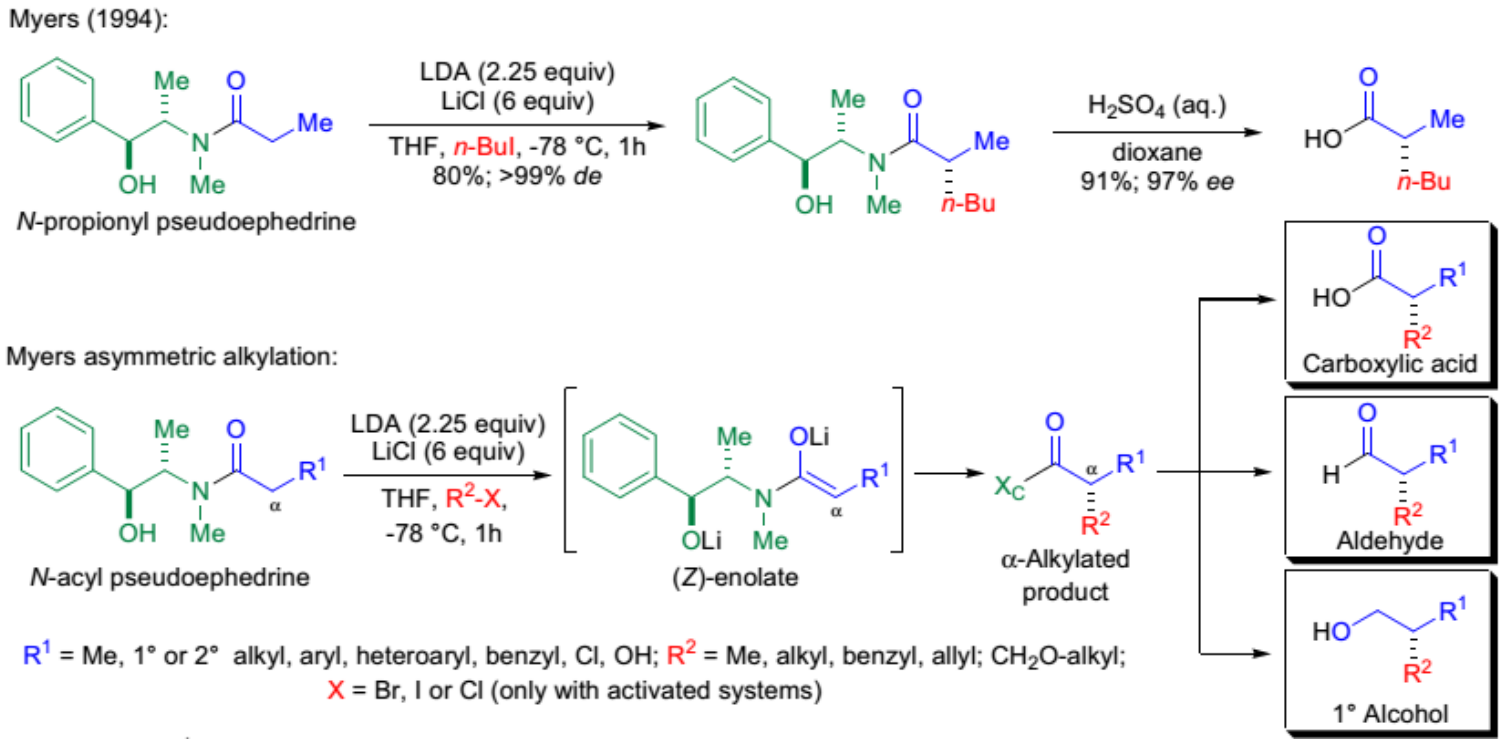
MYERS ASYMMETRIC ALKYLATION

——Chen Peihao

Importance



A.G. Myers et al. developed an efficient alkylation of N-acylated pseudoephedrines , to obtain enantiomerically enriched α-alkylated, aldehydes, ketones, carboxylic acids, and alcohols.

