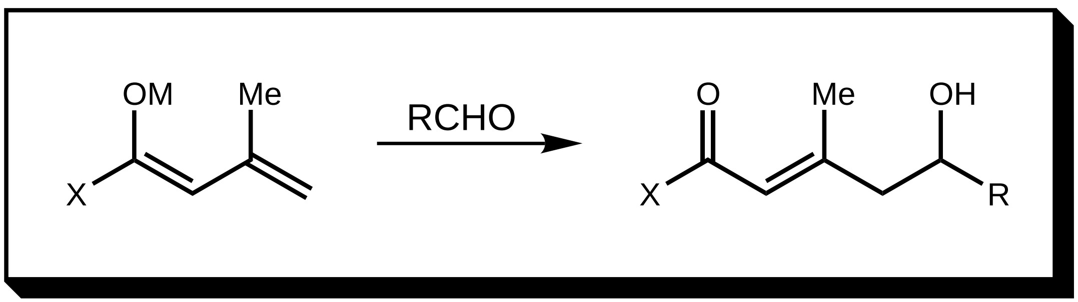
The Vinylogous Aldol Reaction

Synthesis and Methodology

Evans Group Seminar

February 15, 2002

Jason Burch

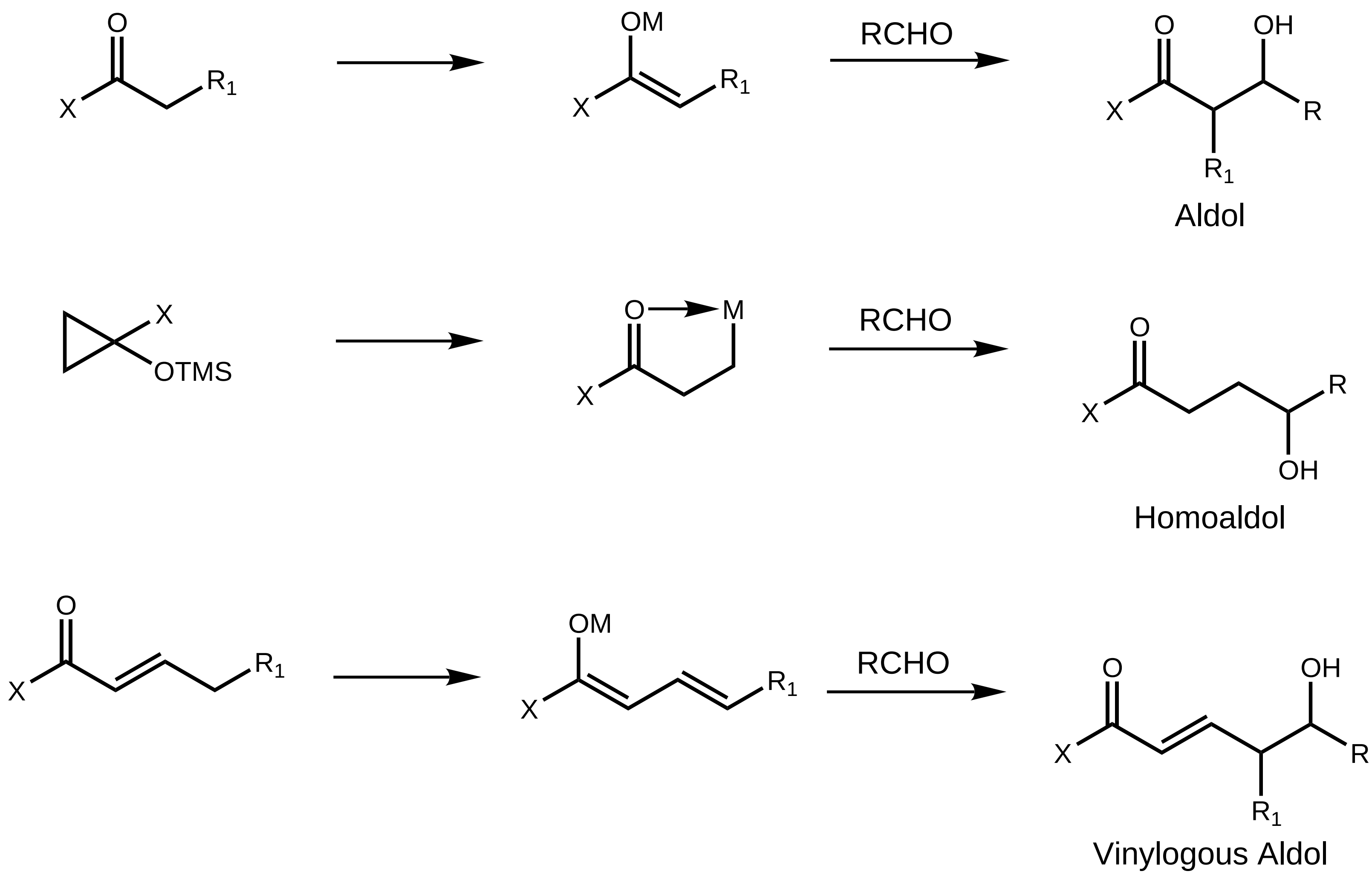


Leading References:

Casiraghi and Rassu, *Chem. Rev.* **2000**, *100*, 1929.
Rassu and Casiraghi, *Chem. Soc. Rev.* **2000**, *29*, 109.
Rassu and Casiraghi, *Synlett* **1999**, 1333.
Martin, *Tetrahedron* **2001**, *57*, 3221. (Mannich rxns.; not covered)

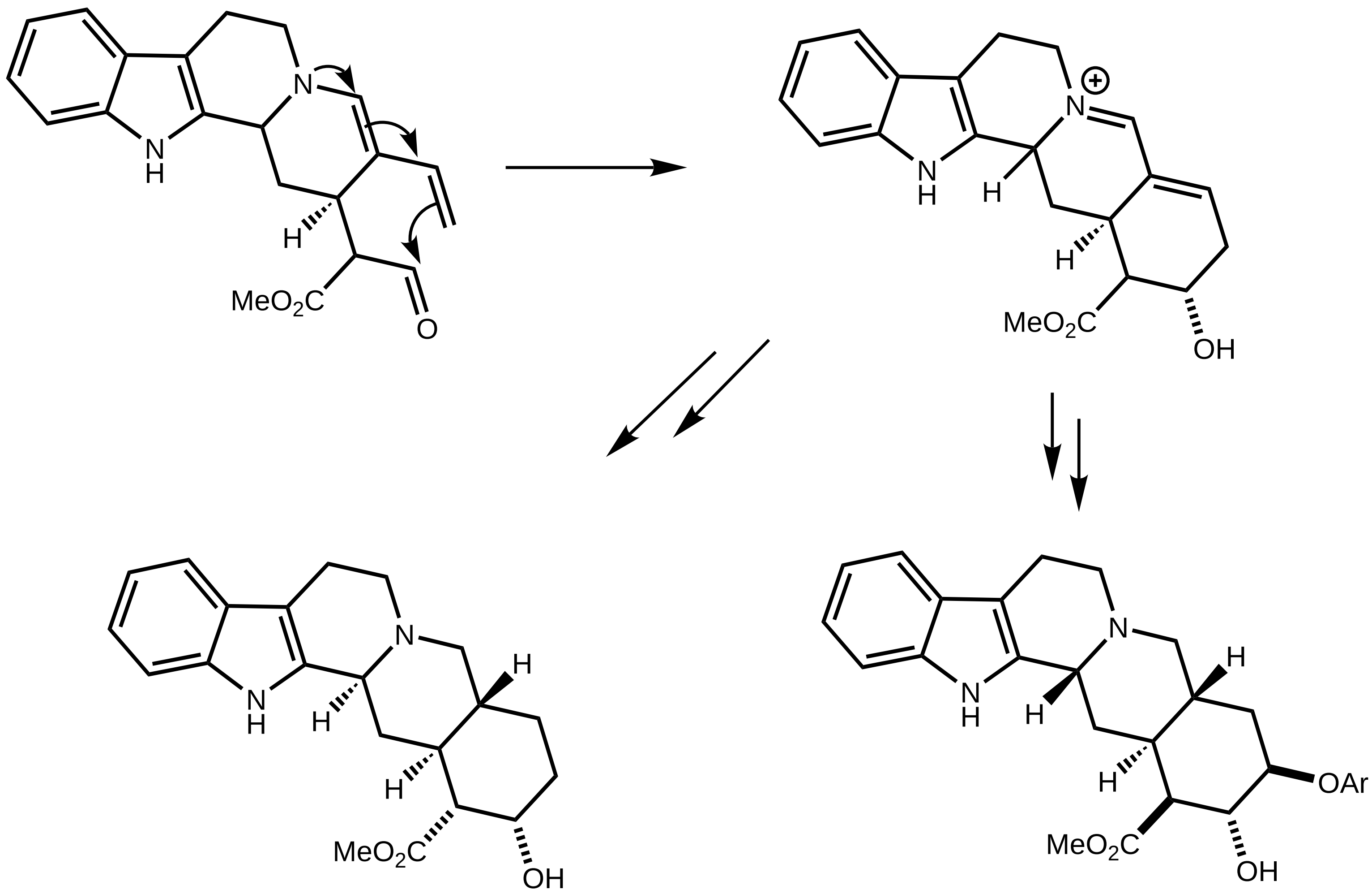
Aldols, Homoaldols and Vinylogous Aldols

A Comparison



The Vinylogous Aldol Reaction in Nature

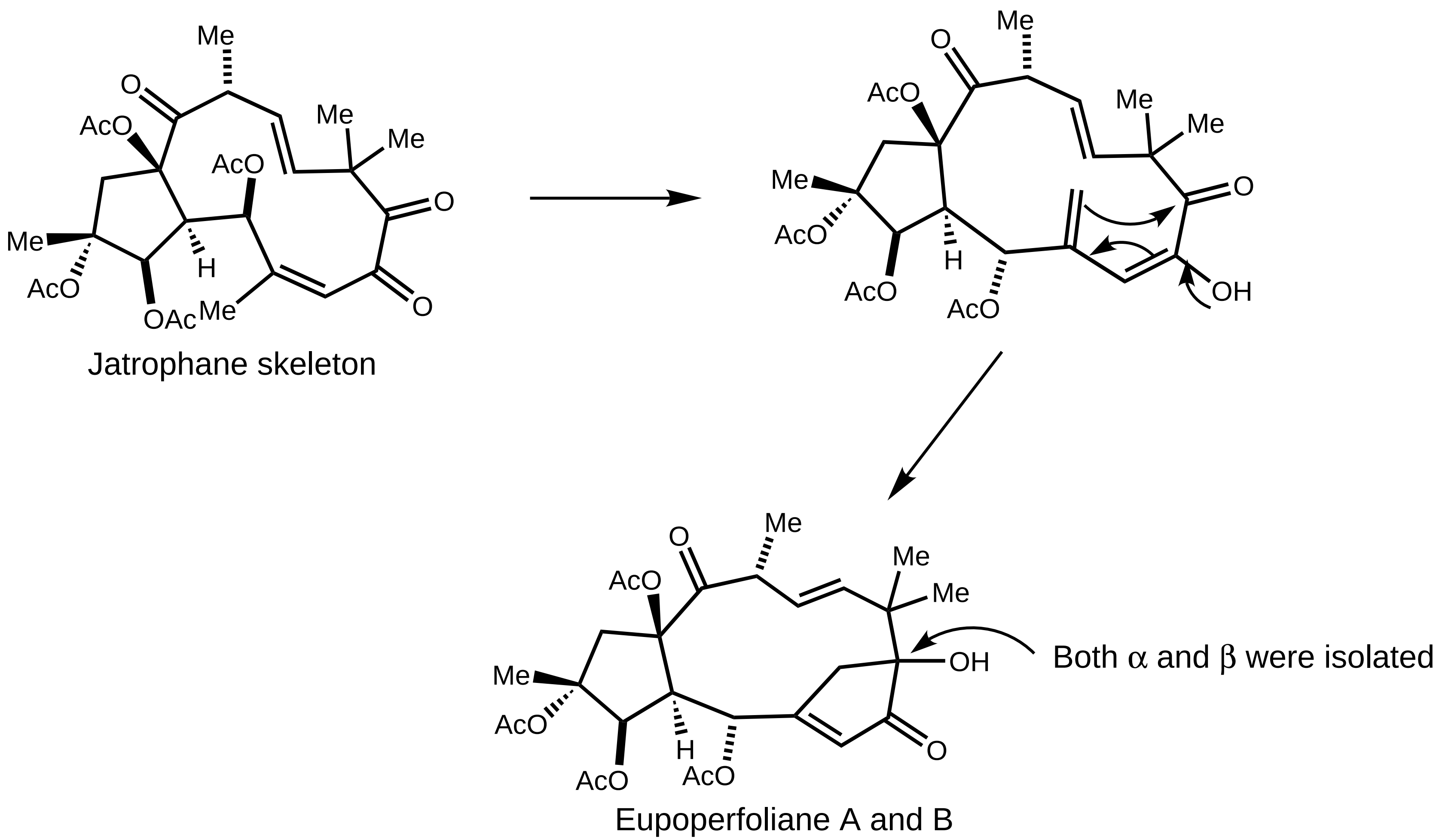
Yohimbine and Reserpine



Cordell, *Introduction to Alkaloids*, Wiley: New York, 1981; pp. 826-828

The Vinylogous Aldol Reaction in Nature

Euphoperfolianes



Appendino, *J. Nat. Prod.* **1998**, *61*, 749.

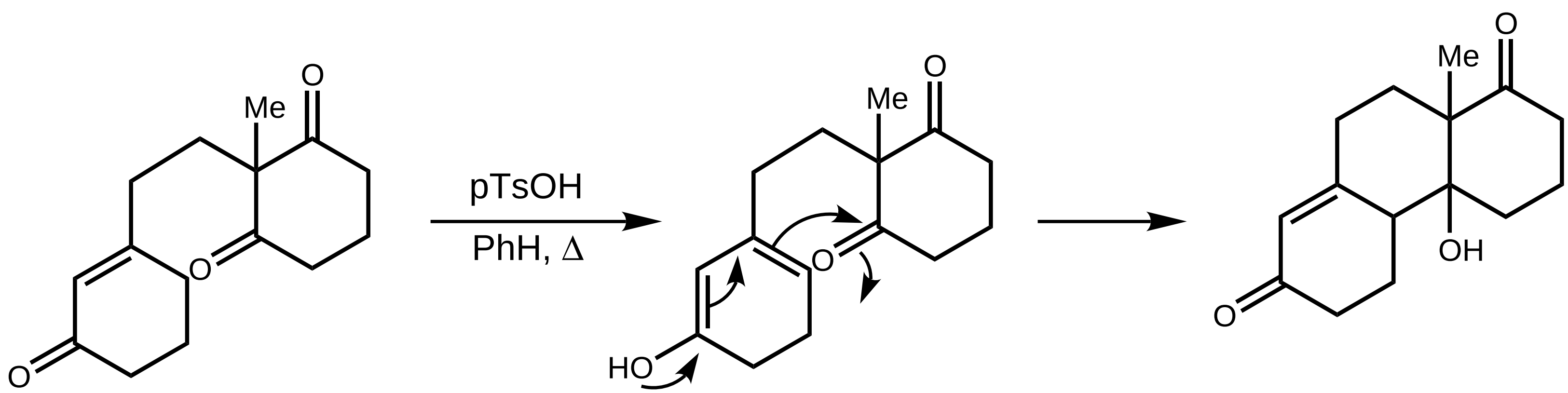
Non-Directed Vinylogous Aldol Reactions

Intramolecular Cyclization

• non-directed aldol reaction: nucleophile (enolate or enol) generated in sub-stoichiometric manner in the presence of the electrophile

• non-directed VAR: very rare since VAR adducts rarely survive conditions of reaction (acid or base catalysis)

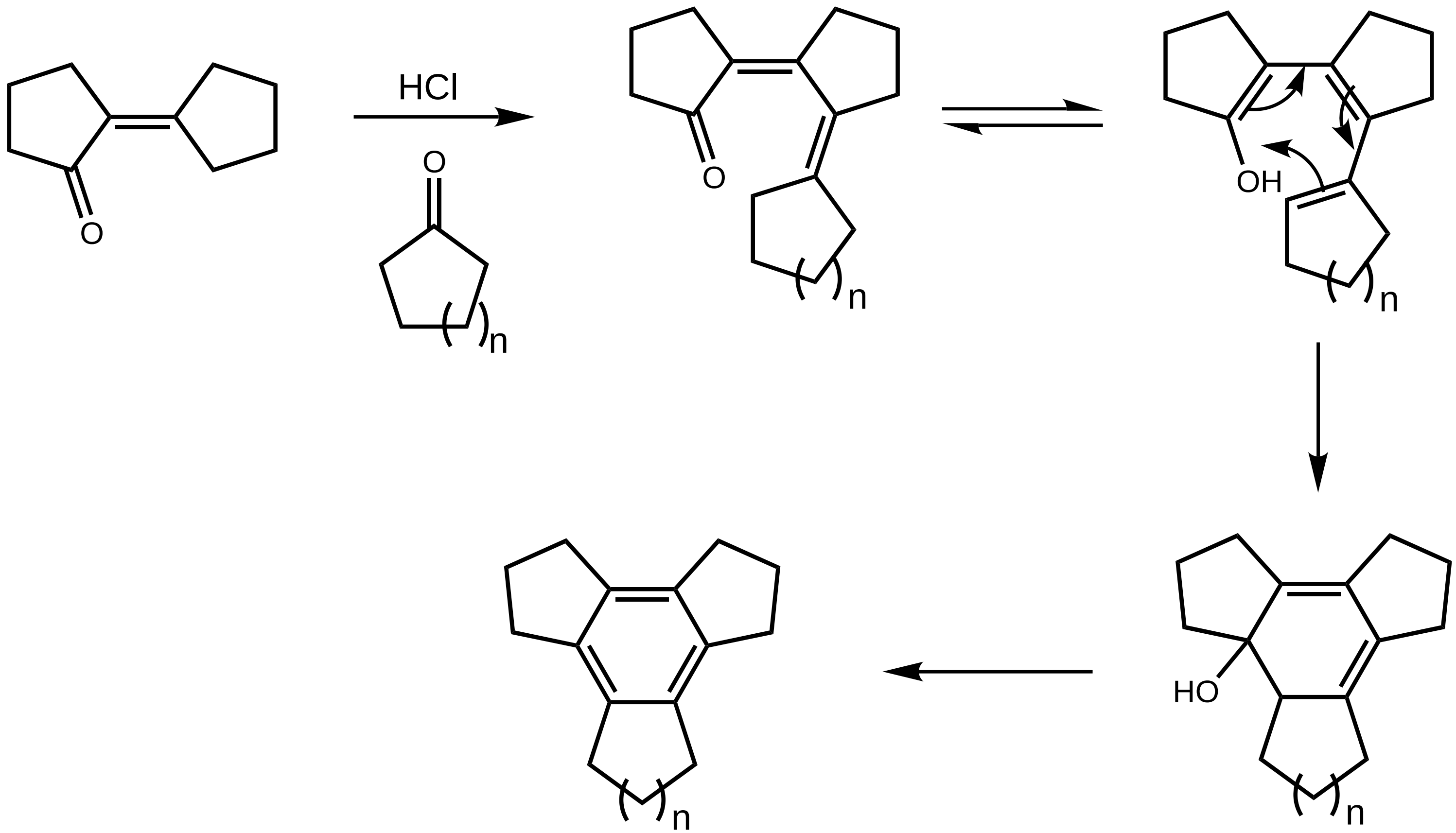
• some special cases:



Torgov, *Izv. Acad. Nauk SSSR* **1964**, 1311.

Non-Directed Vinylogous Aldol Reactions

Cycloaromatization



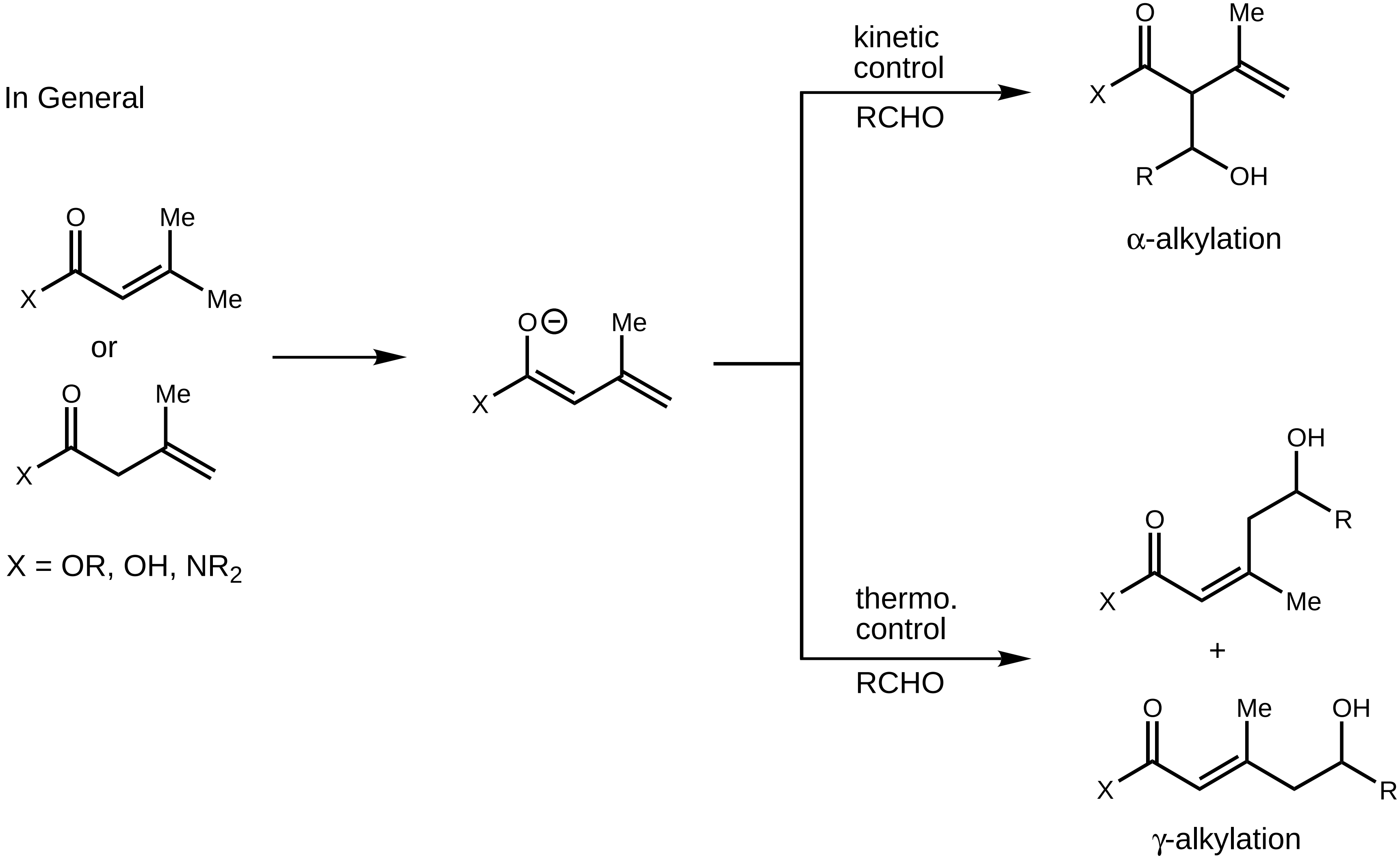
n = 1 (55%)
n = 2 (29%)

Mayer, *Ber*. **1956**, *89*, 1443.

