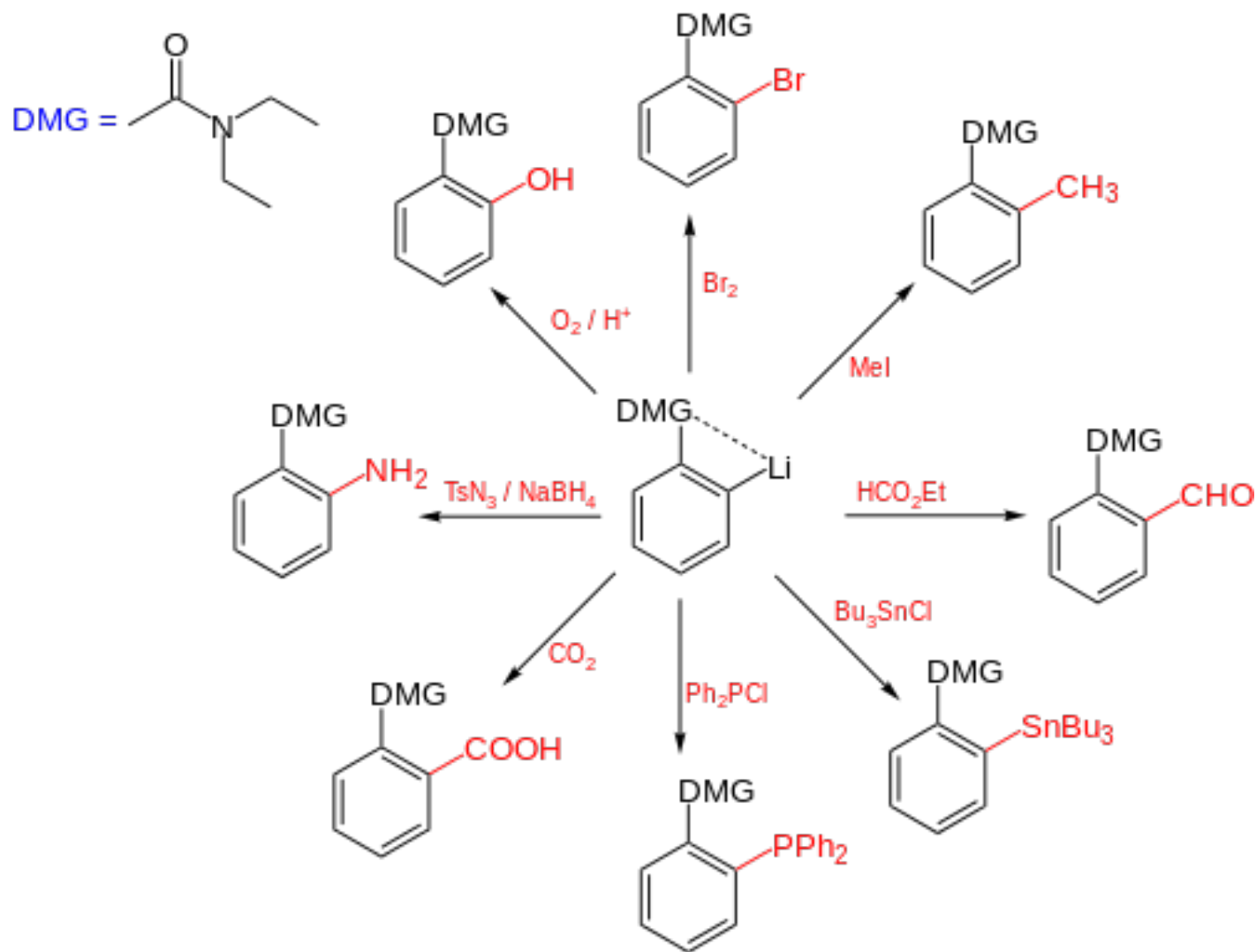


- With appropriate directing groups, lithiation of the pyridine ring can be efficient

