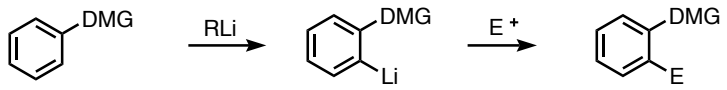
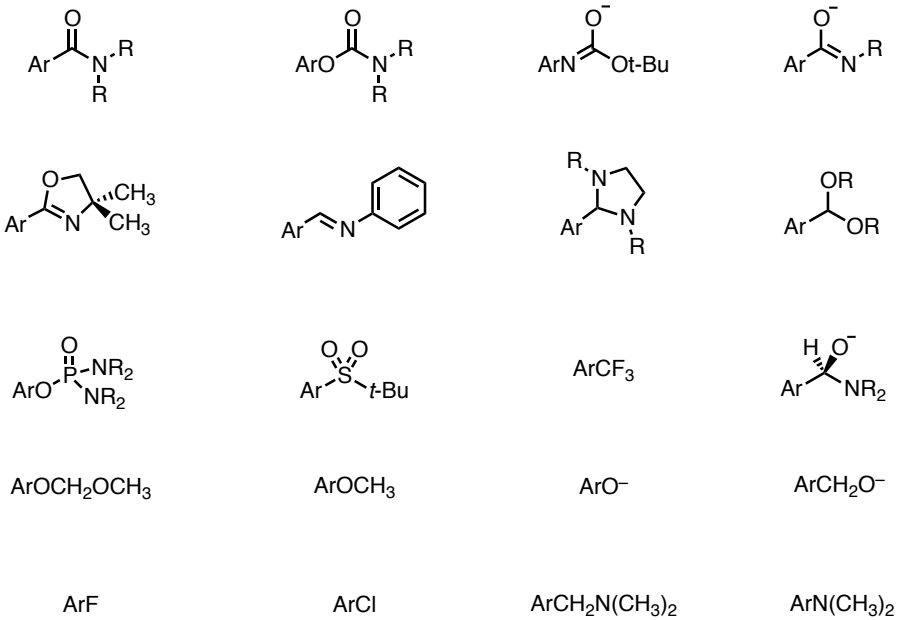
Reviews:

Snieckus, V. *Chem. Rev.* **1990**, 879.
Clayden, J. In *Chemistry of Organolithium Compounds*; Rappoport, Z., Marek, I., Eds.; Wiley: Chichester, 2004; Vol. 1, pp 495–646.



Gliman, H.; Bebb, R. L. *J. Am. Chem. Soc.* **1939**, *61*, 109.
Wittig, G.; Fuhrman, G. *Chem. Ber.* **1940**, *73*, 1197.

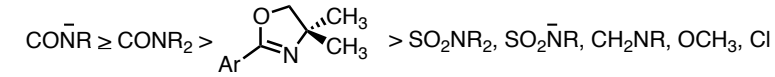
- Directed metalation of anisole with *n*-BuLi was discovered independently in 1939–1940 by Gilman and Wittig. This led to the discovery of more than 40 directing groups.



Relative Rates of Directed Metalation:

$$SO_2NR_2,\ CO\bar{N}R,\ CH_2NR_2 > OCH_3 > CH_2CH_2NR_2,\ CF_3,\ F,\ NR_2$$

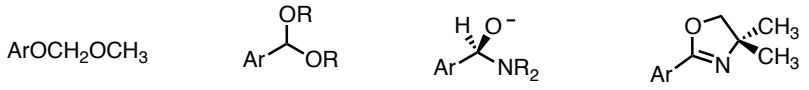
Slocum, D. W.; Jennings, C. A. *J. Org. Chem.* **1976**, *41*, 3653.



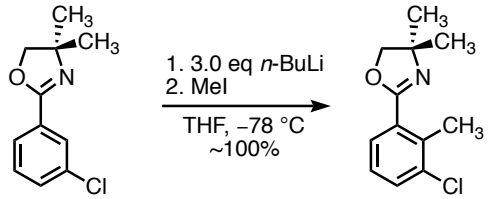
Beak, P.; Brown, R. A. *J. Org. Chem.* **1982**, *47*, 34.

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.

