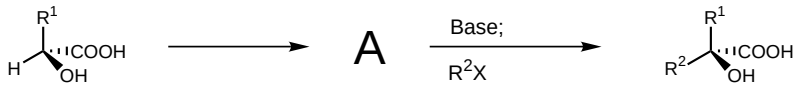
The Principle of Self-Regenerating Stereocenters and its Application to Synthetic Targets



Leading References: Seebach *Angew. Chem. Intl. Ed. Eng.* **1996**, *35*, 2708-2748

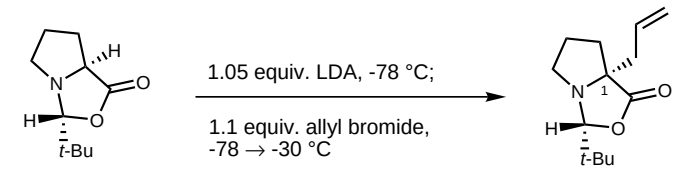
Seebach "EPC Syntheses with C,C Bond Formation via Acetals and Ketals" in *Modern Synthetic Methods 1986* ed. R. Scheffold Springer Verlag: Berlin, **1986**, 125-216.

Gretchen Peterson
Evans Group Afternoon Seminar
Dec. 17, 1999

Seminar Overview

- Introduction to Self-Replication of Stereocenters (SRS) Principle
- Reaction classes rendered stereoselective via SRS acetals
  1. Enolate alkylation and stereochemical induction models
  2. Aldol reactions
  3. α,β-Unsaturated substrates
     a. Conjugate additions
     b. Radical reactions
     c. Diels-Alder cycloadditions
  4. Acyliminium substrates
- Acetal hydrolysis: problems and solutions
- Other manifestations of the SRS principle
  1. Alternative auxiliaries
  2. Transition metal-induced planes of chirality
- Conclusions

Alkylation of Bicyclic Aminals

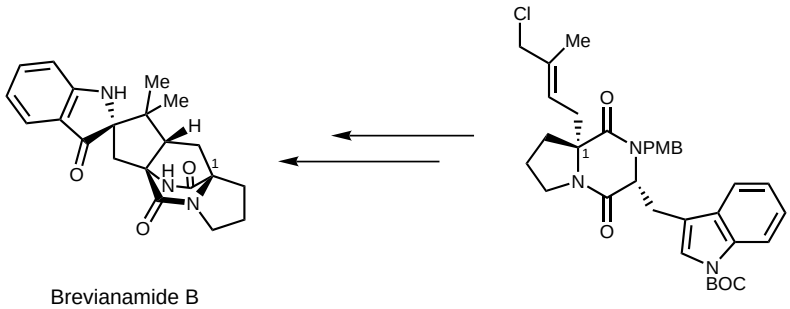


Seebach *JACS* **1983**, *105*, 5390

1 diastereomer formed from condensation with *t*-BuCHO

87% y

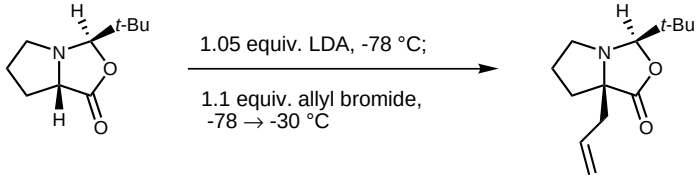
- Alkylation is *cis* to the *t*-Bu group!



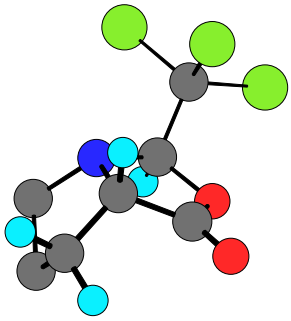
Brevianamide B

Williams *JACS* **1988**,*110*, 5927

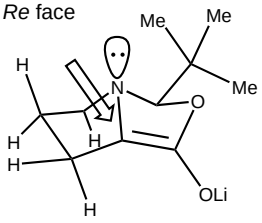
Stereochemistry of Alkylation: Bicyclic Aminals

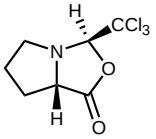


87% y



Re face

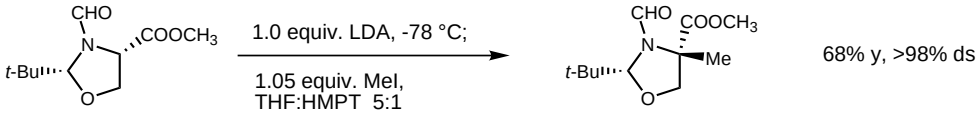




X-ray data: Seebach *HCA* **1992**, *75*, 913

- Deprotonation leads to an enolate in which the pyramidalized N forces the rest of the left ring below the enolate.
- Electrophilic addition is observed exclusively *cis* to the equatorial *t*-Bu group, the enolate face which only has one axial hydrogen.

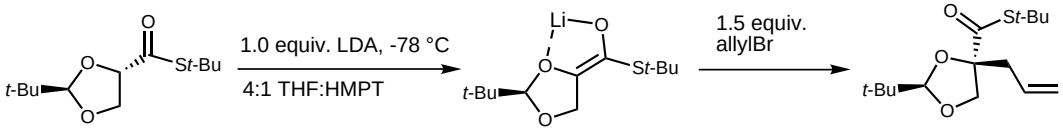
Alkylation of Exocyclic Acetals



68% y, >98% ds

(from serine)

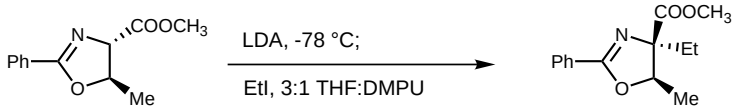
- This is the best result obtained; very few substrates gave above 50% y, but all had excellent diastereoselectivity.
- Low yields due to β-elimination of the alkoxy-group in the enolate intermediate.



(from glyceric acid)

- Note that alkylation has occurred *cis* to the *t*-Bu group.

63% y, 93% ds



(from threonine)

91% y, >98% ds

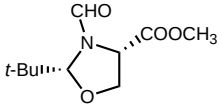
- Sense of induction is controlled by 3-Me.

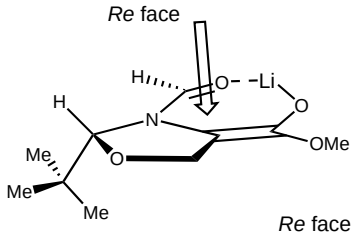
Seebach *HCA* **1987**, *70*, 1194

Stereochemistry of Alkylation: Exocyclic Acetals

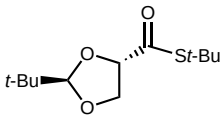
Reactant

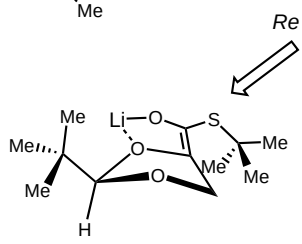
Model of resulting enolate



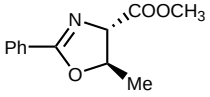


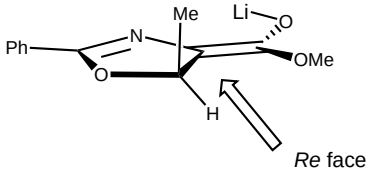
- Planar enolate results in electrophilic attack opposite the *t*-Bu group.





- Puckering of ring causes *t*-Bu group to be equatorial.
- Dioxolane ring and S-*t*-Bu shield bottom face of enolate to give *cis* electrophilic attack.

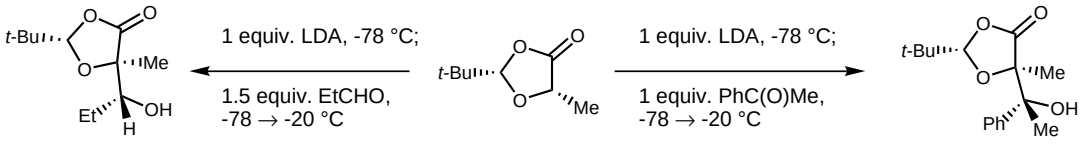




- Adjacent Me group controls electrophilic attack to the opposite face.

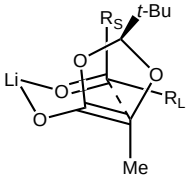
Seebach *HCA* **1987**, *70*, 1194

Aldol Reactions of Endocyclic Enolates



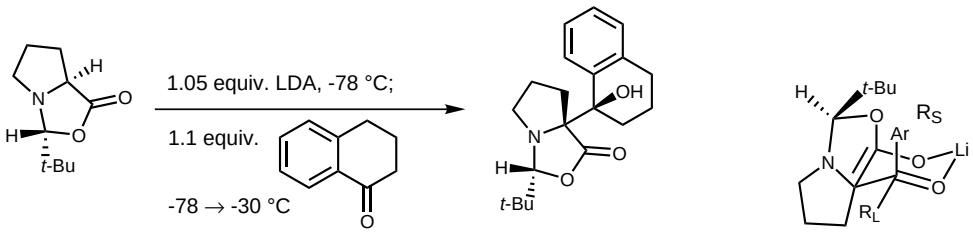
80% y, 60% ds

81% y, >93% ds



- Zimmermann-Traxler transition state diagrams account for observed aldehyde face selectivity.
- *t*-Bu group controls enolate face selectivity.

