α-Oxygenated Aldol Reactions

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Evans Group Meeting

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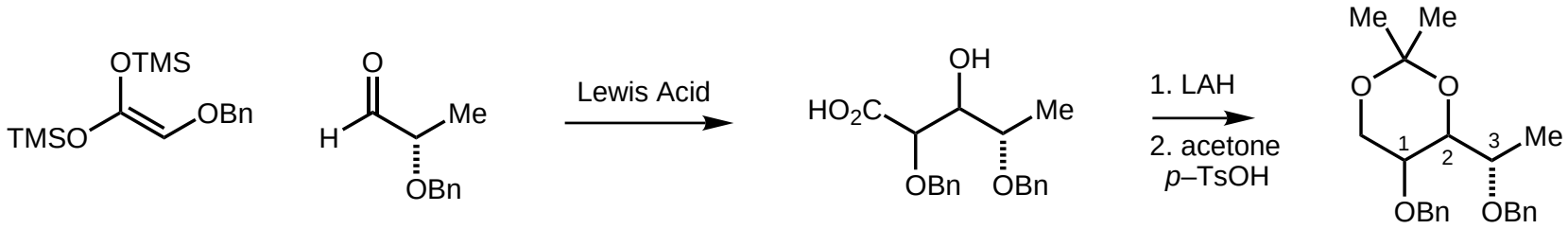
Introduction

1. Aldol Reactions of Glycolate Derivatives
2. Hydroxyketone Aldol Reactions
3. Dihydroxyacetone Aldol Reactions
4. Enzyme Mediated Aldol Reactions

Early Oxygenated Mukaiyama Aldol Study



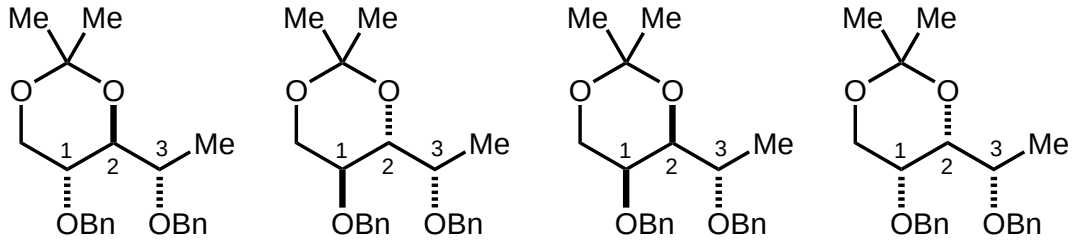
Lewis Acid = BF_3•OEt_2, $SnCl_4$, $TiCl_4$, $MgBr_2$, $ZnCl_2$, $ZnCl_2$•OEt_2, $Eu(fod)_3$, Lithium Enolate

26–54%

Best Results:

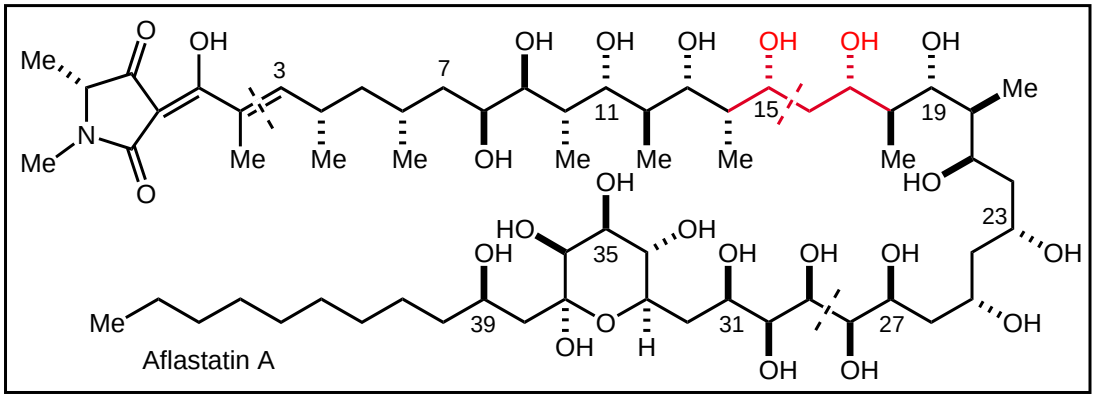
$MgBr_2$ provided 28% yield of a 0:19:1:80 ratio of products which favors the all *syn* product.
This is reaction shows a diastereoselection of 19:81 for C1,C2 and 1:99 for C2,C3. (antiperiplanar)

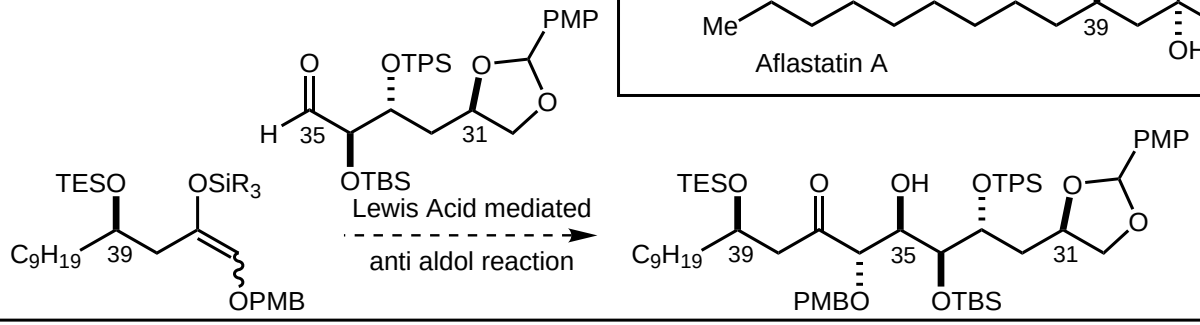
$Eu(fod)_3$ provided a 53% yield of a 0:80:11:9 ratio of products which favors the *anti*,*syn* product.
This reaction shows a diastereoselection of 80:20 for C1,C2 and 11:89 for C2,C3. (synclinal)

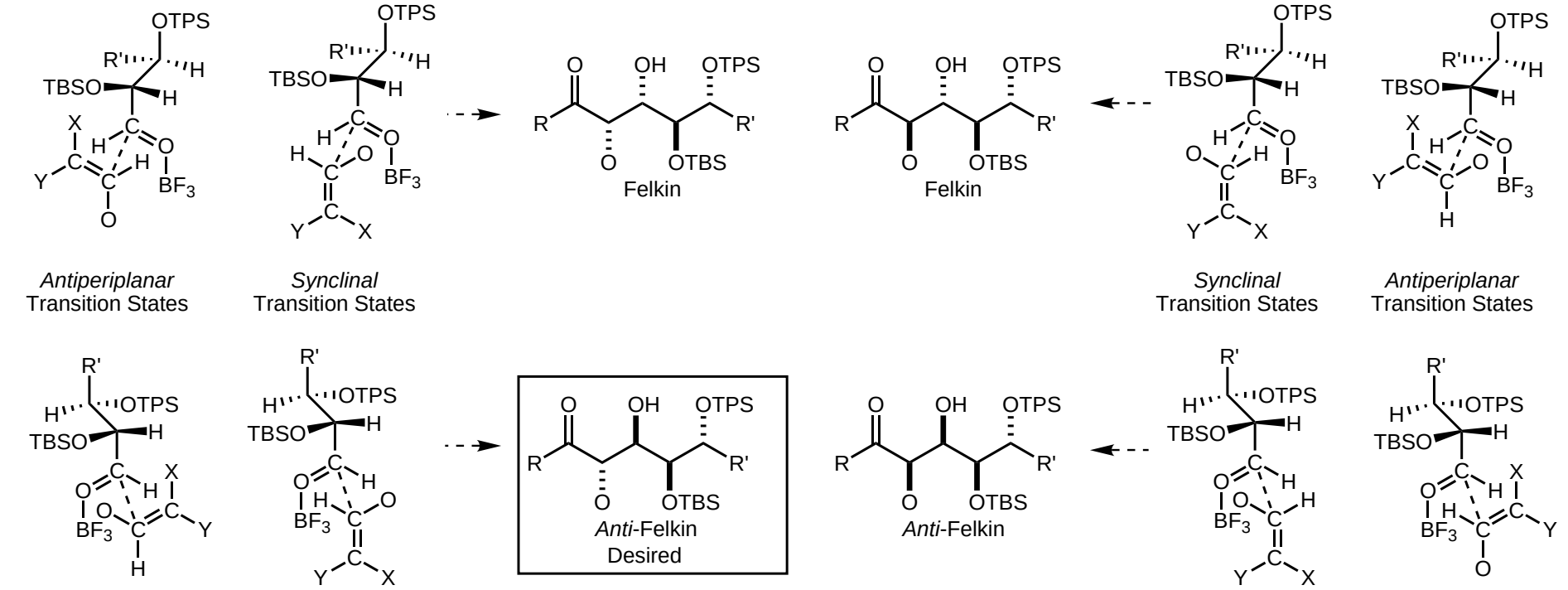


Takai, K.: Heathcock, C. H. *J. Org. Chem.* **1985**, *53*, 3247–3251.

