Massachusetts Institute of Technology

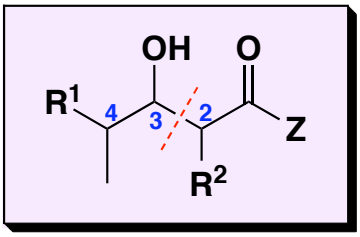
Organic Chemistry 5.512

April 27, 2007
Prof. Rick L. Danheiser

Unit 6

Stereocontrolled Aldol Reactions

- ★ Overview of the Stereochemistry of the Aldol Reaction and Substrate Control
- ★ Reagent Control: Chiral Auxiliary Strategies
- ★ Reagent Control: Chiral Controller Strategies
- ★ Reagent Control: Chiral Lewis Acid Catalyzed Aldol Reactions

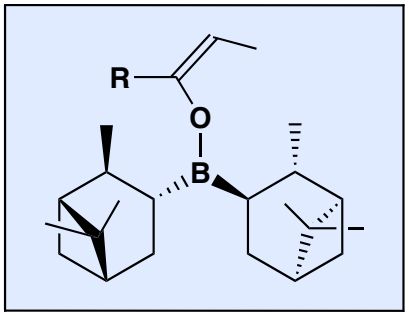


The Aldol Retron

Review:
"Modern Aldol Methods for the Total Synthesis of Polyketides"
Schetter, B.; Mahrwald, R.
Angew. Chem. Int. Ed. **2006**, *45*, 7506

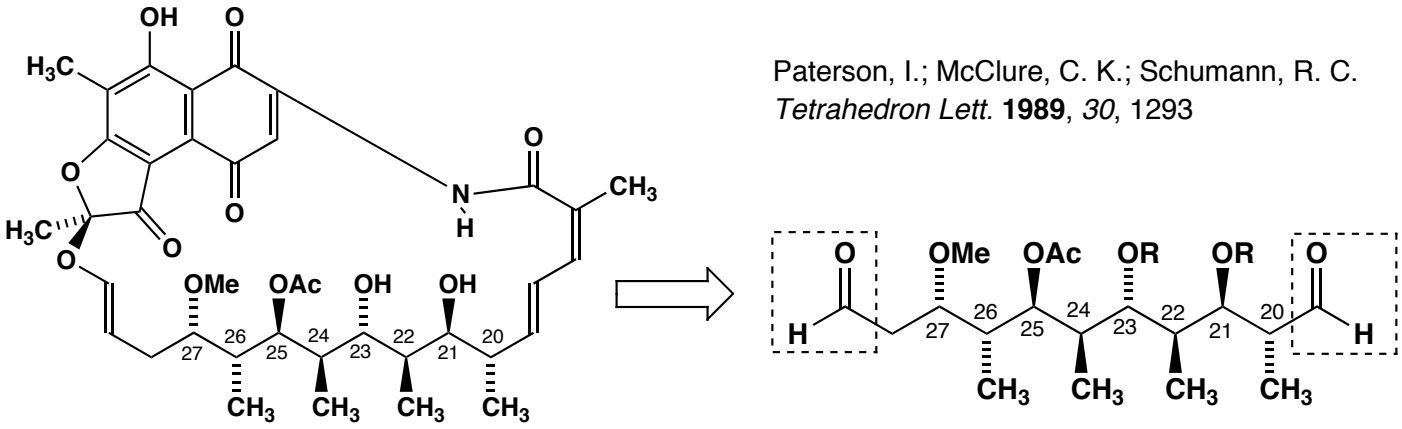
III. Chiral Controller Strategies

(1) Paterson Boron Enolates



Ian Paterson
Cambridge University

Case Study: C_{19}-C_{27} Segment of Rifamycin S



Paterson, I.; McClure, C. K.; Schumann, R. C. *Tetrahedron Lett.* **1989**, *30*, 1293