Seebach *Tetrahedron* **1984**, *40*, 1313

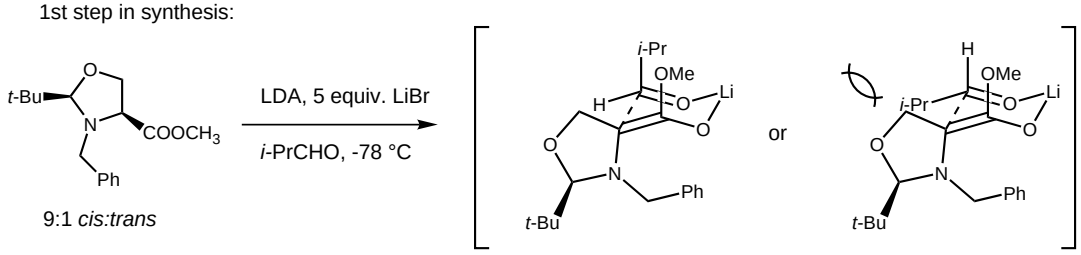


70% y, 73% ds

Seebach *JACS* **1983**, *105*, 5390

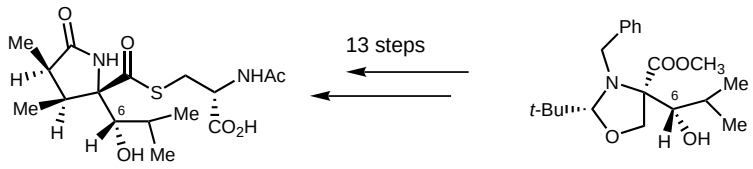
Synthetic Applications of Aldol Addition

1st step in synthesis:



9:1 *cis*:*trans*

- Steric clash between CH_2 and *i*-Pr forces the *i*-Pr (R_L) to be axial.

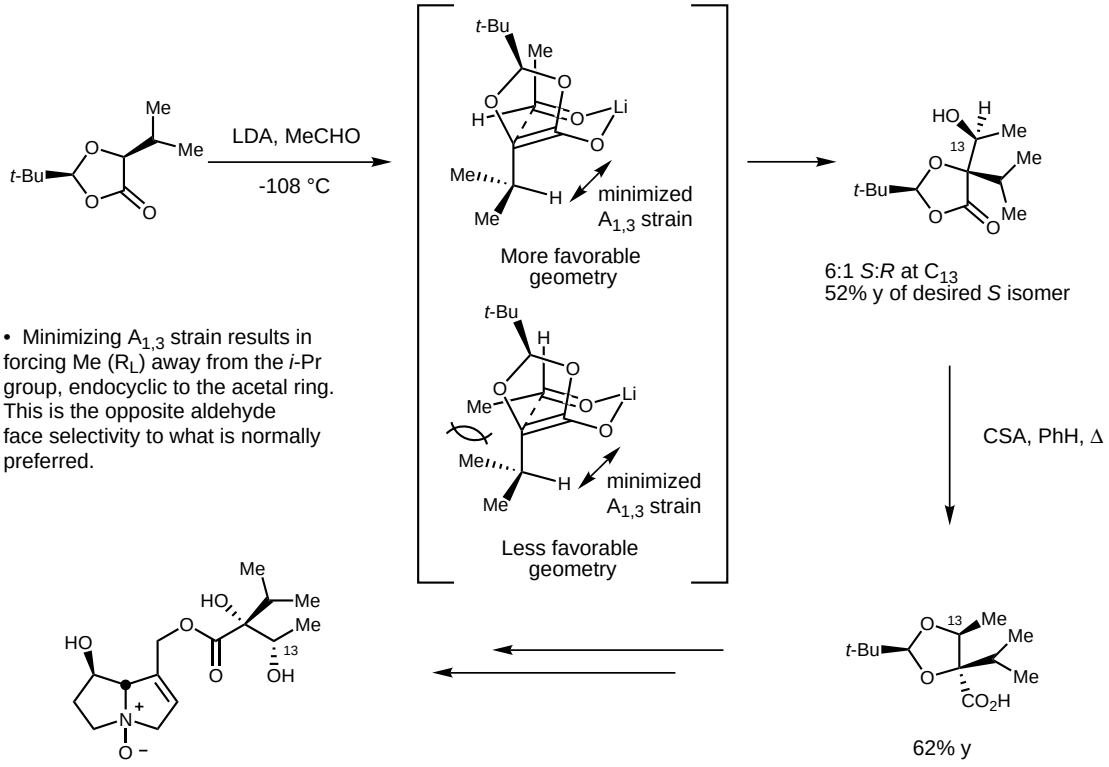


Lactacystin

77% y, >98% ds

Corey *JACS* **1992**, *114*, 10677

Reversal of Predicted Aldehyde Facial Selectivity

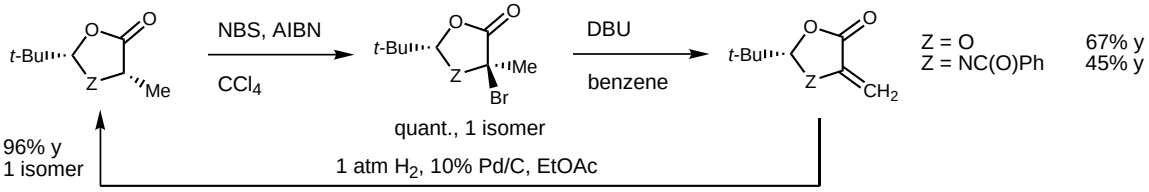


• Minimizing $A_{1,3}$ strain results in forcing Me (R_L) away from the *i*-Pr group, endocyclic to the acetal ring. This is the opposite aldehyde face selectivity to what is normally preferred.

Indicine N-oxide

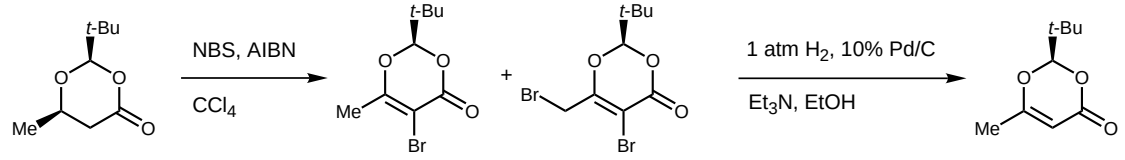
Yamada *Tetrahedron* **1993**, *49*, 1571

Synthesis of α,β-Unsaturated Acetals



• The endocyclic serine-derived α,β-unsaturated ester **A** can also be formed via the bromination/elimination methodology: Seebach *Chem. Ber.* **1989**, 2365

A



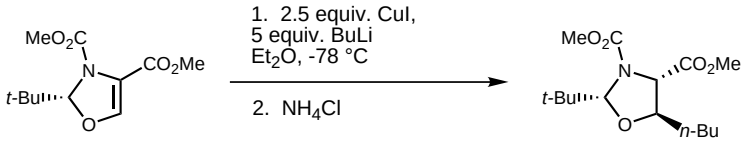
Made in 55% y from *R*-3-hydroxybutanoic acid and pivaldehyde

B **C**

89% y
4:1 **B**:**C**

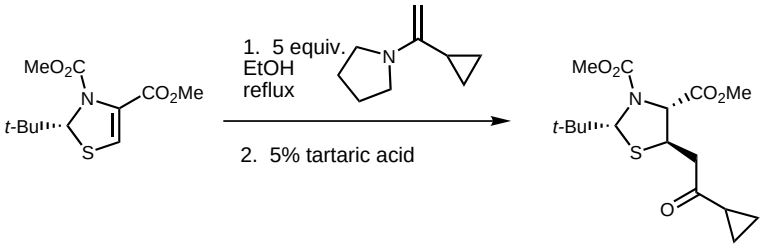
Seebach *HCA* **1987**, *70*, 1104

Stereoselective Acetal Conjugate Additions



87% y, 1 isomer

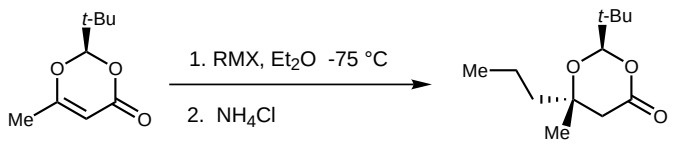
Seebach *Chem. Ber.* **1989**, 2365



70% y, 1 isomer

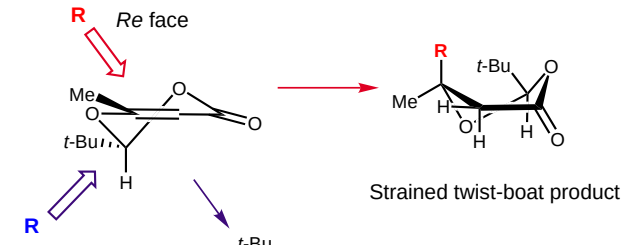
Seebach *J. Chem. Soc. Perk. Trans. 1* **1991**, 2291