Proposed Modes of Addition for the Mukaiyama Aldol of Poly-oxygenated Systems

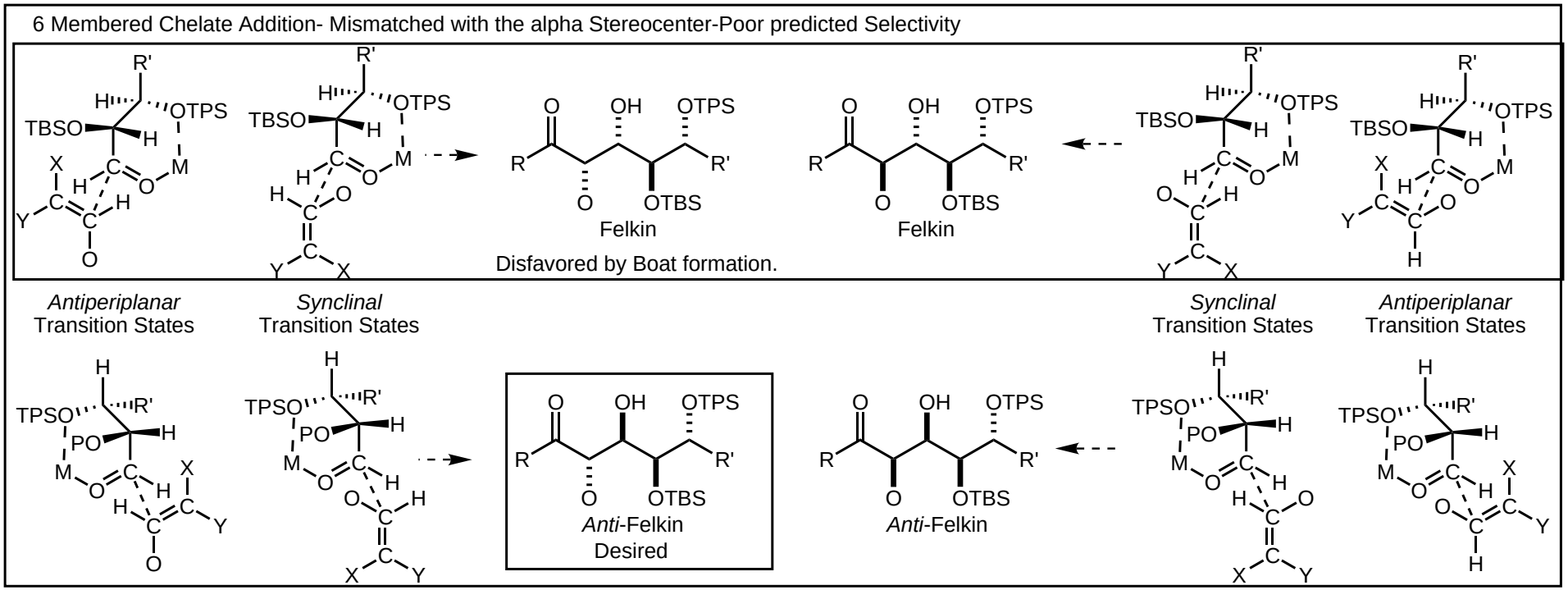


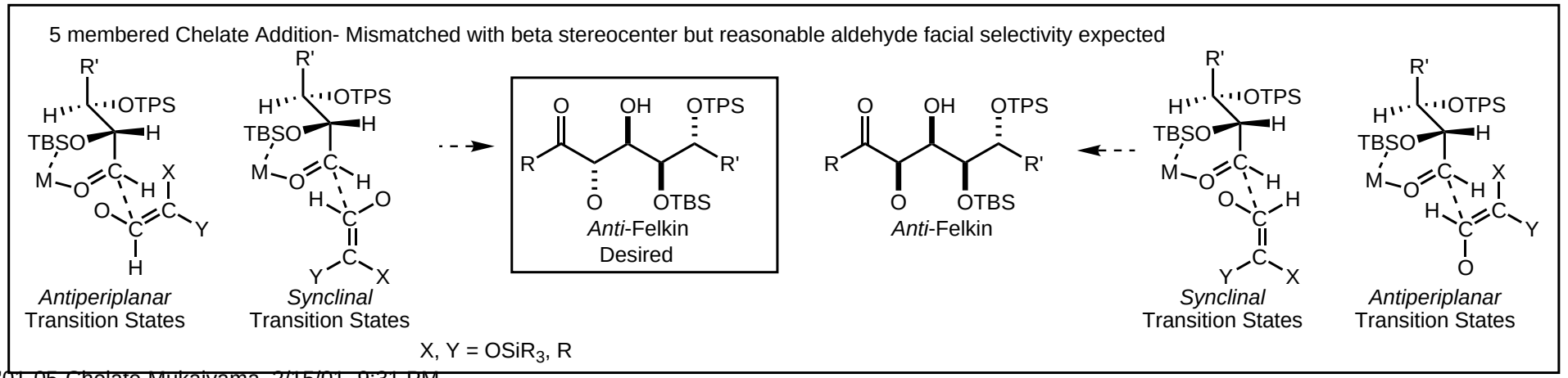




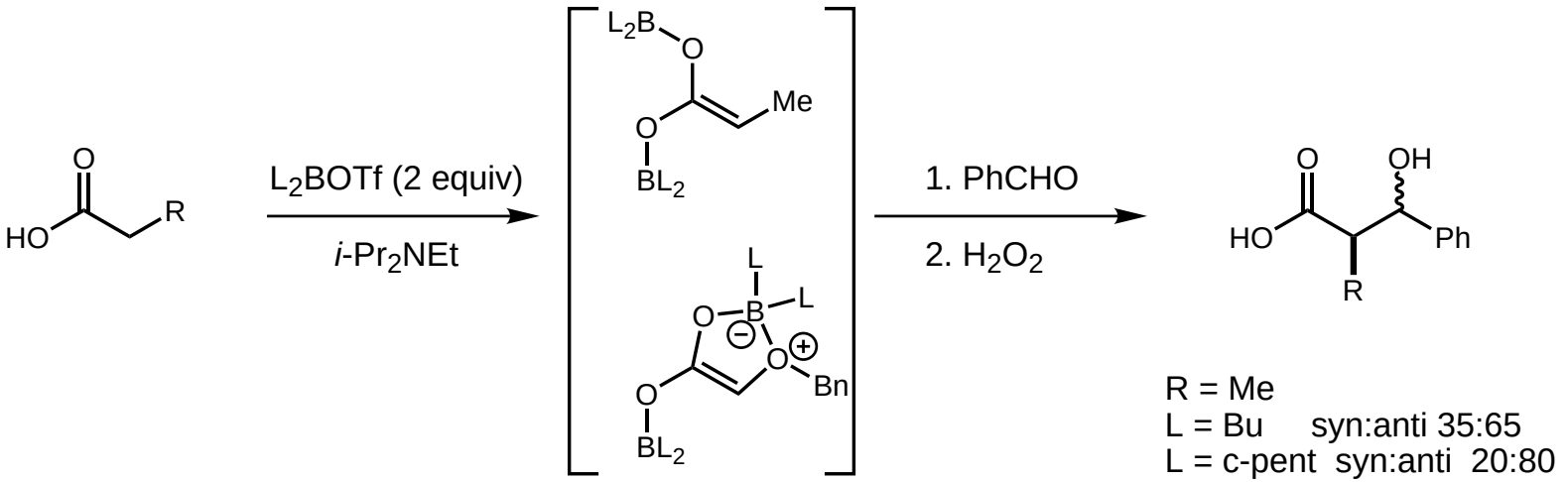
'01-04-Coupling Strategy 2/5/00 1:36 PM

Proposed Modes of Chelate Controlled Addition (6 and 5 membered chelate)





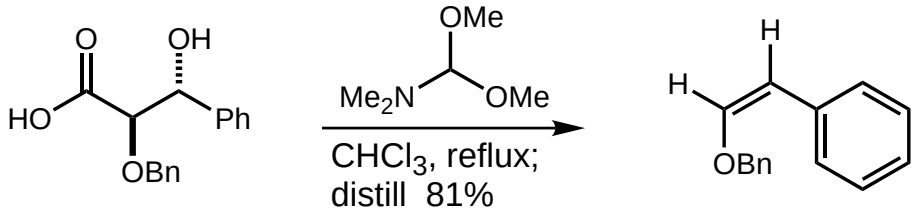
Diastereoselective Addition of Boron Ene-diolates



R = Me
L = Bu syn:anti 35:65
L = c-pent syn:anti 20:80

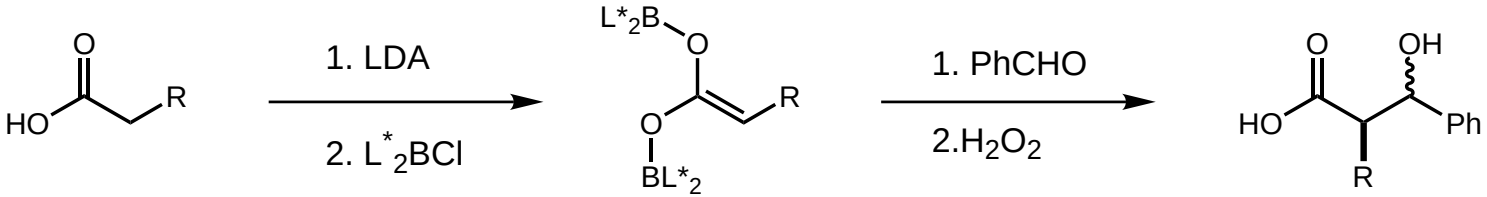
R = OBn
L = Bu only anti 85% yield

Stereochemical Proof:



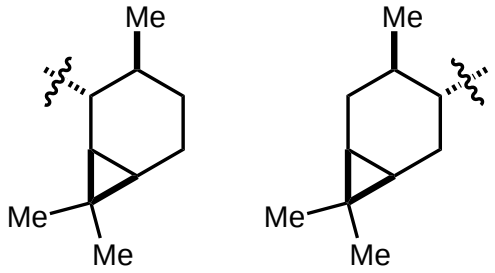
Evans, D. A.; Nelson, J. V.; Vogel, E.; Taber, T. R. *J. Am. Chem. Soc.* **1981***, 103*, 3099-3111.

Diastereoselective Addition of Chiral Boron Ene-diolates



R = H, Me, Ph, SMe
syn:anti ~10:1(2-^{d}Icr) 1:1–10(4-^{d}Icr)
%ee syn 90–99 anti 20–61
yield 50–90%

L* =



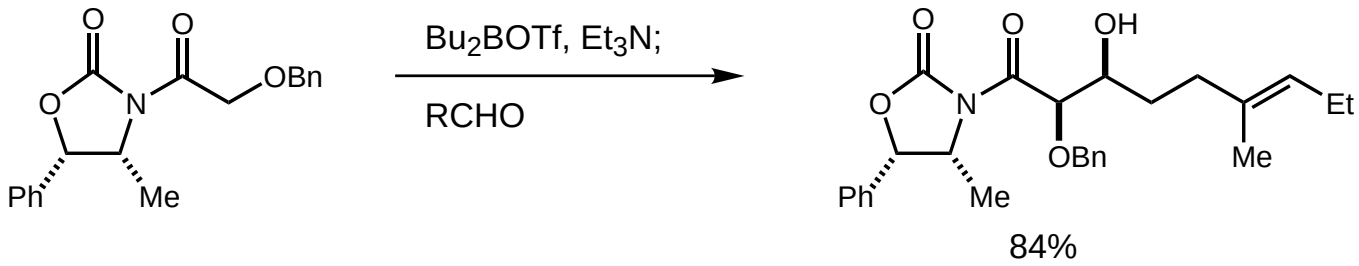
(2-^{d}Icr) (4-^{d}Icr)

R = OPh
L* = 2-^{d}Icr
syn:anti 4:1
%ee syn 98 anti 50
combined yield 68%

R = OPh
L* = 4-^{d}Icr
syn:anti 1:4
%ee syn 96 anti 80
combined yield 70%

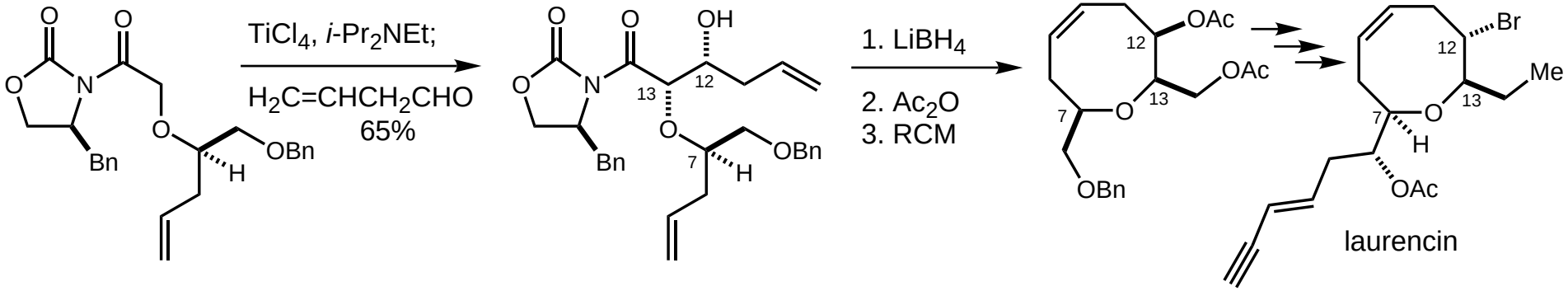
Fringuelli, F.; Piermatti, O.; Pizzo, F. *J. Org. Chem.* **1995***, 60*, 7006-7009.

Evans Boron Mediated Aldol Reaction



This methodology is general has been widely adopted and utilized in many syntheses.

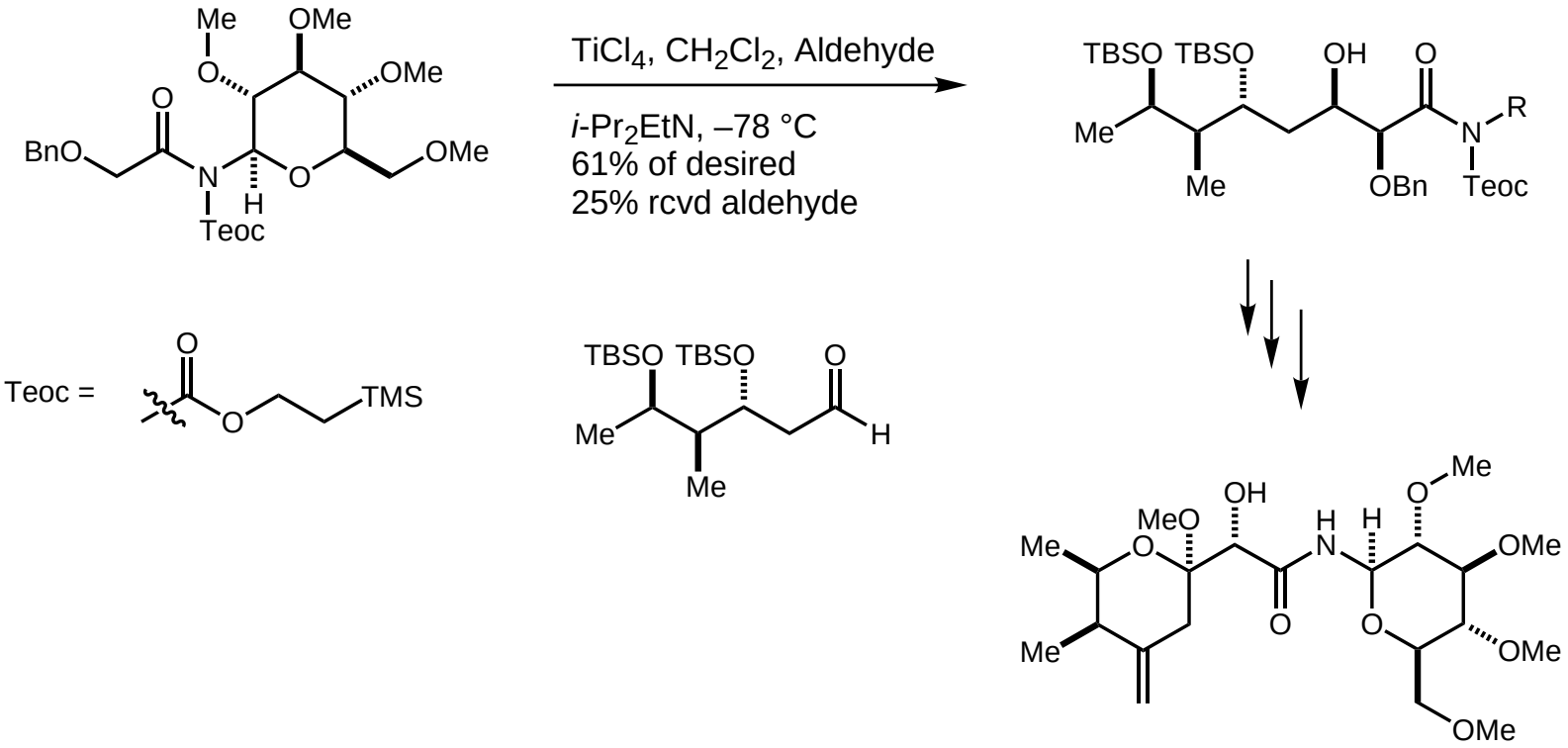
Benzyl, methyl, aryl, allyl and alkyl ethers are all tolerated.



This example is from Crimmins' formal total synthesis of laurencin

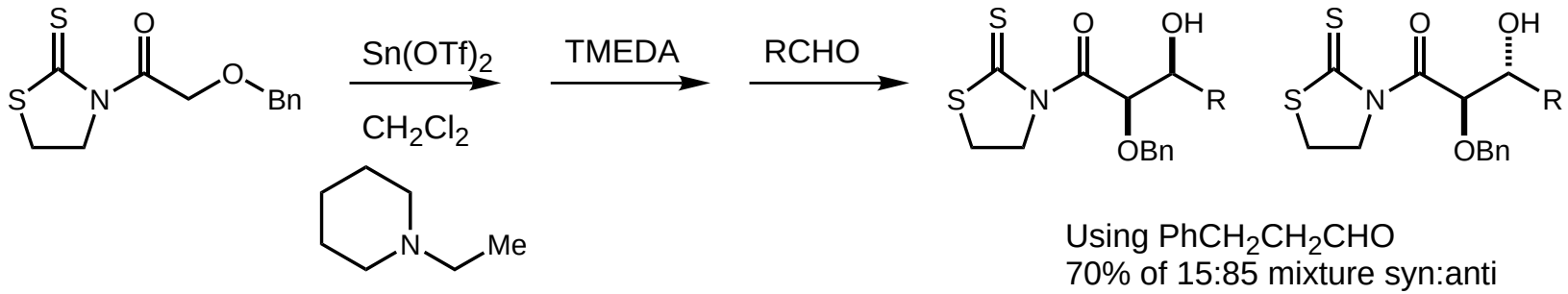
Evans, D. A.; Bender, S. L. *Tet. Lett.* **1986**, *27*, 799–802.
Evans, D. A.; Bender, S. L.; Morris, J. *J. Am. Chem. Soc.* **1988**, *110*, 2506–2526.
Crimmins, M. T.; Choy, A. L. *J. Am. Chem. Soc.* **1999**, *121*, 5653–5660.

