Massachusetts Institute of Technology

Organic Chemistry 5.512

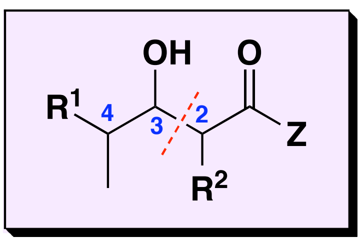
December 3, 2007
Prof. Rick L. Danheiser

Lecture 18

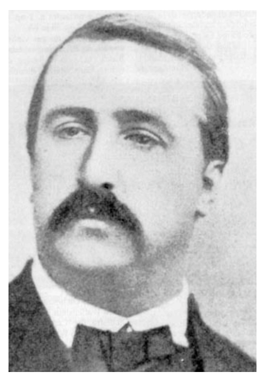
Unit 6

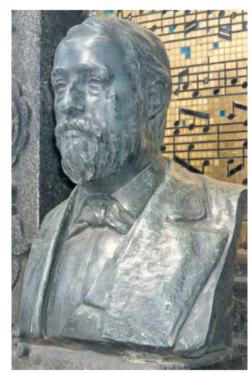
Stereocontrolled Aldol Reactions

- ★ 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





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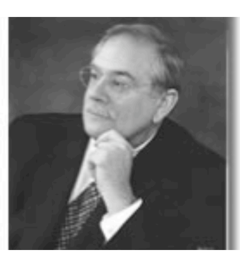

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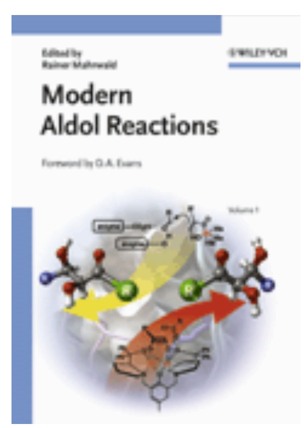

General References on Aldol Chemistry

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"Asymmetric Aldol Reactions Using Boron Enolates"
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Carreira, E. M. In *Modern Carbonyl Chemistry*; Otera, J., Ed.; Wiley-VCH, 2000, pp 227-248.

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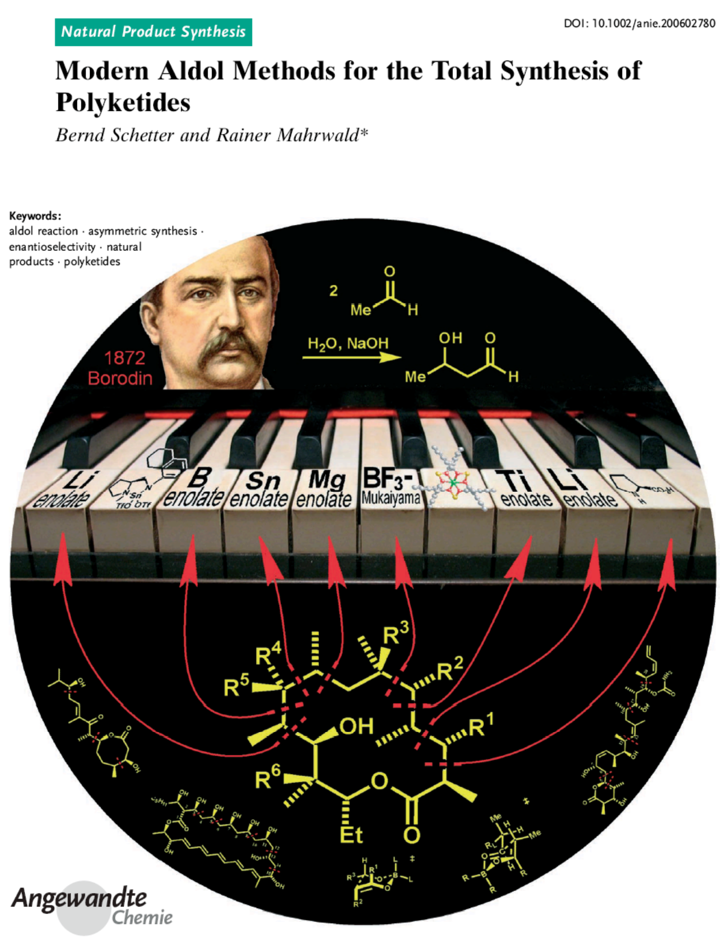
Paterson, I.; Cowden, C. J.; Wallace, D. J.; In *Modern Carbonyl Chemistry*; Otera, J., Ed.; Wiley-VCH, 2000, pp 249-298.

