

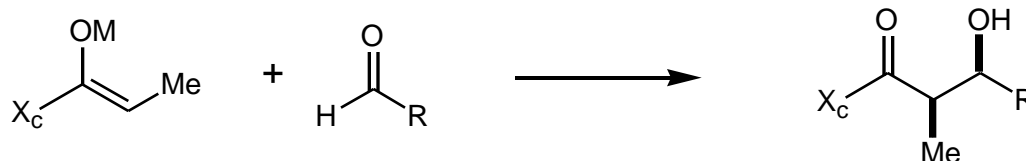
Denmark's Base Catalyzed Aldol/Allylation

Evans' Group Seminar
November 21th, 2003
Jimmy Wu

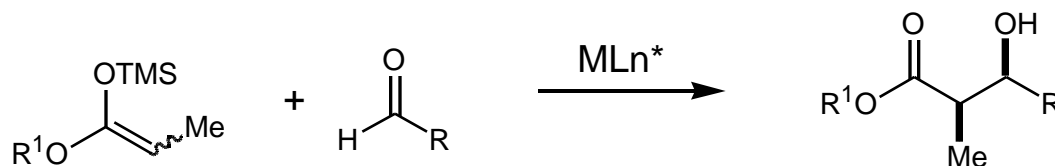
Lead References:

- Denmark, S. E. *Acc. Chem. Res.*, **2000**, 33, 432
- Denmark, S. E. *Chem. Comm.* **2003**, 167
- Denmark, S. E. *Chem. Rev.* **2003**, 103, 2763
- Denmark, S. E. *JOC*, **1998**, 63, 9517

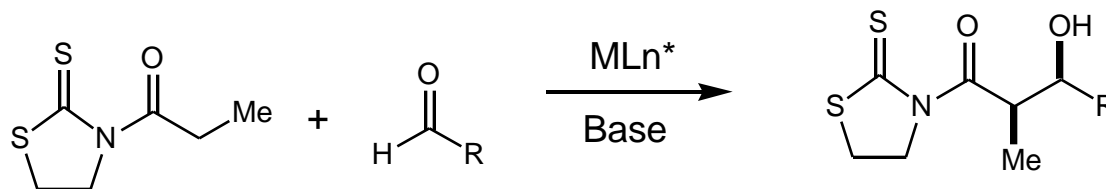
Background



- Requires stoichiometric amounts of covalently bound auxiliaries

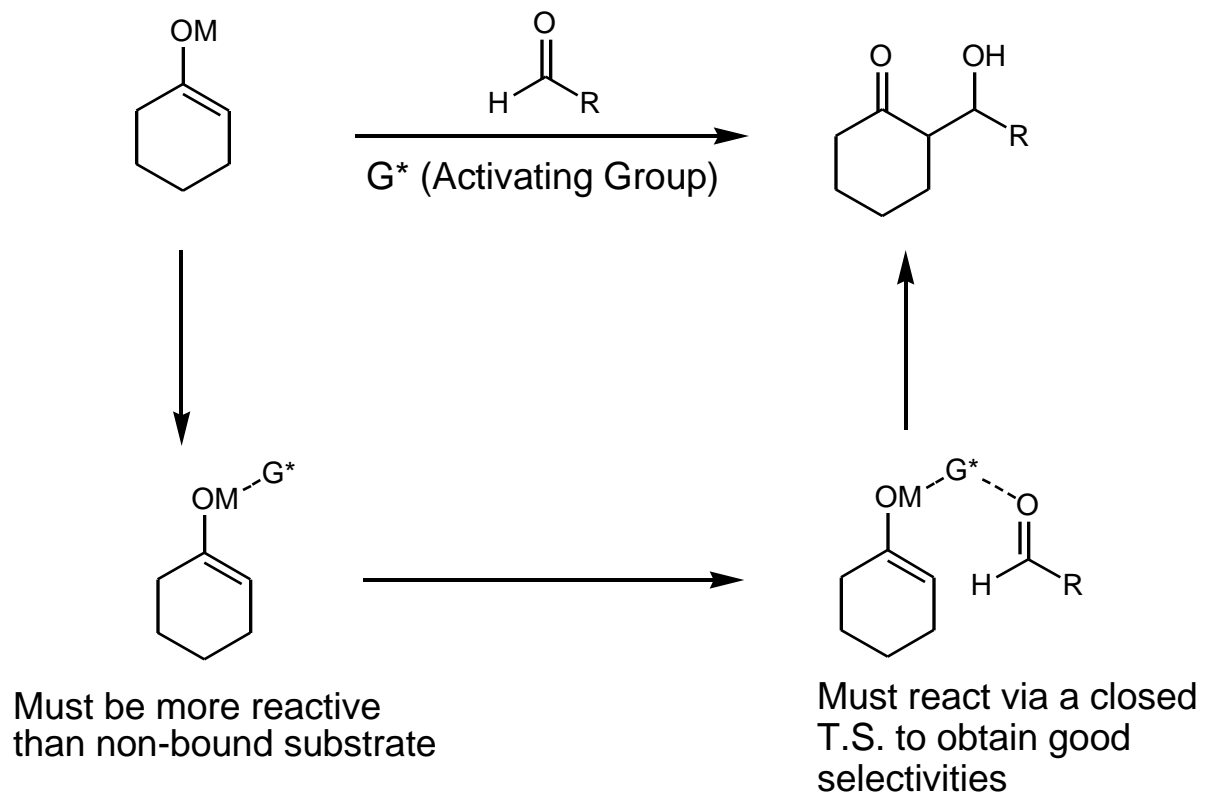


- Ligand is often deactivating
- Diastereoselectivity can be high but are often variable

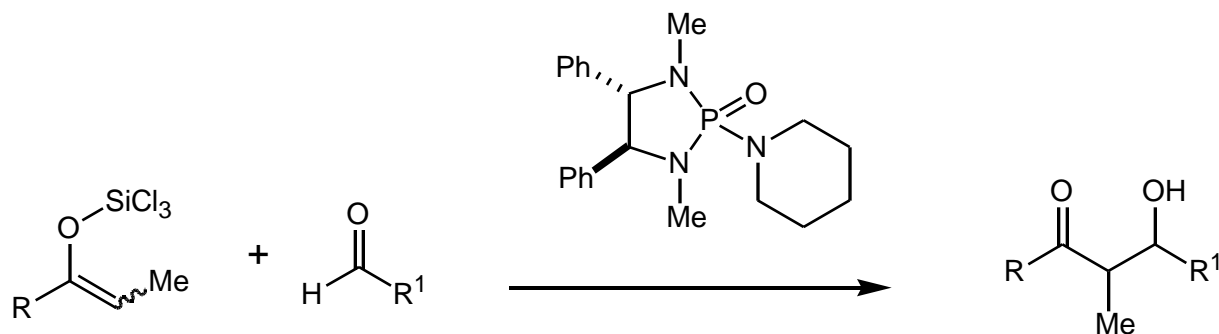


- Number of literature examples is still limited.

Lewis Base Activated Aldol

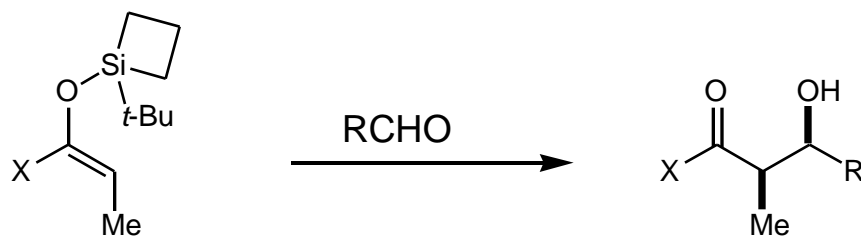


General Reaction Overview

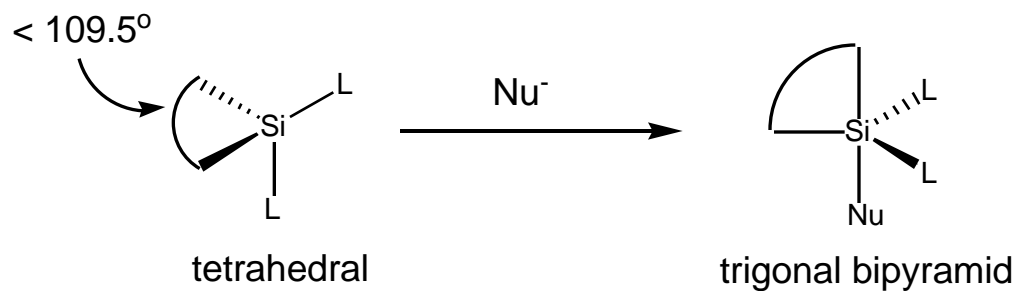


- *E* enolsilane ---> anti product
 - Highly diastereoselective (up to 99:1 anti/syn)
 - Highly enantioselective (up to 98% ee)
-
- *Z* enolsilane ---> syn product
 - Highly diastereoselective (up to 18:1 syn/anti)
 - Highly enantioselective (up to 98% ee)

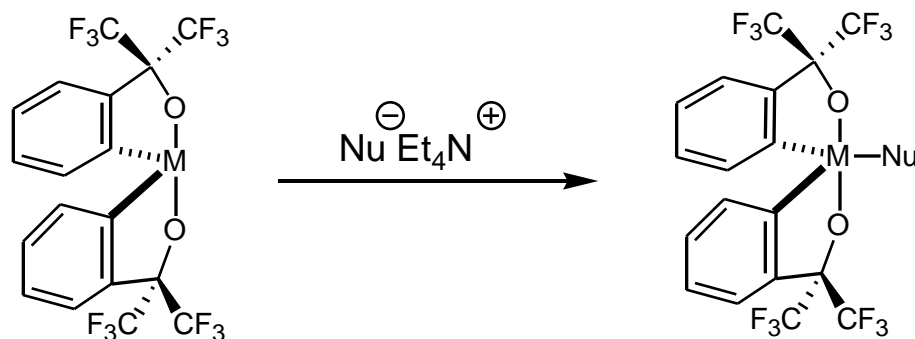
How It All Started



- Wanted to exploit the concept of “strain-release Lewis acidity”



Literature Examples

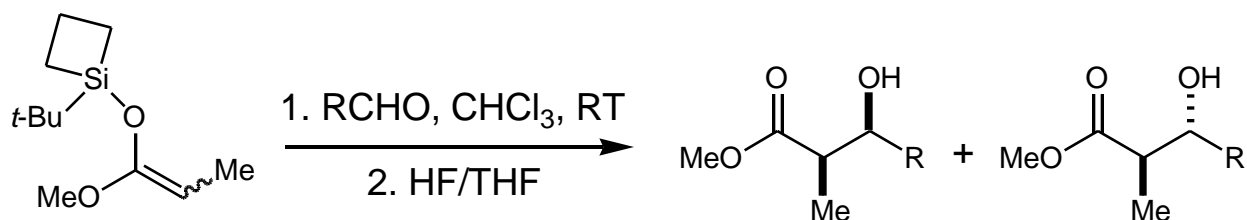


M = Si and Ge
Ligand C-O(Ge) -2.6°

- Germanium compound is able to catalyze the ene reaction while silicon is not.

