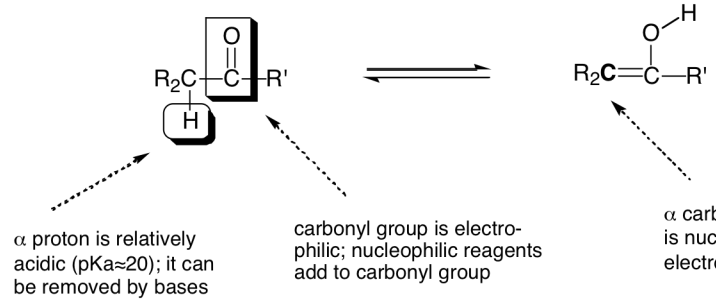
I. Basic Principles

IB. Enolates & Enamines

- G. Stork, R. A. Kretchmer, R. H. Schlessinger, *J. Am. Chem. Soc.* **1968**, *90*, 1647-1649.

1. Introduction



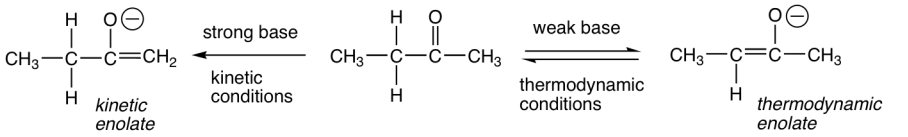
α proton is relatively acidic (pKa≈20); it can be removed by bases

carbonyl group is electrophilic; nucleophilic reagents add to carbonyl group

α carbon atom of enol is nucleophilic; it attacks electrophilic reagents

Carbonyl compounds exist in equilibrium with their tautomers, which are enols. They can express a variety of different kinds of chemical reactivity.

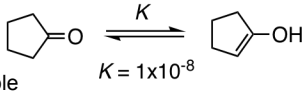
The enol tautomer is quite reactive toward electrophiles, and the above equilibrium rapidly regenerates new enols in the presence of acid or base catalysts. However, most reactions of electrophiles with carbonyl compounds take advantage of the higher nucleophilicity of the deprotonated enol, the enolate anion.



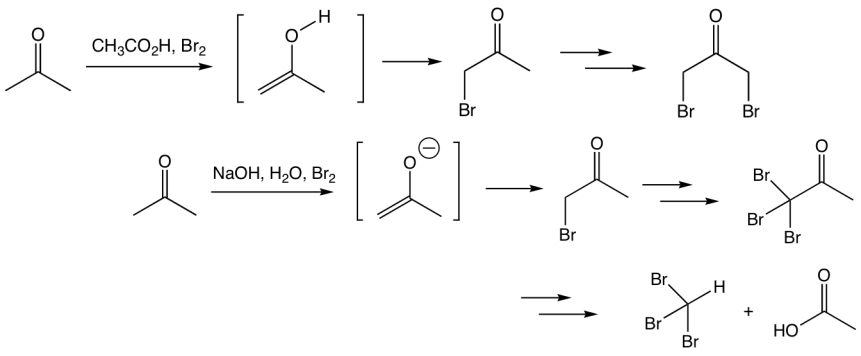
When unsymmetrical carbonyl compounds are converted to their enolates under conditions that allow equilibrium to be established (high temperatures and weak bases) the enolate anion with the more highly substituted double bond is formed. This ion is the more stable of the two possible enolates and is called the thermodynamic enolate. If the carbonyl compound is added to an excess of a strong base (usually LDA) at low temperatures, the least hindered hydrogen atom is removed. The ion with the less substituted double bond forms; it is the less stable of the two possible enolates but is the one that forms faster. For this reason, it is called the kinetic enolate.