Dienolates from Unsaturated Acid Equivalents

Kinetic vs. Thermodynamic Control

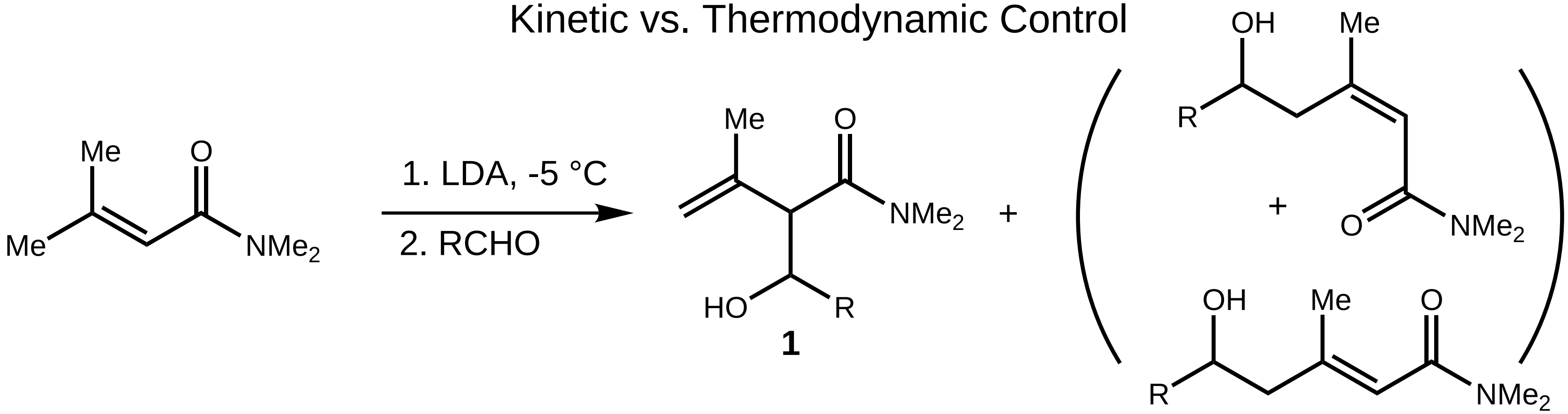
• In General

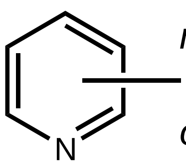


Casiraghi, *Chem. Rev.* **2000**, *100*, 1929.

Metal Dienolates of Amides

Kinetic vs. Thermodynamic Control

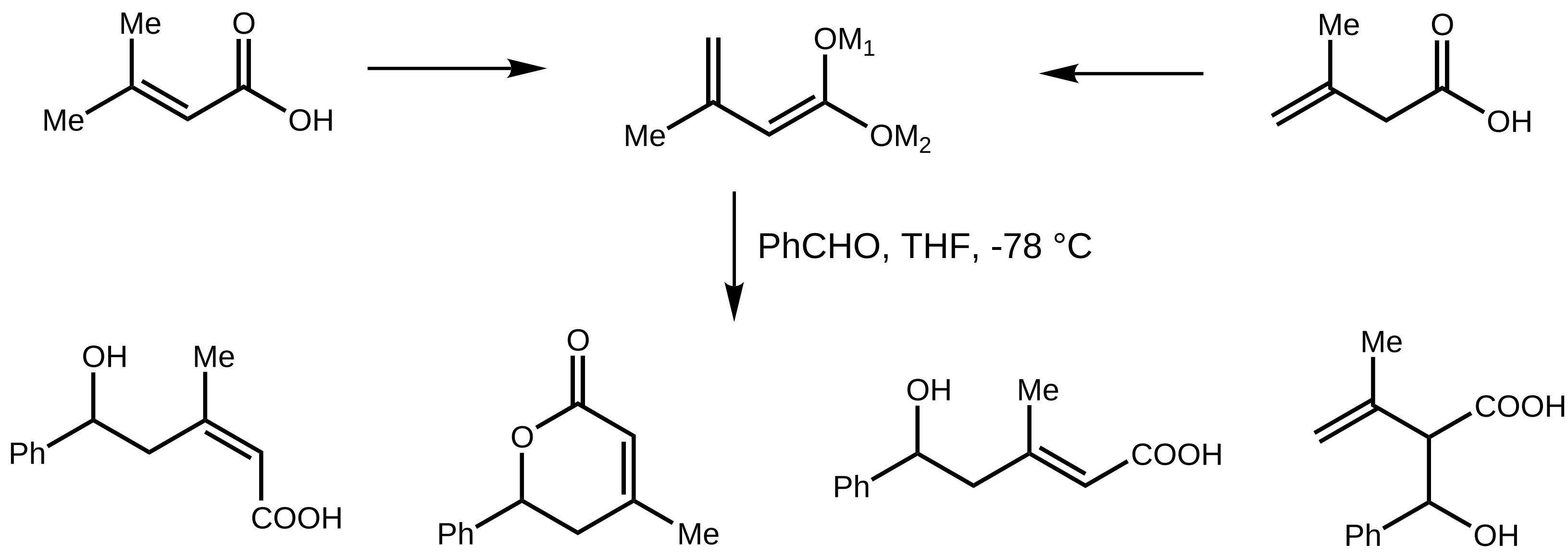


R	-5 °C, 5 min 1 : 2	-5 °C to rt, overnight 1 : 2
Ph	80 : 20	0 : 100
^{n}Pr	100 : 0	13 : 87
 *meta*	100 : 0	15 : 85
ortho / para	100 : 0	100 : 0
(E)-CH=CHPh	100 : 0	100 : 0

Snieckus, *J. Org. Chem.* **1981**, *46*, 2029.

Dienolates from Unsaturated Carboxylic Acids

Vinylogous Aldol Selectivity Highly Dependant on Metal(s)



A **B** **C** **D**

M	M'	relative yield A	B	C	D
Li	$SnBu_3$	-	-	-	100
Li	Li	19	27	-	54
Na	Li	5	44	5	46
K	Li	54	24	-	22
K	K	100	-	-	-

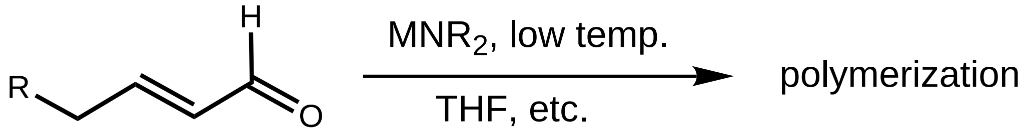
Conclusion: vinylogous aldol adducts favored with more ionic character

Cainelli, *J. Chem. Soc. Perkin Trans. 1* **1973**, 400.

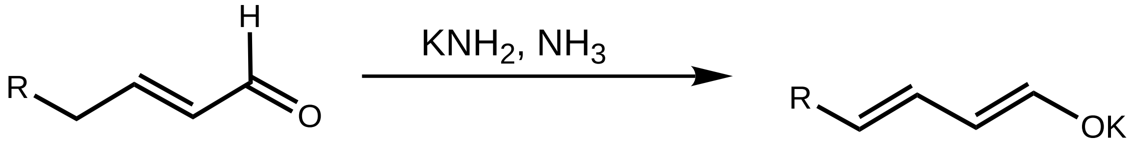
Metal Dienolates of Aldehydes

Methods of Enolate Generation

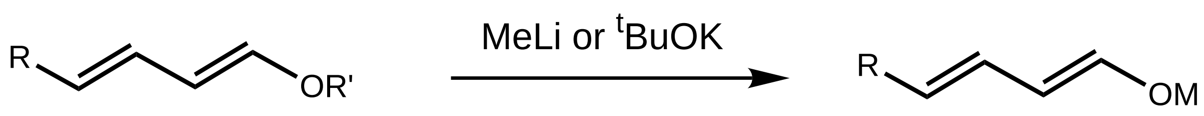
• "traditional" methods of enolization not synthetically useful



• enolate can be generated in liquid ammonia; highly stable in these conditions but reactivity in these conditions not studied



• most common method: cleavage of silyl dienol ethers and dienol acetates

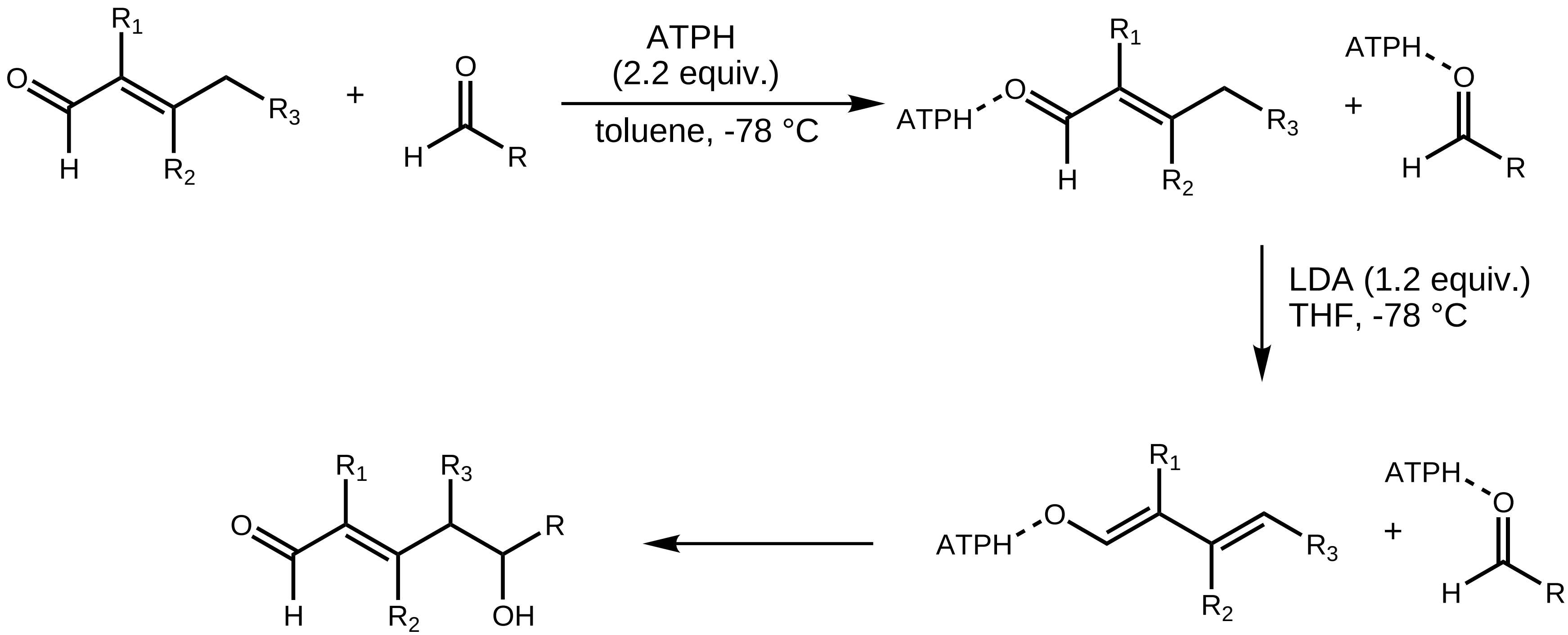


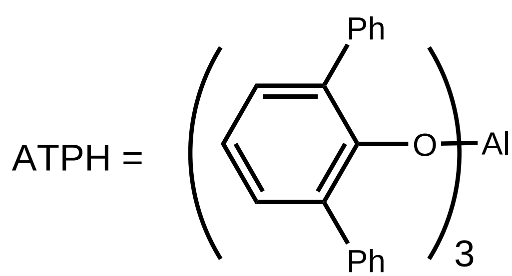
R' = TMS or Ac

van der Gen, *Tetrahedron Lett.*. **1978**, 491.
Stork, *J. Am. Chem. Soc.* **1968**, *90*, 4464.
House, *J. Org. Chem.* **1969**, *34*, 2324.

Metal Dienolates of Aldehydes

Yamamoto's Al-mediated VAR

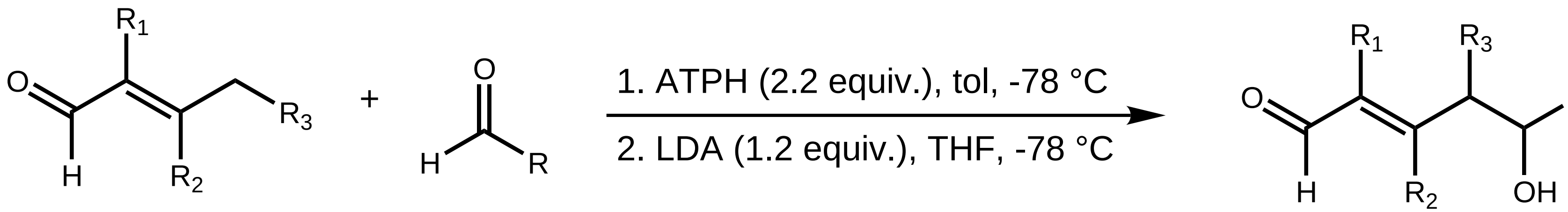


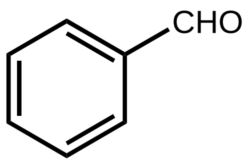
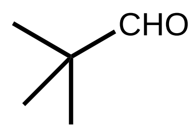
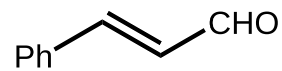
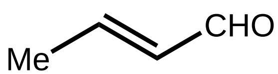
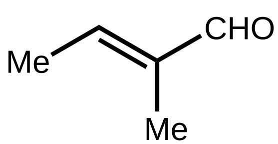
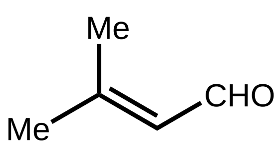


Yamamoto, *J. Am. Chem. Soc.* **1998**, *120*, 813.

Metal Dienolates of Aldehydes

Yamamoto's Al-mediated VAR



conj. aldehyde \ aldehyde				
	99%	99%	55%	83%
	97%	91%	90%	83%
	99%	99%	77%	83%

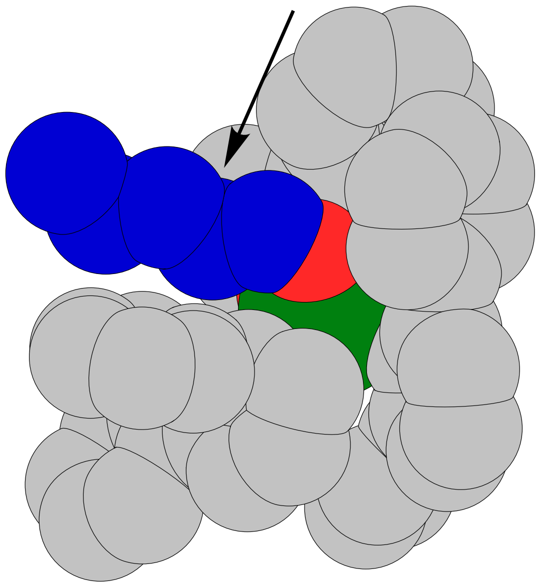
Yamamoto, *J. Am. Chem. Soc.* **1998**, *120*, 813.

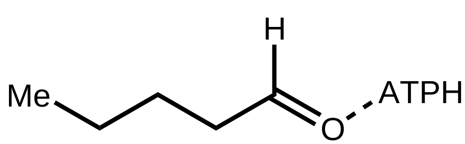
Metal Dienolates of Aldehydes

Yamamoto's Al-mediated VAR

• Rational for enolatization selectivity

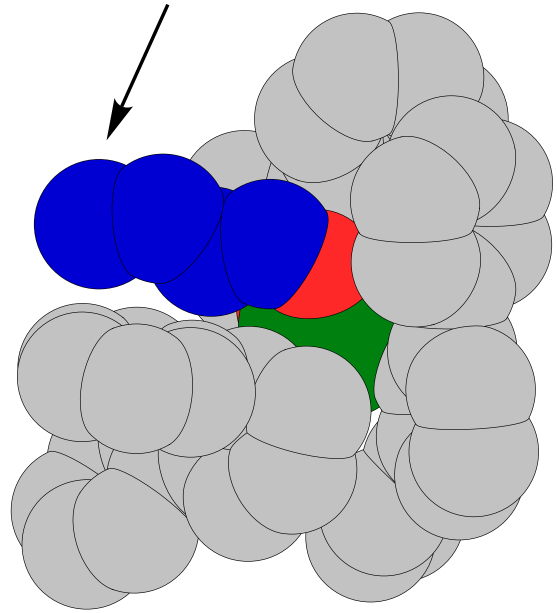
Hydrogens not accessible to base

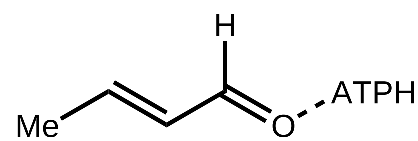




MM2
Models
(Chem3D)

Hydrogens accessible to base



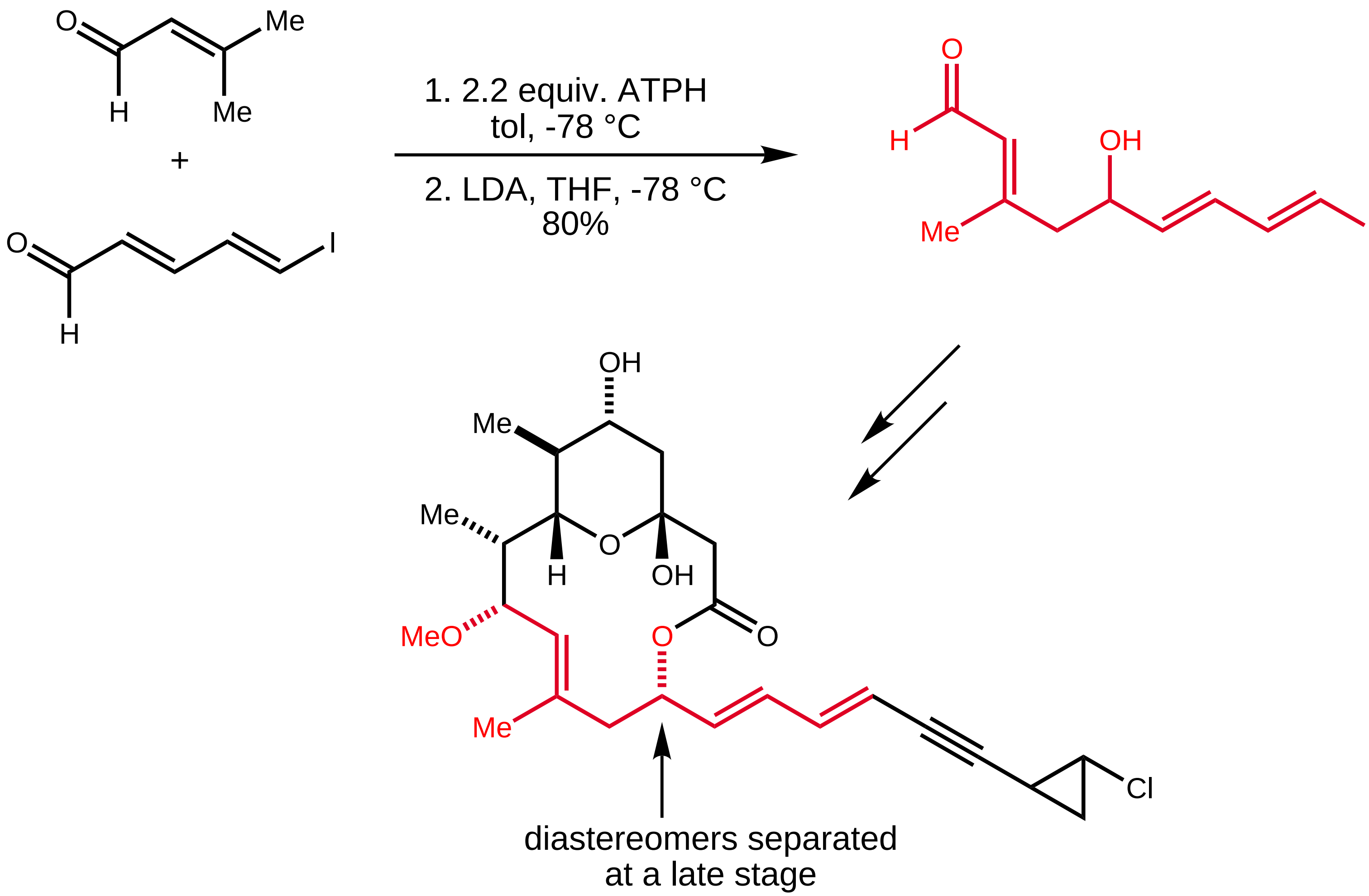


• has also been suggested that aldol occurs only with *uncomplexed* aldehyde due to this steric hindrance
→carbonyls complexed with ATPH even resistant to addition by MeLi

Yamamoto, *J. Am. Chem. Soc.* **1998**, *120*, 813.
Casiraghi, *Chem. Rev.* **2000**, *100*, 1929.
Maruoka, *Angew. Chem. Int. Ed.* **1998**, *37*, 3039.

