

Massachusetts Institute of Technology
Organic Chemistry 5.511

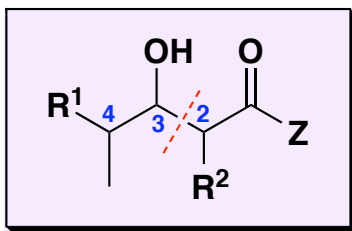
December 7, 2007
Prof. Rick L. Danheiser

Lecture 20

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

Catalytic Asymmetric Aldol Reactions

- ★ Chiral Controller Strategies
- ★ Catalytic Chiral Auxiliary Strategies
- ★ Chiral Lewis Acid Catalyzed Aldol Reactions

Catalytic Asymmetric Aldol Reactions

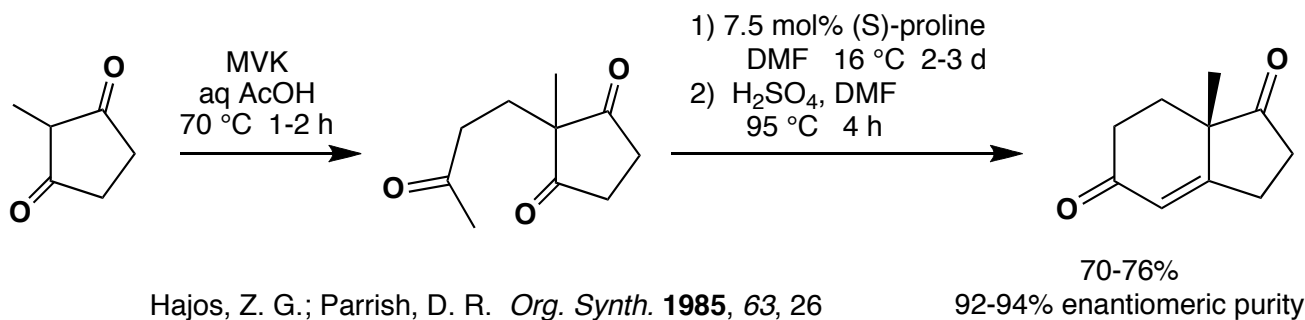
I. Chiral Controller Strategies

Enamine Aldol Reactions

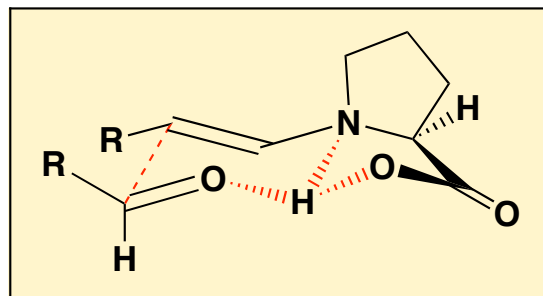
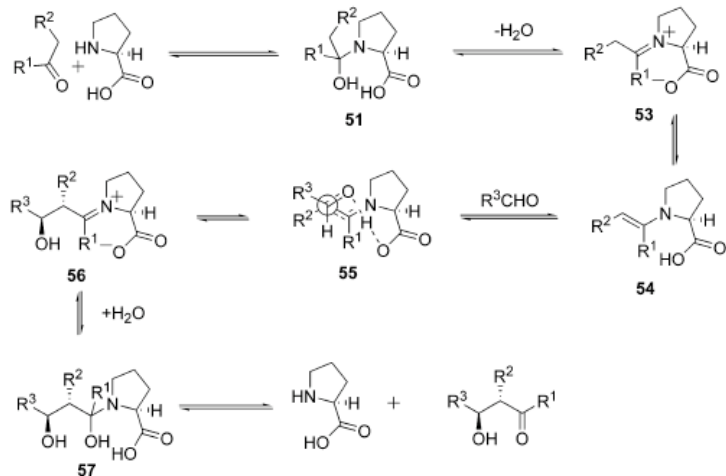
Reviews