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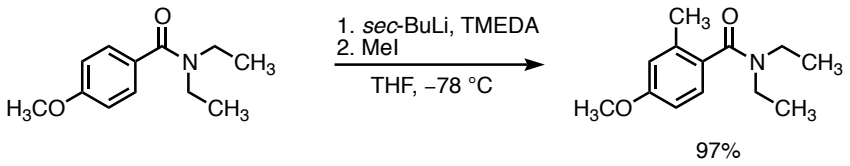
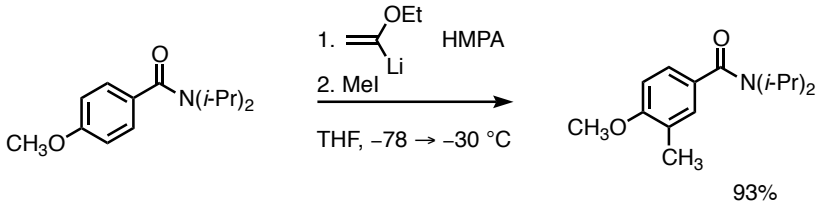
- Lithiation occurs ortho to the stronger directing group in cases where two lithiation sites are possible.



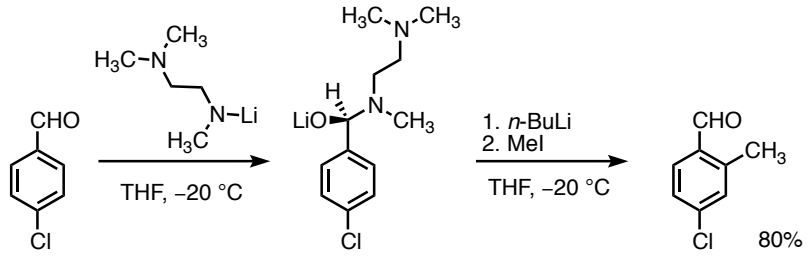
Mills, R. J.; Snieckus, V. *J. Org. Chem.* **1989,** 5*4,* 4386.

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



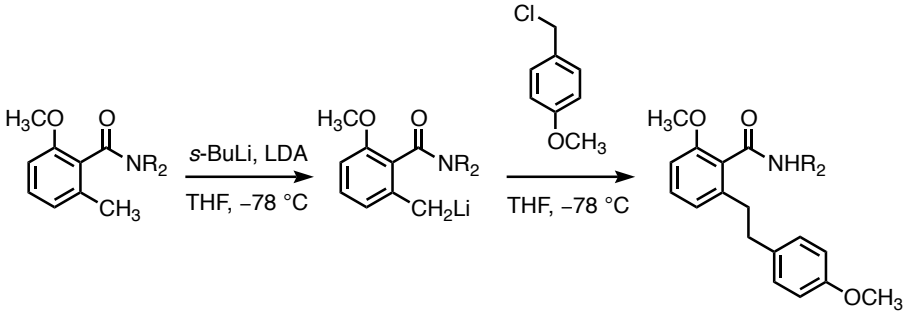
Shimano, M.; Meyers, A. I. *J. Am. Chem. Soc.* **1994**, *116*, 10815.

- 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.

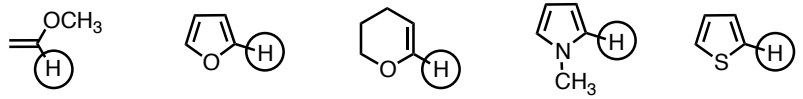
- Ortho tolyl anion formation is facile by directed metalation.



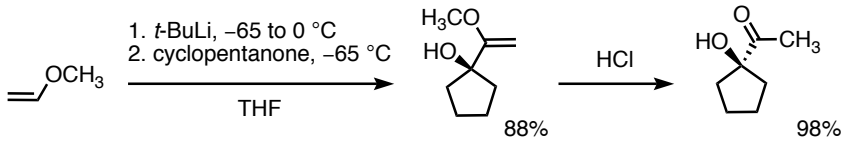
Reitz, D. B.; Massey, S. M. *J. Org. Chem.* **1990**, *55*, 1375.

Heterocycle and Vinyl Ether Metalation:

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

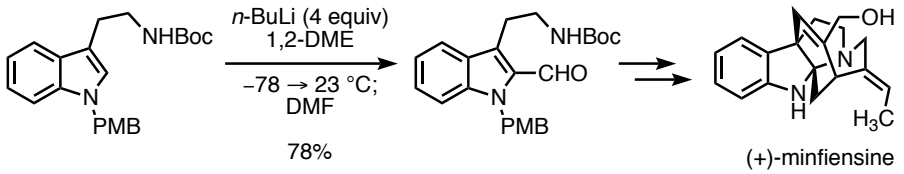


- Vinyl ether anions provide an acyl anion equivalent.



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

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



Jones, S. B.; Simmons, B. S.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2009**, *131*, 13606.

