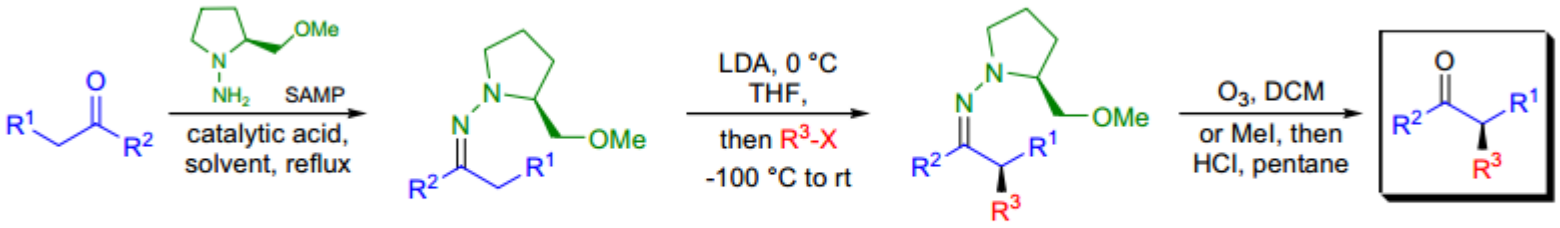
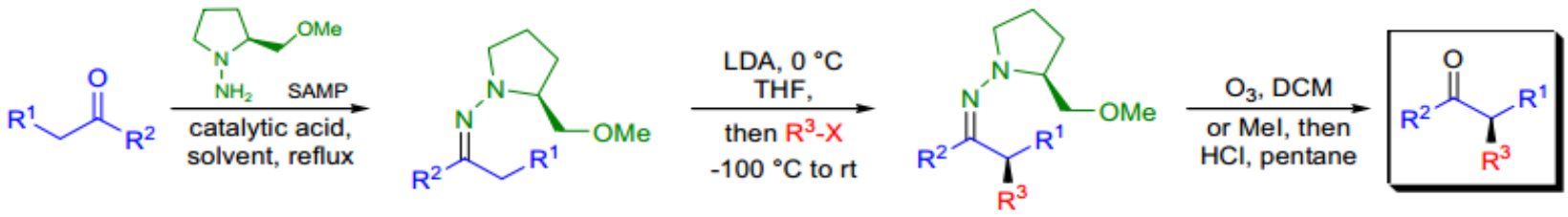
ENDERS SAMPRAMP HYDRAZONE ALKYLATION



R^1 = alkyl, aryl; R^2 = H, alkyl, R^1 = R^2 = $-(CH_2)_3-$, $-(CH_2)_4-$, $-(CH_2)_5-$, $-(CH_2)_6-$, $-CH=CH(CH_2)_2-$; R^3 = alkyl, benzyl, allyl; X = I, Br;
solvent: benzene, cyclohexane