Reactions of aldehydes and ketones that involve enol or enolate ion intermediates include:

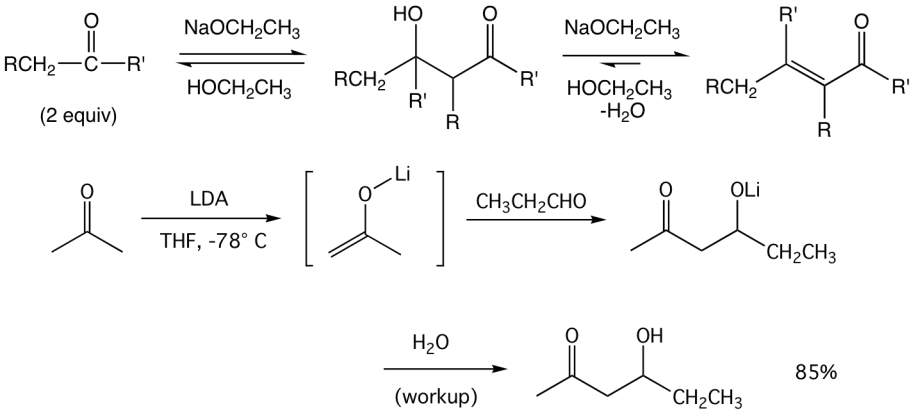
Enolization. Aldehydes and ketones exist in equilibrium with their enol forms. The rate at which equilibrium is achieved is increased by acidic or basic catalysts. The enol content of simple aldehydes and ketones is quite small; β-diketones, however, are extensively enolized.



α-Halogenation. Halogens react with aldehydes and ketones by substitution; An acid catalyst (or base) increases the rate of enolization (enolate formation), which is the rate-determining step. The reaction of a methyl ketone with a halogen in base is known as the haloform reaction. Once one of the α-H's is replaced by a halogen atom, the remaining H's are more acidic and are more easily substituted. C,C-bond cleavage is facilitated by the e-withdrawing effect of the halogens.

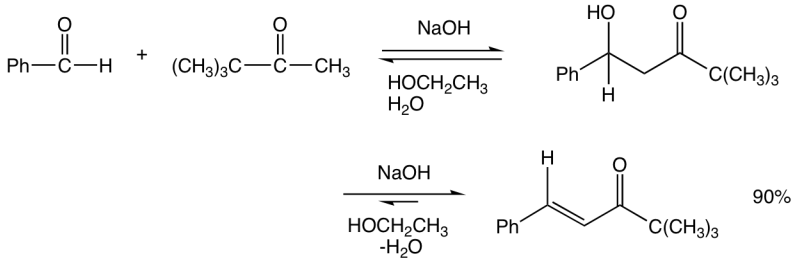


Aldol condensation. A reaction of great synthetic value for C,C-bond formation. Nucleophilic addition of an enolate ion (or an enol in the acid-catalyzed version of this process) to a carbonyl group leads to a β-hydroxy aldehyde or ketone (reversible!). Subsequent dehydration (acid- or base-catalyzed) yields an α,β-unsaturated carbonyl compound.

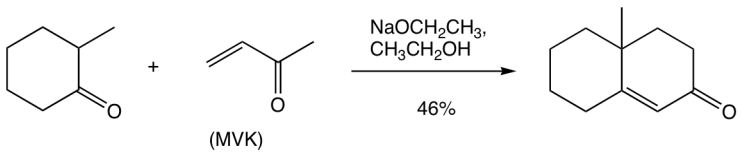


The irreversible, rapid enolization of carbonyl compounds with very strong base (LDA), followed by addition of aldehydes or ketones, allows the direct formation of a single aldol product in **crossed aldol** condensations.

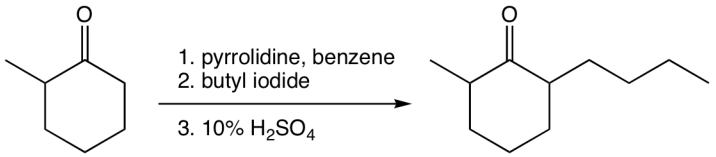
Claisen-Schmidt reaction. A crossed aldol condensation in which a non-enolizable aldehyde reacts with an enolizable aldehyde or ketone.