Stereoselective Conjugate Additions into Dioxinones

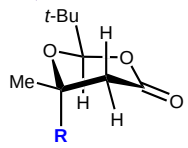


RMX	y
1.1 equiv. CuI 2.2 equiv. PrLi	79%
2 equiv. PrMgBr 0.2 equiv. CuI	91%

1 isomer

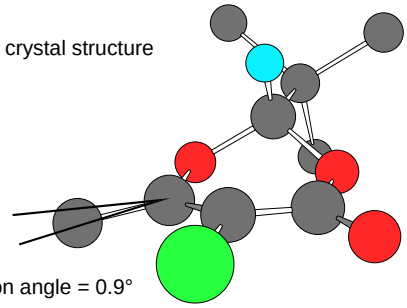


Strained twist-boat product

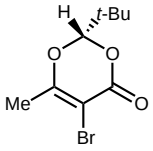


Preferred chair product

X-ray crystal structure



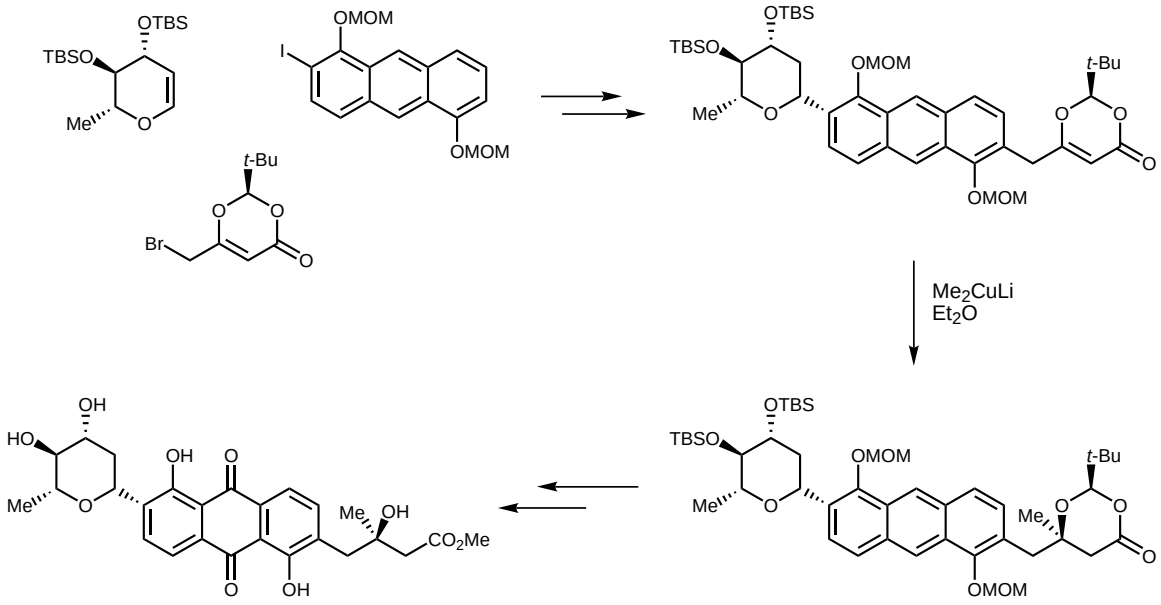
pyramidalization angle = 0.9°



- Seebach: Nucleophilic attack is observed from the "more hindered" side due to development of stabilizing $n_O \rightarrow \sigma^*_{C\text{-}Nu}$ interaction and the inherent pyramidalization of the β-carbon towards the acetal center. Alternative view: Attack occurs to give stereoelectronically preferred chair conformation.

Seebach *JACS* **1988**, *110*, 4763

Synthetic Application of Dioxinone Conjugate Addition

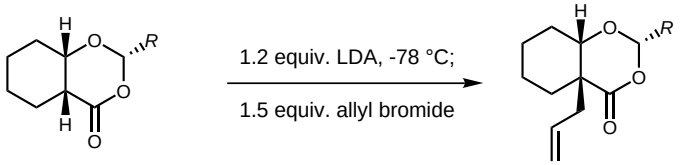


Vineomycinone B2

60% y, 1 isomer

Tius *JACS* **1990**, *112*, 8188

Enolate Alkylation of Bicyclic Dioxinones

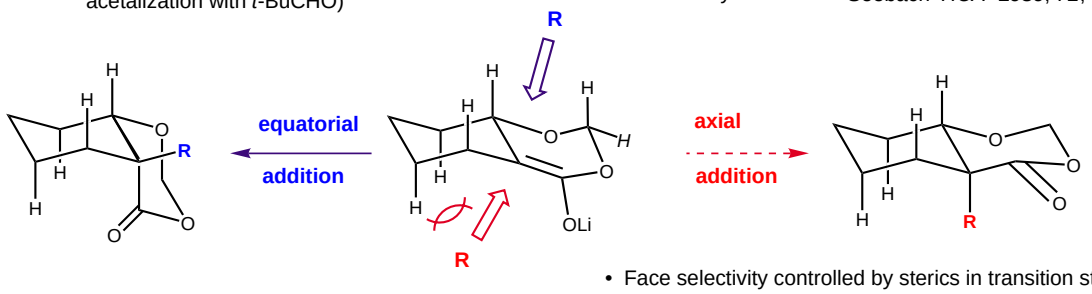


R	ds
H	93
t-Bu	57

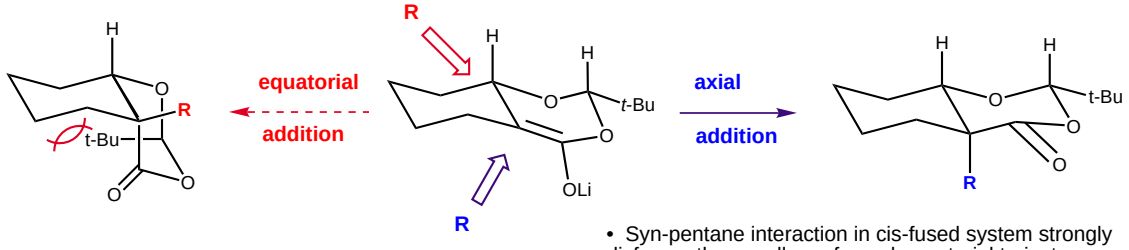
(exclusive product from acetalization with *t*-BuCHO)

80% y

Seebach *HCA* **1989**, *72*, 690

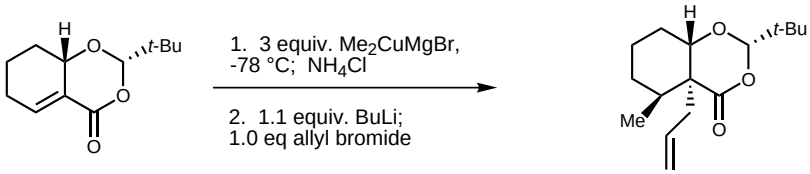


- Face selectivity controlled by sterics in transition state.

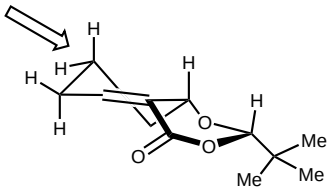


- Syn-pentane interaction in cis-fused system strongly disfavors the usually preferrred equatorial trajectory.

Conjugate Addition to Bicyclic Dioxinones



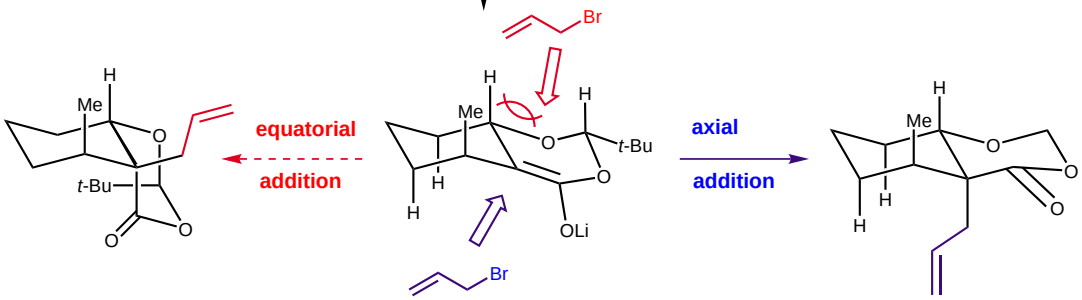
axial attack preferred to give chair transition state



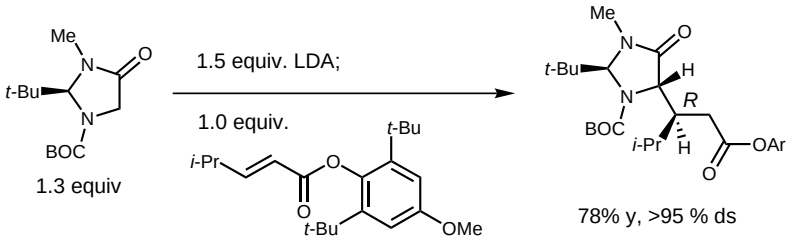
82% y, 1 isomer

Seebach *HCA* **1989**, *72*, 690

- Face selectivity controlled by sterics in transition state for both conjugate addition and enolate alkylation.



