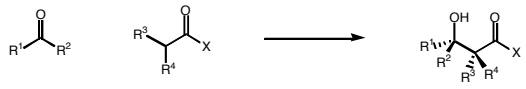
# The Selective Aldol Reaction



Alan B. Northrup

MacMillan Group Meeting

September 18, 2002

**A Brief Recent General Review:**

Palomo, C.; Oiarbide, M.; García, J. M. "The Aldol Addition Reaction: An Old Transformation at Constant Rebirth" *Chem. Eur. J.* **2002**, *8*, 36.

**Review Focusing on Enzymatic and other Catalytic Aldols:**

Machajewski, T. D.; Wong, C.- H. "The Catalytic Asymmetric Aldol Reaction" *Angew. Chem. Int. Ed.* **2000**, *39*, 1352.

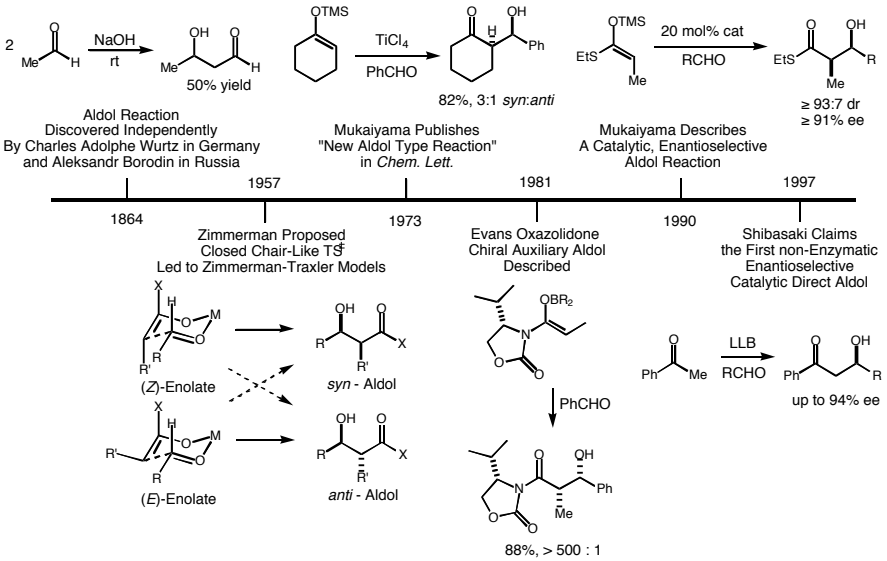
**Classic Reviews**

Evans, D. A.; Nelson, J. V.; Taber, T. R. "Stereoselective Aldol Condensations," in *Topics in Stereochemistry*, New York, 1982; Vol. 13, p. 2.

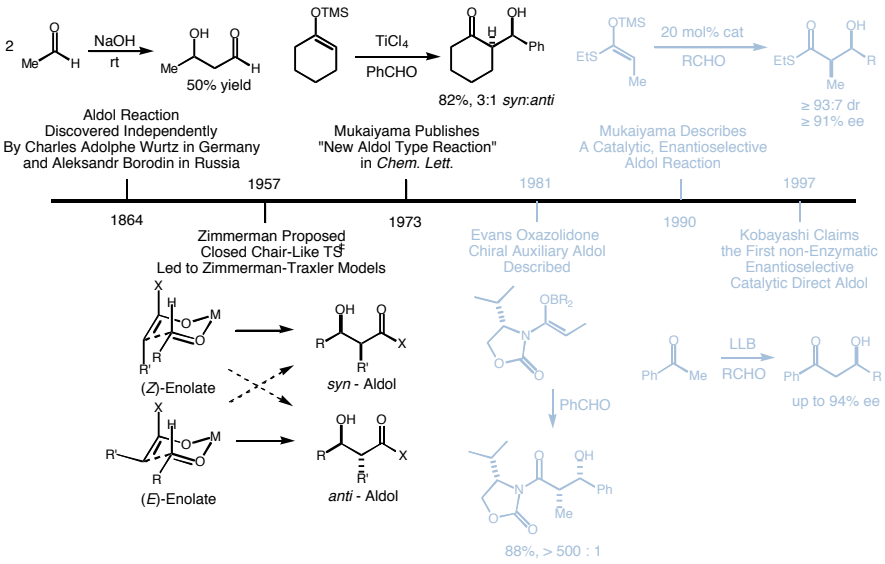
Mukaiyama, T. "The Directed Aldol Reaction," in *Organic Reactions*, New York, 1982; Vol. 28, p 203.

Heathcock, C. H. *Asymmetric Synthesis*; Morrion, J. D., Ed.; Academic Press: New York, 1984; Vol. 3, part B, p 111.

## *Aldol Reaction Time-Line*

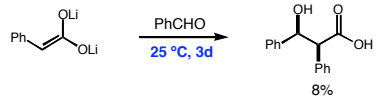


## *Racemic Aldol Technology*




## *Enolate Geometry Correlates with Product Diastereoselectivity Under Kinetic Control*

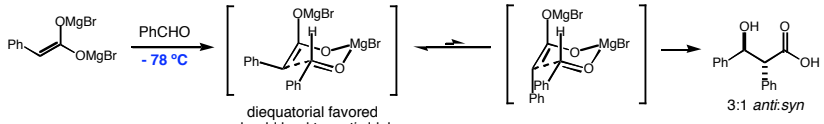
- The *anti* - Aldol Stereochemistry is Thermodynamically Favored:




Subsequent cross-over experiments implicate aldol-retro-aldol equilibration rather than epimerization

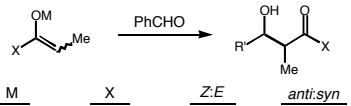
Mulzer, *et al. Tet. Lett.*, **1977**, 4651.

- Zimmerman Proposed a Chair Transition State for Kinetic Selectivity of the Ivanov Reaction:

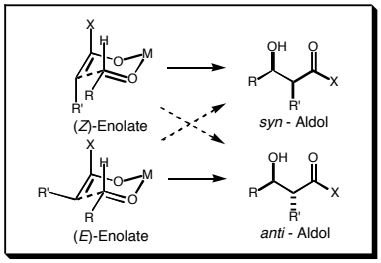



Zimmerman, H. E.; Traxler, M. D. *J. Am. Chem. Soc.* **1957**, *79*, 1920.

- Model Holds for a Variety of Enolates Both *E* and *Z*

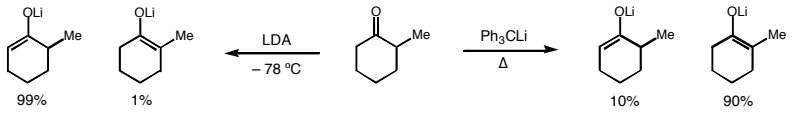



| M | X | *Z*:*E* | *anti*:*syn* |
|---|---|---|---|
| Li | *i*-Pr | >98:2 | 90:10 |
| Li | Mesityl | 5:95 | 8:92 |
| B | *i*-Pr | >99:1 | >97:3 |
| B | S*t*-Bu | 5:95 | 5:95 |
| Mg | *t*-Bu | >99:1 | >97:3 |



## *Selective Enolization Can Be Achieved*

■ Kinteic vs. Thermodynamic Acidity:

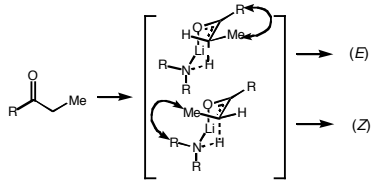



For other examples, see Evans 206 Kinetic Acidity

■ Structure of Carbonyl Compound Can Influence Ratio of Enolates Formed under Kinetic Control:


| R | *E* : *Z* |
|---|---|
| OR, SR | 95 : 5 |
| Et | 77: 23 |
| *t*-Bu | 0 : 100 |
| $NR_2$ | 0 : 100 |

These result can be rationalized with the Ireland model:




Ireland *et al. J. Am. Chem. Soc.*, **1976**, *98*, 2868
Ireland, *J. Org. Chem.* **1991**, *56*, 650

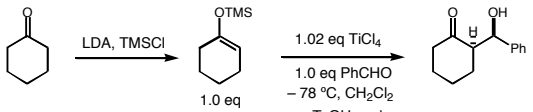
■ Solvent Can Impact Enolate Ratios:

| R | Solvent | *E* : *Z* |
|---|---|---|
| OMe | THF | 95 : 5 |
| OMe | THF/HMPA | 16 : 84 |

⟹ *Difference due to Enolate Equilibration*

## *The Mukaiyama Aldol Reaction*

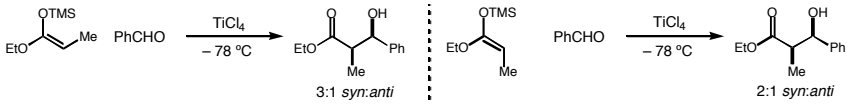
■ Mukaiyama's Report of a New Aldol-Type Process:



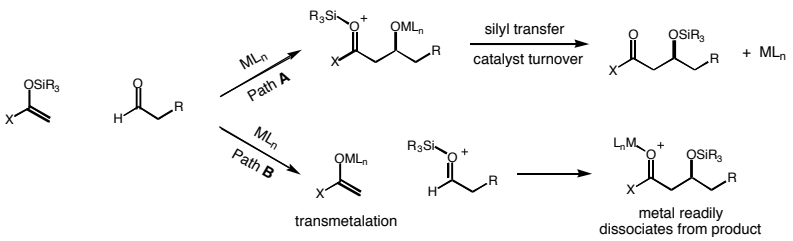

- Broad Range of Ketone Nucleophiles
- Range of Aldehyde + Ketone Electrophiles
- 50-93% yield
- 1:1 to 3:1 *syn*:*anti*
- Open Transition State
- Use of SKA or thio-SKA can increase the dr

Mukaiyama, T.; Narasaka, K.; Banno, K. *Chem. Lett.* **1973**, 1011
Mukaiyama, T.; Banno, K.; Narasaka, K. *J. Am. Chem. Soc.* **1974**, *96*, 7503