Martin, J. C. *JOC*, **1981**, *46*, 1049
Denmark, S. E. *Organometallics*, **1990**, *9*, 3015

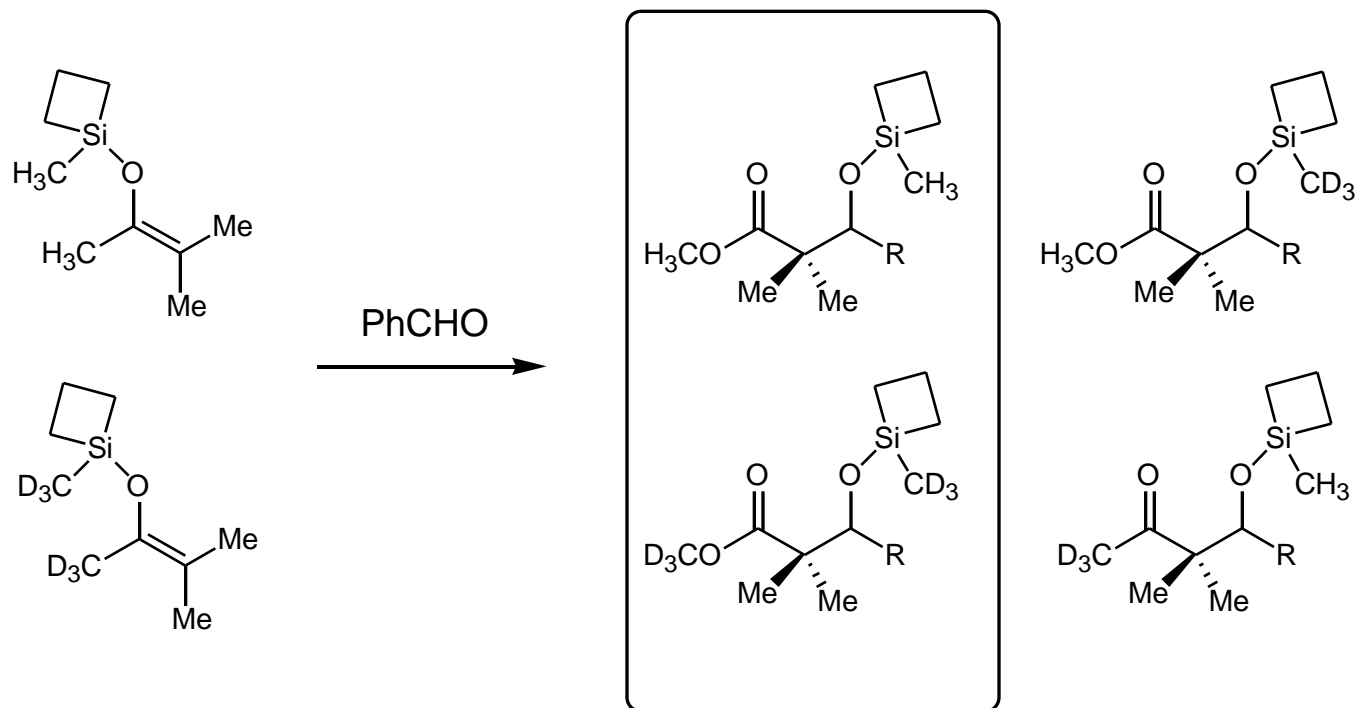
Strain-Release Catalyzed Aldol



| entry | R | <i>E/Z</i> | yield | syn/anti |
|-------|------------------|------------|-------|----------|
| 1 | Ph | 0/100 | 80 | 42/58 |
| 2 | Ph | 95/5 | 94 | 95/5 |
| 3 | cinnamyl | 89/11 | 95 | 93/7 |
| 4 | <i>n</i> -pentyl | 89/11 | 91 | 93/7 |
| 5 | cyclohexyl | 89/11 | 85 | >99/1 |

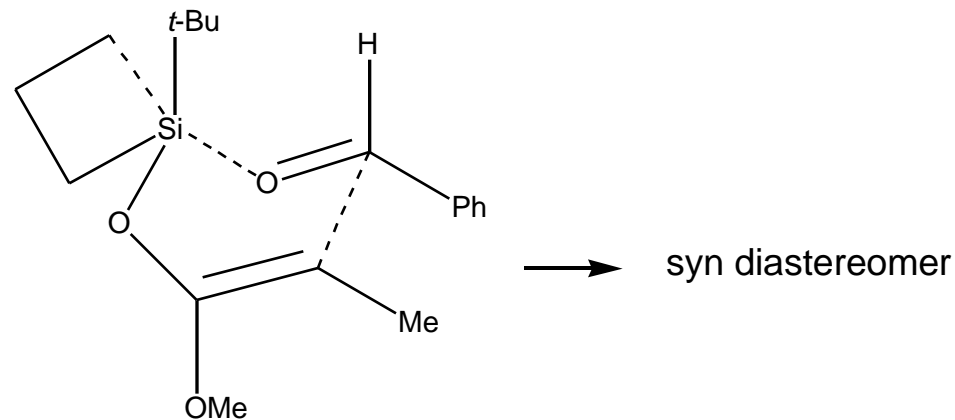
- Also worked for thiosilylketene acetals but both *E* and *Z* gave syn selectivity.
- Amide derived enolsilanes were unselective.

Mechanistic Studies



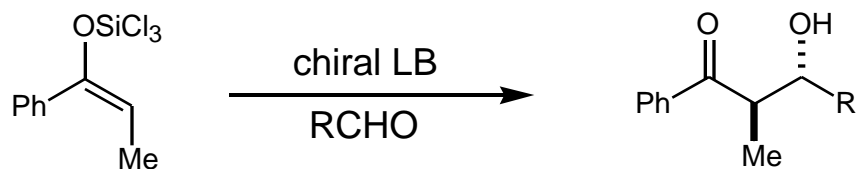
- Must go through a trigonal bipyramidal T.S. with internal transfer of silicon
- Analogous studies with KO*t*-Bu as a catalyst revealed complete deuterium scrambling. Cannot go through an octahedral T.S.

T.S. Models



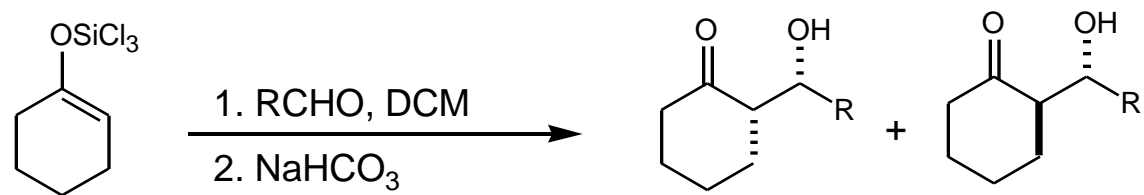
- Closed boat-like T.S.
- Pentacoordinate silicon
- Evans proposes similar T.S. in Zr based aldol (Evans, D. A. *TL*, **1980**, 21, 3975).

2nd Generation of LB Catalyzed Aldol



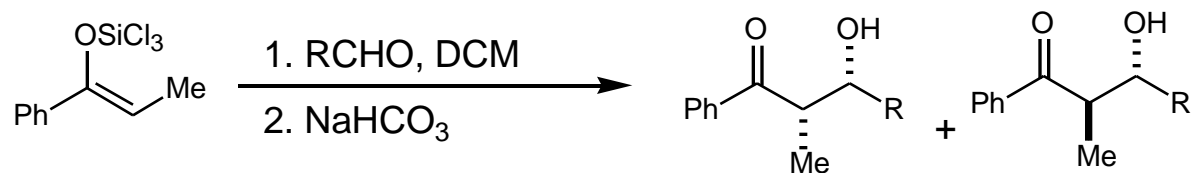
- Trichlorosilane required for sufficient Lewis acidity
- Silicon can expand valency by 2
- Simultaneous activation of Nu⁻ and E⁺ via closed T.S.
- Facial selectivity comes from chiral base

Uncatalyzed Reactions: *E* Enolsilanes



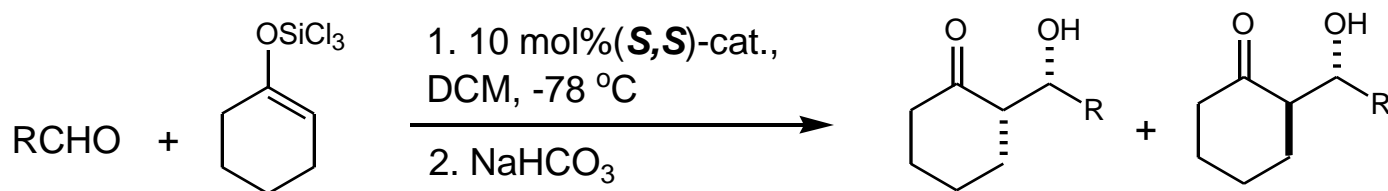
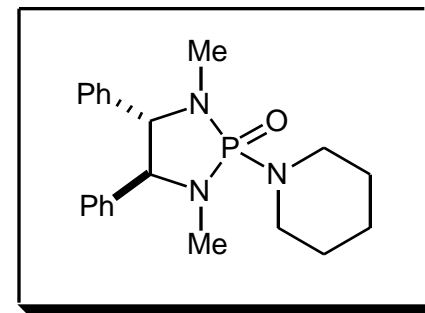
| entry | R | time, hr | syn/anti | yield |
|-------|------------------|----------|----------|-------|
| 1 | Ph- | 6 | 49/1 | 92 |
| 2 | 1-Naphthyl- | 8 | 16/1 | 90 |
| 3 | cinnamyl- | 1 | 49/1 | 83 |
| 4 | -methylcinnamyl- | 11 | 5.7/1 | 86 |
| 5 | Phenylpropargyl- | 2 | 36/1 | 91 |
| 6 | dihydrocinnamyl- | 12 | 5.3/1 | 82 |
| 7 | cyclohexyl- | 36 | 1/1 | 92 |

Uncatalyzed Reaction: *Z* Enolsilanes



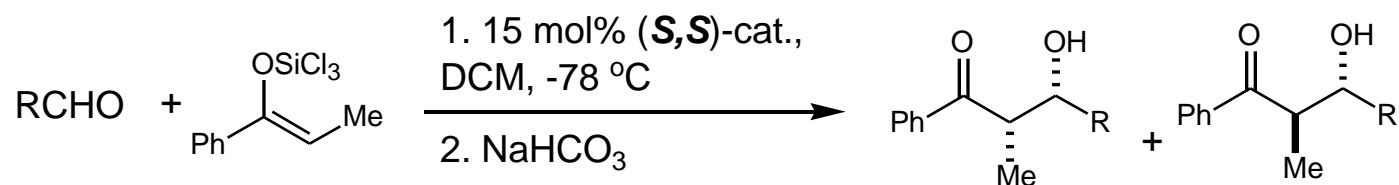
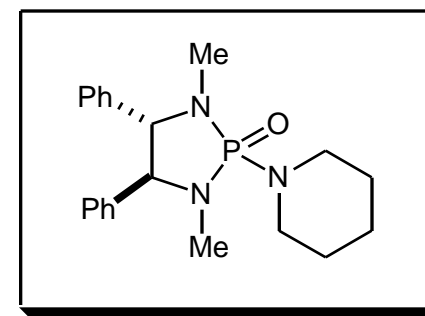
| entry | R | time, hr | syn/anti | yield |
|-------|------------------|----------|----------|-------|
| 1 | Ph- | 10 | 1/2.3 | 97 |
| 2 | 4-BrPh- | 10 | 1/2.9 | 93 |
| 3 | 1-Naphtyl- | 16 | 1/1.3 | 95 |
| 4 | cinnamyl- | 10 | 1/1.9 | 95 |
| 5 | -methylcinnamyl- | 12 | 1/2.2 | 64 |
| 6 | crotyl- | 16 | 1/1.9 | 89 |
| 7 | Phenylpropargyl- | 11 | 1/2.2 | 89 |

