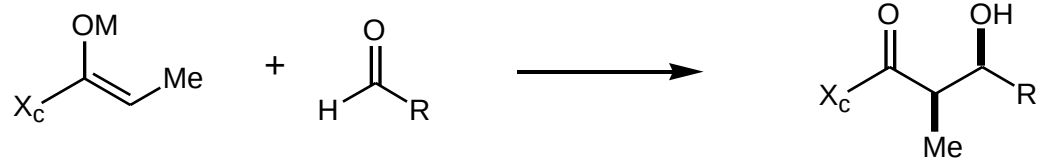
Denmark's Base Catalyzed Aldol/Allylation

Evans' Group Seminar
November 21th, 2003
Jimmy Wu

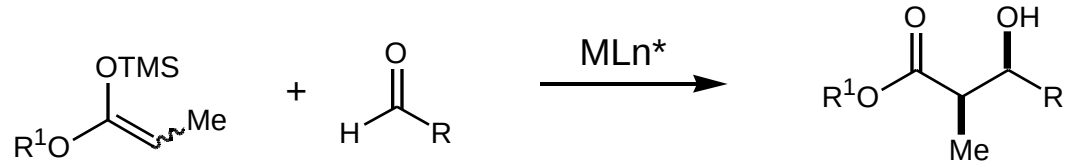
Lead References:

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

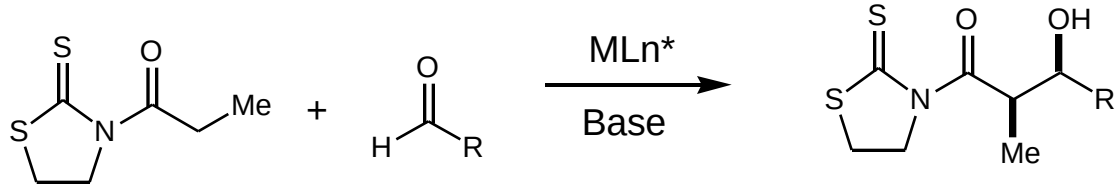
Background



• Requires stoichiometric amounts of covalently bound auxiliaries

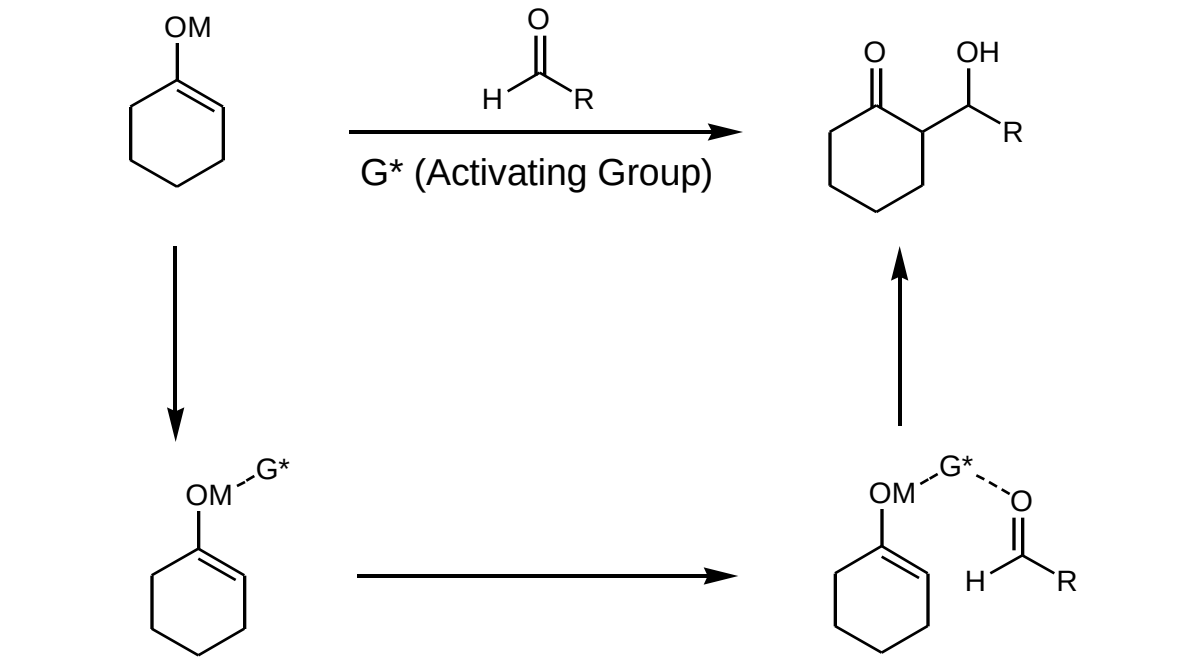


• Ligand is often deactivating
• Diastereoselectivity can be high but are often variable



• Number of literature examples is still limited.

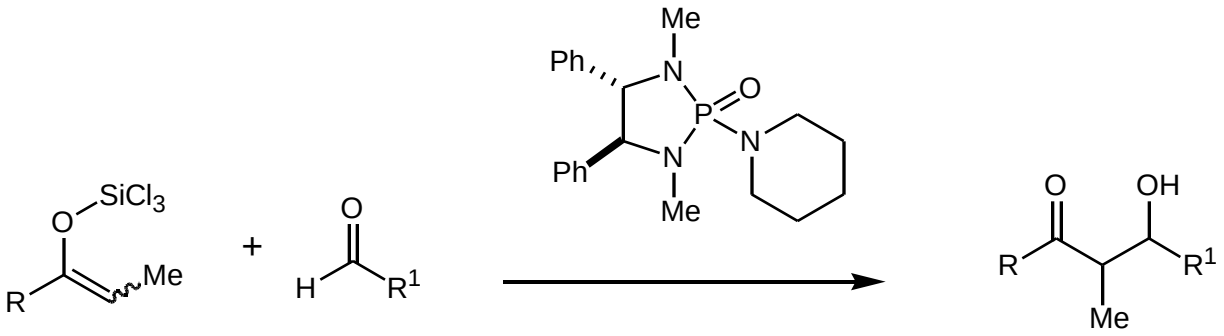
Lewis Base Activated Aldol



Must be more reactive
than non-bound substrate

Must react via a closed
T.S. to obtain good
selectivities

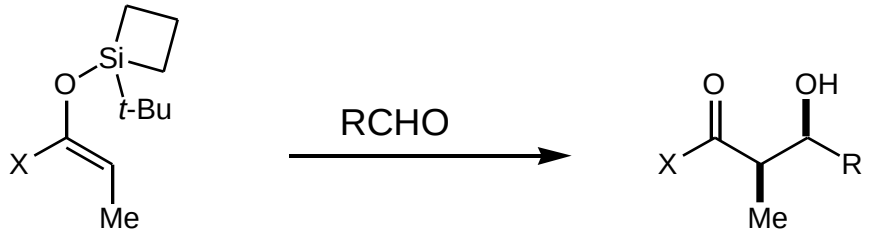
General Reaction Overview



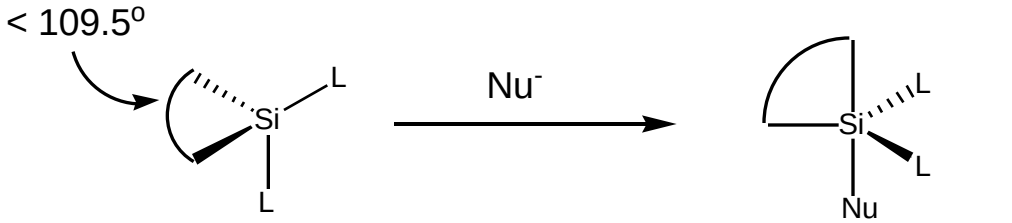
- *E* enolsilane ---> anti product
- Highly diastereoselective (up to 99:1 anti/syn)
- Highly enantioselective (up to 98% ee)

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

How It All Started



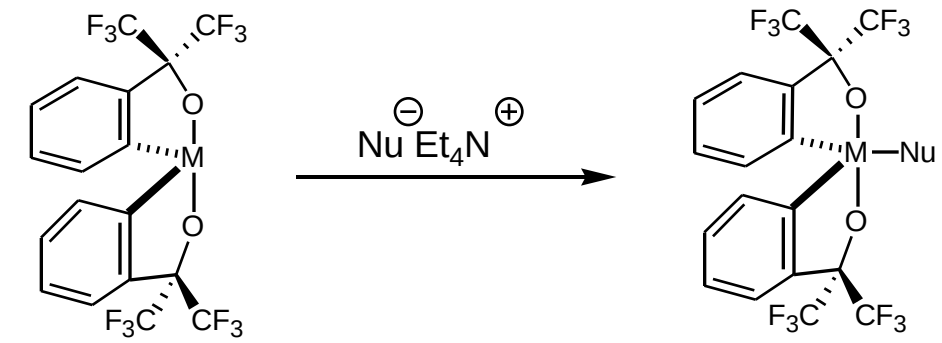
- Wanted to exploit the concept of “strain-release Lewis acidity”