(2) Enamine Aldol Reactions

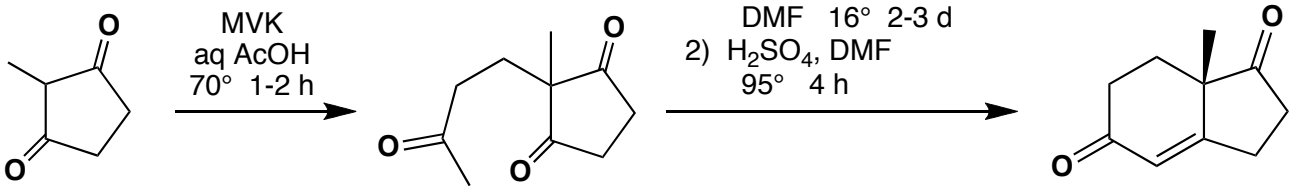
Reviews

(1) "Proline-Catalyzed Asymmetric Reactions" List, B. *Tetrahedron* **2002**, *58*, 5573

(2) "Enamine Catalysis Is a Powerful Strategy for the Catalytic Generation and Use of Carbanion Equivalents" List, B. *Acc. Chem. Res.* **2004**, *37*, 548

(3) "Enamine-Based Organocatalysis with Proline and Diamines" Notz, W.; Tanaka, F.; Barbas, C. F. *Acc. Chem. Res.* **2004**, *37*, 580

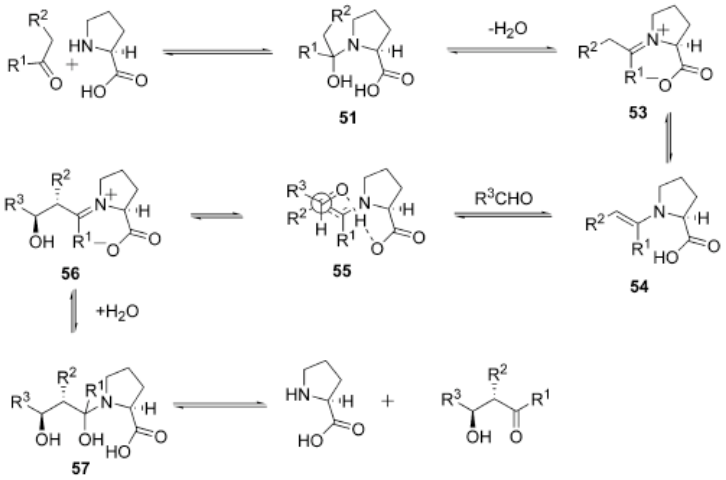
Hajos-Parrish-Eder-Sauer-Wiechert Reaction

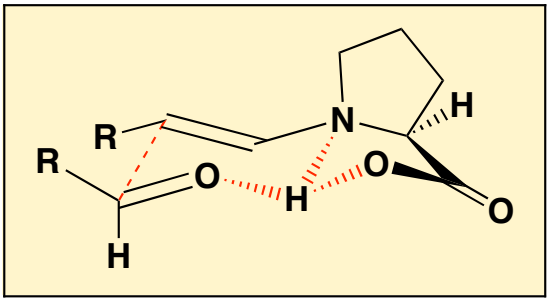


Hajos, Z. G.; Parrish, D. R. *Org. Synth. Coll. Vol.* **7**, 363

70-76%
92-94% enantiomeric purity

Scheme 8. Proposed Mechanism of the Proline-Catalyzed Intermolecular Aldol Reaction





IV. Chiral Lewis Acid Strategies

(1) Carreira Chiral Ti Catalyst

Carreira, E. M.; Singer, R. A.; Lee, W. *J. Am. Chem. Soc.* **1994,** *116*, 8837