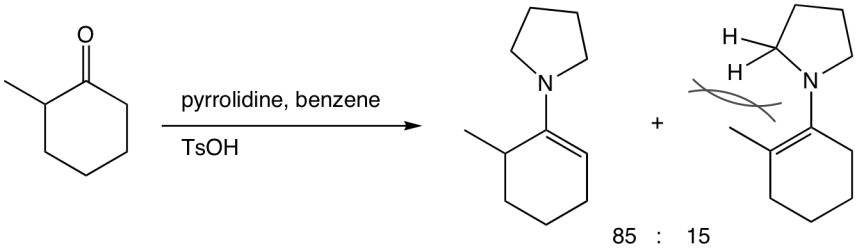


Robinson annulation. A combination of conjugate addition of an enolate anion to an α,β-unsaturated ketone (**Michael addition**) with subsequent intramolecular aldol condensation. Michael additions are typical for soft nucleophiles, including enols, cyanides, cuprates and thiol(ate)s. In contrast, hard nucleophiles (hydrides, Grignard and lithium reagents) prefer 1,2-addition.



Alkylation reactions. Treatment of enolates with halides provides a means for carbon chain extensions at the α-position. However, polyalkylation can be a problem, and the use of a strong, nucleophilic base or the enamine is recommended.





85 : 15

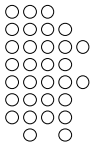
2. Enolate Alkylation

A major, general side reaction with alkylation is the multiple introduction of alkyl groups.

Evidence supports an earlier hypothesis by House that alkylation of an enolate is frequently accompanied by extensive polyalkylation because the less-substituted enolates are more aggregated: Streitwieser, A.; Kim, Y.-J.; Wang, D. Z.-R., "Why is alkylation of an enolate accompanied by so much polyalkylation?" *Org. Lett.* **2001**, *3*, 2599-2601.

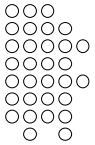
Diastereoselective Alkylation of Aluminum Enolates

Saito, S.; Ito, M.; Yamamoto, H. *J. Am. Chem. Soc.* **1997**, *119*, 611.



Diastereoselective Alkylation of Lithium Enolates

Wipf, P.; Kim, Y.; Goldstein, D. M. *J. Am. Chem. Soc.* **1995**, *117*, 11106.



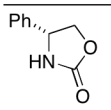
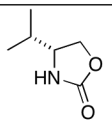
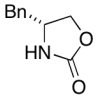
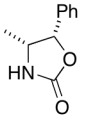
Frater Alkylation

