

Asymmetric Catalysis with Chiral Lewis Bases

I. Catalysis of the allylation of aldehydes

- A. Phosphoramides
- B. Formamides
- C. Amine*N*-oxides

II. Catalysis of the aldol reaction

III. Kinetic resolutions of alcohols/amines

- A. Phosphines
- B. Planar-chiral DMAP analogs

IV. Catalysis of the ring opening of *meso*-epoxides

- A. Phosphoramides
- B. Amine*N*-oxides

V. TMS-CN additions and ketone reductions

Karl Scheidt
Evans Group Friday Seminar
March 9, 2001

Reviews:

Denmark, S. E.; Stavenger, R. A.; Su, X.; Wong, K.-T.; Nishigaichi, Y. *Pure Appl. Chem.* **1998**, *70*, 1469-1476.

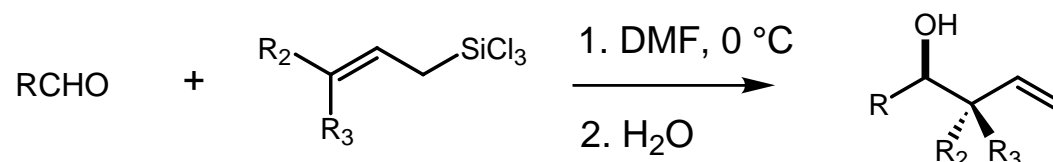
Denmark, S. E.; Stavenger, R. A. *Acc. Chem. Res.* **2000**, *33*, 432-440.

Fu, G. C. *Acc. Chem. Res.* **2000**, *33*, 412-420.

Buono, G.; Chiodi, O.; Wills, M. *Synlett* **1999**, 377-388.

Seminal Observation: DMF Promotes Allylations

General Reaction:

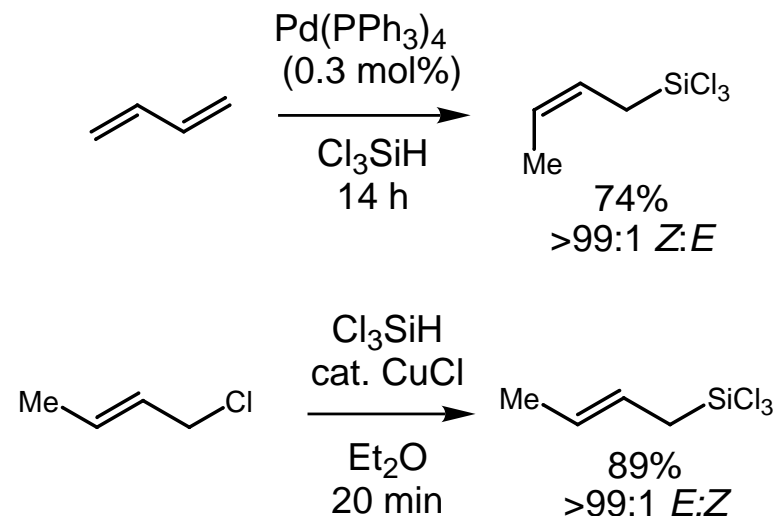


1:1 CH₂Cl₂/DMF as solvent provides product in 97% yield in 4h

RCHO = PhCHO, cinnamaldehyde, hydrocinnamaldehyde, cyclohexanecarboxaldehyde

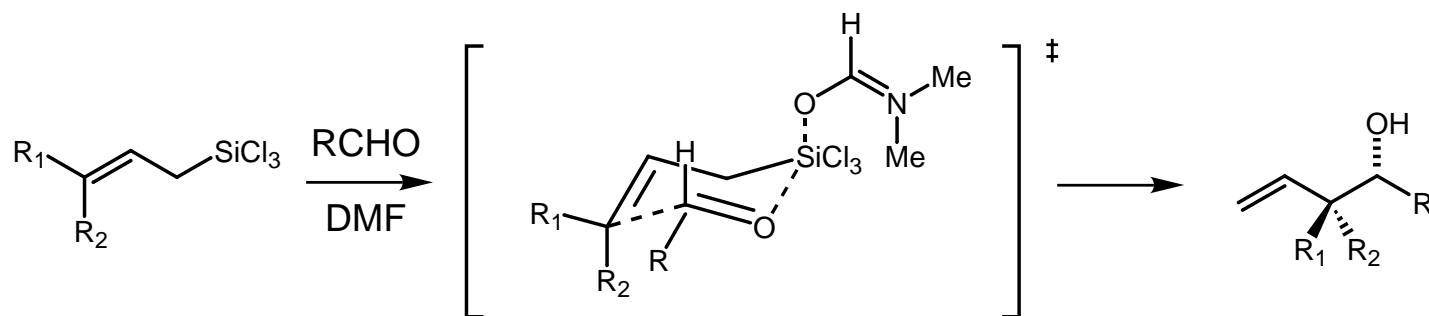
²⁹Si NMR Chemical Shifts of (Z)-Crotyltrichlorosilane in Various Solvents

solvent	chemical shift (ppm)
CDCl ₃	+8.0
CD ₃ CN	+8.6
C ₆ D ₆	+7.9
THF- <i>d</i> ₈	+8.5
DMF-<i>d</i>₇	-170
HMPA	-22



Kobayashi, S.; Nishio, K. *Tetrahedron Lett.* **1993**, 34, 3453-3456.
Kobayashi, S.; Nishio, K. *J. Org. Chem.* **1994**, 59, 6620-6628.

Proposed Transition State for Allylation

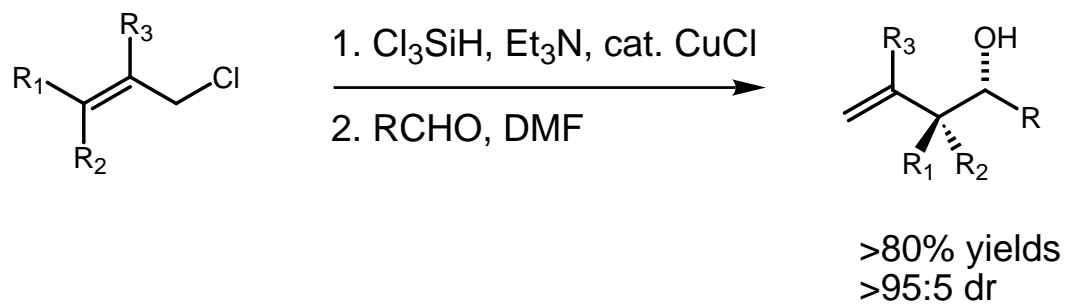


E crotyltrichlorosilane gives >99:1 anti product

Z crotyltrichlorosilane gives >99:1 syn product

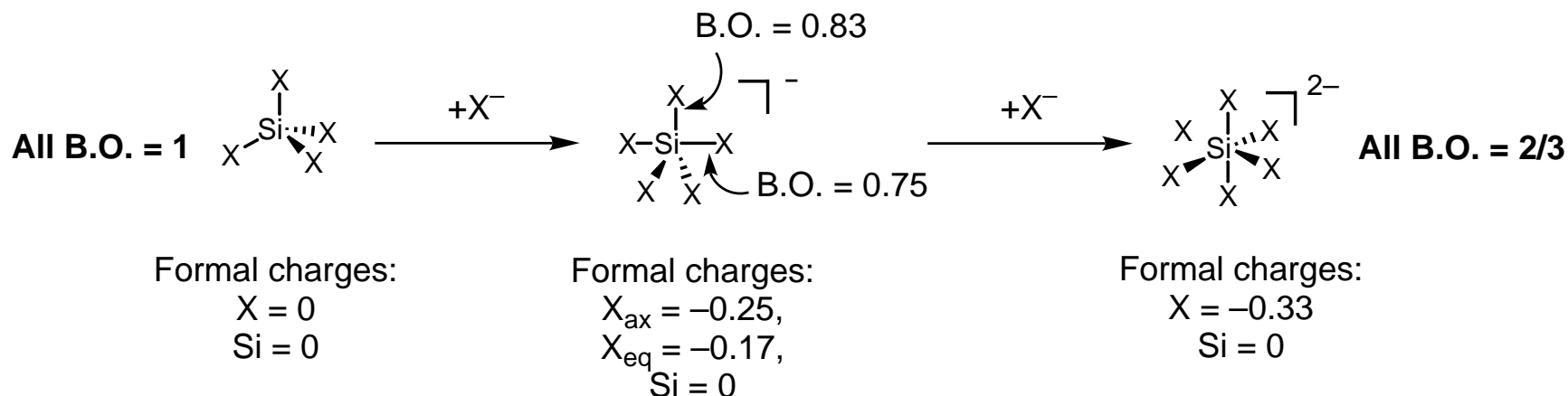
Kobayashi invokes 1:1 DMF/allylsilane complex in transition state, but no kinetic data provided

One-Pot Procedure from Allylic chloride:



Why are pentacoordinate compounds more electrophilic?

Slide taken from Forrest Michael's Seminar : Hypercoordinate Main-Group Compounds 1999



Ab initio study:

Species	Si charge	Ligand charge
SiH ₄	+0.63	-0.16
SiH ₅ ⁻	+0.84	-0.29(eq), -0.49(ax)
SiH ₃ F	+1.10	-0.15(H), -0.67(F)
SiH ₃ F ₂ ⁻	+1.26	-0.26(H), -0.74(F)
SiF ₄	+1.434	-0.358
SiF ₄ •NH ₃	+1.470	-0.397(F, eq), -0.385(F, ax), +0.084(NH ₃)
SiF ₄ •2NH ₃	+1.463	-0.463(F), +0.196(NH ₃)

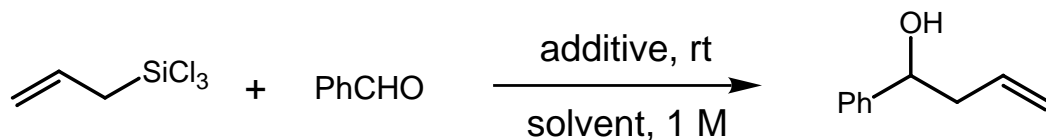
This phenomenon is termed the "spillover effect", and is widely seen in donor-acceptor complexes.

Although the formal charge does not change, the number of electronegative substituents increases upon increasing coordination.

Voronkov, M. *Top. Curr. Chem.* **1986**, 131, 99.
Corriu, R. et al. *Chem. Rev.* **1993**, 93, 1371.