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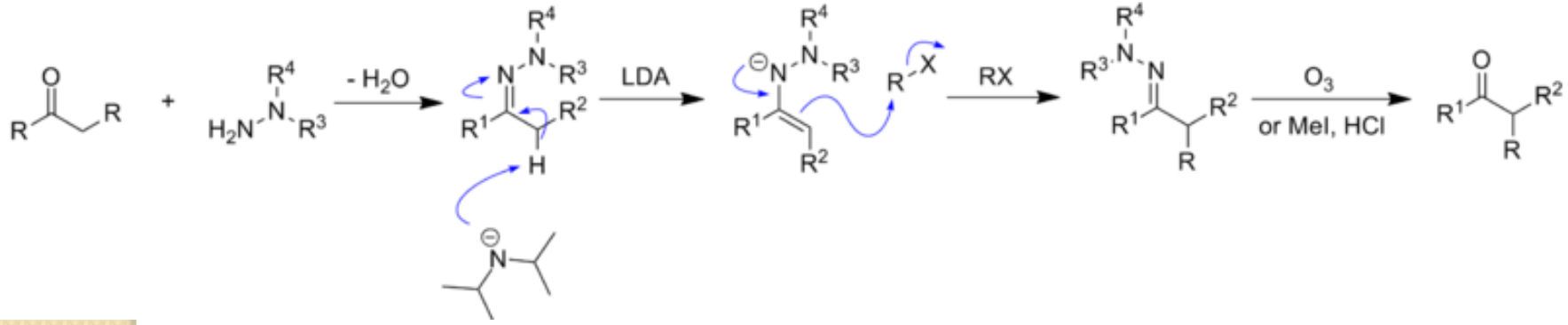
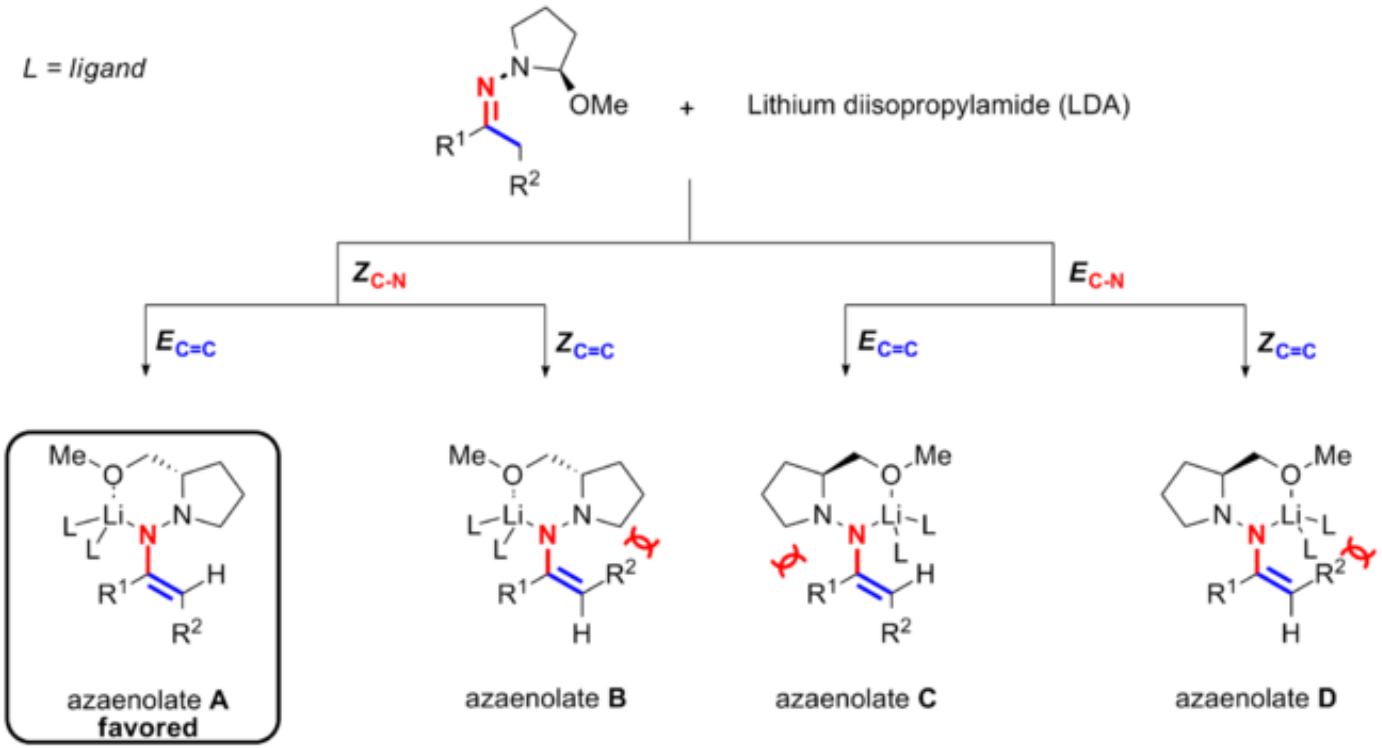
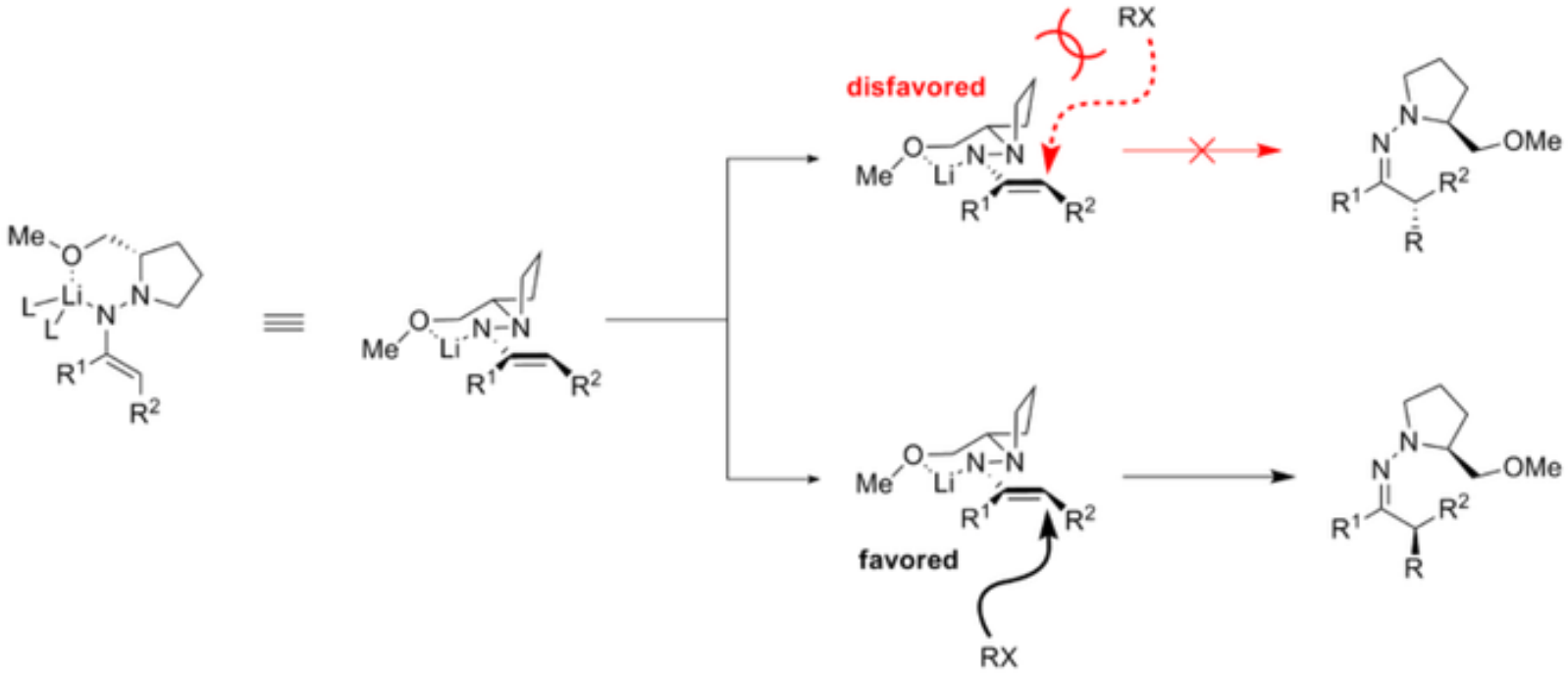
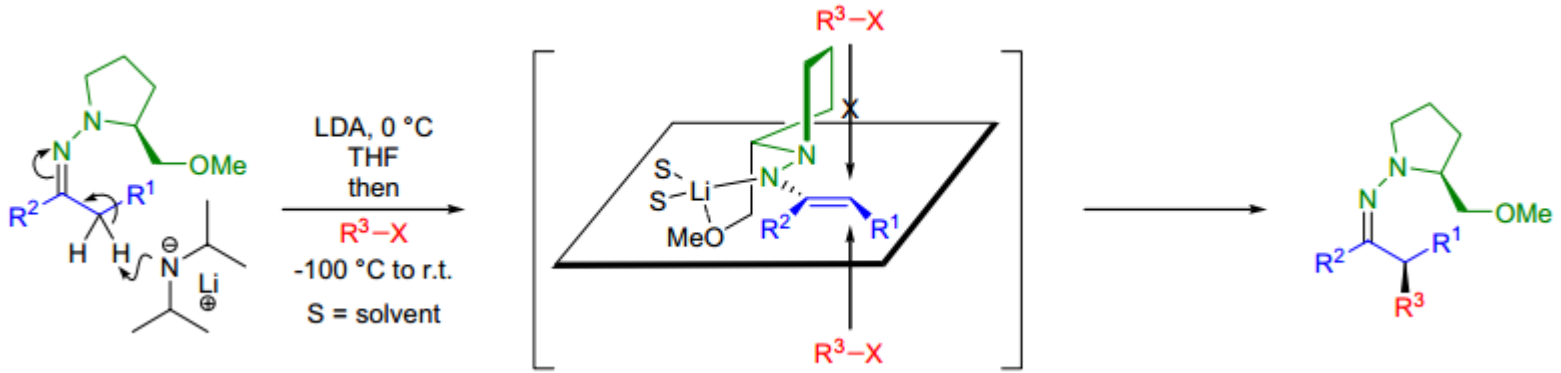
- 1) The SAMP/RAMP hydrazones of aldehydes can be formed by mixing the aldehyde with the hydrazone derivative at 0 ^{O}C, while ketones need to be heated to reflux in the presence
- 2) The hydrazones can be purified by distillation or chromatography, although purification is not always necessary, and they can be stored at -20 ^{O}C under inert atmosphere without decomposition;
- 3) Cyclic and acyclic ketones and aldehydes undergo the transformation; deprotonation can be effected with lithium bases, most commonly with lithium diisopropylamide;
- 4) The alkylating reagents are alkyl-, benzyl-, and allyl bromides and iodides;
- 5) Upon completion of the alkylation, the ketone can be regenerated by ozonolysis or methylation with methyl iodide and subsequent acidic hydrolysis;