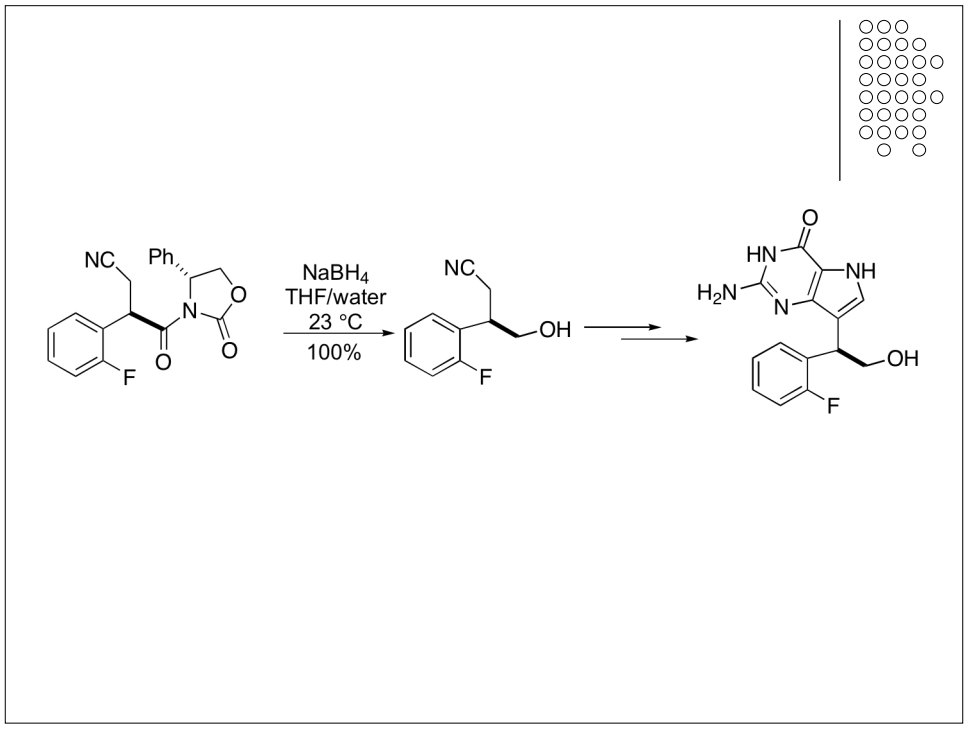
Ali, S. M.; Georg, G. I. *Tetrahedron Lett.* **1997**, *38*, 1703.

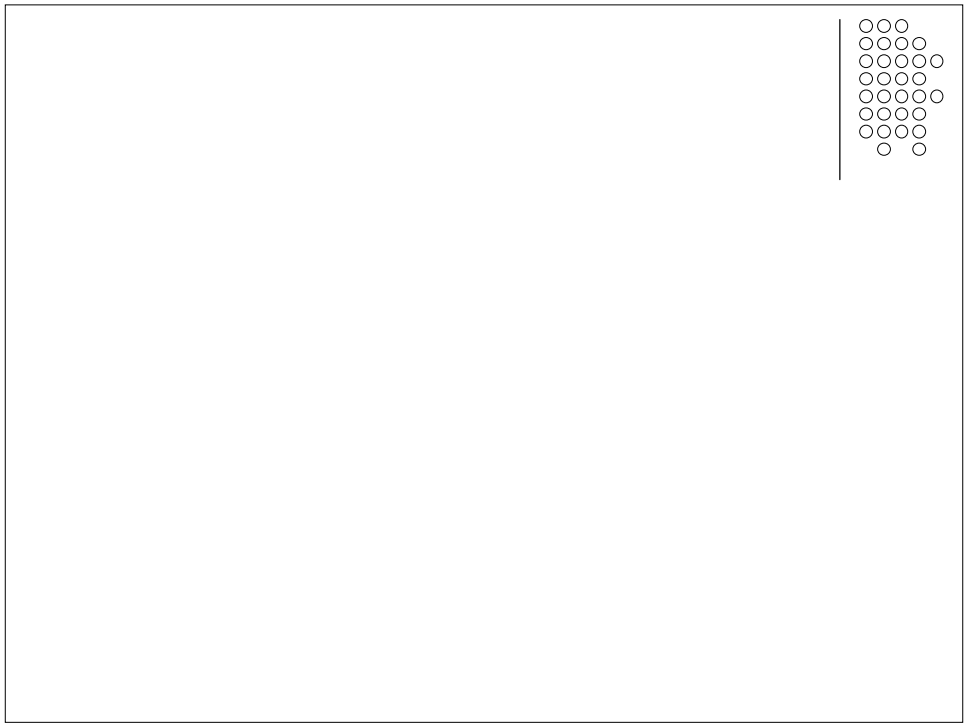
Asymmetric Alkylation of Lithium Enolates