Second on the Scene: Denmark

Re-examination of allylation promoters:

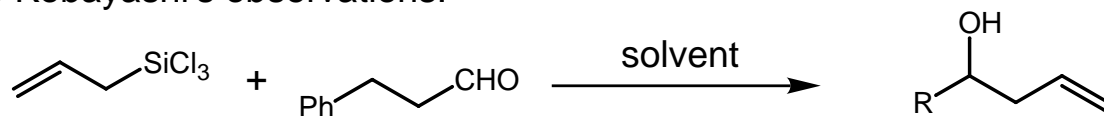


entry	additive (equiv)	solvent	$t_{1/2}$ (min)	conversion (time)	yield
1	DMF (1)	C_6D_6	nd	83 (70 h)	nd
2	HMPA (1)	C_6D_6	18	nd	77
3	HMPA (1)	CDCl_3	nd	63 (4 min)	85
4	HMPA (1)	CD_3CN	nd	63 (4 min)	86
5	HMPA (0.1)	C_6D_6	529	60 (46 h)	nd
6	HMPA (0.1)	$\text{THF}-d_8$	350	80 (124 h)	nd

HMPA superior to DMF →

DMSO and pyridine *N*-oxide were "incompatible" with trichloroallylsilane

In contrast to Kobayashi's observations:

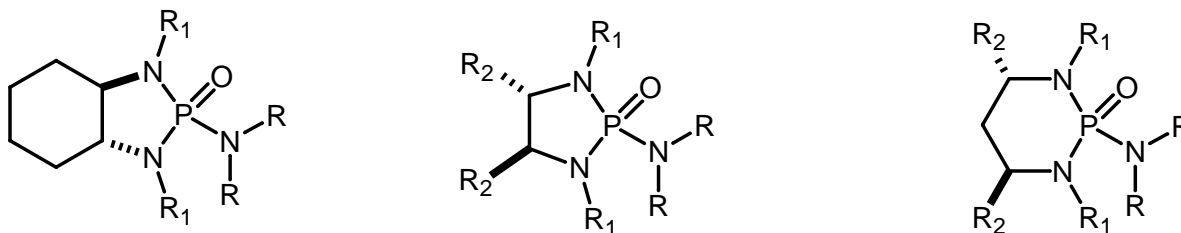


DMF: 2 h, 90% yield
HMPA: 3 h, 28% yield

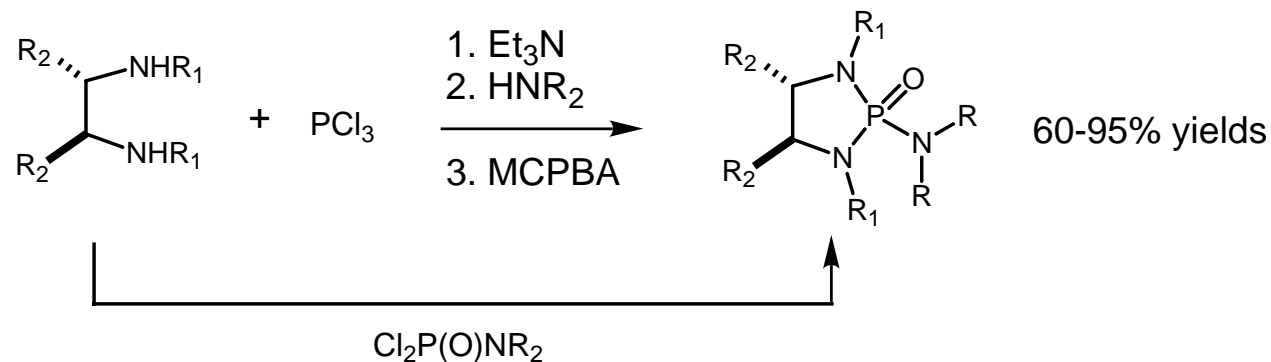
Denmark, S. E.; Coe, D. M.; Pratt, N. E.; Griedel, B. D. *J. Org. Chem.* **1994**, 59, 6161-6163.

Development of Asymmetric Allylation: Synthesis of Chiral Phosphoramides

Catalyst structures screened by Denmark:



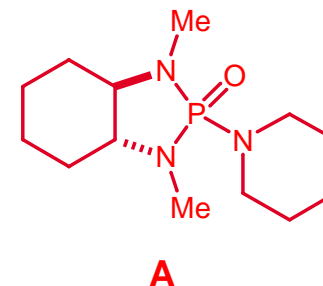
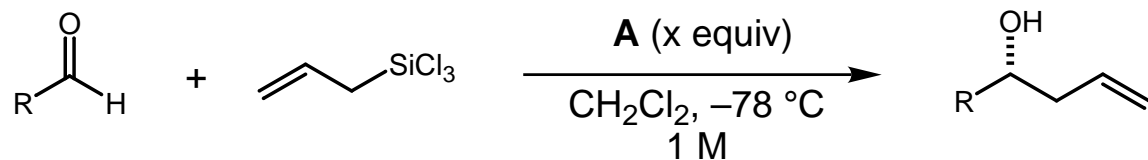
General synthesis of chiral phosphoramides:



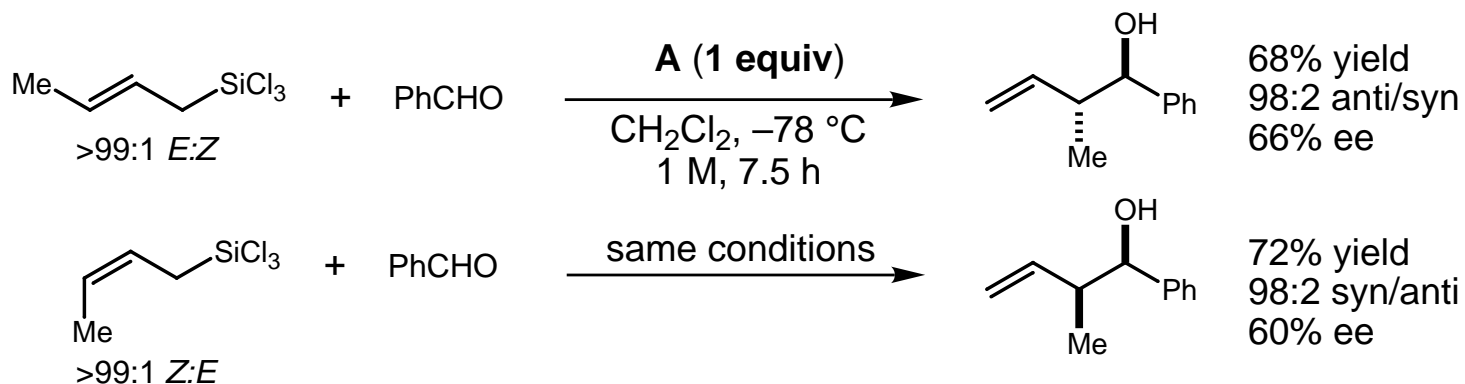
Syntheses of chiral phosphoramides: Denmark et al. *J. Org. Chem.* **1999**, *64*, 1958-1967.
Hanessian et al. *J. Am. Chem. Soc.* **1984**, *106*, 5754-5757; Normant et al. *Synthesis* **1988**, 255-257.

For a review of 1,2-diamines see Bennani, Y. L.; Hanessian, S. *Chem. Rev.* **1997**, *97*, 3161.

Asymmetric Allylation with Chiral Phosphoramides

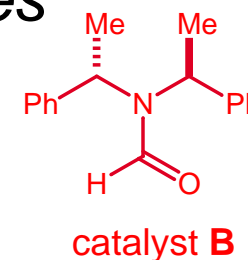
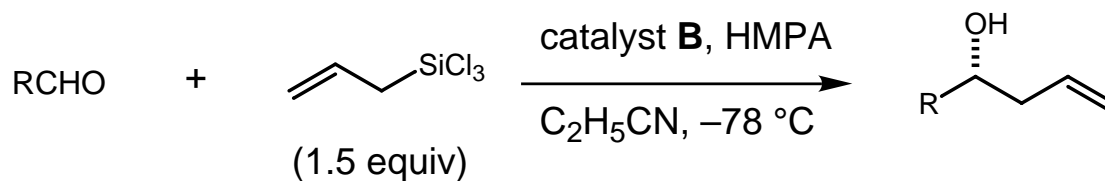


entry	R	equiv A	time	yield	% ee (config)
1	Ph	1.0	6 h	81	60 (<i>R</i>)
2	Ph	0.5	24 h	78	57 (<i>R</i>)
3	Ph	0.1	24 h	40	53 (<i>R</i>)
4	2-MeC ₆ H ₄	1.0	6 h	81	65 (<i>R</i>)
5	4-NO ₂ -C ₆ H ₄	1.0	6 h	76	21 (<i>R</i>)
6	4-MeOC ₆ H ₄	1.0	6 h	80	50 (<i>R</i>)
7	4-NMe ₂ -C ₆ H ₄	1.0	6 h	69	33 (<i>R</i>)
8	(<i>E</i>)-PhCH=CH	1.0	6 h	67	38 (<i>R</i>)



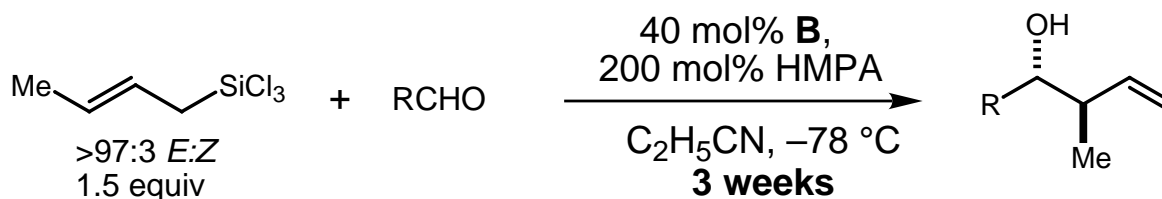
Denmark, S. E.; Coe, D. M.; Pratt, N. E.; Griedel, B. D. *J. Org. Chem.* **1994**, *59*, 6161-6163.

Asymmetric Allylation with Chiral Formamides



entry	R	B (mol%)	HMPA (mol%)	time (weeks)	yield (%)	% ee (config)
1	cyclopentyl	20	100	2	72	91
2	PhCH ₂ CH ₂	20	100	3	84	95 (S)
3	(C ₂ H ₅) ₂ CH	20	100	3	74	93
4	(CH ₃) ₃	40	200	4	61	98
5	CH ₃ (CH ₂) ₅	40	200	4	53	68
6	CH ₂ =CH(CH ₂) ₂	20	100	3	56	86
7	3-butynyl	40	200	3	51	88
8	Ph	20	100	1	94	8

catalyst recovered in >95% by chromatography

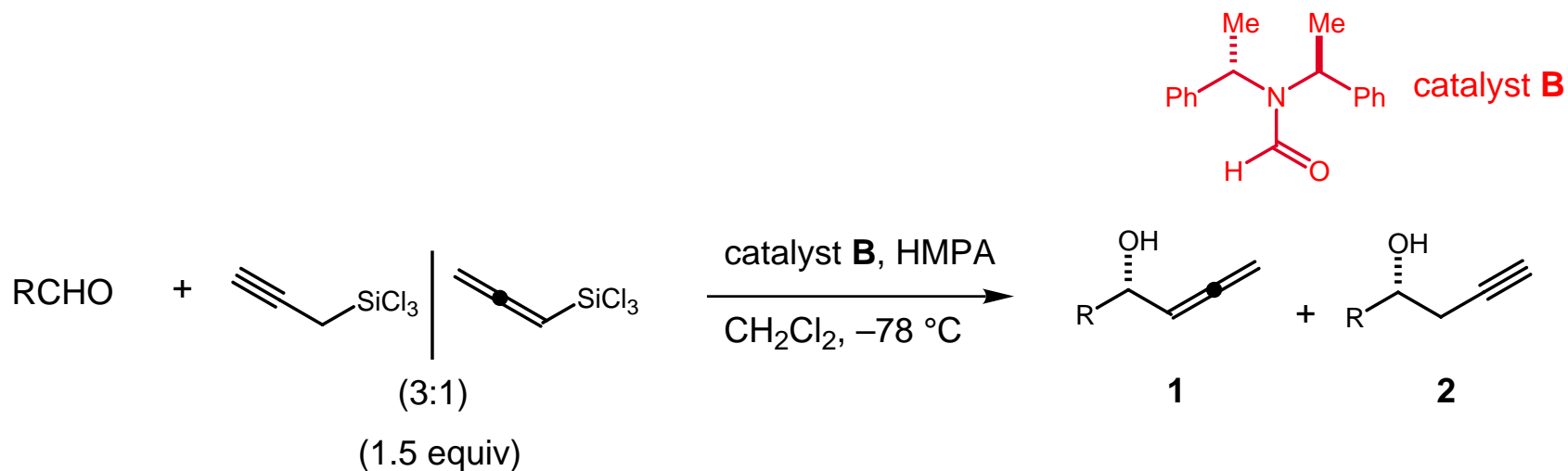


R = cyclohexyl: 92% yield, >99:1 anti/syn, 98% ee

R = PhCH₂CH₂: 97% yield, >99:1 anti/syn, 94% ee

Iseki, K.; Mizuno, S.; Kuroki, Y.; Kobayashi, Y. *Tetrahedron Lett.* **1998**, *39*, 2767-2770