- H_2O
LDA
RX
O_3
or MeI, HCl

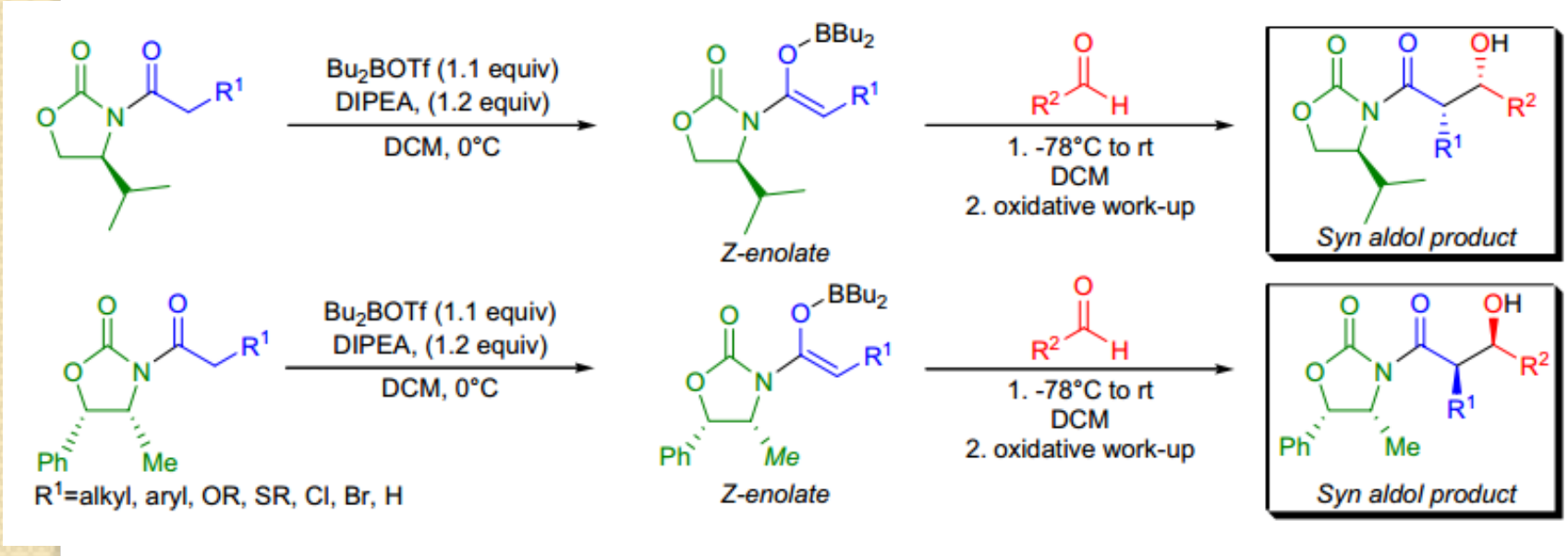
L = ligand


OMe
+
Lithium diisopropylamide (LDA)
Z_{C-N}
E_{C-N}
$E_{C=C}$
$Z_{C=C}$
$E_{C=C}$
$Z_{C=C}$
azaenolate **A** **favored**
azaenolate **B**
azaenolate **C**
azaenolate **D**