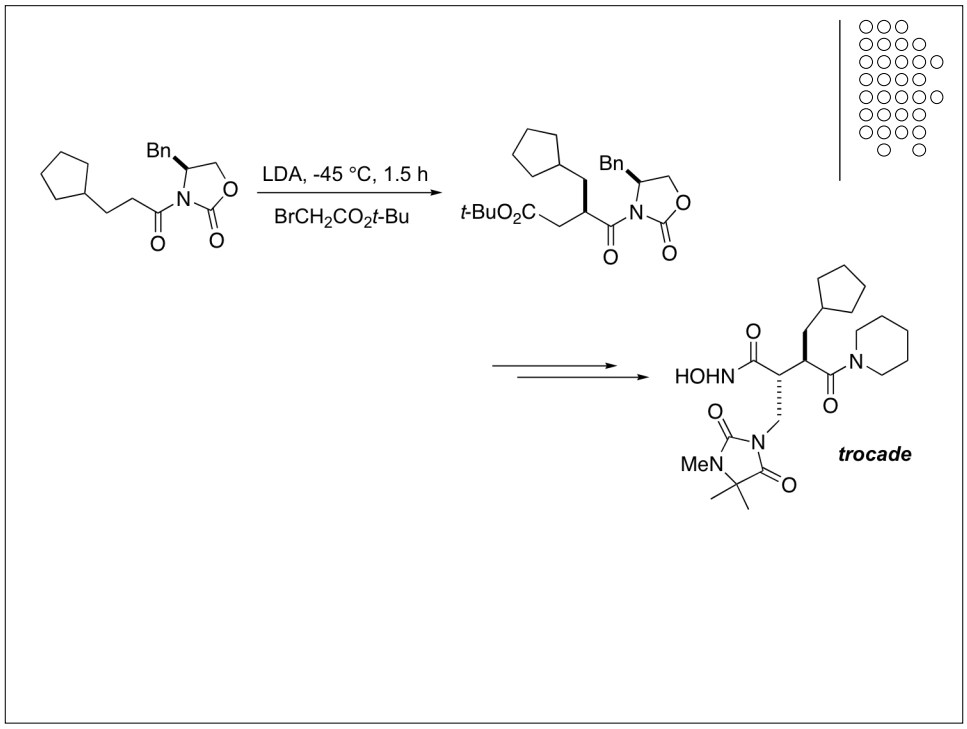
Farina, V.; Reeves, J. T.; Senanayake, C. H.; Song, J. J., "Asymmetric synthesis of active pharmaceutical ingredients." *Chem. Rev.* **2006**, *106*, 2734-2793.

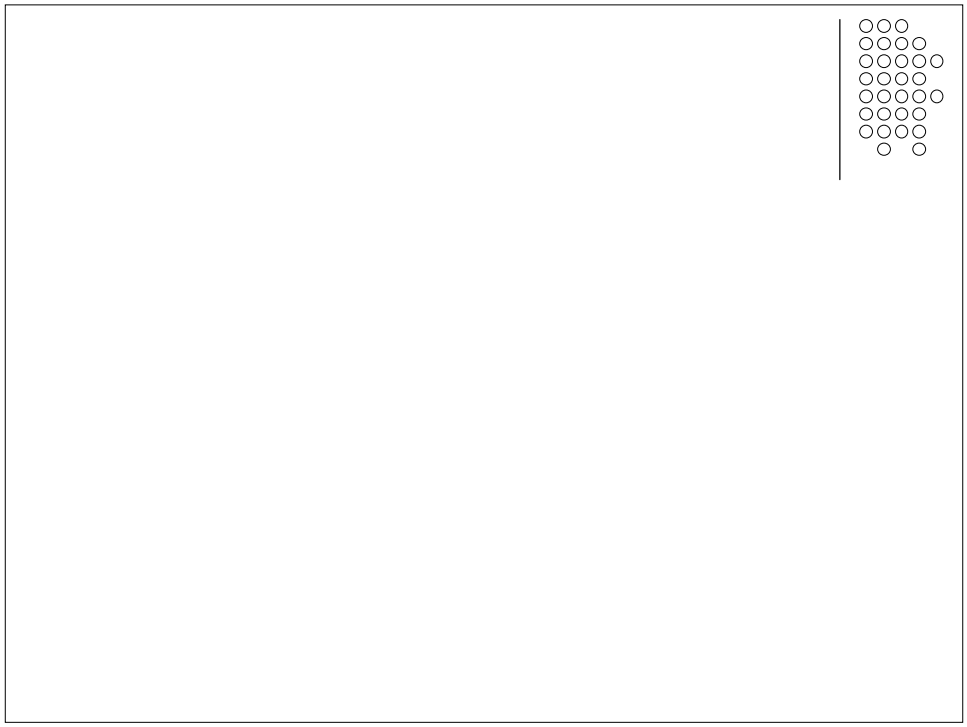
Survey of Different Oxazolidinones for Alkylation