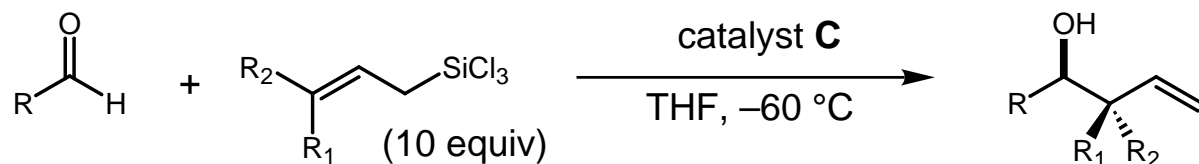
Asymmetric Allenylation with Chiral Formamides



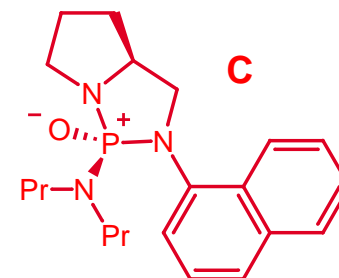
entry	R	B (mol%)	HMPA (mol%)	time (days)	yield (%)	1/2	% ee (config)
1	cyclohexyl	20	100	14	71	98/2	79 (S)
2	cyclohexyl	10	50	14	35	98/2	79 (S)
3	cyclohexyl	10	0	7	28	98/2	43
4	PhCH ₂ CH ₂	20	100	14	71	99/1	79
5	(C ₂ H ₅) ₂ CH	20	100	14	70	96/4	77
6	(CH ₃) ₃	20	100	14	55	94/6	95
7	CH ₃ (CH ₂) ₅	20	100	14	37	93/7	56
8	Ph	40	200	4	59	96/4	0

Iseki, K.; Kuroki, Y.; Kobayashi, Y. *Tetrahedron: Asymmetry* **1998**, 9, 2889-2894.

Catalytic Asymmetric Allylation with Chiral Phosphoramides

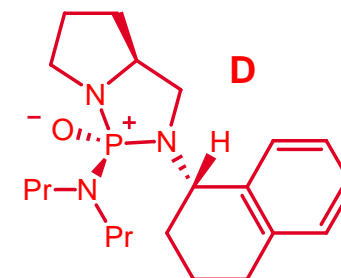
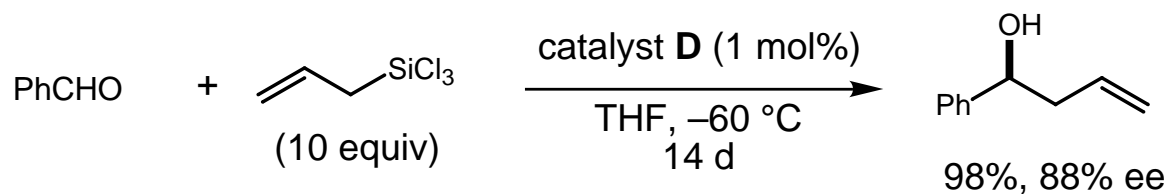


3 $\text{R}_1 = \text{R}_2 = \text{H}$
(Z)-4 $\text{R}_1 = \text{Me}, \text{R}_2 = \text{H}$
(E)-4 $\text{R}_1 = \text{H}, \text{R}_2 = \text{Me}$



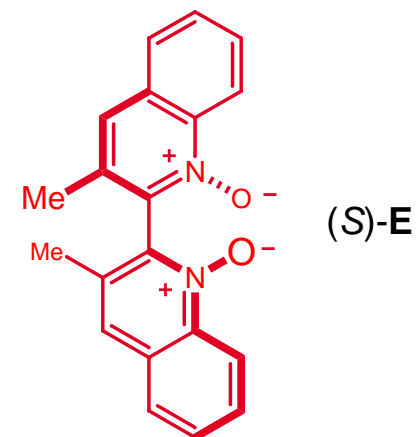
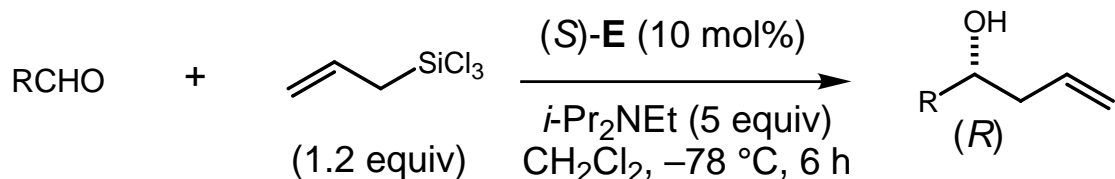
entry	R	mol% C	silane	time (h)	yield (%)	syn/anti	% ee (config)
1	Ph	10	3	168	83	—	88 (S) ^a
2	2-MeC ₆ H ₄	20	3	72	86	—	81
3	Ph	20	(Z)-4	96	80	98/2	77
4	Ph	20	(E)-4	96	90	2/98	83
5	2-MeC ₆ H ₄	20	(Z)-4	120	78	99/1	83
6	4- <i>t</i> -BuC ₆ H ₄	20	(Z)-4	120	72	95/5	82

^a Reaction run @ -78 °C



Iseki et al. *Tetrahedron Lett.* **1996**, 37, 5149-5150.
 Iseki et al. *Tetrahedron* **1997**, 53, 3513-3526.

Catalytic Asymmetric Allylation with Pyridine N-Oxides

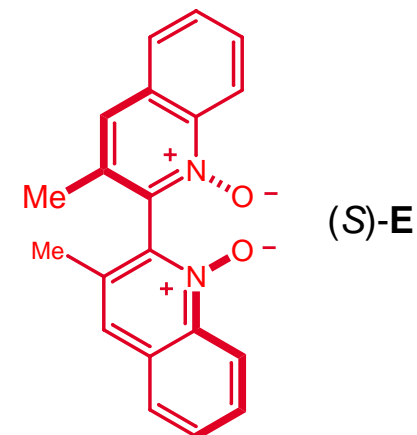
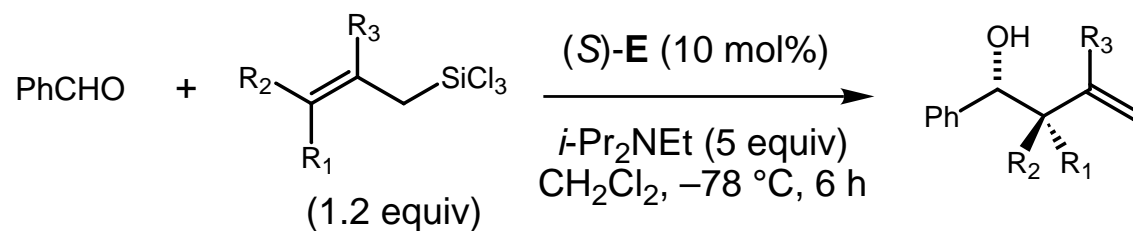


entry	R	yield (%)	ee%
1	Ph	85	88
2	4-MeOC ₆ H ₄	91	92
3	4-CF ₃ -C ₆ H ₄	71	71
4	2-MeC ₆ H ₄	70	90
5	1-naphthyl	68	88
6	(E)-C ₇ H ₁₅ CH=CH	74	81
7	(E)-PhCH=CH	87	80
8	PhCH ₂ CH ₂	30	7 ^a
9	c-Hex	27	28 ^a

^a Provided (S)-homoallylic alcohol

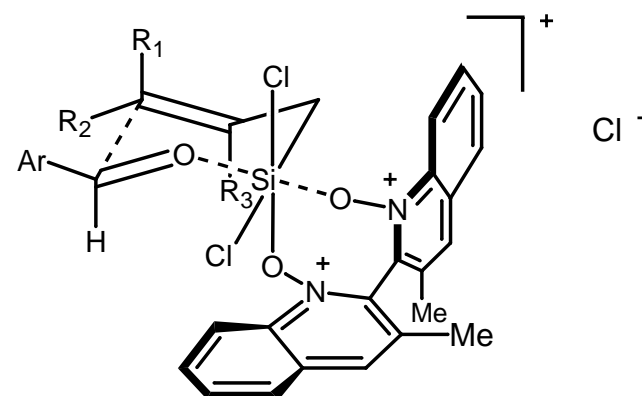
i-Pr₂NEt only amine that accelerates productive reaction- most likely promotes turnover since it does not influence enantioselection.