Modern Aldol Reactions (2 Vols); Mahrwald, R., Ed.; Wiley-VCH, 2004.

"Current Progress in the Asymmetric Aldol Addition Reaction"
Palomo, C.; Oiarbide, M.; Garcia, J. M. *Chem. Soc. Rev.* **2004**, *33,* 65.

"Catalytic Enantioselective Aldol Addition Reactions"
Carreira, E. M.; Fettes, A.; Marti, C. *Org. React.* **2006,** *67*, 1.

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


Natural Product Synthesis

DOI: 10.1002/anie.200602780

Modern Aldol Methods for the Total Synthesis of Polyketides

*Bernd Schetter and Rainer Mahrwald**

Keywords:
aldol reaction · asymmetric synthesis · enantioselectivity · natural products · polyketides

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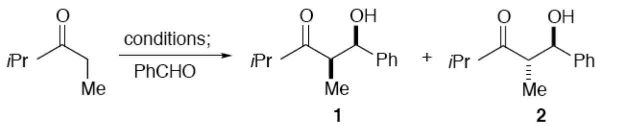
Aldol Reaction Stereochemistry: Recent Examples

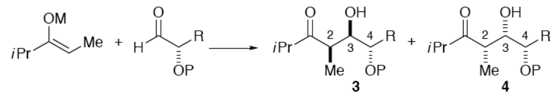
Evans, D. A.; Siska, S. A.; Cee, V. J. *Angew. Chem. Int. Ed.* **2003**, *42*, 1761. See also Evans, D. A. et. al *J. Am. Chem. Soc.* **2006**, *128*, 2920

Table 1: Enolization and aldol addition of 2-methyl-3-pentanone.

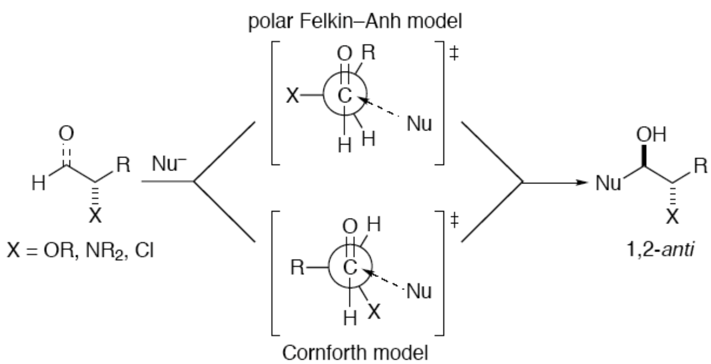


Conditions[a]	Solvent	Configuration (Z:E)[d]	1:2[d]	Yield [%][e]
9-BBNOTf, DIPEA	Et_2O	95:05[b]	94:06	82
(c-Hex)$_2$BCl, TEA	Et_2O	07:93[b]	04:96	79
LiHMDS	THF	95:05[c]	90:10	66
LiNTMS(tBu)	THF	09:91[c]	48:52	86

Table 2: Aldol reactions of Z enolates.[a]

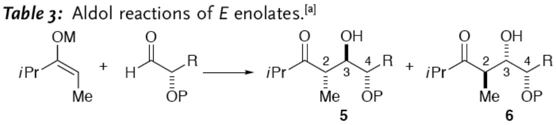


M	P	R	2,3-*syn*:2,3-*anti*	3:4	Yield [%][c]
9-BBN	Bn	Me	95:05[b]	89:11[b]	95
9-BBN	Bn	*i*Pr	95:05	98:02	73
9-BBN	TBS	Me	93:07	98:02	77
9-BBN	TBS	*i*Pr	94:06	98:02	72
Li	Bn	Me	93:07[b]	89:11[b]	67
Li	Bn	*i*Pr	98:02	98:02	77
Li	TBS	Me	96:04	95:05	65
Li	TBS	*i*Pr	98:02	99:01	71



Scheme 1. Stereochemical models for 1,2-induction in α-heteroatom-substituted aldehydes.