Catalyzed Aldol: *E* Enolsilanes



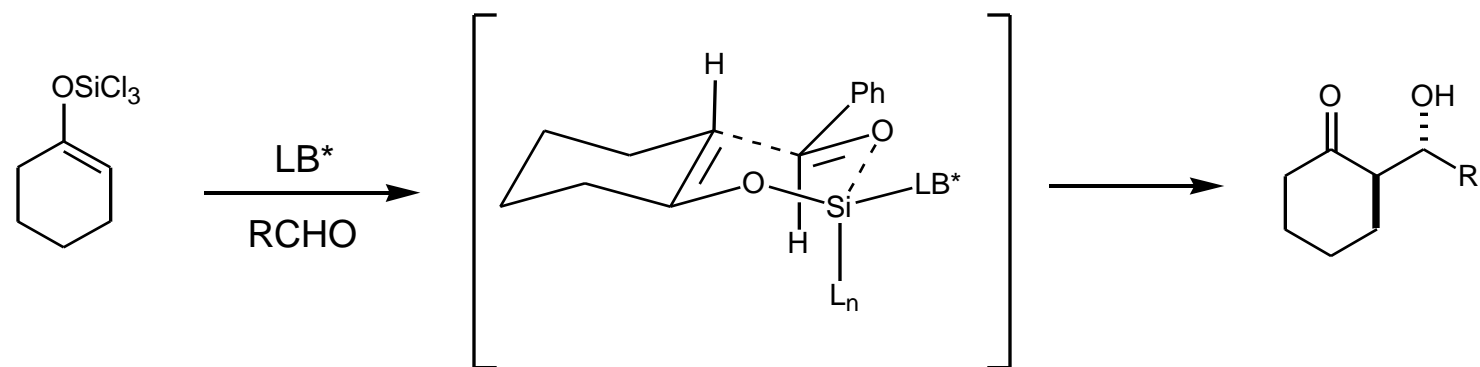
| entry | R | syn/anti | anti ee% | yield, % |
|-------|------------------|----------|----------|----------|
| 1 | Ph- | 1/61 | 93 | 95 |
| 2 | 1-Naphthyl- | <1/99 | 97 | 94 |
| 3 | cinnamyl- | <1/99 | 88 | 94 |
| 4 | -methylcinnamyl- | <1/99 | 92 | 98 |
| 5 | Phenylpropargyl- | 1/5.3 | 82 | 90 |

Catalyzed Aldol: *Z* Enolsilanes

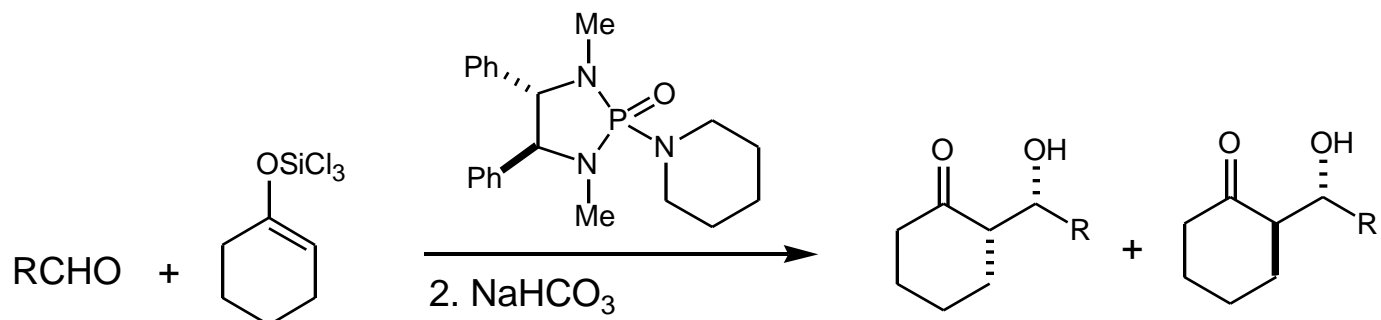


| entry | R | syn/anti | syn ee% | yield, % |
|-------|------------------|----------|---------|----------|
| 1 | Ph- | 18/1 | 95 | 95 |
| 2 | 4-BrPh- | 12/1 | 96 | 89 |
| 3 | 1-Napthyl- | 3/1 | 84 | 96 |
| 4 | cinnamyl- | 9.4/1 | 92 | 97 |
| 5 | crotyl- | 7/1 | 91 | 94 |
| 6 | Phenylpropargyl- | 1/3.5 | 58 | 92 |

Current T.S. Model - Too Simplistic



Mechanistic Clues



| entry | loading | conc. | syn/anti | yield |
|-------|---------|-------|----------|-------|
| 1 | 10% | 0.5 | 1/14 | 94 |
| 2 | 5% | 0.5 | 1/10 | 90 |
| 3 | 2% | 0.5 | 1/2.4 | 84 |

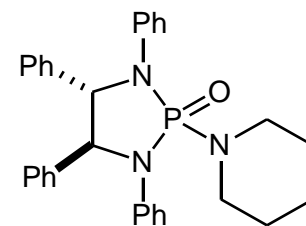
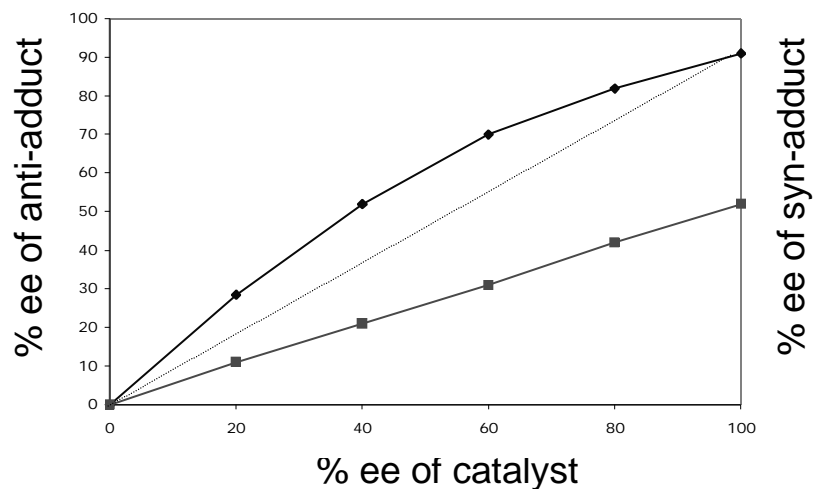
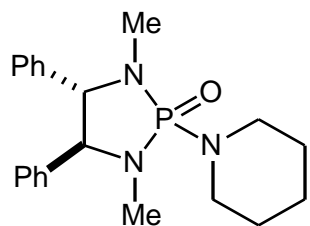
- Syn/anti ratio is highly dependent on catalyst loading
- Simple change in silicon valency cannot account for rate acceleration
- Bulkier catalysts lowers and even switches diastereoselectivities

Denmark, S. E. *JACS*, **1998**, *120*, 12990

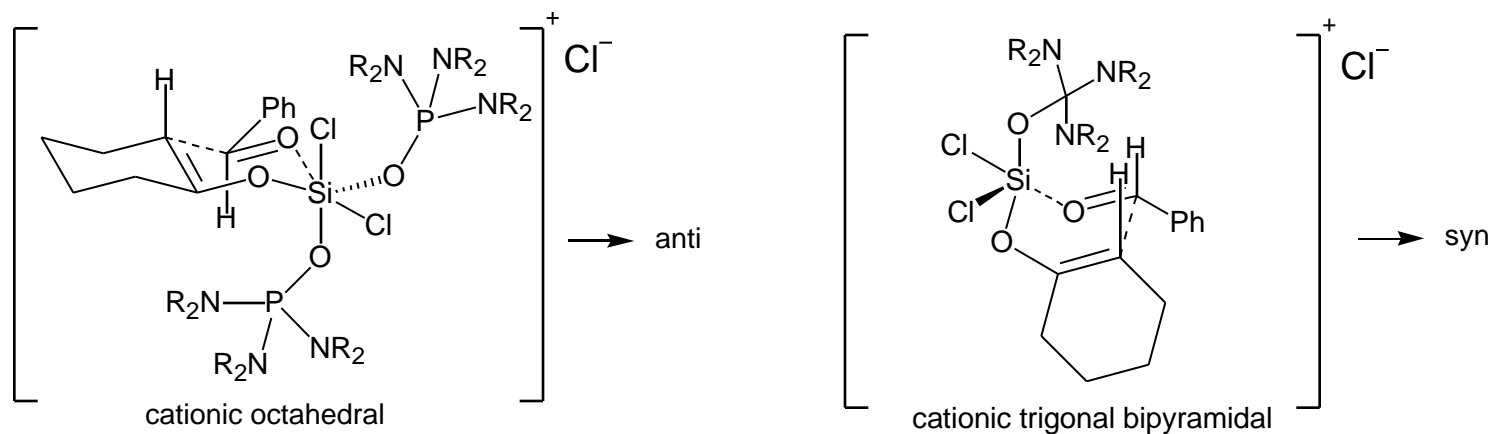
Denmark, S. E. *JACS*, **1999**, *121*, 4982

Mechanistic Proposal

- Two competitive pathways, one for the formation of each diastereomer
- Anti diastereomer dominates with less bulky ligands and higher conc.
- Syn diastereomer dominates with more bulky ligands and lower conc.