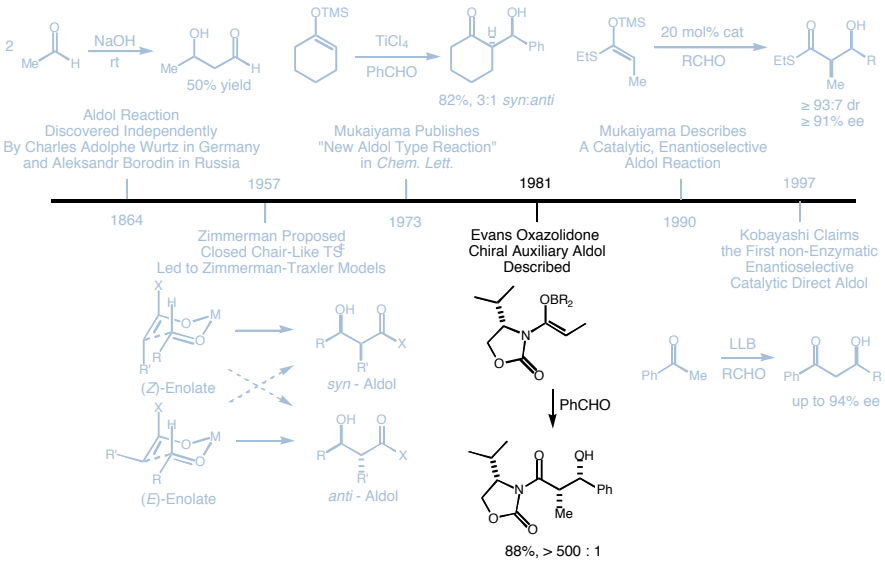
■ Reaction is *syn*-Selective Regardless of Enolsilane Geometry




■ Attractive Prospects for Catalysis...More on this Later

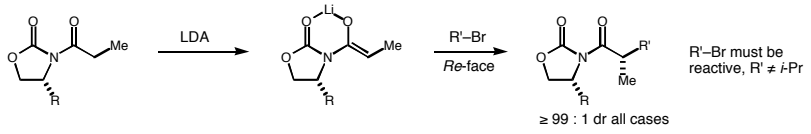


## *Chiral Auxiliary Technology*




## *The Evans Aldol Reaction*

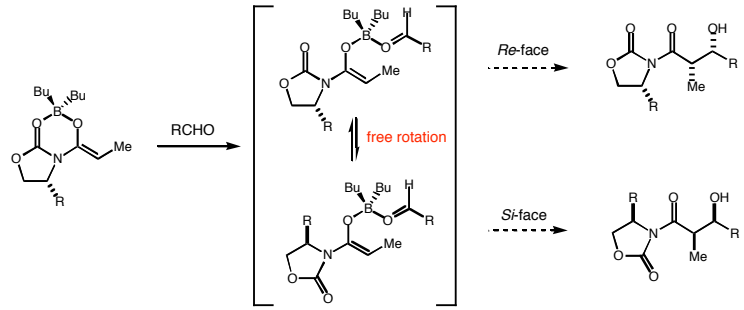
- Chelate Organization Allowed for Highly Diastereoselective Alkylations of Imide Enolates




≥ 99 : 1 dr all cases

Evans, D. A.; Ennis, M. D.; Mathre, D. J. *J. Am. Chem. Soc.* **1982**, *104*, 1737

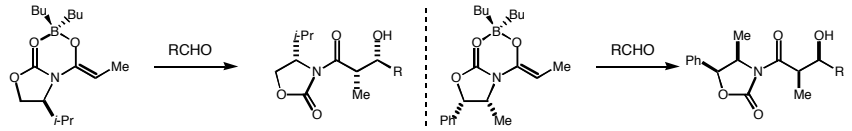
- Chelate Organization Precluded in Aldol Process




- Will this Reaction be Selective Given Lack of Chelate Control?

## *The Evans Aldol Reaction*

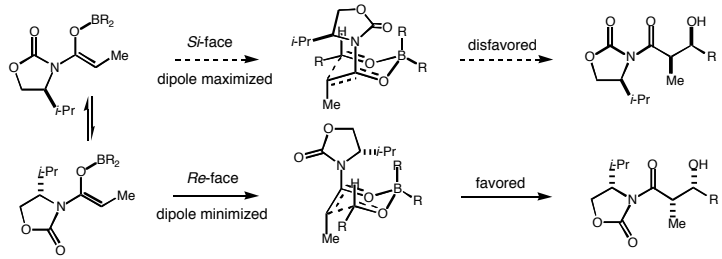
- Surprisingly, This Reaction is Highly Enolate Face-Selective:




Evans, D. A.; Bartroli, J.; Shih, T. L. *J. Am. Chem. Soc.* **1981**, *103*, 2127

- Reaction is Highly Diastereoselective in all propionate cases (141 : 1 to > 500 : 1)
- Reaction is Tolerant of a Broad Range of Aldehydes; R = Alkyl, Aryl, hindered, unhindered
- Acetyl-done provides poor selectivity—1 : 1 for the two diastereomers; Acetate aldol product via desulfurization
- One of the most reliable and predictable reactions in organic synthesis; industrially useful

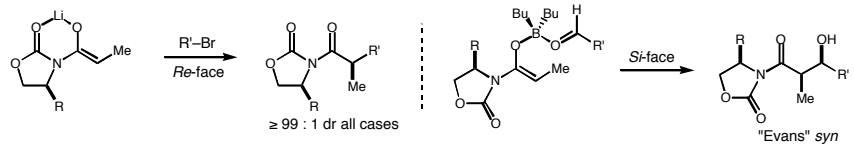
- Possible Model for Asymmetric Induction:



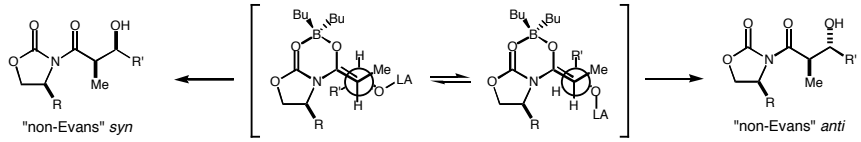

- Model does not account for the impact of the acyl-done α-substituent on diastereoselectivity. Perhaps a boat TS should be considered for smaller acyl donors as a competitive pathway

## *Heathcock's Modification to the Evans Aldol*

- Chelated *S*-imides give *Re*-face attack and Non-Chelated Imides give *Si*-Face Attack




- Based on that Observation, Heathcock Developed a "non-Evans" *syn* or *anti* Aldol: *J. Org. Chem.* **1991**, *56*, 5747



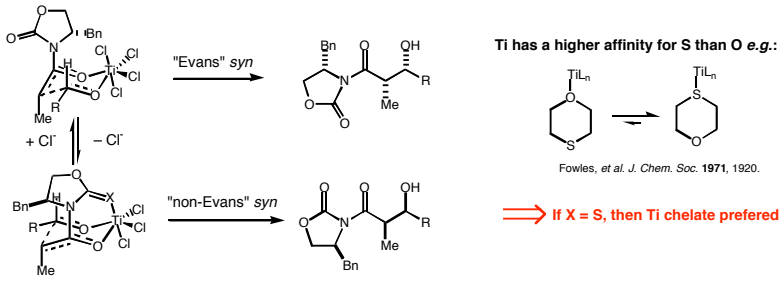

| Method | R | R' | Lewis Acid | equiv. | *syn*: *anti* | "non-Evans" : "Evans" |
|---|---|---|---|---|---|---|
| A or C | *t*-Bu | *i*-Pr | $TiCl_4$ | 2.0 | 94 : 6 | 100 : 0 |
| B | *t*-Bu | *i*-Pr | $SnCl_4$ | 2.0 | 93 : 7 | 100 : 0 |
| C | *i*-Pr | *i*-Pr | $Et_2AlCl$ | 3.0 | 5 : 95 | 100 : 0 |

Method A: Lewis acid added to enolate at – 78°C followed by slow addition of isobutyraldehyde
Method B: Aldehyde added to enolate at – 78°C followed by slow addition of Lewis acid
Method C: Precomplexed aldehyde and Lewis acid cannulated into solution of enolate at – 78°C

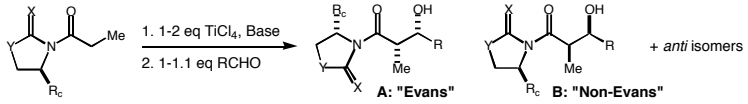
- "Size" of Lewis acid affects selectivity; propionaldehyde, isovaleraldehyde work well, benzaldehyde *syn*-only

## *Crimmins's Modification of the Evans Aldol*

- Crimmins's Hypothesis for Observed Lower Selectivities with Titanium Imide Enolates (88-96% de):




- Evans vs non-Evans Path Dictated by Auxiliary and Stoichiometry of Amine Base: *J. Org. Chem.* **2001**, *66*, 894.