Metal Dienolates of Aldehydes - Synthetic Applications

Callipeltoside Aglycone - Patterson

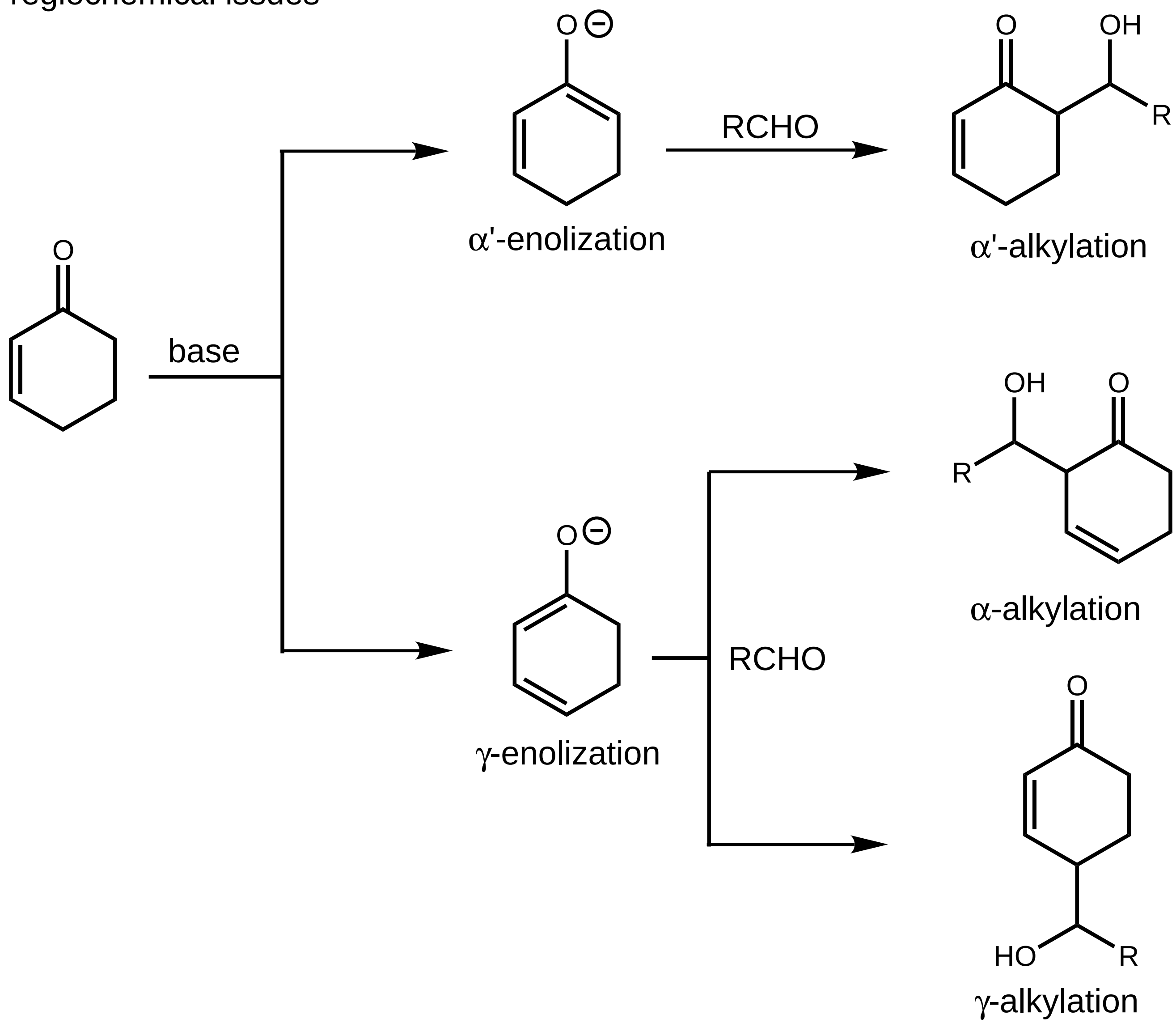


Patterson, *Angew. Chem. Int. Ed.* **2001**, *40*, 603.

Metal Dienolates of Enones

Methods of Enolate Generation

• regiochemical issues

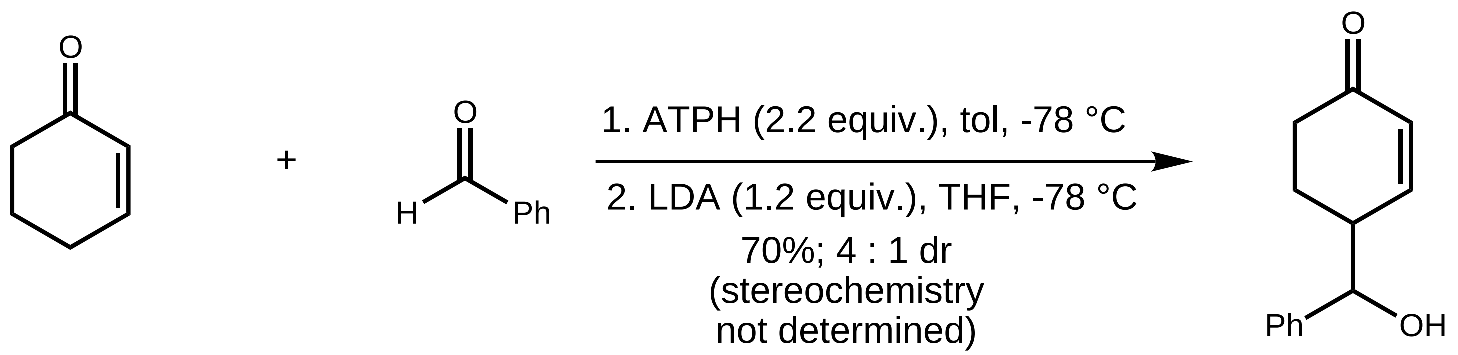


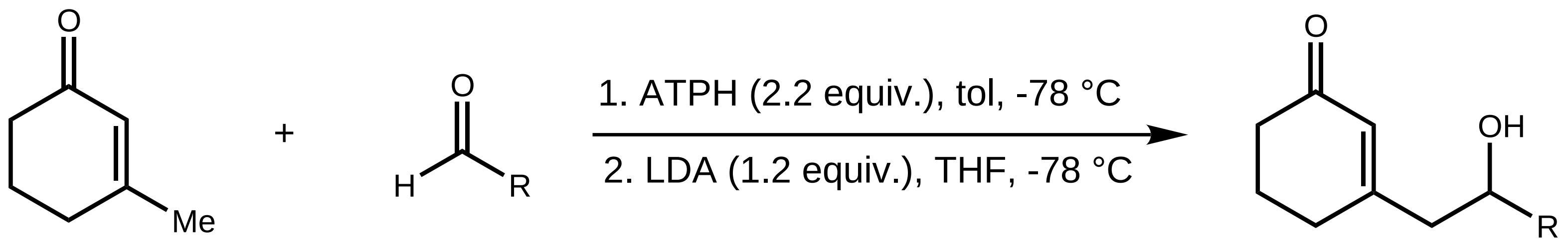
Only product observed under kinetic conditions (i.e. LDA, cold temp)

Can be observed under equilibrating conditions; usually accompanied by elimination (aldol condensation)

Metal Dienolates of Enones

Yamamoto's Al-mediated VAR



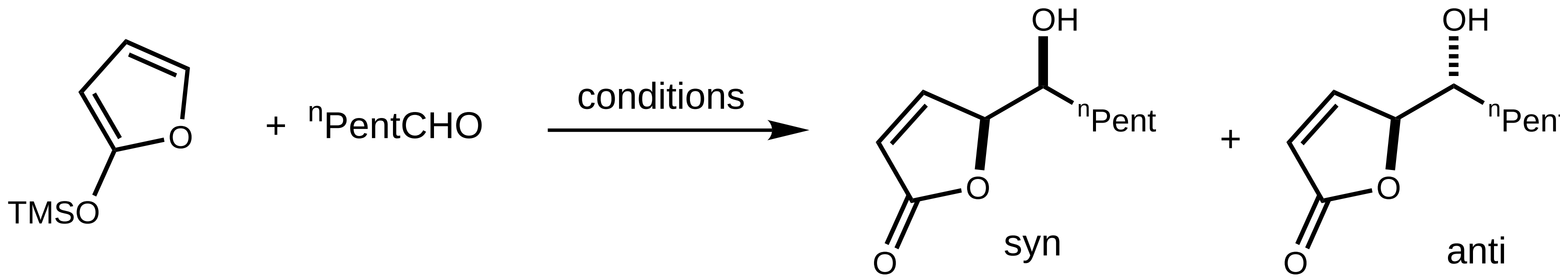


R = Ph : 86%
R = ^{t}Bu : 99%
R = ^{n}Bu : 73%
R = (E)-CH=CHPh : 68%

Yamamoto, *J. Am. Chem. Soc.* **1998**, *120*, 813.

Vinylogous Aldol Reactions of Siloxyfurans

Effect of Lewis Acid / Promoters

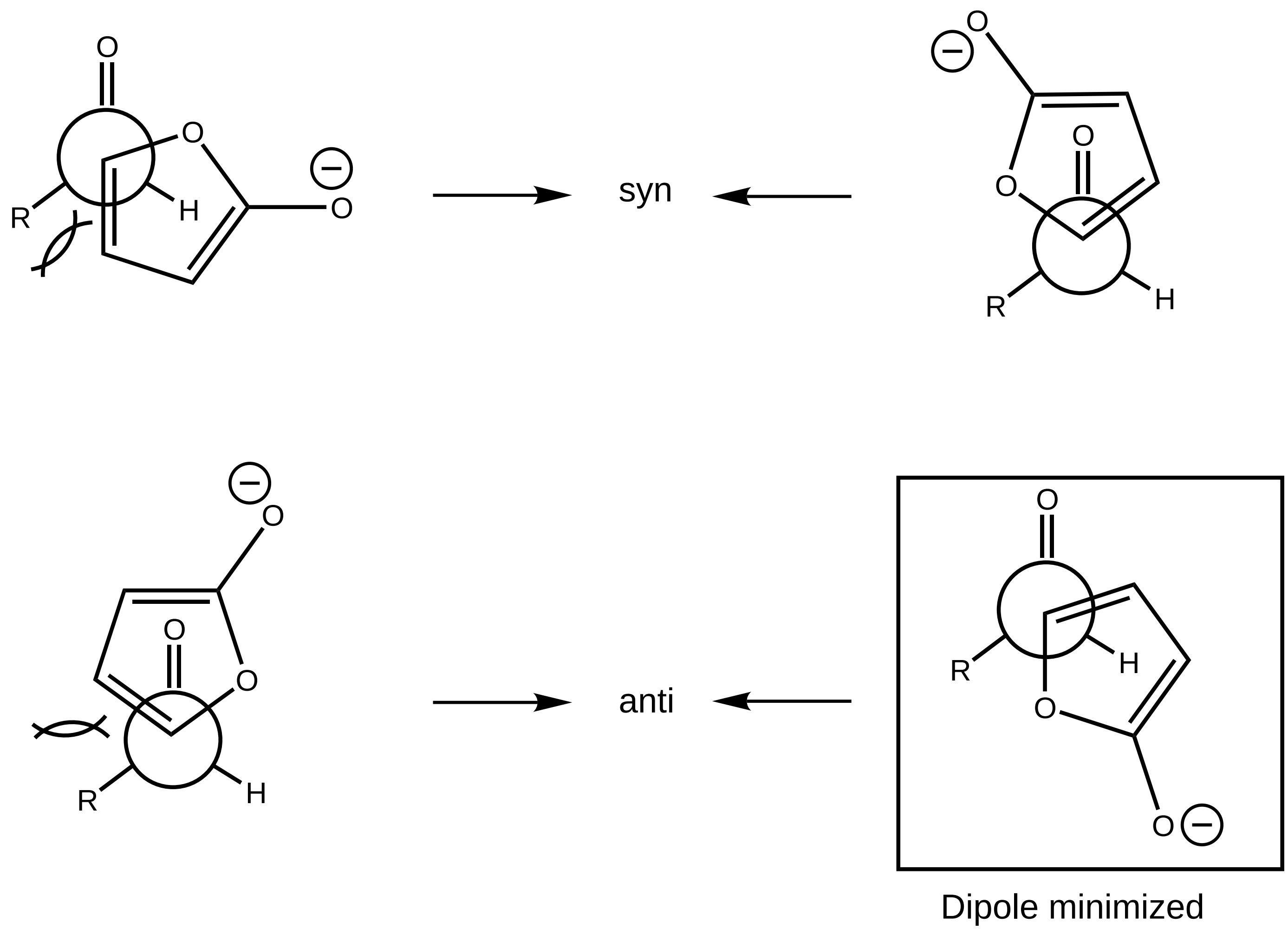


Conditions	syn : anti	yield (%)
$SnCl_4$ (0.4 equiv.), -78 °C	76 : 24	88
$ZnBr_2$ (0.4 equiv.), 0 °C	66 : 34	94
$ZnCl_2$ (0.5 equiv.), 0 °C	68 : 32	82
BF_3•OEt_2 (0.6 equiv.), -78 °C	81 : 19	95
$TrClO_4$ (0.1 equiv.), -78 to 0 °C	79 : 21	92
TMSOTf (0.2 equiv.), -78 °C	82 : 18	95
TESOTf (0.2 equiv.), -78 °C	82 : 18	93
CsF (1.3 equiv.), -78 to 0 °C	27 : 73	68
TBAF (0.06 equiv.), -78 °C	33 : 67	74

Jefford, *Tetrahedron Lett.* **1987**, *28*, 4037.

Vinylogous Aldol Reactions of Siloxyfurans

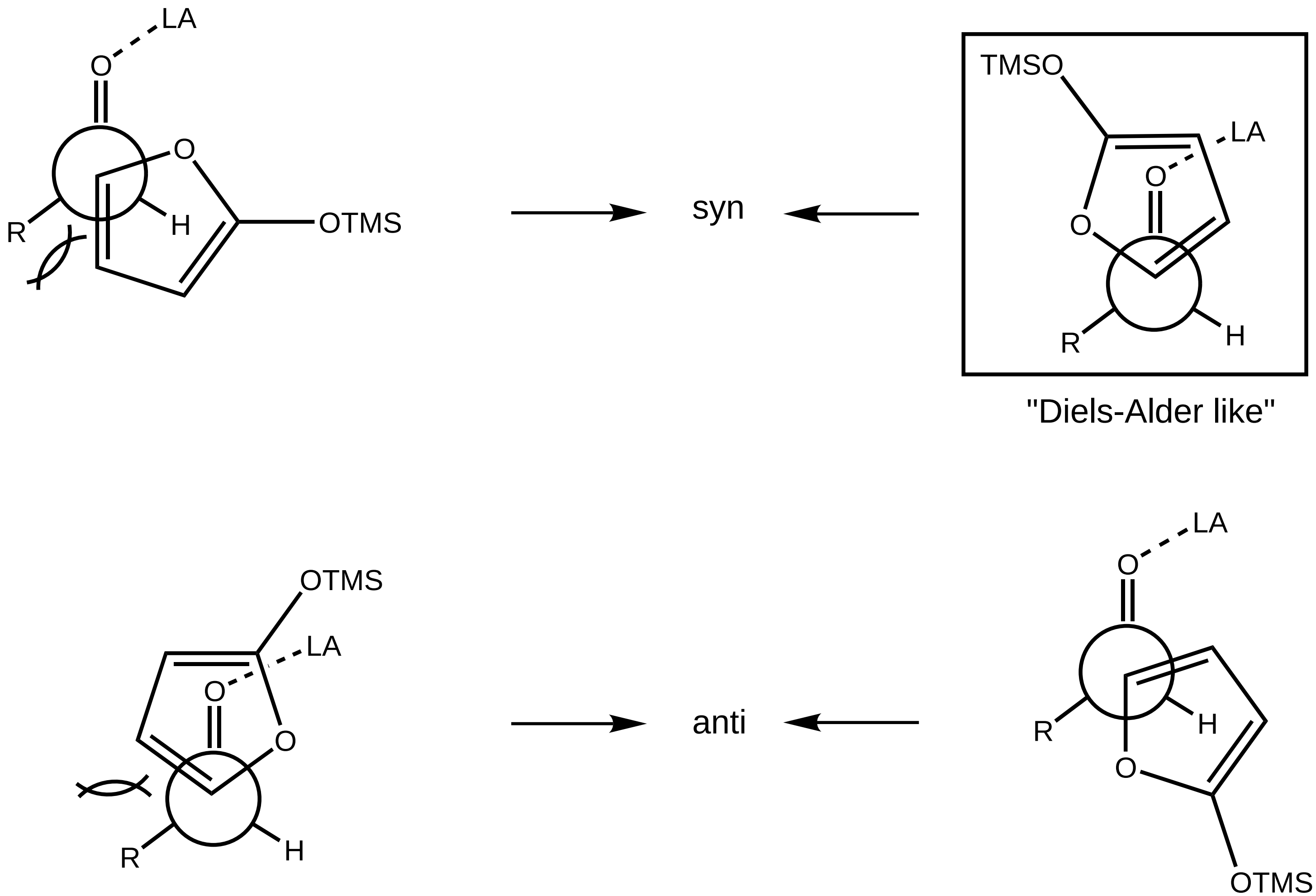
Rationale of Stereoselectivity - "naked" dienolates



Jefford, *Tetrahedron Lett.* **1987**, *28*, 4037.

Vinylogous Aldol Reactions of Siloxyfurans

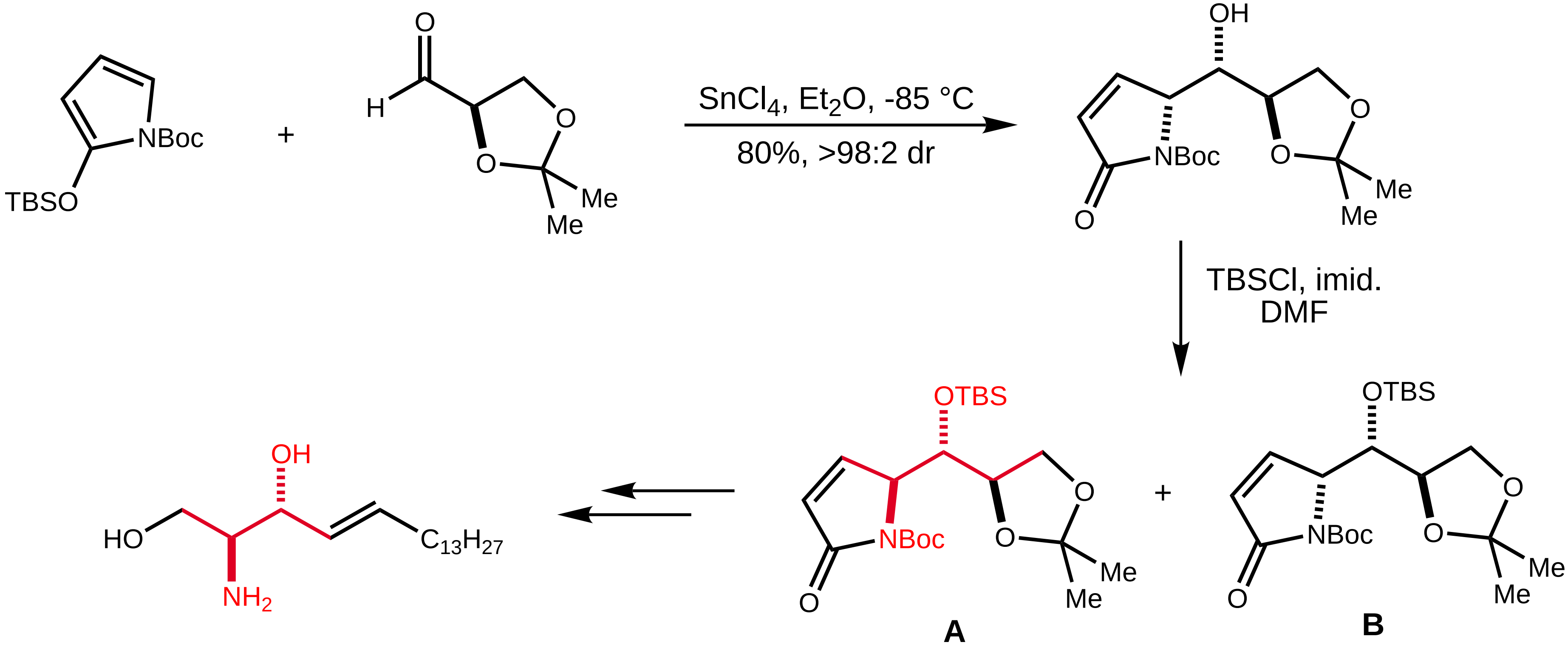
Rationale of Stereoselectivity - Mukaiyama VARs



Jefford, *Tetrahedron Lett.* **1987**, *28*, 4037.