BOC-BMI as Nucleophile in Conjugate Additions

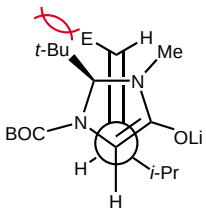


1.3 equiv

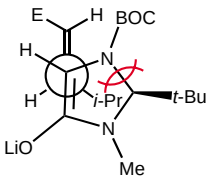
78% y, >95 % ds

- Lower yields and ds are seen with alkyl esters.

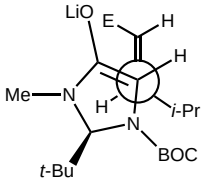
Seebach *Liebigs Ann. Chem.* **1992**, 51



Synclinal: possible interaction between *t*-Bu and E

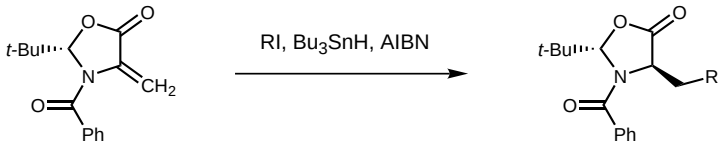


Anitperiplanar: steric strain with *i*-Pr endocyclic



Synclinal: all steric interactions minimized

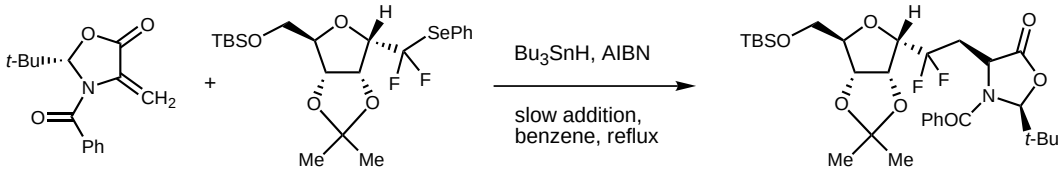
Radical Addition to α,β-Unsaturated Acetals



R	y	ds
t-Bu	70	>96%
c-hex	52	82%
c-hex	89	68%
(with *c*-hexHgH, $NaBH_3CN$)		
Me	58	56%

- Only very bulky radicals gave moderate yields and diastereoselectivity, thus limiting the usefulness of this methodology.

Beckwith *J. Chem. Soc. Chem. Comm.* **1995**, 549

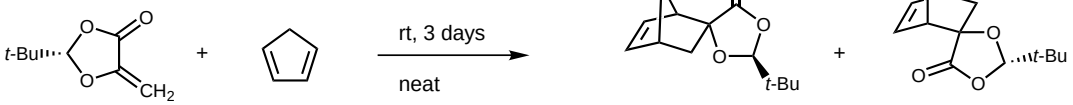


86% y, 70% ds

Glycosidated alanine CF_2 analog

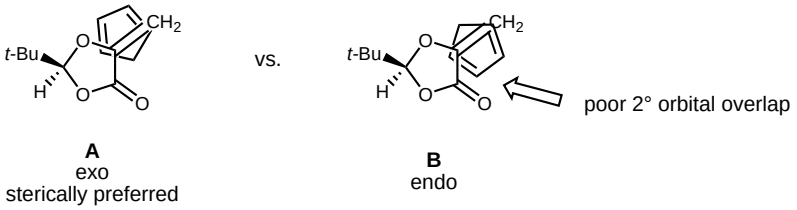
Motherwell *J. Chem. Soc. Chem. Comm.* **1997**, 123

Diels-Alder Cycloadditions of α,β-Unsaturated Acetals



A **B**

86% y, 96:4 **A**:**B**



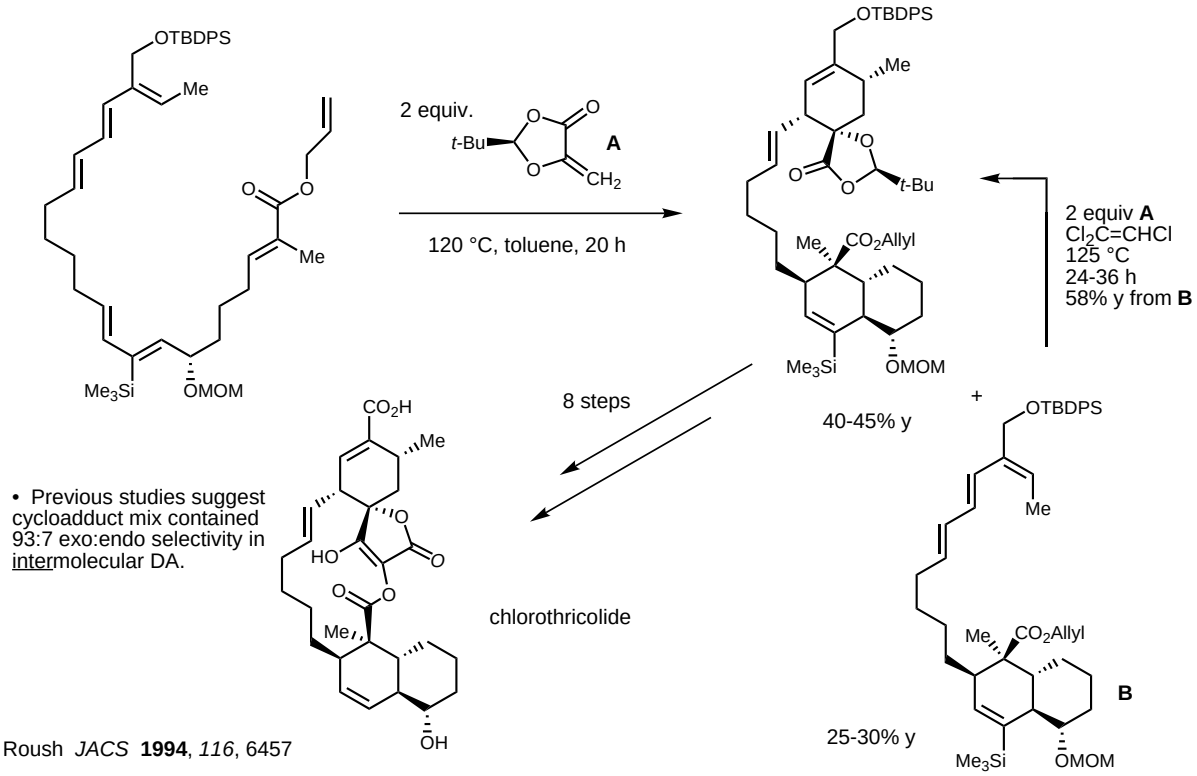
A
exo
sterically preferred

B
endo

- Addition of Lewis acids ($EtAlCl_2$, $TiCl_2(i\text{-}PrO)_2$) or heating to 140 °C results in poorer yield and diastereoselectivity.

Mattay *Chem. Ber.* **1989**, 327

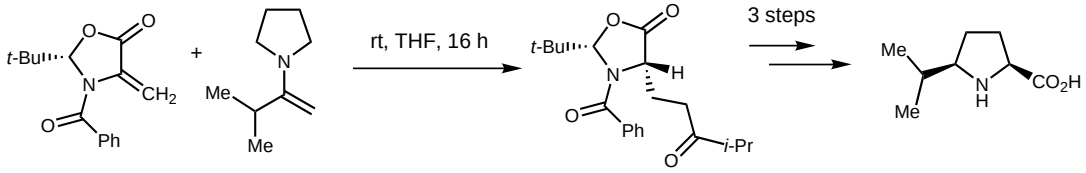
Synthetic Application of SRS Diels-Alder Reaction



- Previous studies suggest cycloadduct mix contained 93:7 exo:endo selectivity in intermolecular DA.

Roush *JACS* **1994**, *116*, 6457

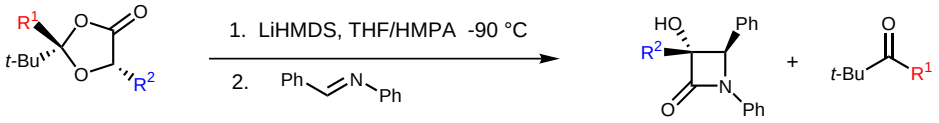
Limitations of Acetal Diastereoselectivity



70% y
66% ds

- Above is the best selectivity seen in this kind of Michael addition.

Pyne *Tetrahedron* **1995**, *51*, 5157

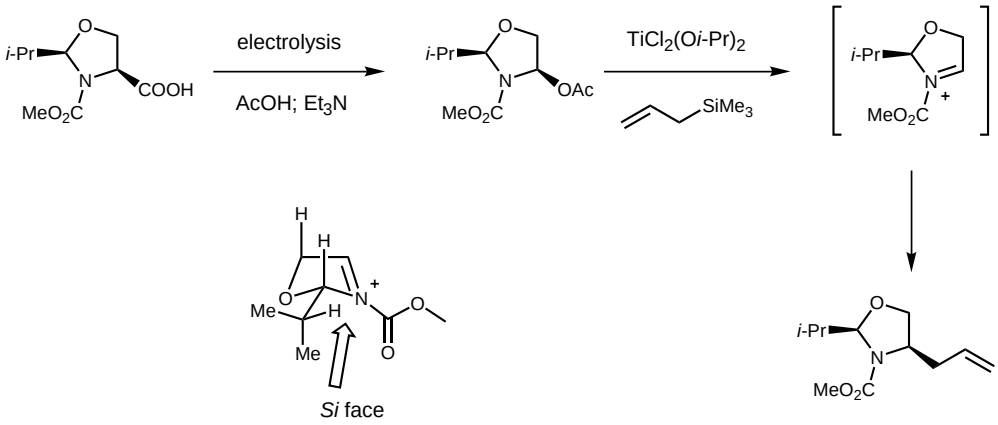


- Using the pinacolone acetal results in a more stable enolate.
- However, diastereoselectivity is still highly variable depending on the imine used.