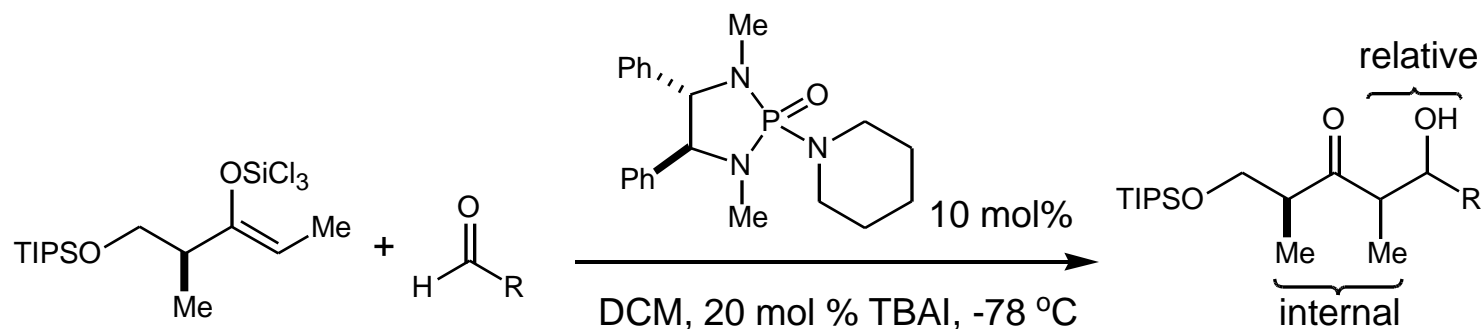


Unified T.S. Model



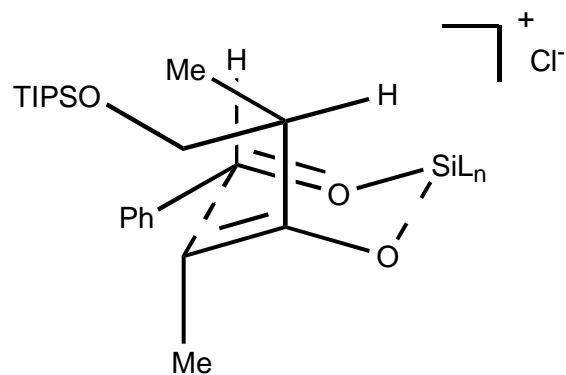
- Ligand binding causes Cl^- to dissociate:
- Bu_4NCl inhibits reaction because of the common ion effect
- Bu_4NOTf and TBAI accelerate reaction rates by increasing ionic strength

Double Stereodifferentiating Reactions I

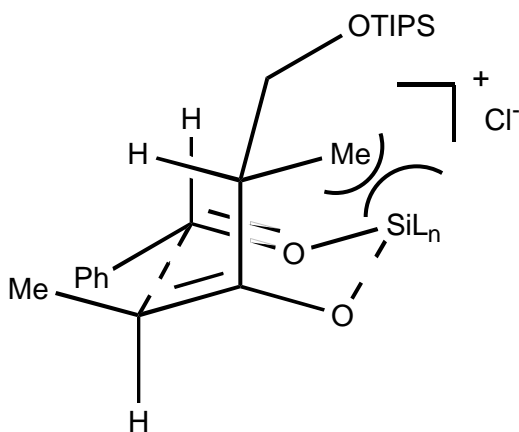


| entry | R | catalyst | relative dr (syn/anti) | internal dr (syn/anti) |
|-------|-------------|----------------|---------------------------|---------------------------|
| 1 | Ph- | (<i>R,R</i>) | 53/1 | 24/1 |
| 2 | Ph- | (<i>S,S</i>) | 32/1 | 1/8 |
| 3 | 1-Naphthyl- | (<i>R,R</i>) | 14/1 | 89/1 |
| 4 | 1-Naphthyl- | (<i>S,S</i>) | 14/1 | 1/17 |
| 5 | cinnamyl- | (<i>R,R</i>) | 9/1 | 14/1 |
| 6 | cinnamyl- | (<i>S,S</i>) | 15/1 | 1/6 |
| 7 | crotyl- | (<i>R,R</i>) | >50/1 | 15/1 |
| 8 | crotyl- | (<i>S,S</i>) | >50/1 | 1/5 |
| 9 | tiglyl- | (<i>R,R</i>) | 13/1 | 13/1 |
| 10 | tiglyl- | (<i>S,S</i>) | 19/1 | 1/5 |
| 11 | Ph | achiral | 27/1 | 5/1 |

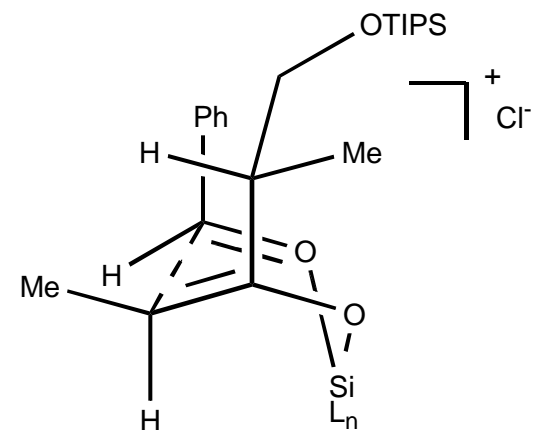
T.S. Models



- Minimizes steric interactions between substituents on enolate and bulky ligands on silicon
- Anti diastereomer may be formed via a boat-like T.S.

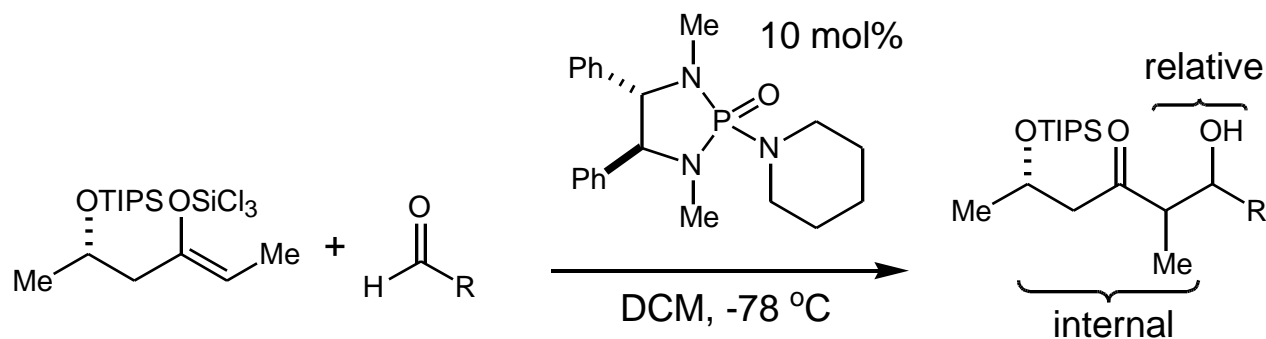


- $A_{1,3}$ strain is minimized but severe non-bonding interactions exist between substrate and ligands on silicon.



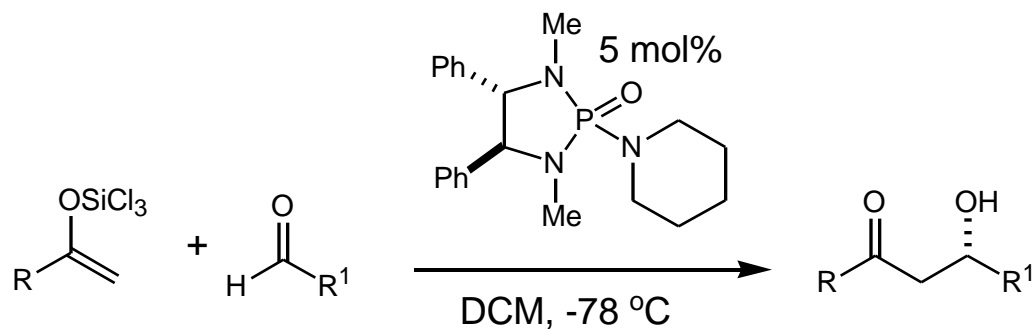
- Non-bonding interactions arising from chair T.S. can give rise to boat-like T.S.

Double Stereodifferentiating Reactions II



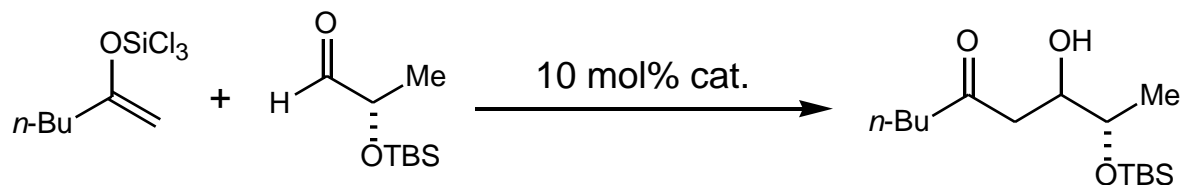
| entry | R | catalyst | relative dr (syn/anti) | internal dr (syn/anti) |
|-------|-------------|----------------|---------------------------|---------------------------|
| 1 | Ph- | (<i>R,R</i>) | 30/1 | 16/1 |
| 2 | Ph- | (<i>S,S</i>) | 26/1 | 1/10 |
| 3 | 1-Naphthyl- | (<i>R,R</i>) | 17/1 | 30/1 |
| 4 | 1-Naphthyl- | (<i>S,S</i>) | 18/1 | 1/10 |
| 5 | cinnamyl- | (<i>R,R</i>) | >50/1 | 10/1 |
| 6 | cinnamyl- | (<i>S,S</i>) | >50/1 | 1/8 |
| 7 | crotyl- | (<i>R,R</i>) | 28/1 | 7/1 |
| 8 | crotyl- | (<i>S,S</i>) | 37/1 | 1/6 |
| 9 | tiglyl- | (<i>R,R</i>) | >50/1 | 3/1 |
| 10 | tiglyl- | (<i>S,S</i>) | >50/1 | 1/3 |
| 11 | Ph | achiral | 29/1 | 1.4/1 |

Methyl Ketones as Nucleophiles

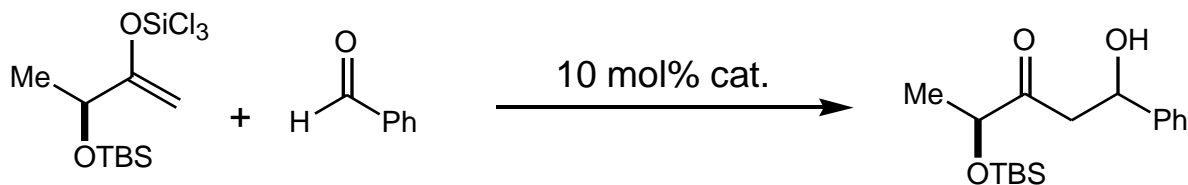


| entry | R | R ¹ | ee % | yield % |
|-------|-----------------------|------------------|------|---------|
| 1 | Me- | Ph- | 87 | 98 |
| 2 | <i>n</i> -Bu- | Ph- | 85 | 98 |
| 3 | <i>i</i> -Pr- | Ph- | 81 | 97 |
| 4 | Ph- | Ph- | 49 | 93 |
| 5 | TBSOCH ₂ - | Ph- | 86 | 94 |
| 6 | <i>n</i> -Bu- | cinnamyl- | 84 | 94 |
| 7 | <i>n</i> -Bu- | -methylcinnamyl- | 91 | 95 |
| 8 | <i>n</i> -Bu- | 1-naphthyl- | 86 | 92 |
| 9 | <i>n</i> -Bu- | cyclohexyl- | 89 | 79 |
| 10 | <i>n</i> -Bu- | <i>t</i> -Bu- | 92 | 81 |