Oxy-aldol Approaches to Pederic Acid Analogs



Roush, W. R.; Pfeifer, L. A.; Marron, T. G. *J. Org. Chem.* **1998**, *63*, 2064-2065.

Sn^{II} Mediated Anti Aldol of Benzyloxy Acyl Thiazolidines

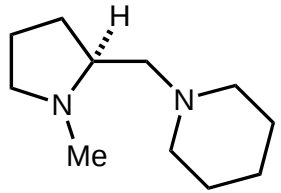


Using $PhCH_2CH_2CHO$
70% of 15:85 mixture syn:anti

Without TMEDA syn:anti 3:1

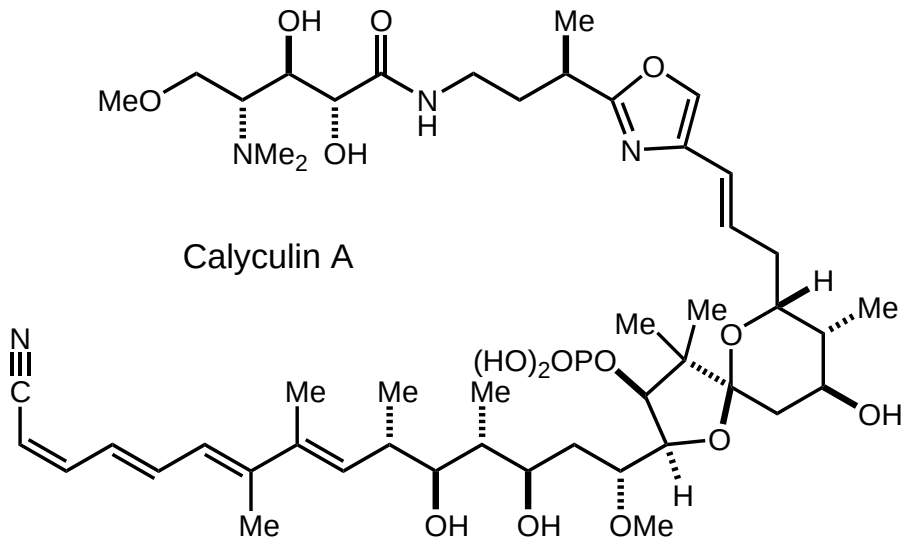
Appears to be fairly general and gives a 17:83–7:93 ratio depending on aldehyde (hexanal, c-HexCHO, *i*-PrCHO, PhCHO).

Use of enantiopure chiral diamine provides the same ratio of syn:anti in good ee 87–94%. (determination of absolute not indicated)

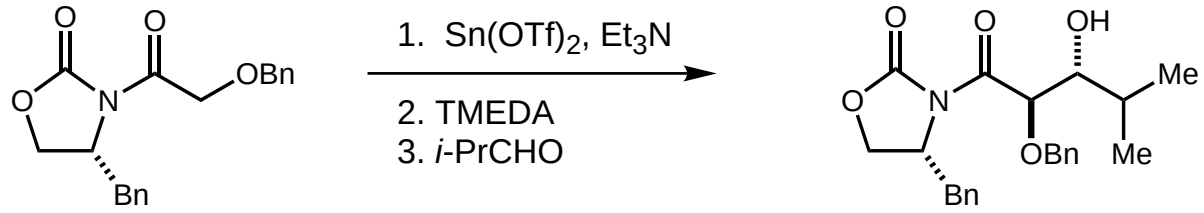


Mukaiyama, T.; Iwasawa, N. *Chem. Lett.* **1984**, 753–756.

Evans Sn^{II} Aldol Reaction



Calyculin A



63% isolated yield
~80:20 of desired:Σ of other ds

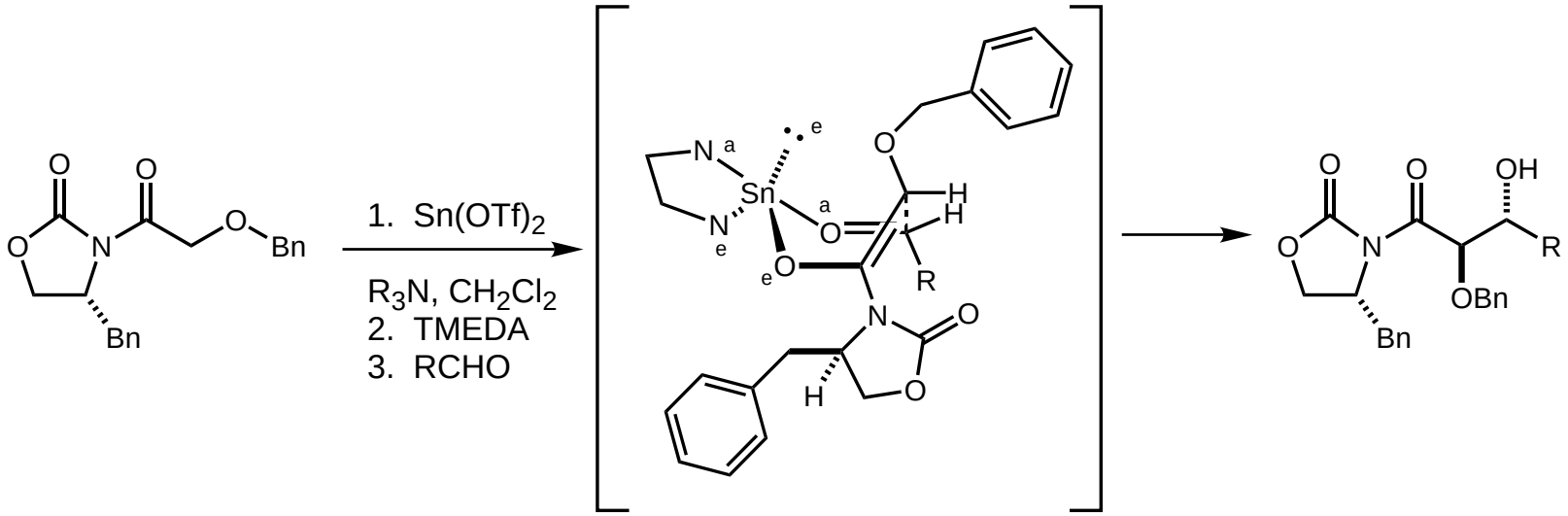
This reaction has been used widely in the synthesis of natural products. It is very general however has the failing of being only modestly stereoselective.

The *p*-OMeBn protected analog works equally.

The silyl protected analogs do not behave well in this reaction (preliminary result F. Glorius)

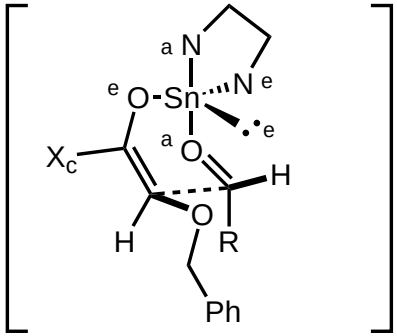
Evans,D. A.; Gage, J. R.; Leighton, J. L.; Kim, A. S. *J. Org. Chem.* **1992**, *57*, 1961–1963.

Rationale for the Stereoselection Observed in the Sn^{II} Mediated Aldol Reaction

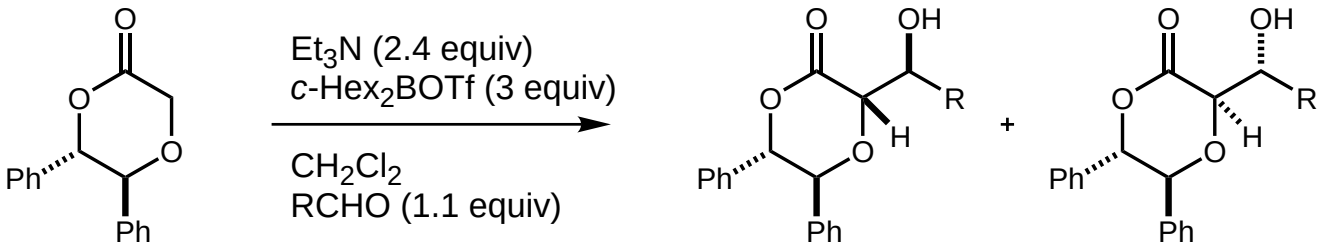


To the best of my knowledge, there has not been a mechanistic model proposed to explain the diastereoselectivity observed in the Sn^{II} mediated aldol reaction of acyloxazolidinones.

This model correctly predicts the stereochemical outcome of the reaction.

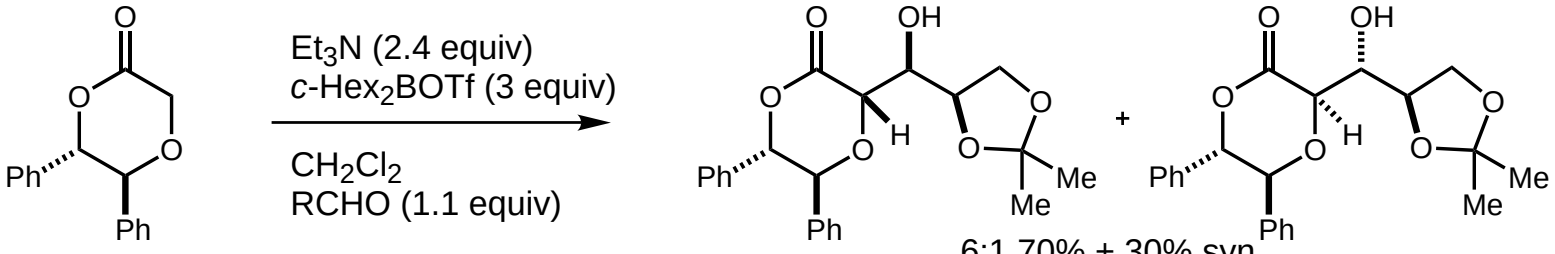


Anti Selective Glycolate Aldol Additions

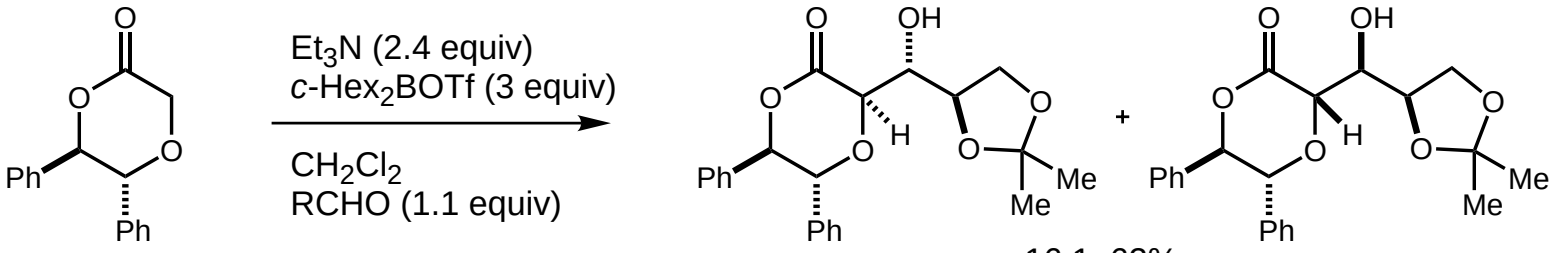


Bu_2BOTf gave lower ds (4:1)
$TiCl_4$ gave 3:1 and lower yield (40%)

yields consistent 71-92% best with aliphatic
ds ratio 8–20:1 with aliphatic aldehydes
4–7:1 with unsaturated aldehydes



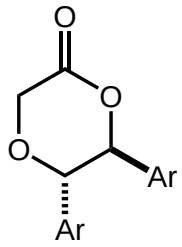
6:1 70% + 30% syn



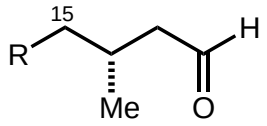
16:1 62%

Andrus, M. B.; Soma Sekhar, B. B. V.; Meredith, E. L.; Dalley, N. K. *Org. Lett.* **2000**, *2*, 3035–3037.