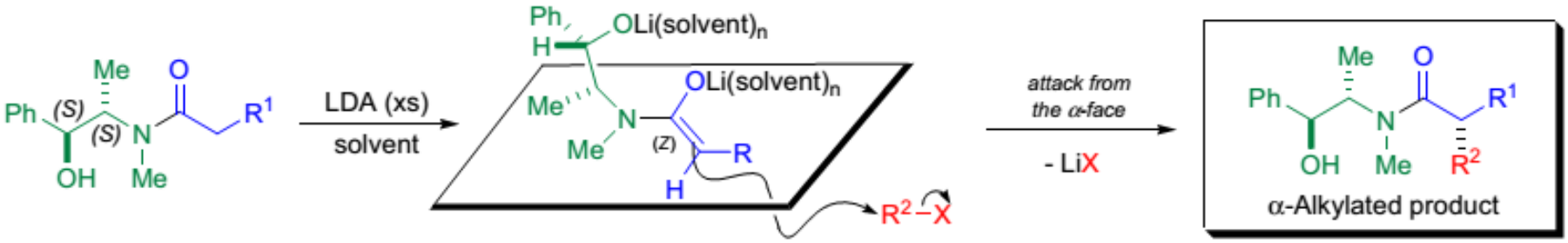
This transformation is known as the Myers asymmetric alkylation.

Features

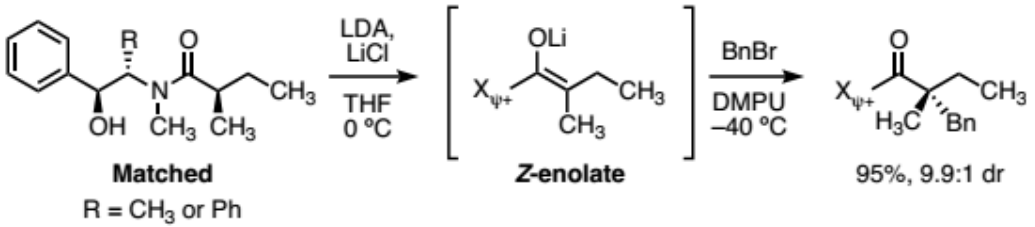
- Pseudoephedrine are inexpensive and commercially.
- N-acylation can be achieved in almost quantitative yields.
- Allylic, benzylic, as well as the less reactive alkyl halides are all good alkylating agents.
- The α-alkylated products are often crystalline and can be enriched by recrystallization to get >99% de.
- In order to obtain high yields and high levels of diastereoselectivity, the use of a large excess (6-10 equivalents) of anhydrous lithium chloride is necessary.
- The role of the LiCl is twofold: it accelerates the rate of the alkylation and suppresses the O-alkylation of the pseudoephedrine hydroxyl group
- When β-branched alkyl iodides are used as alkylating agents the transformation .leads to 1,3-dialkyl substituted alkyl chains,a common motif in a large number of natural products.
- Simple acidic, basic or Lewis acid catalyzed hydrolysis affords carboxylic acids, reduction with lithium pyrrolidide-borane (LPT) or with lithium amidotrihydroborate (LAB) gives primary alcohols, reduction with lithium triethoxyaluminum hydride results in aldehydes, while the addition of alkyllithium reagents followed by an aqueous work-up leads to ketones.

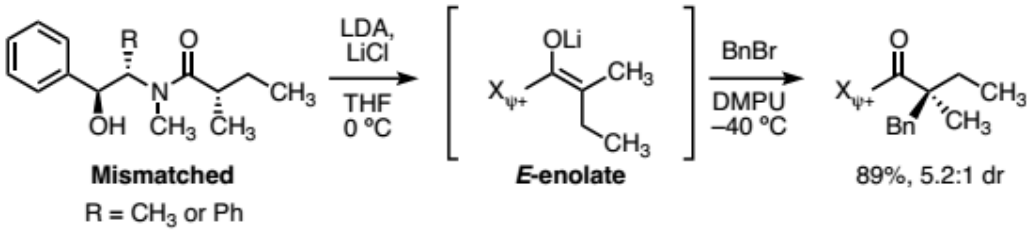
Mechanism

The origin of the high diastereoselectivity in this alkylation is not fully understood. The stereochemical outcome is consistent with a model in which the (*Z*)-enolate is alkylated from the α-face while the β-face is blocked by the solvated lithium alkoxide.