R^1	R^2	ds %	y %	ee % (major)
H	Me	82	69	94
H	*i*-Pr	-71	59	97
Me	Me	92	87	92

Battaglia *J. Org. Chem.* **1999**, *64*, 4643

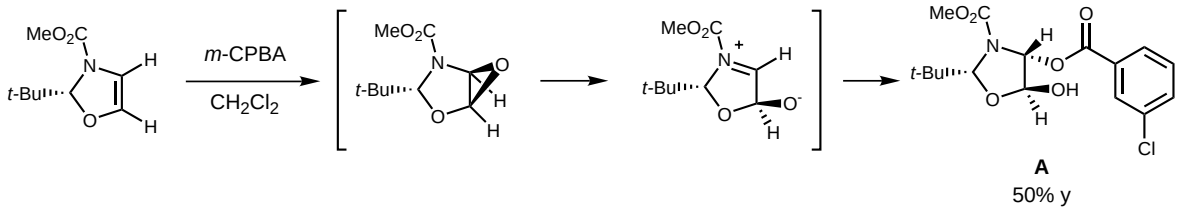
Nucleophilic Addition to Acyliminium Substrates

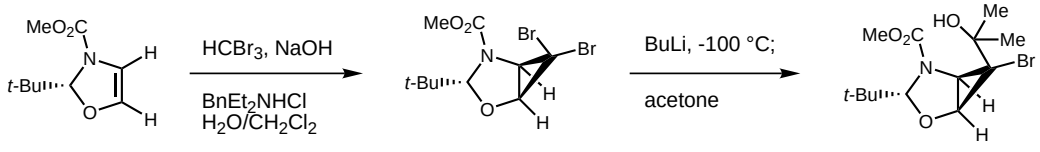


- *Cis* product is the major diastereomer in all nucleophilic additions to the acylimminium substrate.
- Nucleophilic attack from *Si* face avoids steric interference with the 2 axial hydrogens on the ring.
- No selectivity is observed with *t*-Bu acetal, perhaps due to difficulty in acheiving equatorial conformer with N-acyl group twisted out of plane.

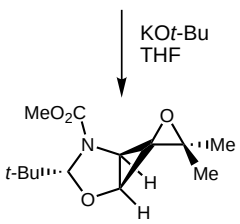
Seebach *ACIEE* **1986**, *25*, 843

Cycloadditions of Oxazolines



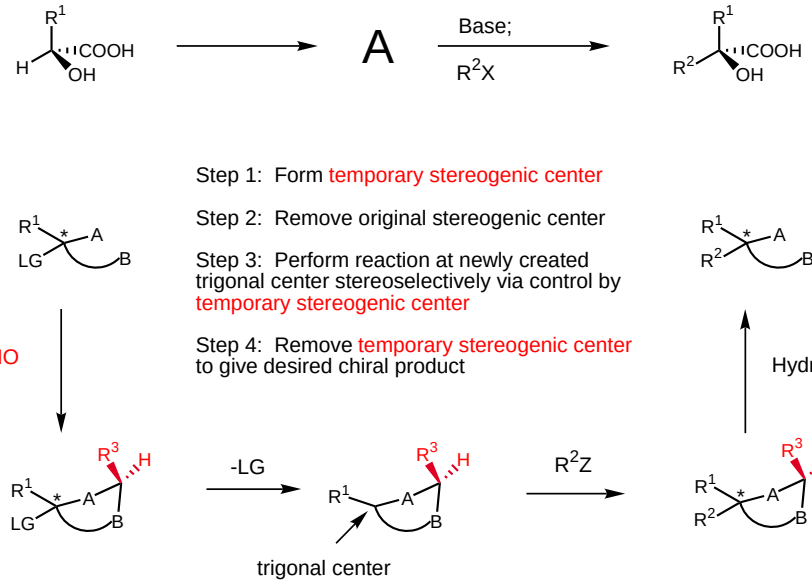


- Performing epoxidation in alcoholic solvent (ROH) results in the *trans* product **A** with OR in place of benzoate ester.
- Aldehyde addition to lithiated bromocyclopropane occurs on the endo face due to stabilization of the lithiated species by the ester and acetal oxygen of the ring.
- In both cases, there is exclusive addition to the olefin face opposite to the *t*-Bu group.



Seebach *Chem. Ber.* **1989**, 2377

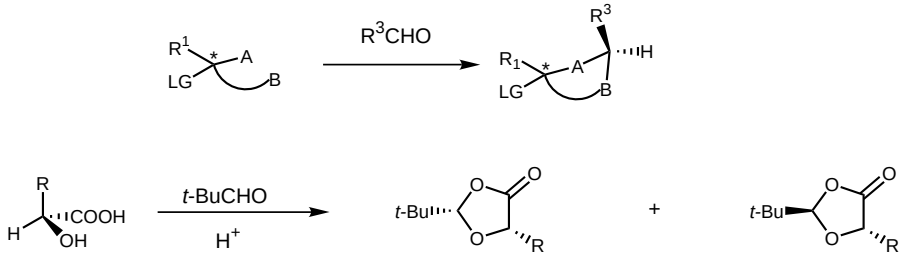
The SRS Principle



- Can have a cation, radical, anion, or π-system at the trigonal carbon

---

Formation of the Acetal

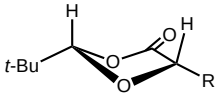


R	yield (%)	*cis:trans*
Me	93	4:1
Bn	87	5:1
Ph	82	20:1

• *t*-Bu acetal is chosen for most applications due to its steric bulk (enabling high ds/ee), reasonable cost, being inert to reaction at the α carbon, and favorable physical properties.

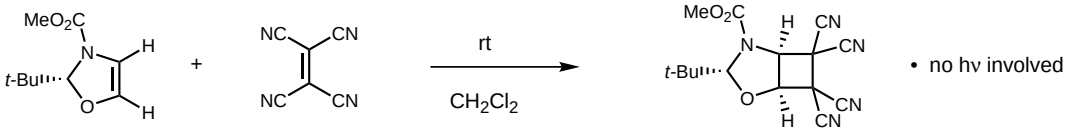
• Pure *cis* or *trans* isomer is isolated by crystallization. Dioxolane acetal diastereoselectivity is typical of acid-catalyzed method of formation for the N,O heterocyclic variants: *HCA* **1985**, *68*, 1243

• *Cis* isomer is preferred under thermodynamic conditions due to favorable placement of substituents in equatorial positions on 5-membered ring.

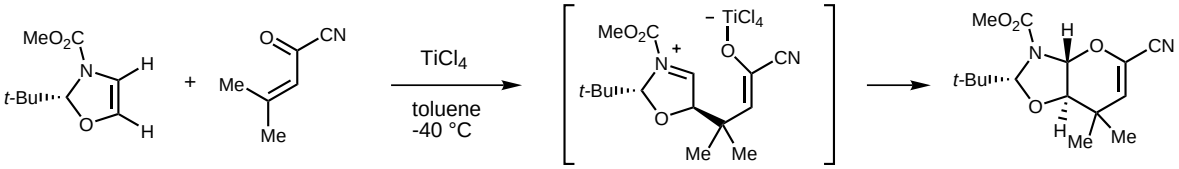


Seebach *Tetrahedron* **1984**, *40*, 1313

Acyliminium Intermediates: Diels-Alder Reaction



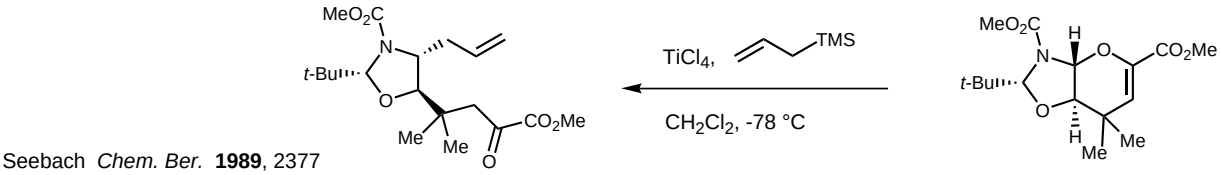
- no hν involved



A

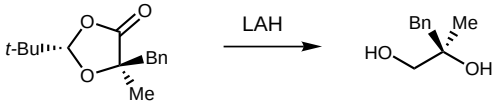
- *Trans* ring fusion in hetero-Diels-Alder suggests cycloaddition is stepwise.
- Greater stability of the iminium ion **A** over the oxonium ion alternative directs the first attack *trans* to the *t*-Bu group to give the observed stereochemistry.