Anti Glycolate Aldol Reaction

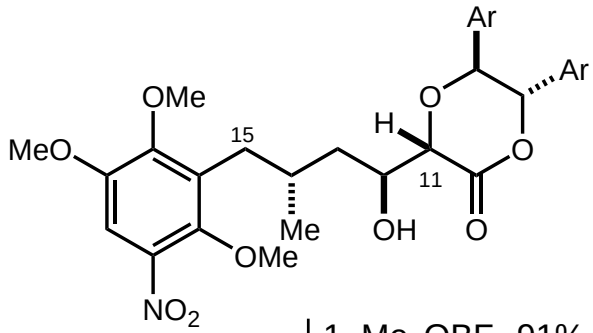


Ar = *p*-OMe-Ph

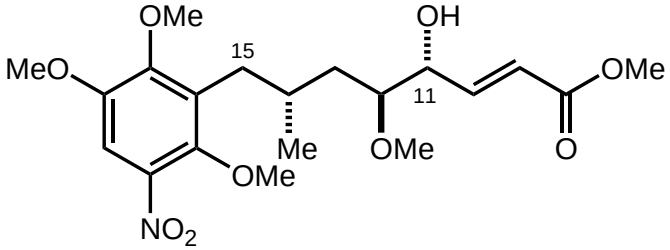


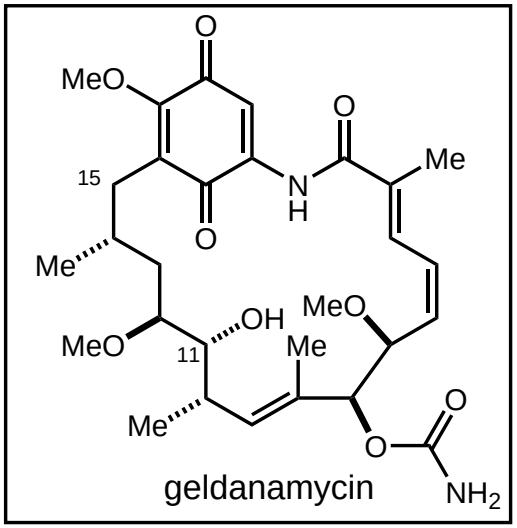
$(c\text{-Hex})_2BOTf$,
Et_3N, CH_2Cl_2,

–78 °C, 70%
ds 15:1 anti:syn

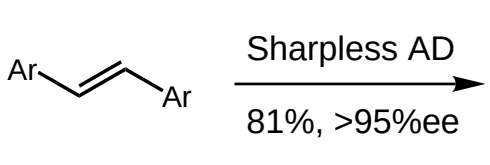


1. Me_3OBF_4 91%
2. Dibal-H 91%
3. LiCl, $Ph_3P{=}CHCO_2Me$
   93%, 19:1
4. CAN 93%

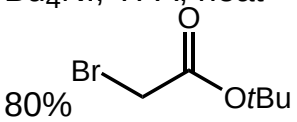




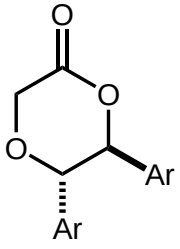
Auxillary Preparation:



Ar = Ph or *p*-OMe-Ph

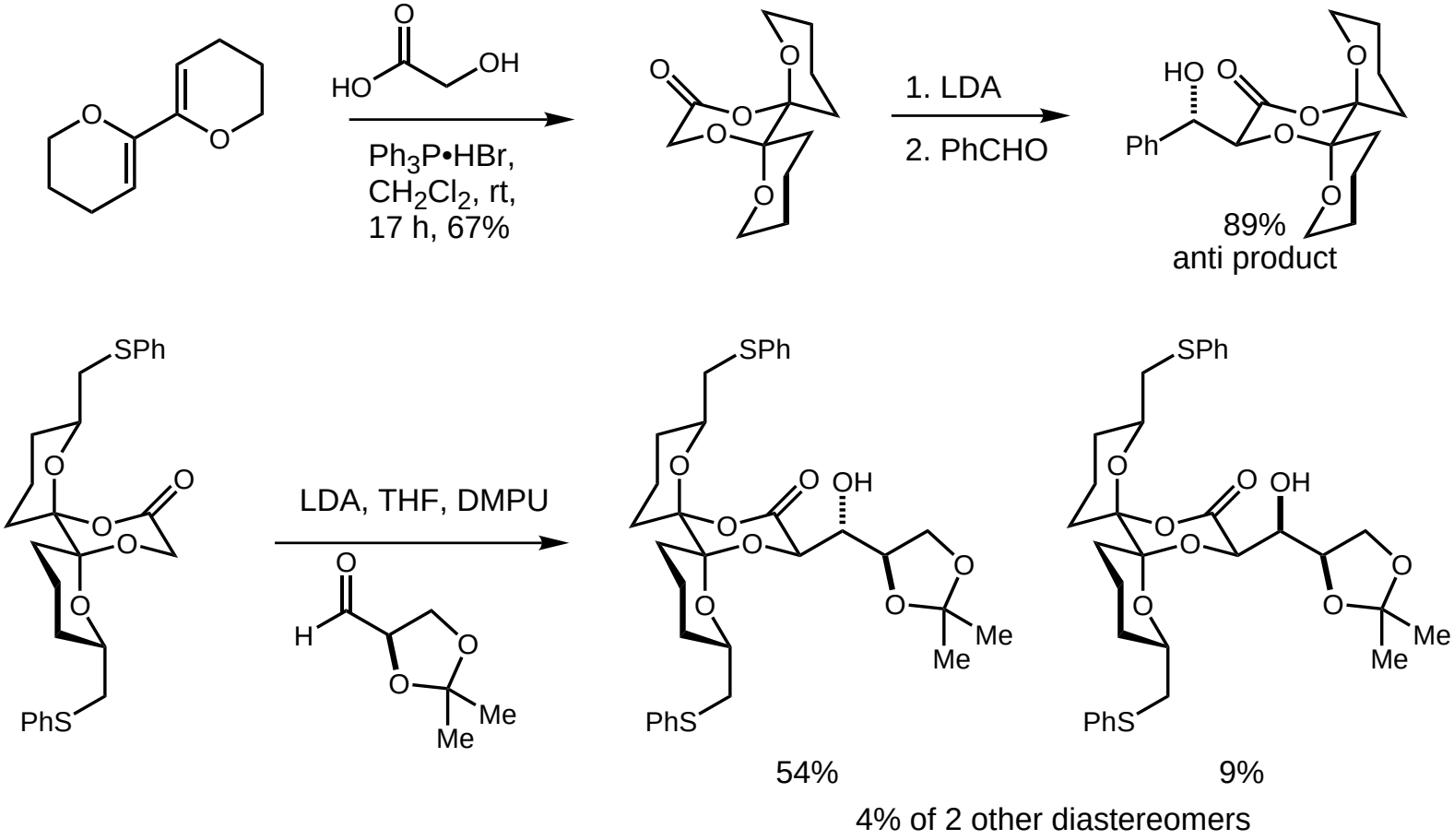


80%



Andrus, M. B.; Meredith, E. L.; Soma Sekhar, B. B. V. *Org. Lett*. **2001**, *3*, 259–262.
Original Report: Andrus, M. B.; Soma Sekhar, B. B. V.; Meredith, E. L.; Dalley, N. K. *Org. Lett.* **2000**, *2,* 3035.

Dispiroketals in Aldol Reactions

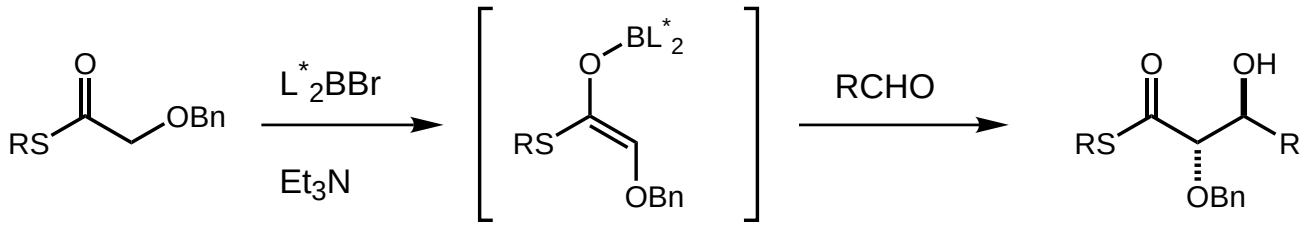


Enantiomer of dispiroketal fails to react with D-glyceraldehyde acetonide (14% of a 3:2 mixture of ds)

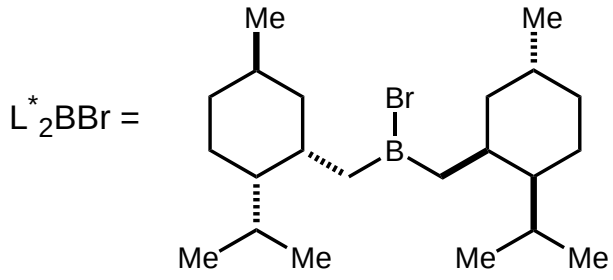
Discussion of these results and evidence for structural assignment is not very convincing.

Fujita, M.; Lainé, D.; Ley, S. V. *J. Chem. Soc., Perk. 1*, **1999**, 1647–1656.

Boron Aldol Reactions of α-Heterosubstituted Thioacetates



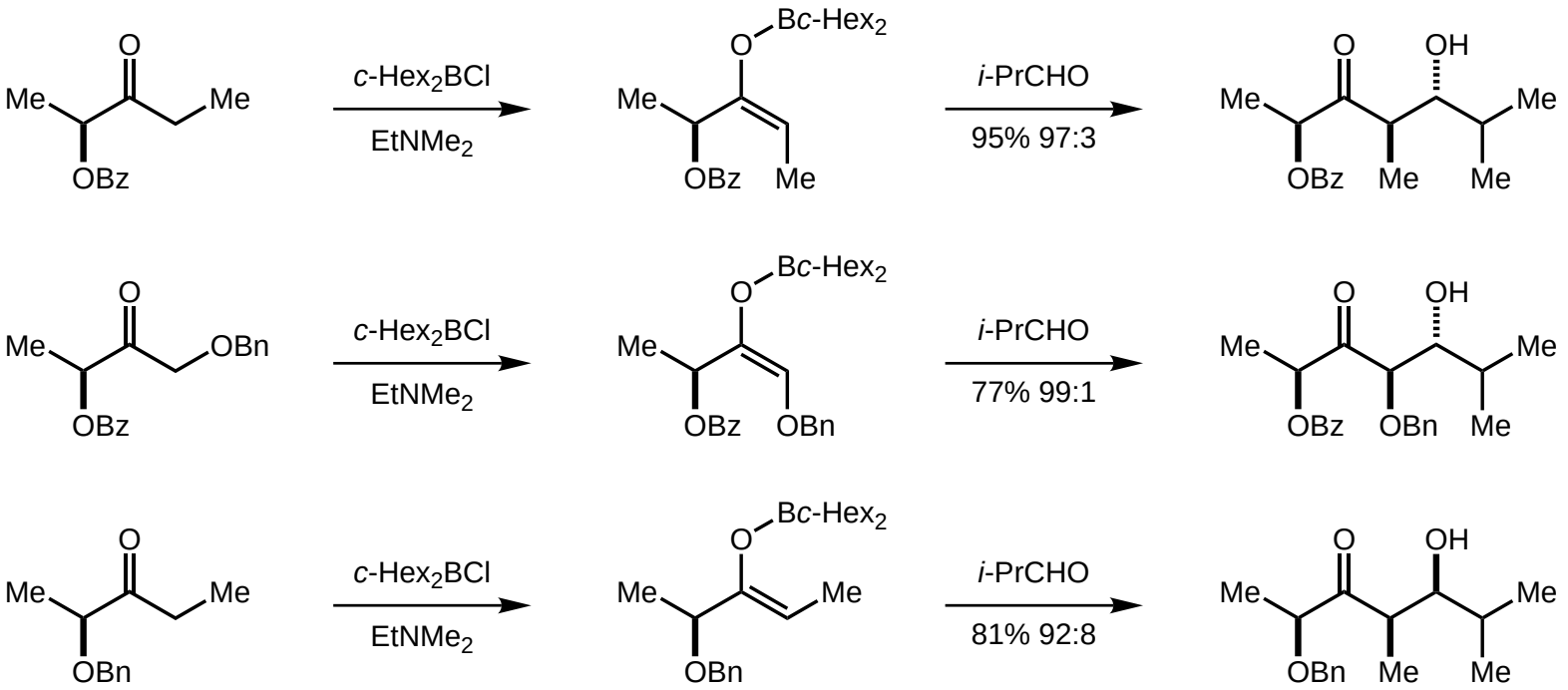
S-*t*Bu and S-Ph esters work equally well. as does a range of aldehydes. (PhCHO, CH_2=C(Me)CHO, *i*-PrCHO, *n*-PrCHO) 3:97–1:>99 syn:anti, ee values range from 94–96% and yields are modest 45–79%.
OTBS has been used in place of OBn with equal results.
This methodology has also been expanded to α-halo thioesters and utilized with imines as the electrophile



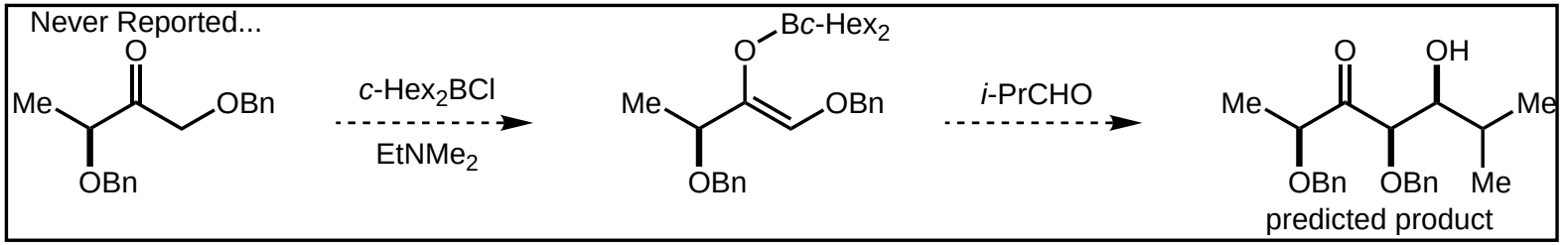
(derived from α-menthone)

Gennari, C.; Vulpetti, A.; Pain, G. *Tetrahedron*, **1997**, *53*, 5909–5924.