Catalytic Asymmetric Allylation with Pyridine N-Oxides



entry	R ₁	R ₂	R ₃	syn/anti	yield (%)	ee%
1	H	CH ₃	H	3:97	68	86
2	CH ₃	H	H	99:1	64	84
3	CH ₃	CH ₃	H	na	52	78
4	H	H	CH ₃	na	70	49

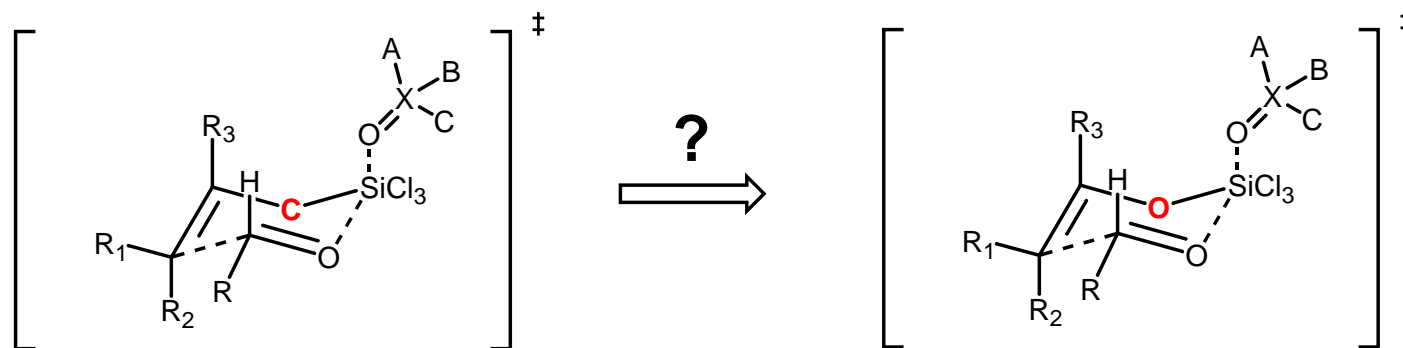
proposed transition state



Nakajima, M.; Saito, M.; Shiro, M.; Hashimoto, S.-i. *J. Am. Chem. Soc.* **1998**, *120*, 6419-6420

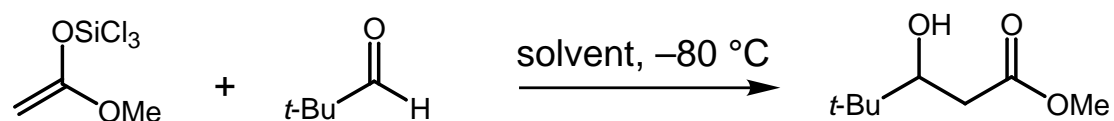
"Inventing" a New Type of Aldol Reaction

"We set for ourselves the goal of inventing a new type of aldol addition reaction which involves the ordered preassembly of enolate, aldehyde and chiral agent for maximum asymmetric influence and which would be catalytic in the chiral reagent." Denmark et al. *J. Am. Chem. Soc.* **1996**, *118*, 7404-7405.



Successful allylation strategy:
Kobayashi, Iseki, Denmark, Nakajima

Cautionary Note: HMPA catalyzed reaction, but background is a potential problem.

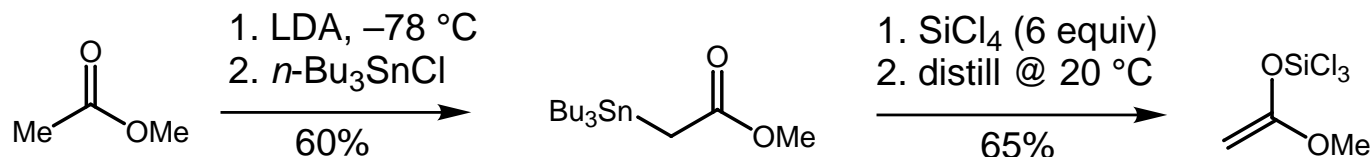


entry	solvent	promoter (equiv)	conversion	time (min)
1	toluene- <i>d</i> ₈	none	18	120
2	CD ₂ Cl ₂	none	50	120
3	THF- <i>d</i> ₈	none	69	120
4	CD ₂ Cl ₂	HMPA (0.1)	100	<3

Denmark, S. E.; Winter, S. B. D.; Su, X.; Wong, K.-T. *J. Am. Chem. Soc.* **1996**, *118*, 7404-7405.

Trichlorosilyl Enolates: Preparation

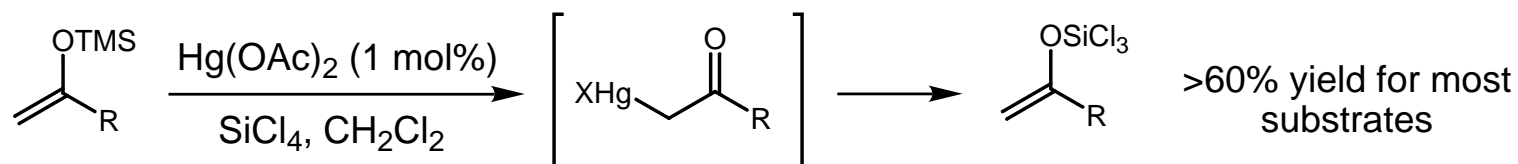
1st generation synthesis:



Baukov and Lustenko et al. *J. Organomet. Chem.* **1966**, 5, 20-28.

Denmark, S. E.; Winter, S. B. D.; Su, X.; Wong, K.-T. *J. Am. Chem. Soc.* **1996**, 118, 7404-7405.

2nd generation synthesis:



Denmark et al. *J. Org. Chem.* **1998**, 63, 9517-9523.

R group

i-Pr

n-Bu

i-Bu

t-Bu

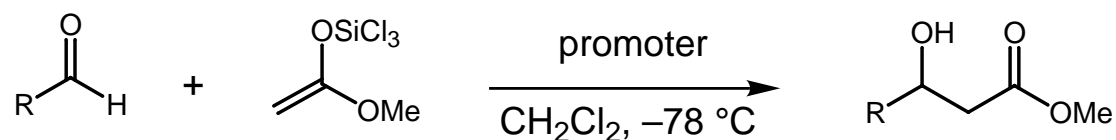
TBSO- CH_2

$\text{CH}_2\text{C}\equiv\text{H}$

Ph

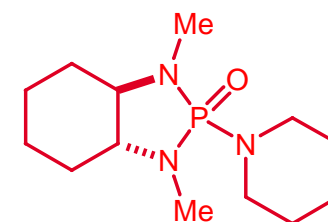
While many other chlorosilyl enolates were generated, only the trichlorosilyl variant was useful

Asymmetric Aldol Reaction with Trichlorosilyl Enolates

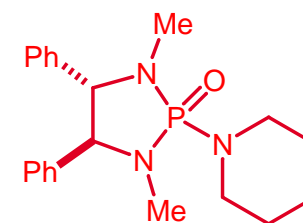


entry	RCHO	promoter (equiv)	config	ee%	yield
1	PhCHO	A (0.1)	(<i>R</i>)	20	88
2	PhCHO	F (0.1)	(<i>S</i>)	33	87
3	PhCHO	G (0.1)	(<i>S</i>)	23	91
4	PhCHO	F (1.0)	(<i>S</i>)	53	84

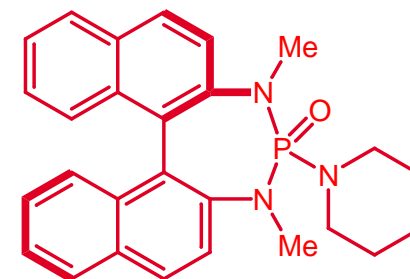
5	<i>t</i> -BuCHO	A (0.1)	(<i>R</i>)	26	76
6	<i>t</i> -BuCHO	F (0.1)	(<i>S</i>)	40	78
7	<i>t</i> -BuCHO	G (0.1)	(<i>S</i>)	49	75
8	<i>t</i> -BuCHO	G (1.0)	(<i>S</i>)	62	77



(*R,R*)-**A**



(*S,S*)-**F**

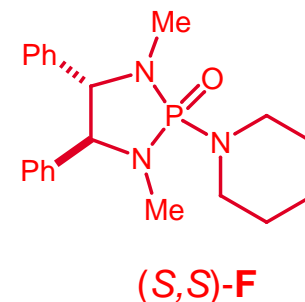
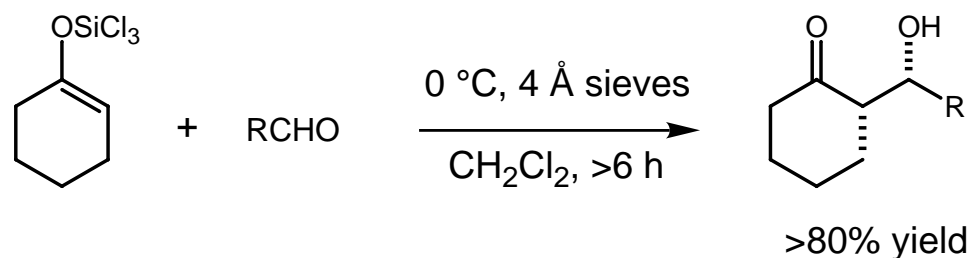


(*R*)-**G**

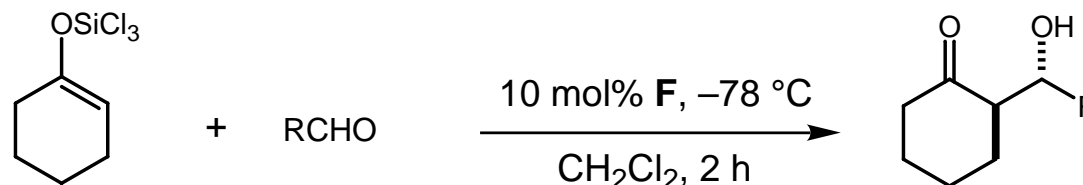
Denmark, S. E.; Winter, S. B. D.; Su, X.; Wong, K.-T. *J. Am. Chem. Soc.* **1996**, *118*, 7404-7405.

Aldol Reactions with Trichlorosilyl Enolsilanes

Uncatalyzed reactions are syn selective (>5:1, max 50:1):



Reactions catalyzed by **F** are highly anti selective:



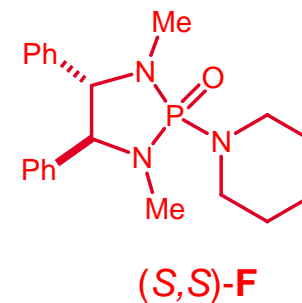
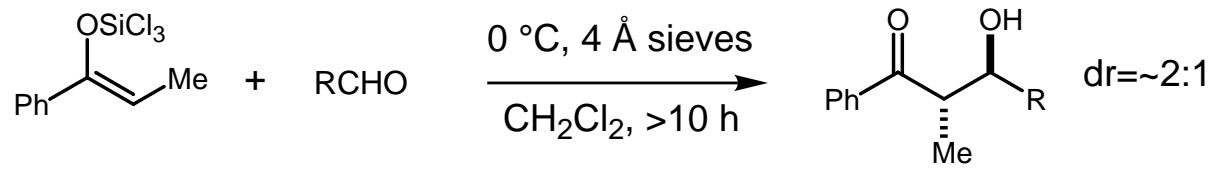
entry	R	syn/anti ^a	ee% (anti)	yield
1	Ph	1:61	93	95
2	1-naphthyl	<1:99	97	94
3	(<i>E</i>)-PhCH=CH	<1:99	88	94
4	(<i>E</i>)-PhCH=C(Me)	<1:99	92	98
5	PhC≡C-	1:5.3	82	90

^a Determined by ¹H NMR (400 MHz) analysis (?)

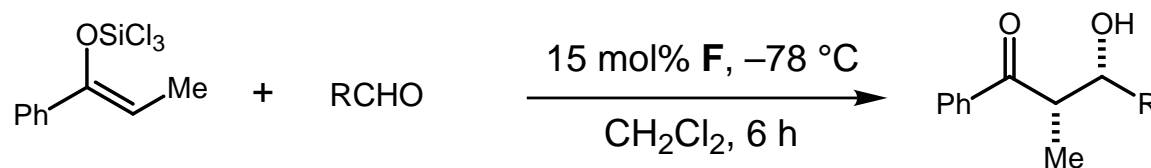
Denmark, S. E.; Wong, K.-T.; Stavenger, R. A. *J. Am. Chem. Soc.* **1997**, *119*, 2333-2334.