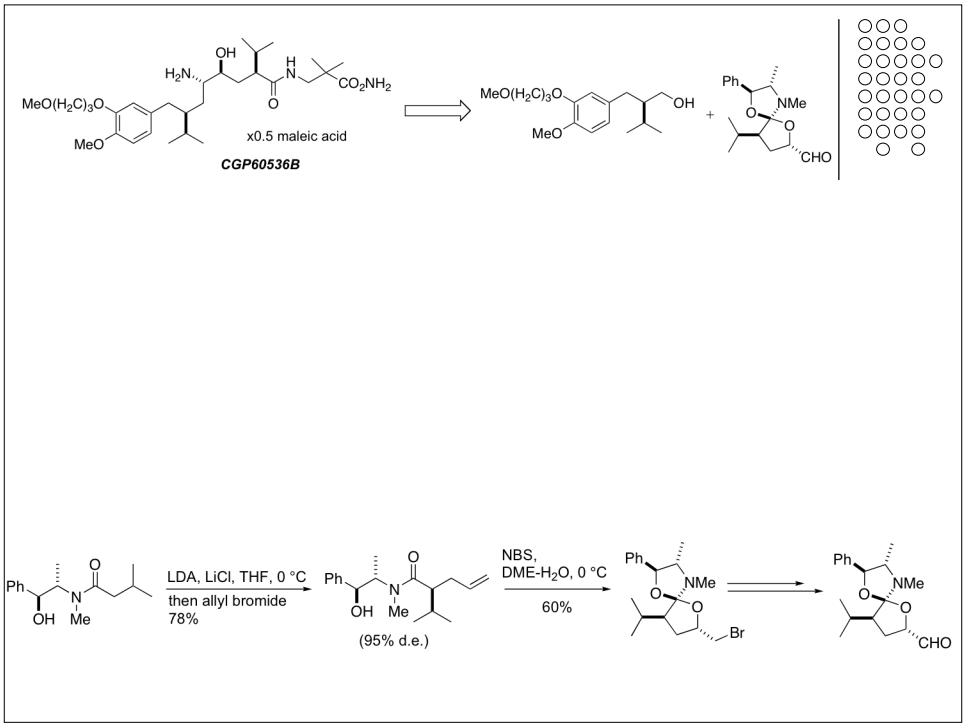
auxiliary	d.r. (yield)	auxiliary	d.r. (yield)
	7:1 (80%)		13:4:1 (81%)
	5:3:1 (56%)		3:7:1 (52%)