tetrahedral

trigonal bipyramid

Literature Examples

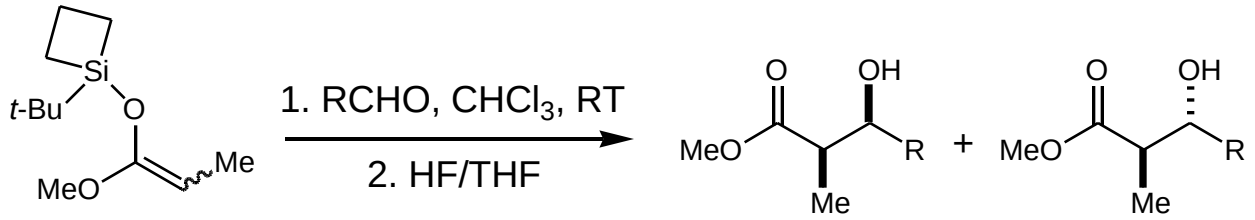


M = Si and Ge
Ligand C-O(Ge) –2.6°

• 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



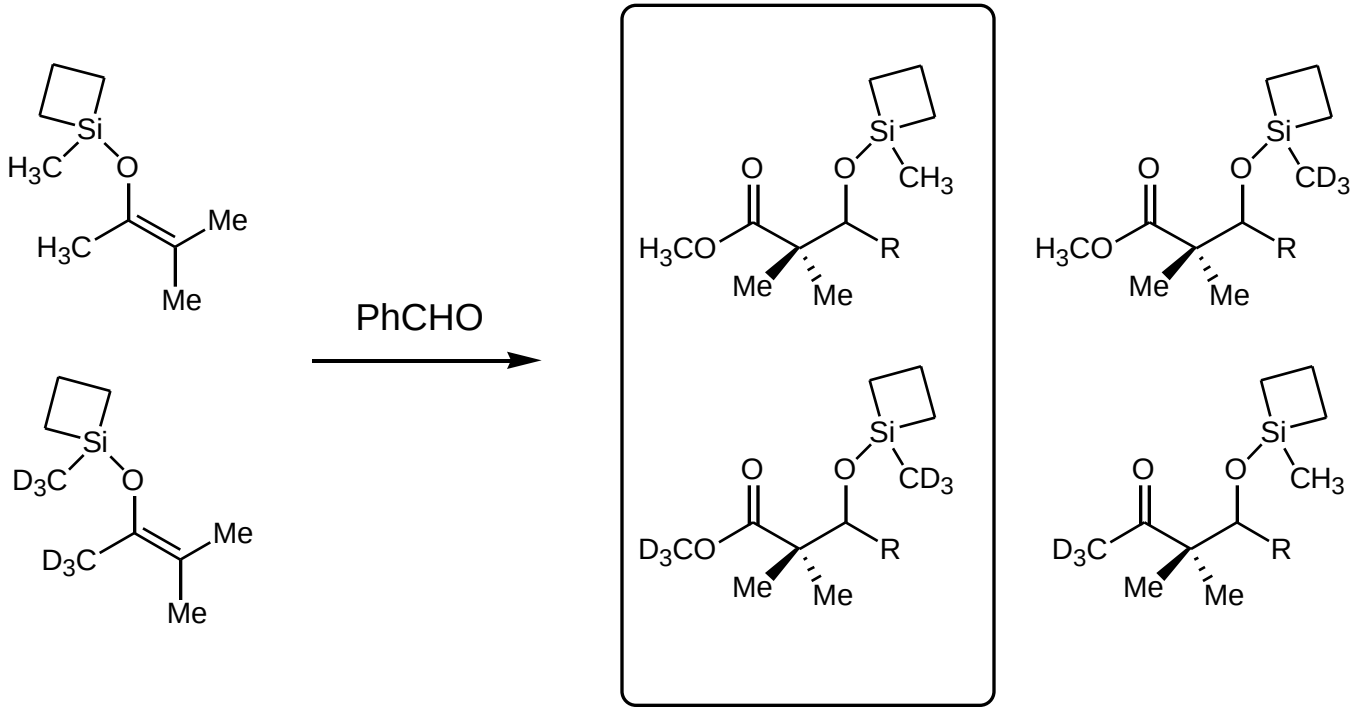
entry	R	*E*/*Z*	yield	syn/anti
1	Ph	0/100	80	42/58
2	Ph	95/5	94	95/5
3	cinnamyl	89/11	95	93/7
4	*n*-pentyl	89/11	91	93/7
5	cyclohexyl	89/11	85	>99/1

- Also worked for thiosilylketene acetals but both *E and Z* gave syn selectivity.

- Amide derived enolsilanes were unselective.

Denmark, S. E. *JACS*, **1994**, *116*, 7026

Mechanistic Studies

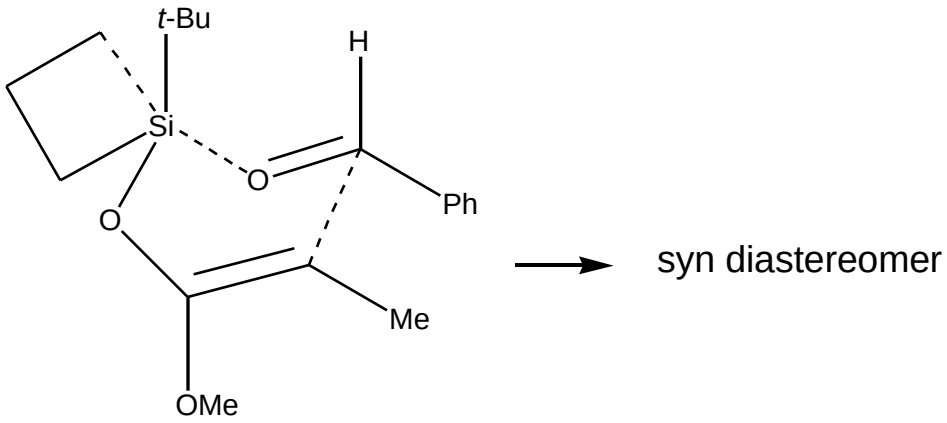


• Must go through a trigonal bipyramidal T.S. with internal transfer of silicon

• Analagous studies with KO*t*-Bu as a catalyst revealed complete deuterium scrambling. Cannot go through an octahedreal T.S.

Denmark, S. E. *JACS*, **1994**, *116*, 7026

T.S. Models

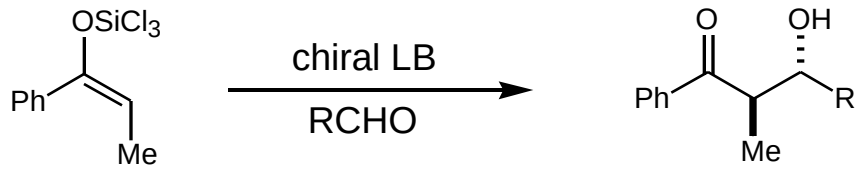


- Closed boat-like T.S.

- Pentacoordinate silicon

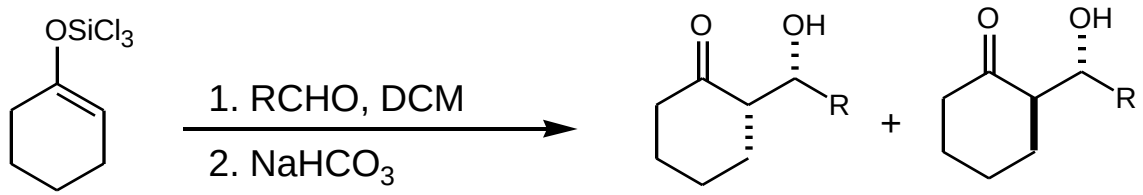
•Evans proposes similar T.S. in Zr based aldol (Evans, D. A. *TL*, **1980**, *21*, 3975.

2nd Generation of LB Catalyzed Aldol



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

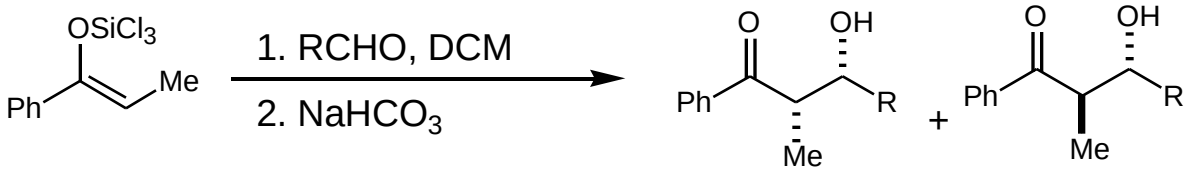
Uncatalyzed Reactions: E Enolsilanes



entry	R	time, hr	syn/anti	yield
1	Ph-	6	49/1	92
2	1-Napthyl-	8	16/1	90
3	cinnamyl-	1	49/1	83
4	α-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

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

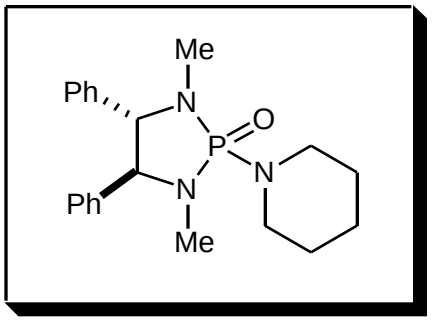
Uncatalyzed Reaction: Z Enolsilanes

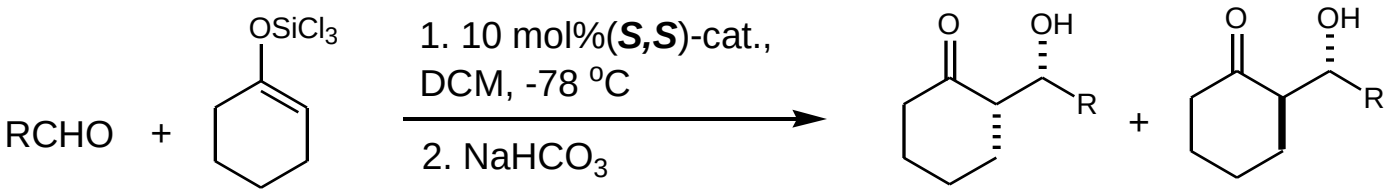


entry	R	time, hr	syn/anti	yield
1	Ph-	10	1/2.3	97
2	4-BrPh-	10	1/2.9	93
3	1-Naphtyl-	16	1/1.3	95
4	cinnamyl-	10	1/1.9	95
5	α-methylcinnamyl-	12	1/2.2	64
6	crotyl-	16	1/1.9	89
7	Phenylpropargyl-	11	1/2.2	89