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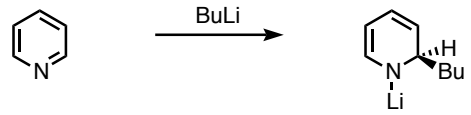
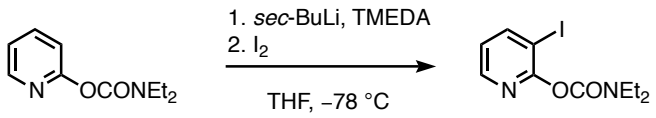
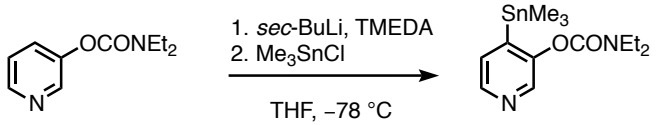
- Metalation of pyridine is complicated by 1,2-addition of the organometallic into the pyridine ring.



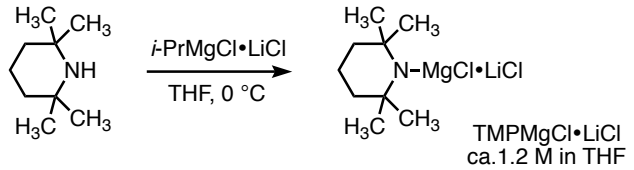
- With appropriate directing groups, lithiation of the pyridine ring can be efficient.

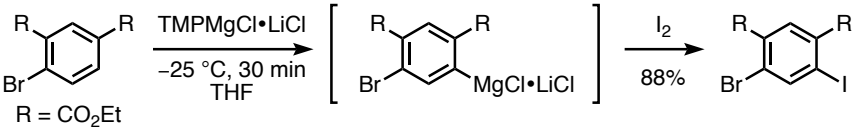




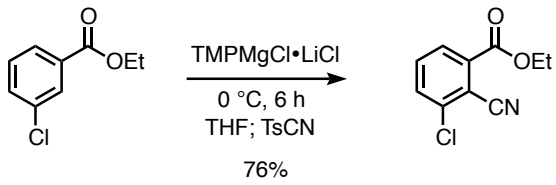
Miah, M. A.; Snieckus, V. *J. Org. Chem.* **1985**, *50*, 5436

- The highly hindered amide base TMPMgCl•LiCl has been shown to effect efficient directed metallation of electron-poor heteroarenes and arenes containing sensitive functional groups.



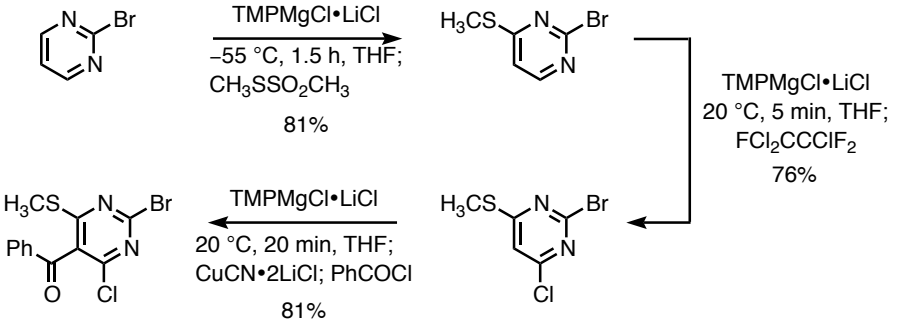


Krasovskiy, A.; Krasovskaya, V.; Knochel, P. *Angew. Chem., Int. Ed.* **2006**, *45*, 2958.



Lin, W.; Baron, O.; Knochel, P. *Org. Lett.* **2006**, *8*, 5673.

- This metallation technology has been employed iteratively in the synthesis of a fully substituted pyrimidine derivative.



Mosrin, M.; Knochel, P. *Org. Lett.* **2008**, *10*, 2497.