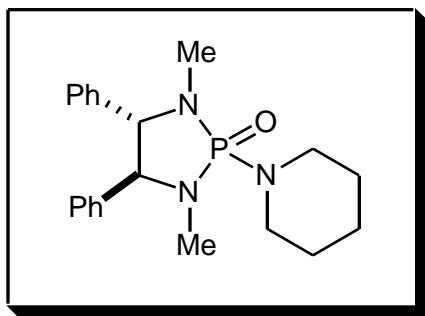
Double Stereodifferentiating Reactions



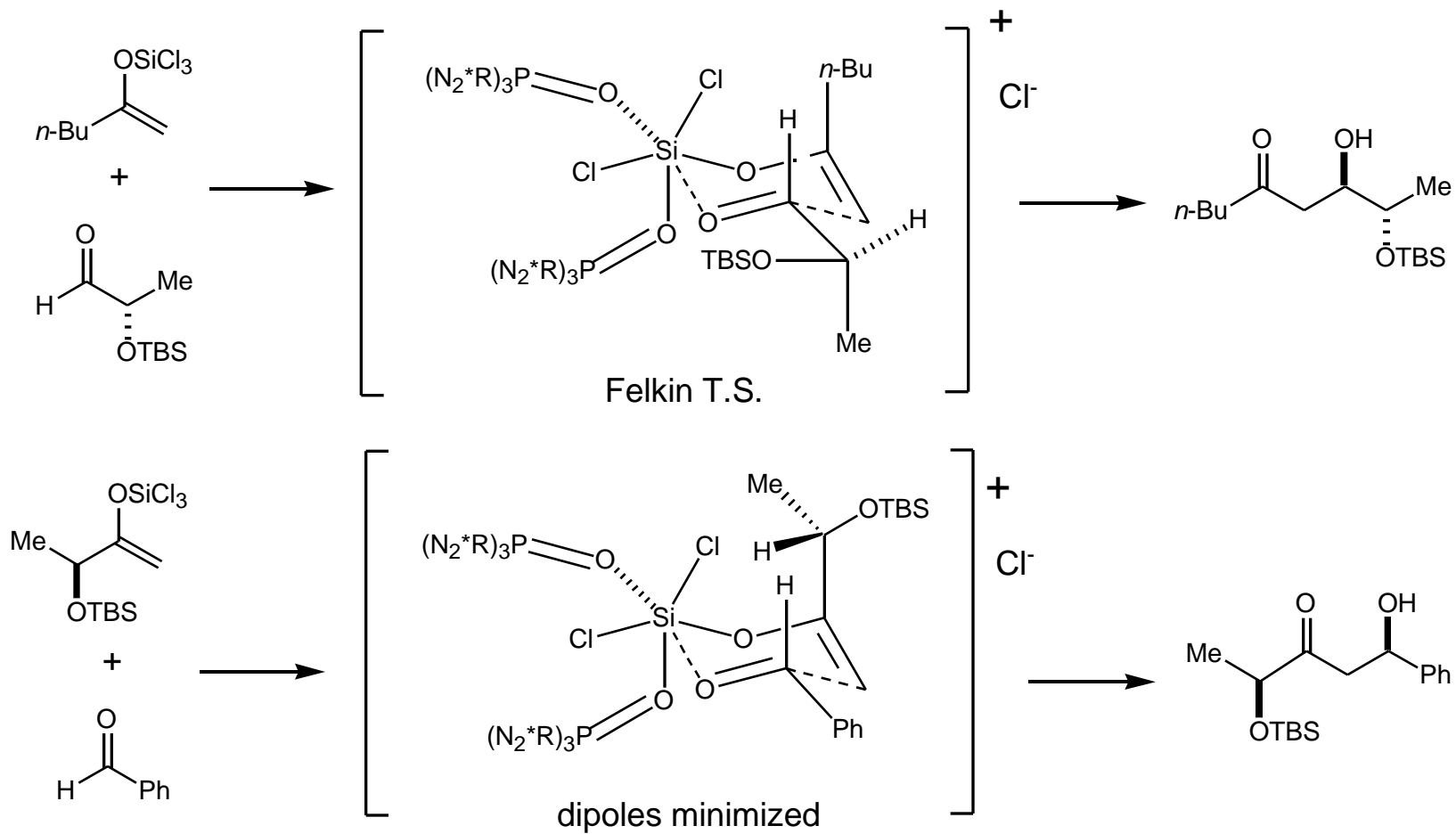
(*R,R*) - 1/15.6 syn/anti, 56% yield
(*S,S*) - 2.7/1 syn/anti, 47% yield
achiral - 1/1.3 syn/anti, 41% yield



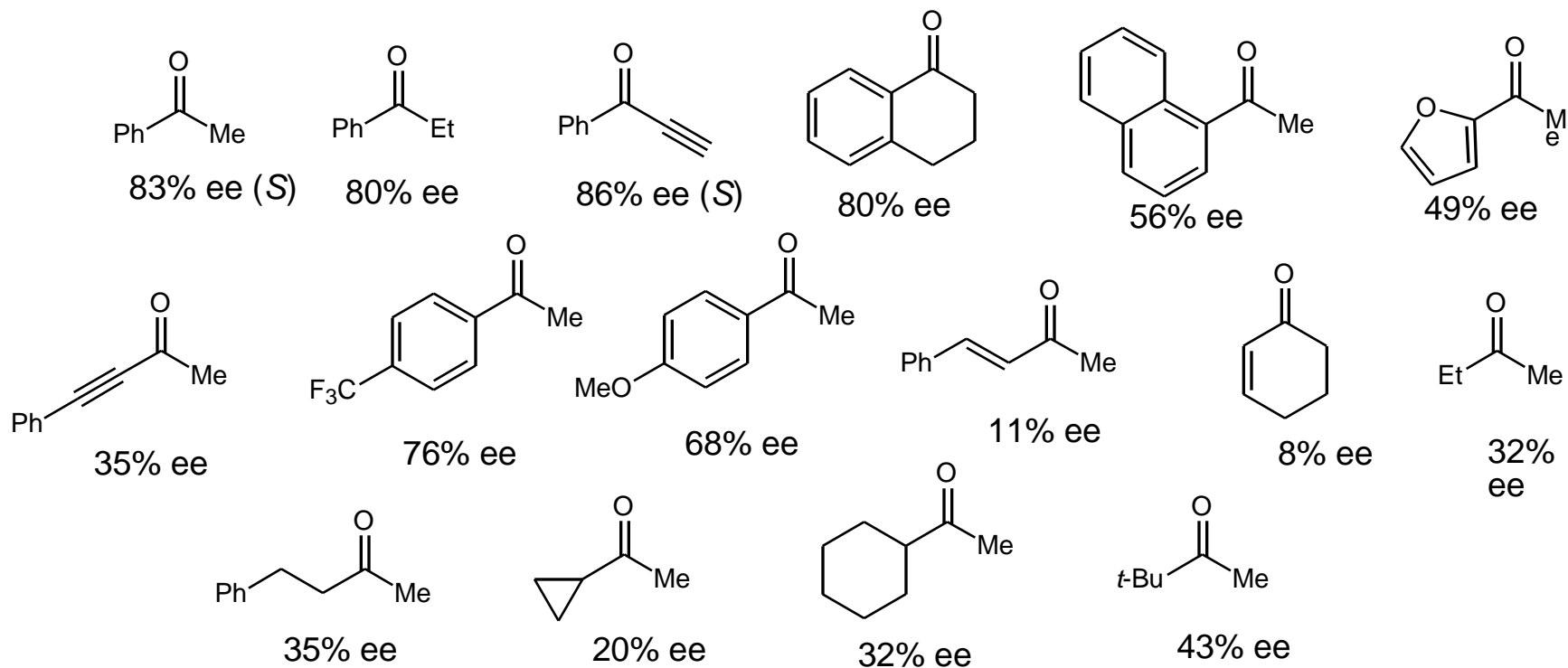
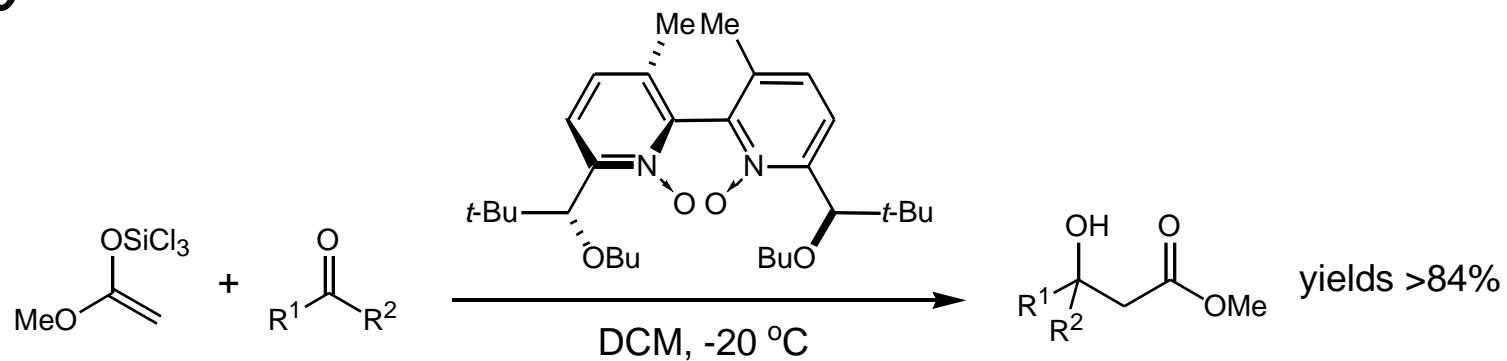
(*R,R*) - 73/1 syn/anti, 85% yield
(*S,S*) - 1.5/1 syn/anti, 85% yield
achiral - 1.2/1 syn/anti, 81% yield



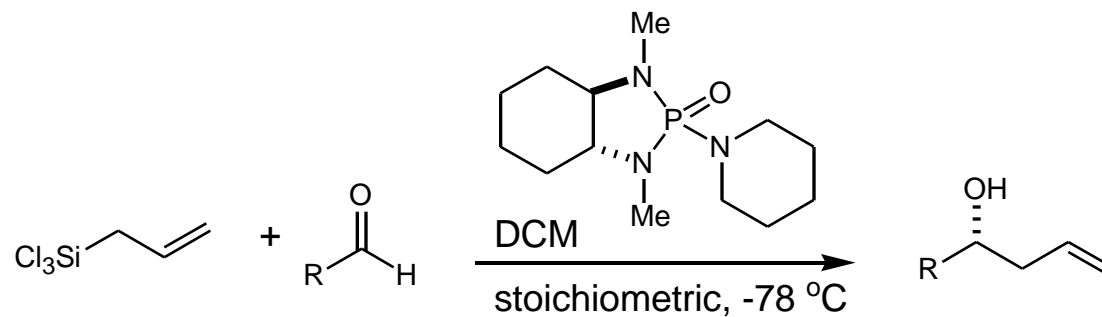
T.S. Models



Silyl Ketene Acetals

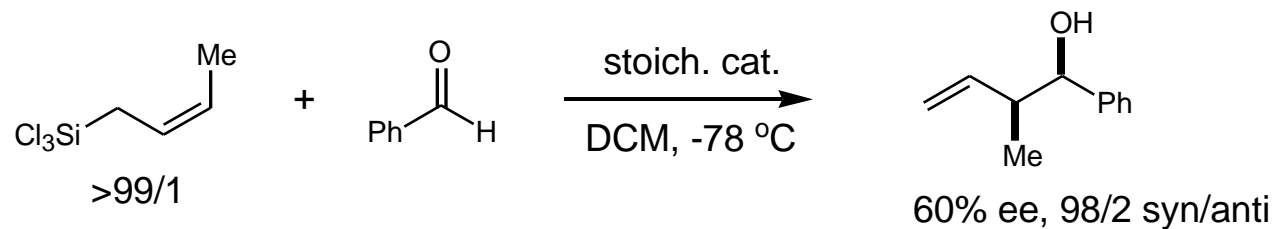
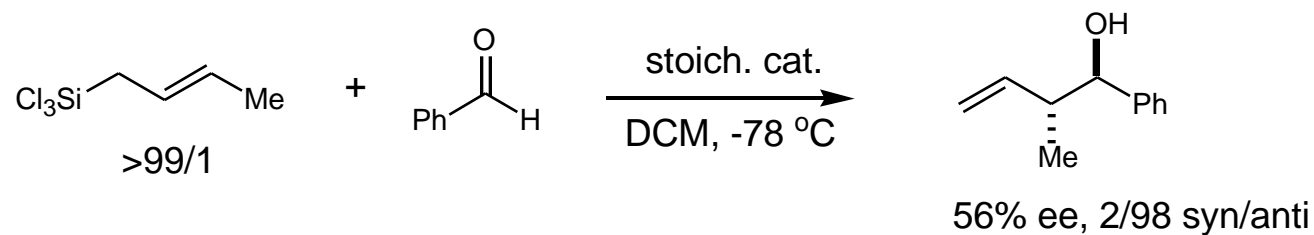
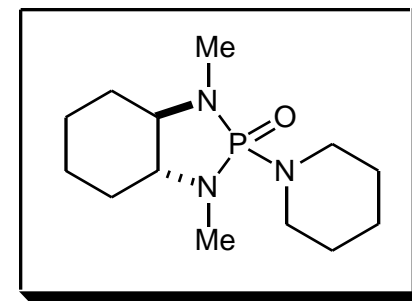