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

Catalyzed Aldol: E Enolsilanes

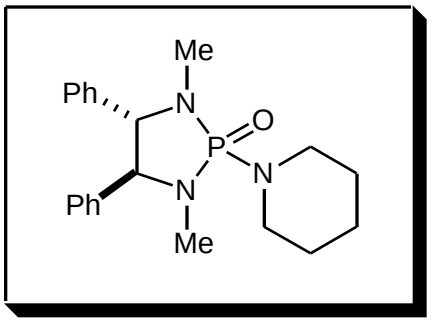


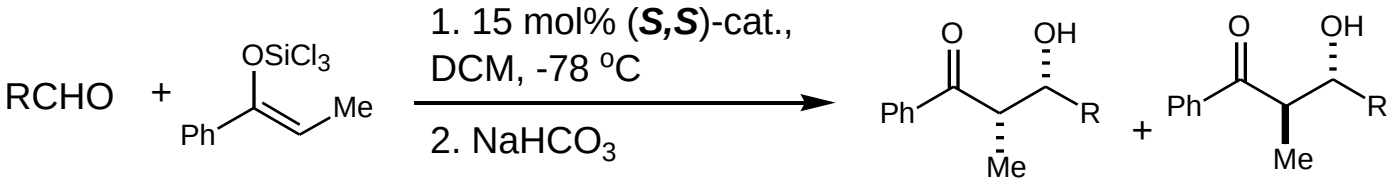


entry	R	syn/anti	anti ee%	yield, %
1	Ph-	1/61	93	95
2	1-Napthyl-	<1/99	97	94
3	cinnamyl-	<1/99	88	94
4	α-methylcinnamyl-	<1/99	92	98
5	Phenylpropargyl-	1/5.3	82	90

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

Catalyzed Aldol: Z Enolsilanes

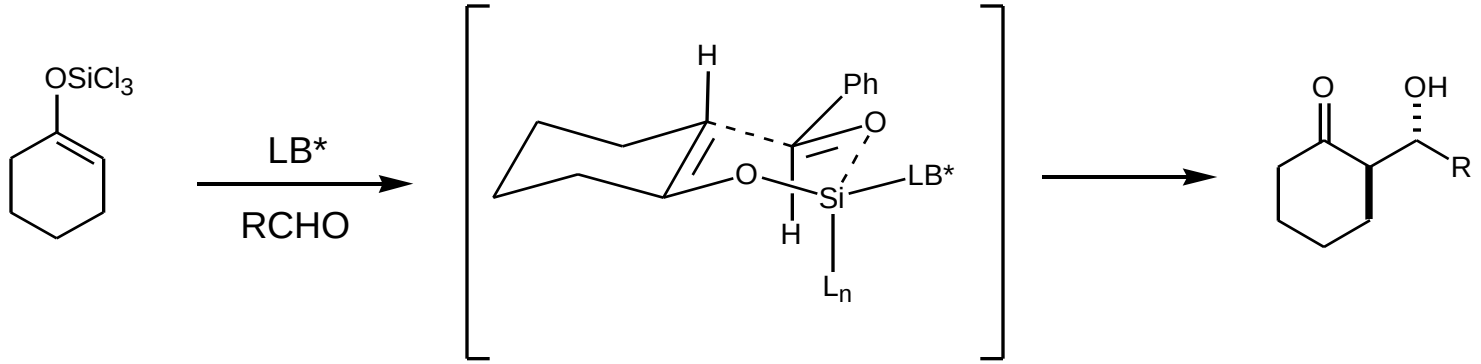




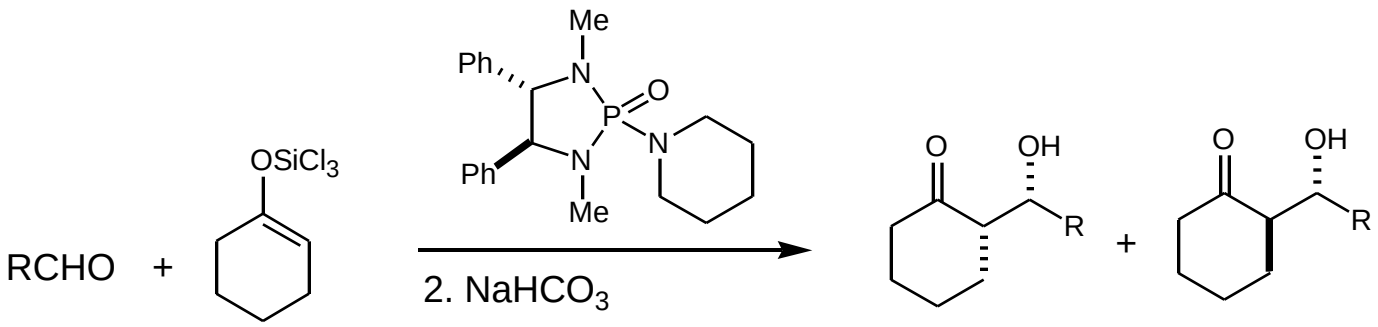
entry	R	syn/anti	syn ee%	yield, %
1	Ph-	18/1	95	95
2	4-BrPh-	12/1	96	89
3	1-Napthyl-	3/1	84	96
4	cinnamyl-	9.4/1	92	97
5	crotyl-	7/1	91	94
6	Phenylpropargyl-	1/3.5	58	92

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

Current T.S. Model - Too Simplistic



Mechanistic Clues



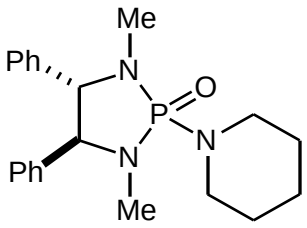
entry	loading	conc.	syn/anti	yield
1	10%	0.5	1/14	94
2	5%	0.5	1/10	90
3	2%	0.5	1/2.4	84

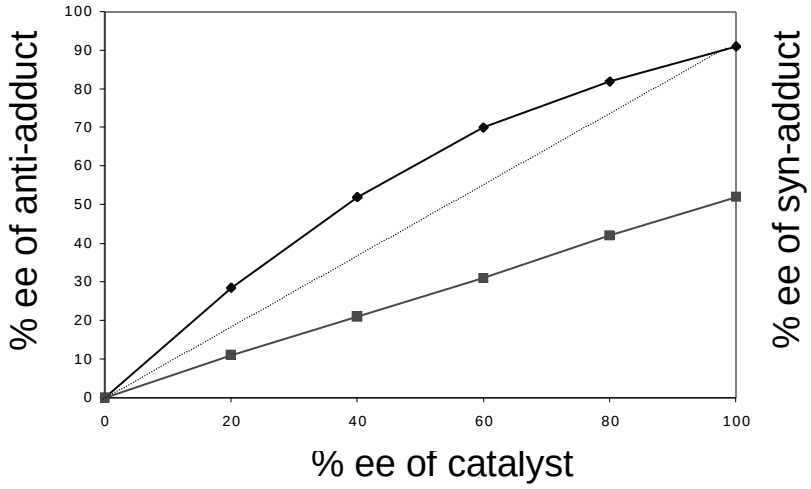
- Syn/anti ratio is highly dependent on catalyst loading
- Simple change in silicon valency cannot account for rate acceleration
- Bulkier catalysts lowers and even switches diastereoselectivities

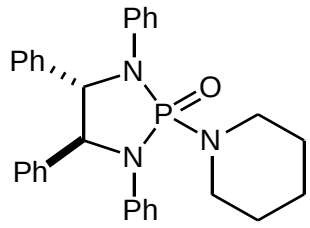
Denmark, S. E. *JACS*, **1998**, *120*, 12990
Denmark, S. E. *JACS*, **1999**, *121*, 4982