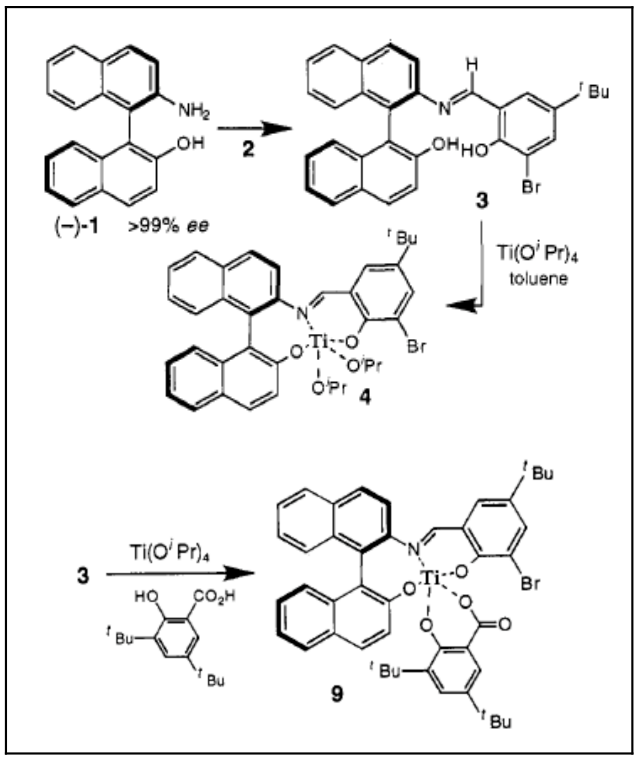
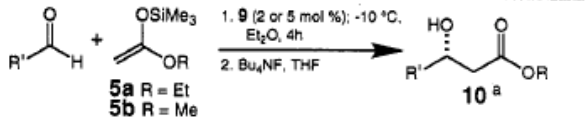


Table 1. Catalytic Asymmetric Aldol Additions of Alkyl Aceate Ketene Acetal[a,c]



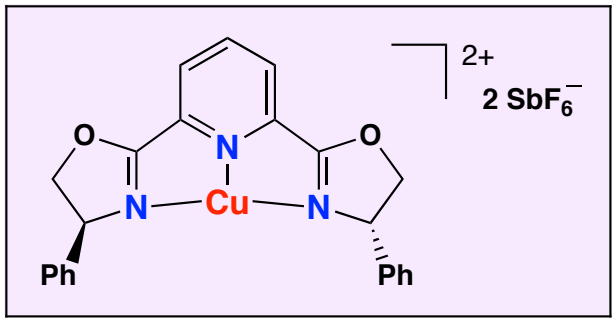
Entry	Aldehyde	ee: R = Et [d]	ee: R = Me [e]
1		92%	97%
2		88%	95%
3		93%	97%
4		89%	94%
5	$C_6H_{11}CHO$	94%	95%
6	PhCHO	93%	96%

[a] Absolute configuration was determined by reduction to the known 1,3-diols.[1b] [b] Yields for two steps (addition and desilylation) range from 72 to 98%. [c] For each entry, the *ee* was determined by preparation of the derived (*S*)-MTPA ester and analysis by ^{1}H NMR spectroscopy. [d] 5 mol % catalyst used. [e] 2 mol % catalyst used.

(2) Evans Copper BOX and PYBOX Catalysts

D. A. Evans et al. *J. Am. Chem. Soc.* **1999,** *121*, 669 and 686. **Reviewed** in: J. S. Johnson and D. A. Nicewicz In *Modern Aldol Reactions,* Vol 2; Mahrwald, R., Ed.; Wiley-VCH, 2004; pp 69-103.