Aldol Reactions with Propiophenone Trichlorosilyl Enolsilanes

Uncatalyzed reactions are slightly anti selective (~2:1):



Reactions catalyzed by **F** are syn selective:

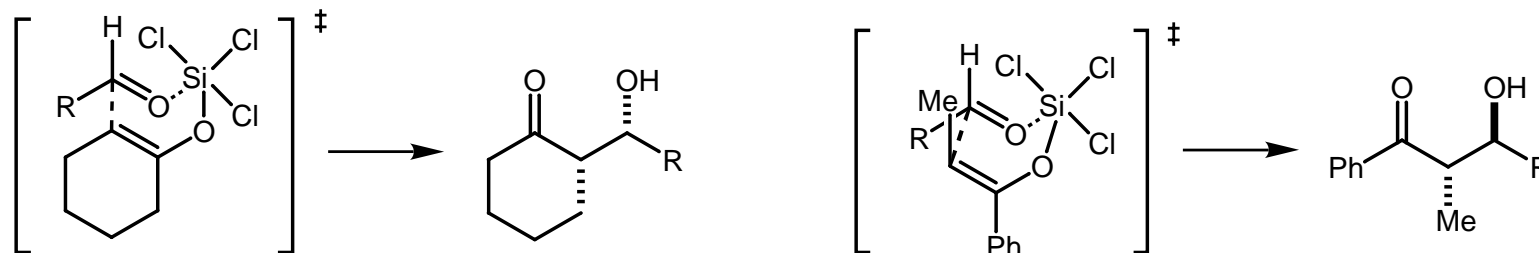


entry	RCHO	syn/anti	ee% (syn)	yield
1	PhCHO	18:1	95	95
2	4-Br-PhCHO	12:1	96	89
3	1-naphthyl	3:1	84	96
4	(<i>E</i>)-PhCH=CH	9.4:1	92	97
5	(<i>E</i>)-MeCH=CH	7:1	91	94
6	PhC≡C	1:3.5	58	92

Aliphatic aldehydes did not react, presumably due to competitive enolization.

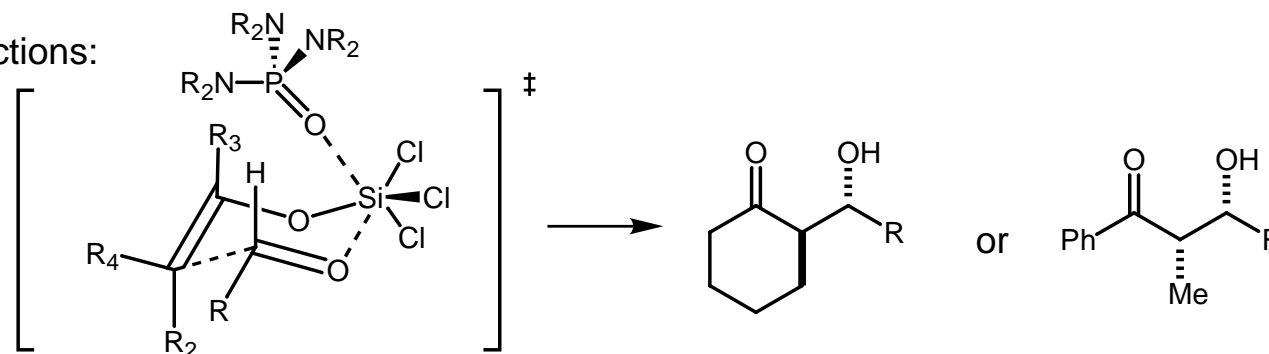
Early Analysis of Trichlorosilyl Enolate Aldol Reactions

Uncatalyzed reactions:



boat-like transition states predominate— pentacoordinate siliconates invoked

Catalyzed reactions:



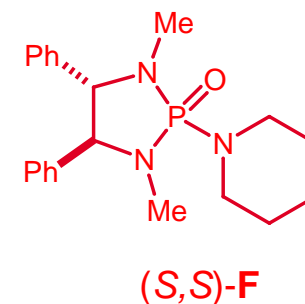
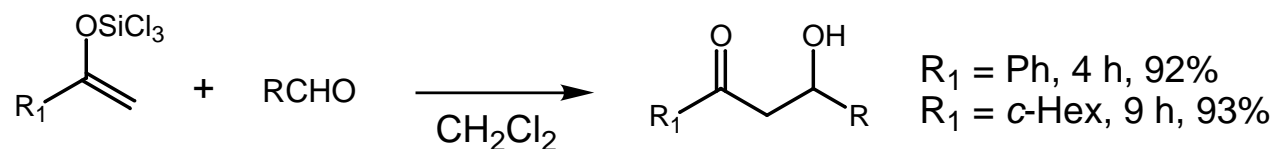
chair-like transition states predominate— octahedral siliconates invoked

"The lack of structural information about the coordination geometry at silicon makes the formulation of a sensible transition structure model tenuous at this stage."

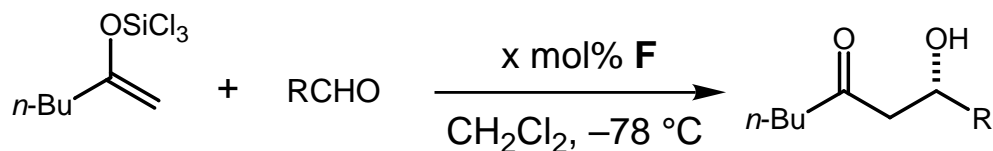
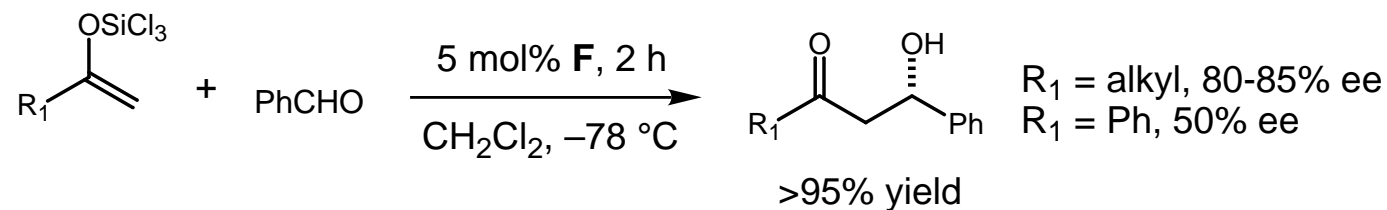
Denmark et al. *J. Am. Chem. Soc.* **1997**, *119*, 2333-2334.

Lewis Base-Catalyzed Methyl Ketone Aldol Reactions

Uncatalyzed reaction:



Catalyzed reaction:

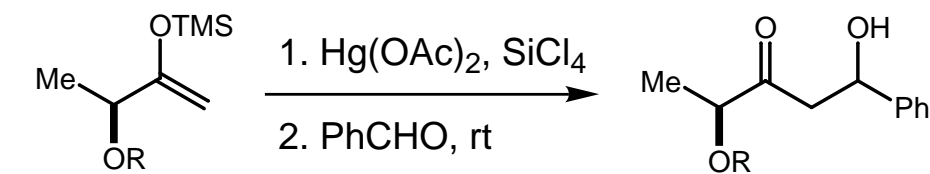


entry	RCHO	mol% F	time (h)	%ee	yield
1	cinnamaldehyde	5	2	84	94
2	α -Me-cinnamaldehyde	5	2	92	95
3	1-naphthaldehyde	5	2	86	92
4	4-Ph-PhCHO	5	2	86	95
enolizable \longrightarrow 5	c-hexCHO	10	6	90	79
6	<i>t</i> -BuCHO	10	6	92	81

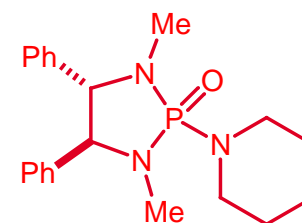
Denmark, S. E.; Stavenger, R. A.; Wong, K.-T. *J. Am. Chem. Soc.* **1998**, 120, 918-919.

Lewis Base-Catalyzed Methyl Ketone Aldol Reactions

Uncatalyzed reaction:

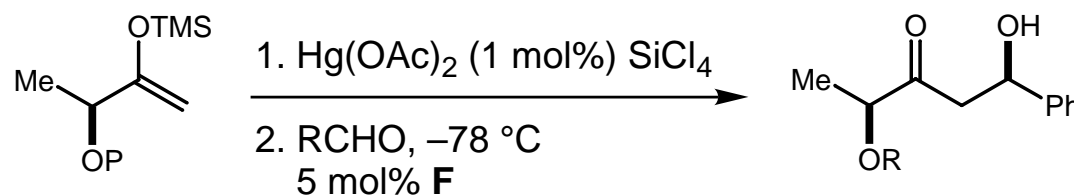


entry	R	Hg(OAc) ₂ (mol%)	syn/anti	yield
1	TBS	0.25	1/1.2	82
2	Piv	0.5	1/2.4	71
3	Bn	0.5	1/3.4	75



(*S,S*)-**F**

Catalyzed reaction:

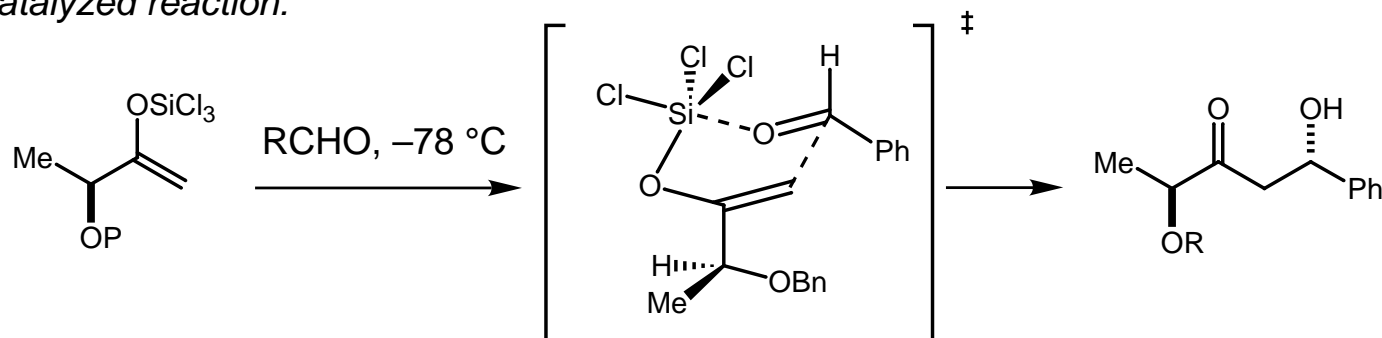


	entry	P	R	catalyst	syn/anti	yield
mismatched	1	TBS	Ph	(<i>S,S</i>)- F	1.5/1	85
	2	Piv	Ph	(<i>S,S</i>)- F	3.4/1	78
	3	Bn	Ph	(<i>S,S</i>)- F	1/1.1	78
matched	4	TBS	Ph	(<i>R,R</i>)- F	73/1	85
	5	Piv	Ph	(<i>R,R</i>)- F	20/1	78
	6	Bn	Ph	(<i>R,R</i>)- F	11/1	77
	7	TBS	(<i>E</i>)-MeCH=CH	(<i>R,R</i>)- F	6.2/1	81

Denmark, S. E.; Stavenger, R. A. *J. Am. Chem. Soc.* **1998**, 120, 9524-9527.