Mechanistic Proposal

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

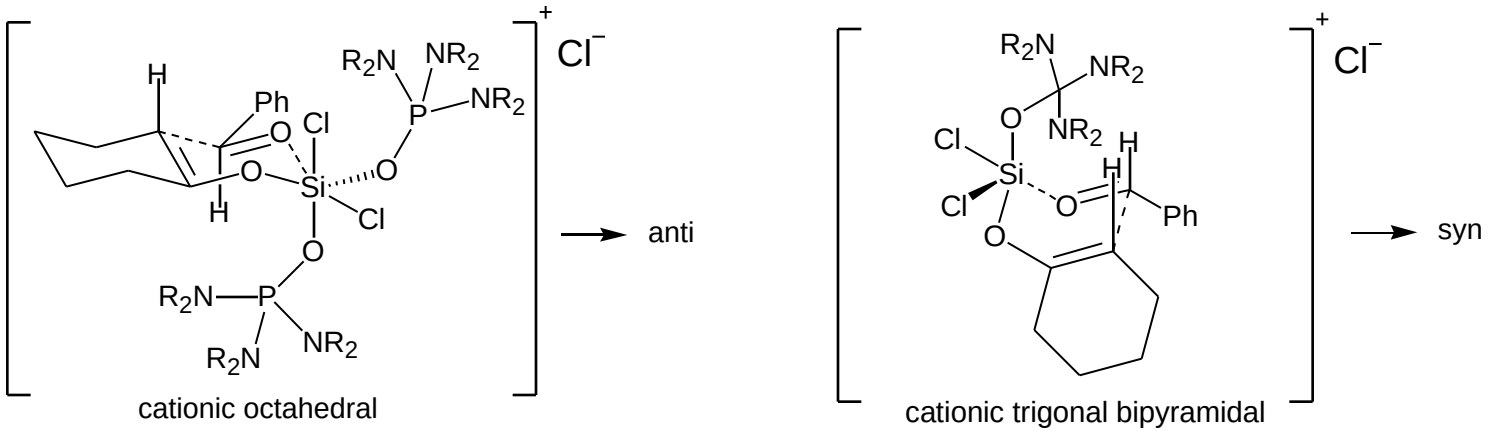






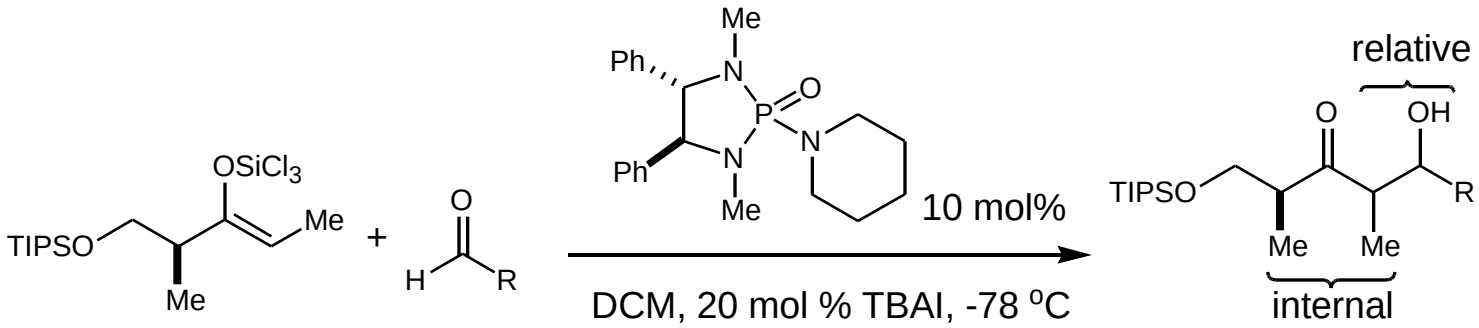
Denmark, S. E. *JACS*, **1998**, *120*, 12990

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

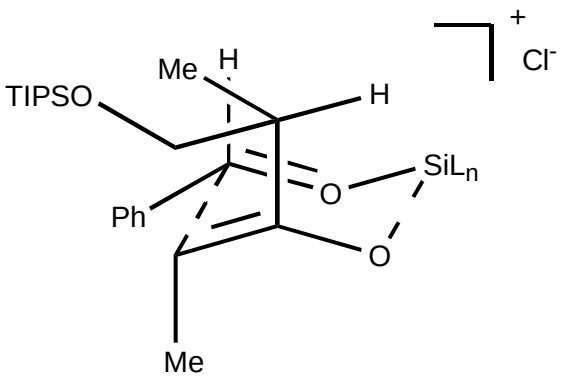
Double Stereodifferentiating Reactions I



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

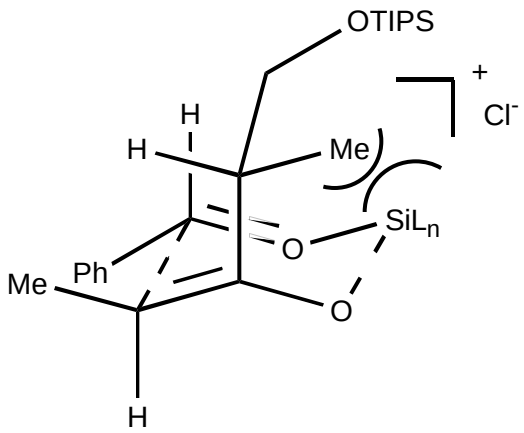
Denmark, S. E. *OL*, **2002**, *4*, 3473

T.S. Models

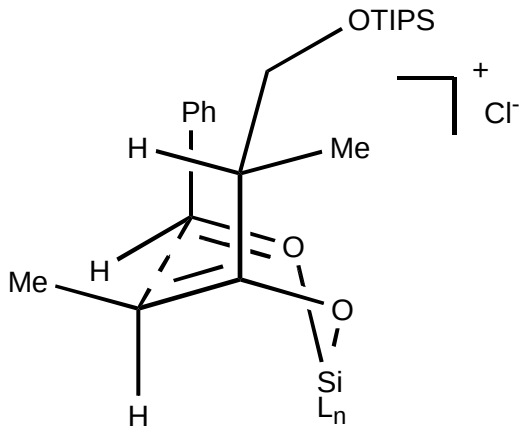


• Minimizes steric interactions between substituents on enolate and bulky ligands on silicon

• Anti diastereomer may be formed via a boat-like T.S.

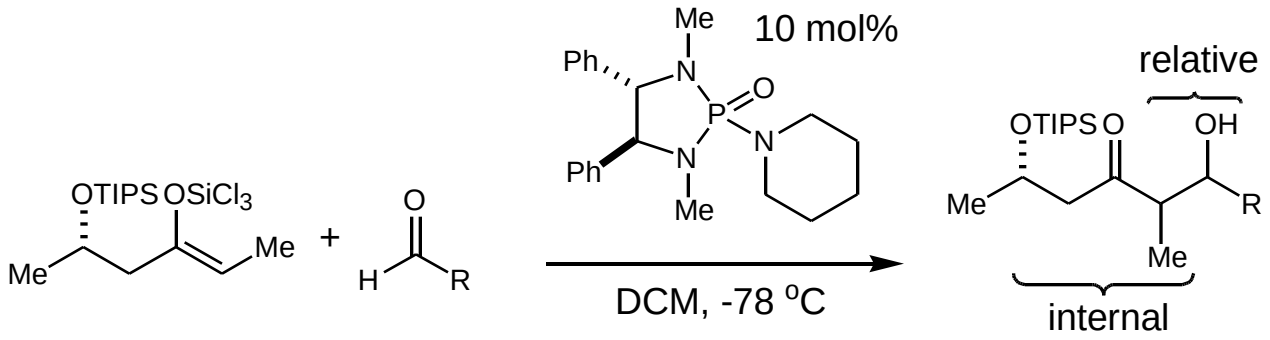


• $A_{1,3}$ strain is minimized but severe non-bonding interactions exist between subtrate and ligands on silicon.



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

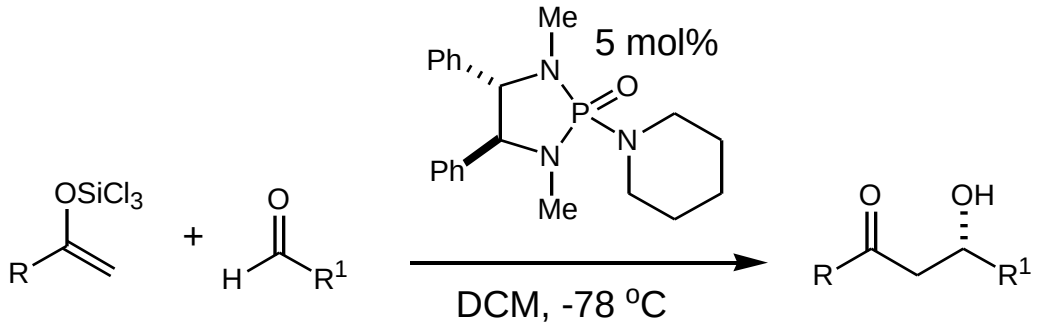
Double Stereodifferentiating Reactions II



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

Denmark, S. E. *OL*, **2002**, *4*, 3477

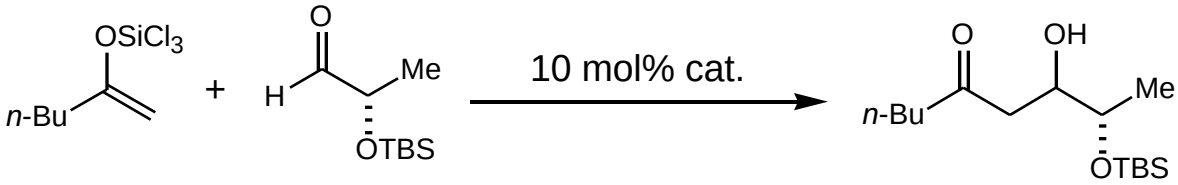
Methyl Ketones as Nucleophiles



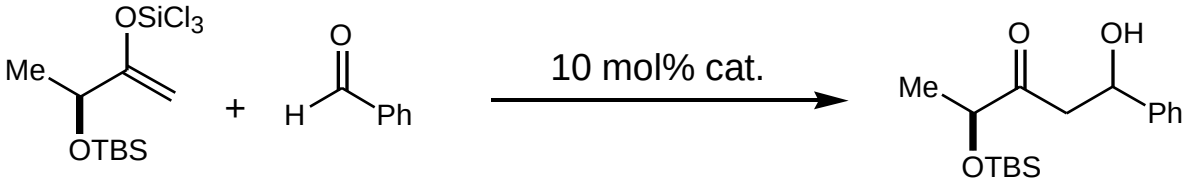
entry	R	R^1	ee %	yield %
1	Me-	Ph-	87	98
2	*n*-Bu-	Ph-	85	98
3	*i*-Pr-	Ph-	81	97
4	Ph-	Ph-	49	93
5	$TBSOCH_2$-	Ph-	86	94
6	*n*-Bu-	cinnamyl-	84	94
7	*n*-Bu-	α-methylcinnamyl-	91	95
8	*n*-Bu-	1-napthyl-	86	92
9	*n*-Bu-	cyclohexyl-	89	79
10	*n*-Bu-	*t*-Bu-	92	81