Addition to (Benzyloxy)acetaldehyde



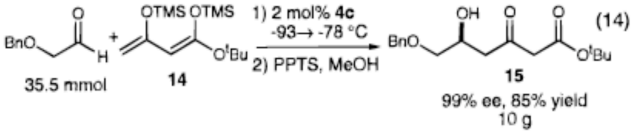
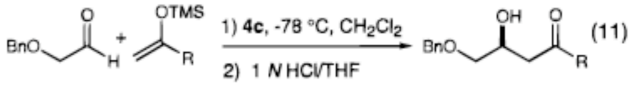


Table 4. Catalyzed Benzyloxyacetaldehyde Aldol Reaction with Representative Acetate Silylketene Acetals (eq 12)[a]

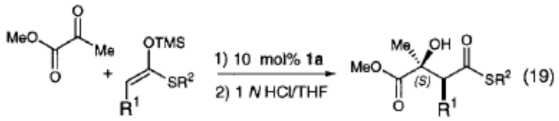


entry	R	catalyst loading	time, h	% ee[b]	% yield
1	S^{t}Bu	0.5 mol%	12-24	99	99
2	SEt	0.5 mol%	12-24	98	95
3	OEt	0.5 mol%	12	98	99[c]

[a]All reactions were 0.2 M in substrate. [b]Enantiomeric excess determined by HPLC using a Chiralcel OD-H column. Absolute configuration determined by independent synthesis (see experimental). [c]The silyl ether was cleaved with TBAF/THF to prevent retroaldol reaction.

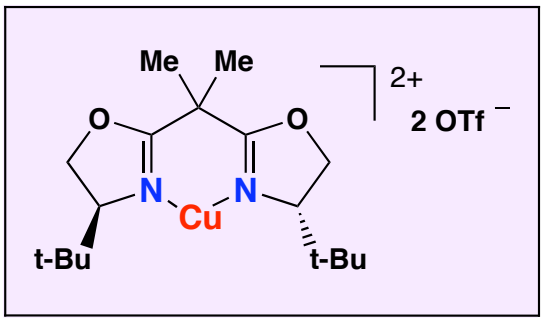
Addition to Pyruvates

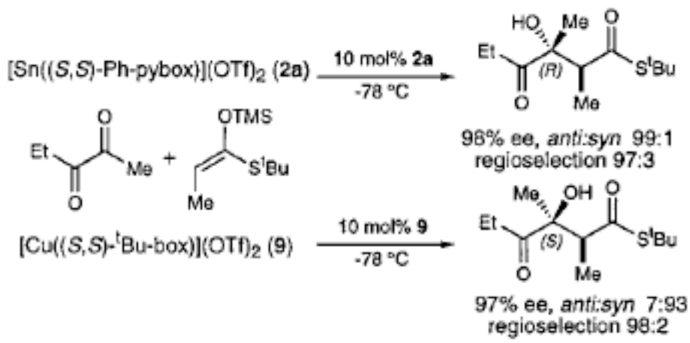
Table 9. Catalyzed Enantioselective Aldol Reactions between Methyl Pyruvate and Representative Enolsilanes (eq 19)[a]



entry	solvent	R^1	R^2	enolsilane geometry[b]	time/ T (°C)	*syn:anti*[c]	ee[c] %	yield %
1	CH_2Cl_2	Me	^{t}Bu	(*Z*)	8 h/-78	94:6	96	96
2	THF	Me	^{t}Bu	(*Z*)	1 d/-78	90:10	93	93
3	CH_2Cl_2	Me	^{t}Bu	(*E*)	1 d/-78	95:5	98	90[d]
4	**THF**	**Me**	**^{t}Bu**	(*E*)	2 d/-78	**97:3**	**99**	**88**[d]
5	CH_2Cl_2	Me	Et	(*Z*)	4 h/-78	90:10	95	95
6	THF	Me	Et	(*Z*)	1 h/-78	94:6	93	90
7	**CH_2Cl_2**	**Me**	**Et**	(*E*)	2 h/-78	**98:2**	**98**	**78(93)**[e]
8	**THF**	**Me**	**Et**	(*E*)	2 h/-78	**98:2**	**98**	**91**
9	CH_2Cl_2	^{i}Bu	^{t}Bu	(*Z*)	2 d/-78	93:7	97[f]	58
10	**CH_2Cl_2**	**^{i}Bu**	**Et**	(*Z*)	1 d/-78	**90:10**[f]	**93**[f]	**88**
11	CH_2Cl_2	^{i}Pr	^{t}Bu	(*Z*)	1 d/rt	66:34[f]	97	71[g,h]
12	**CH_2Cl_2**	**^{i}Pr**	**Et**	(*Z*)	12 h/-50	**90:10**	**99**	**80**[h]