X, Y = O; $R_c$ = Bn

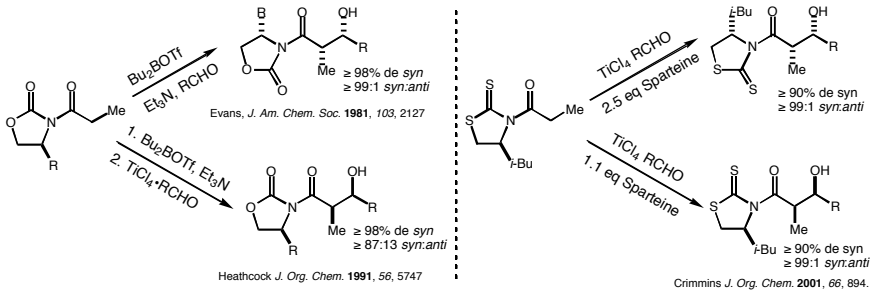
| T (ºC) | R | yield | **A** : **B** : *anti* |
|---|---|---|---|
| 0 | Et | 84 | 99 : 1 : 0 |
| 0 | MeCH=CH | 89 | 97 : 3 : 0 |
| 0 | *i*-Pr | 89 | 98 : 2 : 0 |
| 0 | *t*-Bu | 87 | 97 : 3 : 0 |
| – 78 | *i*-Pr | 98 | 98 : 2 : 0 |

X, Y = S; $R_c$ = *i*-Bu (X = S, Y = O, $R_c$ = Bn gave similar)

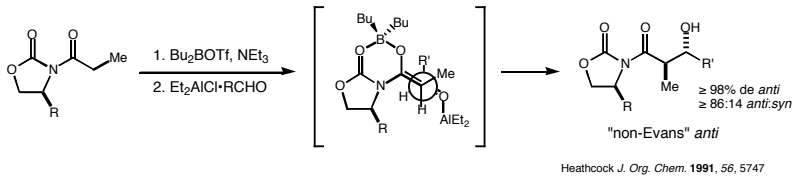
| Base | equiv. | R | yield | **A** : **B** : *anti* |
|---|---|---|---|---|
| DIEA | 2.5 | *i*-Pr | 86 | 86 : 14 : 0.3 |
| DIEA | 1.1 | *i*-Pr | 75 | 5 : 95 : n.a. |
| TMEDA | 2.5 | *i*-Pr | 57 | 96 : 4 : n.a. |
| TMEDA | 1.1 | *i*-Pr | 50 | <1 : >99 : n.a. |
| Sparteine | 2.5 | *i*-Pr | 84 | 95 : 5 : 0 |
| Sparteine | 1.1 | *i*-Pr | 63 | 5 : 95 : n.a. |

## *Summary of Aldols with Imide Auxiliaries*

- *Syn* Aldols:



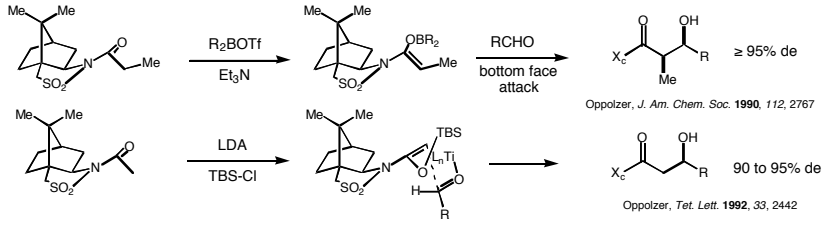

- *Anti* Aldols:




- Auxiliary can be converted to the corresponding alcohols, aldehydes, acids, esters, thioesters, Weinreb amides

## *Other Useful Chiral Auxiliaries*

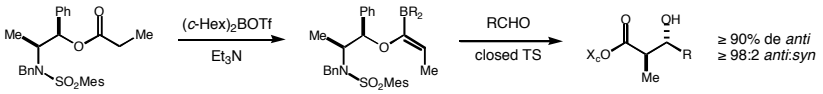
■ Oppolzer's Sultam: Both Propionate and Acetate Aldols Possible




Oppolzer, *J. Am. Chem. Soc.* **1990**, *112*, 2767

Oppolzer, *Tet. Lett.* **1992**, *33*, 2442

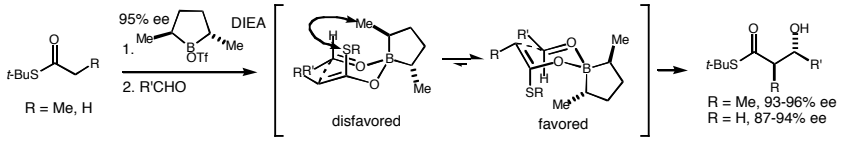
■ Abiko and Masamune's Norephedrine-Derived Auxiliary Gives *anti* Aldols




*E* - enolate

Abiko, A.; Liu, J.- F.; Masamune, S. *J. Am. Chem. Soc.* **1997**, *119*, 2586

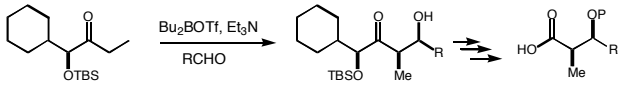
■ Masamune/Reetz Chiral Boron Enolates Give *anti* Aldols




Masamune, *J. Am. Chem. Soc.* **1986**, *108*, 8279
Reetz, *Tet. Lett.* **1986**, 4721

## *Chiral Ethyl Ketone Aldol Reactions (Z)-Enolates*

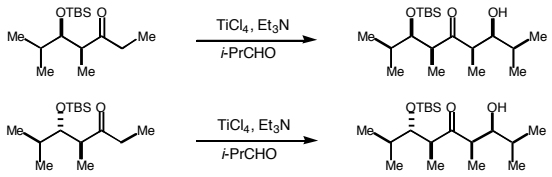
■ Even Simple α-Chiral (*Z*)-Ethyl Ketone Enolates Give High dr's:




| R | dr |
|---|---|
| Ph | 97 : 3 |
| Et | 98 : 2 |
| $BnOCH_2CH_2$ | 96 : 4 |
| *i*-Pr | >99 : <1 |

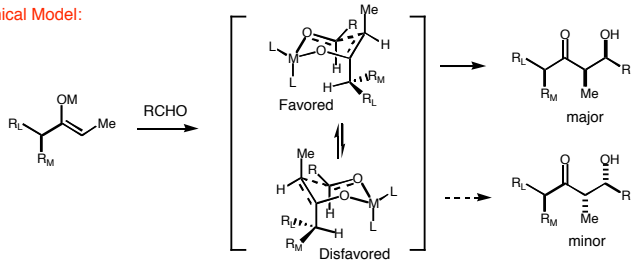
Masamune *J. Am. Che. Soc.* **1981**, *103*, 1566

■ A β-Stereocenter Usually has Little Impact:



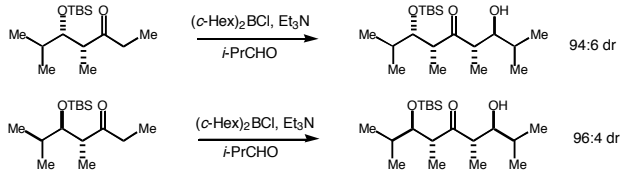

Evans *J. Am. Chem. Soc.* **1991**, *113*, 1047

■ Stereochemical Model:

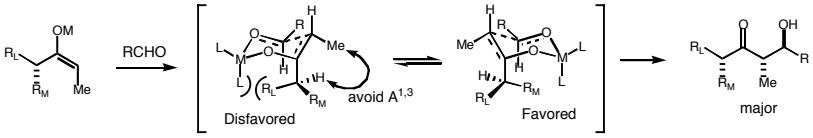


## *Chiral Ethyl Ketone Aldol Reactions (E)-Enolates*

- Simple α-Chiral (*E*)-Ethyl Ketone Enolates also Give High dr's:

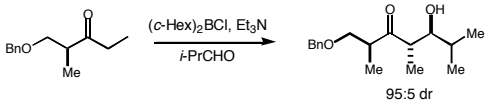



- Stereochemical Model:




Evans, *J. Am. Chem. Soc.* **1991**, *113*, 1047

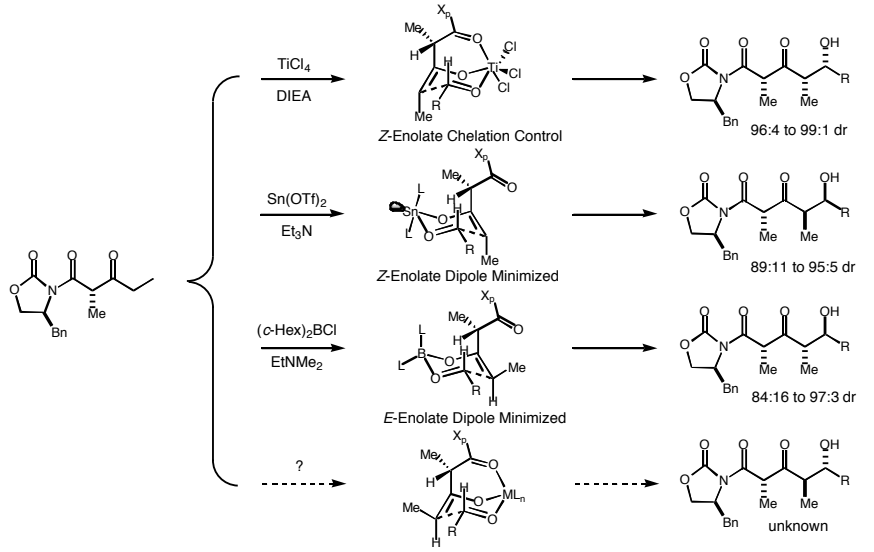
- However, not all (*E*)-enolates are well-behaved




Patterson, I.; Goodman, J. M.; Isaka, M. *Tet. Lett.* **1989**, *30*, 7121

## *Chiral Ethyl Ketone Aldol Reactions—β-Keto Imides*

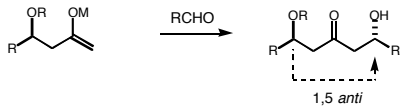
- Diastereomer Depends on Enolate Geometry and Lewis Acid




Evans, *J. Am. Chem. Soc.* **1990**, *112*, 866
Evans, *Tetrahedron*, **1992**, *48*, 2127

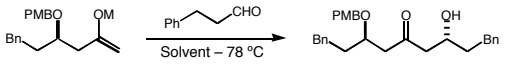
## *Chiral Ketone Aldol Reactions*–1,5 Induction

- Evans and Patterson Independently Observed this Phenomenon:

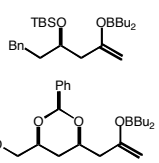



Evans *J. Org. Chem.* **1997**, *62*, 788
Patterson *Tet. Lett.* **1996**, 8585

- Levels of Induction Strongly Dependent on Metal, Protecting Group and Solvent:

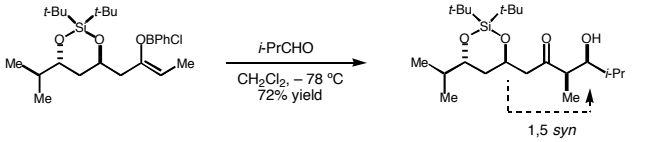



| M | solvent | yield | *anti*:*syn* |
|---|---|---|---|
| Li | THF | 79 | 40:60 |
| TMS/$BF_3$•$Et_2O$ | $CH_2Cl_2$ | 85 | 50:50 |
| $Cy_2B$ | $CH_2Cl_2$ | 85 | 82:18 |
| $Bu_2B$ | $CH_2Cl_2$ | 80 | 87:13 |
| $Bu_2B$ | $Et_2O$ | 85 | 98:02 |




| *anti*:*syn* |
|---|
| 40:60 |
| >95:5 |

- Chiral Ethyl Ketones Exhibit 1,5-*Syn* Induction:




>99:1 *syn*:*anti*

- No Good Models have been Presented to Account for the Observed Selectivities

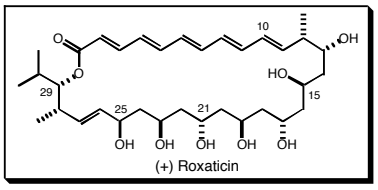
## *Chiral Methyl Ketone Aldol Reactions*–1,5 Induction in Synthesis

**Long-Range Transmission of Stereochemical Information:**

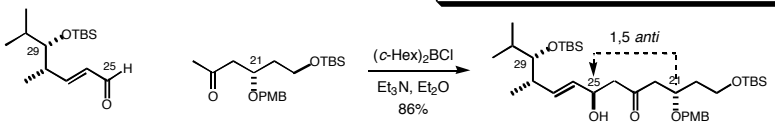
*No proposed model to account for the sense of diastereocontrol*

For a detailed investigation, see Evans *J. Org. Chem.* **1997**, *62*, 788

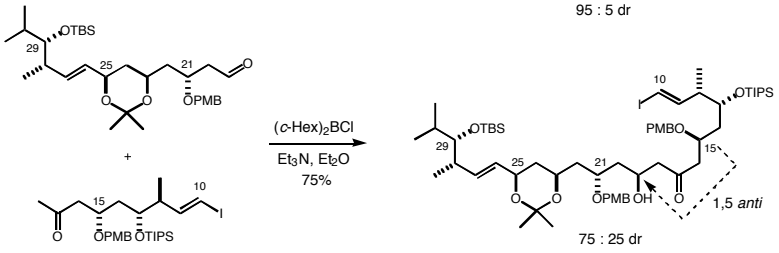
Patterson Roxaticin Synthesis: *C*-10 to *C*-29 Fragment




(+) Roxaticin




95 : 5 dr



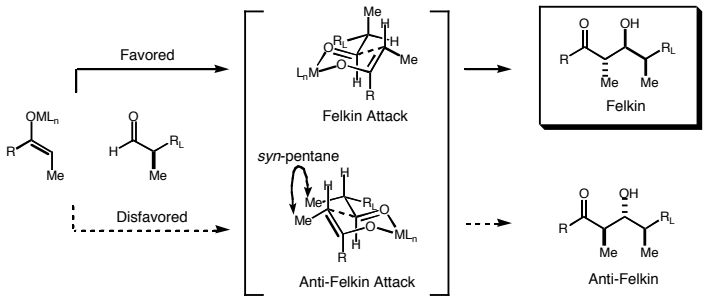

75 : 25 dr

Paterson, I.; Collett, L. A.; *Tet. Lett.*, **2001**, *42*, 1187

- The analogous ethyl ketone enolates give 1,5-*syn* selectivity

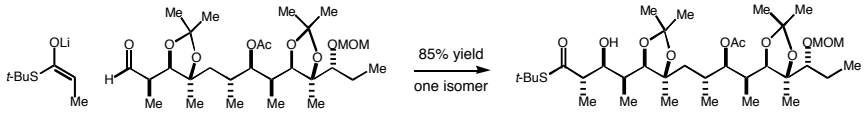
## *Chiral Aldehyde Aldol Reactions–α-Chiral Aldeyhdes*

■ (*E*) Enolates Give the Felkin Product




Evans *Topics in Stereochemistry*, **1982**, *13*, 1-115
Roush *J. Org. Chem.* **1991**, *56*, 4151

■ A Complex Case: Woodward's Erythromycin Synthesis

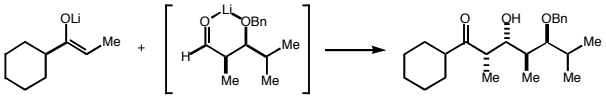



Felkin *anti*-aldol product

Woodward, *et al. J. Am. Chem. Soc.*, **1981**, *103*, 3210

## *Chiral Aldehyde Aldol Reactions–α-Chiral Aldeyhdes*

■ (*Z*) Enolates Give the Anti-Felkin Product:

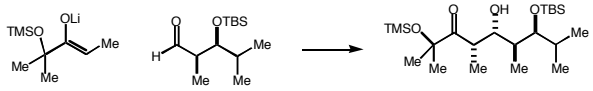


Initially rationalized via a Cram-Chelate Model...

Anti-Felkin 98:2 dr

Masamune *J. Am. Chem. Soc.* **1982**, *104*, 5526

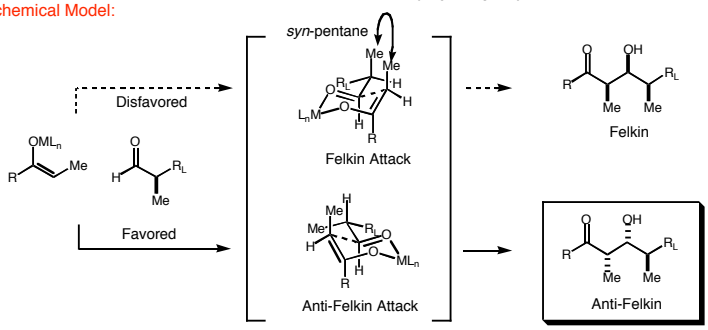
**However...**



Anti-Felkin 73:27 dr

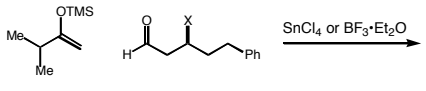
Brooks *Tet. Lett.* **1982**, *23*, 4991

■ Stereochemical Model:



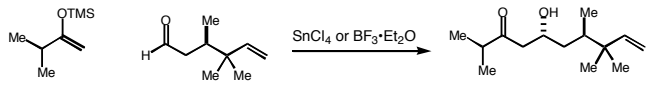
## *Chiral Aldehyde Aldol Reactions*–1,3 Induction

■ Modest Levels of 1,3 *anti* Induction can be achieved with β-Polar Aldehyde Substituents:



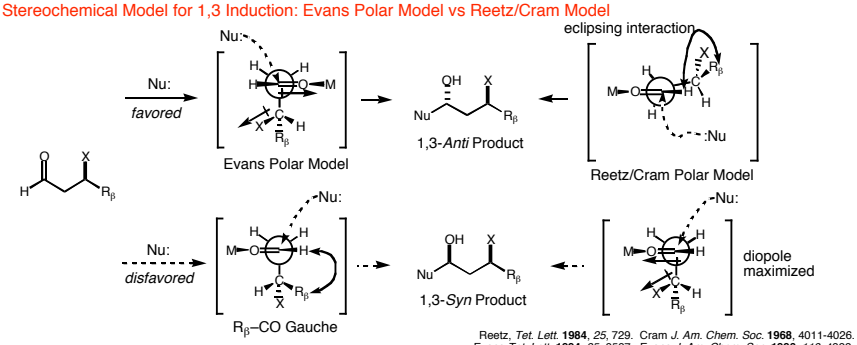

| X | Yield | *anti*:*syn* |
|---|---|---|
| OPMB | 79 | 95 : 5 |
| OTBS | 90 | 73 : 27 |
| OAc | 85 | 89 : 11 |
| Cl | 84 | 83 : 17 |

■ All Alkyl Cases Do Not Give Useful Levels of 1,3 Induction




58 : 42 *anti*:*syn*

■ Stereochemical Model for 1,3 Induction: Evans Polar Model vs Reetz/Cram Model

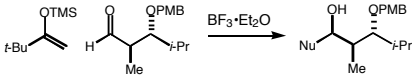



Reetz, *Tet. Lett.* **1984**, *25*, 729. Cram *J. Am. Chem. Soc.* **1968**, 4011-4026.
Evans *Tet. Lett.* **1994**, *35*, 8537. Evans *J. Am. Chem. Soc.* **1996**, *118*, 4322.

## *Chiral Aldehyde Aldol Reactions*–Merged 1,2- and 1,3-Induction

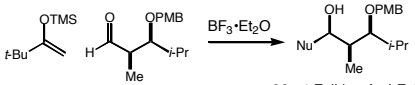
■ An Interesting Observation About α,β-Substituted Aldehydes (*J. Am. Chem. Soc.* **1996**, *118*, 4327)

Matched Case: Large Nucleophile



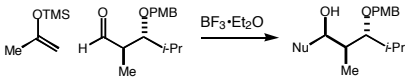

99 : 1 Felkin : Anti-Felkin

Mismatched Case: Large Nucleophile



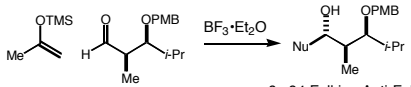

96 : 4 Felkin : Anti-Felkin

Matched Case: Small Nucleophile




97 : 3 Felkin : Anti-Felkin

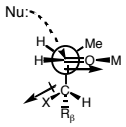
Mismatched Case: Small Nucleophile




6 : 94 Felkin : Anti-Felkin

⟹ For sterically large nucleophiles, Felkin control is more important than 1,3-*anti* induction.
However, the β-stereocenter (if bearing a polar group) can be the dominant control element.