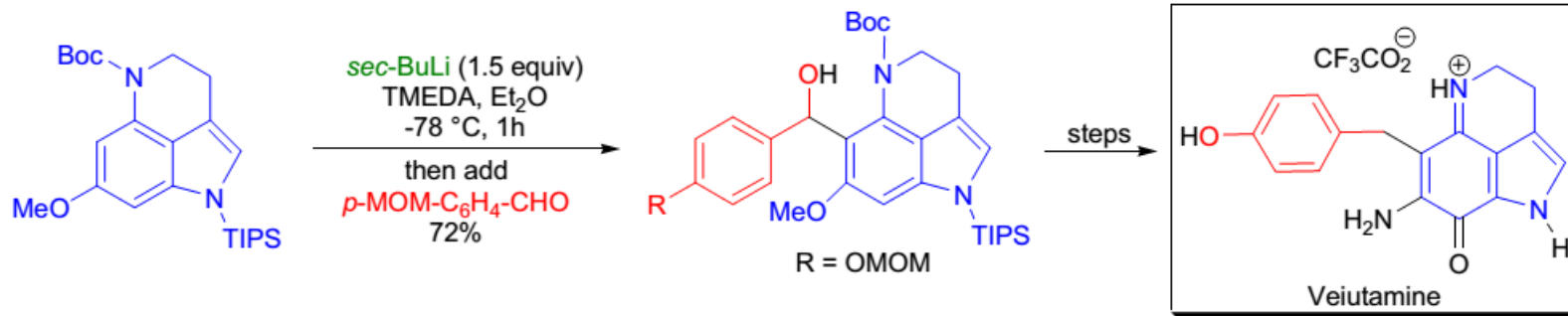
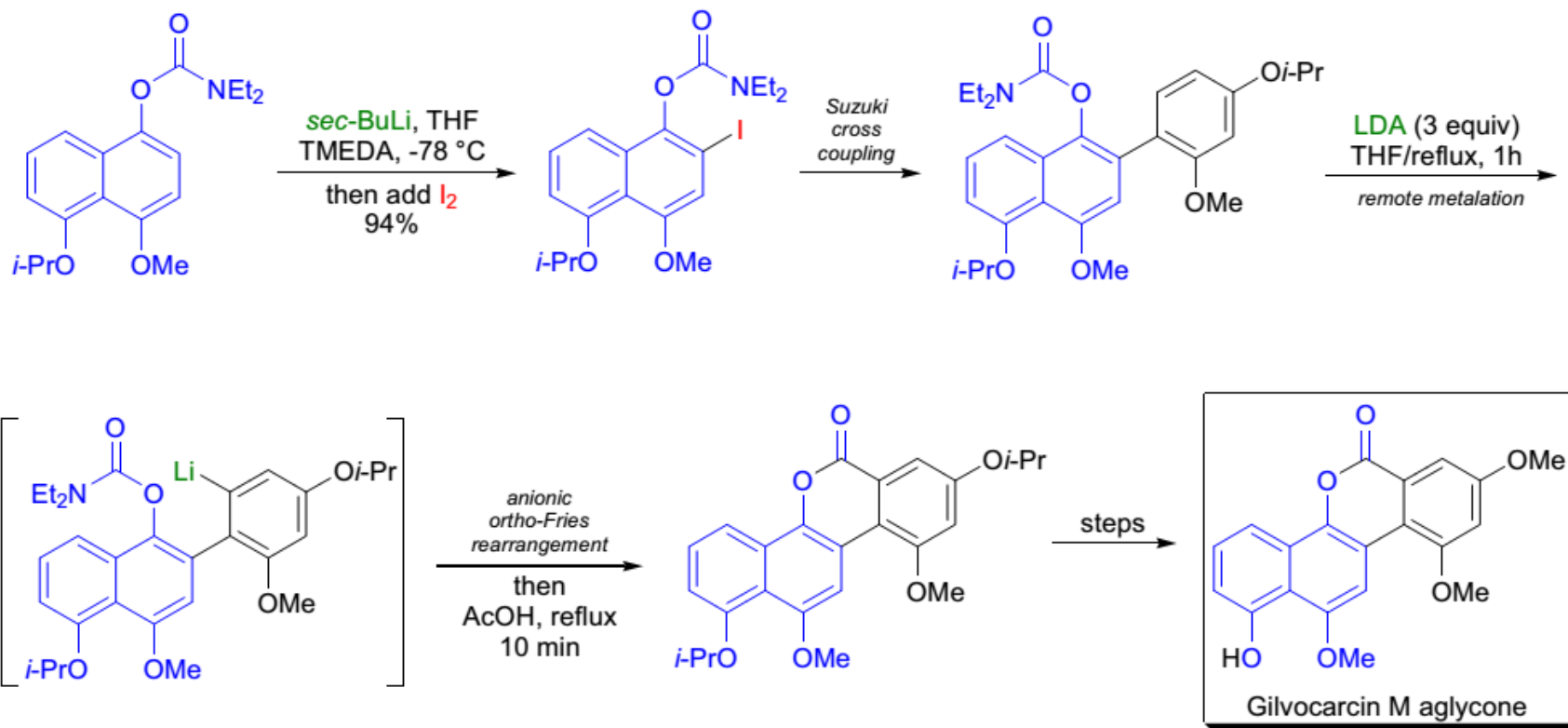