1. NaOMe, MeOH
2. HCl

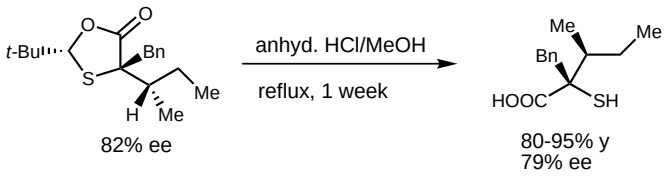


Seebach *Chem. Ber.* **1989**, 2377

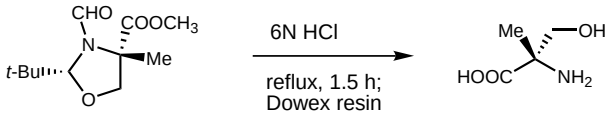
Reality Check: Acetal Hydrolysis



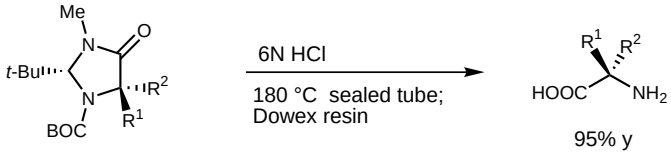
- No yields or experimentals given



- Some acetals cleaved only by basic conditions, which eroded ee.



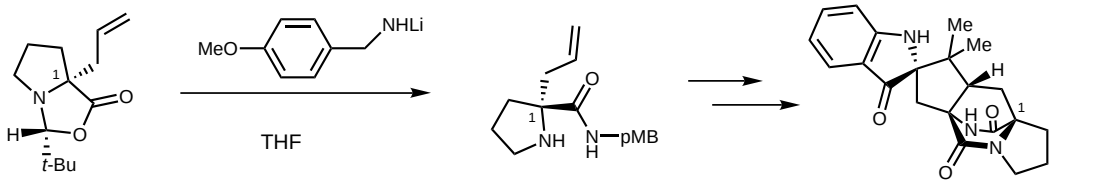
- Conditions "in some cases leave a lot to be desired." --D. Seebach



Seebach *ACIEE* **1996**, *35*. 2708

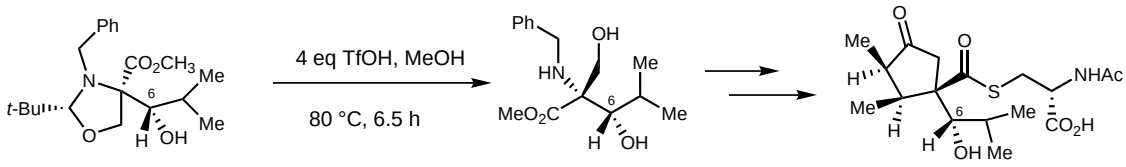
Acetal Hydrolysis in Synthesis

Williams' synthesis of Brevianamide B



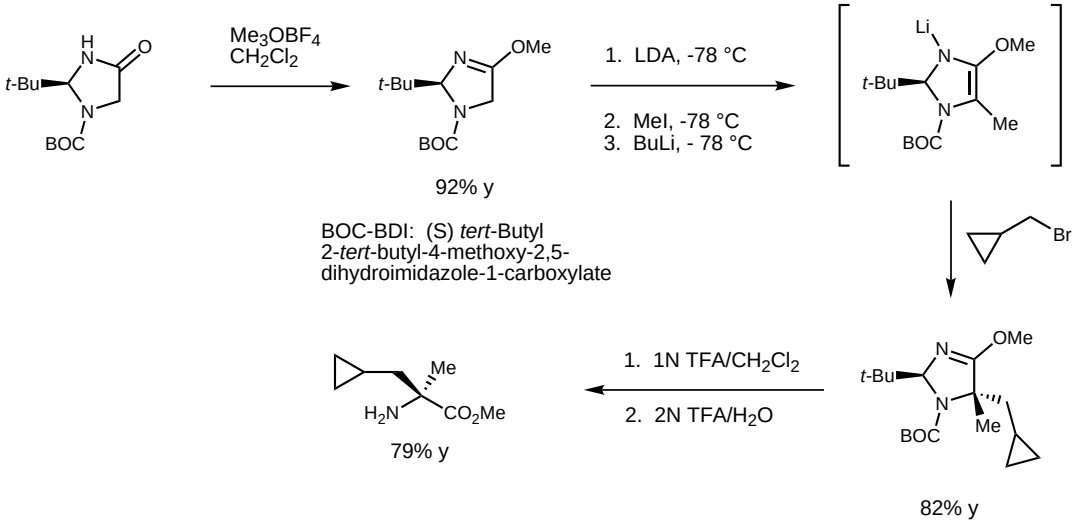
Williams *JACS* **1988**, *110*, 5927

Corey's synthesis of Lactacystin



Corey *JACS* **1992**, *114*, 10677

BOC-BDI: One Solution to the Hydrolysis Problem

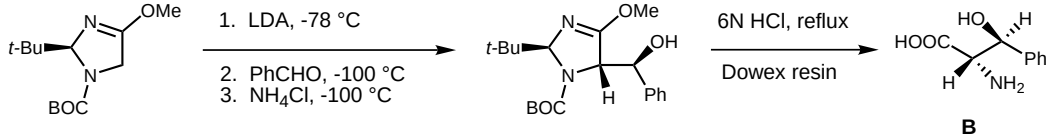


BOC-BDI: (S) *tert*-Butyl 2-*tert*-butyl-4-methoxy-2,5-dihydroimidazole-1-carboxylate

- TFA hydrolysis conditions allow for a wider scope of acid-sensitive electrophiles to be incorporated into amino acid derivatives.

Seebach *Eur. J. Org. Chem.* **1998**, 1337

Extension of BDI Methodology Into the Aldol Reaction

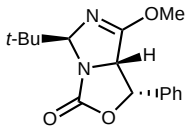


88% y, 82% ds

B

92% y

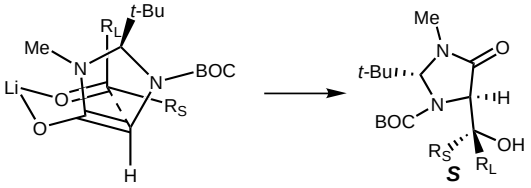
• Addition of aldehyde at -78 °C gives bicyclic derivative **A** which hydrolyzes to **B** under the same conditions.



A

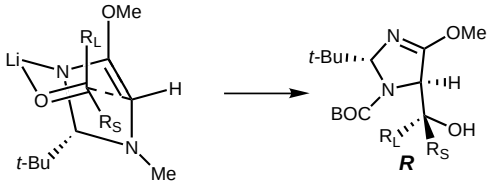
Compare BOC-BMI and BOC-BDI stereochemistry

<u>BOC-BMI</u>



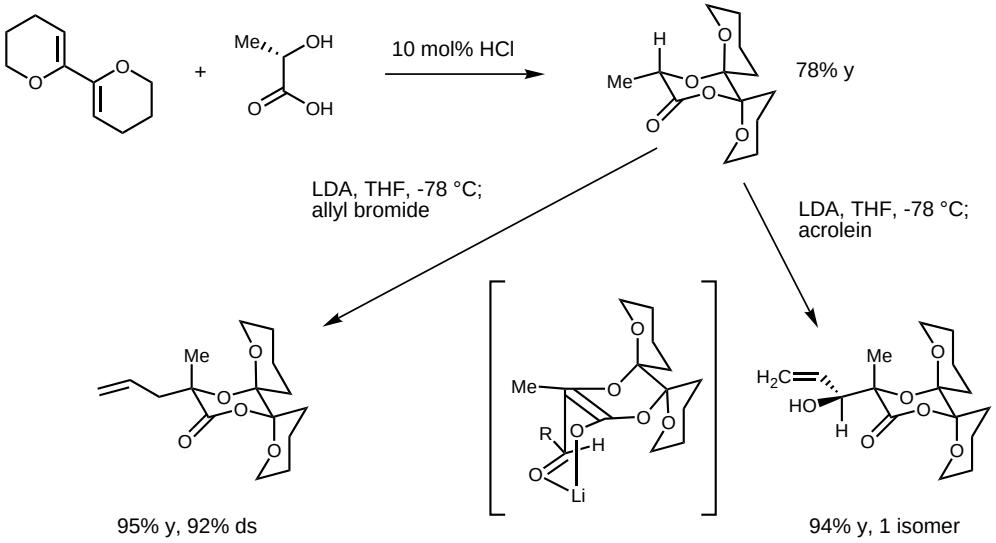
vs.

<u>BOC-BDI</u>



Seebach *Eur. J. Org. Chem.* **1998**, 1337

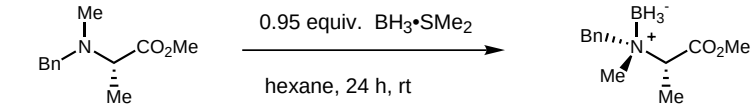
Dispoke Ketal as SRS Temporary Stereogenic Center



- Electrophiles explored thus far includes BnBr, alkyl halides, and simple aldehydes.
- Hydrolysis of ketals with CSA/MeOH gives the chiral α-hydroxy acids.