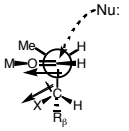
**Analysis of Matched Case**




Felkin and Evans Polar Model
both predict same face of attack

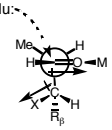
**Analysis of Mismatched Cases**

Favored for Large Nucleophiles




Felkin Attack, 1,3-*syn*

Favored for Small Nucleophiles



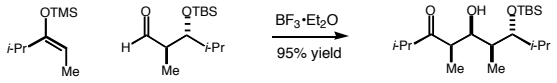

Anti-Felkin Attack, 1,3-*anti*

## *Chiral Aldehyde Aldol Reactions*–Merged 1,2- and 1,3-Induction

■ Propionate Mukaiyama Aldols Also Function Well (*J. Am. Chem. Soc.* **1995**, *117*, 9598)

- (*E*) Propionate nucleophiles give high levels of Felkin Selectivity even in Mismatched cases:
- (*Z*) Enolates generally less selective

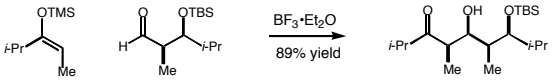
Matched Case:




95: 5 *syn*:*anti*

> 99 : 1 Felkin : Anti-Felkin

Mismatched Case:

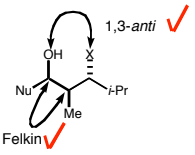



70 : 30 *syn*:*anti*

99 : 1 Felkin : Anti-Felkin

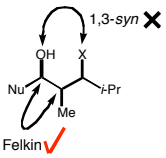
■ Summary of Stereochemical Relationships:

**Matched Case**

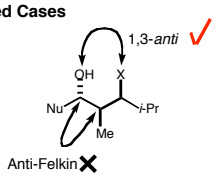



Good selectivity for both large and small Nu

**Mismatched Cases**



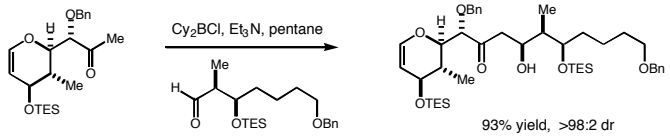

Favored for large Nu for Felkin to dominate 1,3 *anti* effect




Favored for small Nu for 1,3 *anti* to dominate Felkin control

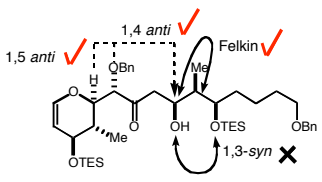
## *Analysis of a Recent Complex Aldol Reaction*

■ A Key Disconnection in Crimmins's Recent Synthesis of the Spongistatins: *J. Am. Chem. Soc.*, **2002**, 5661.




93% yield, >98:2 dr

**Analysis of the Product's Stereochemical Relationships:**




■ 3 of the 4 Known Control Elements are reinforcing

■ For Large Nucleophiles, Felkin beats 1,3 *anti*

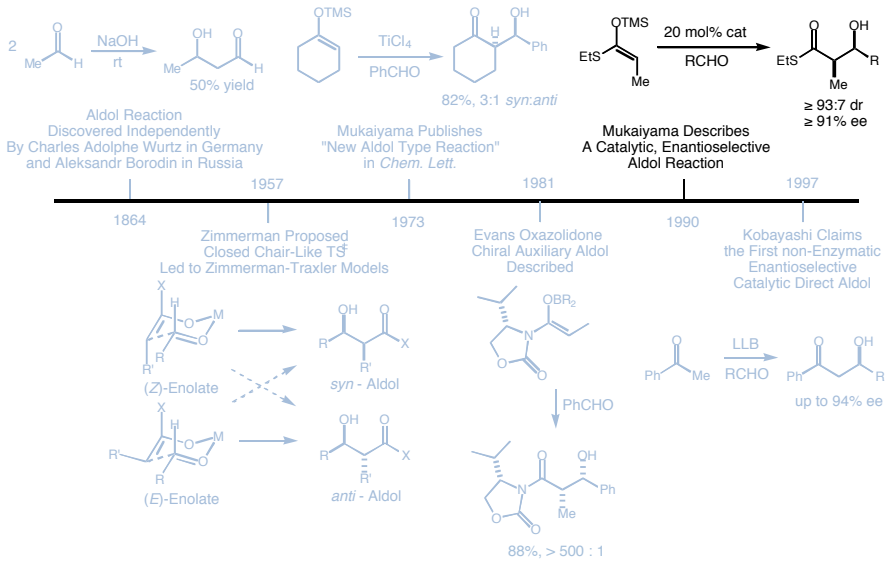
■ 1,3 *anti* Least Effective if 3 PG is Silyl

■ For the 1,4 *anti* Effect, see: Patterson *Tet. Lett.* **1994**, 9083, 9087. Propionates give 1,4 *syn*.

■ Effect of other 2 Stereocenters is Unknown

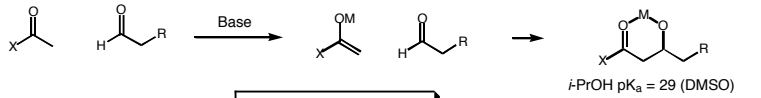
■ Complex Aldol Reactions Generally Require Significant Optimization of Enolization Conditions, Solvent, and PG's

## *Enantioselective Catalysis of the Mukaiyama Aldol Reaction*




## *Catalysis of the Aldol Reaction*

■ Challenges to Metal-Catalysis of the Aldol Reaction: The Direct Aldol

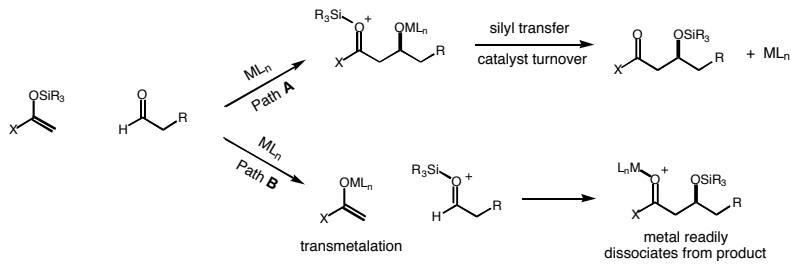



| X | DMSO $pK_a$ |
|---|---|
| Me | 27 |
| Ph | 25 |
| O*t*-Bu | 30 |
| $NMe_2$ | 33 (est) |
| H | 21-24 (est) |

Aldol Acceptor More Acidic ⇩ Chemoselectivity Problem

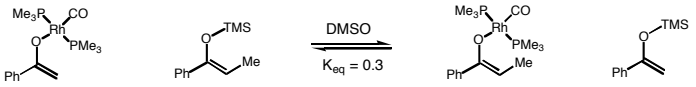
Product More Basic than SM ⇩ Turnover Problem

■ Catalysis of the Mukaiyama Aldol Reaction:

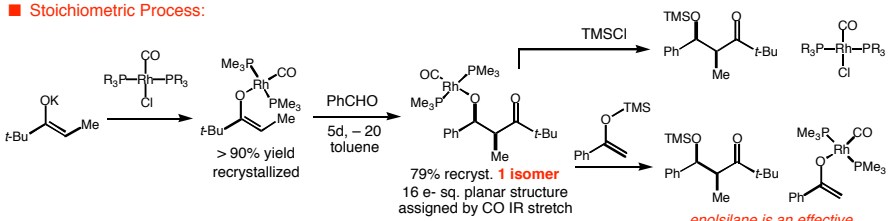


## *The First Catalytic Mukaiyama Aldol Reaction*

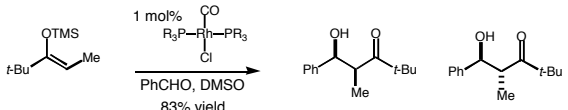
- Bergman and Heathcock *J. Am. Chem. Soc.*, **1989**, *111*, 938.
  - An excellent paper to read for its brilliant logic
- Enolate Equilibration Discovered:




- Stoichiometric Process:




- Catalytic Process is Efficient

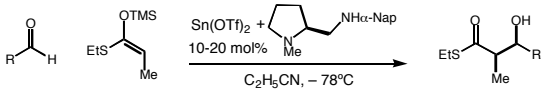



- Reaction scope limited to non-enolizable aldehyde Aldol acceptors due to basicity of Rh enolate
- No crossover experiments preformed to determine origin of loss in dr

- No Reports of Enantioselective Catalysis with this Reaction

## *Enantioselective Catalysis of the Mukaiyama Aldol Reaction–Syn Aldols*

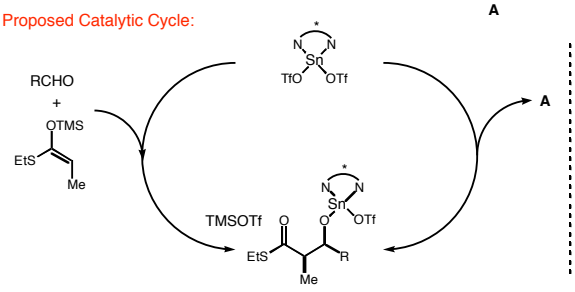
- The First Enantioselective Catalytic Mukaiyama Aldol: Mukaiyama and Kobayashi *Chem Lett.* **1990**, 129, 1455.