Denmark, S. E. *JACS*, **2000**, *122*, 8837

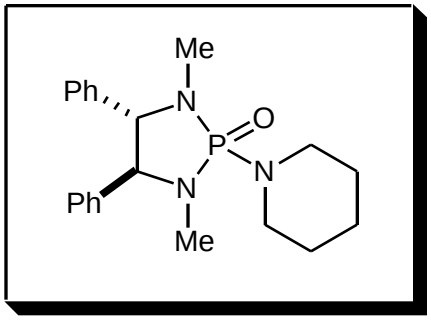
Double Stereodifferentiating Reactions



(*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

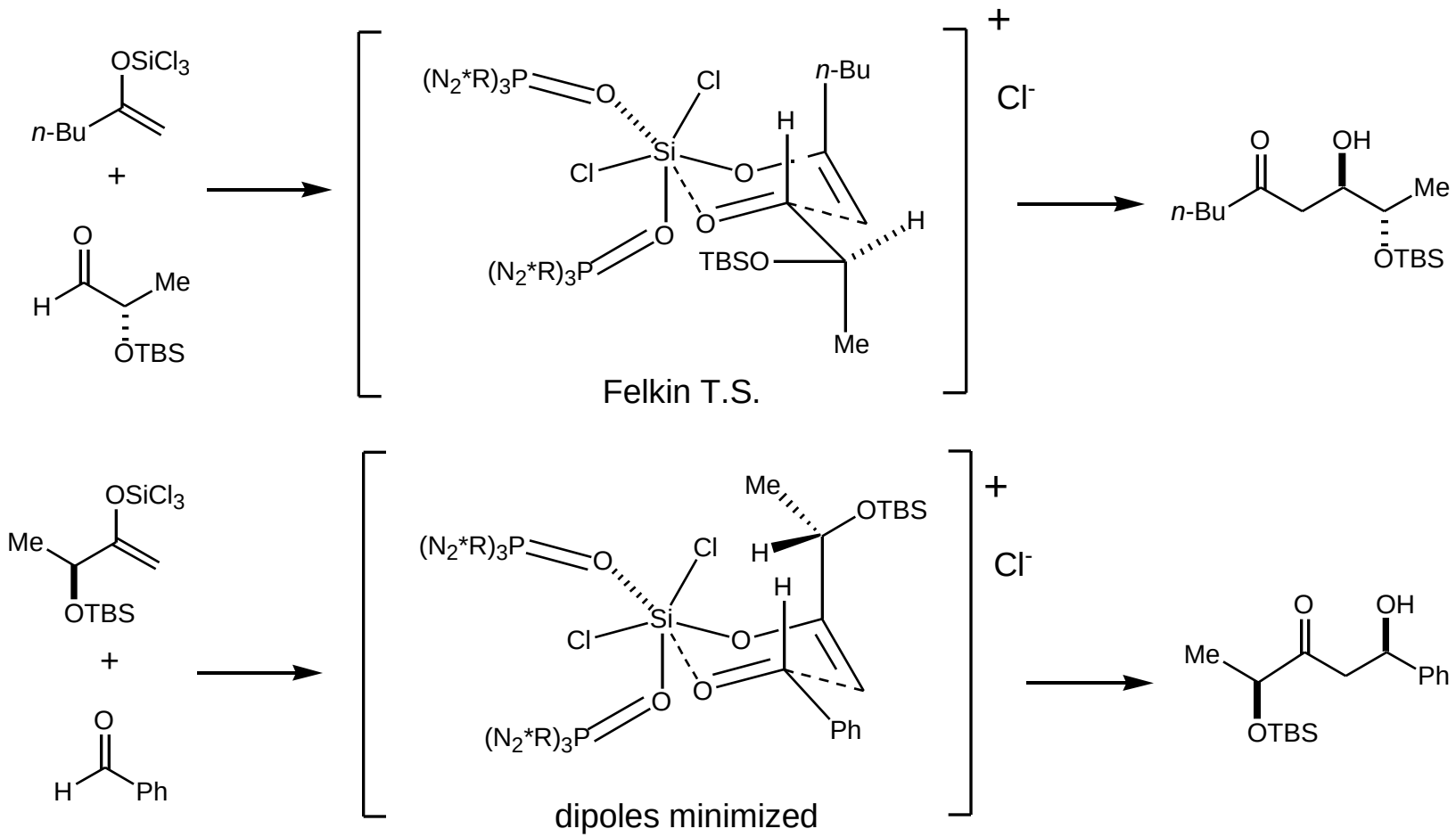


(*R,R*) - 73/1 syn/anti, 85% yield
(*S,S*) - 1.5/1 syn/anti, 85% yield
achiral - 1.2/1 syn/anti, 81% yield



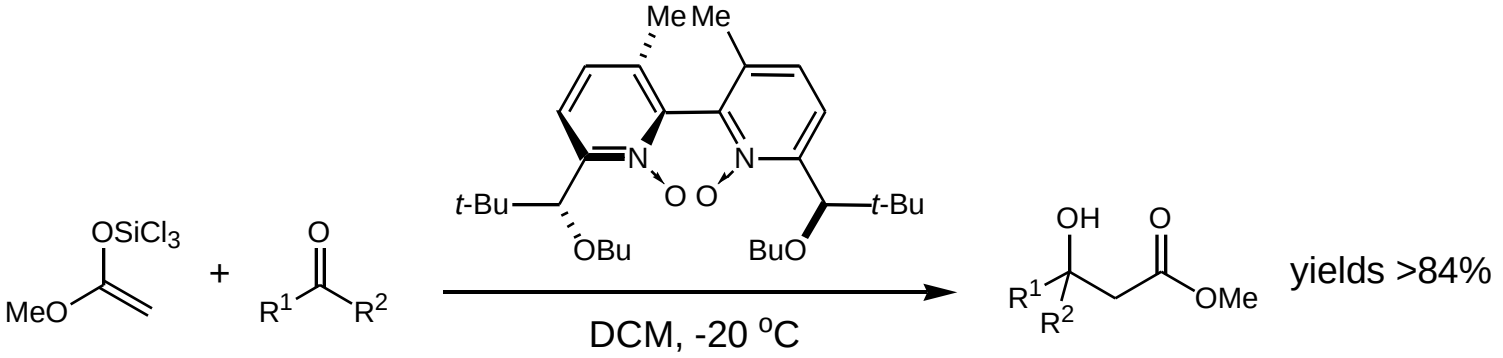
Denmark, S. E. *JACS*, **2000**, *122*, 8837

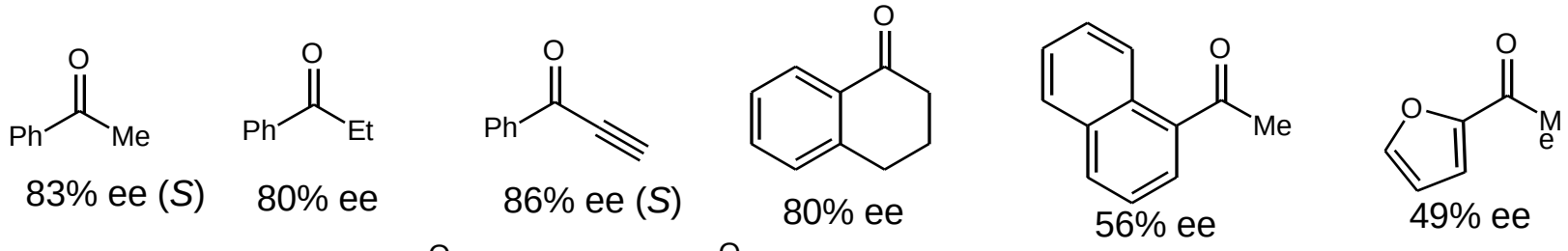
T.S. Models



Denmark, S. E. *JACS*, **2000**, *122*, 8837

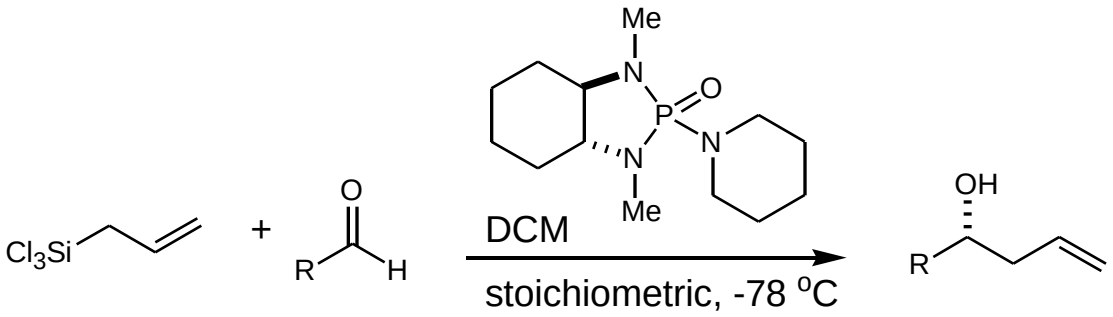
Silyl Ketene Acetals





Denmark, S. E. *JACS*, **2002**, *124*, 4233

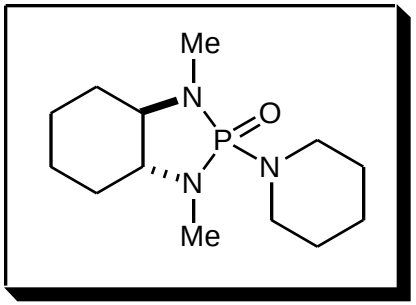
Asymmetric Allylation

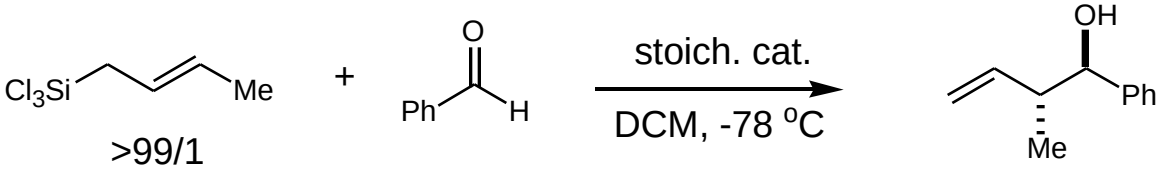


entry	R	ee, %	yield
1	Ph-	60	81
2	*o*-tol-	65	81
3	4-NO_2Ph-	21	76
4	4-MeOPh-	50	80
5	4-NMe_2Ph-	33	69
6	cinnamyl-	38	67