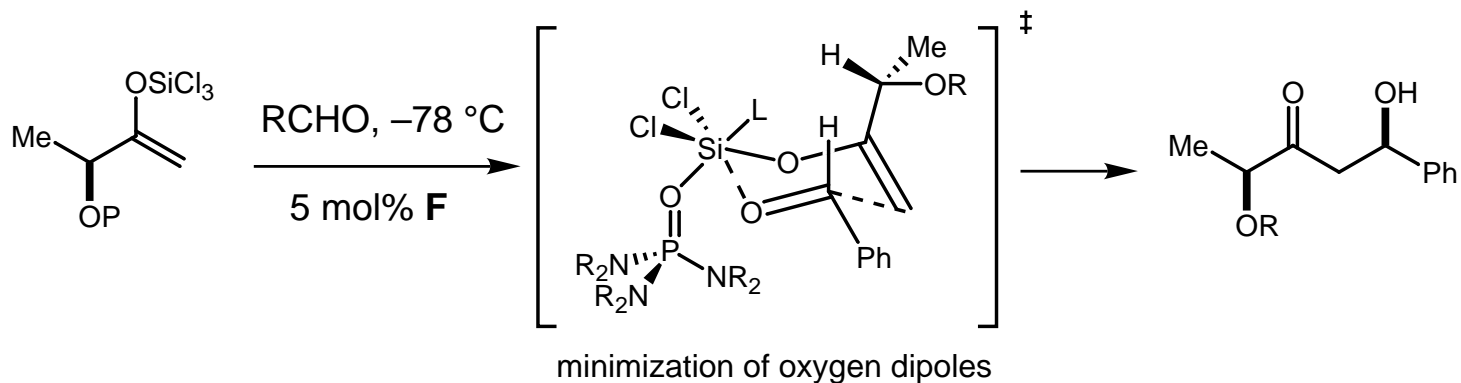
Methyl Ketone Aldol Reactions: Rationale

Uncatalyzed reaction:



"The low diastereoselectivities make proposals for transition structure arrangements speculative at best."

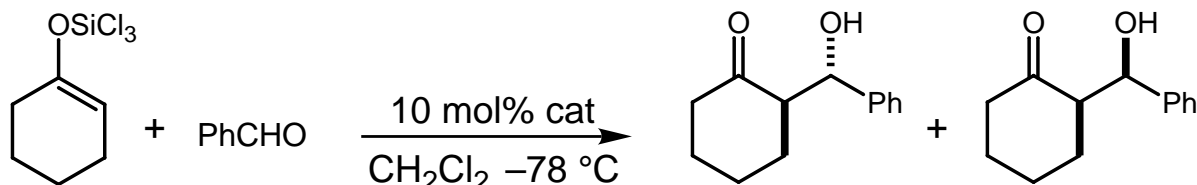
Catalyzed reaction:



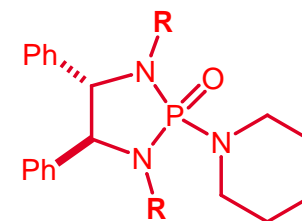
Model does not account for matched and mismatched cases.

Mechanistic Insights on Trichlorosilyl Enolate Aldols

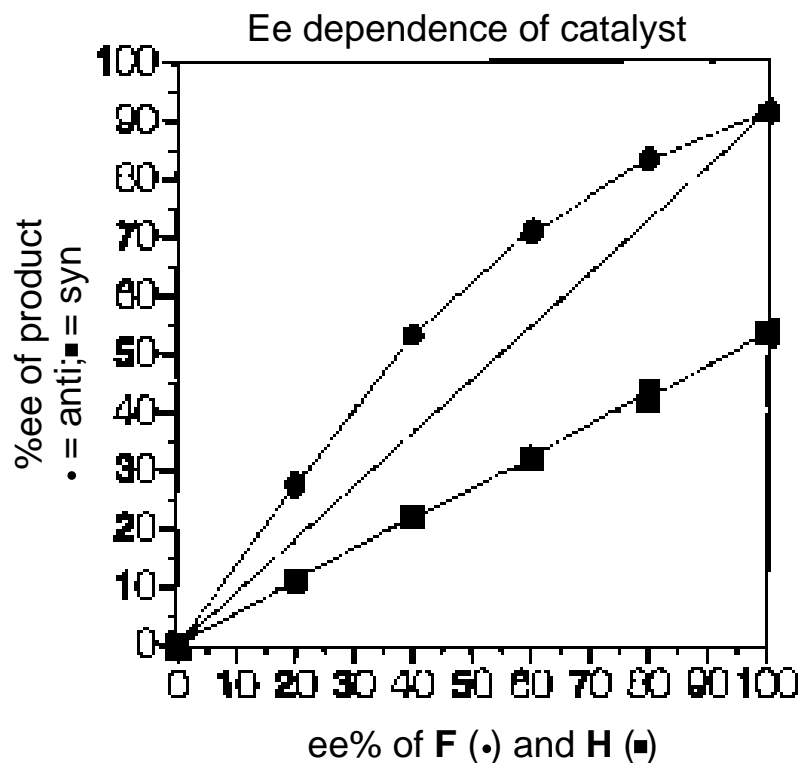
Intriguing switch of diastereoselectivity



cat = **F** (R = Me): anti/syn = 60/1, (anti, 92%ee), 94%
 cat = **H** (R = Ph): anti/syn = 1/97, (syn, 51%ee), 95%



(*S,S*) **F**, R = Me
 (*S,S*) **H**, R = Ph

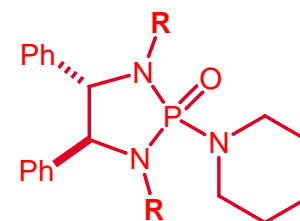
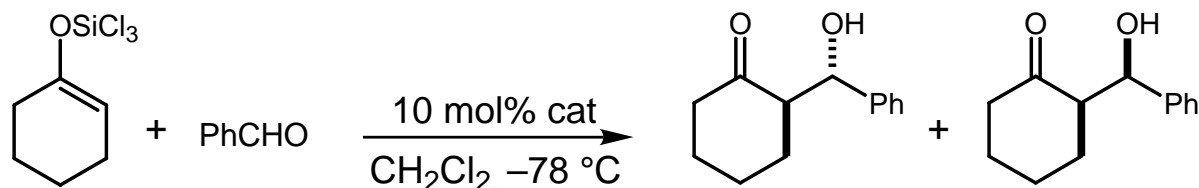


Anti diastereomer favored with less hindered catalysts as well as at higher loadings of achiral **F** analog

Conclusion: Anti product arises from two catalyst molecules in transition state, while syn product arises from one catalyst molecule in the transition state

Mechanistic Insights on Trichlorosilyl Enolate Aldols (cont.)

Intriguing switch of diastereoselectivity

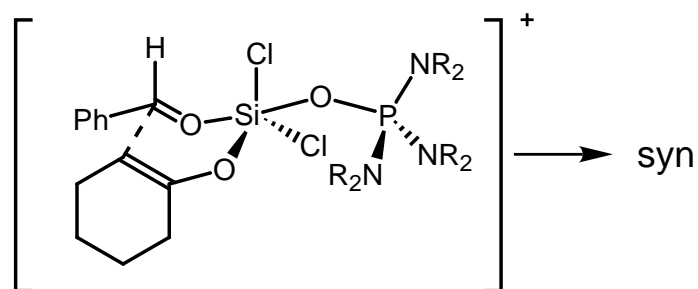


cat = **F** (R = Me): anti/syn = 60/1, (anti, 92%ee), 94%
 cat = **H** (R = Ph): anti/syn = 1/97, (syn, 51%ee), 95%

(*S,S*) **F**, R = Me
 (*S,S*) **H**, R = Ph

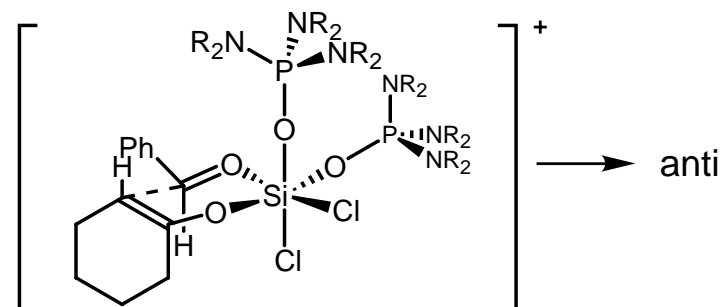
Positive nonlinear dependence on catalyst **F**

Magnitude of nonlinear effect not catalyst concentration dependent– no reservoir effect