Vinylogous Aldol Reactions of Siloxyfurans
Synthetic Applications

D-*erthyro*-C_{18}-sphingosine - Casiraghi



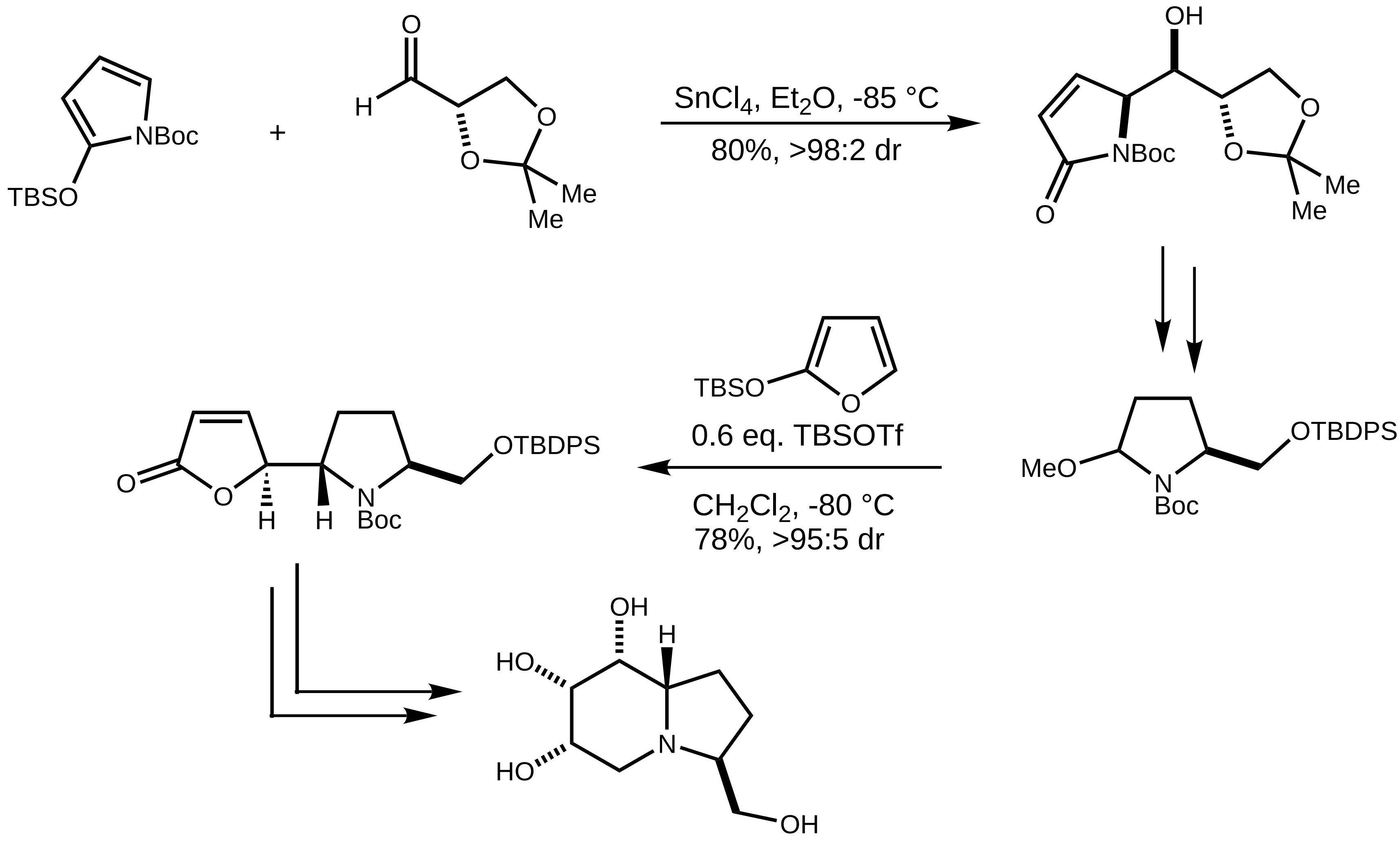
D-*erthyro*-C_{18}-sphingosine

Reaction time	**A : B**
10 hours	12 : 88
4 days	85 : 15

Spanu and Casiraghi, *Tetrahedron Asymm.* **1997**, *8*, 3237.

Vinylogous Aldol Reactions of Siloxyfurans
Synthetic Applications

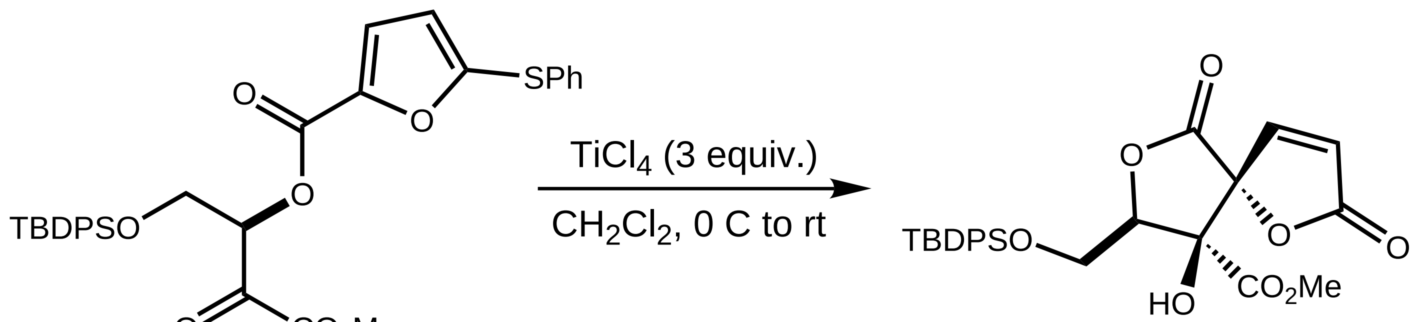
Indolizidine Alkaloid Analogues - Casiraghi



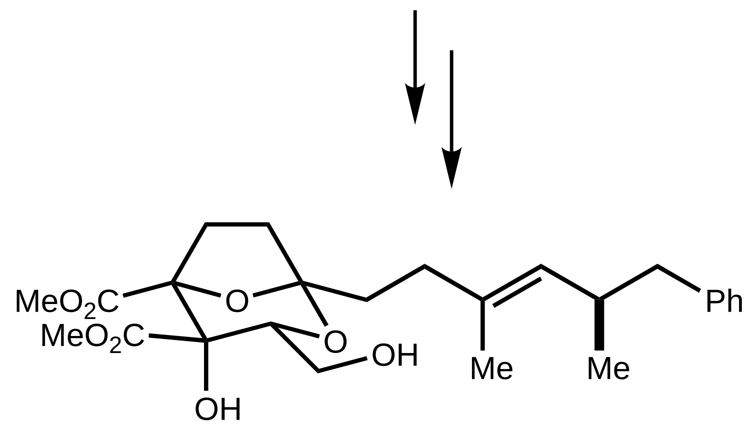
Spanu and Casiraghi, *Eur. J. Org. Chem.* **1999**, 1395.

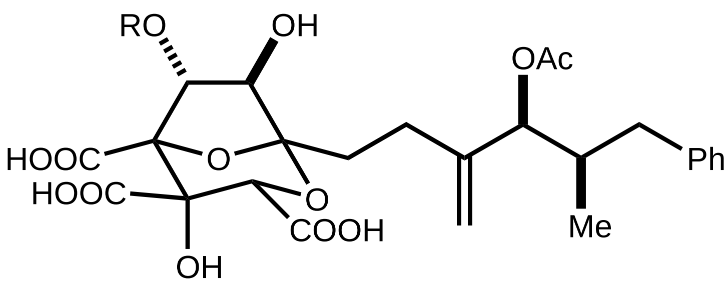
Vinylogous Aldol Reactions of α-heterofurans
Synthetic Applications

Zaragozic Acid Core - Martin



40% (<5% combined of other diast.)
• all other L.A. tried led to decomp. or complex diastereomeric mixtures



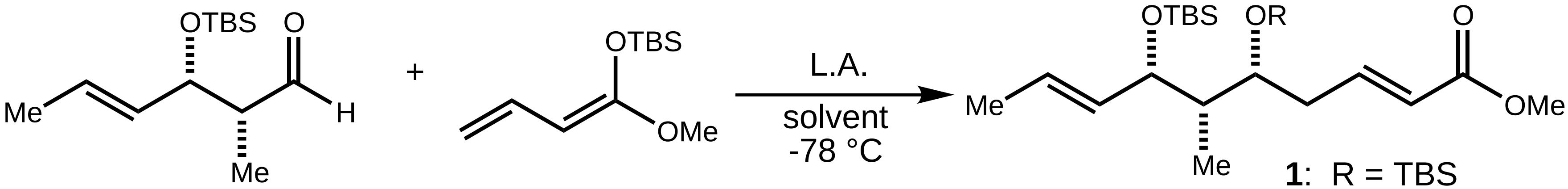


Zaragozic Acid

Martin, *J. Org. Chem.* **1998**, *63*, 7592.

Vinylogous Mukaiyama Aldol Reactions

Effect of Lewis Acid and Solvent



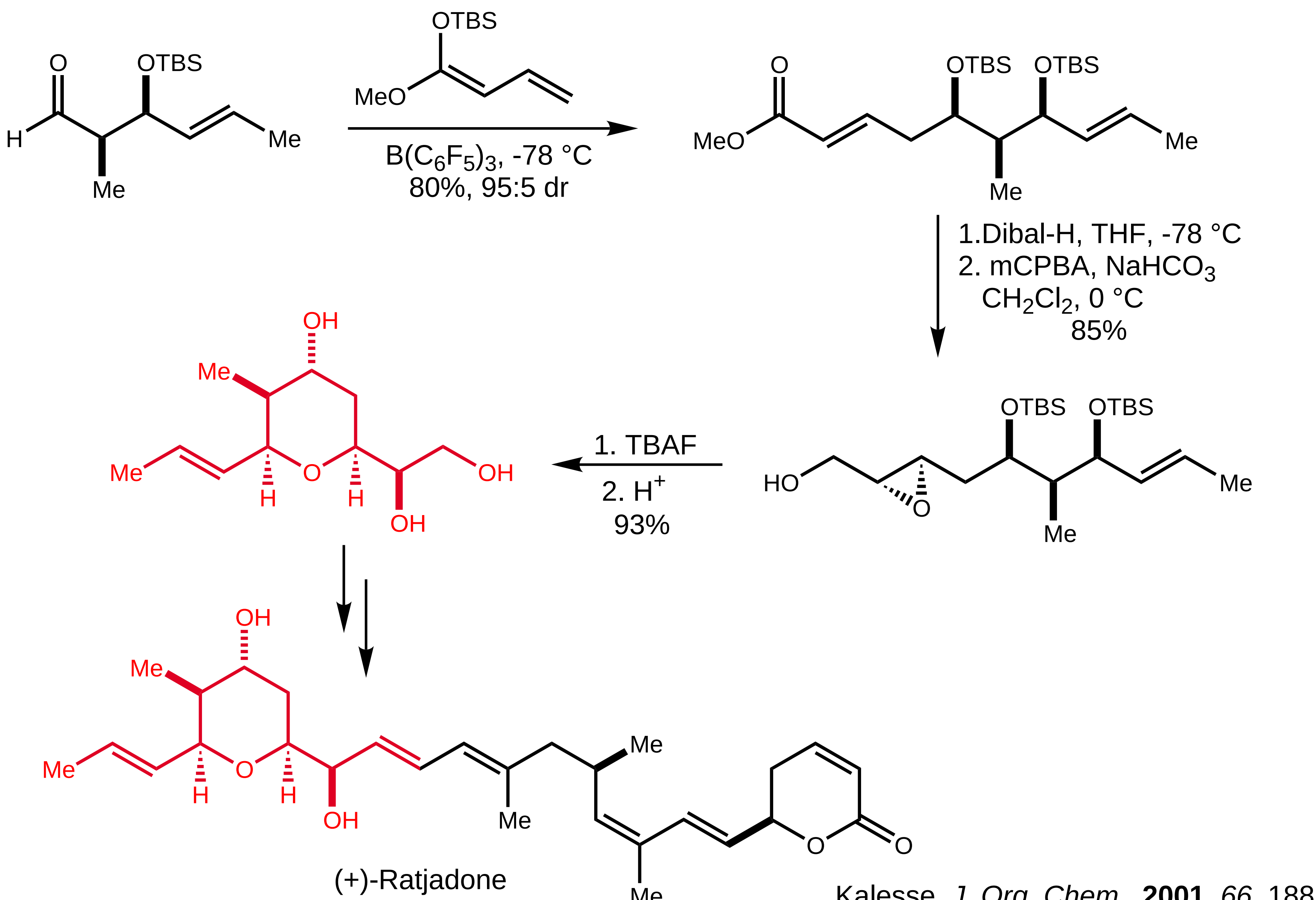
1: R = TBS
2: R = H

Lewis Acid	Equiv.	Solvent	dr	Product (Yield (%))
BF_3•OEt_2	1.5	CH_2Cl_2/Et_2O (9:1)	3:1	**2** (92)
$B(C_6F_5)_3$	1.0	CH_2Cl_2/Et_2O (9:1)	>95:5	**1** (81)
$B(C_6F_5)_3$	0.5	CH_2Cl_2/Et_2O (9:1)	>95:5	**1** (78)
$B(C_6F_5)_3$	0.2	CH_2Cl_2/Et_2O (9:1)	>95:5	**1** (74)
$B(C_6F_5)_3$	0.1	CH_2Cl_2/Et_2O (9:1)	>95:5	**1** (15)
$B(C_6F_5)_3$	0.2	CH_2Cl_2	>95:5	**1** (61), **2** (8)
$B(C_6H_5)_3$	1.0	CH_2Cl_2/Et_2O (9:1)	>95:5	**2** (85)

Kalesse, *Tetrahedron Lett.* **2001**, *42*, 1269.

Vinylogous Mukaiyama Aldol Reactions - Synthetic Applications

(+)-Ratjadone - Kalesse



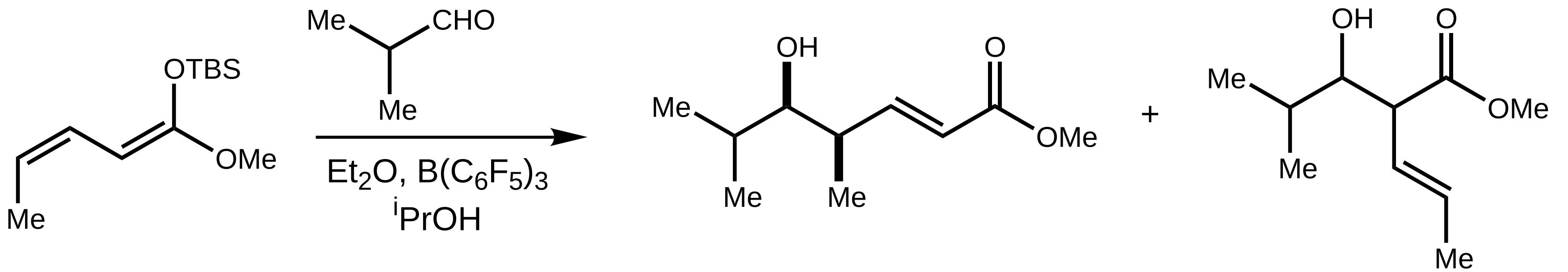
(+)-Ratjadone

Kalesse, *J. Org. Chem.* **2001**, *66*, 1885.

Vinylogous Mukaiyama Aldol Reactions

Effect of Dienolate Stucture

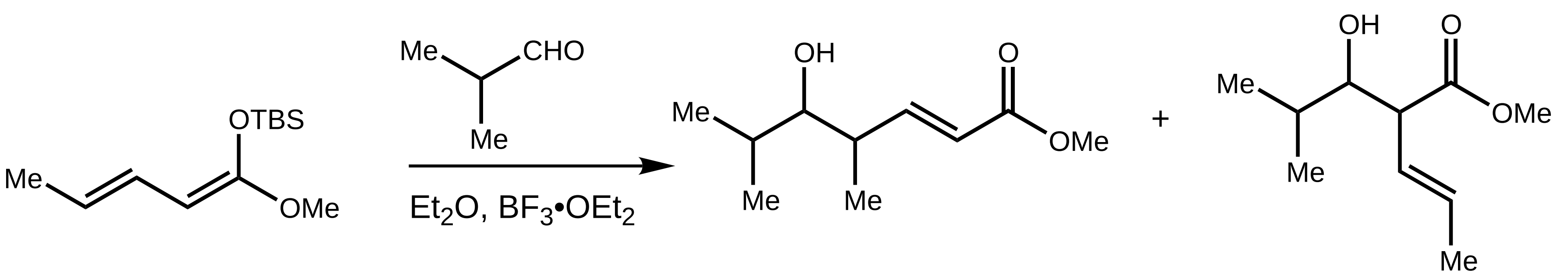
• (Z)-silyl dienolates are good substrates for VMAR



84%; >20:1 syn

<1%; mixture of isomers

• (E)-silyl dienolates, however, are less reactive and unselective



51%; 1:1 syn:anti

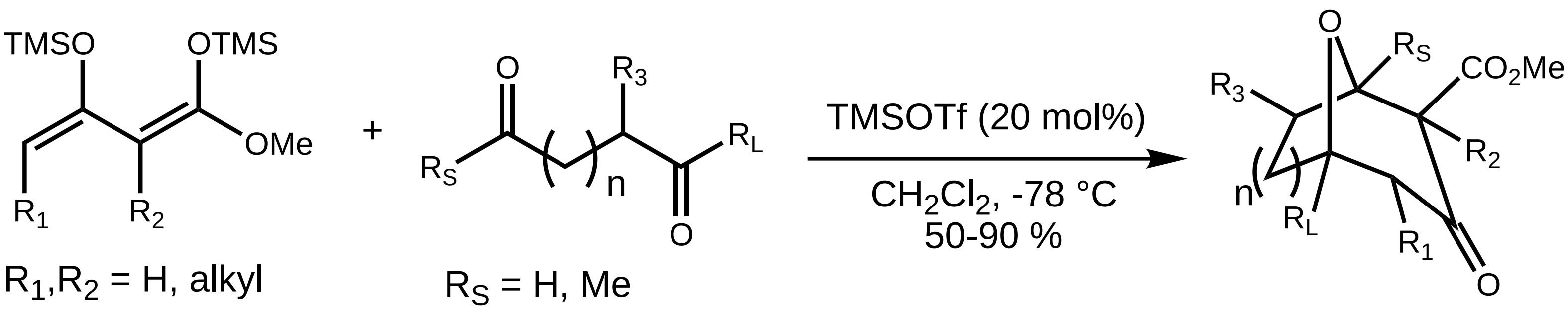
25%; mixture of isomers

• no reaction with B(C$_6$F$_5$)$_3$

Kalesse, *Org. Lett.* **2001**, *3*, 3561.

Vinylogous Enoxy Silane Applications

Molander's [3+4] and [3+5] Annulations



R_1,R_2 = H, alkyl

R_S = H, Me
R_L = alkyl, aryl
R_3 = H, alkyl, OR
n = 1,2

• Representative Examples

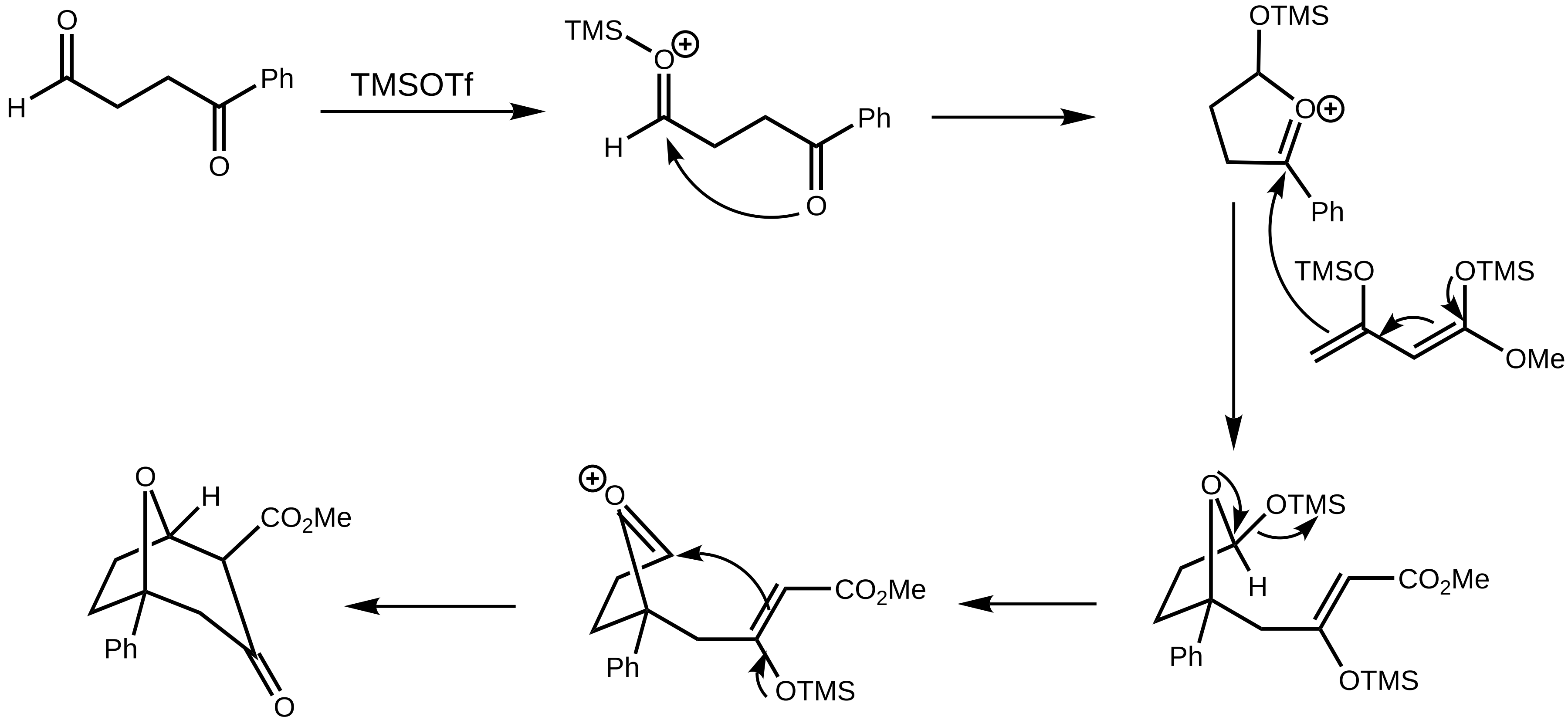
R_1	**R_2**	**R_3**	**R_S**	**R_L**	**n**	**Yield (%)**	**dr**
H	H	H	H	Ph	1	87	>200:1
H	H	H	Me	^{n}Pr	1	58	5:1
H	H	Me	H	Me	1	75	13.5:1
H	^{i}Pr	H	H	^{n}Pr	1	73	25:1
Me	H	H	H	^{n}Pr	1	72	5.4:1
H	H	Me	H	Me	2	72	30:1

Molander, *J. Am. Chem. Soc.* **1993**, *115*, 830.