Table 3: Aldol reactions of E enolates.[a]



M	P	R	2,3-*anti*:2,3-*syn*	5:6	Yield [%]
(c-Hex)$_2$B	Bn	Me	$>$99:01[b]	33:67[b]	59
(c-Hex)$_2$B	Bn	*i*Pr	$>$99:01	67:33	77
(c-Hex)$_2$B	TBS	Me	$>$99:01	21:79	77
(c-Hex)$_2$B	TBS	*i*Pr	$>$99:01	43:57	85
Li	Bn	Me	45:55[b]	93:07[b]	92
Li	Bn	*i*Pr	46:54	80:20	78
Li	TBS	Me	62:38	85:15	78
Li	TBS	*i*Pr	67:33	88:12	80

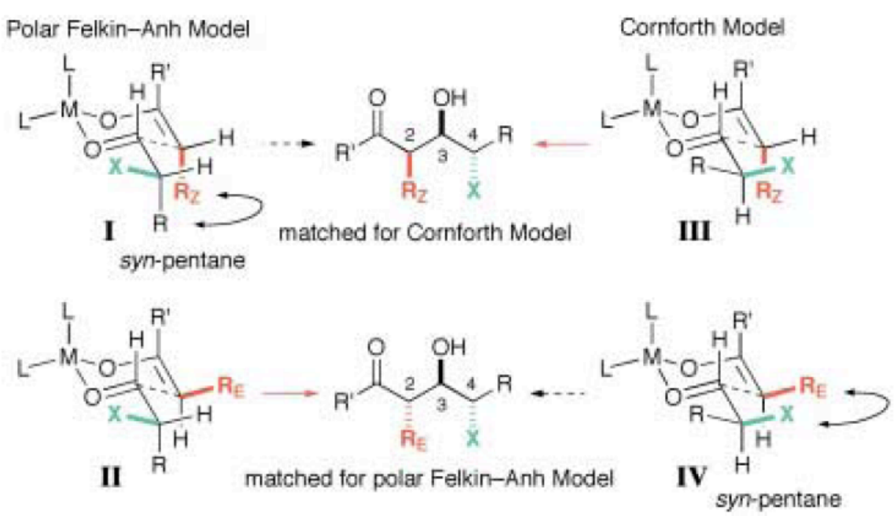


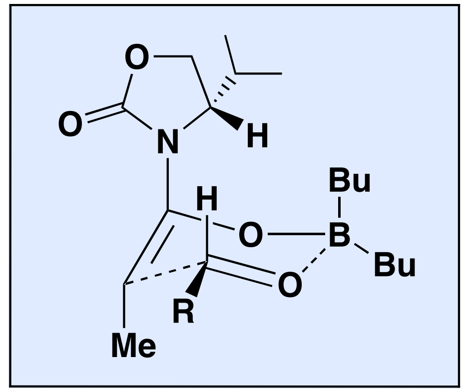
Figure 1. Comparative transition state analysis using the polar Felkin–Anh and Cornforth models.