Asymmetric Allylation

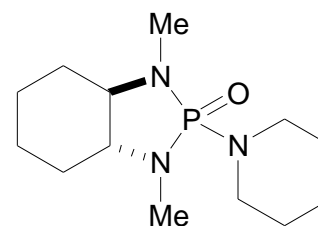
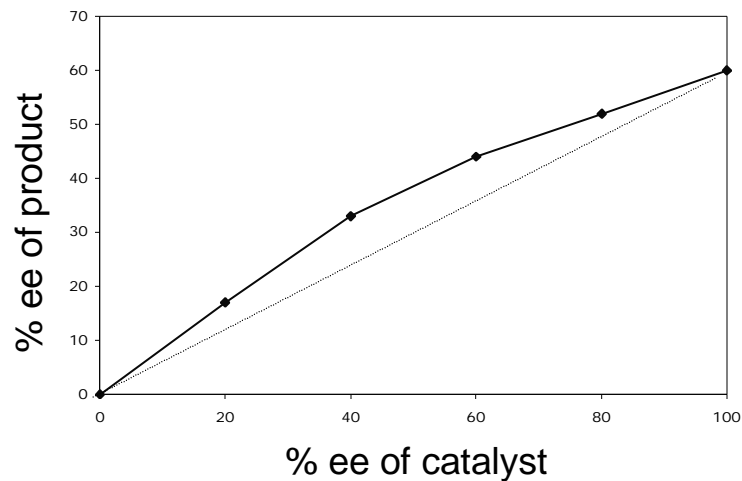


| entry | R | ee, % | yield |
|-------|------------------------|-------|-------|
| 1 | Ph- | 60 | 81 |
| 2 | <i>o</i> -tol- | 65 | 81 |
| 3 | 4-NO ₂ Ph- | 21 | 76 |
| 4 | 4-MeOPh- | 50 | 80 |
| 5 | 4-NMe ₂ Ph- | 33 | 69 |
| 6 | cinnamyl- | 38 | 67 |

Diastereoselective Allylations

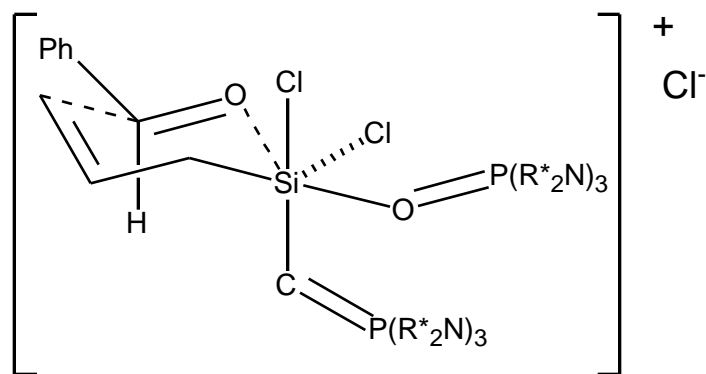


Mechanistic Studies

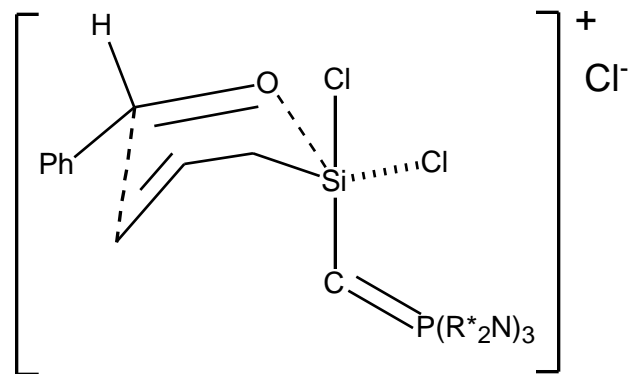


- 1st order in aldehyde
- 1st order in allylsilane
- 1.77th order in catalyst due to competing pathways involving 1 or 2 phosphoramidates bound to silicon.

T.S. Models



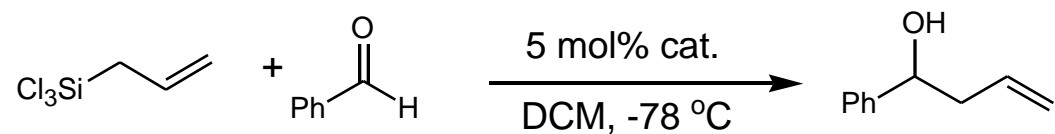
cationic octahedral



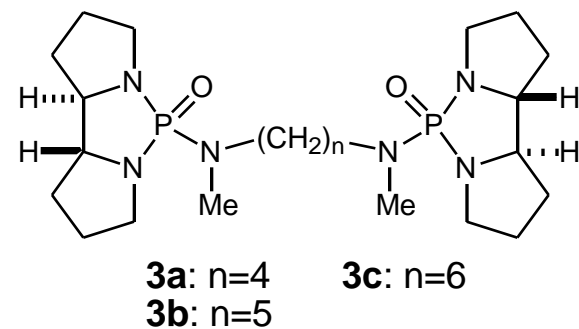
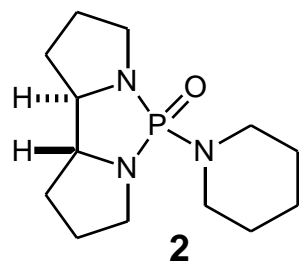
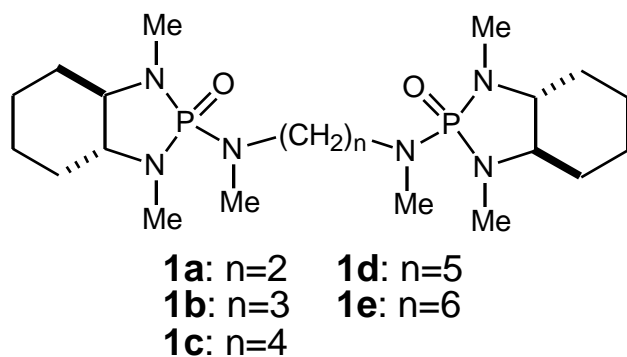
cationic trigonal bipyramidal

- Facial selectivity is lower because the cationic octahedral T.S. gives the opposite facial selectivity as the cationic trigonal bipyramidal T.S.

Bisphosphoramides

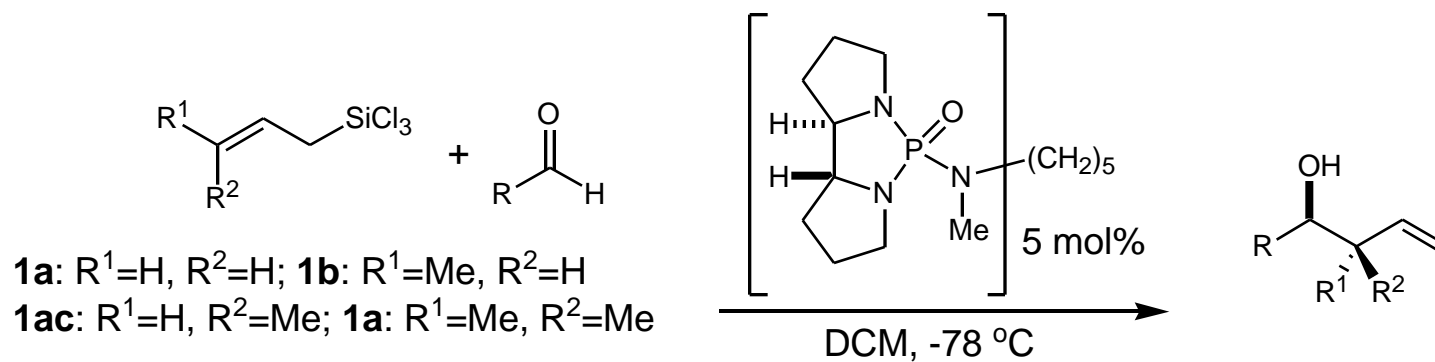


| entry | cat. | ee % | config. | entry | cat. | ee% | config. |
|-------|-----------|------|----------|-------|-----------|-----|----------|
| 1 | 1a | 0 | <i>R</i> | 6 | 2 | 56 | <i>S</i> |
| 2 | 1b | 35 | <i>R</i> | 7 | 3a | 18 | <i>S</i> |
| 3 | 1c | 17 | <i>R</i> | 8 | 3b | 87 | <i>S</i> |
| 4 | 1d | 65 | <i>R</i> | 9 | 3c | 67 | <i>S</i> |
| 5 | 1e | 46 | <i>R</i> | | | | |



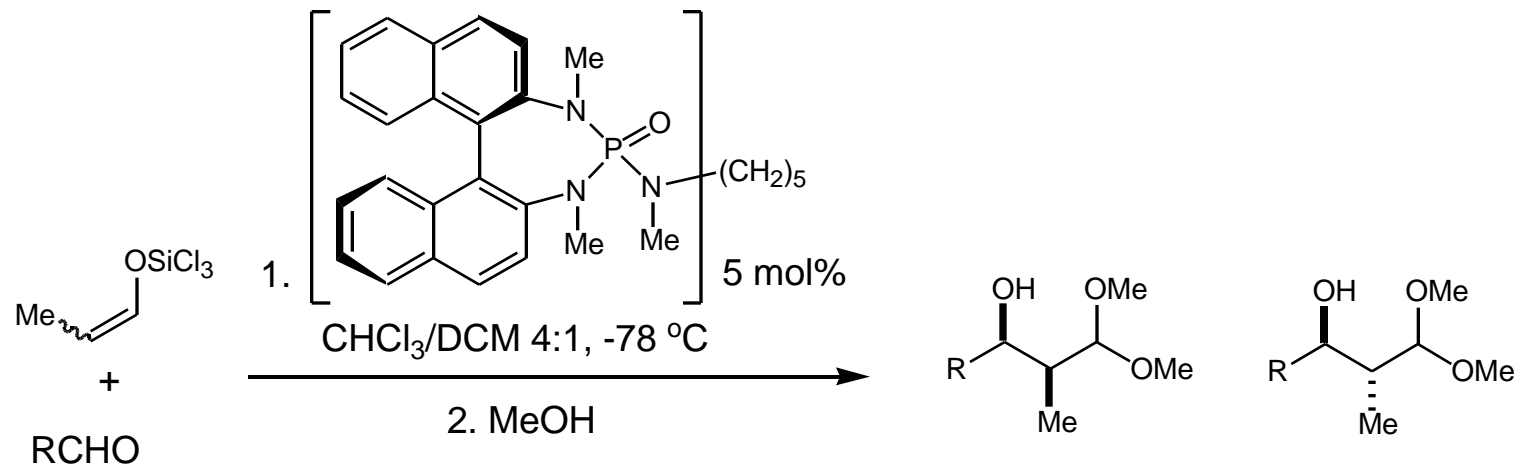
Denmark, S. E. *JACS*, **2000**, 122, 12021
 Denmark, S. E. *JACS*, **2001**, 123, 9488