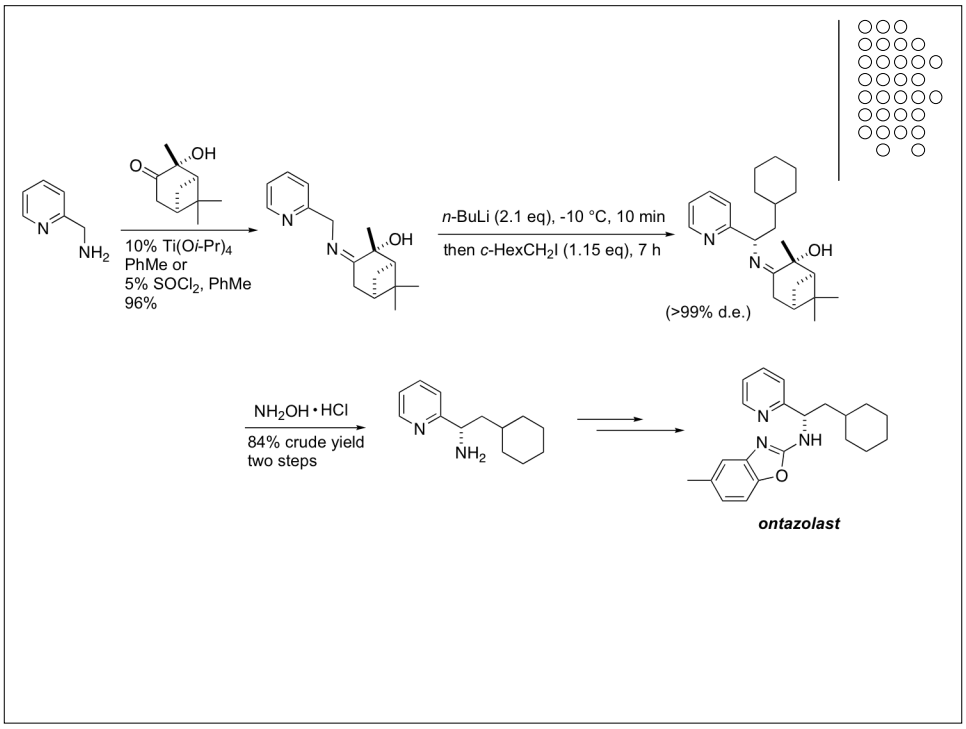

NC
Ph
N
O
O
O
F
NaBH4
THF/water
23 °C
100%
NC
OH
F
O
HN
NH
H2N
N
OH
F




Bn
LDA, -45 °C, 1.5 h
BrCH2CO2t-Bu
t-BuO2C
HOHN
MeN
trocade




MeO(H2C)3O
MeO
H2N
OH
H
N
O
CO2NH2
x0.5 maleic acid
CGP60536B
MeO(H2C)3O
MeO
OH
Ph
NMe
O
O
CHO
Ph
OH
N
Me
O
LDA, LiCl, THF, 0 °C
then allyl bromide
78%
(95% d.e.)
NBS,
DME-H2O, 0 °C
60%
Br

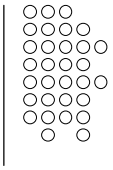


Diastereoselective Alkylation of Boron Enolates

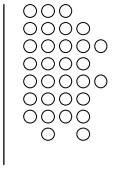
Jacobi, P. A.; Herradura, P., "Enantioselective syntheses of (+)- and (-)-blastmycinolactol." *Tetrahedron Lett.* **1997**, *38*, 6621-6624. *Syn*-selective Nicholas-Schreiber condensation. Interestingly, identical levels of asymmetric induction were obtained employing either the chiral boron enolate (matched condensation) or the achiral enolate. This illustrates the strong directing influence of stereogenic centers on the Nicholas reaction.

Regioselective Alkylation

Heathcock, C. H. *J. Org. Chem.* **1992**, *57*, 2585.