Paterson's Lactate Derived Aldol Reactions

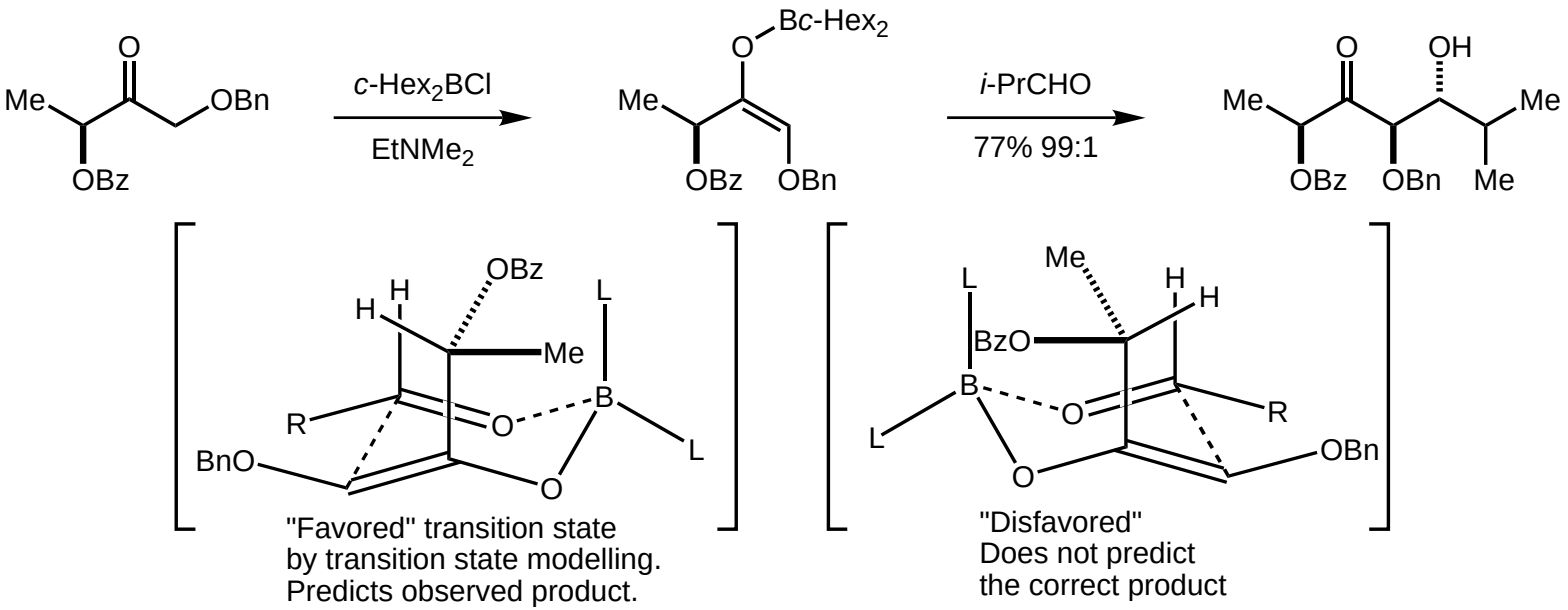


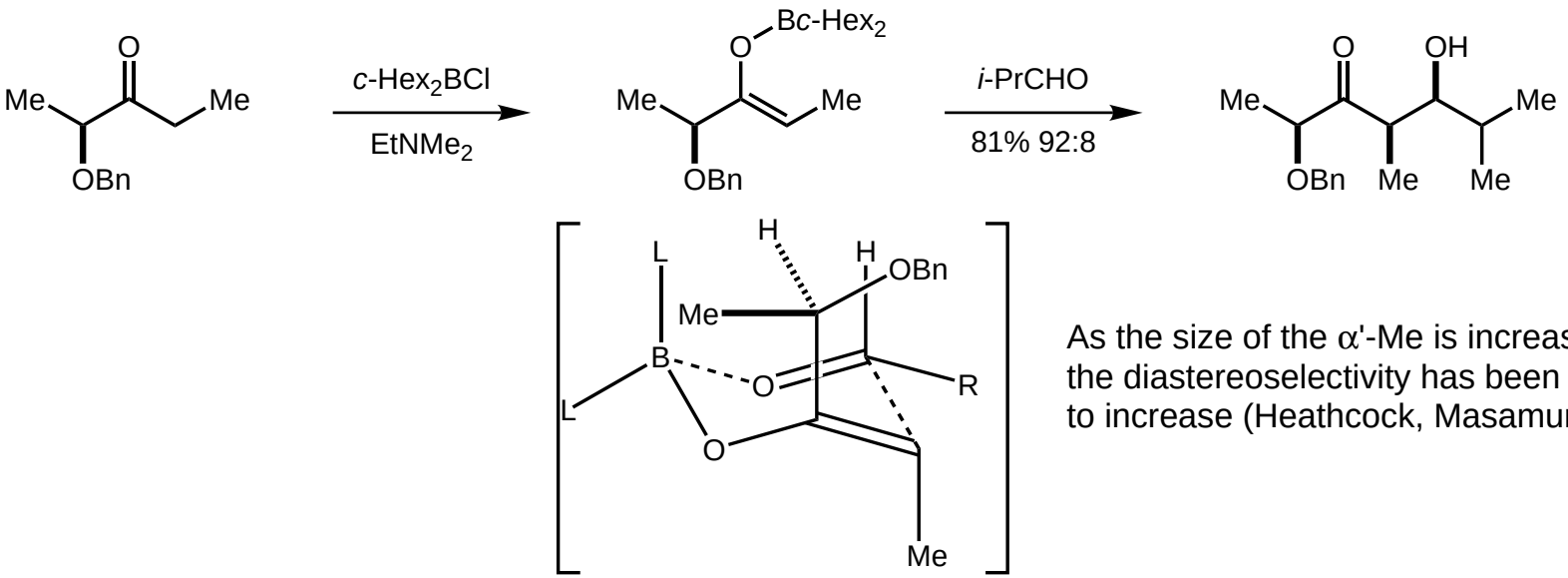
Heathcock and Masamune have shown better pi facial selectivity with alternate *Z* enol borinates.



Paterson, I.; Wallace, D. J.; Velazquez, S. M. *Tet. Lett.* **1994**, *35*, 9083–9086.
Paterson, I.; Wallace, D. J. *Tet. Lett.* **1994**, *35*, 9087–9090.

Models for Predicting the Stereochemical Outcome

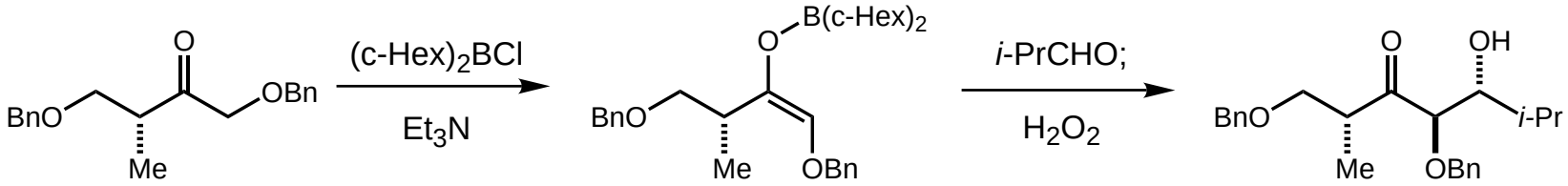




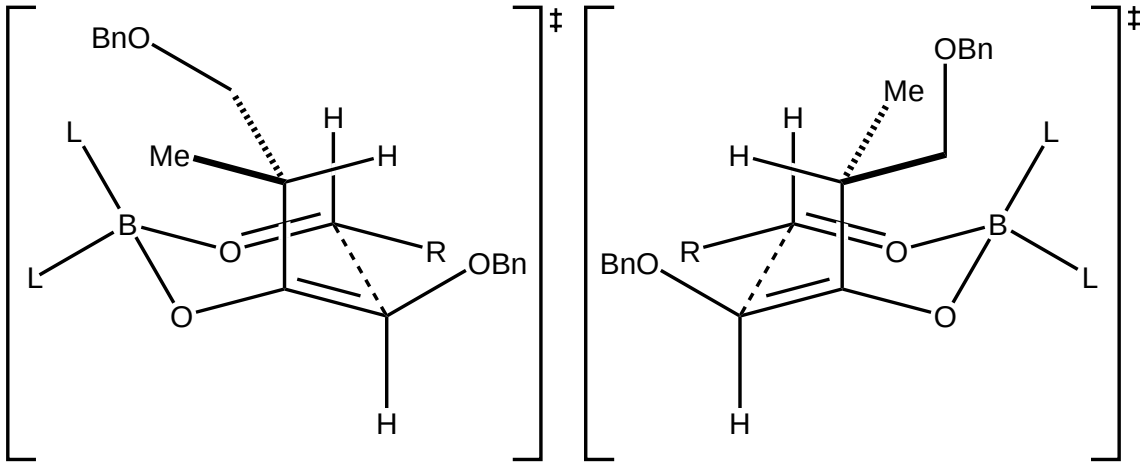
As the size of the α'-Me is increased the diastereoselectivity has been shown to increase (Heathcock, Masamune, Carda)

Paterson, I.; Wallace, D. J.; Velázquez, S. M. *Tet. Lett.* **1994**, *35*, 9083–9086 and references cited therein.

Chiral Alkoxymethyl Ketone Boron Anti Aldol Reactions



95% ds
95% yield

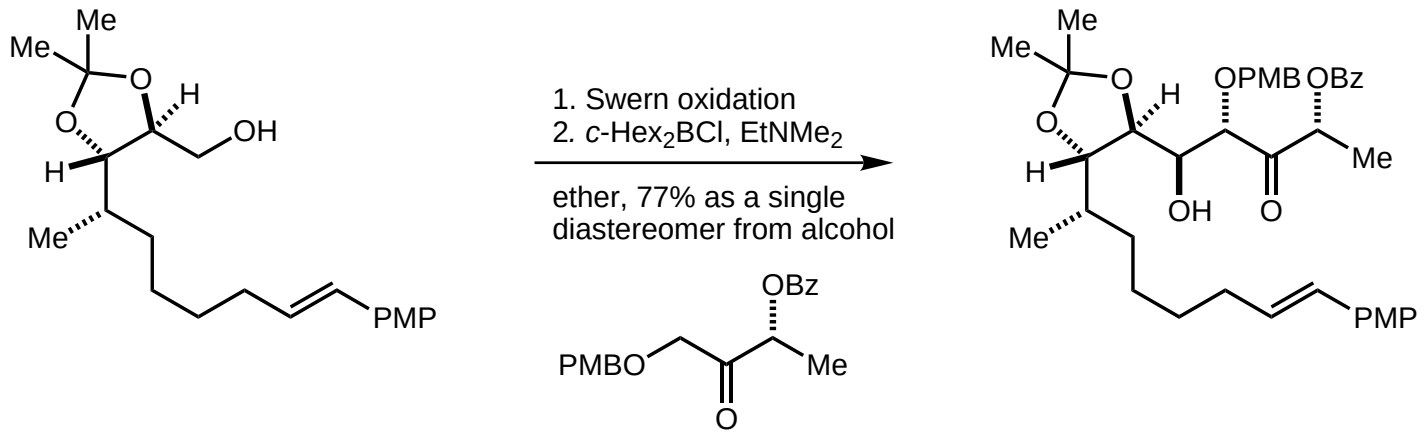


Predicts Observed Product

This reaction is fairly general but it is unclear why it exhibits such high diastereoselectivity.

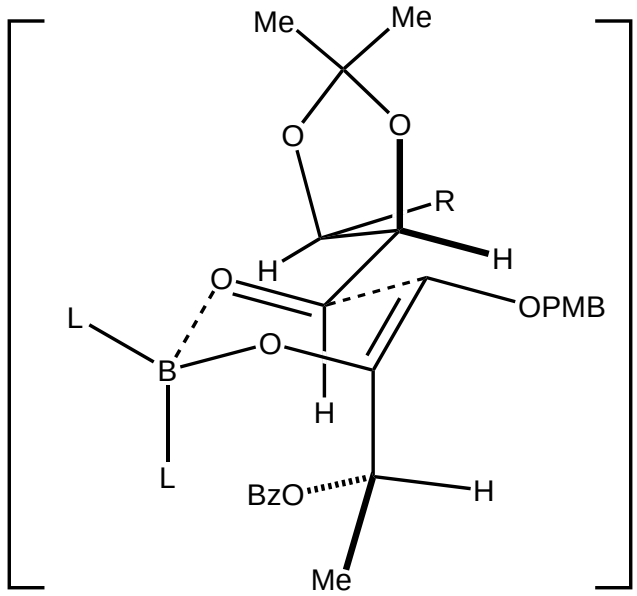
Paterson, I.; Tillyer, R. D. *J. Org. Chem.* **1993**, *58*, 4182–4184.