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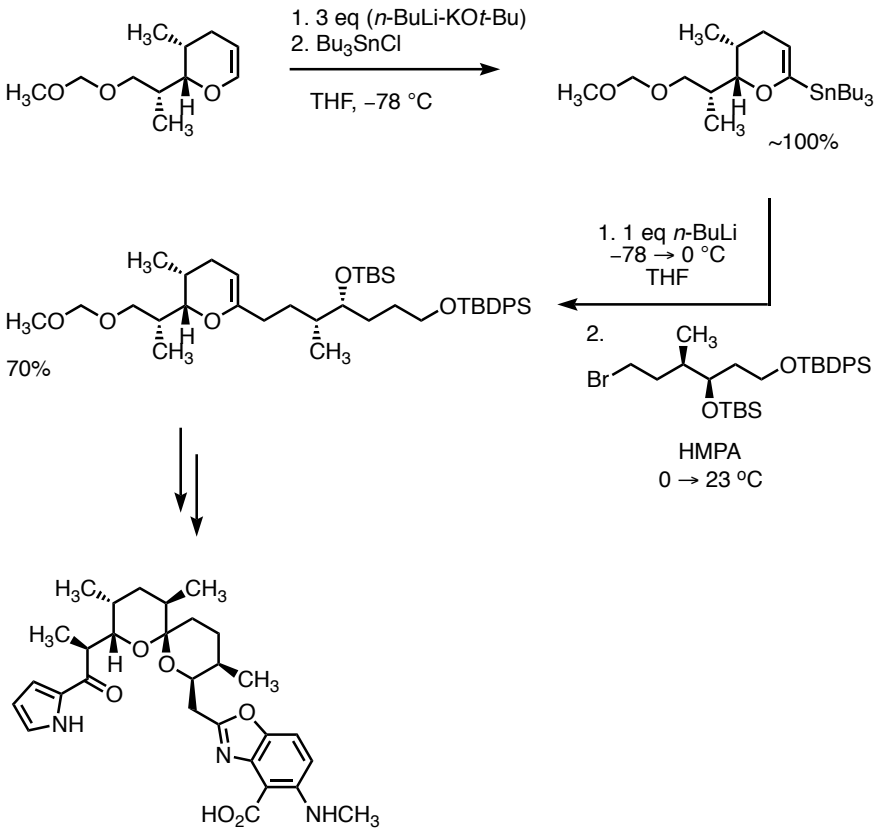
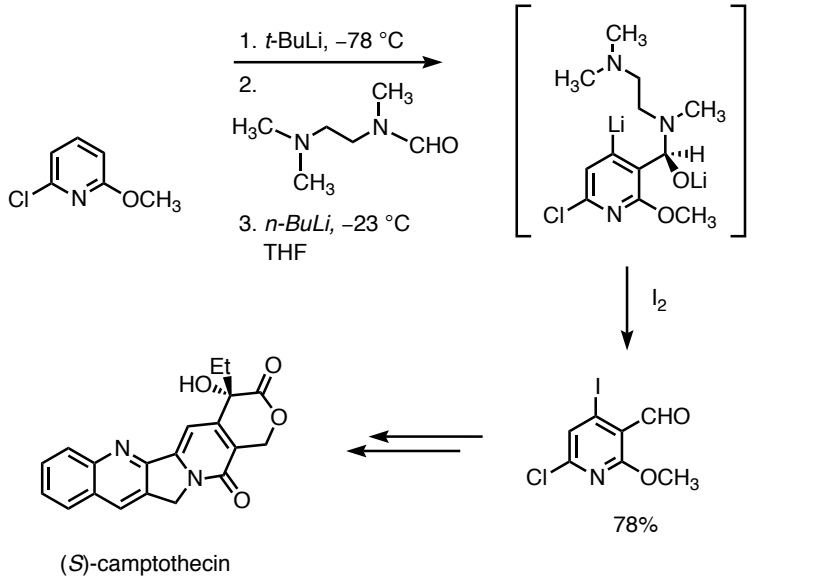
Examples of Directed Ortho Metalation in Synthesis:



- 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.

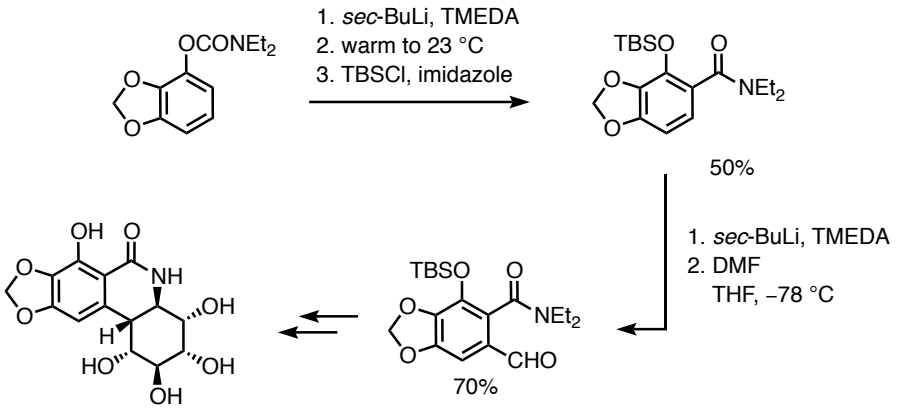
Boeckman, R. K., Jr.; Charette, A. B.; Asberom, T.; Johnston, B. H. *J. Am. Chem. Soc.* **1987**, *109*, 7553.



- Lithiation adjacent to the methoxyl 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.

- 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.

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