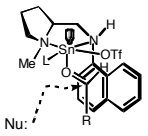

**A**

| R | Yield | *syn*:*anti* | ee |
|---|---|---|---|
| Ph | 77 | 93 : 7 | 90 |
| Tol | 75 | 89 : 11 | 91 |
| Crotyl | 76 | 96 : 4 | 93 |
| Octyl | 80 | 100 : 0 | >98 |
| *c*-Hex | 71 | 100 : 0 | >98 |

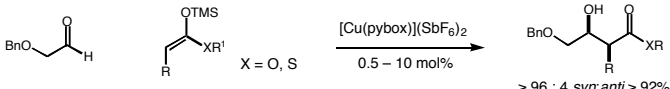
- Proposed Catalytic Cycle:




**Stereochemical Model:**




- State of the Art in *Syn*-Selective Enantioselective Mukaiyama Aldol Reactions:




pyruvate esters function with similar efficiency

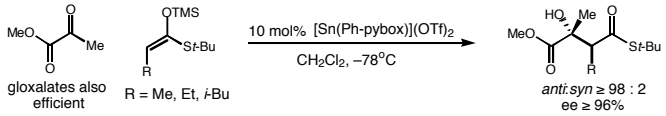
R = H, Me

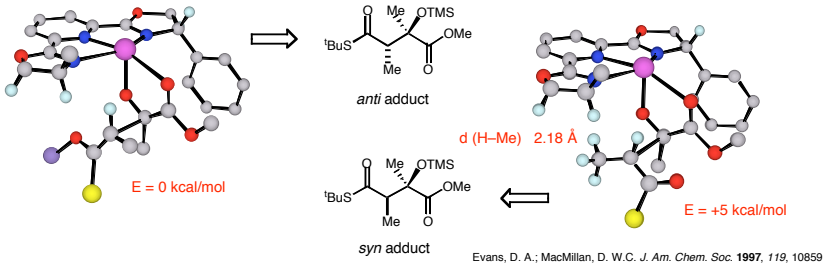
≥ 96 : 4 *syn*:*anti* ≥ 92% ee

Evans *J. Am. Chem. Soc.* **1996**, *118*, 5814
Evans *J. Am. Chem. Soc.* **1997**, *119*, 7893
Evans *J. Am. Chem. Soc.* **1999**, *121*, 686

## *Enantioselective Catalysis of the Mukaiyama Aldol Reaction–Anti Aldols*

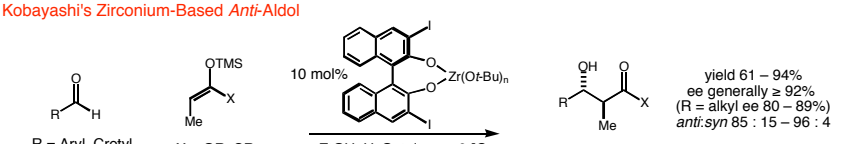
■ The First Efficient *Anti*-Selective Enantioselective Catalytic Mukaiyama Aldol Reaction:




Evans, D. A.; MacMillan, D. W.C. *J. Am. Chem. Soc.* **1997**, *119*, 10859

■ Kobayashi's Zirconium-Based *Anti*-Aldol

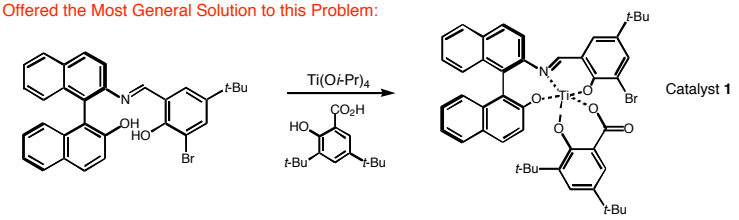



Note: Non-Linear Effect Observed ⇨ Uncertain TS
Dimeric Catalyst Proposed

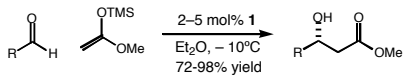
Kobayashi, *J. Am. Chem. Soc.* **2002**, *124*, 3292

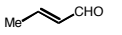
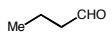
## *Enantioselective Catalysis of the Mukaiyama Aldol Reaction–Acetate Aldols*

■ Carreira Offered the Most General Solution to this Problem:

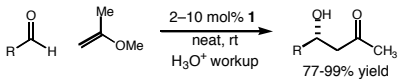


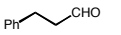
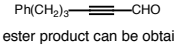

*J. Am. Chem. Soc.* **1994**, *116*, 8837




| Aldehyde | ee |
|---|---|
|  | 97 |
|  | 95 |
| *c*-HexCHO | 95 |
| PhCHO | 96 |
|  | 97 |

*J. Am. Chem. Soc.* **1995**, *117*, 3649



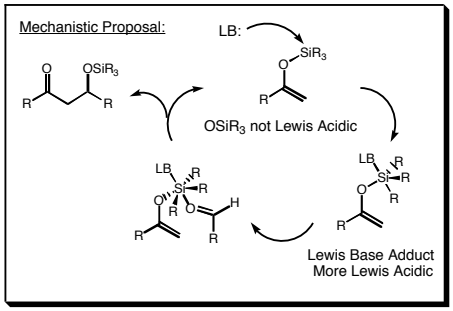

| Aldehyde | ee |
|---|---|
|  | 90 |
| *o*-MePhCHO | 75 |
|  | 93 |
|  | 91 |
|  | 98 |

Methyl ester product can be obtained by ozonolysis workup

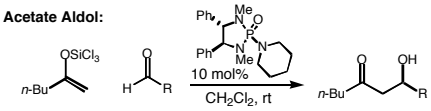
## *Chiral Lewis Base Catalysis of the Mukaiyama Aldol*

An Organocatalytic Approach to the Aldol Reaction:
see Denmark *Acc. Chem. Res.* **2000**, *33*, 432.

- Only trichlorosilylenol ethers are substrates
- There is a background reaction with trichlorosilylenolates
- Ketone & Aldeyhde enolates work well due to low bkgrd
- Phosphoramides and *N*-oxides are effective catalysts
- Reaction is stereospecific—*Z*-enolates give *syn*, *E*-enolates give *anti* products, implicating a closed TS unlike most Mukaiyama-Type processes
- Non-linear effects observed, complicates analysis



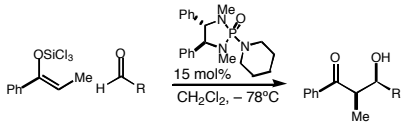

**Acetate Aldol:**




| R | time (h) | yield | ee |
|---|---|---|---|
| Cinnamyl | 2 | 94 | 84 |
| α-Nap | 2 | 92 | 86 |
| *p*-Biphenyl | 2 | 95 | 86 |
| *c*-Hex | 6 | 79 | 89 |
| *t*-Bu | 6 | 81 | 92 |

Denmark *J. Org. Chem.* **1998**, *63*, 918

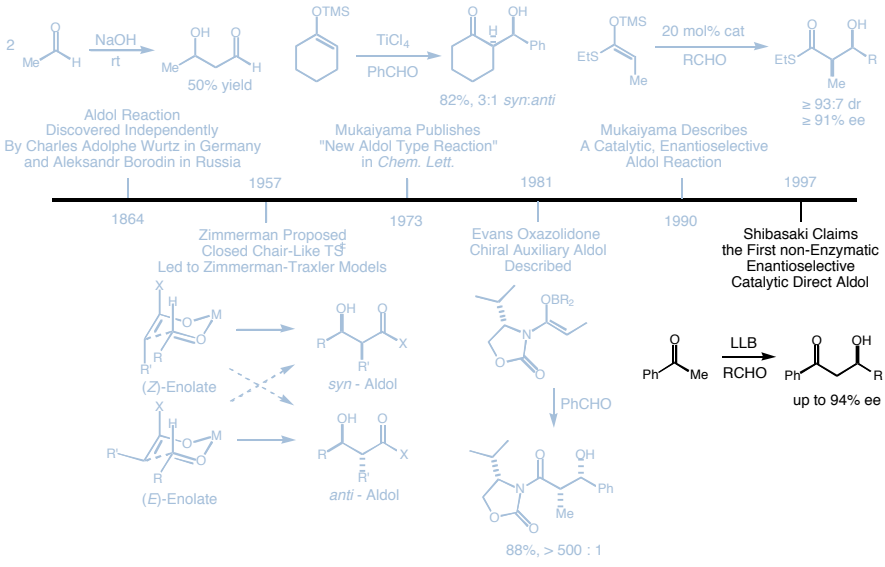
**Propionate Aldol:**




| R | yield | *syn*:*anti* | ee |
|---|---|---|---|
| Ph | 95 | 18 : 1 | 95 |
| α-Nap | 96 | 3 : 1 | 84 |
| Cinnamyl | 97 | 9 : 1 | 92 |

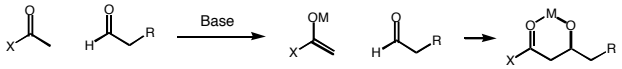
Denmark *Acc. Chem. Res.* **2000**, *33*, 432.

## *Enantioselective Catalytic Direct Aldol Reactions*



## *Catalysis of the Direct Aldol Reaction*

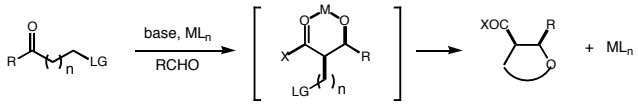
■ Challenges to Metal-Catalysis of the Aldol Reaction: The Direct Aldol



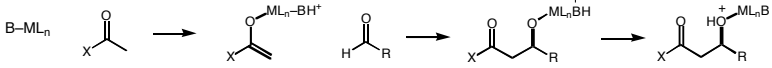

Product More Basic than SM
⇩
Turnover Problem

■ Approaches to the Direct Aldol Problem. Or, How to Quench an Alkoxide.

■ Build an intramolecular trap for the nascent alkoxide (*i.e.* the Ito–Hayashi Gold Aldol)

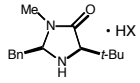



■ Incorporate a proton shuttle on the catalyst (*e.g.,* Shibasaki, and Trost)




■ Silylate the aldolate (*e.g.*, Evans catalytic aldol)

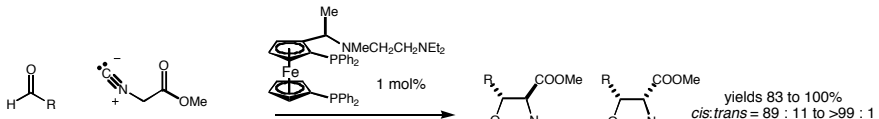

■ Avoid alkoxides altogether by using 2° amine catalysts (*e.g.*, enzymes, proline, *t*-Bu-Bn-Im)




## *The First Catalytic Aldol Reaction*

■ The First Catalytic Aldol-Type Process: Ito and Hayashi *J. Am. Chem. Soc.*, **1986**, *108*, 6405.

Solution to the Catalytic Aldol Problem — Intramolecular Trap for Alkoxide



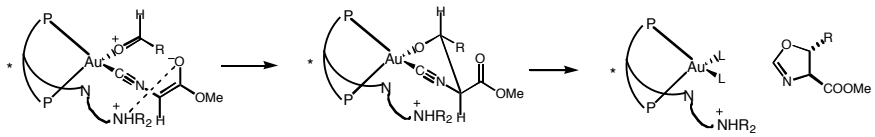

R = Ph, Crotyl, Me, *i*-Pr, *c*-Hex, *t*-Bu

yields 83 to 100%
*cis*:*trans* = 89 : 11 to >99 : 1
ee generally ≥ 95%

*This is a direct, enantioselective catalytic aldol reaction 11 years before the reports of Shibasaki, and Trost!*

⟹ Limitation/Adantage of this process is the α-amino acid functionality. Not applicable to acetate and propionate synthesis, but highly useful for the synthesis of serine derivatives and aminosugars.