An Interesting Example



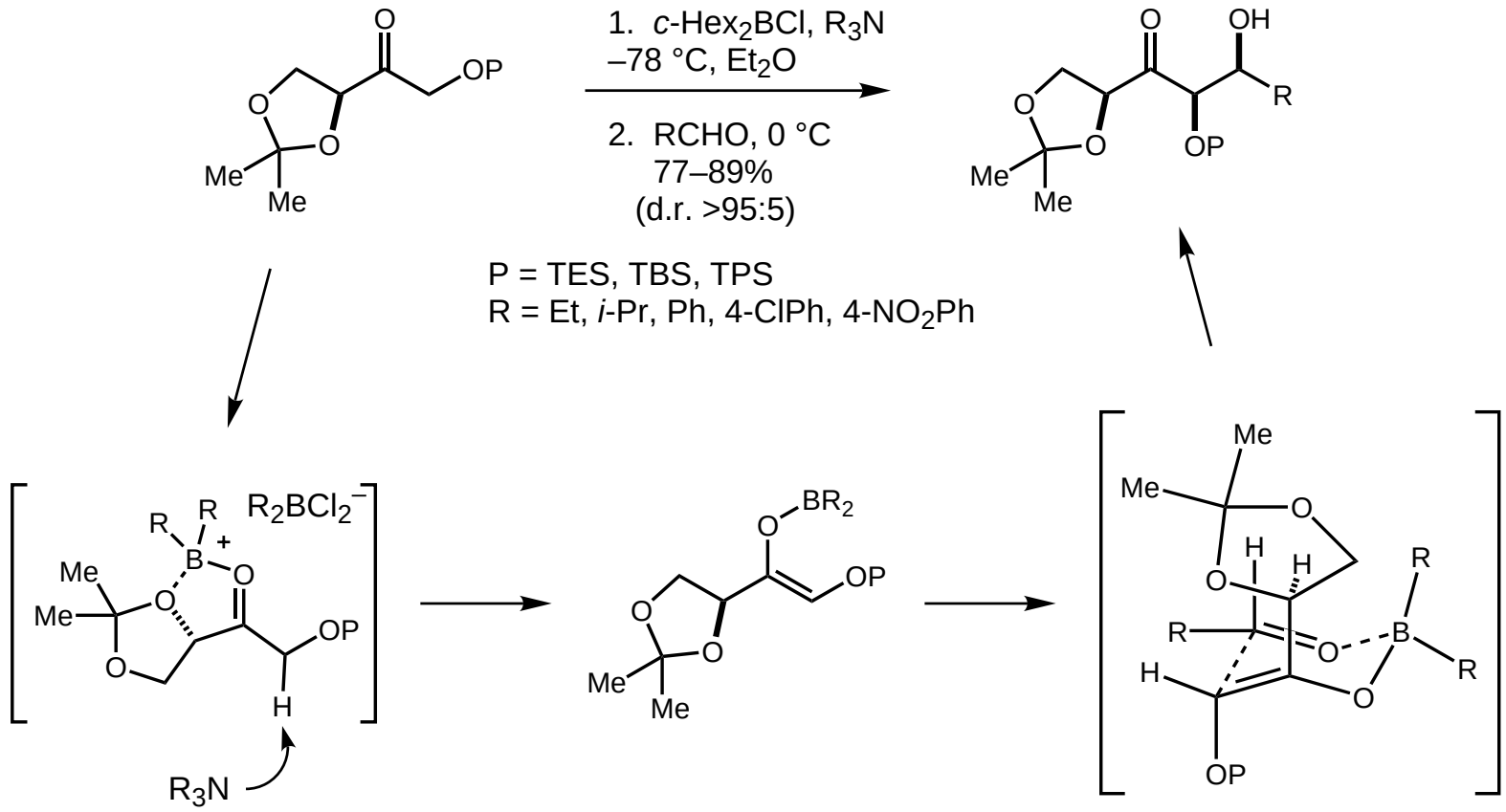
An interesting example that shows the ability of α'-alkoxy enolates to overide the inherent facial selectivity of an aldehyde to give good anti-Felkin selectivity.

It is important to note that the inherent facial bias of the aldehyde may be significantly altered by the acetonide protecting group so this could be a "matched" case.



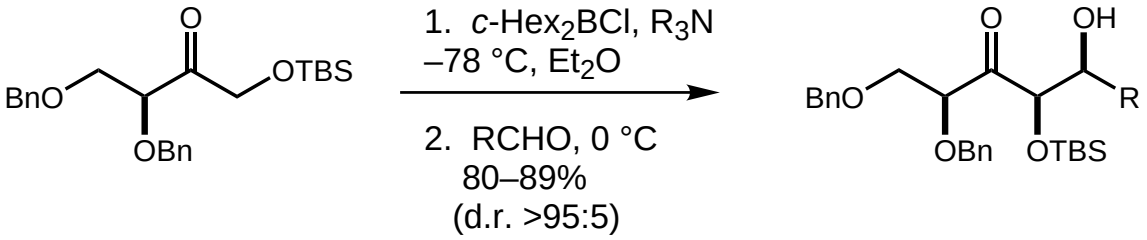
Sasaki, S.; Hamada, Y.; Shioiri, T. *Tet. Lett.* **1999**, *40*, 3187–3190.

Erythrulose Derivatives in Aldol Reactions

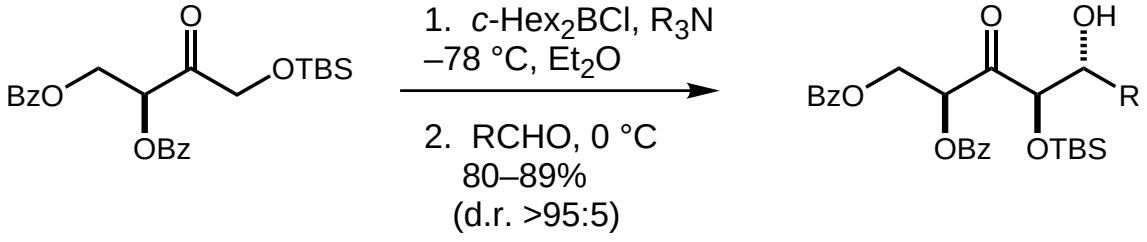


Marco, J. A.; Carda, M.; Falomir, E.; Palomo, C.; Oiarbide, M.; Ortiz, J. A.; Linden, A. *Tet. Lett.* **1999**, *40*, 1065–1068.
Related Paper: Carda, M.; Murga, J.; Falomir, E.; González, F.; Marco, J. A. *Tetrahedron*, **2000**, 677–683.
For Ethyl ketone analog: Carda, M.; Murga, J.; Falomir, E.; González, F.; Marco, J. A. *Tet. Asym*. **2000**, 3211–3220.

Erythrulose Derivatives in Aldol Reactions



R = Et, *i*-Pr, Ph, 4-ClPh, 4-NO_2Ph



R = Et, *i*-Pr, Ph, 4-ClPh

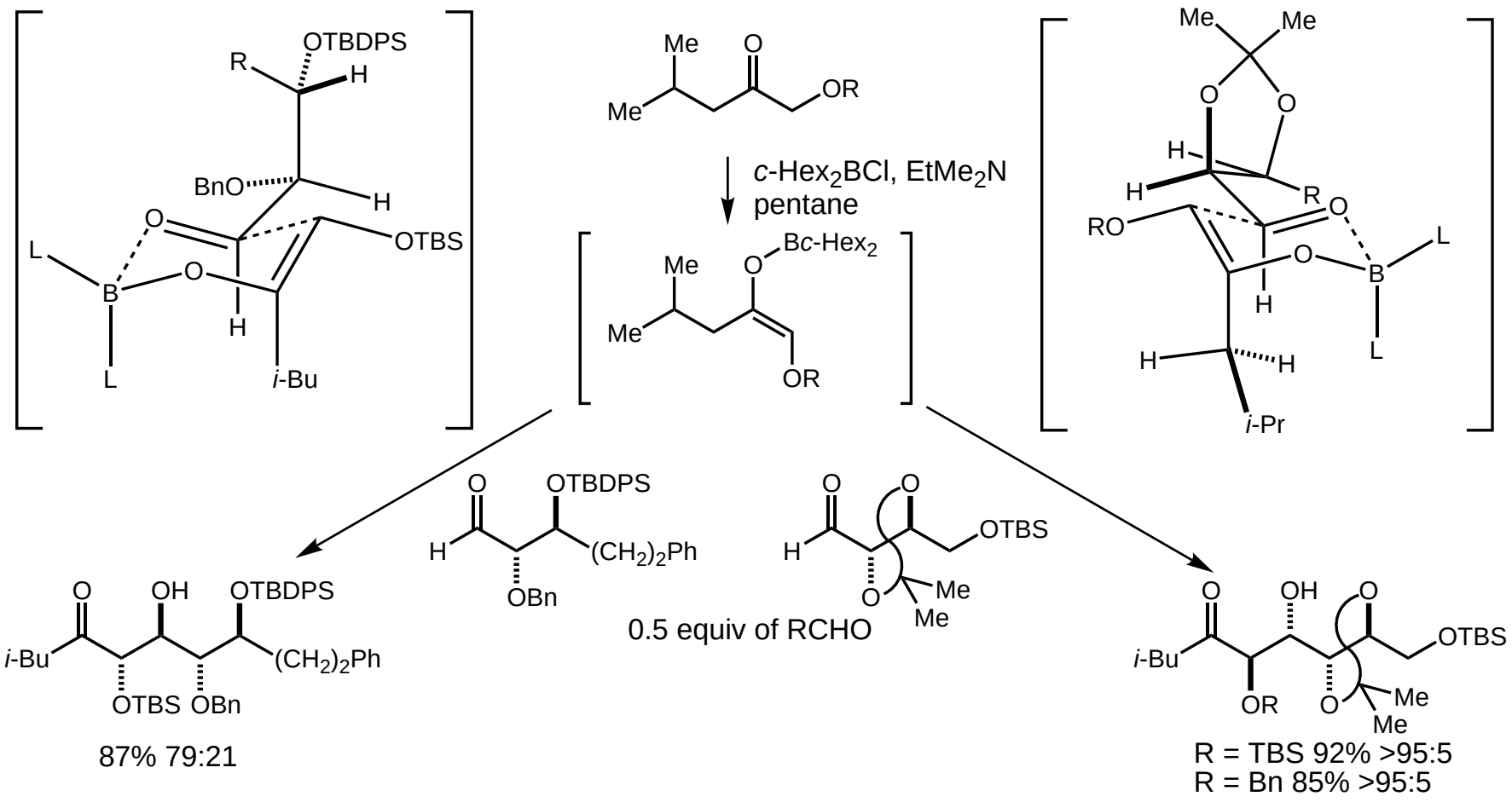
A nice extension of the literature and demonstration of the general applicability of the oxygenated aldol reaction.

These reactions follow the models proposed for the Paterson work.

Note the improved selectivity of the syn aldol with the increased size of the α'-alkyl group.

Carda, M.; Falomir, E.; Murga, J.; Castillo, E.; González, F.; Marco, J. A. *Tet. Lett.* **1999**, *40*, 6845–6848.

Diastereoselective Addition to α,β-Dialkoxyaldehydes

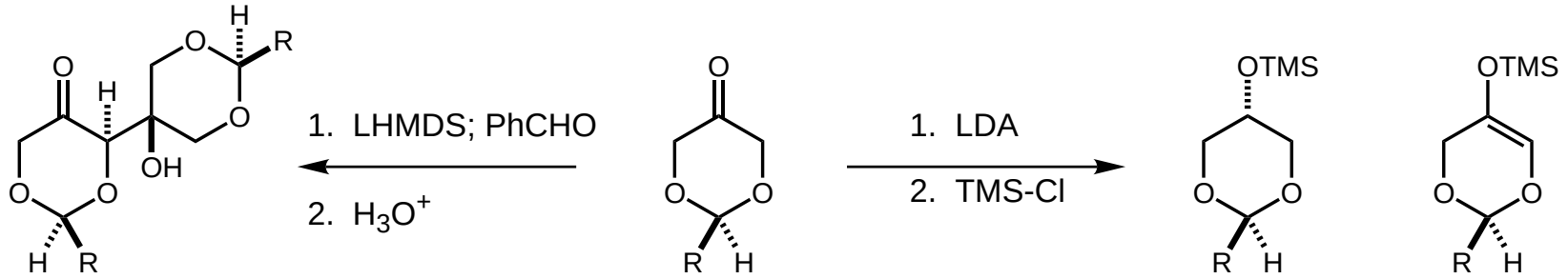


This is an excellent example of how changing the protecting groups can completely turn over diastereoselection.

It also demonstrates that with a simple protecting group swap, one can select for the desire stereotetrad.

Frank Glorius, *Unpublished Results,* DAE group.

Anti-Aldol-Majewski



"major" product

Deprotonation of the acetonide protected dioxanone followed by aqueous quench provided "up to 64%" of self condensation in the absence of aldehyde.

R = Ph, *t*-Bu

Et_2O 81%
THF 63%

Reduction can be avoided using the internal quench method of Corey.

The ketals are reported to be less prone to reduction and cross condensation. Likewise, the acetals were less stable to work up and purification conditions.

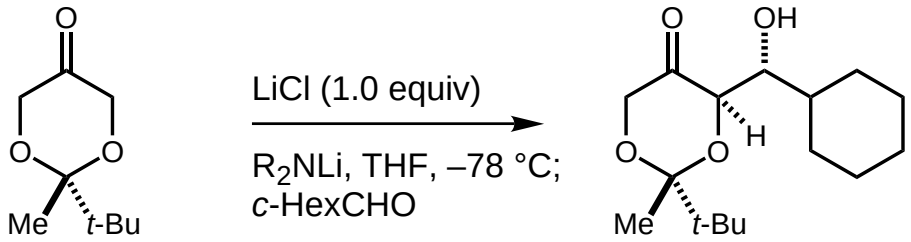
It is noted in this paper that "low yields (40–60%) were presumably due to instability of the products to silica chromatography." They note that there is high conversion in the unpurified reaction mixture, but low mass recovery after purification.

The yield problems were fixed in subsequent publications.

This paper also gives preliminary results of the enantioselective deprotonation work that is fully reported in *J.O.C.* **2000**, *65*, 5152–5160.

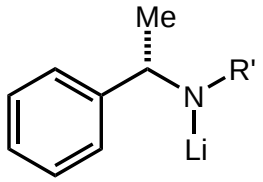
Majewski, M.; Gleave, D. M.; Nowak, P. *Can. J. Chem.* **1995**, *73*, 1616–1626.