-Miah, M. A.; Snieckus, V. *J. Org. Chem.* **1985**, 50, 5436

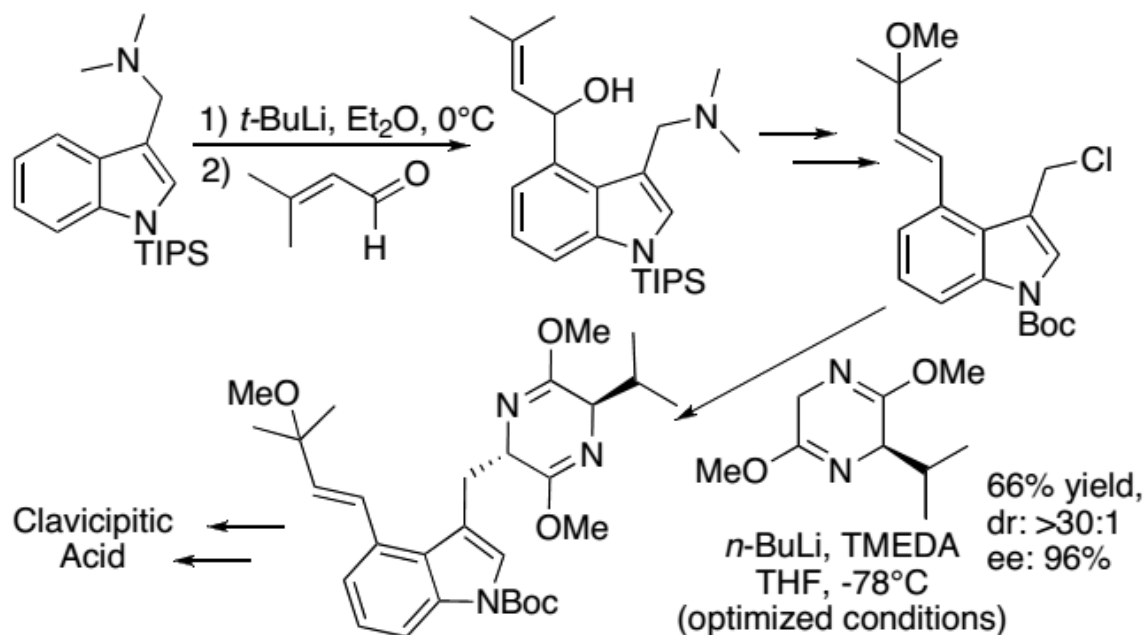
Application



Application

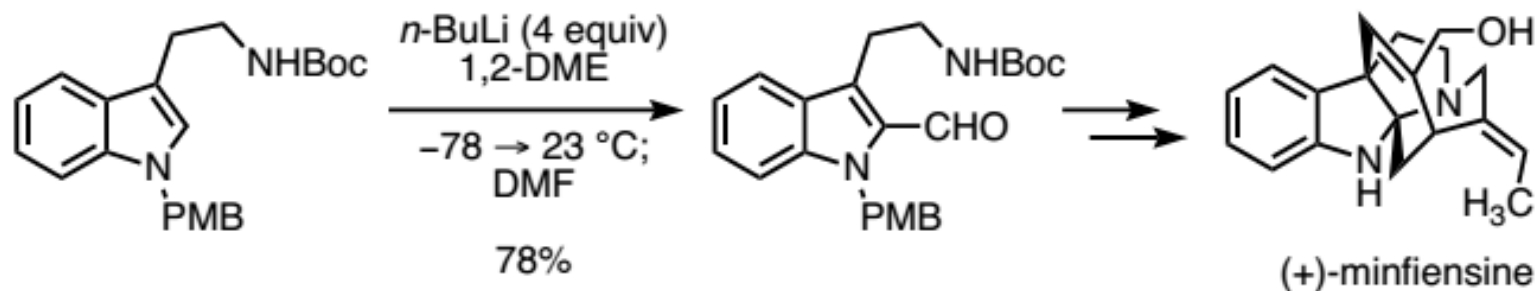


Application



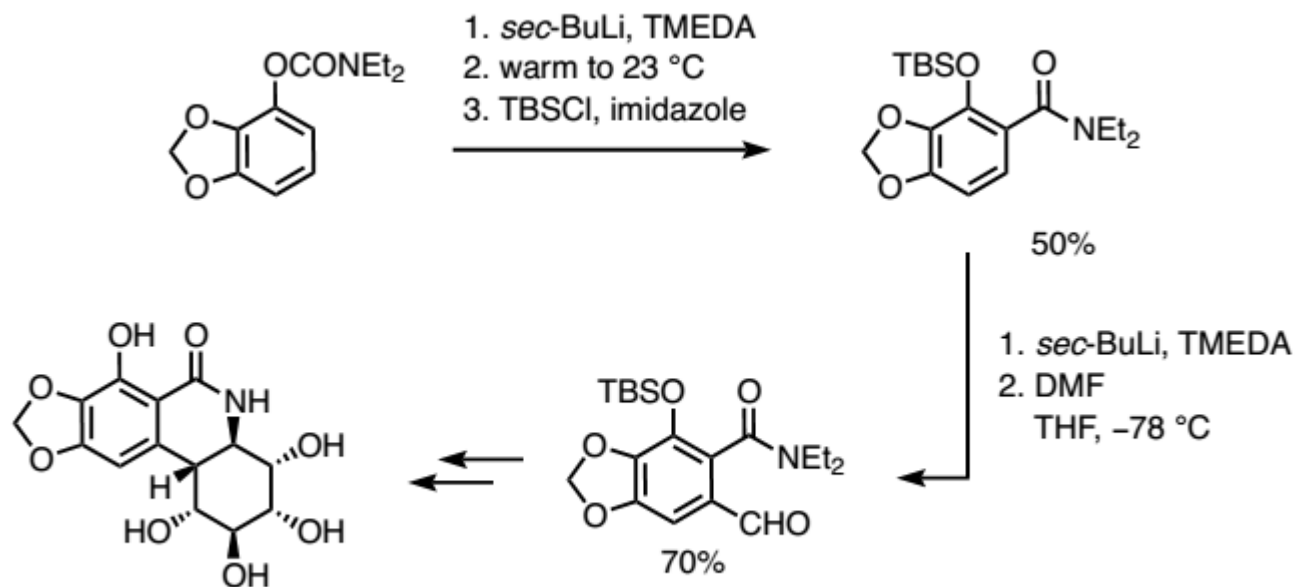
Tetrahedron, **1999**, 55, 10989-11000.

- Directed lithiation of a tryptamine derivative has been employed in the total synthesis of (+)-minfiensine.