Vinylogous Enoxy Silane Applications

Molander's [3+4] and [3+5] Annulations

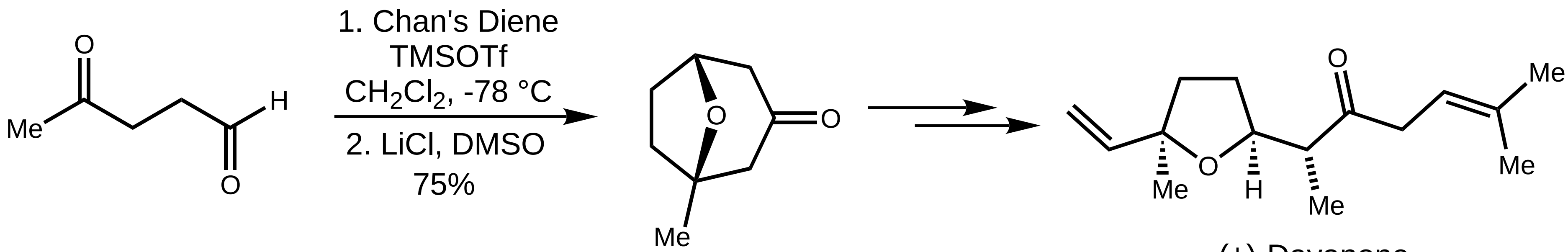
• Mechanism



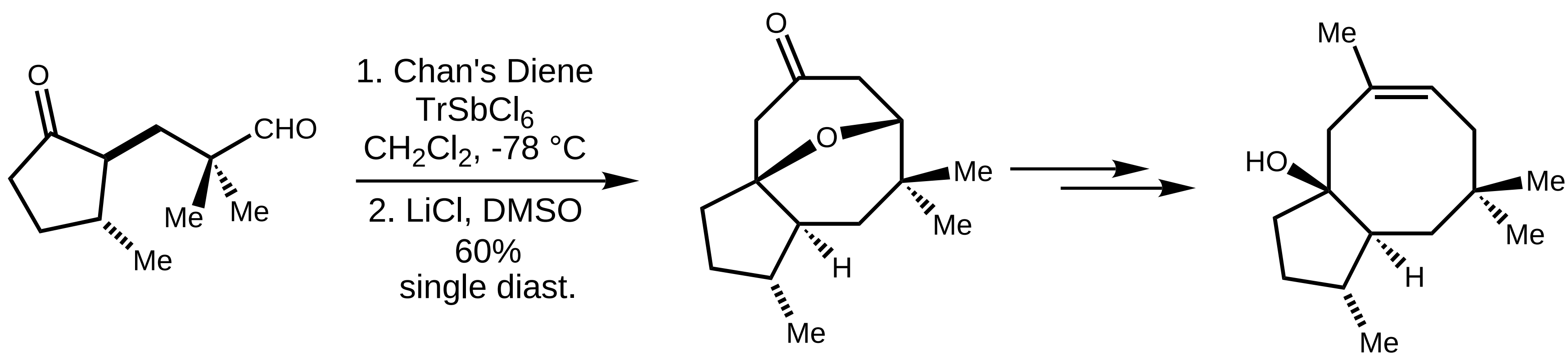
Molander, *J. Am. Chem. Soc.* **1993**, *115*, 830.

[3+n] Enoxy Silane Annulation - Synthetic Applications

Molander's Annulation - Davanone and Dactylol



(±)-Davanone

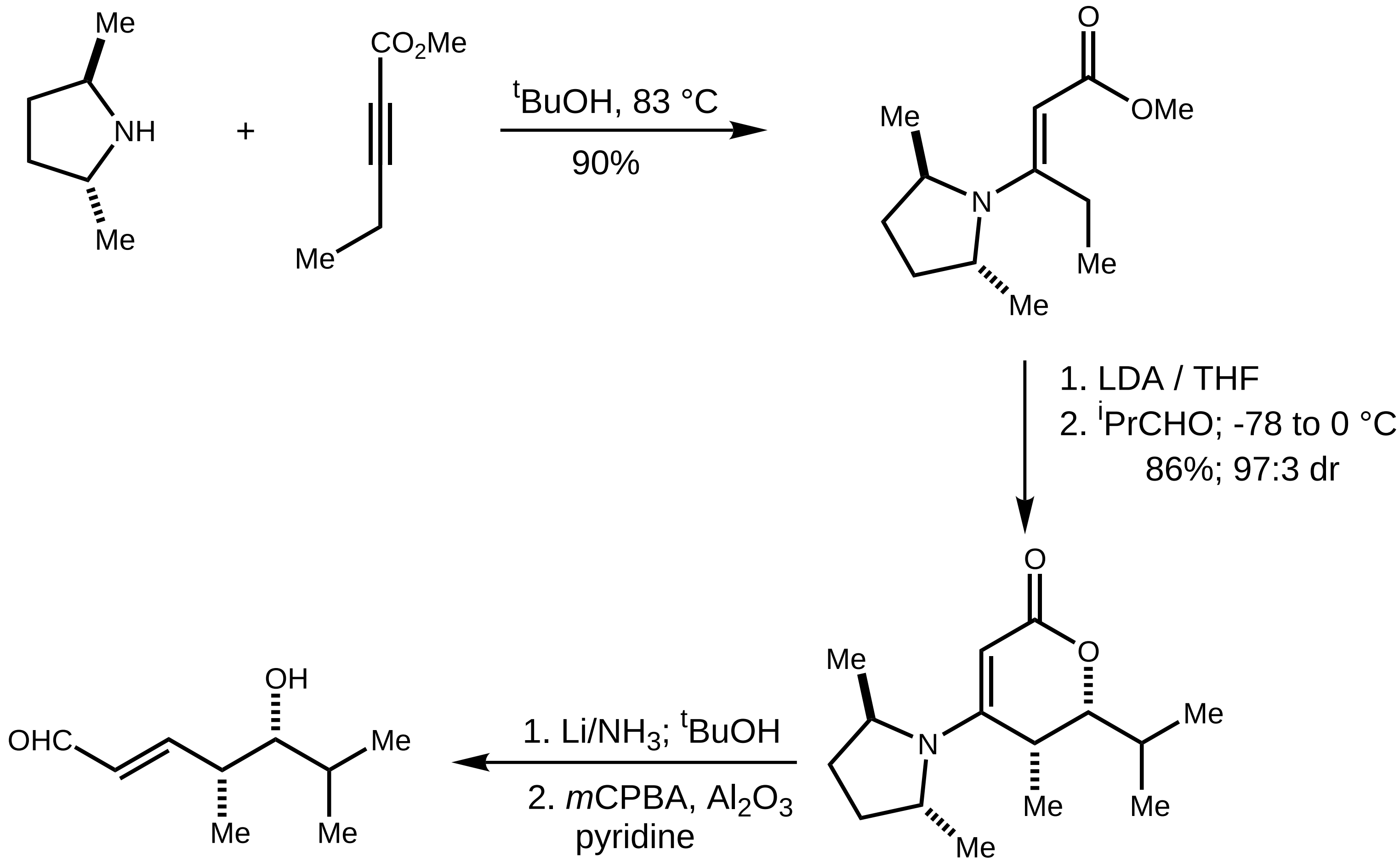


(+)-Dactylol

Molander, *Tetrahedron* **1999**, *55*, 617.
Molander, *J. Org. Chem.* **1995**, *60*, 4559.

Diastereoselective Vinylogous Aldol Reactions

Schlessinger's Chiral Dienolate - First Generation



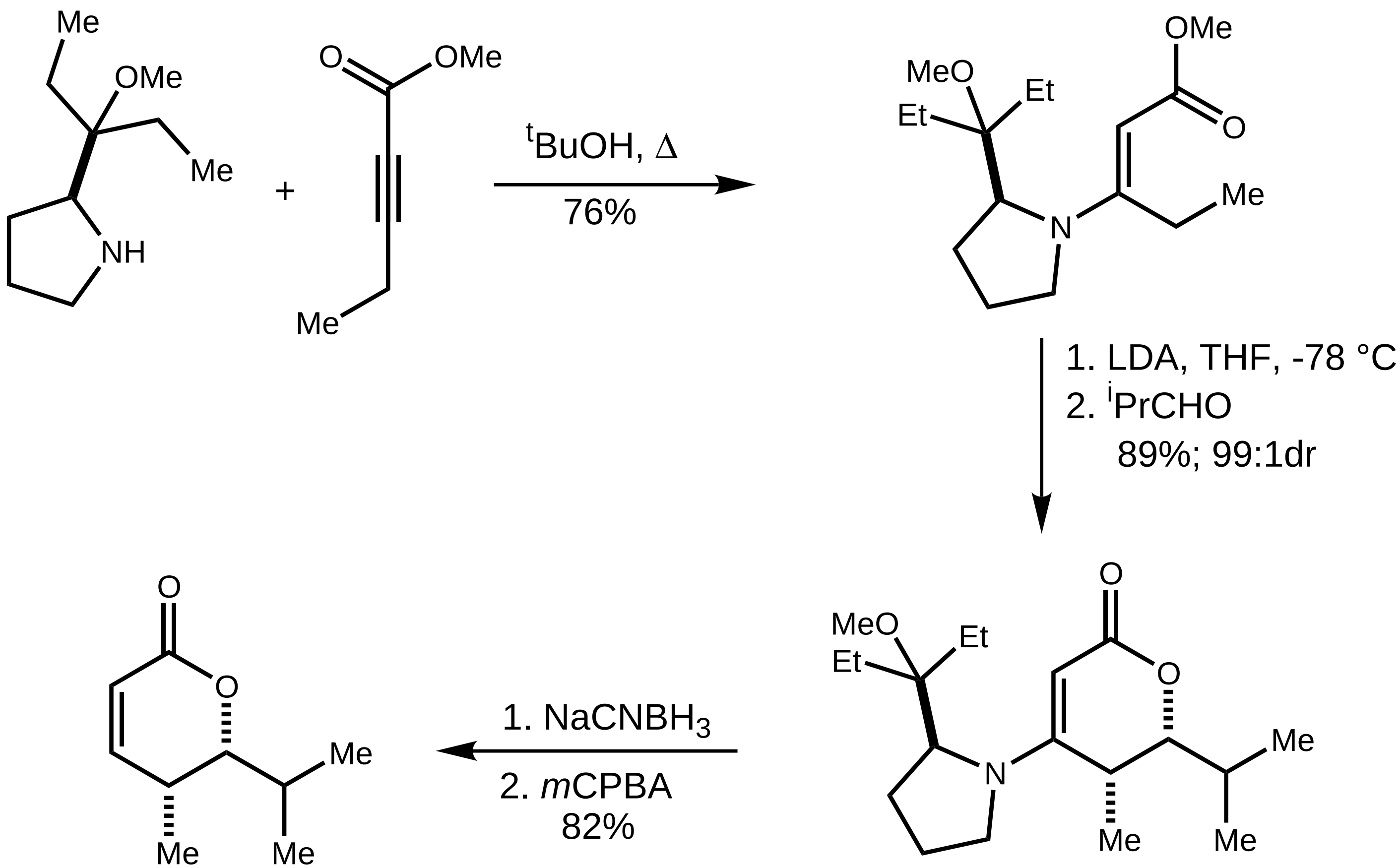
Schlessinger and Springer, *J. Org. Chem.* **1986**, *51*, 3073.

29-Schlessinger 1st Gen 2/11/02 5:10 PM

Diastereoselective Vinylogous Aldol Reactions

Schlessinger's Chiral Dienolate - Second Generation

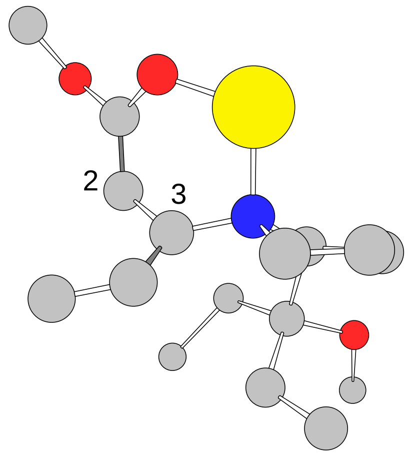
• Problem with previous auxillary: very expensive, and difficult to prepare on large scale
  - solution: proline-derived auxillary

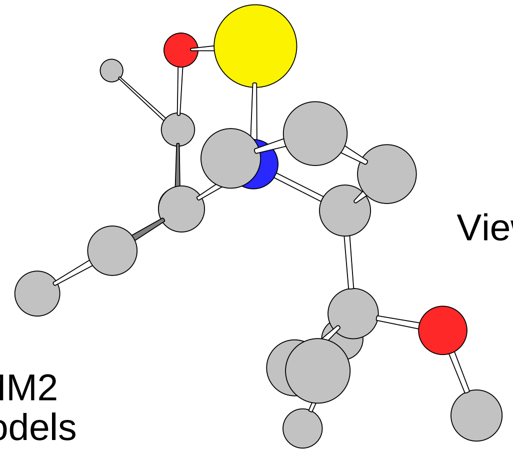


Schlessinger, *J. Org. Chem.* **1996**, *61*, 3226.

Diastereoselective Vinylogous Aldol Reactions

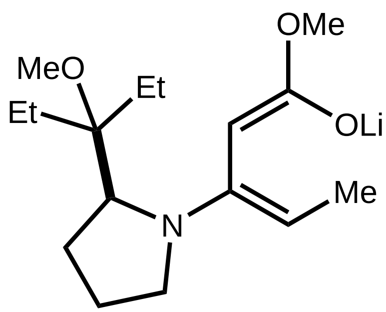
Schlessinger's Chiral Dienolate - Second Generation





View down C_3-C_2 bond

MM2
Models
(Chem3D)



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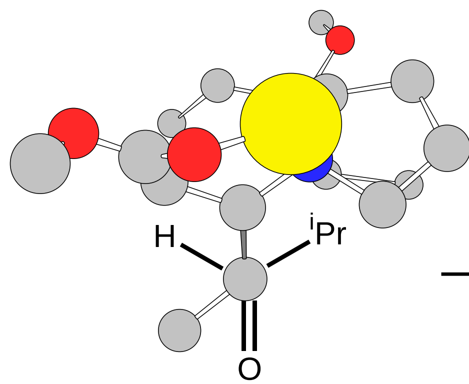
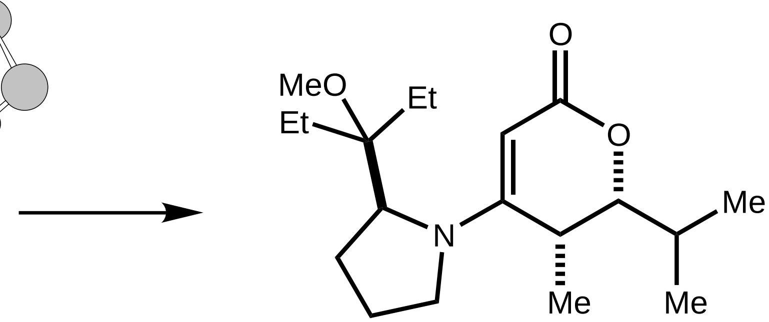


View from top

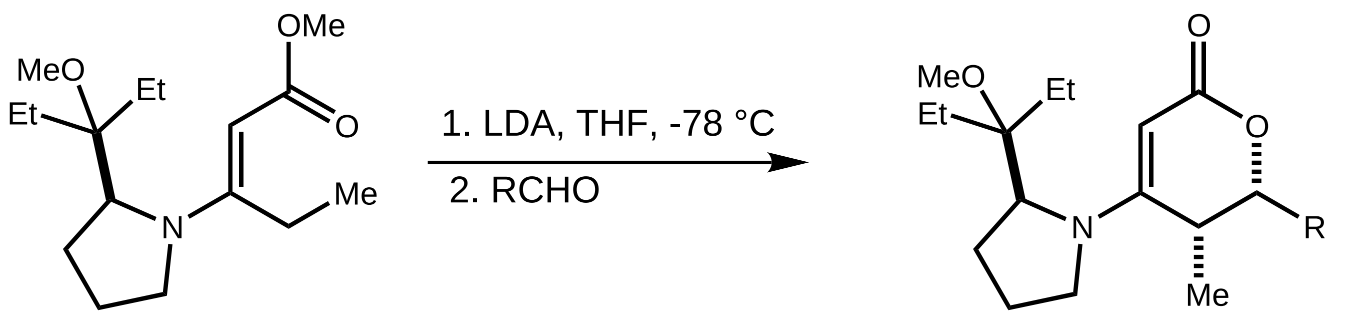


Schlessinger, *J. Org. Chem.* **1996**, *61*, 3226.
Williard and Schlessinger, *J. Am. Chem. Soc.* **1988**, *110*, 7901.

Diastereoselective Vinylogous Aldol Reactions

Schlessinger's Chiral Dienolate - Second Generation

• Substrate Generality

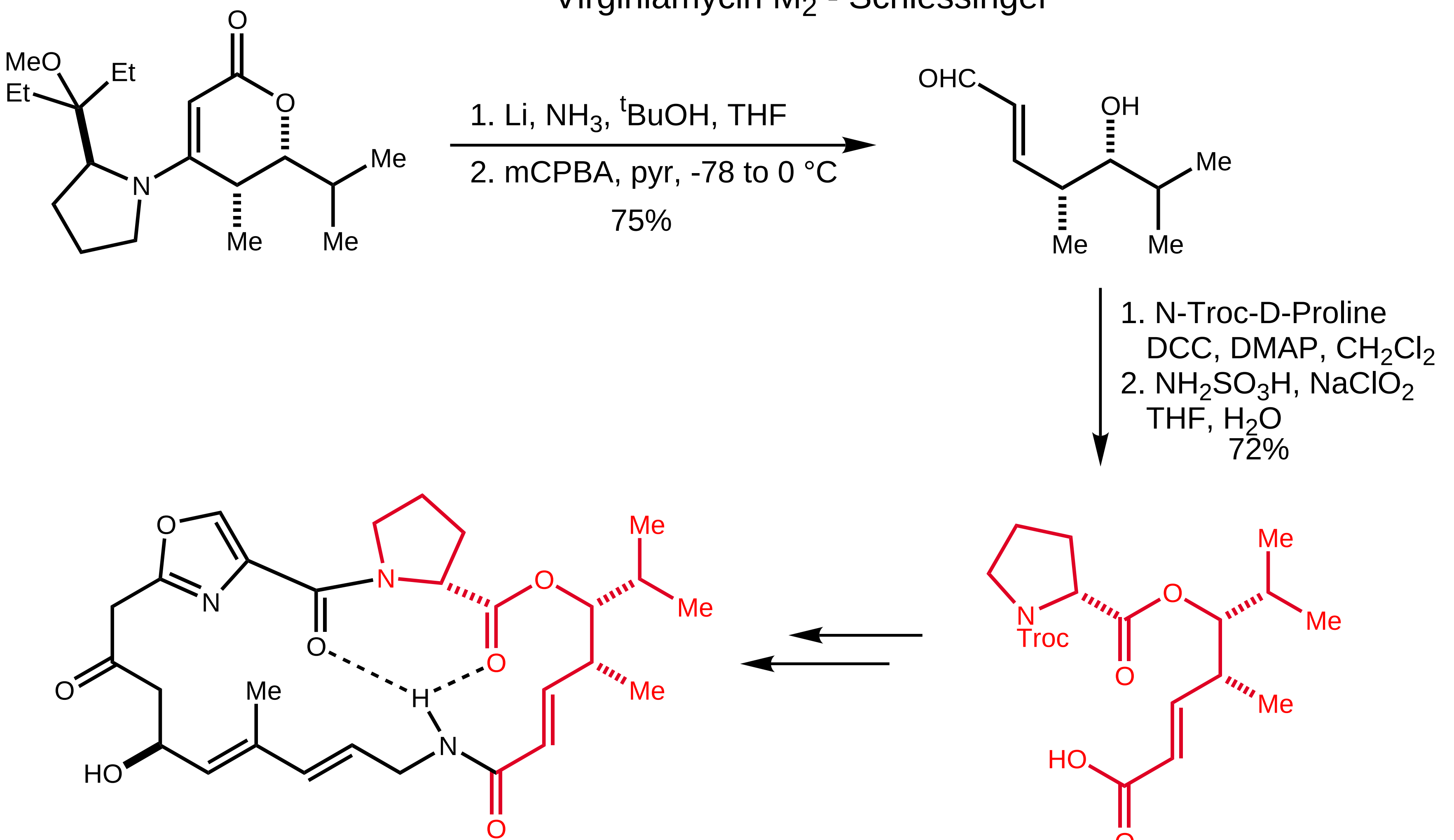


R	Yield (%)	dr
^{t}Bu	83	99:1
Cy	83	99:1
^{n}Pr	57	97:3
(E)-CH=CHMe	74	99:1
(E)-CH=CHPh	74	98:2
(E)-CH=CHSnBu_3	68	99:1

Schlessinger, *J. Org. Chem.* **1996**, *61*, 3226.