II. Chiral Auxiliary Strategies

★ 2,3-Syn Aldols

Evans Oxazolidinone Boron Enolates

Gage, J. R.; Evans, D. A. *Org. Synth.* **1990**, *68*, 83



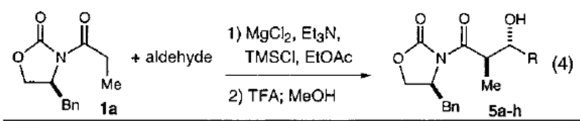
Review
"Asymmetric Aldol Reactions Using Boron Enolates"
Cowden, C. J.; Paterson, I. *Organic Reactions* **1997**, *51*, 1

★ 2,3-Anti Aldols

(1) Evans Dones

D. A. Evans et al.
J. Am. Chem. Soc. **2002** *124*, 392
and *Org. Lett.* **2002**, *4*, 1127

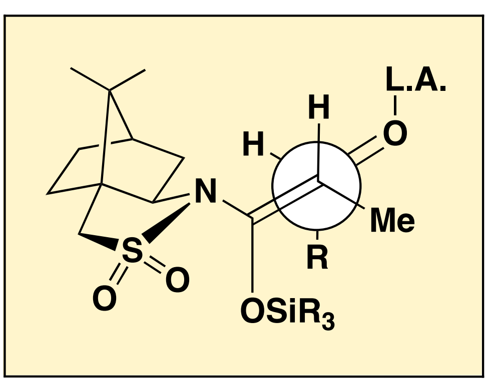
Table 2. Mg-Catalyzed *anti*-Aldol Reactions of **1a** with Representative Aldehydes (Eq 4)[a]

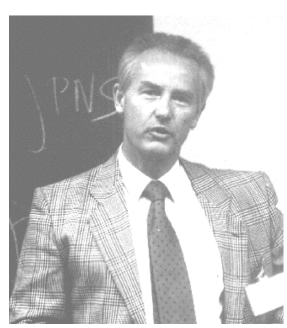


aldehyde		product	procedure[a,b]	dr[c]	yield (%)[d]
X-C$_6$H$_4$-CHO	X = Me	**5a**	A	24:1	-
	X = OMe	**5b**	A	32:1	91
	X = NO_2	**5c**	B	7:1	71
X-CH=C(Y)-CHO	X = Ph, Y = H	**5d**	B	21:1	92
	X = Ph, Y = Me	**5e**	A	28:1	92
	X = H, Y = Me[i]	**5f**	B	16:1	77
α-naphthaldehyde		**5g**	A	14:1	91
furfural		**5h**	B	6:1	80

[a] Procedure A: reactions were conducted with 1.0 equiv **1**, 0.2 equiv $MgCl_2$, 2.0 equiv of triethylamine, 1.5 equiv of TMSCl, 1.2 equiv of RCHO at 0.5 M in EtOAc for 24 h. [b] Procedure B: reaction conducted as in Procedure A but with 0.1 equiv $MgCl_2$ and the addition of 0.3 equiv of $NaSbF_6$ at 0.2 M in ethyl acetate. [c] Table 1 footnote b. [b] Isolated yield of a single diastereomer.

(2) Oppolzer Sultams





(3) Masamune Esters

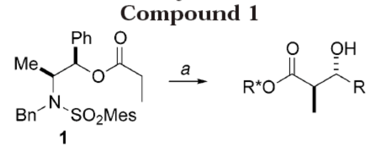
Review

"Boron-Mediated Aldol Reaction of Carboxylic Esters"

Abiko, A. *Acc. Chem. Res.* **2004**, *37*, 387

see also *Org. Synth.* **2002**, *79*, 109 and 116

Table 4. anti-Selective Asymmetric Aldol Reaction of Compound 1



RCHO	yield (%)	ds for anti[b]
MeCHO	92	97:3
EtCHO	90	96:4
n-PrCHO	95	95:5
i-PrCHO	95	98:2
c-HexCHO	91	95:5
t-BuCHO	96	>99:1
PhCHO	93	95:5
(*E*)-$CH_3CH{=}CHCHO$	96	98:2
$CH_2{=}C(CH_3)CHO$	97	96:4
$BnOCH_2CH_2CHO$	94	95:5
$BnOCH_2C(CH_3)_2CHO$	98	96:4

[a] *c*-Hex_2BOTf (2.0 equiv), Et_3N (2.4 equiv), −78 °C for 2 h; then RCHO, −78 °C for 1 h, 0 °C for 1 h. [b] anti/syn = >98:2; ds = diastereoselectivity.