■ Ito and Hayashi Invoke the Following Mechanism for their Bifunctional Catalyst:

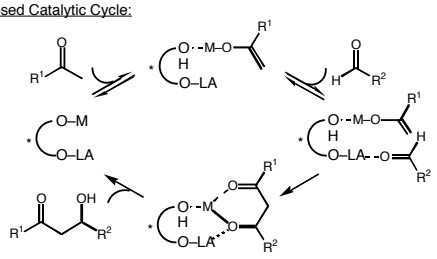


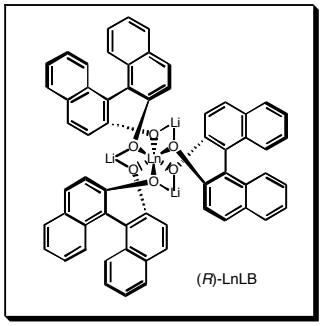
Catalyst Amine Deprotonates Ester | Aldol Reaction | Alkoxide Trapped By Isocyanide, Catalyst Turnover

## *The Direct Aldol Reaction—Proton Shuttle # 1 LnLB*

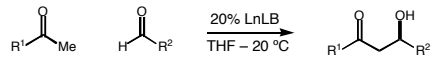
■ Shibasaki Claims the First Direct Catalytic Aldol Reaction:

Proposed Catalytic Cycle:





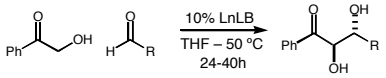

The Methyl Ketone Aldol




| $R^1$ | $R^2$ | Ketone Equiv | t (h) | yield | ee |
|---|---|---|---|---|---|
| Ph | *t*-Bu | 5 | 88 | 76 | 88 |
| Ph | $PhCH_2C(CH_3)_2$ | 7.4 | 87 | 90 | 69 |
| Ph | *c*-Hex | 8 | 169 | 72 | 44 |
| Ph | *i*-Pr | 8 | 277 | 59 | 54 |
| Ph | $Ph(CH_2)_2$ | 10 | 72 | 28 | 52 |
| α-Nap | *t*-Bu | 8 | 253 | 55 | 76 |
| Me | *t*-Bu | 10 | 100 | 53 | 73 |
| Et | $PhCH_2C(CH_3)_2$ | 50 | 185 | 71 | 94 |

Shibasaki *J. Am. Chem. Soc.* **1999**, *121*, 4168

More Acidic Ketones Give Better Results




| R | Ketone Equiv | yield | *syn*:*anti* | ee |
|---|---|---|---|---|
| *i*-Bu | 2 | 86 | 2 : 1 | 90 |
| *n*-Hex | 2 | 84 | 3 : 1 | 94 |
| $Ph(CH_2)_2$ | 2 | 84 | 5 : 1 | 95 |
| *c*-Hex[a] | 2 | 89 | 1 : 6 | 85 |
| *i*-Pr[a] | 2 | 92 | 1 : 5 | 86 |

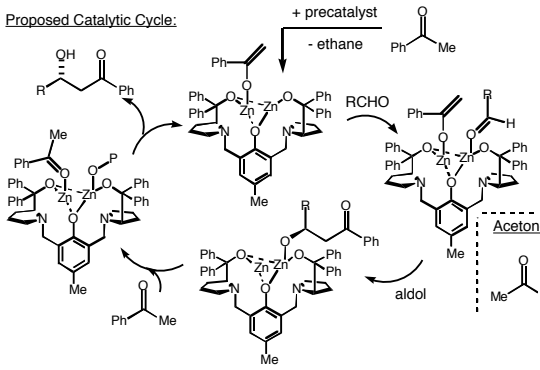
[a]using a modified LnLB ligand

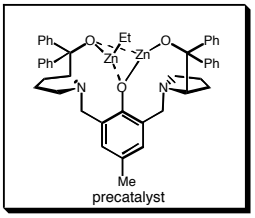
Shibasaki *J. Am. Chem. Soc.* **2001**, *123*, 2467

## *The Direct Aldol Reaction—Proton Shuttle # 2 Trost Ligand*

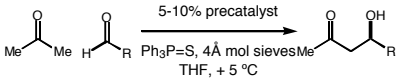
■ Trost's Design Closely Follows Shibasaki's Catalyst

Proposed Catalytic Cycle:



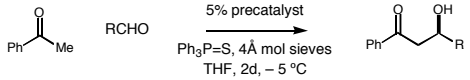




Acetone Functions Surprisingly Well:

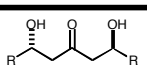



| R | yield | ee |
|---|---|---|
| *c*-Hex | 85 | 93 |
| *i*-Pr | 89 | 91 |
| *t*-Bu | 72 | 94 |
| *i*-Bu | 59 | 84 |
| $Ph(CH_2)_2$ | 59 | 89 |
| *n*-Bu | 56 | 84 |
| Ph | 55 | 88 |

Acetophenone Works With Modest Efficiency




R = unbranched alkyl yield 24-49% ee 56-68
R = *i*-Pr or larger yield 60-79% ee 93-99%
R = aromatic unreactive

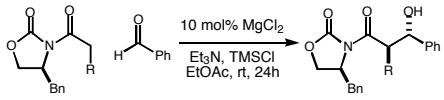
no  reported, elimination major side-product

*J. Am. Chem. Soc.* **2000**, *122*, 12003

Added $Ph_3P=S$ aids in catalyst turnover by reversible competition with product

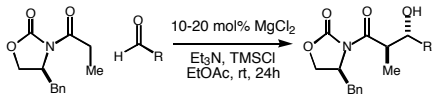
## *The Direct Aldol Reaction—Alkoxide Silylation for Turnover*

■ Evans *et al.* Developed A Catalytic Aldol Based on Silylation of the Aldolate:




| R | dr | yield |
|---|---|---|
| Me | 32 : 1 | 91 |
| Et | 32 : 1 | 88 |
| Bn | 26 : 1 | 94 |
| *i*-Bu | 32 : 1 | 91 |
| Allyl | 28 : 1 | 91 |
| *i*-Pr | 3.5 : 1 | 36 (conv) |

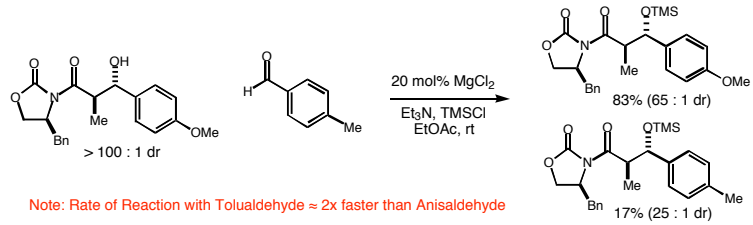
dr = major : Σ isomers
doesn't indicate if dr is mostly due to *anti*:*syn* or *anti* dr




| Aldehyde | Procedure | dr | yield |
|---|---|---|---|
| X = Me | A | 24 : 1 | - |
| X = OMe | A | 32 : 1 | 91 |
| X = $NO_2$ | B | 7 : 1 | 71 |
| X = Ph, Y = H | B | 21 : 1 | 92 |
| X = Ph, Y = Me | A | 28 : 1 | 92 |
| X = H, Y = Me | B | 16 : 1 | 77 |

A : 20 mol % $MgCl_2$, B : 10 mol % $MgCl_2$ 30 mol% $NaSBF_6$

■ Crossover Experiments Show Delicate Balance Between Retro-Aldol and Product Silylation:

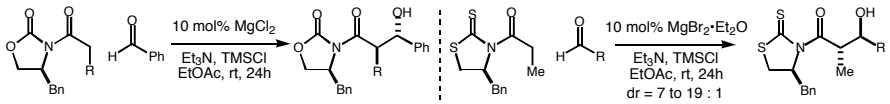



Note: Rate of Reaction with Tolualdehyde ≈ 2x faster than Anisaldehyde

Evans *J. Am. Chem. Soc.* **2002**, *124*, 392

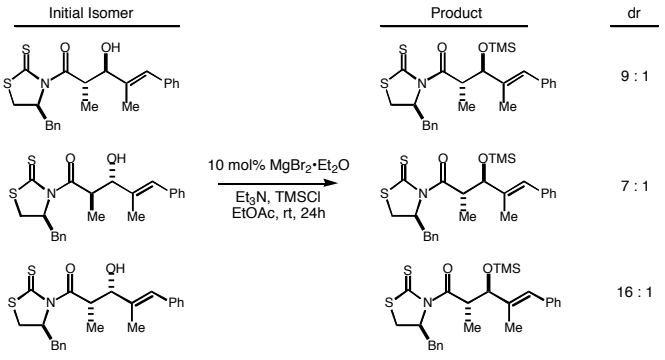
## *The Direct Aldol Reaction—Alkoxide Silylation for Turnover*

■ In Analogy to Crimmins's Work, Thiazolidinthiones Give the Opposite Enantioseries:




scope similar to oxy-done cases

■ Retroaldol Seems to be Faster than Silylation for this Auxiliary:

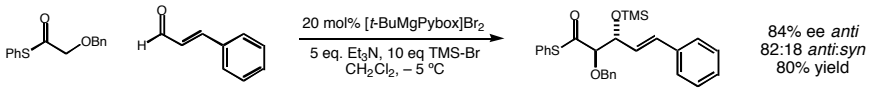



...Although Reaction not necessarily under Thermodynamic Control

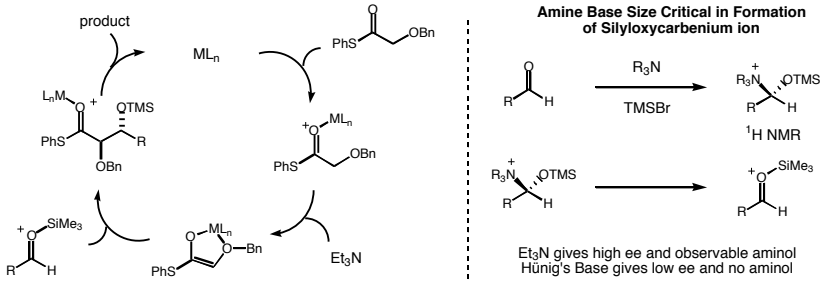
Evans *Org. Lett.* **2002**, *4*, 1127

## *The "Jake Aldol" Enantioselective Catalysis of the Direct Aldol Reaction*

- Acidic Bidentate Thioesters, Non-Enolizeable Aldehydes and Small Amine Bases Function Well