Diastereoselective Vinylogous Aldol Reactions
Synthetic Applications

Virginiamycin M_2 - Schlessinger

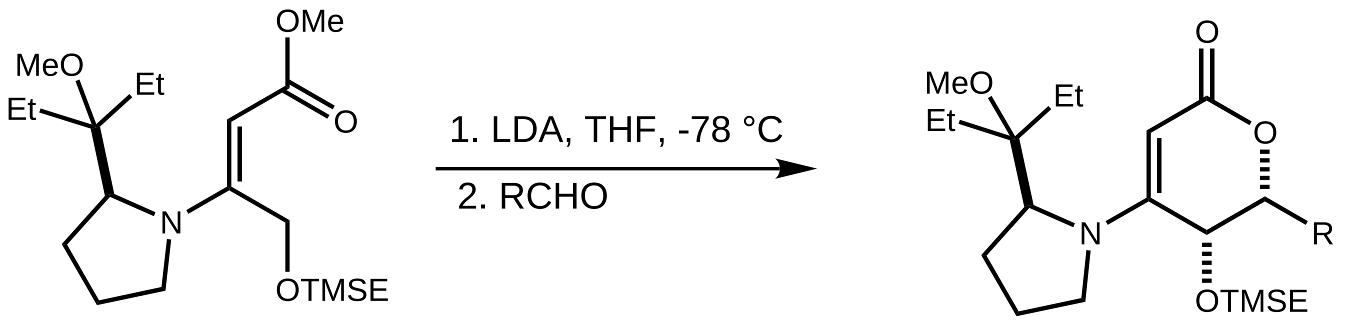


Virginiamycin M_2

Schlessinger, *J. Am. Chem. Soc.* **1996**, ***118***, 3301.

Diastereoselective Vinylogous Aldol Reactions

Schlessinger's Chiral Dienolate - Effect of Oxygenation

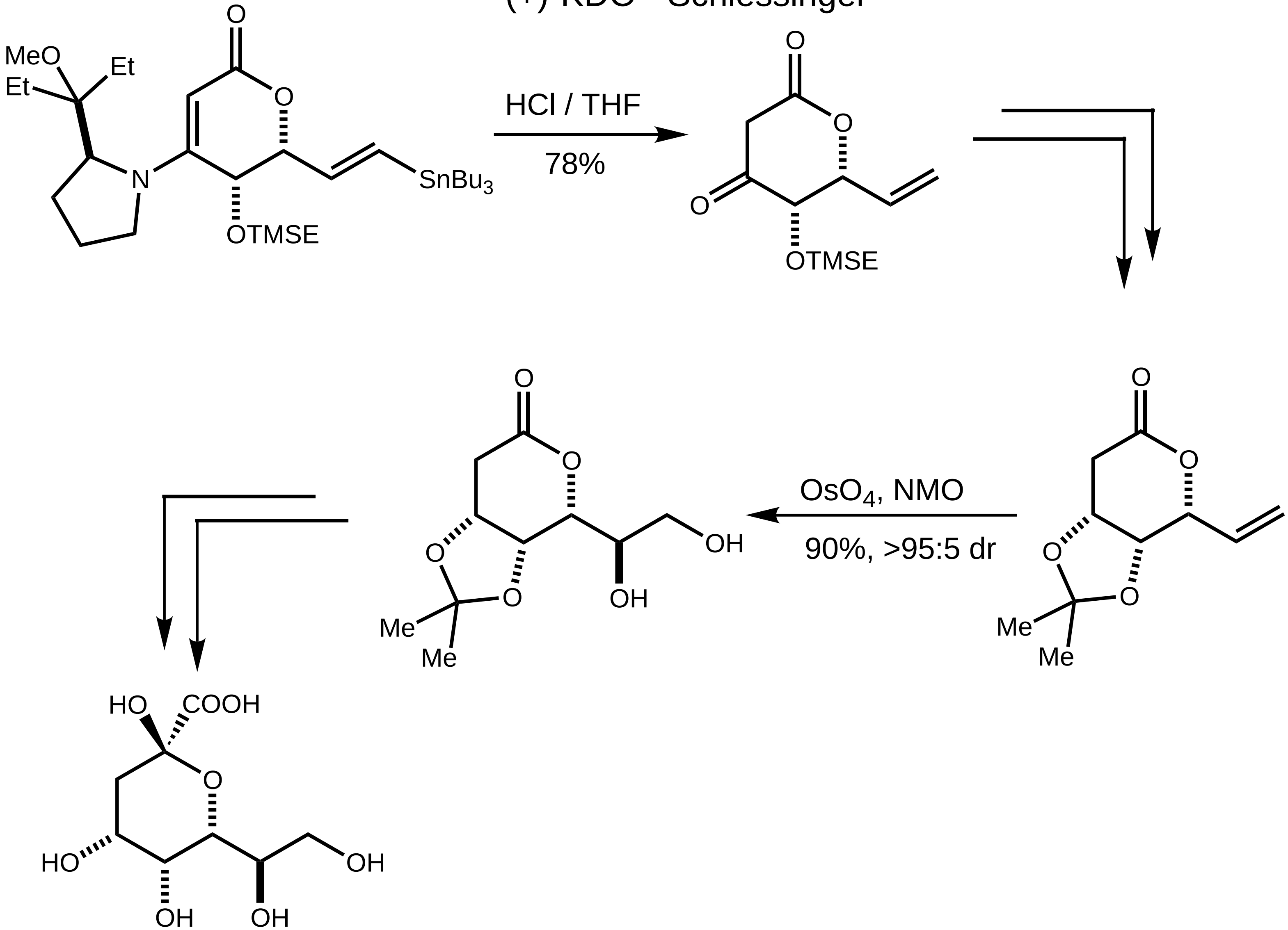


R	Yield (%)	dr
^{t}Bu	93	98:2
^{i}Pr	73	98:2
Ph	84	99:1
(E)-CH=CHEt	78	98:2
(E)-CH=CHSnBu$_3$	76	98:2
(Z)-CH=CHSnBu$_3$	75	99:1

Schlessinger, *J. Org. Chem.*. **1998**, *63*, 9089.

Diastereoselective Vinylogous Aldol Reactions
Synthetic Applications

(+)-KDO - Schlessinger



(+)-KDO

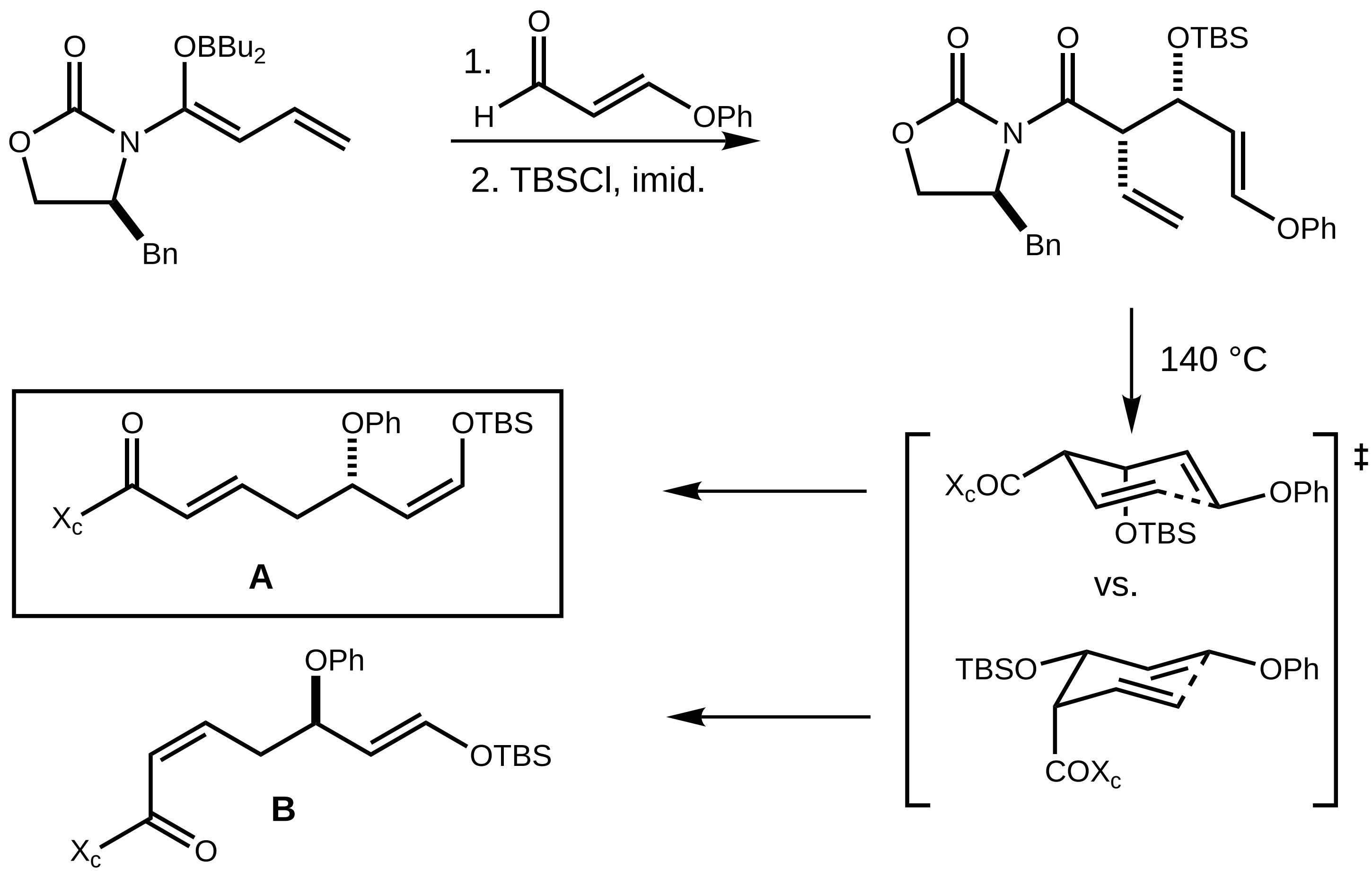
Schlessinger, *J. Org. Chem.* **1998**, *63*, 9089.

Diastereoselective Vinylogous Aldol Reactions

α-alkylation / Cope rearrangement strategy

• Problem: imide auxiliaries give α-alkyation with dienolates

• Solution: aldol followed by siloxy-Cope rearrangement

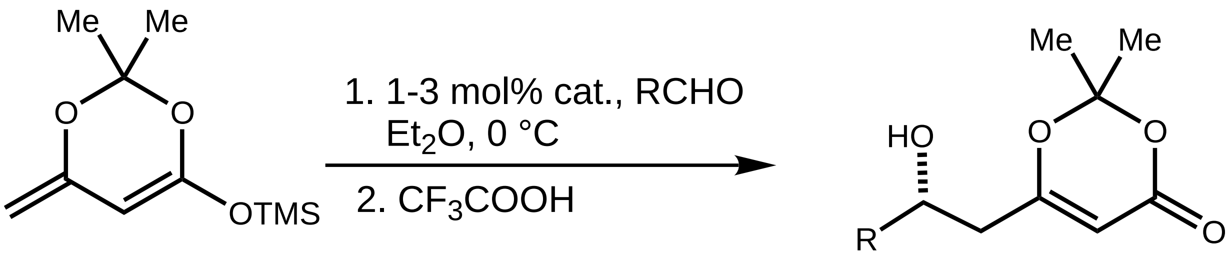


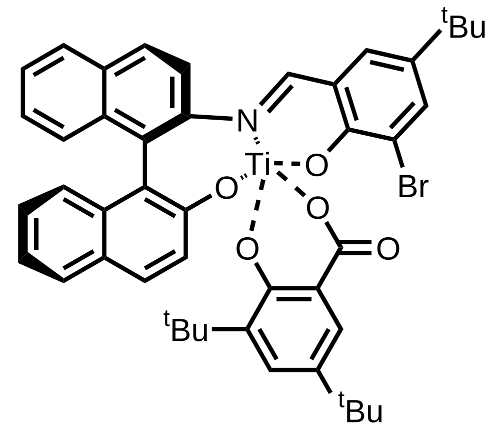
86%, 31:1 **A** : **B**

Black, *Tetrahedron Lett.* **1996**, *37*, 4471.

Catalytic Asymmetric Vinylogous Aldol Reactions

Carreira Ti(IV) Catalyst





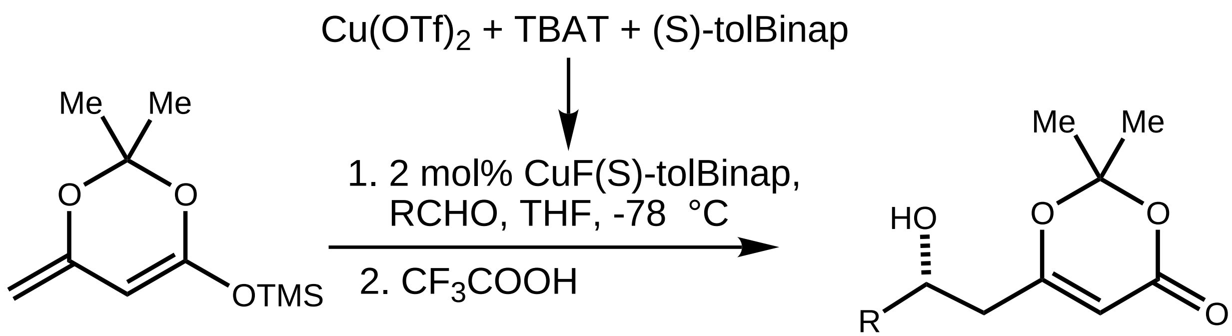
catalyst

Aldehdye	Yield (%)	ee (%)
$^{i}Pr_3Si$–C≡C–CHO	86	91
PhCHO	83	84
Ph–CH=CH–CHO	88	92
Ph–CH$_2$–CH$_2$–CHO	97	80
Bu_3Sn–CH=CH–CHO	79	92

Carreira, *J. Am. Chem. Soc.* **1995**, *117*, 12360.
Carreira, *J. Am. Chem. Soc.* **1994**, *116*, 8837.

Catalytic Asymmetric Vinylogous Aldol Reactions

Carreira Copper Catalyst

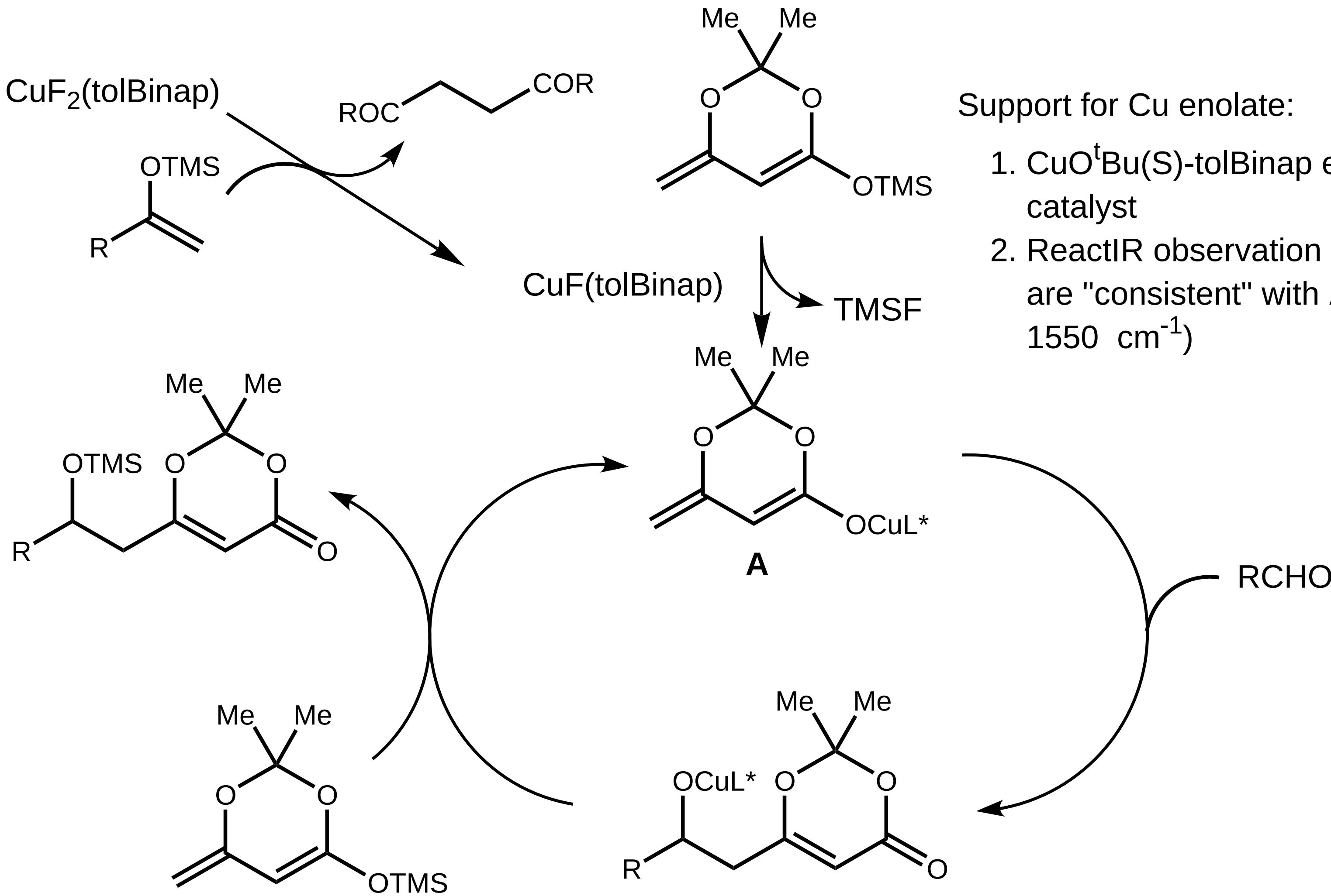


Aldehdye	Yield (%)	ee (%)
PhCHO	92	94
furfural	91	94
p-OMePhCHO	93	94
(E)-PhCH=CHCHO	83	85
(E)-MeCH=CHCHO	48	91

Carreira, *J. Am. Chem. Soc.* **1998**, *120*, 837.

Catalytic Asymmetric Vinylogous Aldol Reactions

Carreira Copper Catalyst - Mechanistic Insights



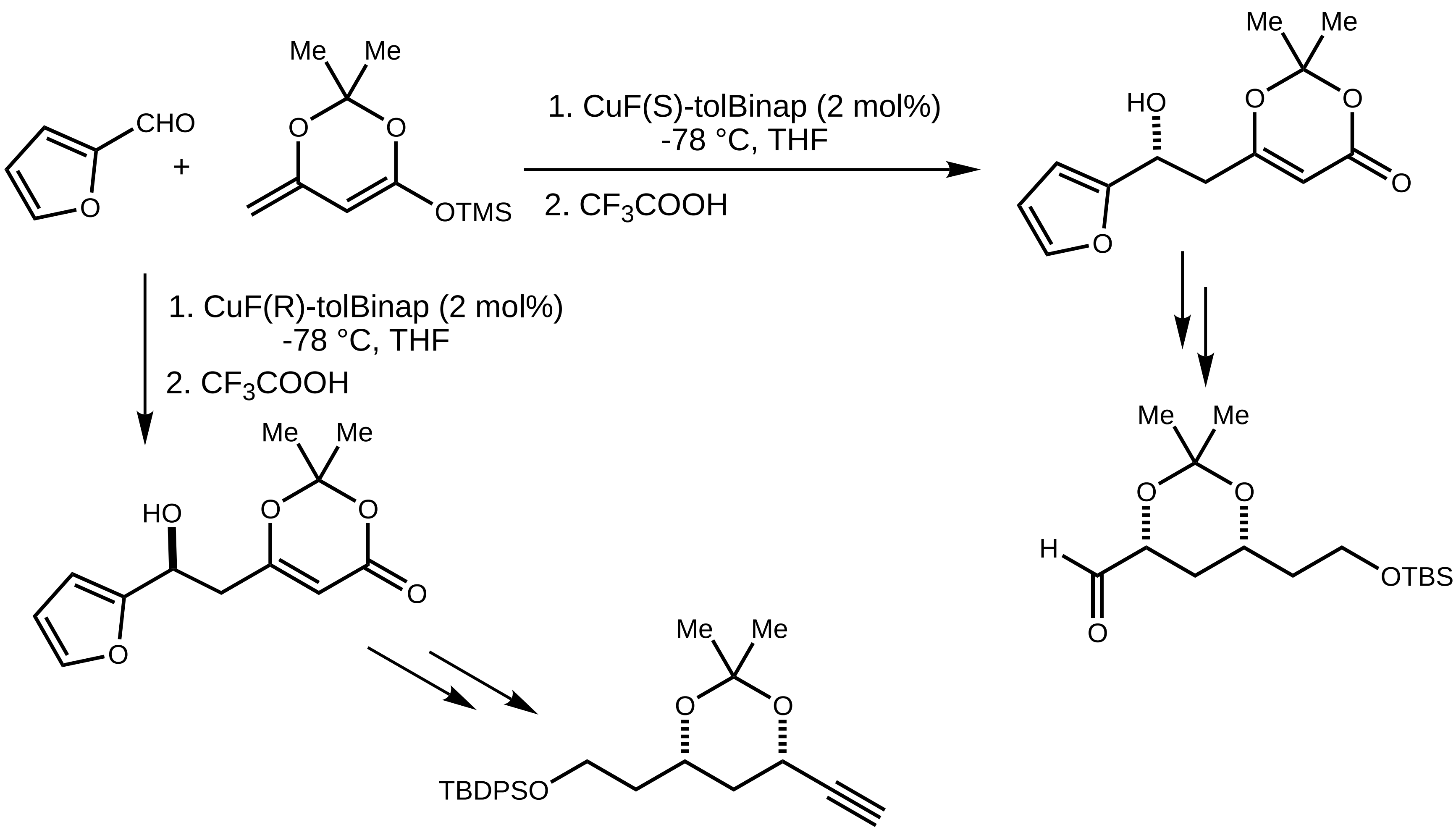
Support for Cu enolate:

1. CuO^tBu(S)-tolBinap equally good catalyst
2. ReactIR observation of signals which are "consistent" with **A** (1690 and 1550 cm^{-1})

Carreira, *Angew. Chem. Int. Ed.* **1998**, *37*, 3124.