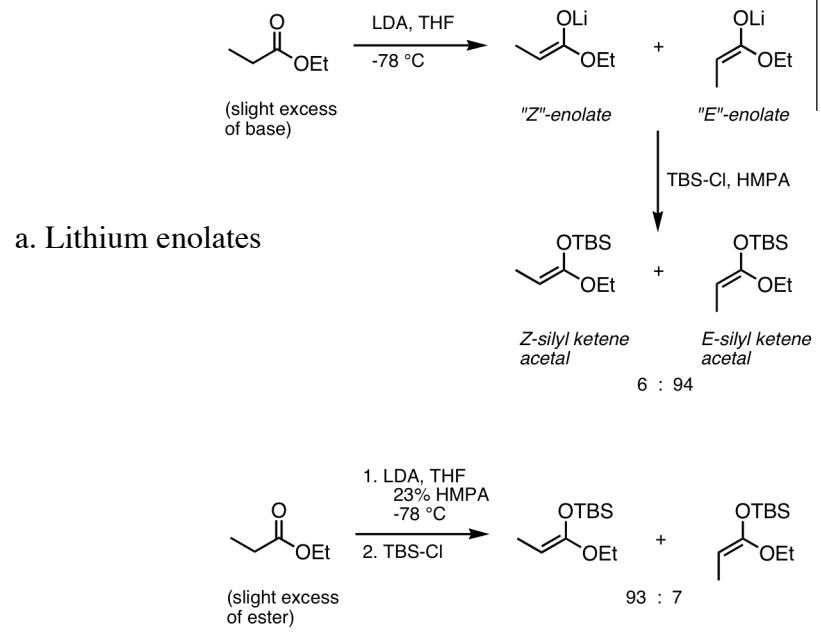


Nicolaou, K. C.; Li, A.; Edmonds, D. J., "Total synthesis of platensimycin." *Angew. Chem., Int. Ed.* **2006**, *45*, 7086-7090.
This is a strategy for 4,4-disubstituted cyclohexenone synthesis analogous to the protocol by Hayashi et al.

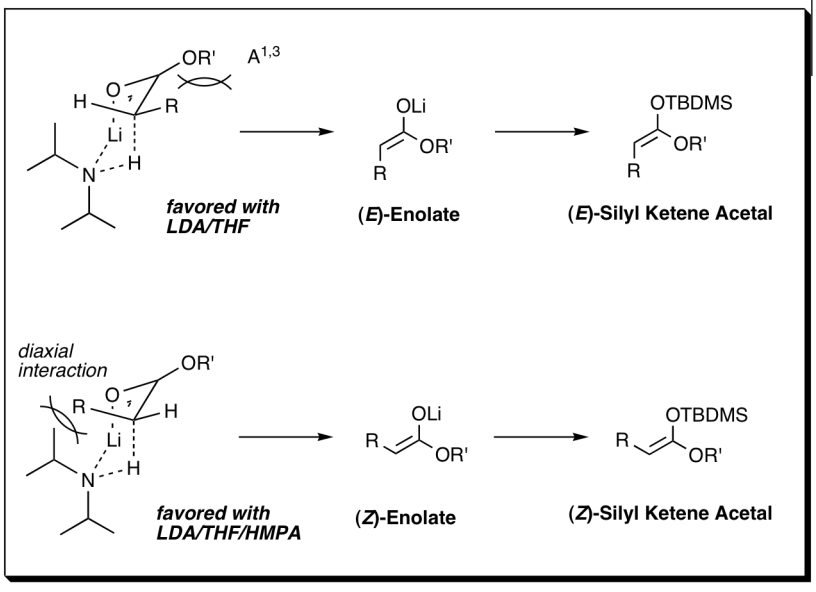


3. E/Z-Selective Enolization

a. Lithium enolates



Transition states for enolization:



Kinetic ratios for LDA/THF enolization:

	E/Z	
OMe	95 : 5	
O-*t*-Bu	95 : 5	
Et	50 : 50	
i-Pr	40 : 60	
t-Bu	0 : 100	
Ph	0 : 100	
NEt_2	0 : 100	(cf. Dauben, *JACS* **1985**, *107*, 2264)

Busch-Petersen, J.; Corey, E. J., "Sterically shielded secondary N-tritylamines and N-tritylamide bases, readily available and useful synthetic reagents." *Tetrahedron Lett.* **2000**, *41*, 2515-2518.