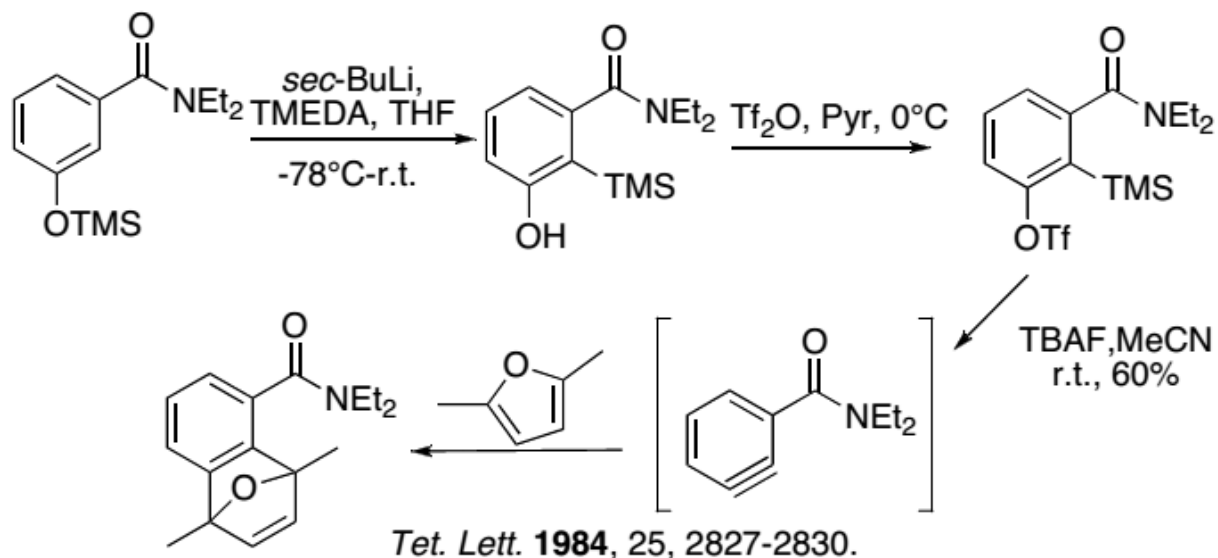


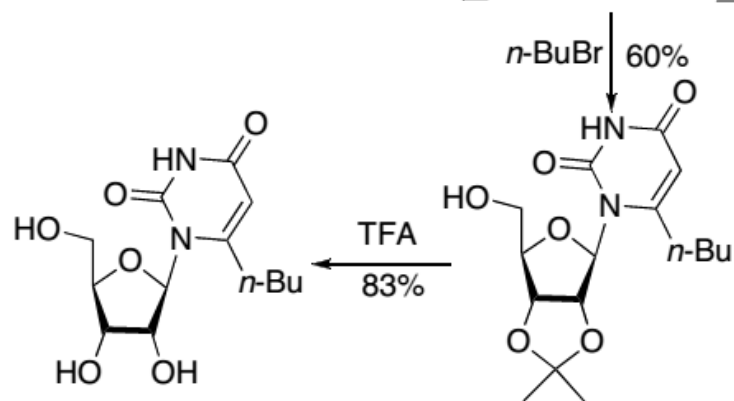
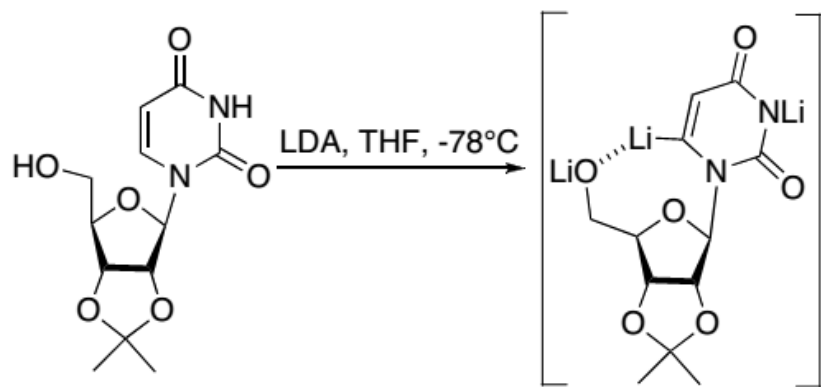
-MacMillan, D. W. C. *J. Am. Chem. Soc.* **2009**, 131, 13606.

Application