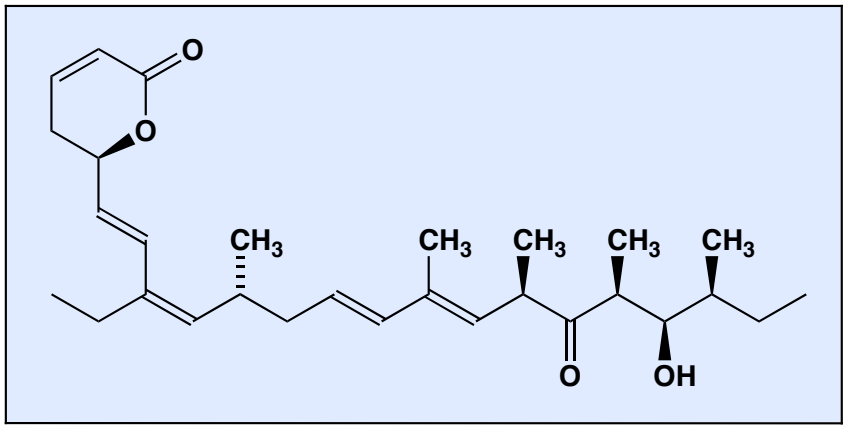
[a]Reactions were typically 0.2-0.3 M in substrate. [b]Isomeric purity ≥90%. [c]Product ratios determined by HPLC using a Chiralcel OD-H or AD column; enantiomeric excess is reported for the major product diastereomer. Unless otherwise stated, the relative and absolute stereochemistry was determined by independent synthesis (see experimental). [d]Reaction required 0.9 equiv of TMSOTf for complete conversion. [e]Reaction performed on a 10 mmol scale with 2.5 mol% catalyst and 0.5 equiv TMSOTf. [f]Configuration assigned by analogy. [g]Reaction required 0.5 equiv of TMSOTf for complete conversion. [h]No reaction when conducted in THF

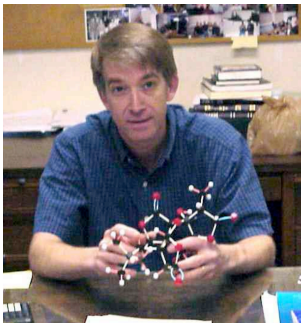




Case Study: C_{13}-C_{22} Segment of Callystatin *A*

Crimmins, M. T.; King, B. W. *J. Am. Chem. Soc.* **1998**, *120*, 9084
Murakami, N.; Wang, W.; Aoki, M.; Tsutsui, Y.; Sugimoto, M.; Kobayashi, M. *Tetrahedron Lett.* **1998**, *39*, 2349
Review: "The Chemistry and Biology of the Leptomycin Family"
Kalesse, M.; Christmann, M. *Synthesis* **2002**, 981