cationic trigonal bipyramidal

Favored for bulky catalyst **H**



cationic octahedral

Favored for smaller catalyst **F**

Bu₄NCl inhibits the reaction– inhibits ionization of enolsilane-catalyst complex

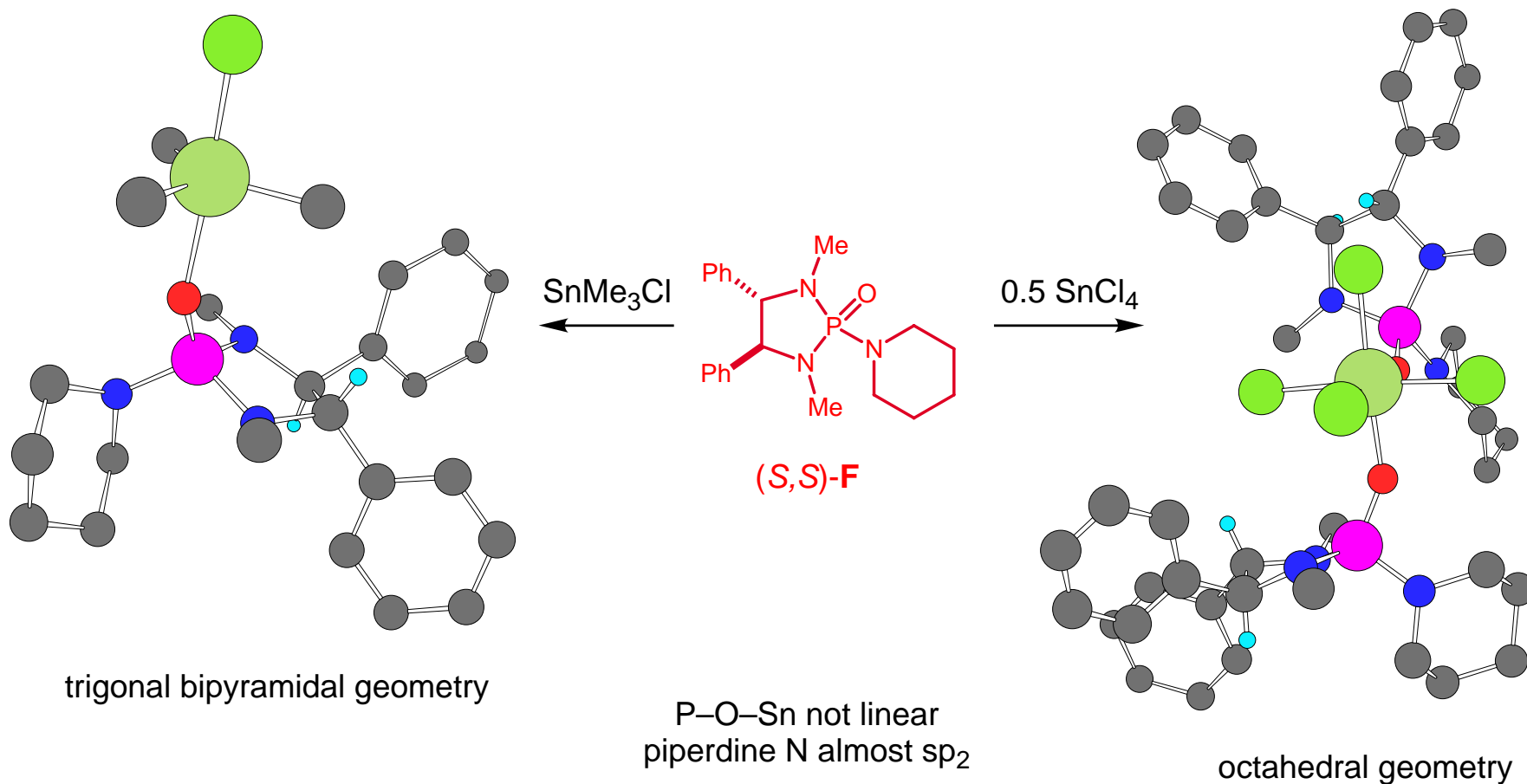
Bu₄NOTf accelerates the reaction by increasing the ionic strength of the medium

Lewis base promotion of ionization of allyltrichlorosilanes: Berrisford et al. *Tetrahedron Lett.* **1997**, 38, 2351-2354.

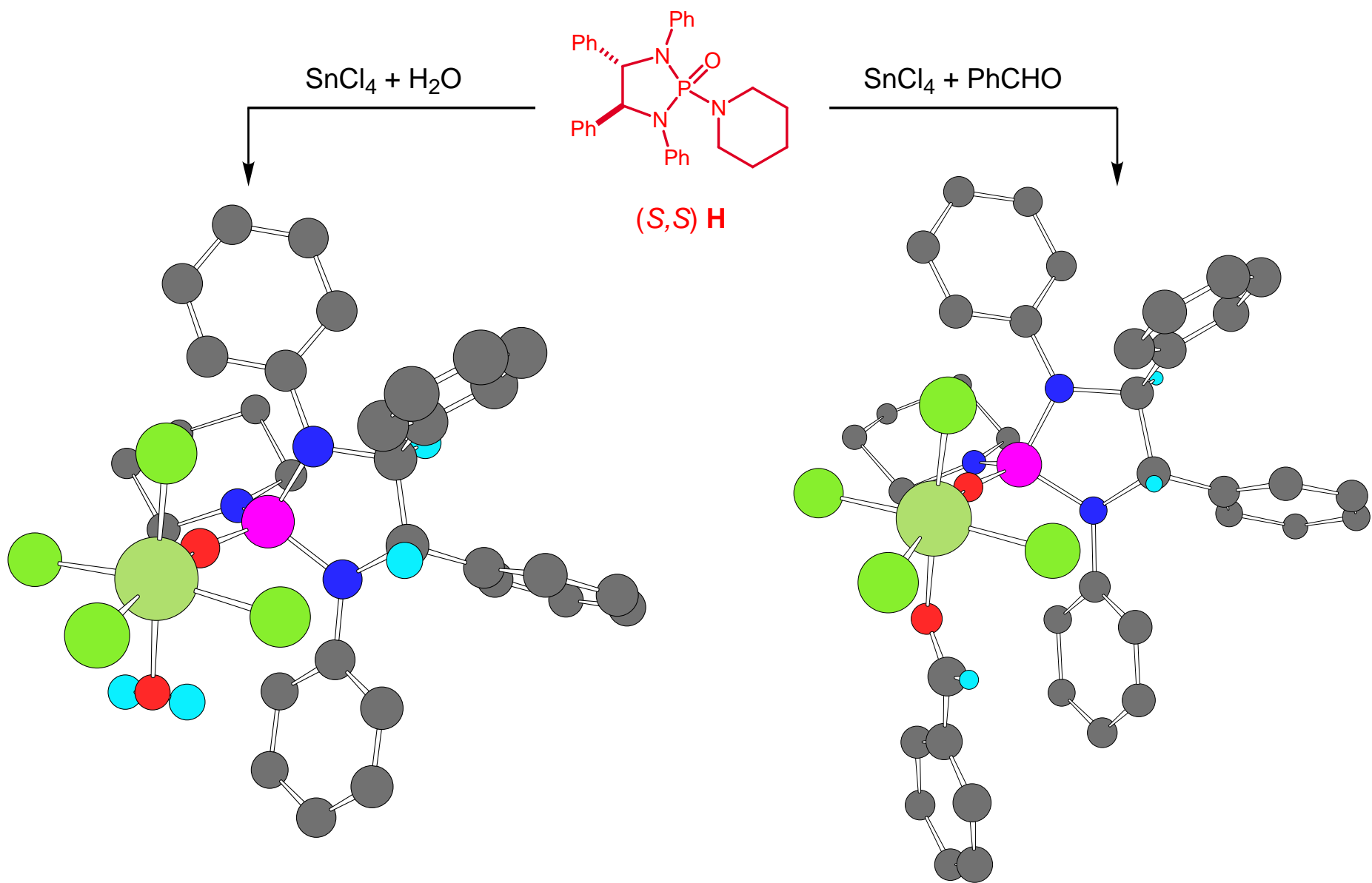
For a review of nonlinear effects see: Fenwick, D.; Kagan, H. B. *Top. Stereochem.* **1999**, 22, 257.

Structural Insights of Trichlorosilyl Enolate Aldols

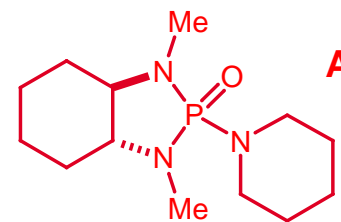
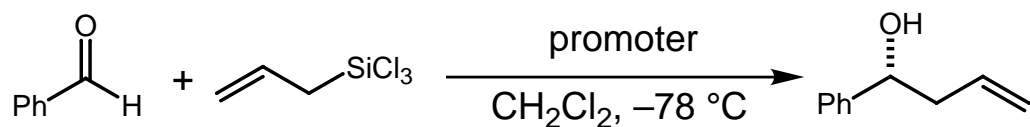
Complexation between phosphoramides and SiCl_4 or trichlorosilylenol silanes were very weak judged by ^1H and ^{29}Si NMR. Use Sn as a surrogate for Si (^{119}Sn NMR and X-ray)



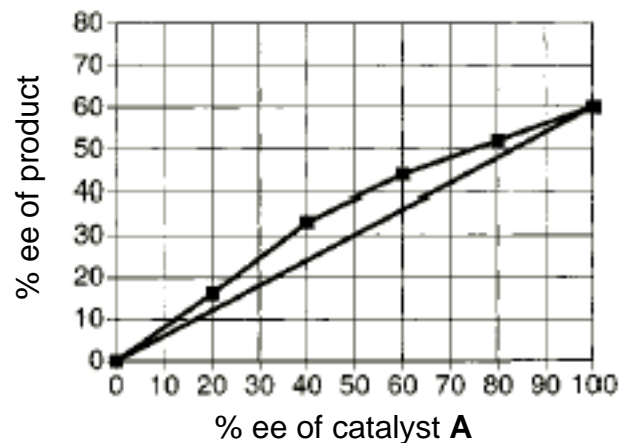
Structural Insights on Trichlorosilyl Enolate Aldols



Allyltrichlorosilane Additions Revisited: New and Improved



Positive nonlinear effect observed

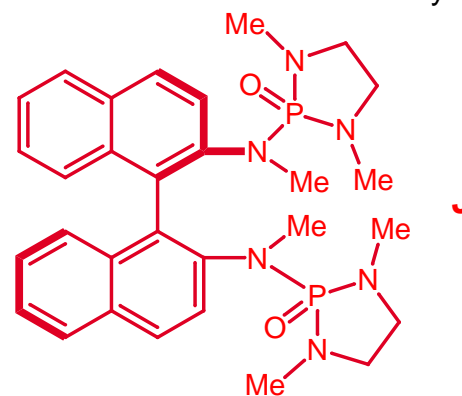
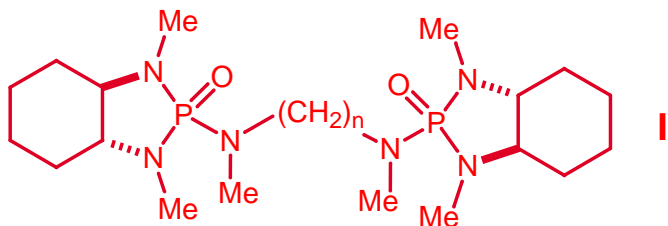


	entry	promoter	tether (n)	equiv	yield (%)	%ee
Denmark 1994	1	A	—	1.0	81	60
	2	A	—	0.1	49	53

	3	I	2	0.5	60	0
	4	I	3	0.5	72	35
	5	I	4	0.5	82	17
	6	I	4	0.1	52	10
	7	I	5	0.5	78	65
	8	I	5	0.1	54	72
	9	I	6	0.5	75	46

	10	J	—	0.1	49	80
	11	J^a	—	0.1	67	80
	12	J^a	—	0.5	76	80
	13	J^a	—	0.05	43	79

^a 5.0 equiv of *i*-Pr₂NEt added for turnover



Denmark, S. E.; Fu, J. *J. Am. Chem. Soc.* **2000**, *122*, 12021-12022.