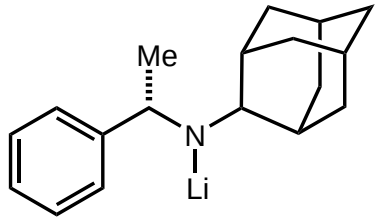
Enantioselective Anti-Aldol-Majewski



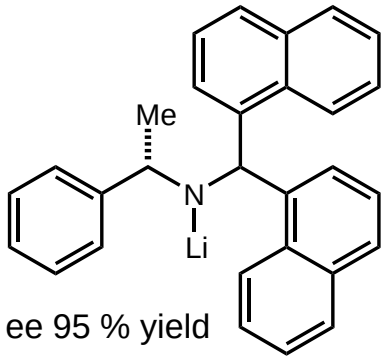
4–95% ee 32–95% yield

R_2NLi =





80% ee 91% yield



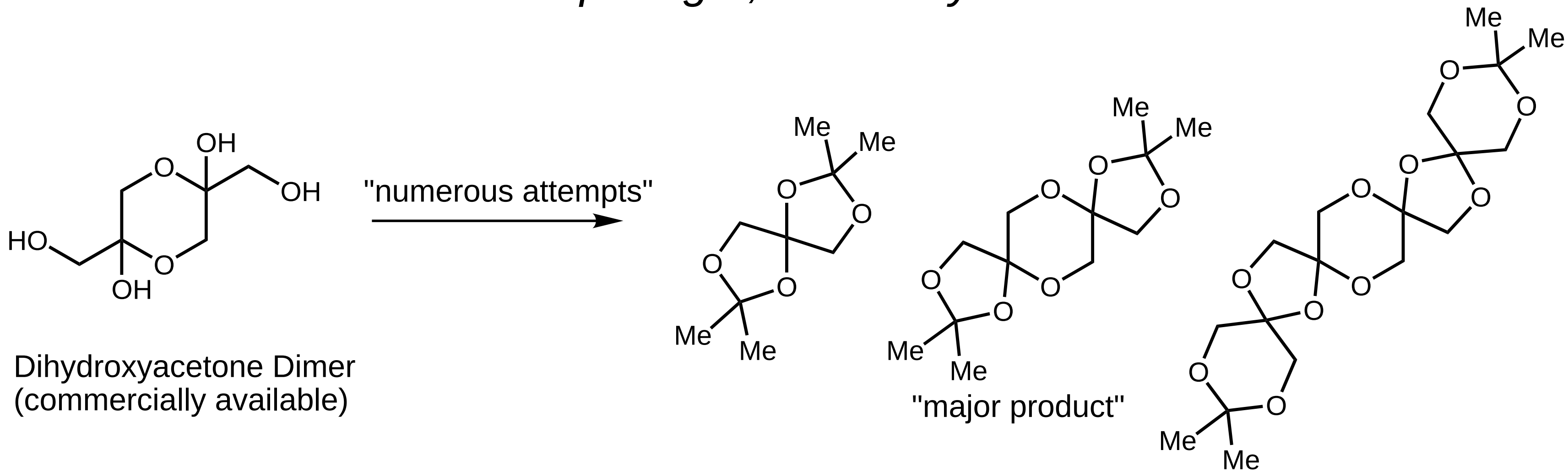
90% ee 95 % yield

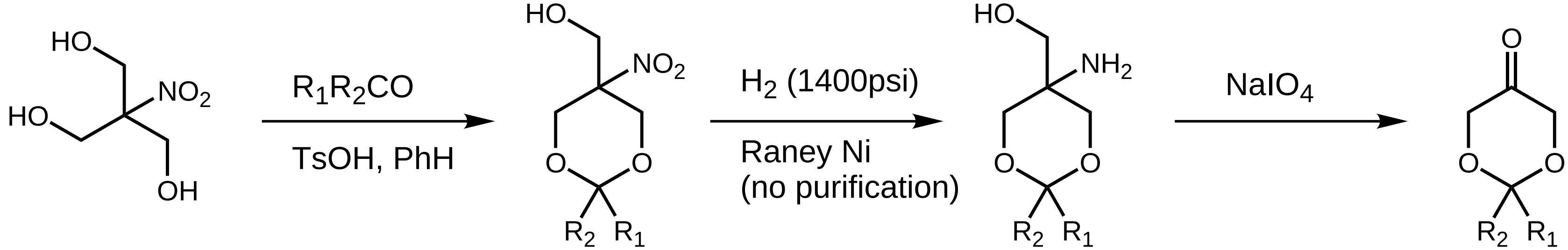
R' = CH_2*t*-Bu, Bn, *c*-Hex, $CH(Ph)_2$, $CH(Bn)_2$, CH_2CF_3 (90% ee 86%)

1. LiCl (1 equiv) leads to more reproducible results and (greatly) enhanced ee.
2. Enantioselective deprotonations are case dependant.
3. *c*-HexCHO was chosen since it exhibits high ds with the Li enolate of the dioxanone.
4. Paper presents a study of the effect of boron reagent and work-up conditions on observed diastereoselectivity for the boron mediated aldol reaction.

Majewski,M.; Nowak, P. *J. Org. Chem.* **2000**, *65*, 5152–5160.
For an earlier report see: Majewski, M.; Gleave, D. M.; Nowak, P. *Can. J. Chem.* **1995**, *73*, 1616–1626.
For a study of LiX effect see: Majewski, M.; Lazny, R.; Nowak, P. *Tet. Lett.***1995**, *36*, 5465–5468.

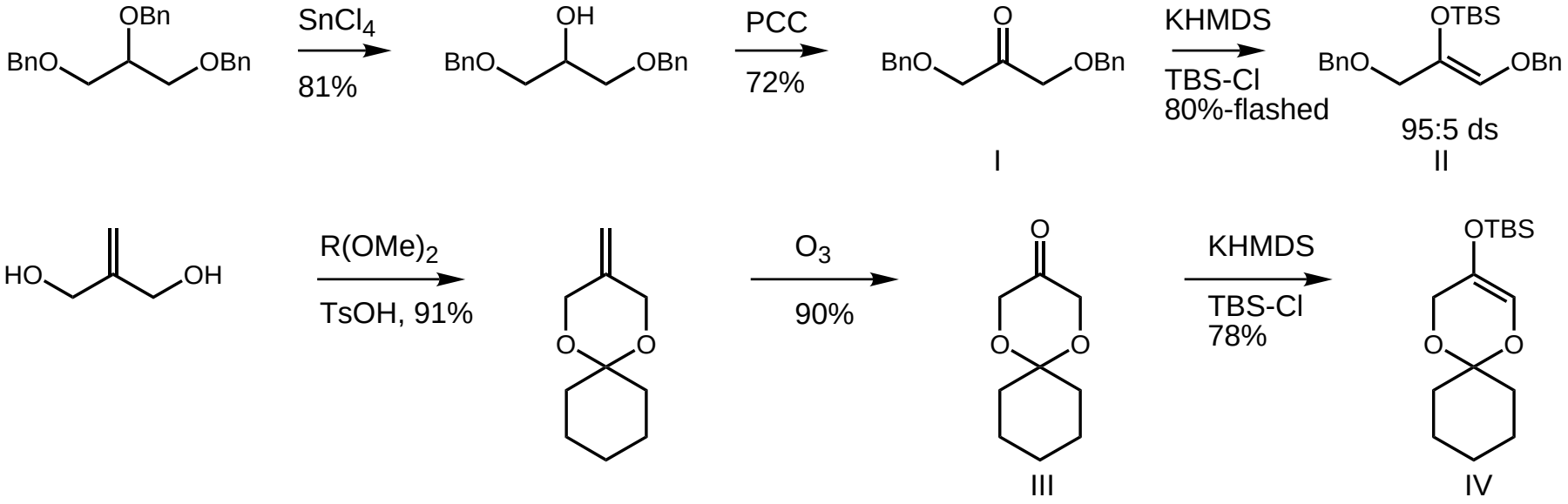
Difficulties in Preparing 2,2-Dimethyldioxan-5-one





Majewski, M.; Gleave, D. M.; Nowak, P. *Can. J. Chem.* **1995**, *73*, 1616–1626.

Aldol Reaction of Dihydroxyacetone Derivatives



R = CH_2CH_3 or CH_2OBn

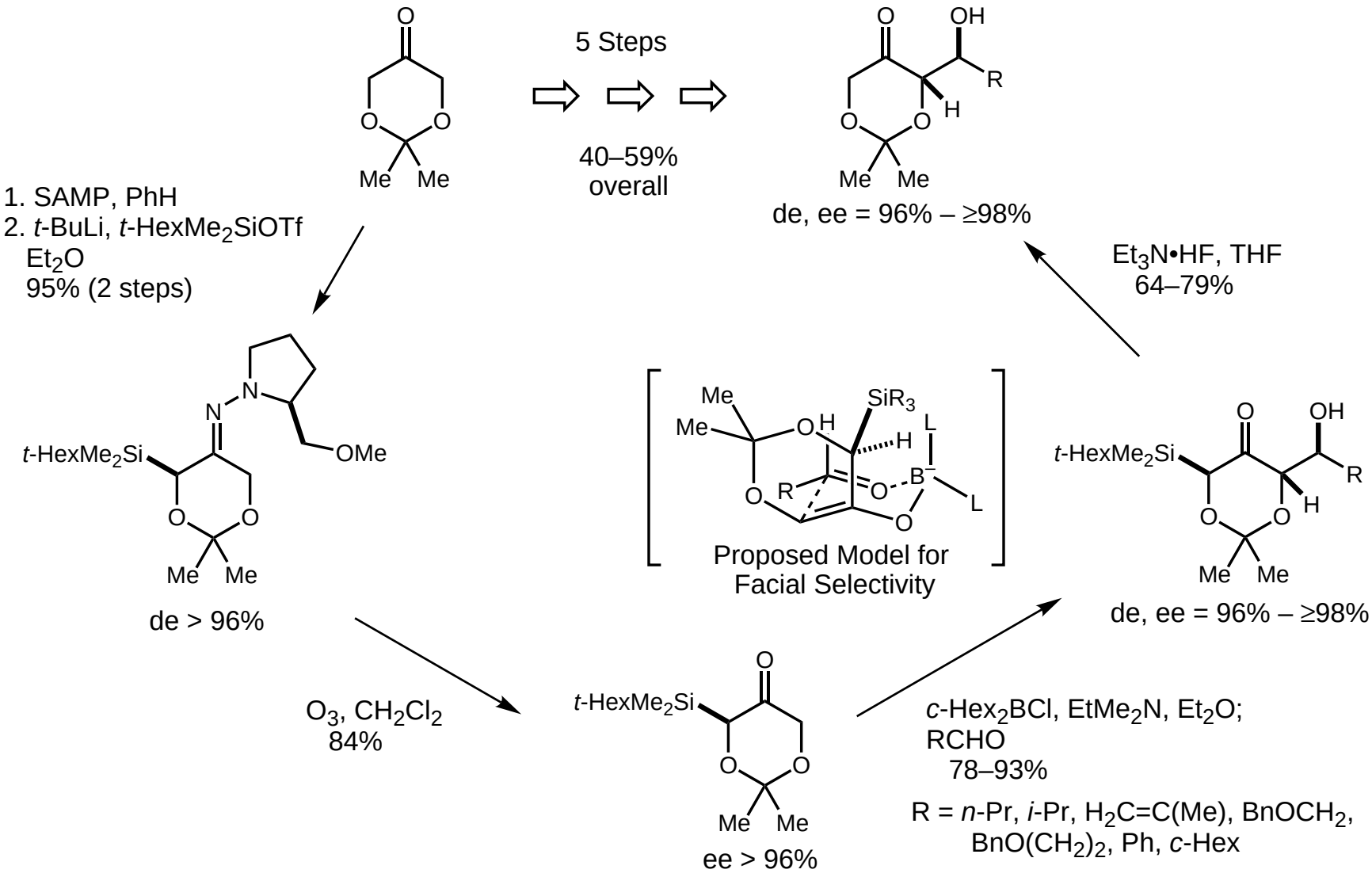
LDA mediated aldol reaction of I provided a 3:2 syn:anti ratio of products (80%).
LDA mediated aldol reaction of III provided exclusively the anti aldol product (~80%).

Mukaiyama aldol reaction of II with a variety of Lewis acid gave a mixture of results with $TiCl_4$ giving good syn selectivity (95:5) while BF_3 and $SnCl_4$ gave poor ds (1:1–85:15 syn:anti).
Mukaiyama aldol reaction of IV gave exclusively the anti diastereomer with all three Lewis acids 73–82%.

It should be noted that these results are entirely consistent with the other literature in this area of research.

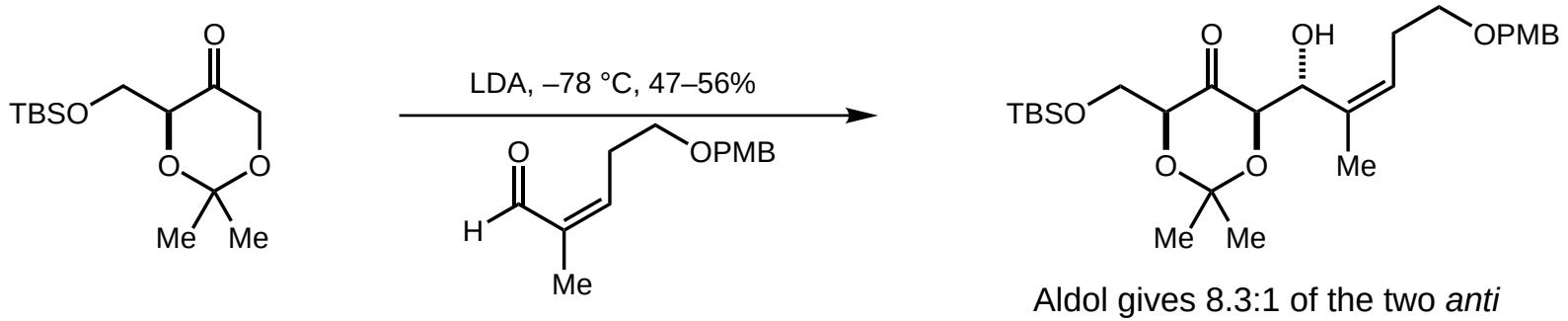
Kim, K. S.; Hong, S. D. *Tet. Lett.* **2000**, *41*, 5909–5913.