Denmark, S. E. *JOC*, **1994**, *59*, 6161

Diastereoselective Allylations





>99/1

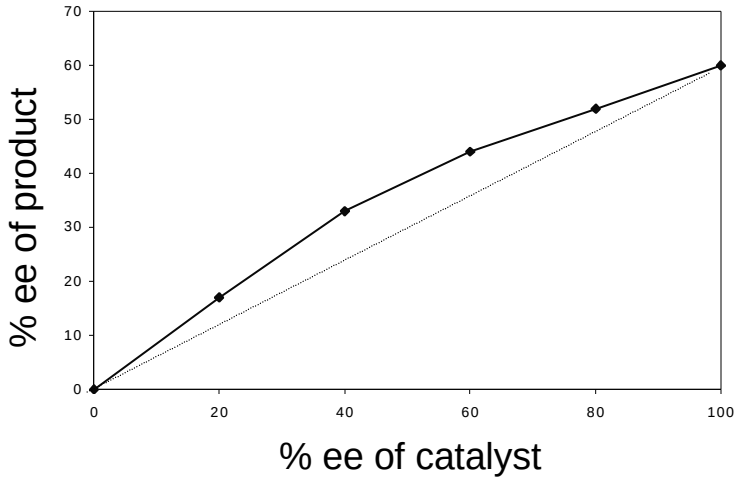
56% ee, 2/98 syn/anti

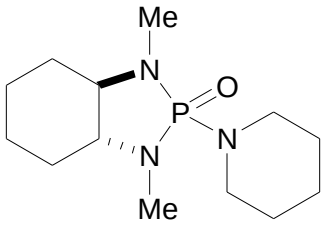
>99/1

60% ee, 98/2 syn/anti

Denmark, S. E. *JOC*, **1994**, *59*, 6161

Mechanistic Studies

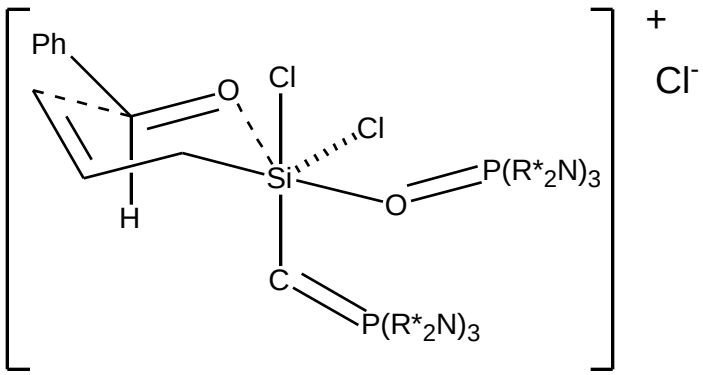




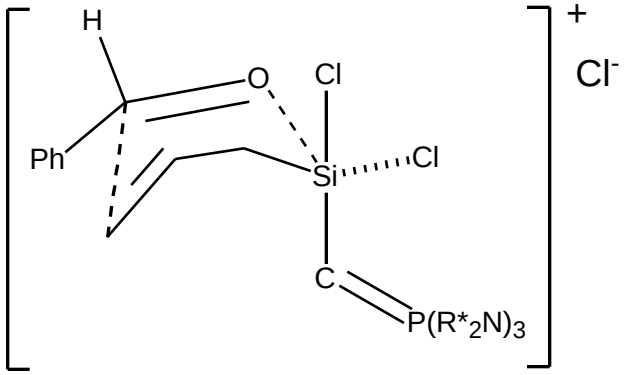
- 1st order in aldehyde
- 1st order in allylsilane
- 1.77th order in catalyst due to competing pathways involving 1 or 2 phosporamides bound to silicon.

Denmark, S. E. *JACS*, **2000**, *122*, 12021

T.S. Models



cationic octahedral

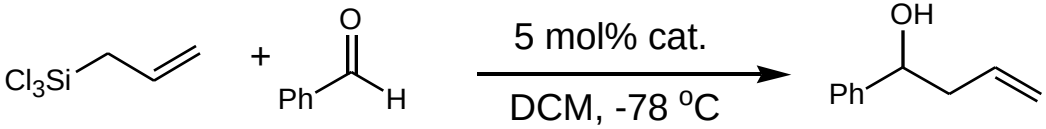


cationic trigonal bipyramidal

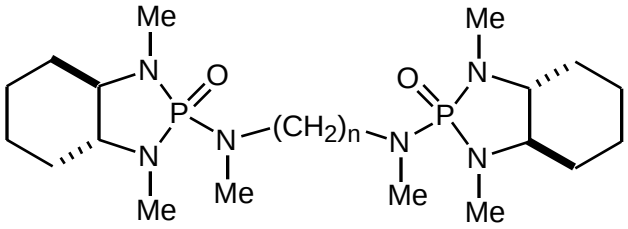
• Facial selectivity is lower because the cationic octahedral T.S. gives the opposite facial selectivity as the cationic trigonal bipyramidal T.S.

Denmark, S. E. *JACS*, **2000**, *122*, 12021

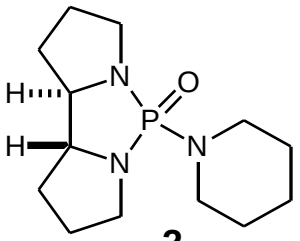
Bisphosphoramides



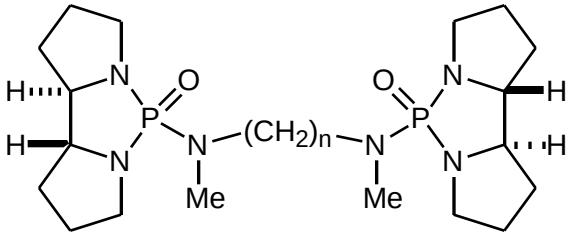
entry	cat.	ee %	config.	entry	cat.	ee%	config.
1	**1a**	0	*R*	6	**2**	56	*S*
2	**1b**	35	*R*	7	**3a**	18	*S*
3	**1c**	17	*R*	8	**3b**	87	*S*
4	**1d**	65	*R*	9	**3c**	67	*S*
5	**1e**	46	*R*				



1a: n=2
1b: n=3
1c: n=4
1d: n=5
1e: n=6



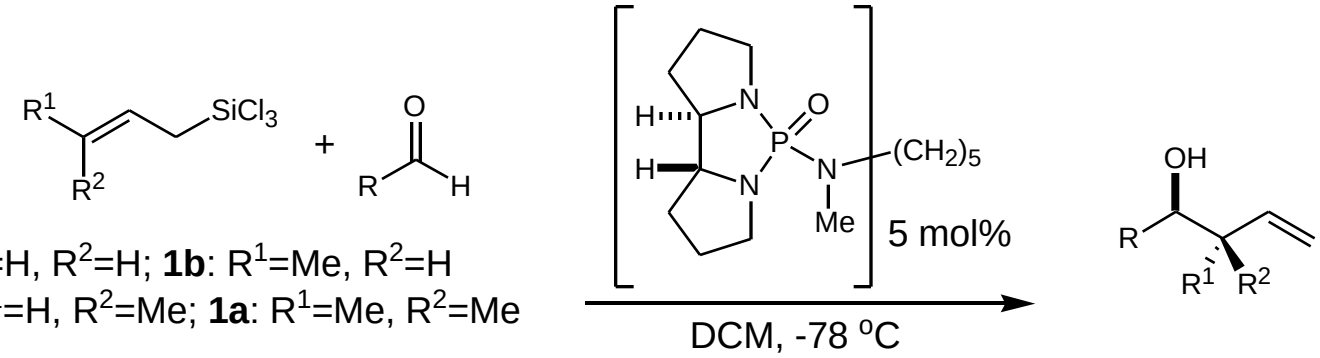
2



3a: n=4
3b: n=5
3c: n=6

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

Allylations Revisited

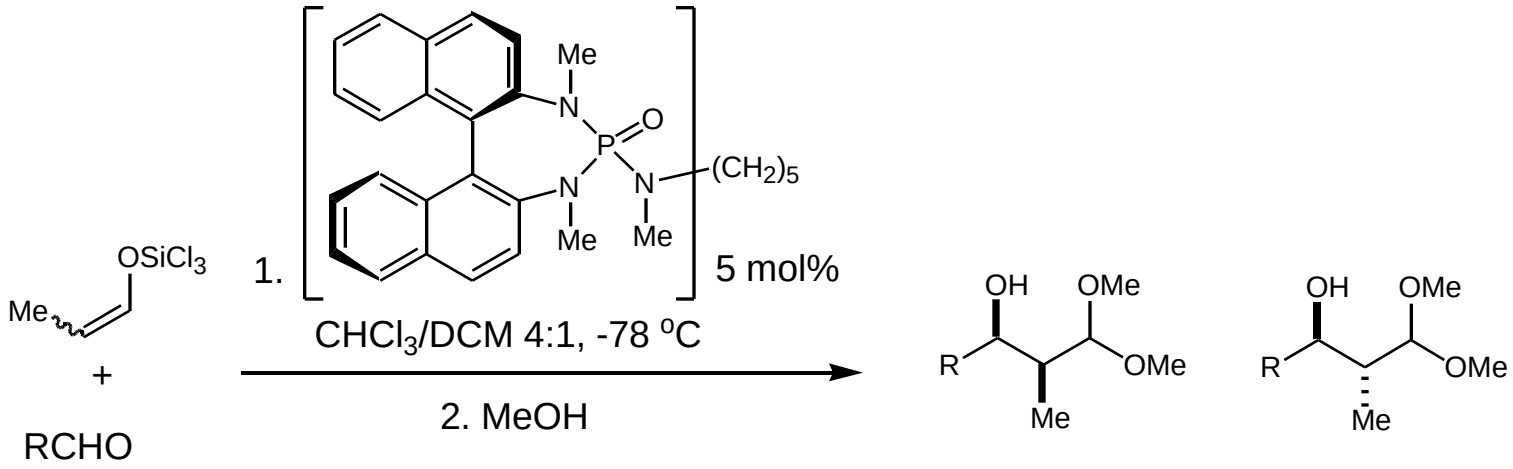


1a: R^1=H, R^2=H; **1b**: R^1=Me, R^2=H
1ac: R^1=H, R^2=Me; **1a**: R^1=Me, R^2=Me