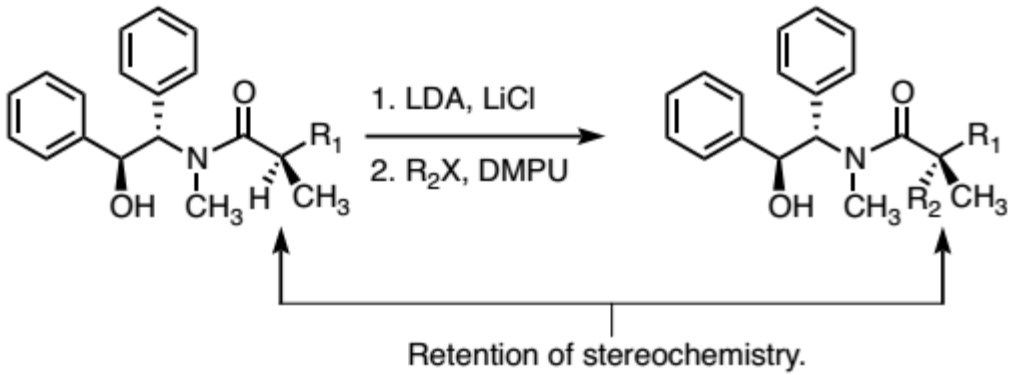
Formation of Quaternary carbons



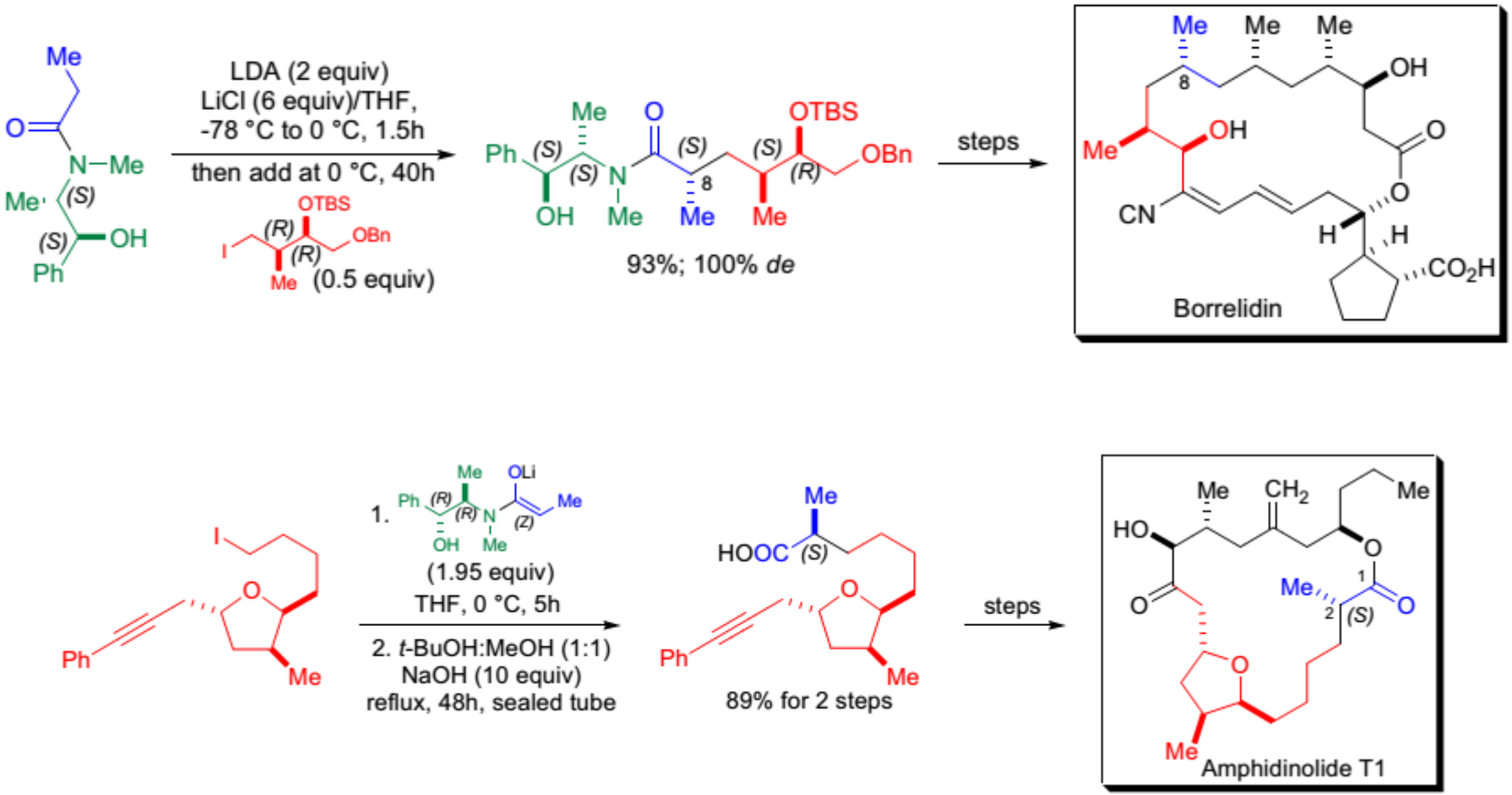


Kummer, D. A.; Chain, W. J.