Carreira's CAVM - Synthetic Applications

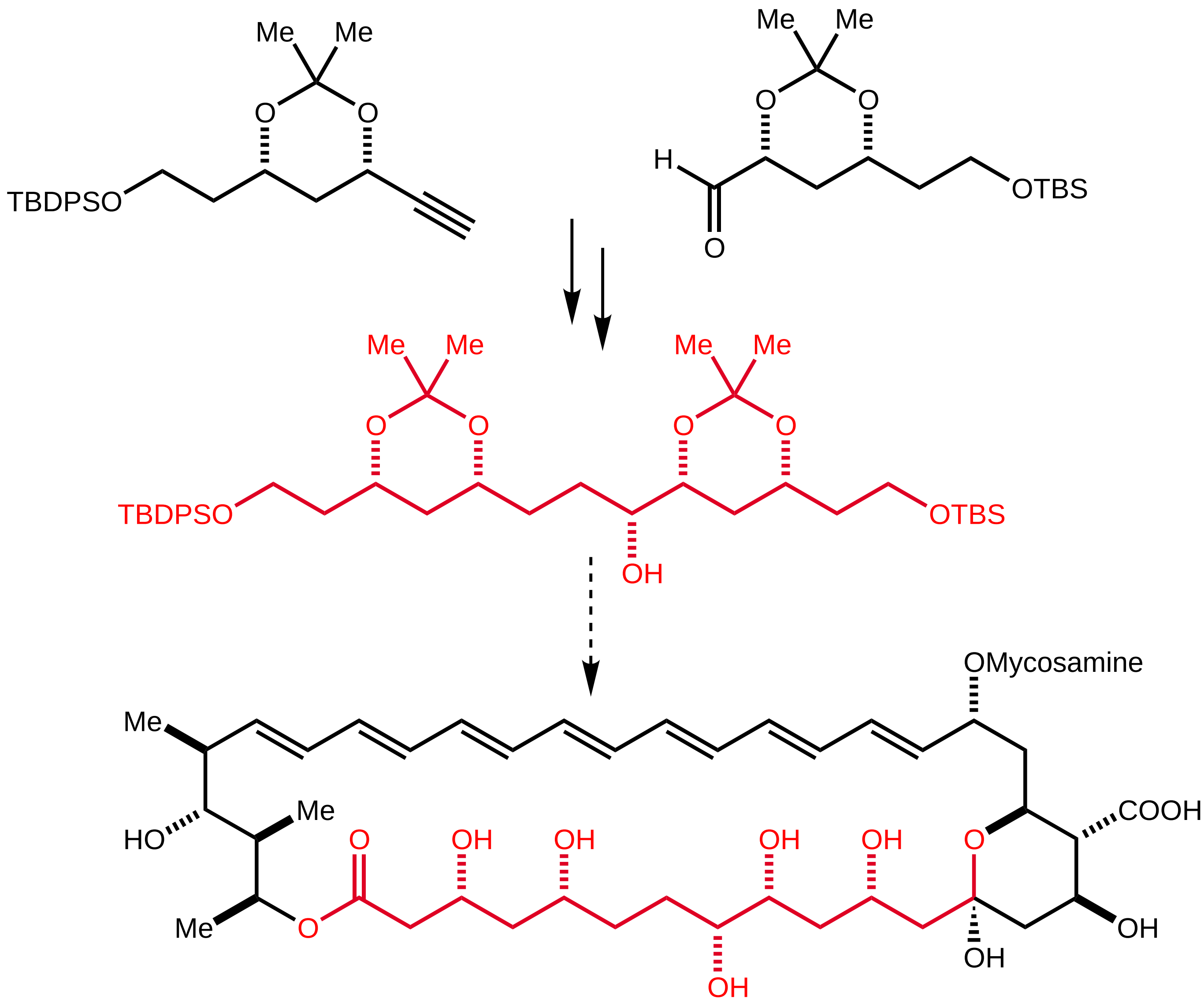
Towards Amphotericin - Carreira



Carreira, *Tetrahedron Lett.* **1998**, *39*, 7013.

Carreira's CAVM - Synthetic Applications

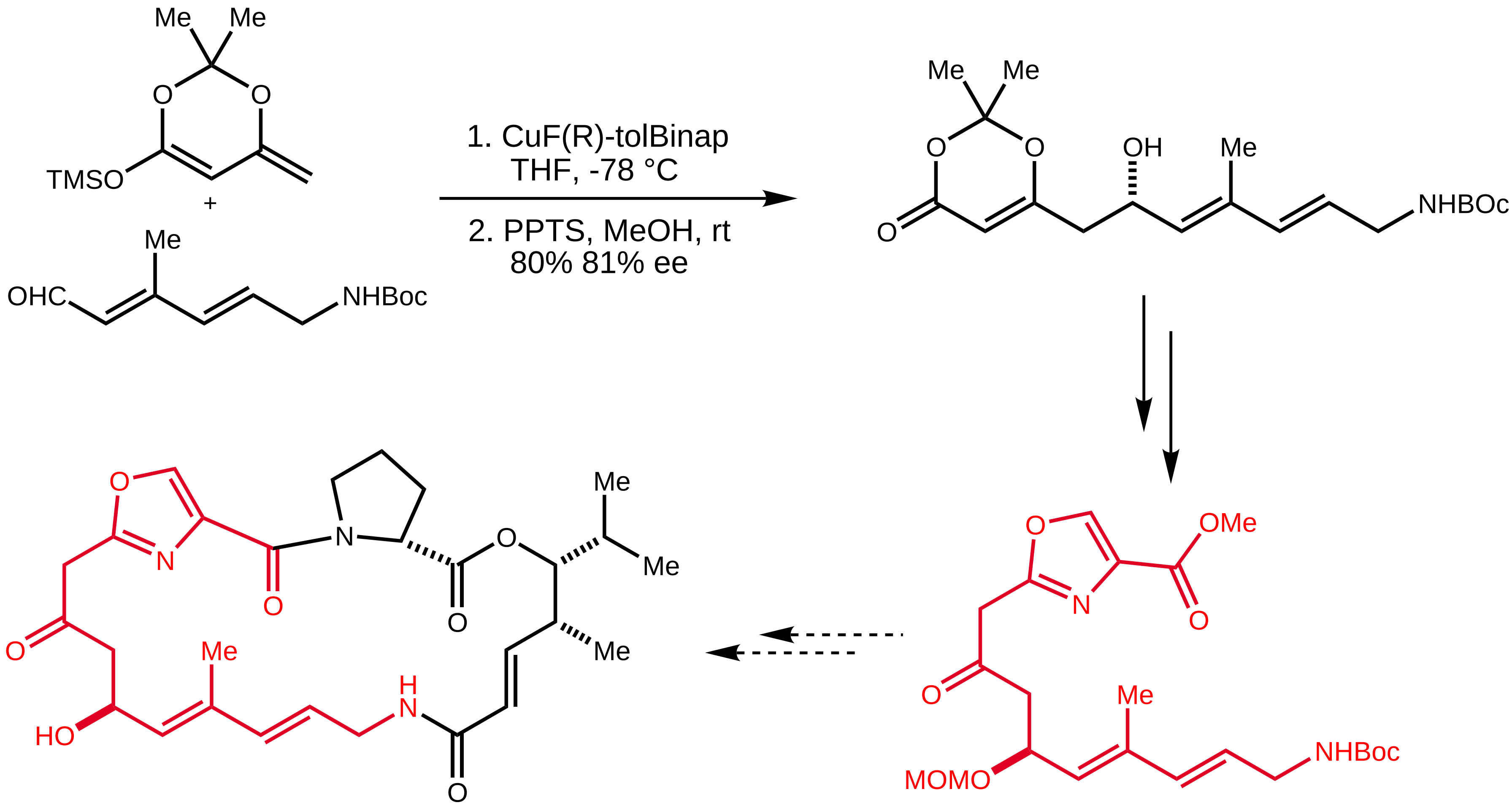
Towards Amphotericin - Carreira



Carreira, *Tetrahedron Lett.* **1998**, *39*, 7013.

Carreira's CAVM - Synthetic Applications

Virginiamycin M_2 - Campagne

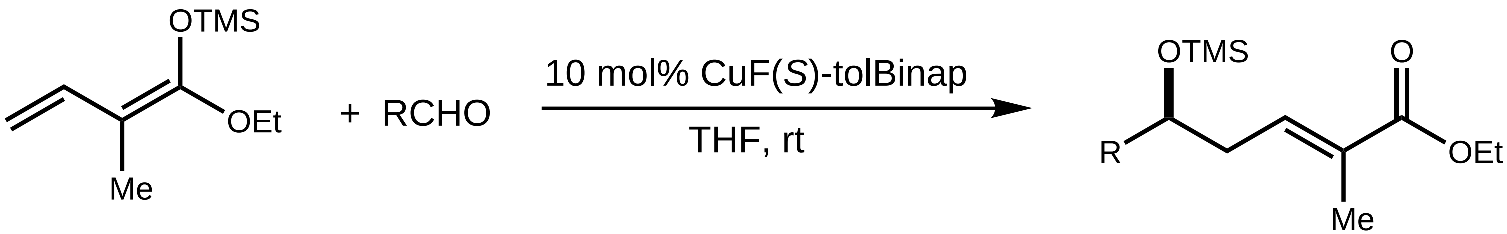


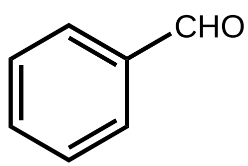
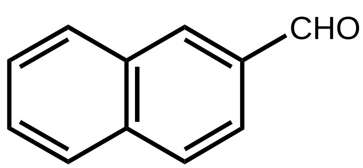
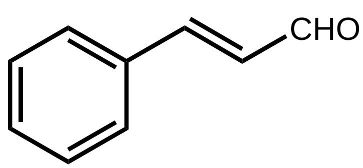
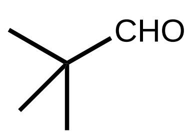
Virginiamycin M_2

Campagne, *Tetrahedron Lett.* **2001**, *42*, 5195.

Catalytic Asymmetric Vinylogous Aldol Reactions

Carreira's Catalyst for Other Dienolates - Campagne

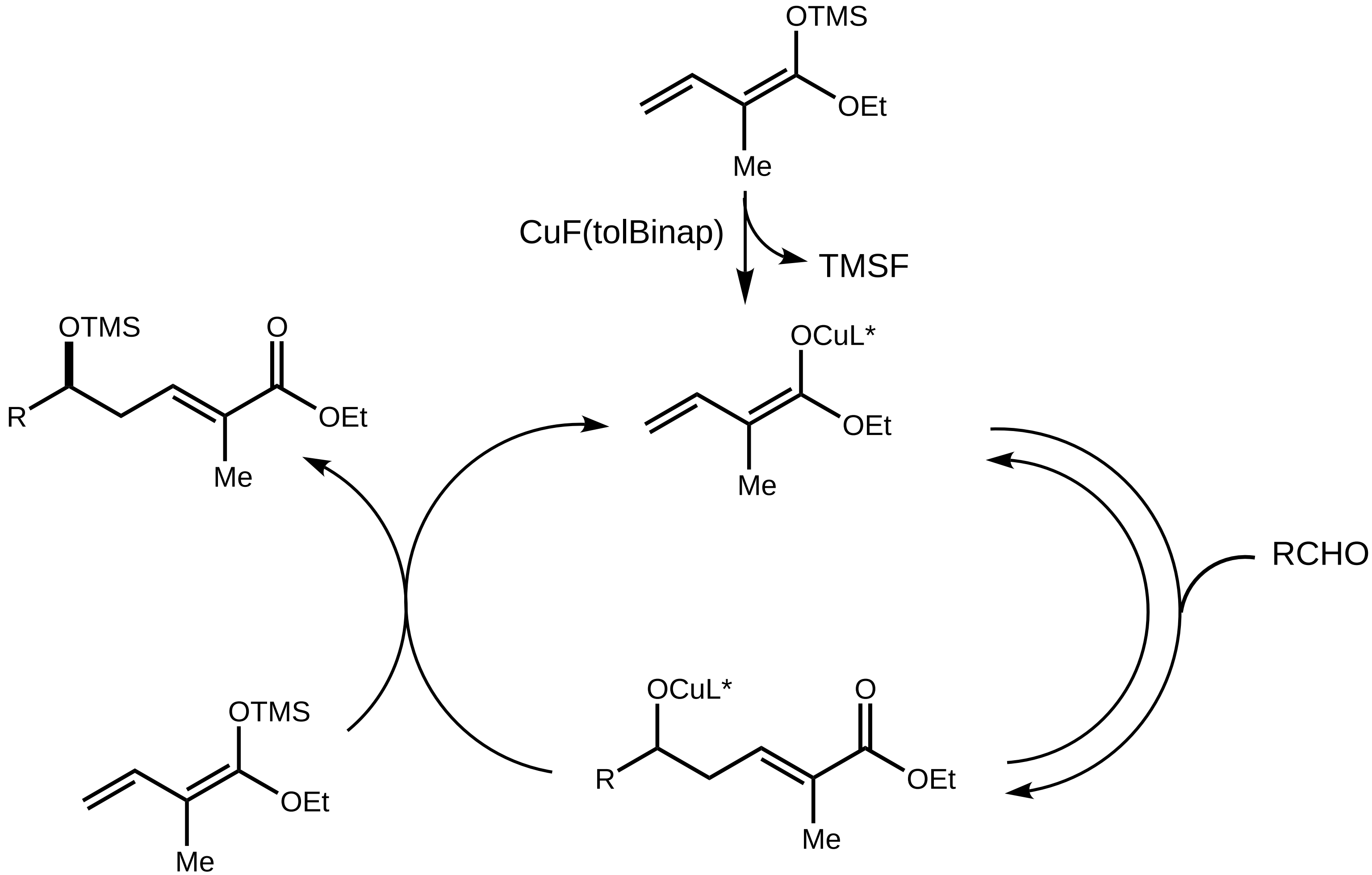


Aldehyde	Yield (%)	ee (%)
	80	70
	70	48
	35	56
	68	77

Campagne, *Tetrahderon Lett.* **1999**, *40*, 5507.

Catalytic Asymmetric Vinylogous Aldol Reactions

Carreira's Catalyst for Other Dienolates - Campagne

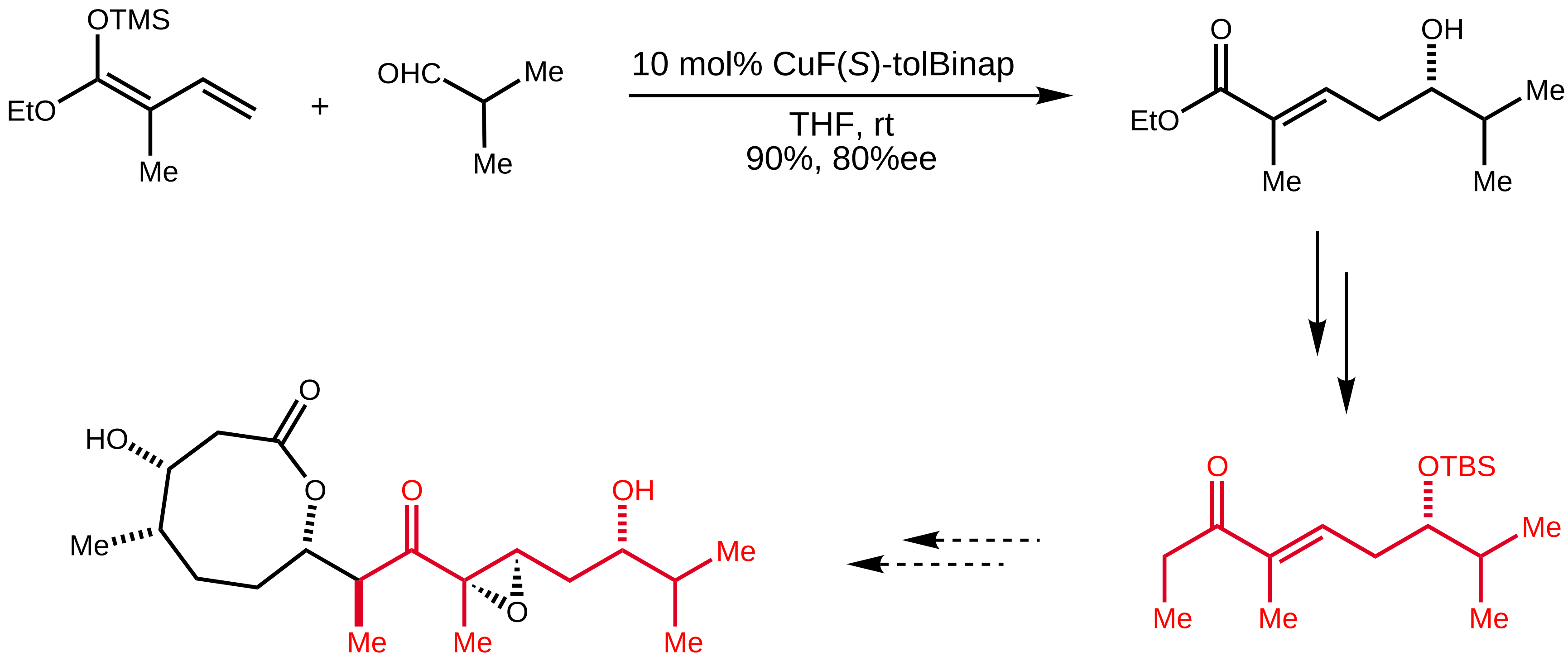


Is Silylation Important in Selectivity???

Campagne, *J. Org. Chem.* **2001**, *66*, 4295.

Campagne's CAVM - Synthetic Applications

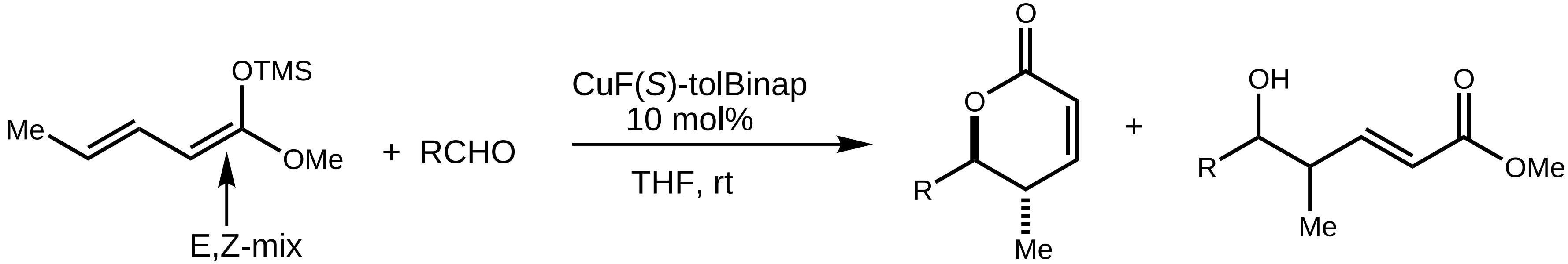
Octalactin A - Campagne



Campagne, *Synlett* **2000**, 221.