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

Denmark, S. E. *JACS*, **2001**, *123*, 9488

Crossed-Aldol Reactions of Aldehydes

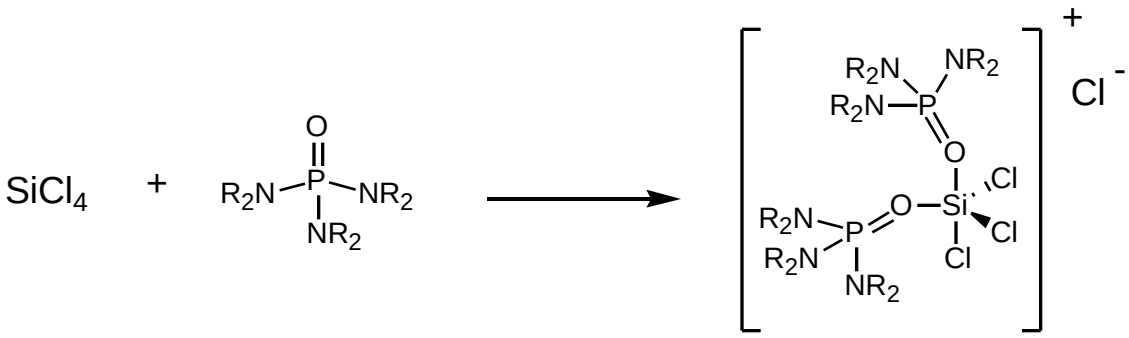


entry	enolate	R	syn/anti	ee %	yield
1	*Z*	Ph-	98/2	81	95
2	*E*	Ph-	1/99	59	97
3	*Z*	cinnamyl-	99/1	42	86
4	*E*	cinnamyl-	1/99	26	88
5	*Z*	crotyl-	99/1	5	85
6	*E*	crotyl-	2/98	52	91
7	*Z*	phenylpropargyl-	98/2	7	98
8	*E*	phenylpropargyl-	2/98	76	99
9	*Z*	dihydrocinnamyl-	95/5	8	47
10	*E*	dihydrocinnamyl-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

Denmark, S. E. *ACIEE*, **2001**, *40*, 4759

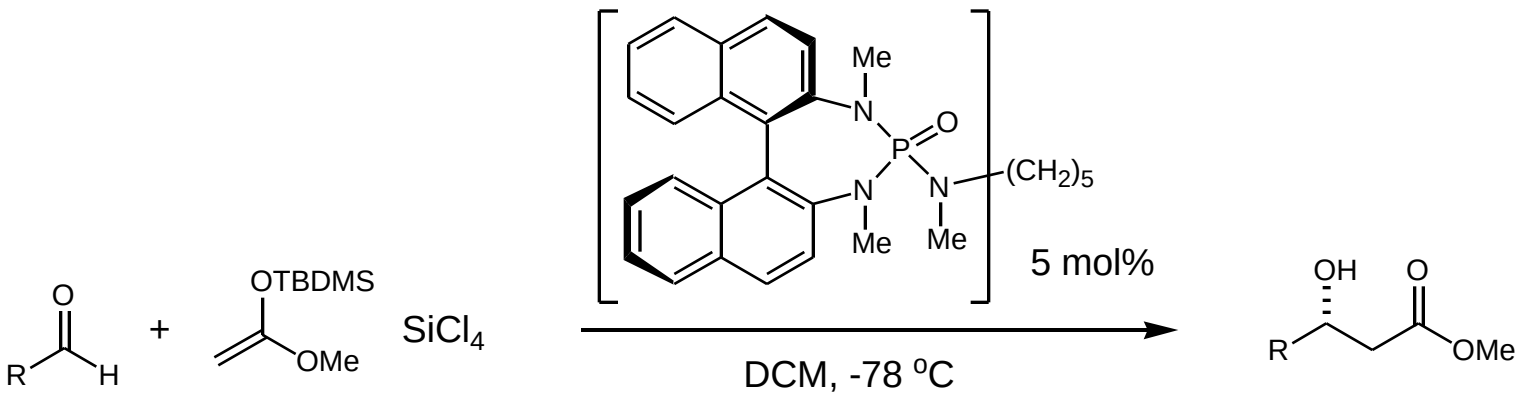
3rd Generation of LB Catalyzed Aldol

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



Lewis Acidic?

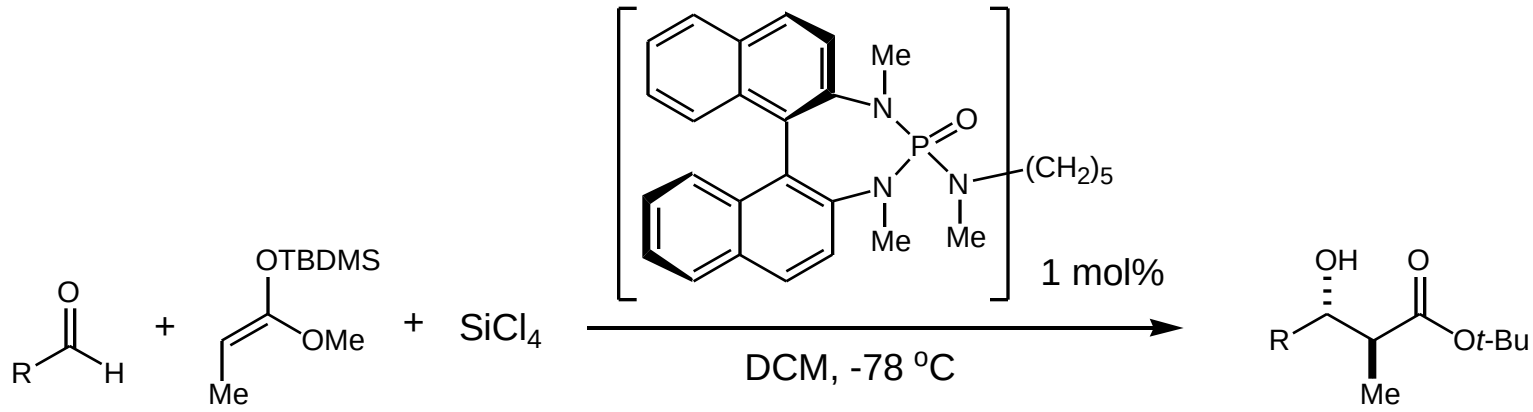
Acetate Aldols



entry	R	ee	yield	entry	R	ee	yield
1	Ph-	93	97	6	4-CF_3Ph-	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

Denmark, S. E. *JACS,* **2002**, *124*, 13405

Propanate Aldols

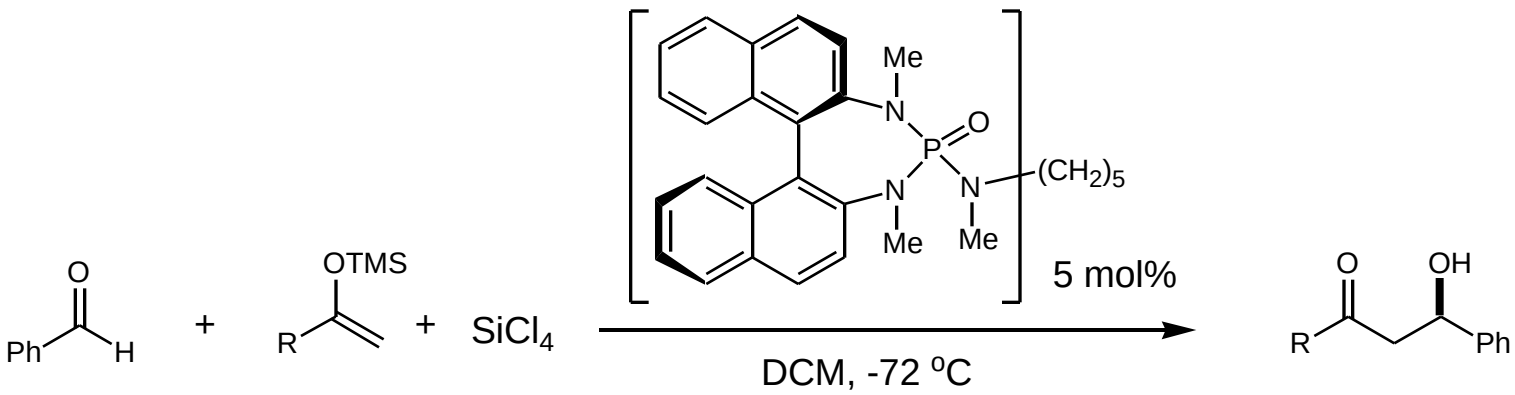


entry	R	dr	ee	yield
1	Ph-	99/1	98	93
2	1-naphthyl-	96/4	94	98
3	2-naphnthyl-	>99/1	98	95
4	4-MeOPh-	>99/1	98	88
5	4-CF_3Ph-	>99/1	92	93
6	cinnamyl-	>99/1	98	98
7	phenylpropargyl-	96/4	68	92
8	dihydrocinnamyl[a]-	93/7	89	55