; Morales, M. R.; Quiroga, O.; Myers, A. G. *J. Am. Chem. Soc.* **2008**, *130*, 13231–13233.

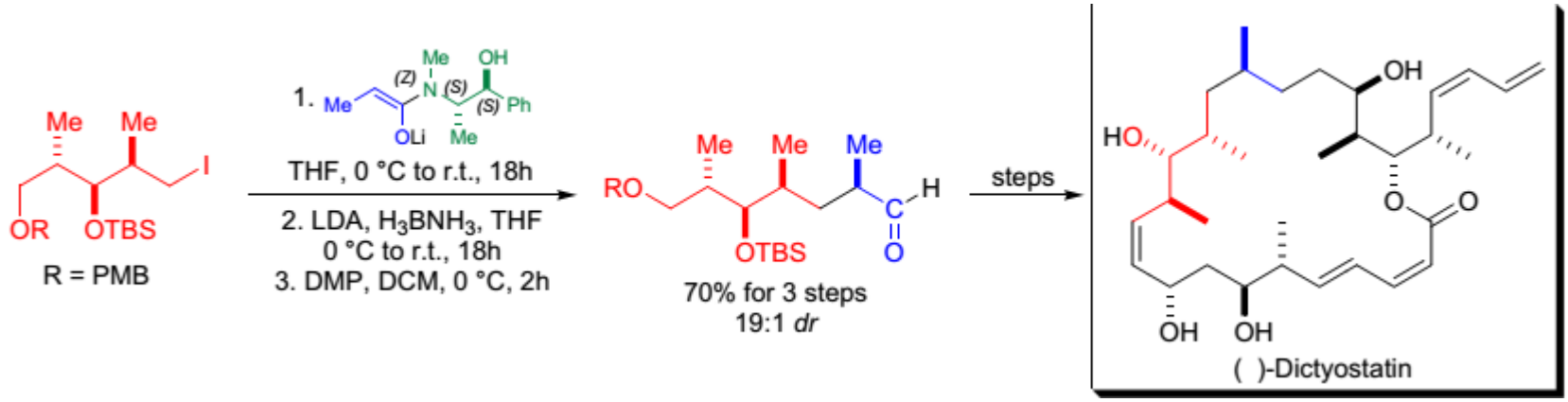
Mnemonic:

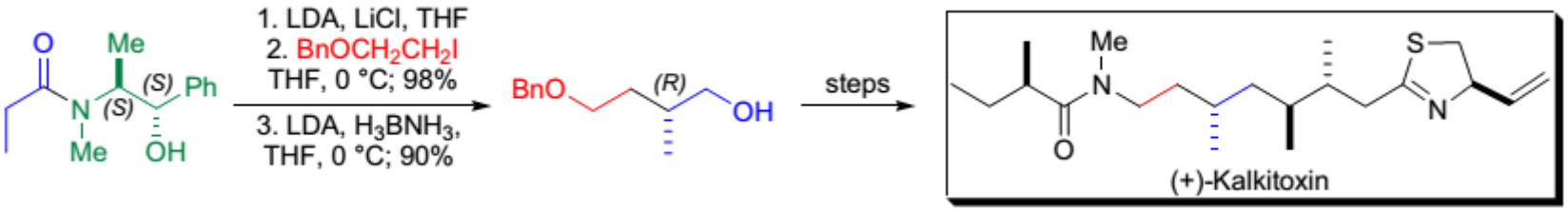


Synthetic Applications



Synthetic Applications

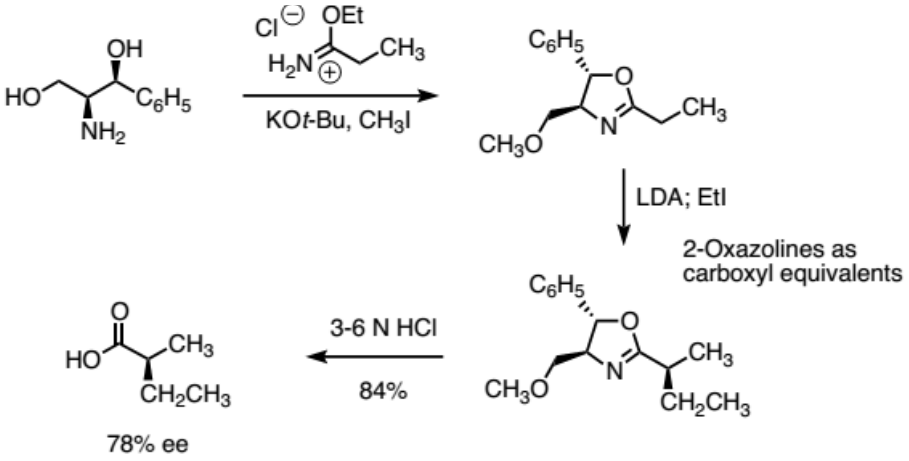




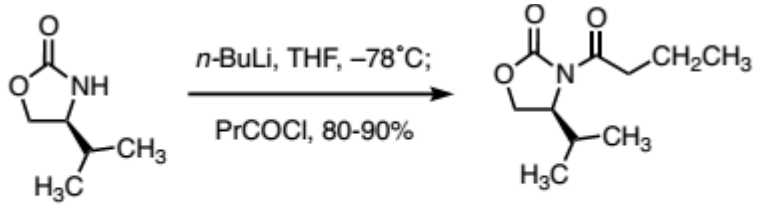
Asymmetric Alkylation

- Need to introduce asymmetry
  - Chiral Auxiliary
  - Chiral Catalyst

Chiral Auxiliaries

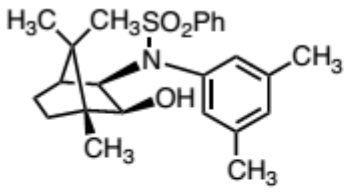


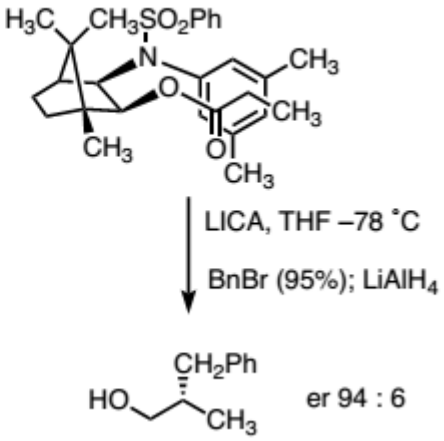
Meyers, A. I.; Knaus, G.; Kamata, K.; Ford, M. E. *J. Am. Chem. Soc.* **1976**, *98*, 567-576.