- (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



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



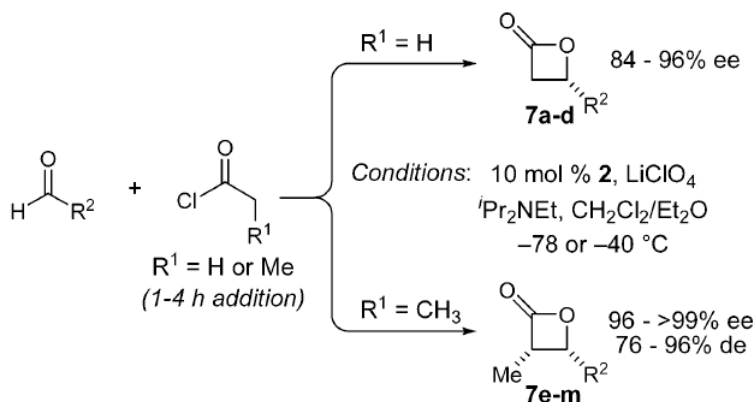
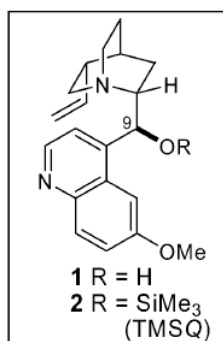
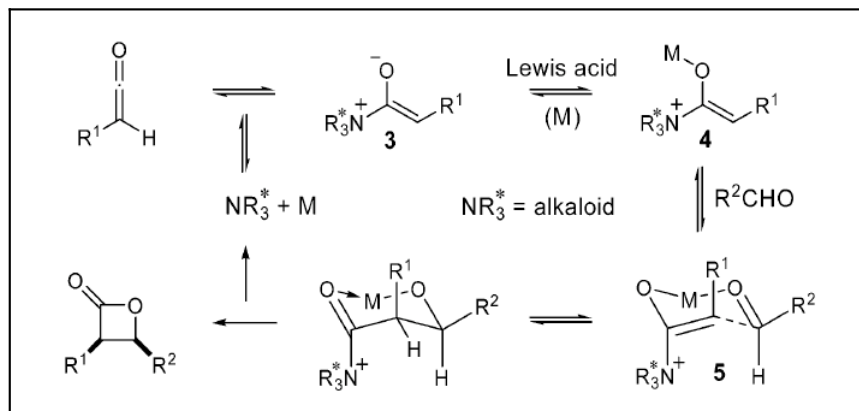
Catalytic Asymmetric Aldol Reactions

II. Catalytic Chiral Auxiliary Strategies

Zhu, C.; Shen, X.; Nelson, S. G. *J. Am. Chem. Soc.* **2004**, *126*, 5352



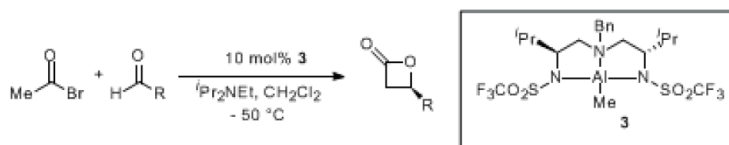
Scott Nelson



III. Chiral Lewis Acid Strategies

(1) Nelson Ketene-Aldehyde Condensations

Nelson, S. G.; Peelen, T. J.; Wan, Z. *J. Am. Chem. Soc.* **1999**, *121*, 9742
 Nelson, S. G.; Zhu, C.; Shen, X. *J. Am. Chem. Soc.* **2004**, *126*, 14
 Nelson, S. G.; Mills, P. M. *Organic Syntheses* **2005**, *82*, 170



Aldehyde (R)	% yield	% ee
-(CH ₂) ₈ CH=CH ₂	99	99
-CH ₂ CH(CH ₃) ₂	80	93
-CH ₂ OCH ₂ Ph	91	92
-CH ₂ OSiPh ₂ tBu	74	89
-CH ₂ CH ₂ OCH ₂ Ph	90	91
-C≡CCH ₂ OCH ₂ Ph	86	93
-C ₆ H ₄ NO ₂	93	95

III. Chiral Lewis Acid Strategies

(2) Carreira Chiral Ti Catalyst

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

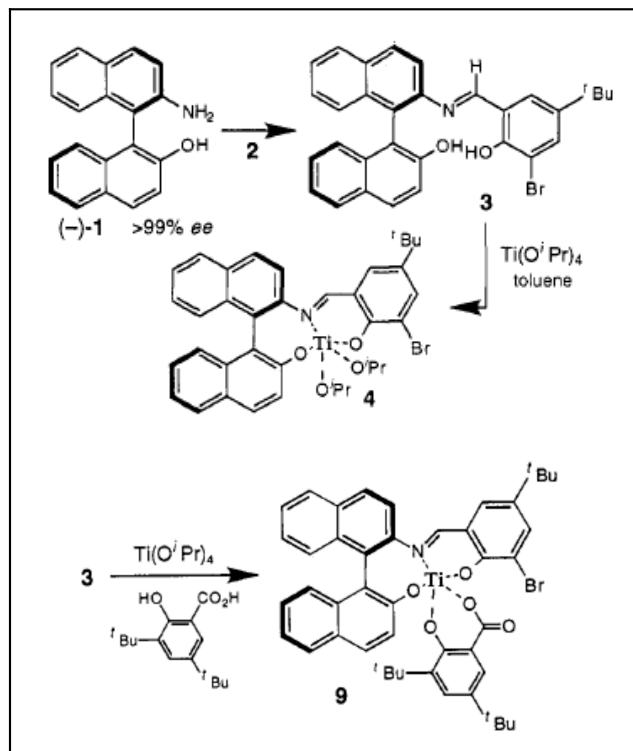


Table 1. Catalytic Asymmetric Aldol Additions of Alkyl Acetate Ketene Acetal^{a,c}

