

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

General References

"Catalyzed Enantioselective Aldol Additions of Latent Enolate Equivalents", Nelson, S. G. *Tetrahedron: Asym*

"Diastereoselection in Lewis-Acid-Mediated Aldol Additions", Mahrwald, R. *Chem. Rev.* **1999**, *99*, 1095-1120

"The Catalytic Asymmetric Aldol Reaction", Machajewski, T. D.; Wong, C. -H. *Angew. Chem. Int. Ed.* **2000**, *39*, 1111-1115

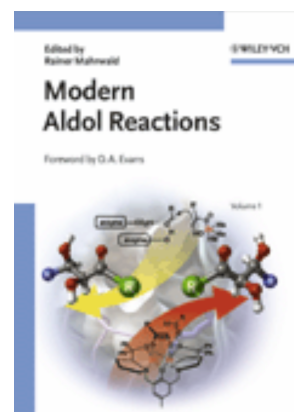
"Recent Developments in Asymmetric Aldol Methodology", Franklin, A. S.; Paterson, I. *Contemp. Org. Syn.* **1**

"Recent Advances in Asymmetric Aldol Addition Reactions", Carreira, E. M. In *Catalytic Asymmetric Syntheses*

"Aldol Reactions: Methodology and Stereochemistry", Carreira, E. M. In *Modern Carbonyl Chemistry*; Otera, J., Ed.

"Stereoselective Aldol Reactions in the Synthesis of Polyketide Natural Products", Paterson, I.; Cowden, C. J.; Wallace, D. J.; In *Modern Carbonyl Chemistry*; Otera, J., Ed.; Wiley-VCH, 2000, pp 249-298.

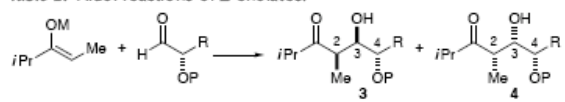
Modern Aldol Reactions (2 Vols); Mahrwald, R., Ed.; Wiley-VCH, 2004.



Aldol Reaction Stereochemistry: Recent Examples

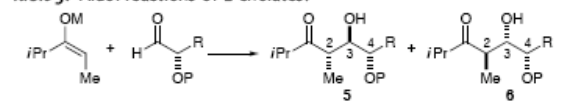
Evans, D. A.; Siska, S. A.; Cee, V. J. *Angew. Chem. Int. Ed.* **2003**, 42, 1761

Table 2: Aldol reactions of *Z* enolates.^[4]

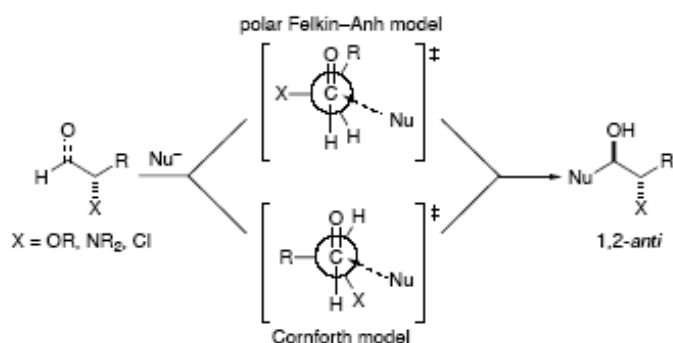


M	P	R	2,3- <i>syn</i> :2,3- <i>anti</i>	3:4	Yield [%] ^[4]
9-BBN	Bn	Me	95:05 ^[4]	89:11 ^[4]	95
9-BBN	Bn	<i>i</i> Pr	95:05	98:02	73
9-BBN	TBS	Me	93:07	98:02	77
9-BBN	TBS	<i>i</i> Pr	94:06	98:02	72
Li	Bn	Me	93:07 ^[4]	89:11 ^[4]	67
Li	Bn	<i>i</i> Pr	98:02	98:02	77
Li	TBS	Me	96:04	95:05	65
Li	TBS	<i>i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

Table 3: Aldol reactions of *E* enolates.^[4]



M	P	R	2,3- <i>anti</i> :2,3- <i>syn</i>	5:6	Yield [%]
(<i>c</i> -Hex) ₂ B	Bn	Me	> 99:01 ^[4]	33:67 ^[4]	59
(<i>c</i> -Hex) ₂ B	Bn	<i>i</i> Pr	> 99:01	67:33	77
(<i>c</i> -Hex) ₂ B	TBS	Me	> 99:01	21:79	77
(<i>c</i> -Hex) ₂ B	TBS	<i>i</i> Pr	> 99:01	43:57	85
Li	Bn	Me	45:55 ^[4]	93:07 ^[4]	92
Li	Bn	<i>i</i> Pr	46:54	80:20	78
Li	TBS	Me	62:38	85:15	78
Li	TBS	<i>i</i> Pr	67:33	88:12	80



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