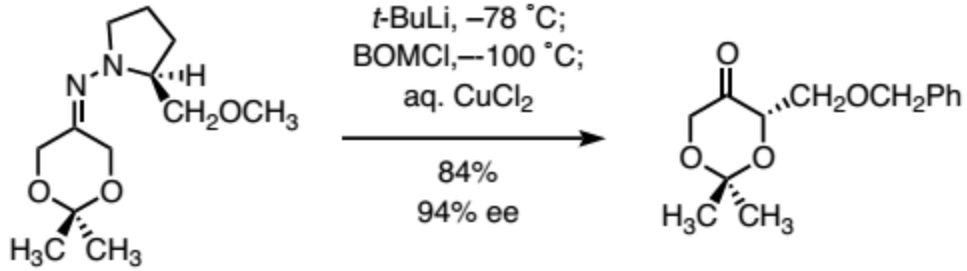
Evans, D. A.; Bartroli, J.: Shih, T. L. *J. Am. Chem. Soc.* **1981**, *103*, 2127-2129.

Chiral Auxiliaries





Schmierier, R.; Grotemeier, G.; Helmchen, G.; Selim, A. *Angew. Chem., Int. Ed. Engl.* **1981**, *20*, 207-208.

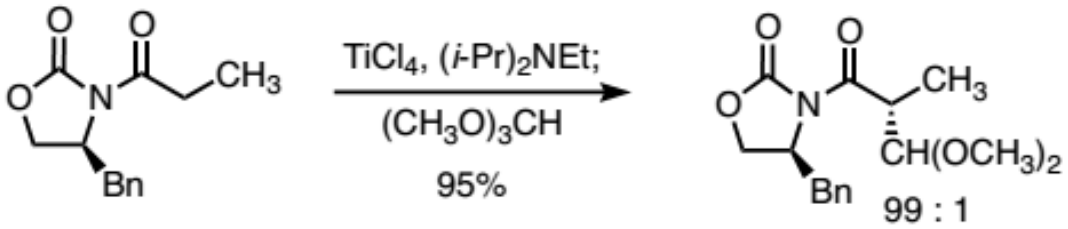


(S)-(+)-1-Amino-2-(methoxymethyl) pyrrolidine [SAMP-Hydrazone]

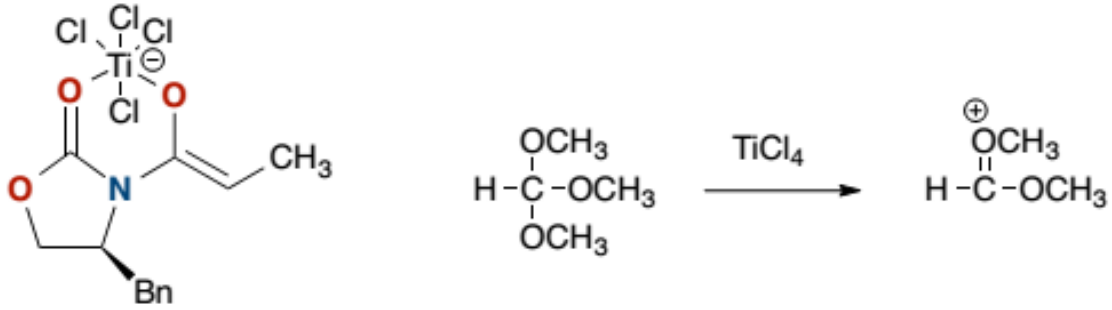
Enders, D.; Hundertmark, T.; Lazny, R. *Syn. Comm.* **1999**, *29*, 27-33.