$\text{R}'\text{CHO} + \text{OSiMe}_3 \xrightarrow[2. \text{Bu}_4\text{NF, THF}]{1. \text{9 (2 or 5 mol \%), -10}^\circ\text{C, Et}_2\text{O, 4h}} \text{R}'\text{CH(OH)CH}_2\text{C(=O)OR}$			
	5a R = Et 5b R = Me		10 ^a
Entry	Aldehyde	ee: R = Et ^d	ee: R = Me ^e
1	Me-CH=CH-CHO	92%	97%
2	Me-CH=CH-CHO	88%	95%
3	Ph-CH=CH-CHO	93%	97%
4	Ph-CH=CH-CHO	89%	94%
5	C ₆ H 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 ¹H NMR spectroscopy. ^d 5 mol % catalyst used. ^e 2 mol % catalyst used.

(3) 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

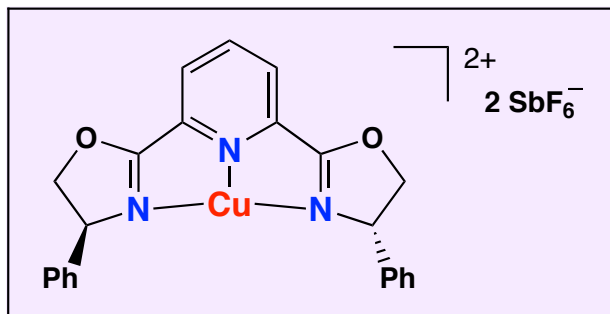
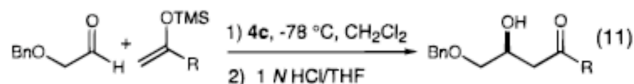


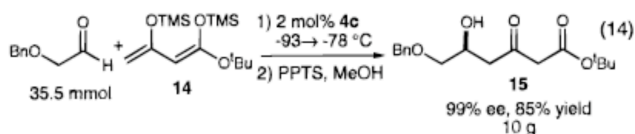
Table 4. Catalyzed Benzyloxyacetaldehyde Aldol Reaction with Representative Acetate Silylketene Acetals (eq 12)^a



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

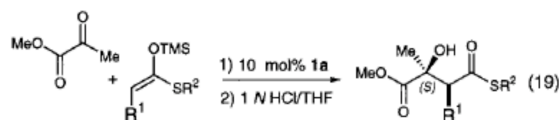
^aAll reactions were 0.2 M in substrate. ^bEnantiomeric excess determined by HPLC using a Chiralcel OD-H column. Absolute configuration determined by independent synthesis (see experimental).

^cThe silyl ether was cleaved with TBAF/THF to prevent retroaldol reaction.



Addition to Pyruvates

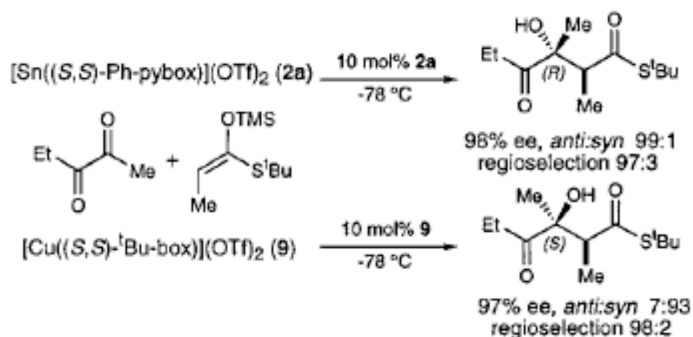
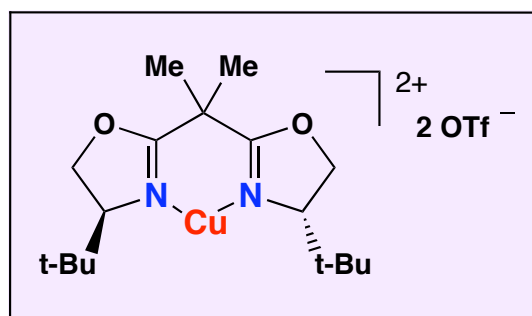
Table 9. Catalyzed Enantioselective Aldol Reactions between Methyl Pyruvate and Representative Enolsilanes (eq 19)^a