Allylations Revisited



| entry | silanes | R | syn/anti | ee % | yield % |
|-------|-----------|------------|----------|------|---------|
| 1 | 1a | Ph- | | 87 | 85 |
| 2 | 1a | 2-naphthyl | | 87 | 92 |
| 3 | 1a | cinnamyl- | | 81 | 86 |
| 4 | 1b | Ph- | 1/99 | 86 | 82 |
| 5 | 1b | cinnamyl- | 1/99 | 80 | 57 |
| 6 | 1c | Ph- | 99/1 | 94 | 89 |
| 7 | 1c | cinnamyl- | 99/1 | 88 | 78 |
| 8 | 1d | Ph- | | 96 | 89 |
| 9 | 1d | cinnamyl- | | 88 | 70 |

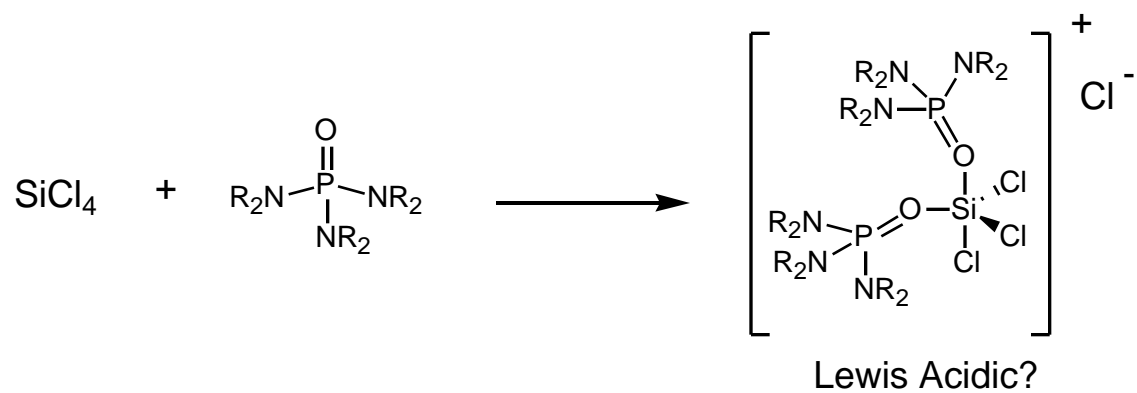
Crossed-Aldol Reactions of Aldehydes



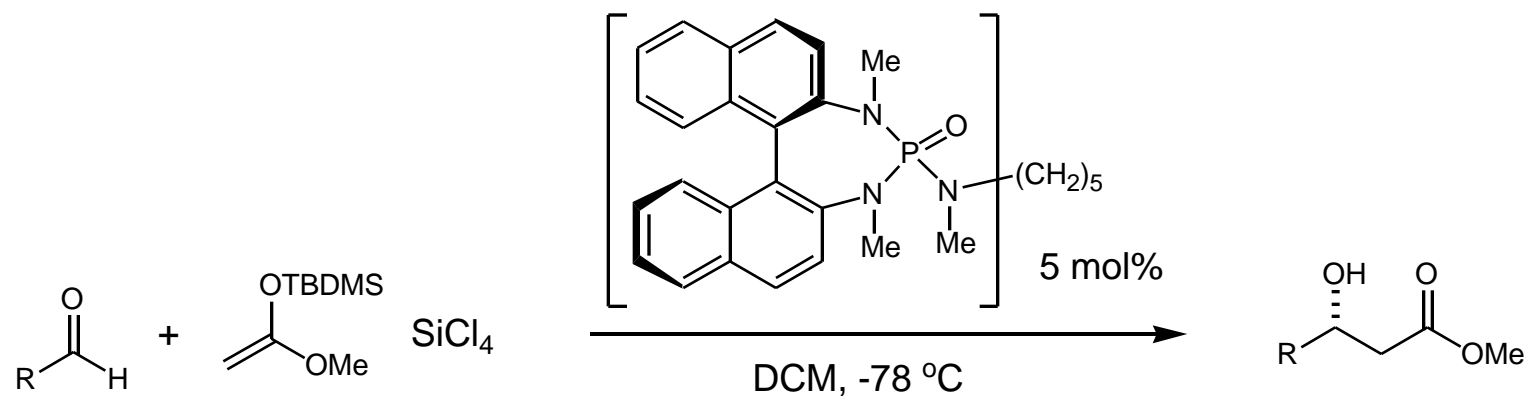
| entry | enolate | R | syn/anti | ee % | yield |
|-------|----------|------------------|----------|------|-------|
| 1 | <i>Z</i> | Ph- | 98/2 | 81 | 95 |
| 2 | <i>E</i> | Ph- | 1/99 | 59 | 97 |
| 3 | <i>Z</i> | cinnamyl- | 99/1 | 42 | 86 |
| 4 | <i>E</i> | cinnamyl- | 1/99 | 26 | 88 |
| 5 | <i>Z</i> | crotyl- | 99/1 | 5 | 85 |
| 6 | <i>E</i> | crotyl- | 2/98 | 52 | 91 |
| 7 | <i>Z</i> | phenylpropargyl- | 98/2 | 7 | 98 |
| 8 | <i>E</i> | phenylpropargyl- | 2/98 | 76 | 99 |
| 9 | <i>Z</i> | dihydrocinnamyl- | 95/5 | 8 | 47 |
| 10 | <i>E</i> | dihydrocinnamyl- | 1/99 | 66 | 79 |

3rd Generation of LB Catalyzed Aldol

- Limitation of current methodology is the ability to prepare the required trichlorosilanes.

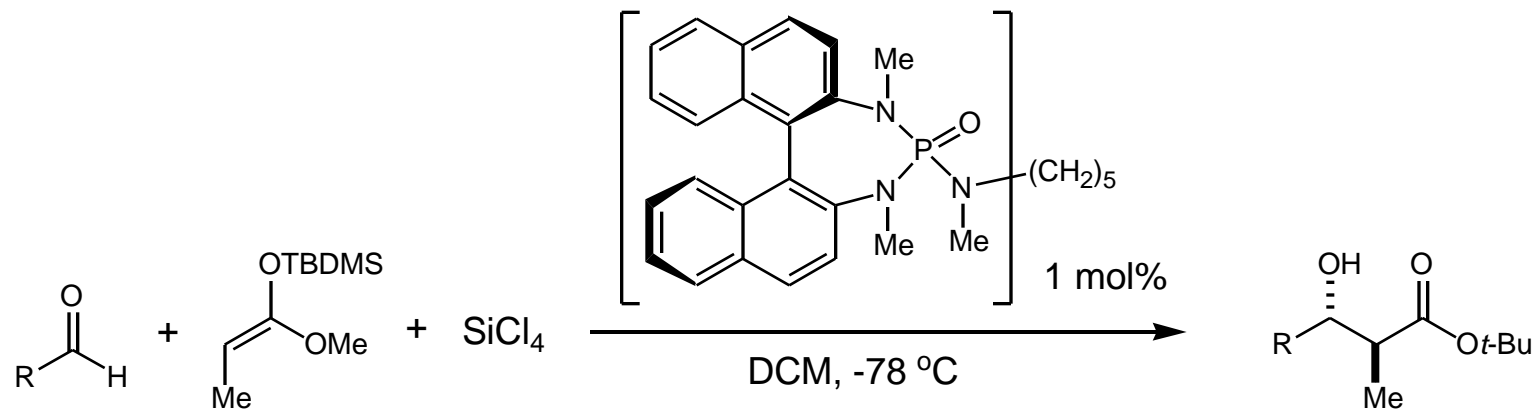


Acetate Aldols



| entry | R | ee | yield | entry | R | ee | yield |
|-------|-------------|----|-------|-------|-----------------------|----|-------|
| 1 | Ph- | 93 | 97 | 6 | 4-CF ₃ Ph- | 91 | 97 |
| 2 | 1-naphthyl- | 80 | 98 | 7 | cinnamyl- | 94 | 95 |
| 3 | 2-naphthyl- | 94 | 98 | 8 | 2-furyl- | 87 | 94 |
| 4 | 4-MePh- | 94 | 97 | 9 | cyclohexyl- | 88 | 86 |
| 5 | 4-MeOPh- | 97 | 97 | 10 | dihydrocinnamyl- | 81 | 72 |

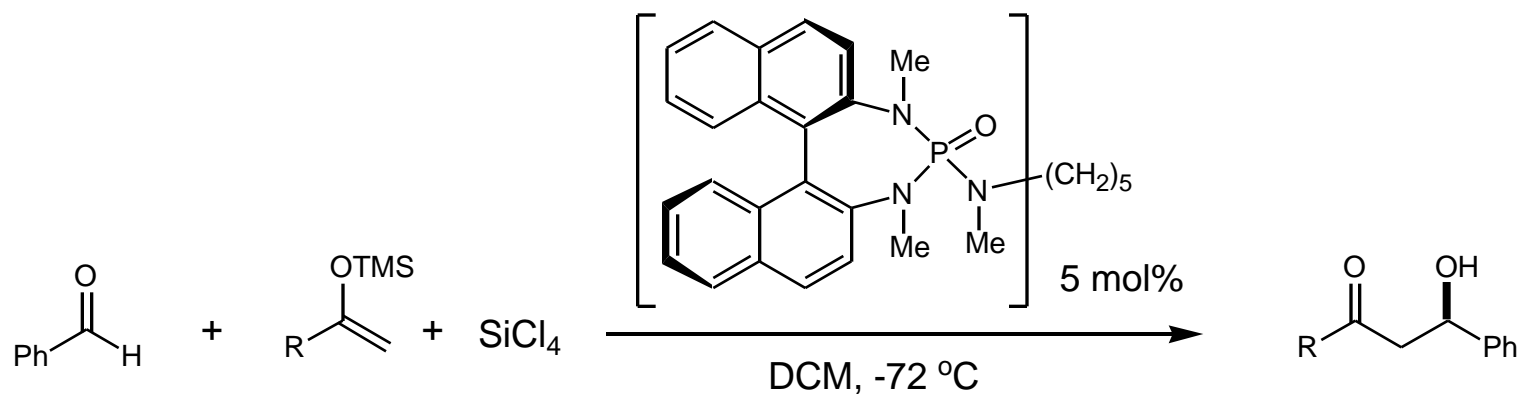
Propanate Aldols



| entry | R | dr | ee | yield |
|-------|--------------------------------|-------|----|-------|
| 1 | Ph- | 99/1 | 98 | 93 |
| 2 | 1-naphthyl- | 96/4 | 94 | 98 |
| 3 | 2-naphthyl- | >99/1 | 98 | 95 |
| 4 | 4-MeOPh- | >99/1 | 98 | 88 |
| 5 | 4-CF ₃ Ph- | >99/1 | 92 | 93 |
| 6 | cinnamyl- | >99/1 | 98 | 98 |
| 7 | phenylpropargyl- | 96/4 | 68 | 92 |
| 8 | dihydrocinnamyl ^a - | 93/7 | 89 | 55 |