[a]Reaction run with 0.1 equiv of TBAI

Denmark, S. E. *JACS,* **2002**, *124*, 13405

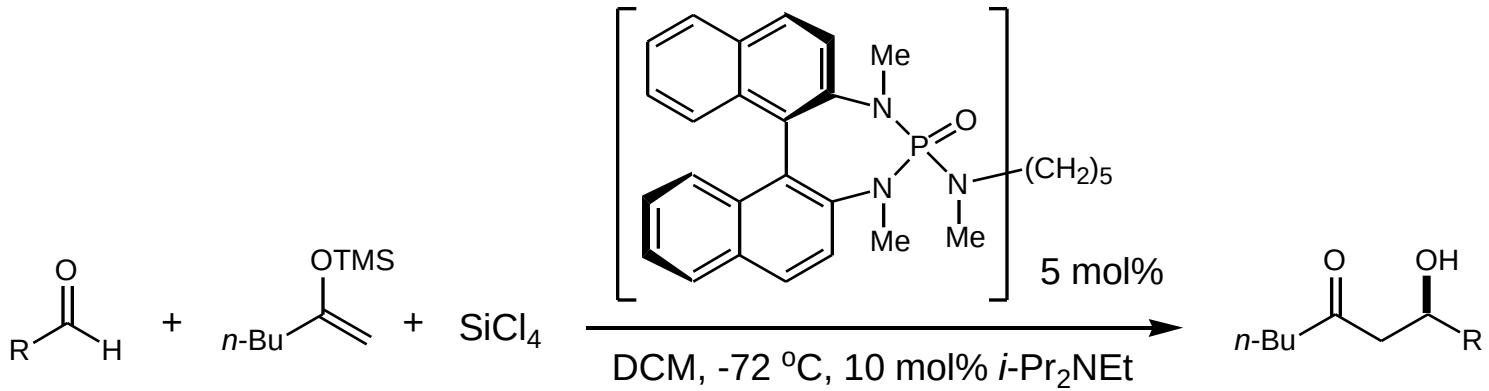
Aldol Additions with Methyl Ketones I



entry	R	ee %	yield
1	*n*-Bu-	98	81
2	*sec*-Bu-	98	70
3	*t*-Bu-	–	–
4	*i*-Pr-	99	72
5	Ph-	94	76

Denmark, S. E. *OL,* **2003**, *5*, 2303

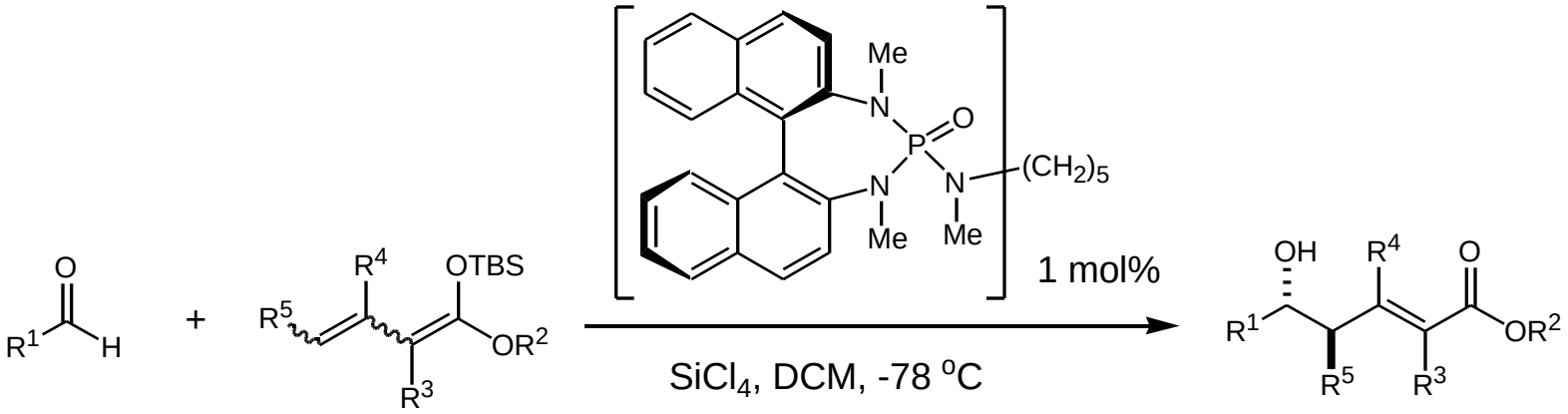
Aldol Additions with Methyl Ketones II



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_3Ph-	99	96
7	2-furyl-	90	88
8	2-thiophenyl-	89	79
9	dihydrocinnamyl-	–	–

Denmark, S. E. *OL,* **2003**, *5*, 2303

Vinylogous Aldol

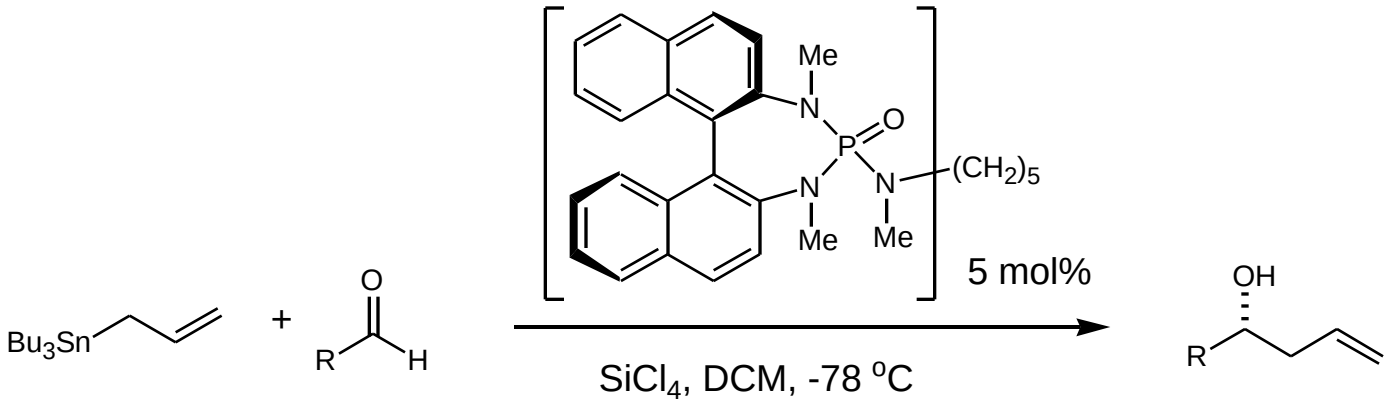


entry	R^1	R^2	R^3	R^4	R^5	ee %	yield
1	Ph-	Et-	H-	H-	H-	98	89
2	cinnamyl-	Et-	H-	H-	H-	96	84
3	dihydrocinnamyl-	Et-	H-	H-	H-	90	68
4	Ph-	Me-	Me-	H-	H-	99	93
5	cinnamyl-	Me-	Me-	H-	H-	99	88
6	Ph	Et-	H-	Me-	H-	92	91
7	cinnamyl-	Et-	H-	Me-	H-	88	97
8	dihydrocinnamyl-	Et-	H-	Me-	H-	95	73
9	Ph-	*t*-Bu-	H-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

[a]Diastereoselectivity >99/1

Denmark, S. E. *JACS,* **2003**, *125*, 7800

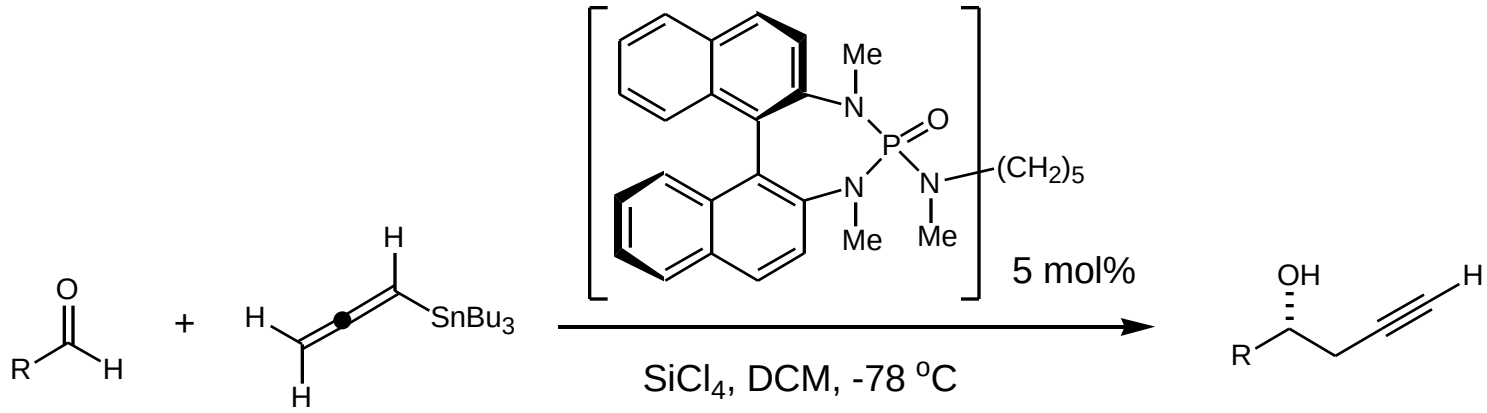
Allylation Revisited, Again



entry	R	ee %	yield %
1	Ph-	94	91
2	4-NO_2Ph-	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

Denmark, S. E. *JACS,* **2001**, *123*, 6199

Propargylation



R = Ph	81% (97% ee (*R*))
R = cinnamyl	90% (87% ee (*R*))
R = 2-naphthyl	95% (93% ee (*R*))

Denmark, S. E. *JACS,* **2001**, *123*, 6199