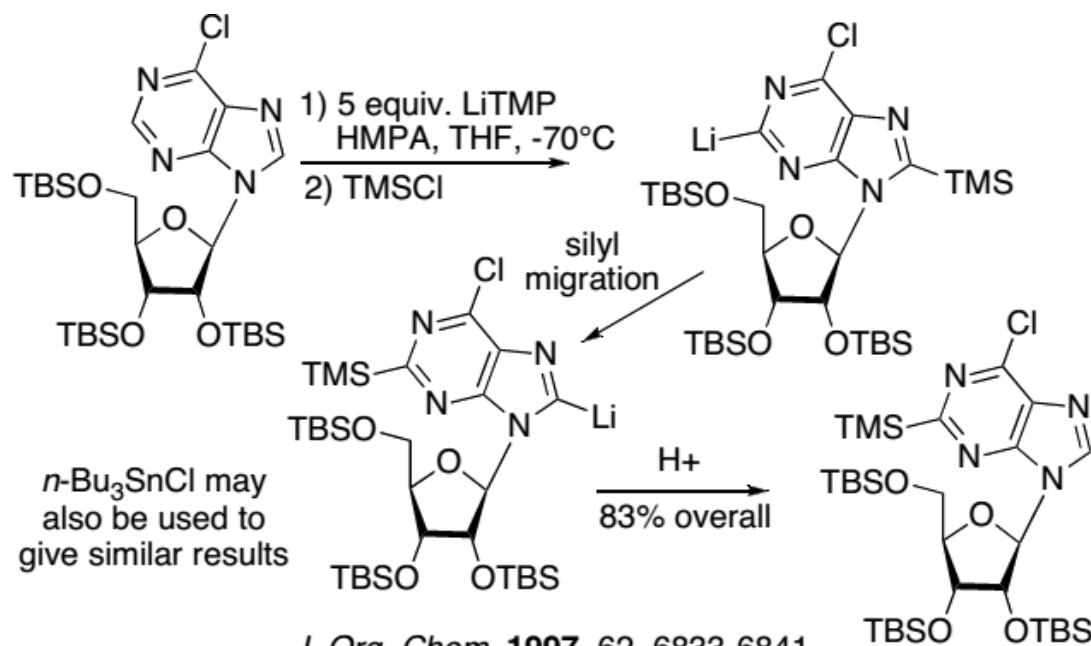


-Danishefsky, S.; Lee, J. Y. *J. Am. Chem. Soc.* **1989**, 111, 4829





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



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