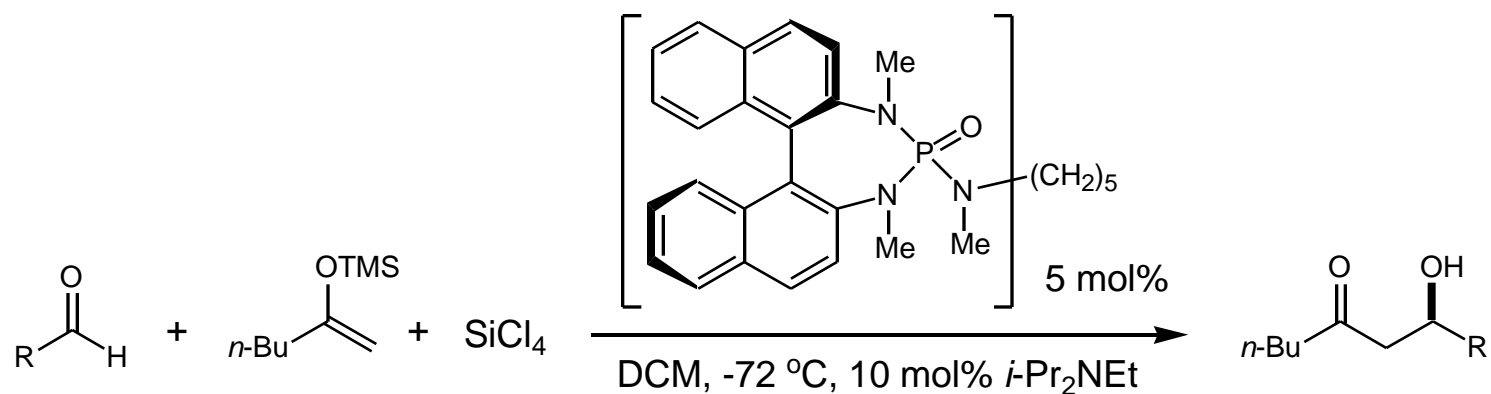
^aReaction run with 0.1 equiv of TBAI

Aldol Additions with Methyl Ketones I



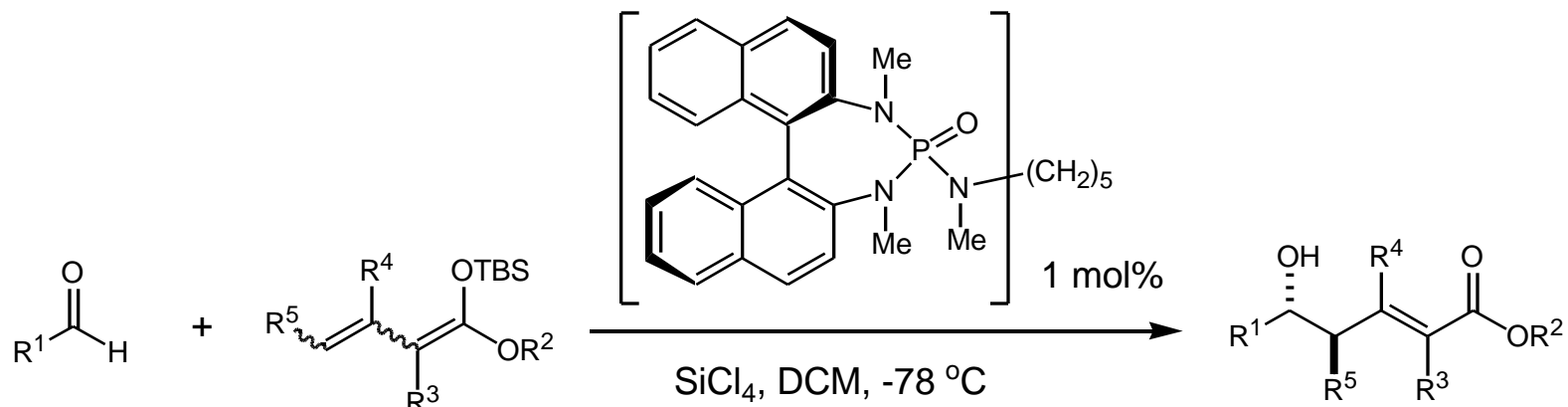
| entry | R | ee % | yield |
|-------|-----------------|------|-------|
| 1 | <i>n</i> -Bu- | 98 | 81 |
| 2 | <i>sec</i> -Bu- | 98 | 70 |
| 3 | <i>t</i> -Bu- | — | — |
| 4 | <i>i</i> -Pr- | 99 | 72 |
| 5 | Ph- | 94 | 76 |

Aldol Additions with Methyl Ketones II



| entry | R | ee % | yield |
|-------|-----------------------|------|-------|
| 1 | Ph- | 99 | 99 |
| 2 | cinnamyl- | 99 | 98 |
| 3 | 1-naphthyl- | 92 | 95 |
| 4 | 2-naphthyl- | 99 | 92 |
| 5 | 4-MeOPh- | 99 | 98 |
| 6 | 4-CF ₃ Ph- | 99 | 96 |
| 7 | 2-furyl- | 90 | 88 |
| 8 | 2-thiophenyl- | 89 | 79 |
| 9 | dihydrocinnamyl- | — | — |

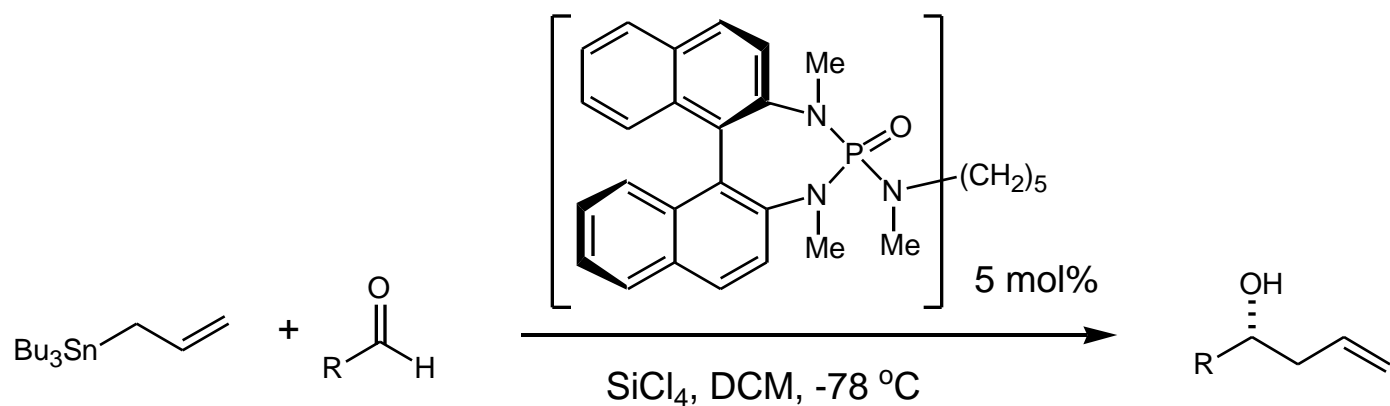
Vinylogous Aldol



| entry | R ¹ | R ² | R ³ | R ⁴ | R ⁵ | ee % | yield |
|-------|------------------|----------------|----------------|----------------|-------------------|------|-------|
| 1 | Ph- | Et- | H- | H- | H- | 98 | 89 |
| 2 | cinnamyl- | Et- | H- | H- | H- | 96 | 84 |
| 3 | dihydrocinnamyl- | Et- | H- | H- | H- | 90 | 68 |
| 4 | Ph- | Me- | Me- | H- | H- | 99 | 93 |
| 5 | cinnamyl- | Me- | Me- | H- | H- | 99 | 88 |
| 6 | Ph | Et- | H- | Me- | H- | 92 | 91 |
| 7 | cinnamyl- | Et- | H- | Me- | H- | 88 | 97 |
| 8 | dihydrocinnamyl- | Et- | H- | Me- | H- | 95 | 73 |
| 9 | Ph- | <i>t</i> -Bu- | H- | H- | Me ^a - | 89 | 92 |
| 10 | cinnamyl- | <i>t</i> -Bu- | H- | H- | Me ^a - | 82 | 71 |

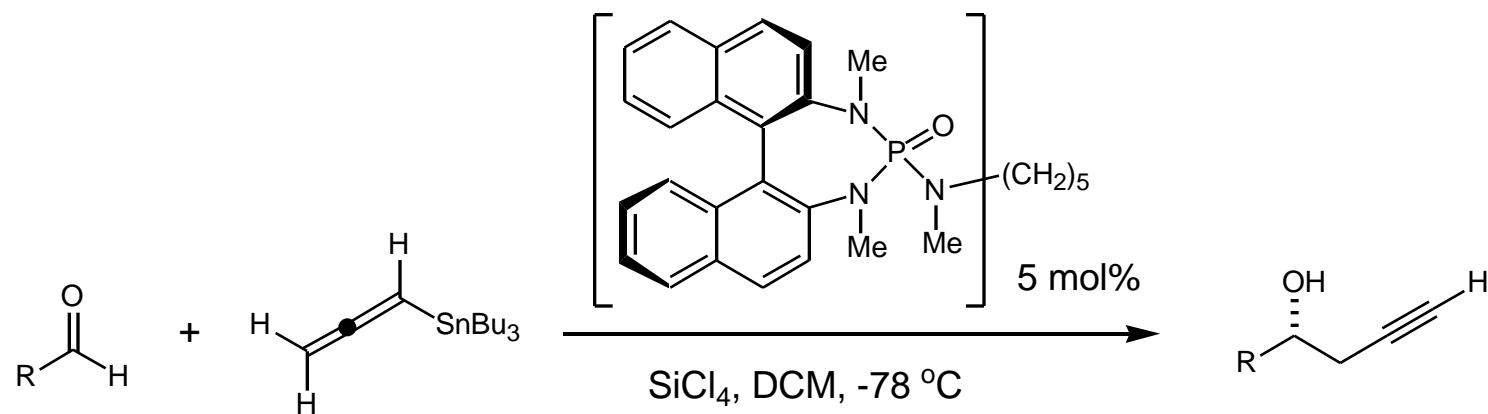
^aDiastereoselectivity >99/1

Allylation Revisited, Again



| entry | R | ee % | yield % |
|-------|-----------------------|------|---------|
| 1 | Ph- | 94 | 91 |
| 2 | 4-NO ₂ Ph- | 83 | 90 |
| 3 | cinnamyl- | 65 | 91 |
| 4 | phenylpropargyl- | 22 | 92 |
| 5 | 1-naphthyl- | 94 | 94 |
| 6 | 2-naphthyl- | 93 | 92 |
| 7 | 2-furyl- | 62 | 65 |

Propargylation



| | |
|----------------|---------------------------|
| R = Ph | 81% (97% ee (<i>R</i>)) |
| R = cinnamyl | 90% (87% ee (<i>R</i>)) |
| R = 2-naphthyl | 95% (93% ee (<i>R</i>)) |