Highly Diastereoselective Boron-Mediated Anti-Aldol-Enders



Enders, D.; Prokopenko, O. F.; Raabe, G.; Runsink, J. *Synthesis* **1996**, 1095-1100.

Lithium Mediated Aldol Reaction

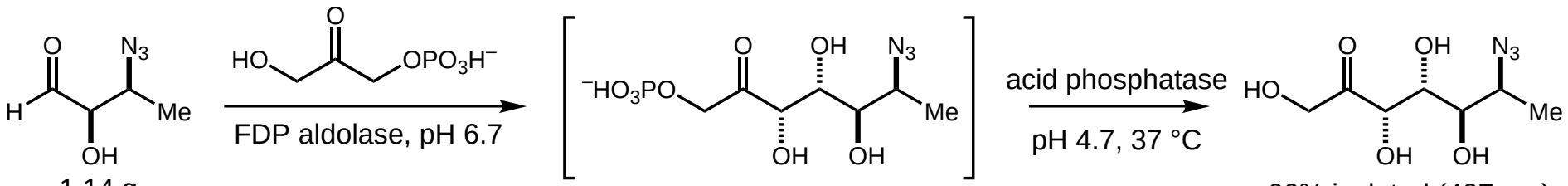


Aldol gives 8.3:1 of the two *anti* aldol adducts with 47–56% isolated yield of the major product

NOTE: This Lithium mediated aldol reaction gives the OPPOSITE product from what is expected in the Boron reaction.

Hirama, M.; Noda, T.; Ito, S. *J. Org. Chem.* **1988**, *53*, 708–710.

Enzyme Catalyzed Aldol Reaction of Dihydroxyacetone Phosphate



The enzymatic based approach is attractive since protecting groups are not required.

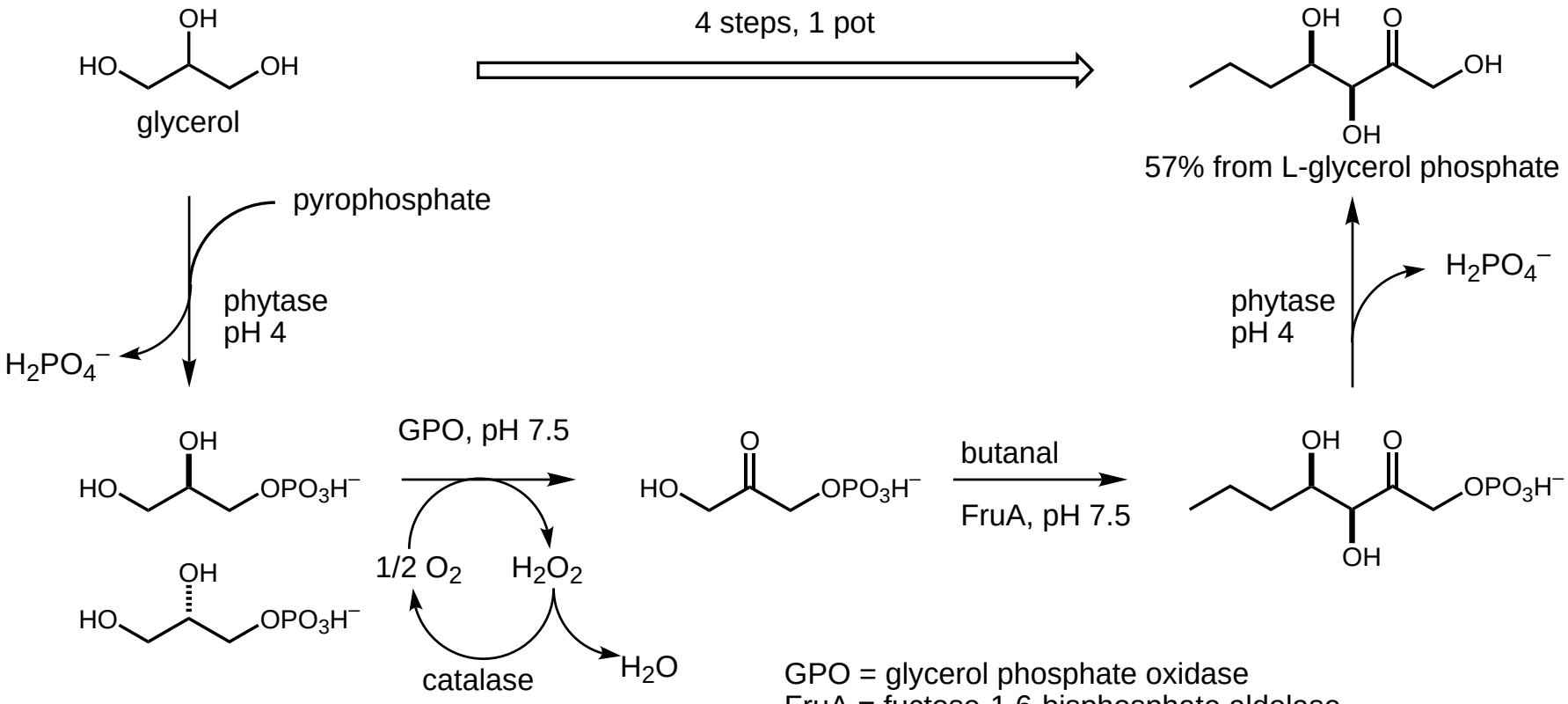
I have not seen many examples of enzyme catalyzed reactions on substrates with protecting groups and this may a limitation due to solubility considerations since the reaction medium is aqueous.

One disadvantage is that dihydroxyacetone phosphate (DHAP) must be made using an enzyme mediated route.

It is important to read the experimentals since I have found that the true diastereomeric ratio is not reported. Instead authors choose to report the isolated yield of the desired.

Qiao, L.; Murray, B. W.; Shimazaki, M.; Schultz, J.; Wong, C.-H. *J. Am. Chem. Soc.* **1996**, *118*, 7653–7662.
For a recent review of aldolase-catalyzed reactions see: Gijsen, H. J. M.; Qiao, L.; Fitz, W.; Wong, C.-H. *Chem. Rev.* **1996**, *96*, 443–473.

Carbohydrates from Glycerol: An Enzymatic Four-step, One Pot Synthesis

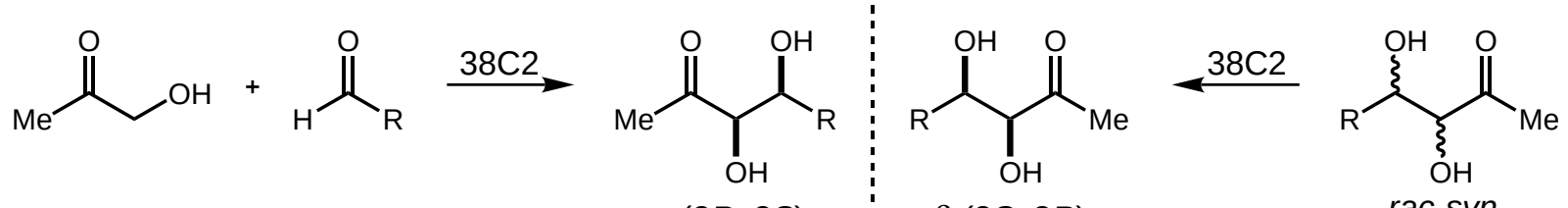


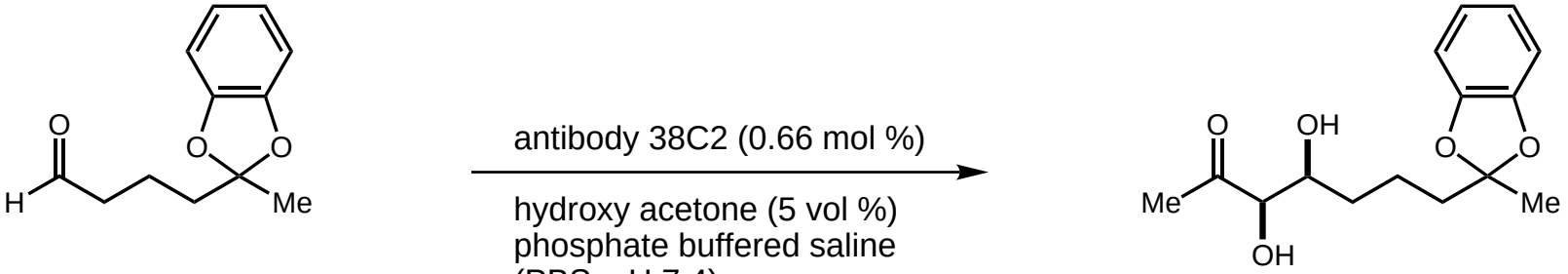
GPO = glycerol phosphate oxidase
FruA = fuctose-1,6-bisphosphate aldolase
phytase from *Aspergillus ficuum* (commercially available)

This is a significant advance in enzyme mediated synthesis and is an elegant solution to problems (and costs) associated with the use of dihydroxyacetone phosphate

Schoevaart, R.; van Rantwijk, F.; Sheldon, R. A. *J. Chem. Soc. Chem. Comm.* **1999**, 2464–2466.
Article gives good lead references.

Antibody Catalyzed Aldol Reaction of Hydroxyacetone



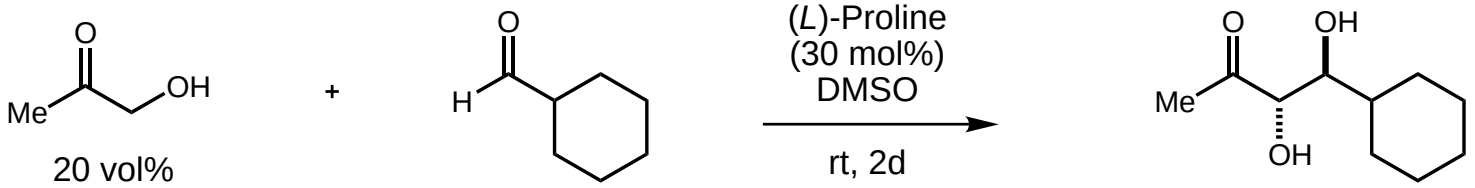


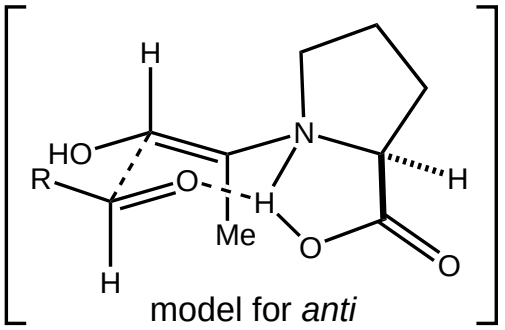
The authors make special note that antibody 38C2 is the only catalyst (chemical or biological) which catalyzes the aldol reaction of hydroxyacetone.

Antibody 38C2 also exhibits broad substrate acceptance for the catalyzed aldol in contrast to naturally occuring aldolases which are often substrate specific.

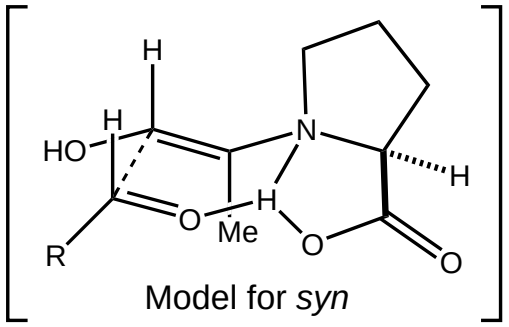
Shabat, D.; List, B.; Lerner, R. A.; Barbas III, C. F. *Tet. Lett.* **1999**, *40*, 1437–1440 and ref. cited therein.
List, B.; Shabat, D.; Barbas III, C. F.; Lerner, R. A. *Chem. Eur. J.* **1998**, *4*, 881–885 and ref. cited therein.

Catalytic Asymmetric Synthesis of Anti-1,2-Diols



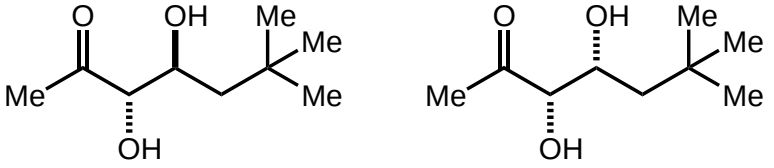


model for *anti*

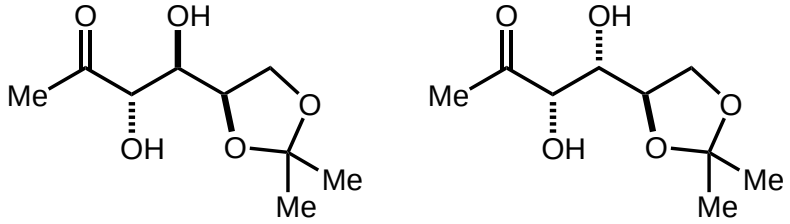


Model for *syn*

60% yield based on RCHO
>20:1 regioselectivity
>20:1 diastereoselectivity
>100:1 enantioselectivity



38% combined yield based on RCHO
1.7:1 dr >97% ee and 84% ee



40% combined yield based on RCHO
2:1 dr >97% ee for *anti*

Reaction needs bulk a to aldehyde for good yields and diastereoselection.

Aromatic Aldehyde (1 case) gives reduced enantioselection (67% ee)

Notz, W.; List, B. *J. Am. Chem. Soc.* **2000**, *122*, 7386–7387.

Conclusion

1. Syn aldol reaction of glycolate oxazolidinones are a well behaved and established method for the synthesis of syn polyols.

2. There is no general method for the anti aldol reaction of glycolate derivatives

3. Ene-diolate chemistry has been underutilized.

4. The diastereoselectivity of polyoxygenated ketones is being elucidated in the literature and is developing into a powerful method for the synthesis of polyols.

5. Enzyme mediated synthesis of polyols is reaching