Alkylation under Lewis acidic (SN1) conditions

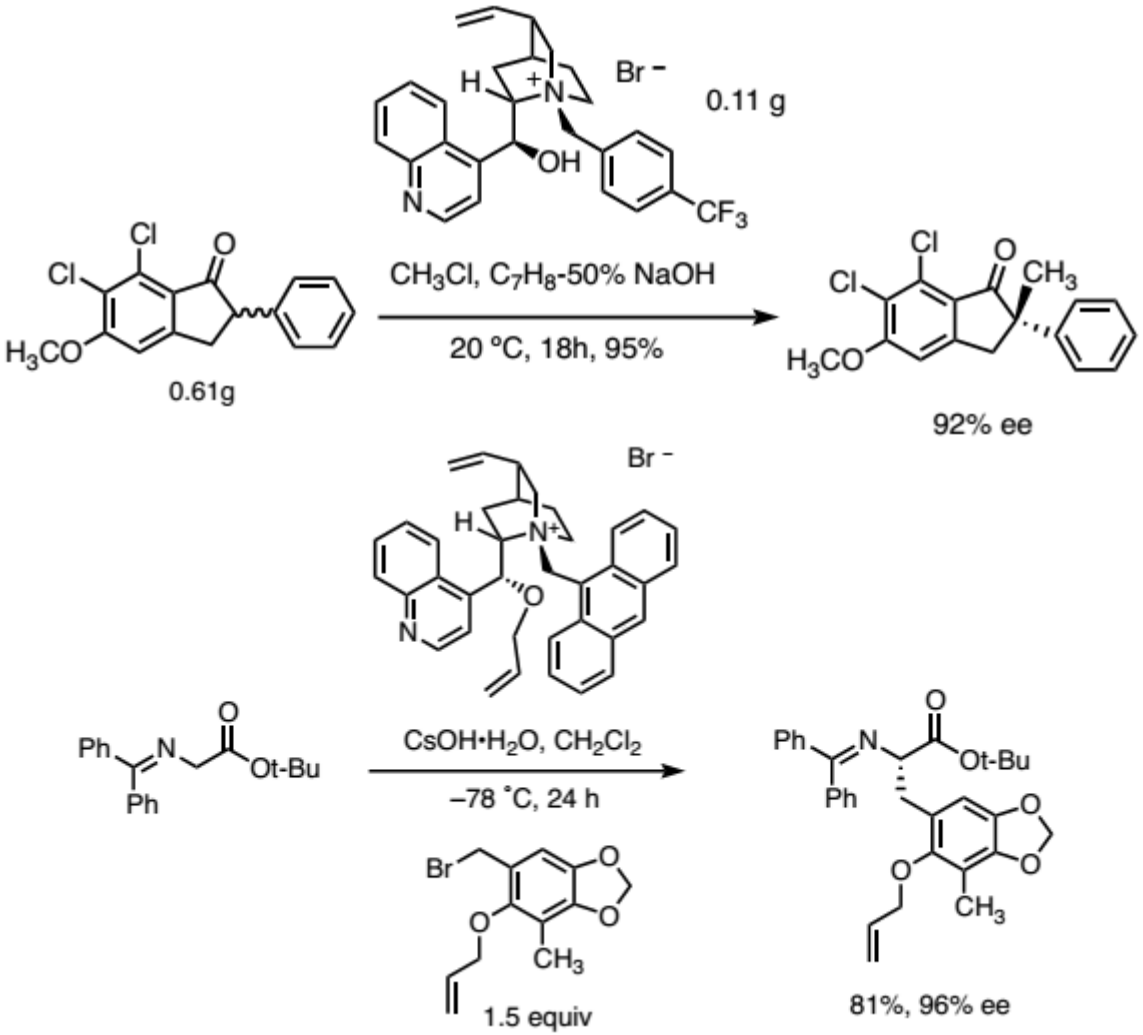
• Titanium enolates provide a route for diastereoselective S_N1-like coupling reactions:



Evans, D. A.; Urpi, F.; Somers, T. C.; Clark, J. S.; Bilodeau, M. T. *J. Am. Chem. Soc.* **1990**, *112*, 8215-8216.



Chiral catalysts



Corey, E. J.; Xu, F.; Noe, M. C. *J. Am. Chem. Soc.* **1997**, *119*, 12414-12415.