Catalytic Asymmetric Vinylogous Aldol Reactions

Synthesis of Lactones with Other Silyl Dienolates - Campagne



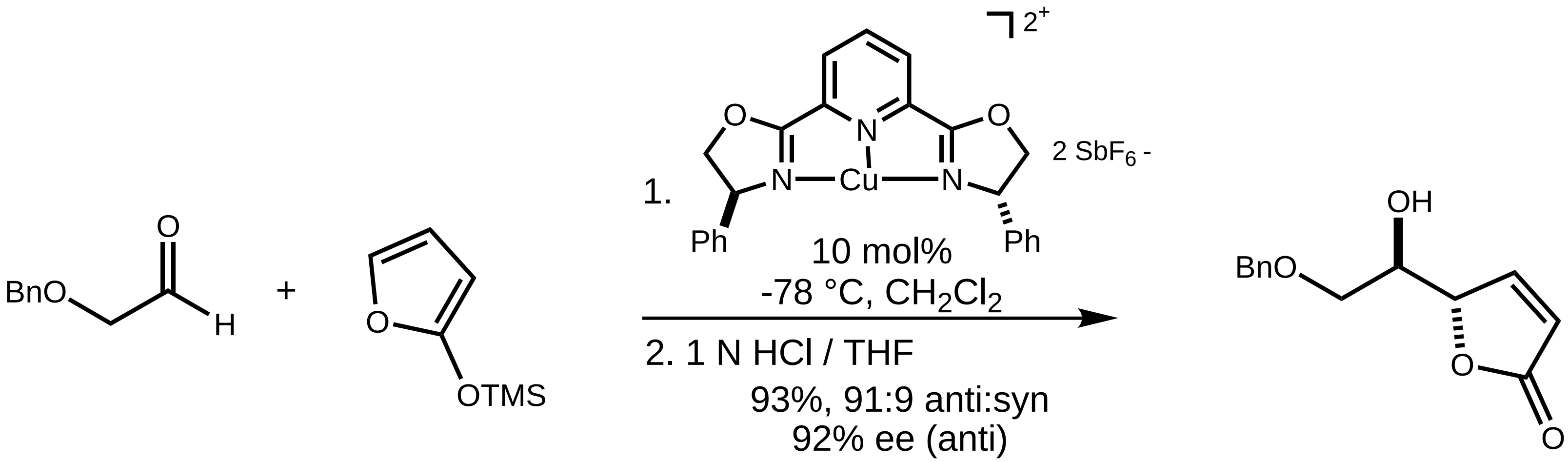
1 **2**

Aldehyde	Yield (%) (**1** + **2**)	ratio (**1**/**2**)	ee (%) of **1**
Benzaldehyde	85	86/14	87
2-napthaldehyde	95	80/20	85
2,3-dimethoxybenzaldehyde	87	81/19	91
2-furaldehdye	60	50/50	86
(E)-cinnamaldehyde	60	70/30	82
isobutyraldehyde	95	64/36	91

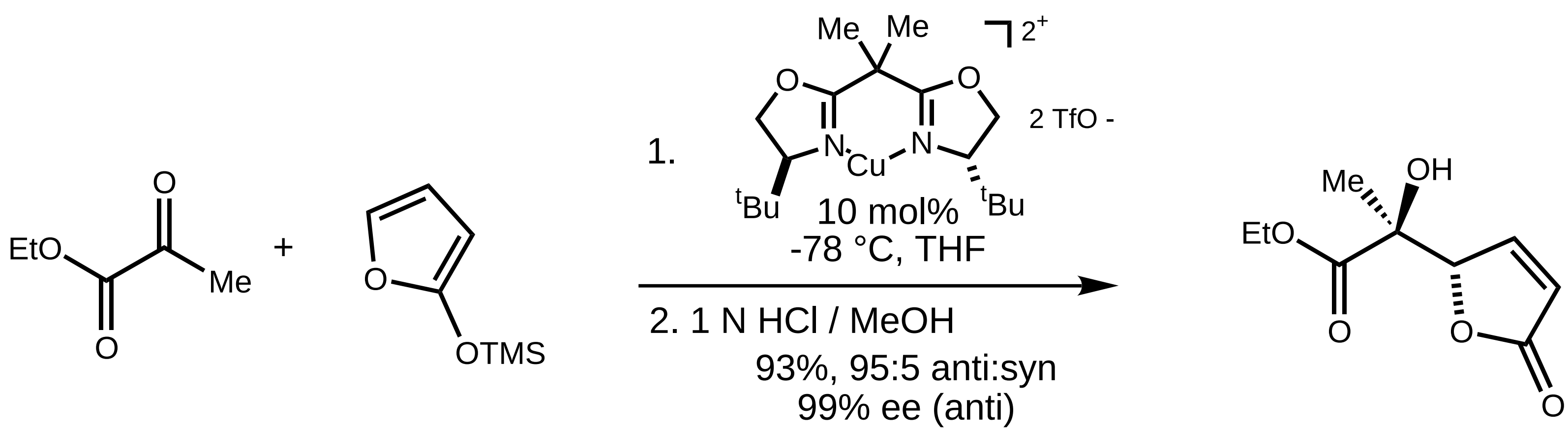
Campagne, *Org. Lett.* **2001**, *3*, 3807.

Catalytic Asymmetric Vinylogous Aldol Reactions

Evans' Cu(II)box and pybox Catalysts



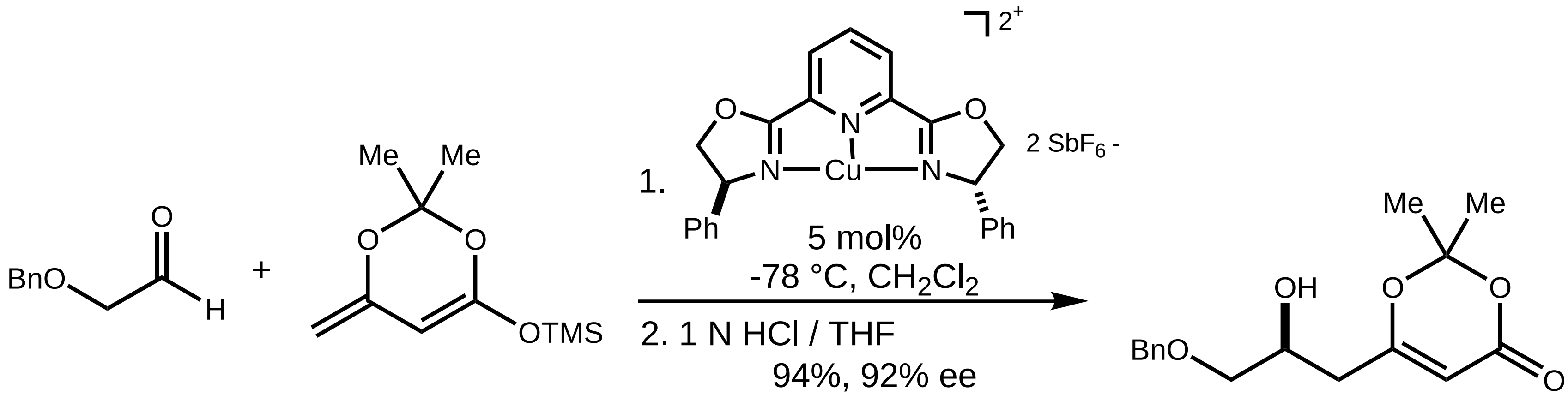
• addition of CF_3CH_2OH makes reaction amenable to large scale

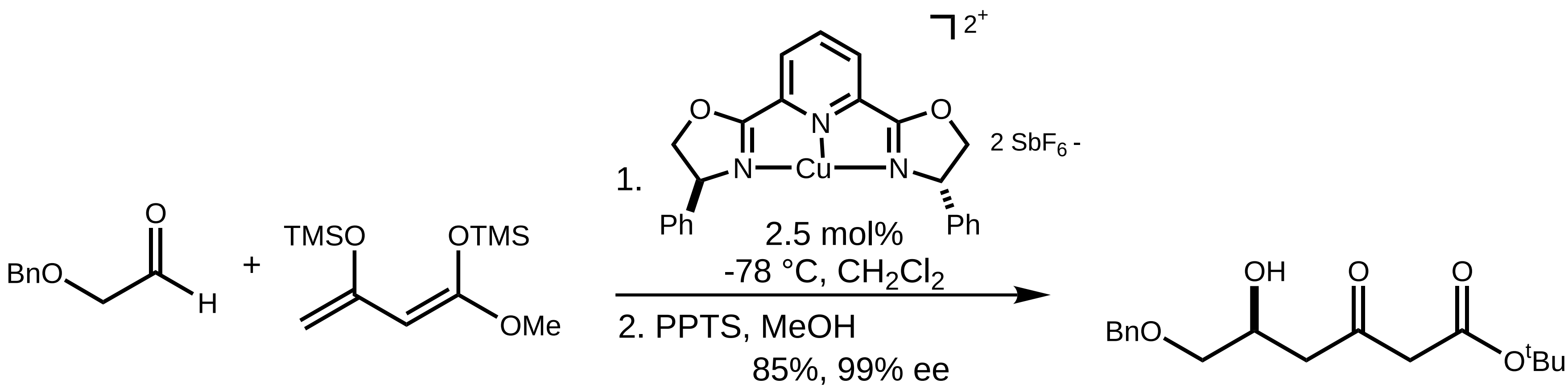


Evans, *J. Am. Chem. Soc.* **1999**, *121*, 669.
Evans, *J. Am. Chem. Soc.* **1999**, *121*, 686.

Catalytic Asymmetric Vinylogous Aldol Reactions

Evans' Cu(II)box and pybox Catalysts



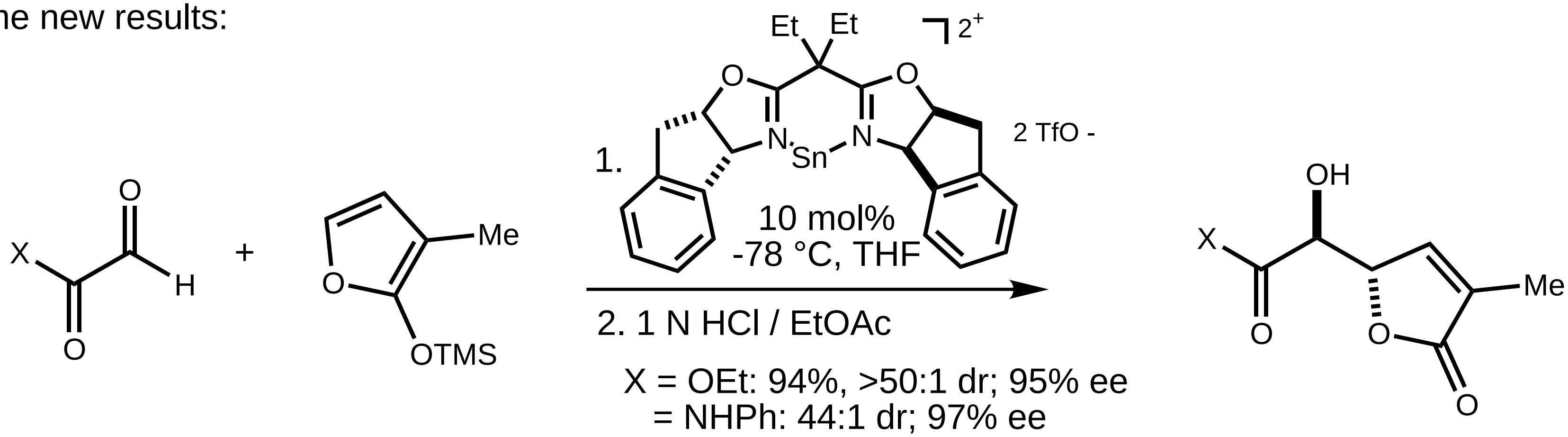


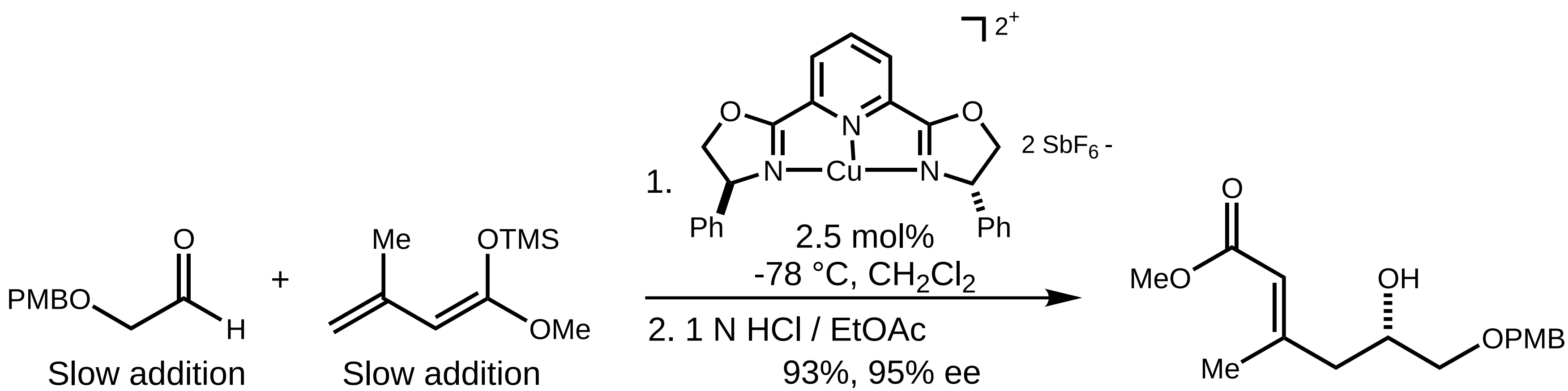
Evans, *J. Am. Chem. Soc.* **1999**, *121*, 669.

Catalytic Asymmetric Vinylogous Aldol Reactions

Evans' Sn(II)box and Cu(II)pybox Catalysts

• some new results:

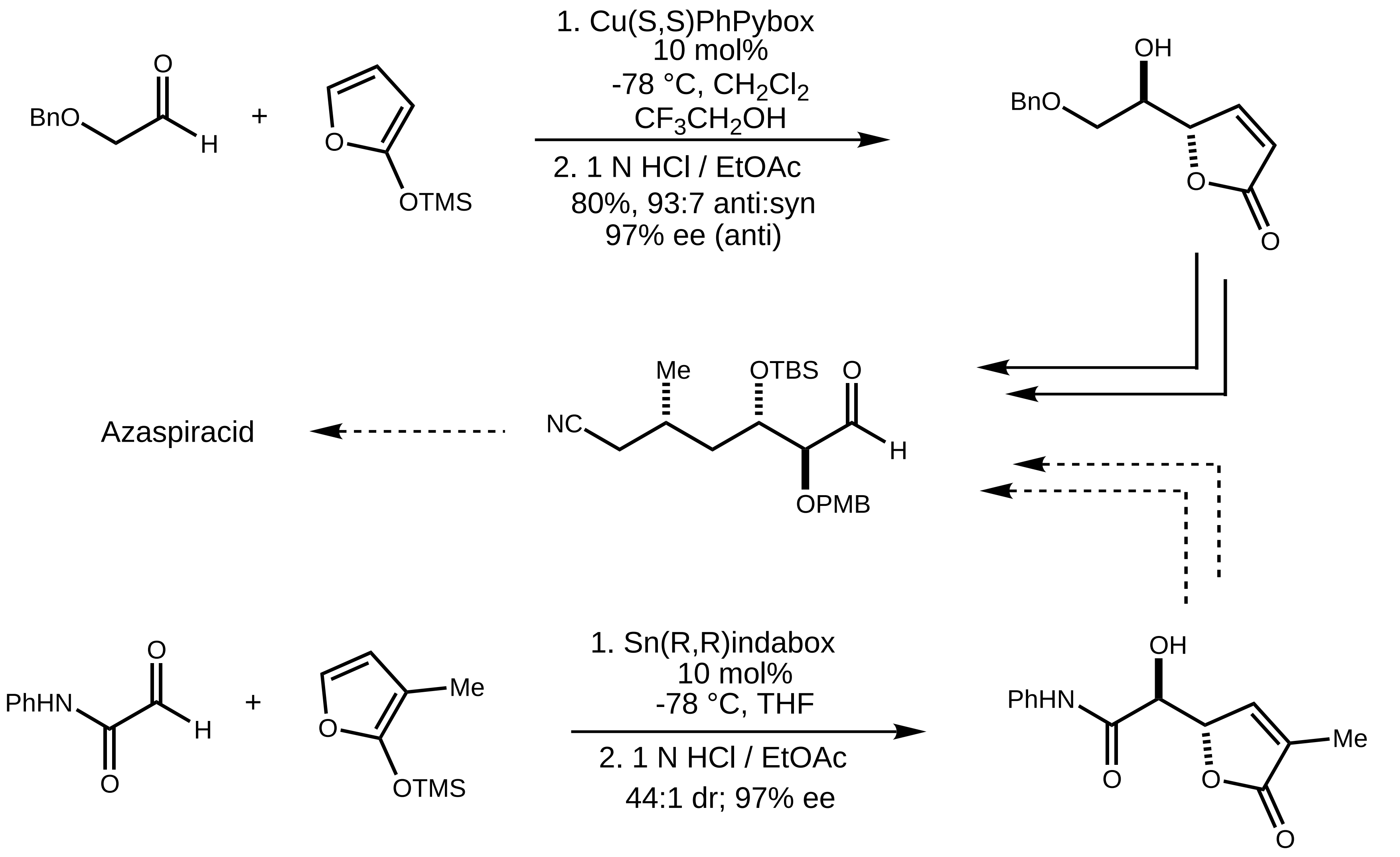




Evans, Favor, Beauchemin, Hu and Burch; unpublished results

Evans' CAVM - Synthetic Applications

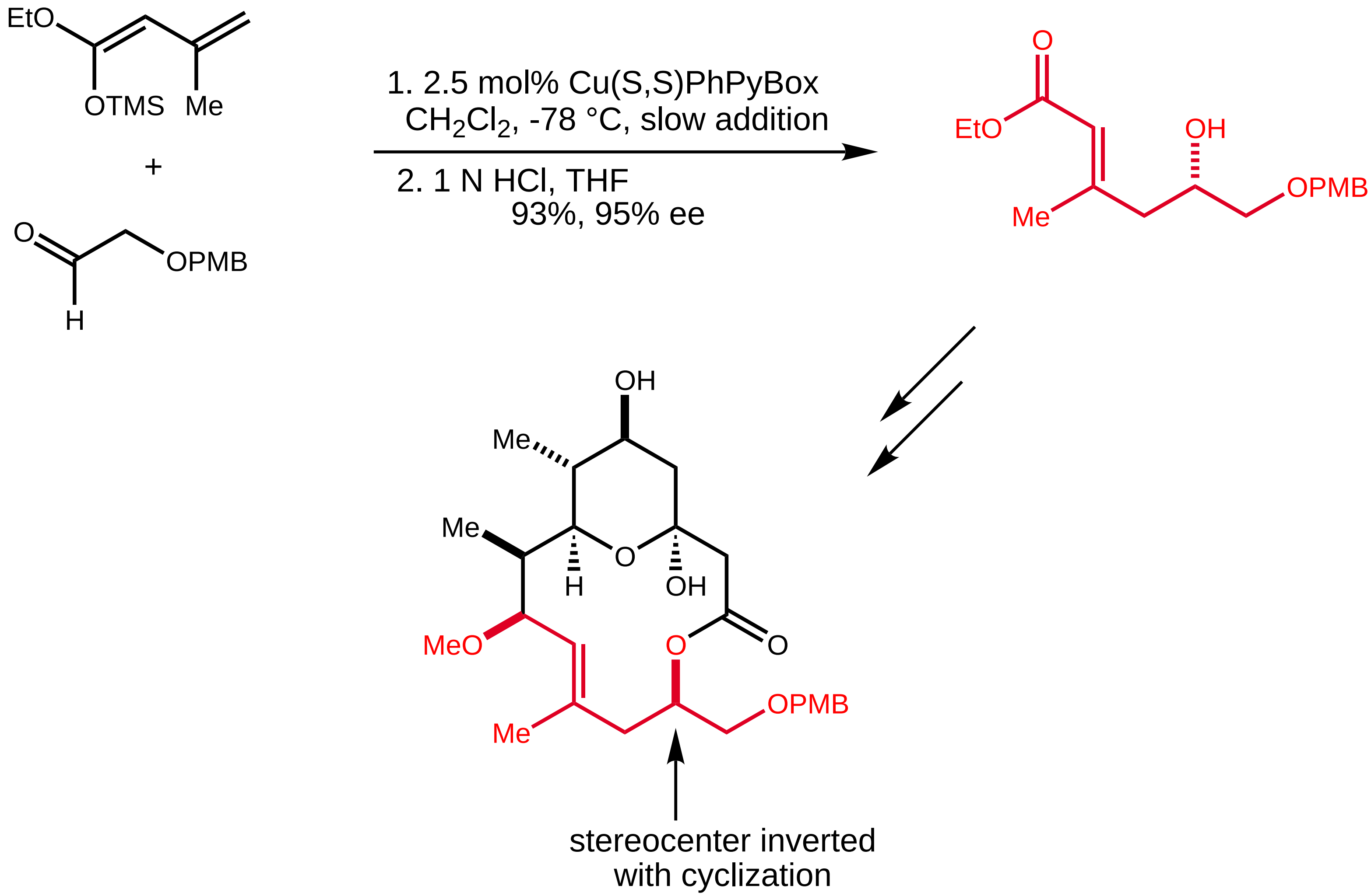
Azaspiracid - Evans



Evans, Dunn and Beauchemin; unpublished results

Evans' CAVM - Synthetic Applications

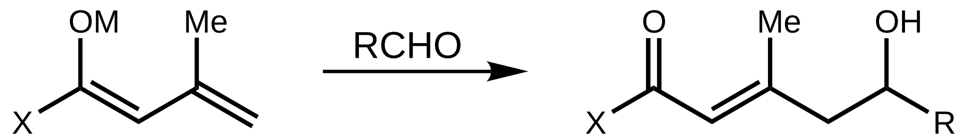
Callipeltoside - Evans



Evans, Hu and Burch; unpublished results

The Vinylogous Aldol Reaction

A Summary



• in general, metal dienolates favor α-alkylation under kinetic conditions and γ-alkylation under thermodynamic conditions

• exception: Yamamoto's ATPH-mediated vinylogous aldol conditions

• in general, siloxyfurans vinylogous aldol favor syn adducts under lewis acid catalysis and anti adducts with "naked" dienolates

• exception: Evans' Cu(II) catalyzed additions of siloxyfurans

• Schlessinger's proline-derived auxilliary useful for diastereoselective vinylogous aldol reacitons

• Carreira's Ti(IV) and Cu(I) catalysts and Evans' Cu(II) and Sn(II) catalysts useful for enantioselective vinylogous aldol reactions of β-oxygenated dienolates; non-oxygenated cases also showing promise