entry	solvent	R ¹	R ²	enolsilane geometry ^b	time/T (°C)	syn:anti ^c	ee ^c %	yield %
1	CH ₂ Cl 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 ₂ Cl 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 ₂ Cl 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 ₂ Cl 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 ₂ Cl ₂	ⁱ Bu	^t Bu	(Z)	2 d/-78	93:7	97 ^f	58
10	CH ₂ Cl ₂	ⁱ Bu	Et	(Z)	1 d/-78	90:10 ^f	93 ^f	88
11	CH ₂ Cl ₂	ⁱ Pr	^t Bu	(Z)	1 d/rt	66:34 ^f	97	71 ^{g,h}
12	CH ₂ Cl ₂	ⁱ Pr	Et	(Z)	12 h/-50	90:10	99	80 ^h

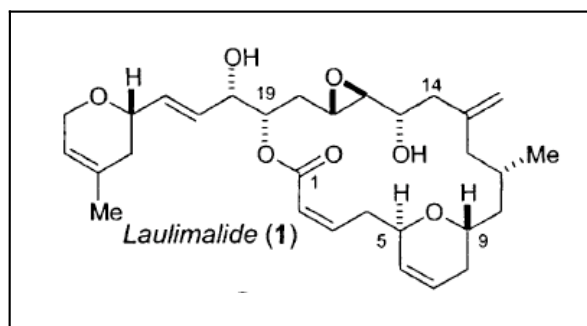
^aReactions were typically 0.2-0.3 M in substrate. ^bIsomeric purity ≥90%.

^cProduct 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). ^dReaction required 0.9 equiv of TMSOTf for complete conversion. ^eReaction performed on a 10 mmol scale with 2.5 mol% catalyst and 0.5 equiv TMSOTf. ^fConfiguration assigned by analogy. ^gReaction required 0.5 equiv of TMSOTf for complete conversion. ^hNo reaction when conducted in THF.



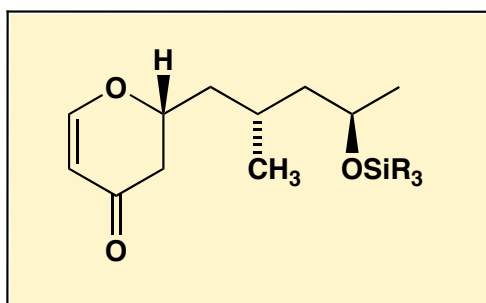
Case Study

Synthesis of (-)-Laulimalide

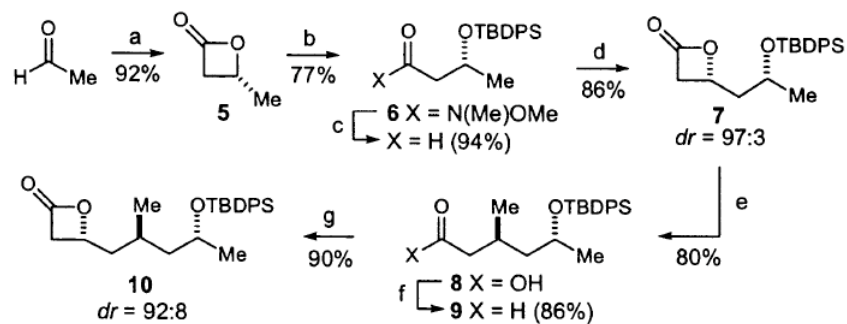


Nelson, S. G.; Cheung, W. S.; Kassick, A. J.; Hilfiker, M. A.
J. Am. Chem. Soc. **2002**, 124, 13654

Laulimalide
subtarget



Scheme 1^a



^a a) 10 mol % **4**, MeCOBr, *i*Pr₂NEt, *n*Bu₄NBr, -78 °C. b) i. Me₂AlCl, (MeO)MeNH₂Cl; ii. *t*BuPh₂SiCl, imidazole. c) *i*Bu₂AlH. d) 10 mol % **4**, MeCOBr, *i*Pr₂NEt, -50 °C. e) MeMgBr, CuBr·DMS. f) i. BH₃·SMe₂; ii. PCC. g) 15 mol % **4**, MeCOBr, *i*Pr₂NEt, -50 °C.

Scheme 2^a