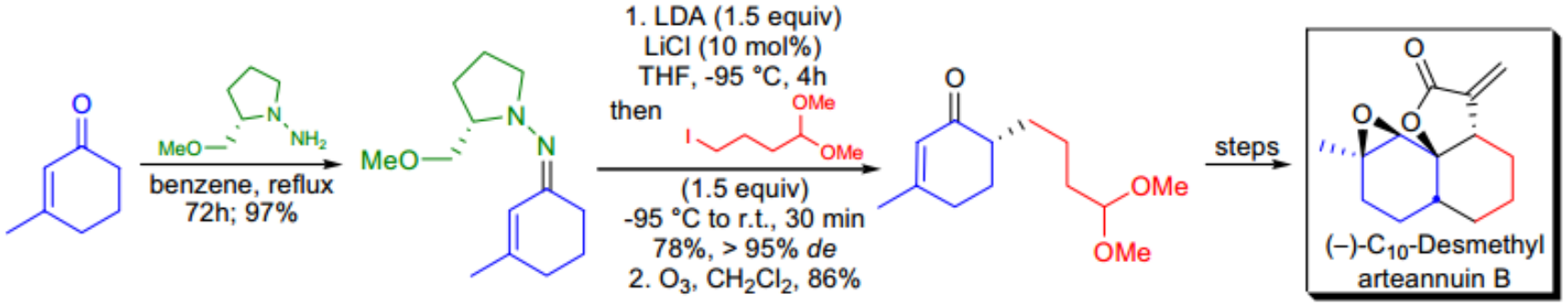

RX
disfavored
favored
RX


LDA, 0 °C
THF
then
R3–X
-100 °C to r.t.
S = solvent
R3–X
R3–X

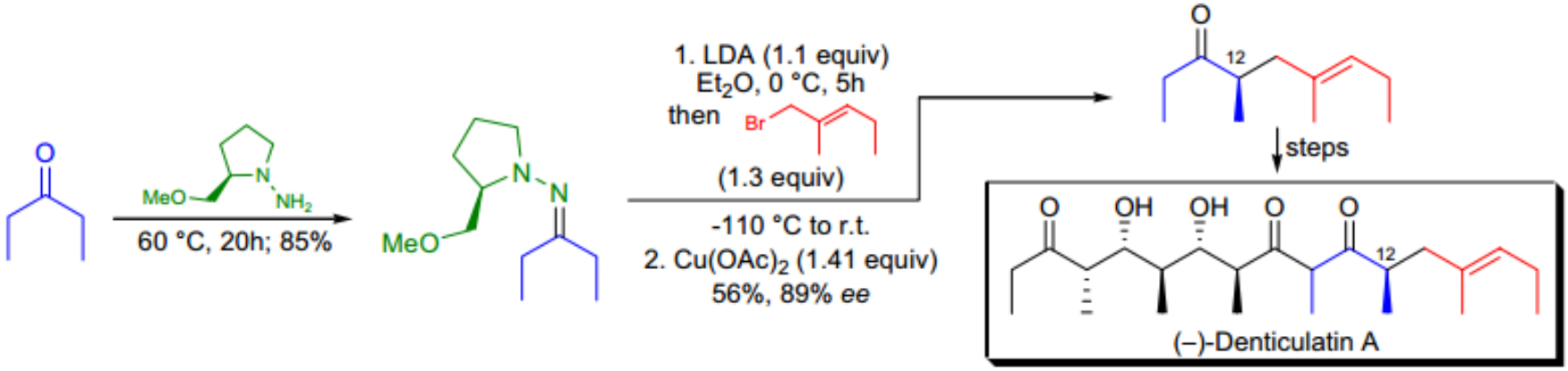
EVANS ALDOL REACTION

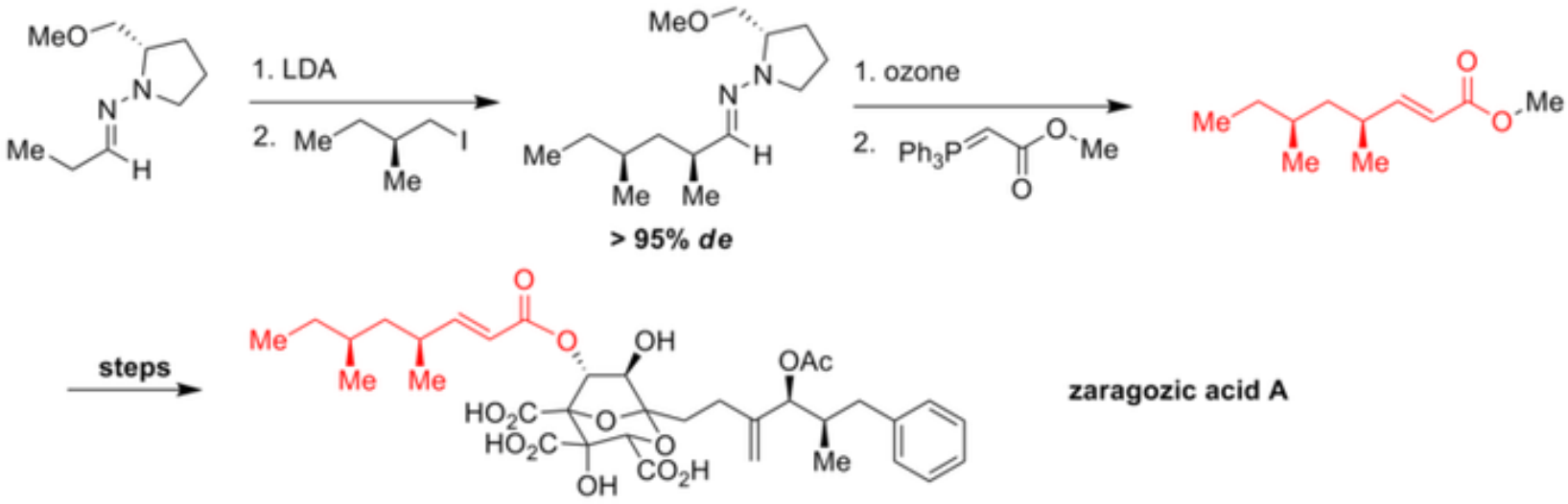


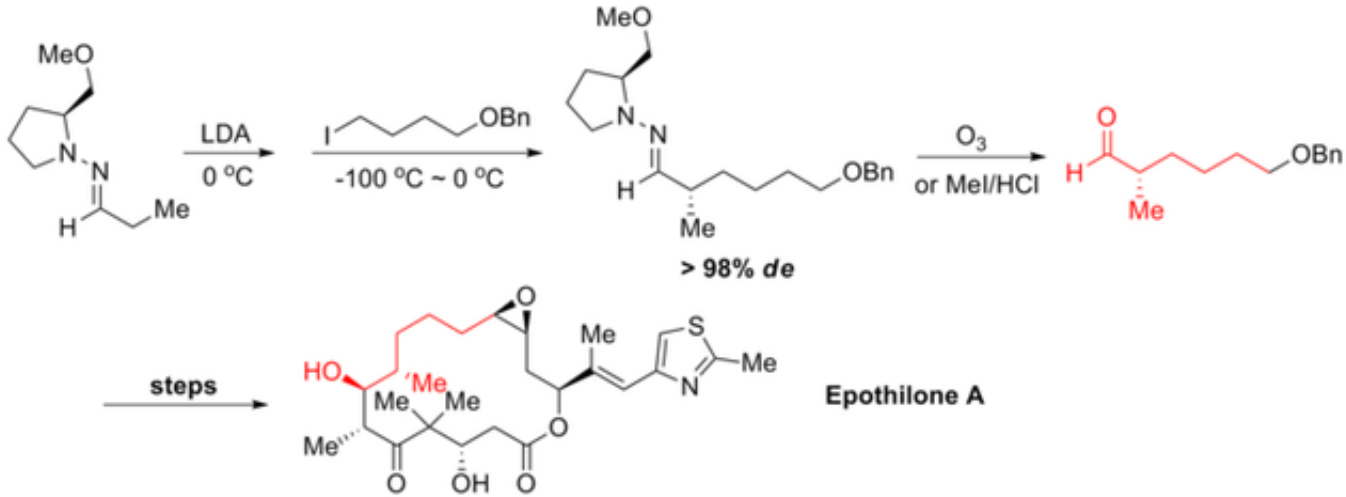
The synthesis of (–)-C_{10}-desmethyl arteannuin B, a structural analog of the antimalarial artemisinin, was developed by D. Little et al.[30] In their approach, the absolute stereochemistry was introduced early in the synthesis utilizing the *Enders SAMP/RAMP hydrazone alkylation* method. The sequence begins with the conversion of 3-methylcyclohexenone to the corresponding (*S*)-(–)-1-amino-2-(methoxymethyl)pyrrolidine (SAMP) hydrazone. Deprotonation with lithium diisopropylamide, followed by alkylation in the presence of lithium chloride at -95 °C afforded the product as a single diastereomer. The SAMP chiral auxiliary was removed by ozonolysis.



The total synthesis of (–)-denticulatin A, a polypropionate metabolite, was accomplished in the laboratory of F.E. Ziegler.[31] To establish the absolute stereochemistry at C12, they utilized the *Enders SAMP/RAMP hydrazone alkylation*. To this end, the RAMP hydrazone of 3-pentanone was successfully alkylated with 1-bromo-2-methyl-2(*E*)-pentene. Hydrolysis of the hydrazone under standard acidic conditions led to loss of the enantiomeric purity. This problem was avoided by using cupric acetate for the cleavage.




MeO
1. LDA
2. Me
I
Me
> 95% de
1. ozone
2. Ph3P
O
Me
steps
OH
OAc
HO2C
HO2C
CO2H
zaragozic acid A


MeO
LDA
0 °C
I
OBn
-100 °C ~ 0 °C
O3
or MeI/HCl
> 98% de
steps
HO
S
N
Epothilone A