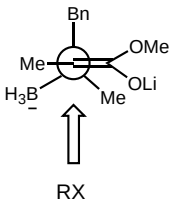
Ley *Tetrahedron* **1994**, *50*, 7157

Borane-Amines as Temporary Stereogenic Center



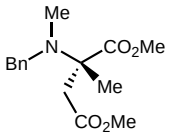
(from alanine Me ester)

90% ds
78% y major isomer



RX

1.1 equiv. LDA, -78 °C;
1.5 equiv. $BrCH_2CO_2Me$,
HMPA, toluene

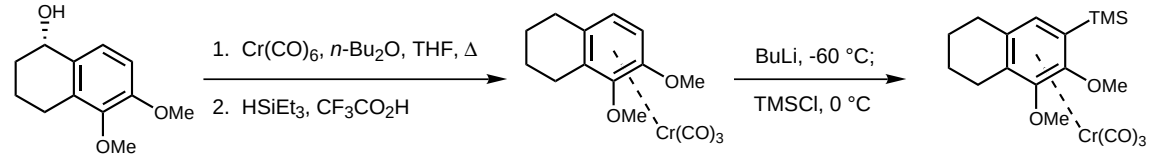


82% y, 80% ee

- The temporary stereogenic center is the borane-amine, which is removed under the alkylation conditions.
- Authors suggest Felkin type transition state to predict the observed stereochemistry as the electrophile adds opposite to the large Bn group.

Mioskowski *ACIEE* **1996**, *35*, 430

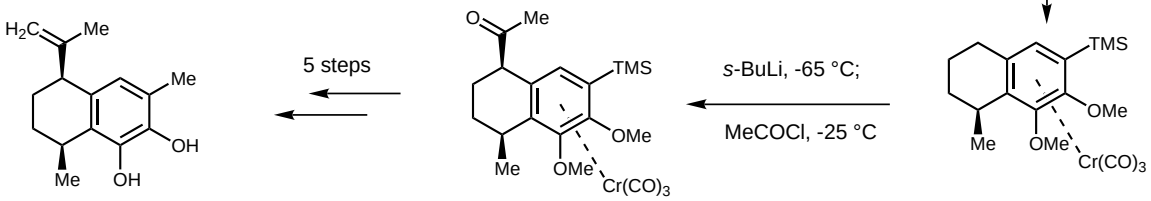
Self-Regenerating Planes of Chirality



74% y

98% y

BuLi, THF/HMPT, -60 °C;
MeI, -40 °C



cis-7,8-Dihydroxy-11,12-dehydrocalamenene

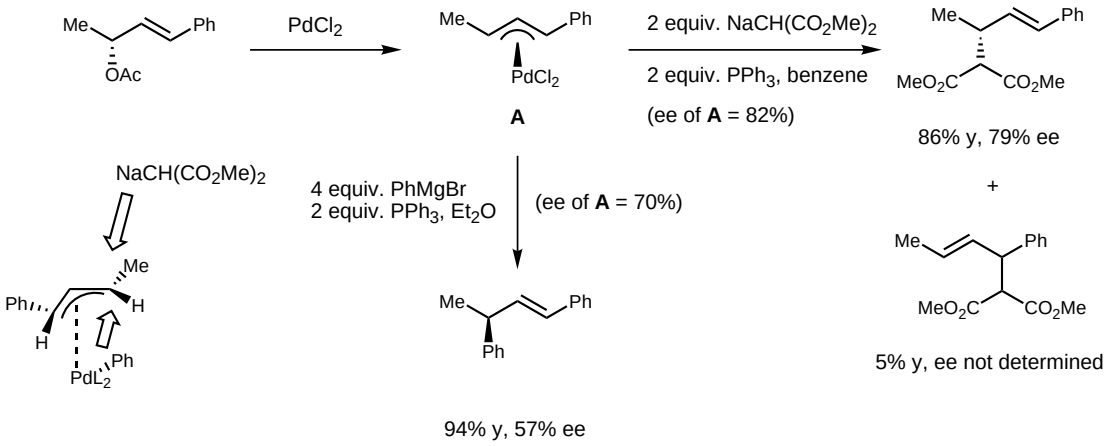
74% y

95% y

- $Cr(CO)_3$ creates a plane of chirality which functions as the temporary stereogenic center in the previous reactions.
- Steric shielding of the bottom face of the tetralin ring by $Cr(CO)_3$ allows for completely diastereoselective alkylation and acylation at benzylic positions.

Schmalz *ACIEE* **1994**, *33*, 109

Palladium-mediated Allylic Substitution



- Reaction is the first use of an optically active Pd complex to determine stereochemistry of nucleophilic addition to Pd-allyl substrates.

- Product stereochemistry indicates reaction controlled by selective binding of $PdCl_2$ to allyl face opposite the OAc leaving group.

Hayashi *J. Chem. Soc. Chem. Comm.* **1984**, 107

Conclusions

1. Alkylations (single or double) can be performed on a variety of heterocyclic acetals

   a. If the resultant alkylated product is not acid sensitive, BOC-BMI methodology is the most widely used to date.
   b. If the product is acid-sensitive, the use of BOC-BDI methodolgy is recommended.
   c. Exocyclic and bicyclic enolates can be alkylated in good yield and diastereoselectivity. Resultant stereochemistry is often <u>opposite</u> to that seen in mono-endocyclic cases.

2. Conjugate additions proceed with complete ds in good to excellent yields for a variety of donor-acceptor motifs.

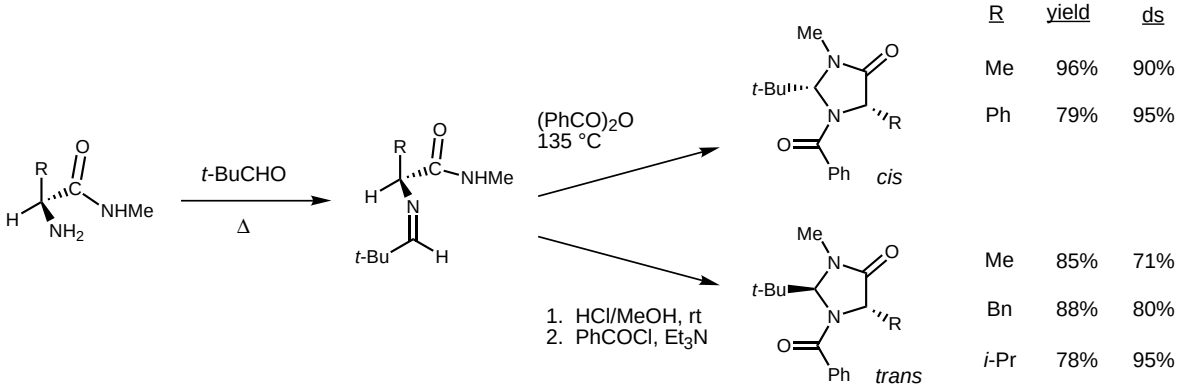
3. Radical reactions proceed with good yield and selectivity only for bulky radicals.

4. Diels-Alder reactions proceed in good yield with high exo selectivity.

5. The vast majority of these reactions occur on the acetal side *trans* to the *t*-Bu group.

6. The SRS principle can be applied to other temporary stereogenic centers besides acetals.

Control of Imidazolidinone Formation

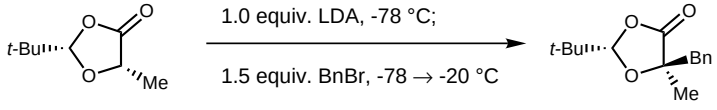


R	yield	ds
Me	96%	90%
Ph	79%	95%
Me	85%	71%
Bn	88%	80%
i-Pr	78%	95%

- More stable *cis* isomer arises from thermodynamic control, while the *trans* isomer is formed under kinetic control.
- Both diastereomers can be purified by crystallization to >95:5 ds.

