Massachusetts Institute of Technology

Organic Chemistry 5.512

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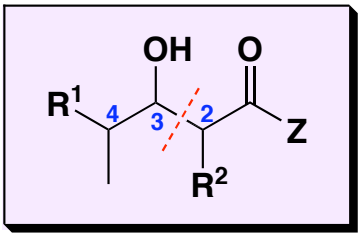
Unit 6

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

III. Chiral Lewis Acid Strategies

(1) Carreira Chiral Ti Catalyst

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

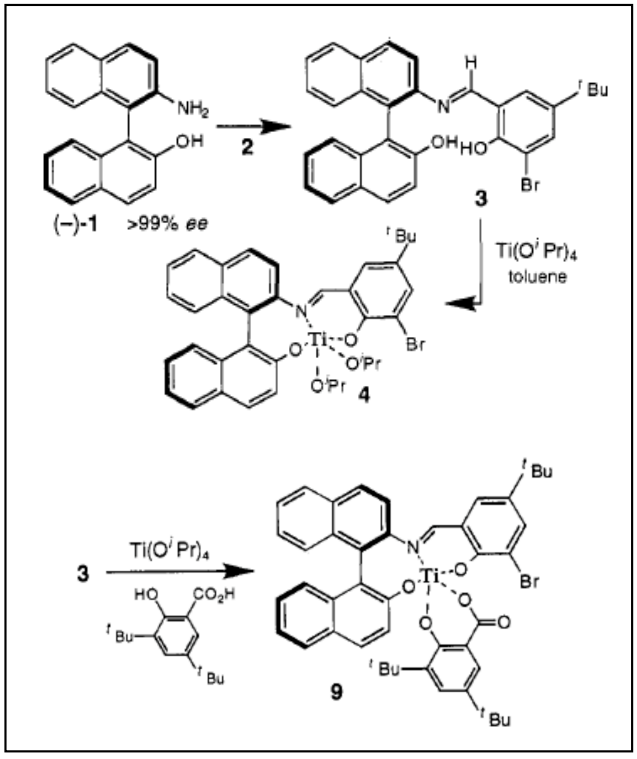
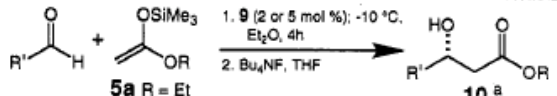


Table 1. Catalytic Asymmetric Aldol Additions of Alkyl Acetate Ketene Acetal[b,c]



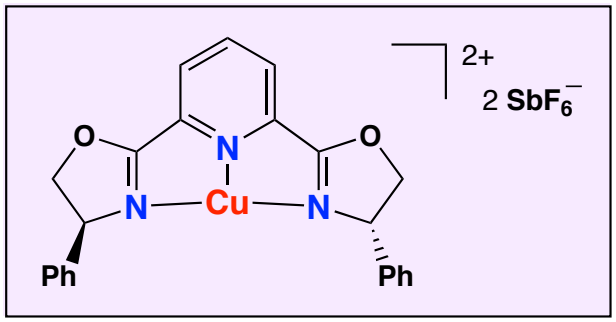
Entry	Aldehyde	ee: R = Et [d]	ee: R = Me [e]
1	Me, CHO	92%	97%
2	Me, CHO	88%	95%
3	Ph, CHO	93%	97%
4	Ph, CHO	89%	94%
5	$C_6H_{11}CHO$	94%	95%
6	PhCHO	93%	96%

[a] Absolute configuration was determined by reduction to the known 1,3-diols.[1h] [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



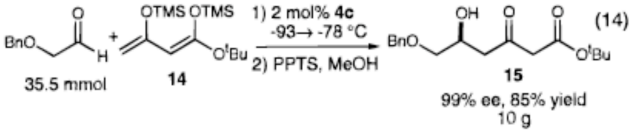
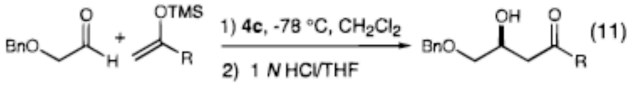


Table 4. Catalyzed Benzyloxyacetaldehyde Aldol Reaction with Representative Acetate Silylketene Acetals (eq 12)[a]

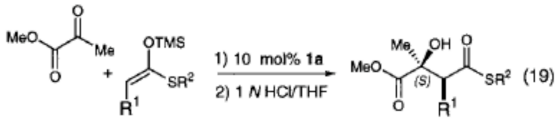


entry	R	catalyst loading	time, h	% ee[b]	% yield
1	S^{t}Bu	0.5 mol%	12-24	99	99
2	SEt	0.5 mol%	12-24	98	95
3	OEt	0.5 mol%	12	98	99[c]

[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