- Mechanistic Investigations Support it not beign a Mukaiyama Aldol:



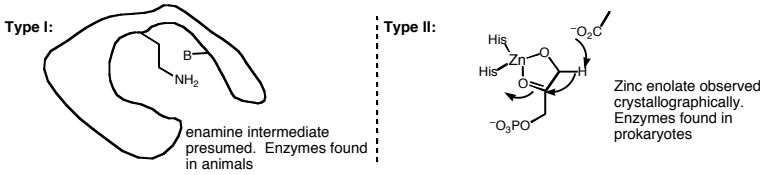

- Reaction Scope Yet to be Determined

Wiener, MacMillan, *Unpublished Results.*

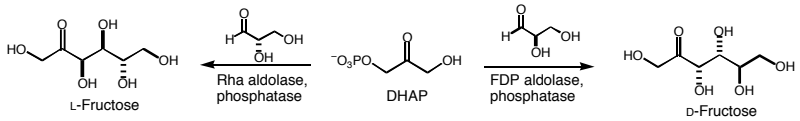
## *Enzymatic Aldol Reactions—A Summary*

- The Original Organic Catalysts: For an excellent review, see: Wong, *Angew. Chem. Int. Ed.* **2000**, *39*, 1352.

Two Types of Aldolases:

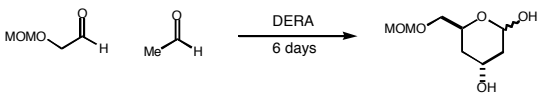



- Synthesis of D-Fructose and L-Fructose With Type II DHAP Dependant Aldolases:




Wong *J. Org. Chem.* **1995**, *60*, 4294

- The Type I Enzyme 2-Deoxyribose-5-Phosphate Aldolase (DERA) Catalyzes an Interesting Aldol Trimerization:

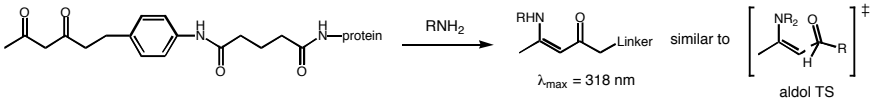



DERA is an acetaldehyde dependant aldolase.
While many aldehydes are good aceptors, only acetaldehyde is an efficient aldol donor

Wong, *J. Am. Chem. Soc.* **1995**, *117*, 3333

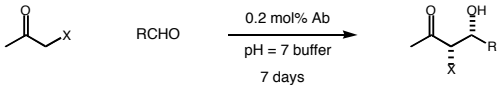
## *Antibody Catalyzed Aldol Reactions—A Summary*

■ Antibodies Raised with Haptens Designed to Place an Amine at the Binding/Active Site (Type I Mimic):



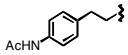
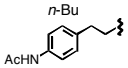

Lerner, Barbas *Science* **1995**, *270*, 1797

■ 2 of 20 generated antibodies showed Strong UV abs. at 316 nm, 38C2 and 33F12:




yields listed for 2 of >20 examples
67, 82% yields

Lerner, Barbas *J. Am. Chem. Soc.* **1998**, *120*, 2768

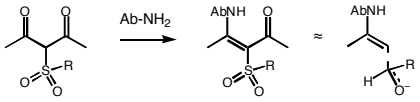
| Substrates | | ee | |
|---|---|---|---|
| X | R | 38C2 | 33F12 |
| H | Ph | >99 | >99 |
| H | *p*-$NO_2$Ph | 98 | 99 |
| H | *p*-$NO_2$Cinnamyl | 99 | 98 |
| H |  | 20 | 3 |
| OH | *n*-Bu | >98* | 89* |
| OH |  | 77* | 70* |

*syn:anti >99:1; opposite enantioseries!

■ Antibody 38C2 available through Aldrich
10mg $108.70 (MW = 150,000) should give 0.03mmol

■ Retroaldol kinetic resolution possible $k_{rel}$ 2 – >200 with similar substrate types: Lerner, Barbas *Angew. Chem. Int. Ed.* **1998**, *37*, 2481

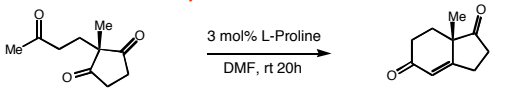
■ New Hapten raises antibodies (93F3) giving opposite sense of induction and similar scope:




Lerner, Barbas *Angew. Chem. Int. Ed.* **1999**, *38*, 3738

## *Proline Catalyzed Aldol Reactions*

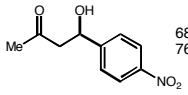
■ The Eder-Sauer-Wiechert-Hajos-Parrish Reaction:



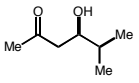

84% yield, 96% ee

Eder, Sauer, Wiechert *Angew. Chem. Int. Ed.* **1971**, *10*, 496
Hajos, Parrish *J. Org. Chem.* **1974**, *39*, 1615

■ Barbas (with List and Lerner) became Interested Based on Ab Catalysis and Extended to Intermolecular Cases:




68% yield
76% ee




97% yield
96% ee

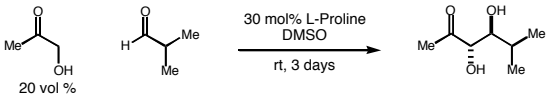
■ Uses 20 mol% cat, 20 vol% acetone, 24 – 48h at +4 °C or rt

■ Cyclic and Acyclic Ketones good

■ Linear unbranched aldehydes low yield

List, Lerner, Barbas *J. Am. Chem. Soc.* **2000**, *122*, 2395

■ Hydroxyacetone Requires Harsher Conditions to Give the *Anti*-Aldol Product:

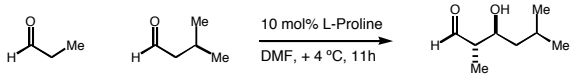



62% yield
99% ee
>95:5 *anti:syn*

6 examples
yields 38-62%
67 to >99%ee
1.5:1 to >95:5 *anti:syn*

List *J. Am. Chem. Soc.* **2000**, *122*, 7386

■ Aldehydes also Function Chemoselectively as Aldol Donors in High ee and Modest to Good *Anti* Selectivity



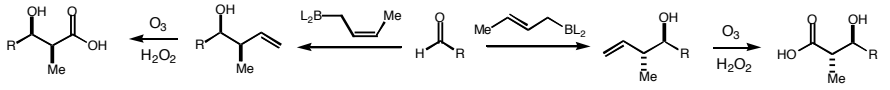

88% yield
97% ee
3:1 *anti:syn*
one regioisomer

*reaction tolerates a range of alkyl and α-oxy aldehyde donors and both alkyl and aromatic aldol acceptors*

Northrup, MacMillan *J. Am. Chem. Soc.* **2002**, *124*, 6798

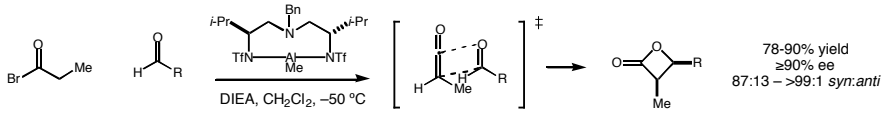
## *A Brief Survey of Other Methods to Produce β-Hydroxy Carbonyl Compounds*

■ Allylation/Crotylation–Ozonolysis Sequence:




Review: Bubnov *Pure Appl. Chem.* **1987**, *21*, 895

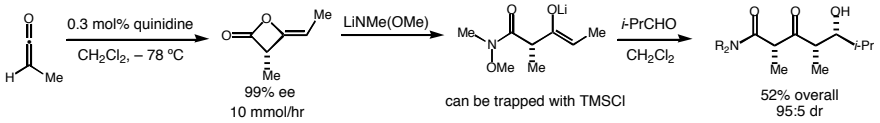
■ Nelson's Acyl Halide–Aldehyde Cyclocondensation:




*R = aromatic, $CH_2OBn$, mostly alkynyl*

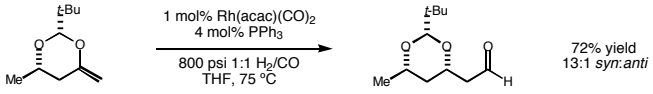
Nelson *Org. Lett.* **2000**, *2*, 1883

■ Calter's Enantioselective, Catalytic Ketene Dimerization/Aldol Sequence:




Calter *Org. Lett.* **2001**, *3*, 1499

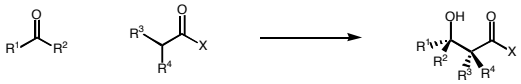
■ Leighton's Hydroformylation of Enol Ethers Builds Polyacetates in Opposite Direction:




*See CJB Strained Cyclosilane Grp. Meeting for More Leighton Chemistry*

Leighton *J. Am. Chem. Soc.* **1997**, *119*, 11118

## *Summary*




■ The Aldol Reaction is a Fundamental C-C Bond Forming Technology

■ Enolate Geometry Dictates *Syn*:*Anti* Selectivity except for Mukaiyama Aldols

■ Chiral Auxiliary Still Most Common Method for Inducing Chirality in the Aldol Reaction

■ Many Predicitve Models Available for Diastereoselective Aldol Reactions—Beware! Very Case-Specific

■ Several Good Enantioselective Catalytic Mukaiyama Aldols (both *Syn* and *Anti*) Available

■ Direct, Enantioselective Catalytic Aldol Reactions Generally Not Amenable to an Itterative Aldol Sequence due to Reliance on Ketone Aldol Donors to solve $pK_a$ Problem