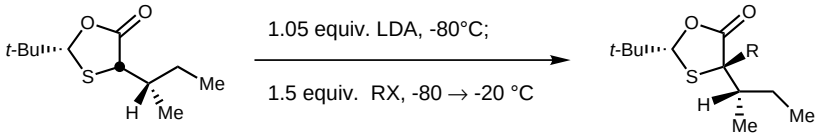
Seebach *HCA* **1985**, *68*, 135

Alkylation of α-Substituted Heterocyclic Substrates



81% y, 96% ds

Seebach *Tetrahedron* **1984**, *40*, 1313

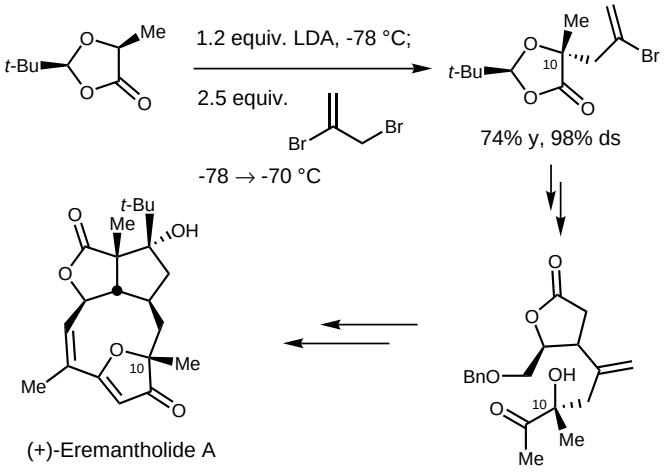


RX = MeI 85% y, 60% ds
RX = BnBr 90% y, >95% ds

Kellogg *Tetrahedron* **1987**, *43*, 5039

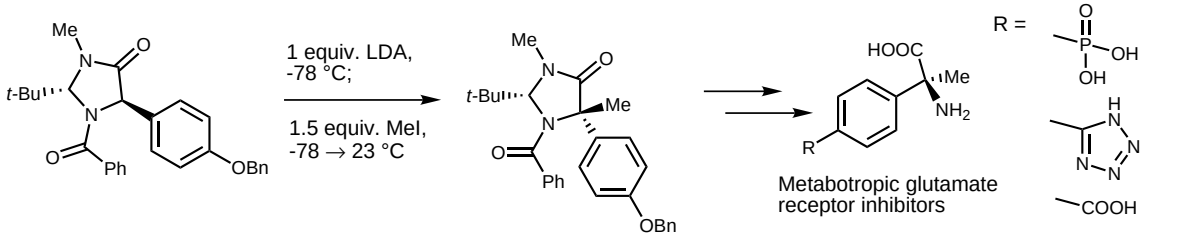
- Dioxolane alkylations with other aliphatic halides gave comparable yields and selectivities to above example; however, these enolates are less stable than their imidazolinone counterparts.
- Use of N,O or N,N variants leads to synthesis of non-natural amino acid derivatives with useful biological applications.
- O,S acetal allowed for first enantioselective synthesis of tertiary thiols after acidic hydrolysis.

Synthetic Applications of SRS Alkylation



• Either product enantiomer is available from alkylation of the appropriate heterocyclic precursor.

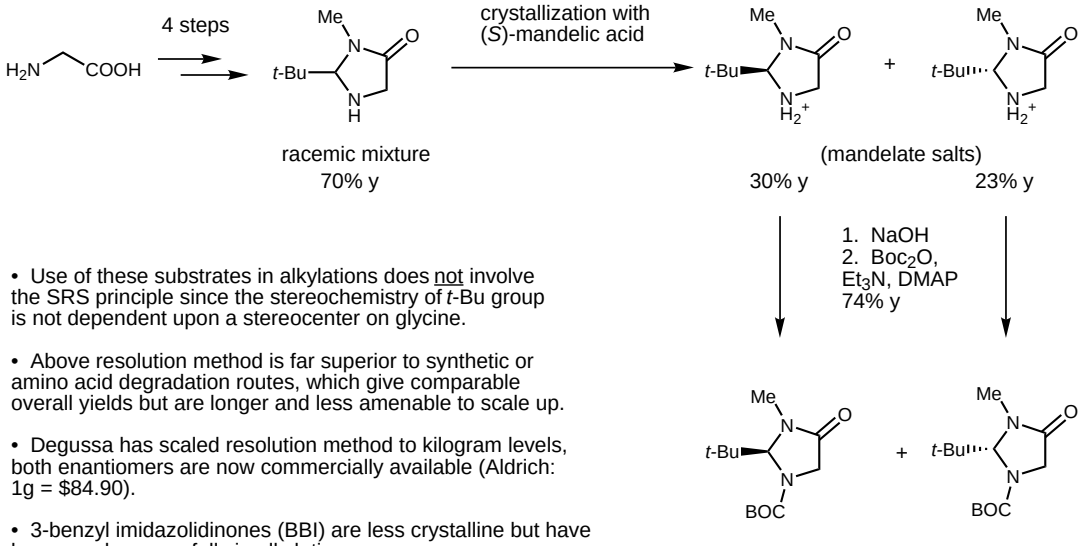
Boeckman *JACS* **1991**, *113*, 9682



Ma *J. Chem. Soc. Perk. Trans. 1* **1997**, 3493

BOC-BMI: Even Better than SRS Methodology

Synthesis of BOC-BMI (BMI = 2-*tert*-butyl-3-methyl-1,3-imidazolidin-4-one):



• Use of these substrates in alkylations does not involve the SRS principle since the stereochemistry of *t*-Bu group is not dependent upon a stereocenter on glycine.

• Above resolution method is far superior to synthetic or amino acid degradation routes, which give comparable overall yields but are longer and less amenable to scale up.

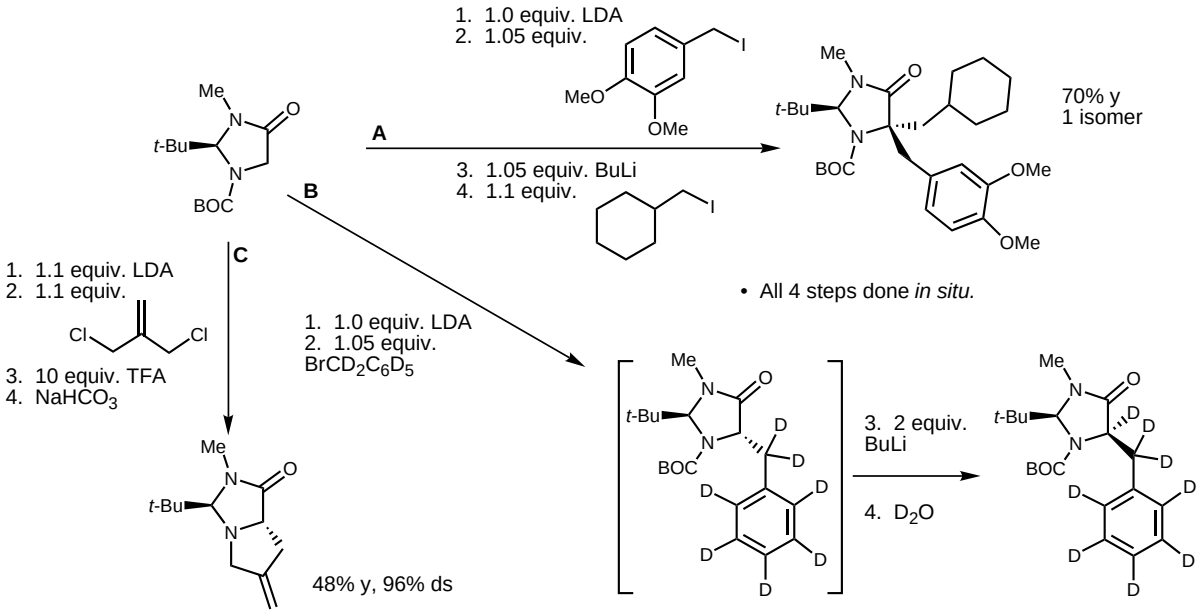
• Degussa has scaled resolution method to kilogram levels, both enantiomers are now commercially available (Aldrich: 1g = $84.90).

• 3-benzyl imidazolidinones (BBI) are less crystalline but have been used successfully in alkylations.

Seebach *Tetrahedron* **1988**, *44*, 5277

Alkylation with BOC-BMI: Improved Flexibility

Application to unnatural amino acid derivatives:

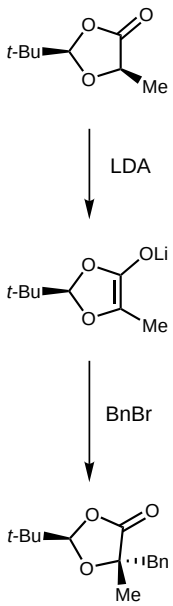


• Products are hydrolyzed to their free amino acid counterparts.

A and **B**: Seebach *Liebigs Ann. Chem.* **1989**, 1215
C: Najera *Tet. Asymm.* **1997**, *8*, 1855

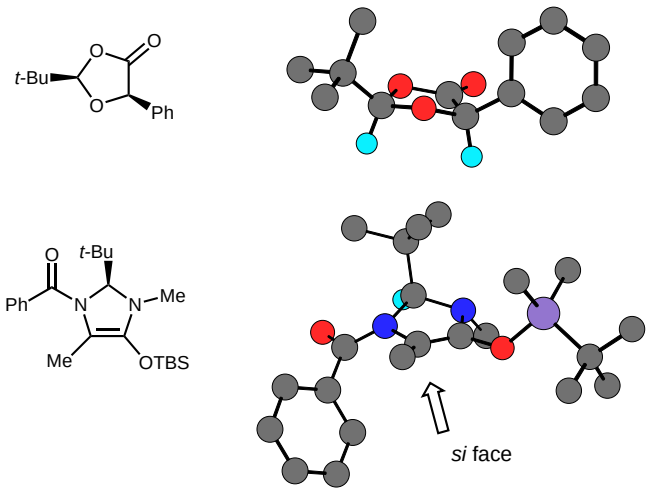
Stereochemistry of Alkylation: Monocyclic Acetals

Monocyclic acetal alkylation



Seebach *Tetrahedron* **1984**, *40*, 1313

X-ray structure data supports observed facial selectivity



X-ray data: Seebach *HCA* **1992**, *75*, 913

• Bulky *t*-Bu group blocks the top face of the enolate so that alkylation occurs ***trans*** to the acetal substituent.

• This sense of induction observed for all electrophilic additions to <u>monocyclic</u> acetals of N,N; N,O; O,O; O,S with <u>endocyclic</u> enolates.