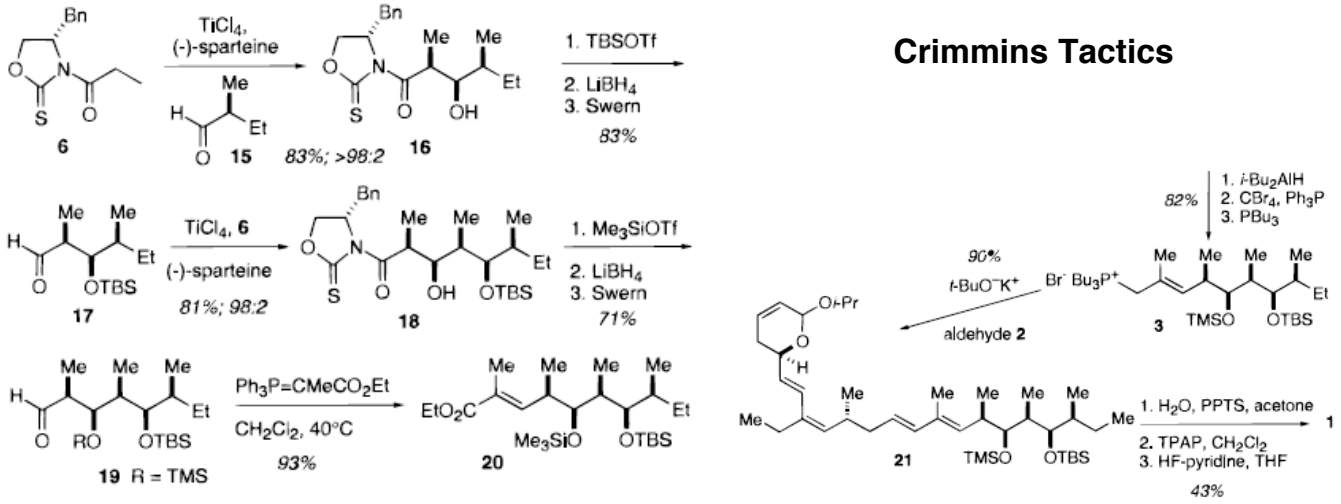




Mike Crimmins
University of North Carolina

Crimmins Tactics

Scheme 4



Kobayashi Tactics

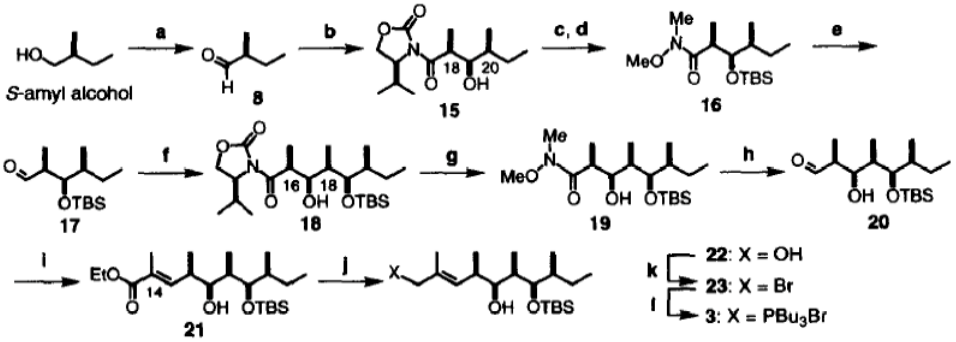


Chart 3: Synthesis of Segment C_{13}-C_{22} (**3**)
Reagents and conditions: **a)** PCC, CH_2Cl_2, 0°C, 23%, **b)** **7**, $^nBu_2BOTf$, Et_3N, THF, -78~0°C, 98% (9:1), **c)** $AlMe_3$, MeONHMe•HCl, CH_2Cl_2, -20~0°C, 95%, **d)** TBSOTf, 2,6-lutidine, CH_2Cl_2, -20°C, quant., **e)** DIBAL-H, THF, -78°C, 76%, **f)** **7**, $^nBu_2BOTf$, Et_3N, THF, -78~0°C, 85%, **g)** $AlMe_3$, MeONHMe•HCl, CH_2Cl_2, -78~0°C, 92%, **h)** $LiAlH_4$, Et_2O, 0°C, 96%, **i)** **6**, toluene, 94%, **j)** DIBAL-H, CH_2Cl_2, -78°C, quant., **k)** CBr_4, Ph_3P, 2,6-lutidine, CH_3CN, 99 %, **l)** $^nBu_3P$, CH_3CN, quant.