Kinetic Resolutions: Theory and Practice

Basic math:

$$s = \frac{\ln[(1-c)(1-ee)]}{\ln[(1-c)(1+ee)]} = \frac{k_{\text{fast-reacting enantiomer}}}{k_{\text{slow-reacting enantiomer}}}$$

$$s = \text{selectivity} \quad c = 1 - \frac{A + B}{A_0 + B_0}$$

c = conversion

ee = %ee of recovered substrate

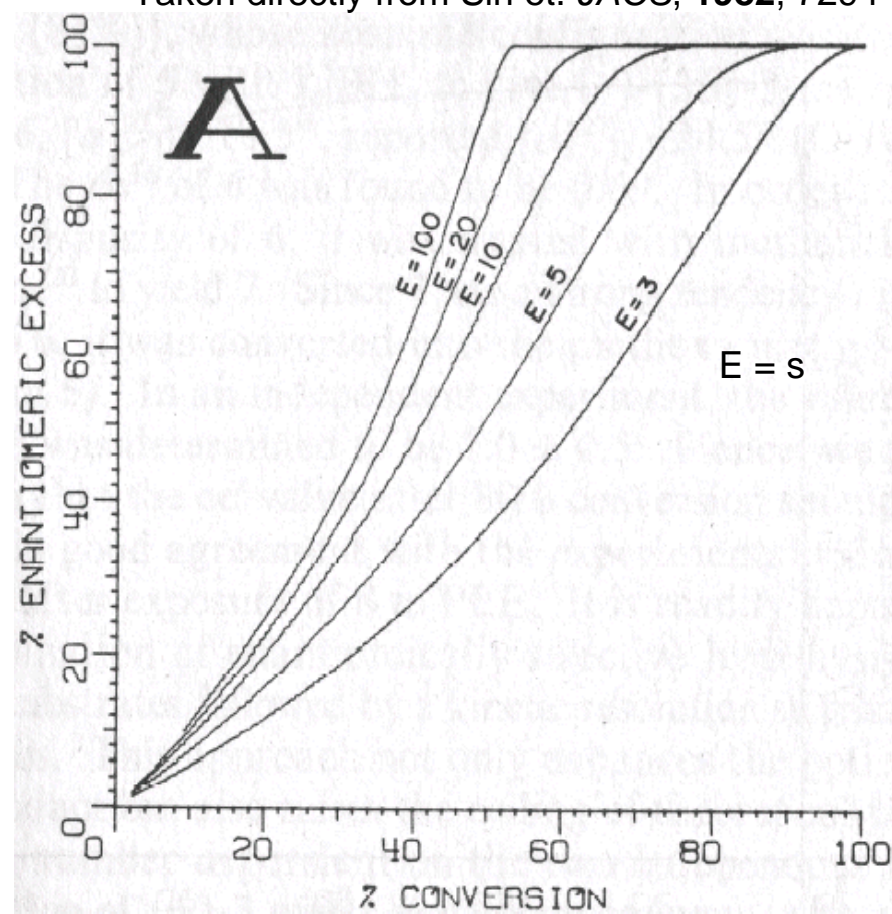
A_0 = initial amt. of fast-reacting enantiomer

B_0 = initial amt. of slow-reacting enantiomer

A = amt. of fast-reacting enantiomer @ time T

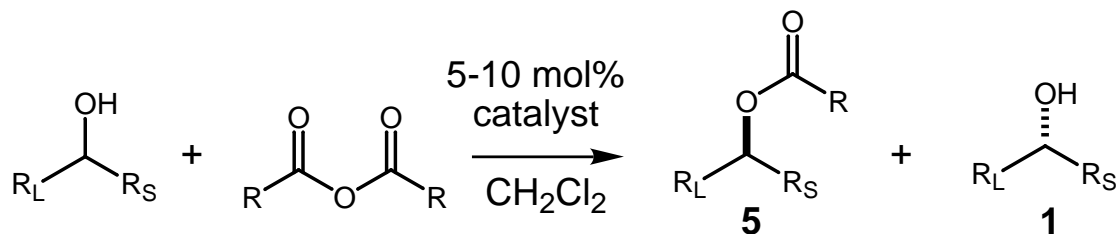
B = amt. of slow-reacting enantiomer @ time T

Taken directly from Sih et. *JACS*, **1982**, 7294



For an excellent analysis of kinetic resolution, see: Sih et al. *J. Am. Chem. Soc.* **1982**, 104, 7294-7299.
For a review of kinetic resolutions, see: Kagan, H. B.; Fiaud, J. C. *Top. Stereochem.* **1998**, 18, 249-330.

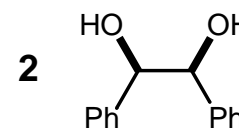
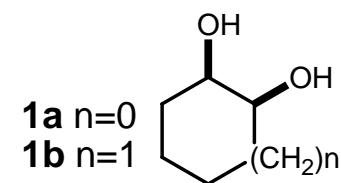
Enantioselective Acylations Catalyzed by Chiral Phosphines



entry	substrate	catalyst	anhydride	%ee 5 (conv.)	selectivity (s)
1	1b	3	Ac ₂ O	9 (40)	1.2
2	1b	4	Ac ₂ O	11 (60)	1.3
3	1b	6a	Ac ₂ O	65 (66)	4.5
4	1b	6b	Ac ₂ O	42 (80)	2.6
5	1a	6a	Ac ₂ O	52 (10)	3.2

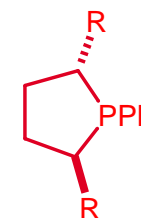
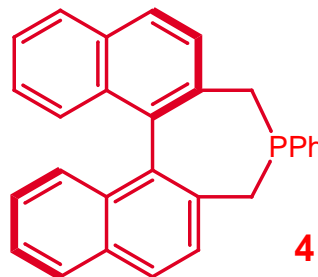
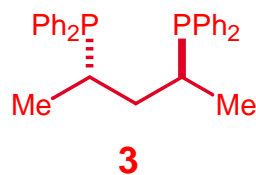
6	2	3	Ac ₂ O	50 (40)	2.9
7	2	6a	Ac ₂ O	27 (22)	1.2
8	2	4	Bz ₂ O	22 (31)	1.6
9	2	6a	Bz ₂ O	68 (84)	5.5
10	2	6b	Bz ₂ O	58 (70)	4.7
11	PhCH(OH) <i>t</i> Bu	6a	3-CIBz ₂ O	81 (25)	12-15 ←

meso substrates



perdeuterated Ac₂O
give monoacetate without
loss of deuterium: no ketene
mechanism operative

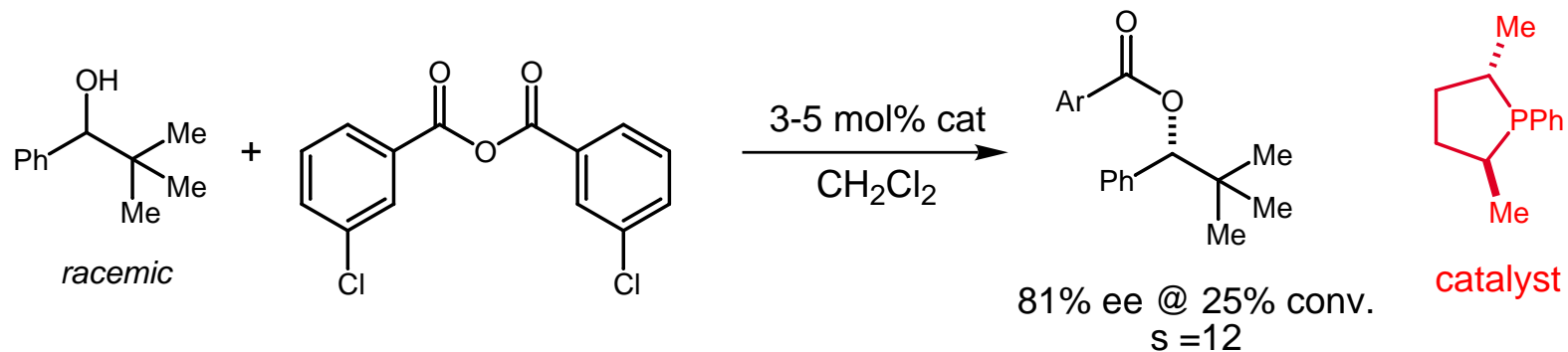
chiral phosphines:



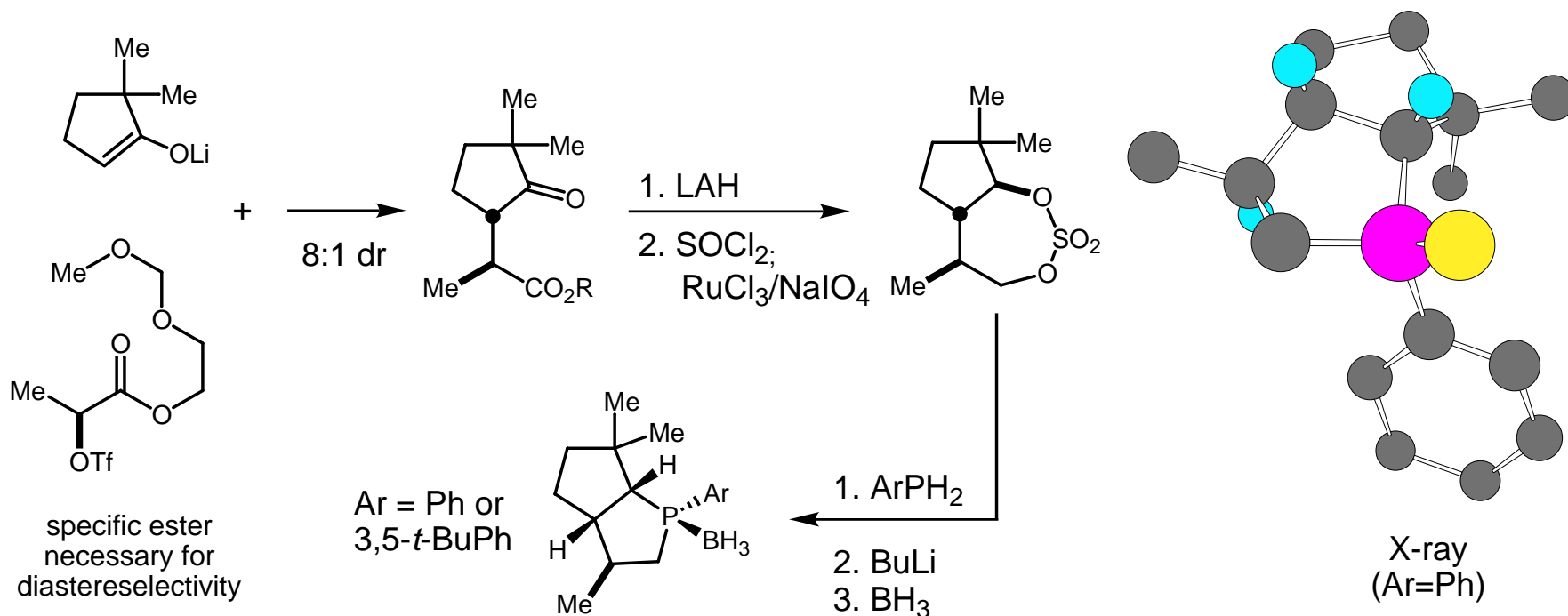
Vedejs, E.; Daugulis, O.; Diver, T. S. *J. Org. Chem.* **1996**, *61*, 430-431.

Improved Chiral Phosphine for Kinetic Resolutions

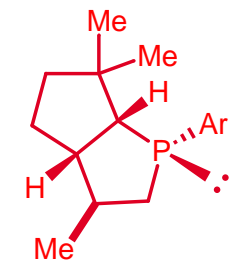
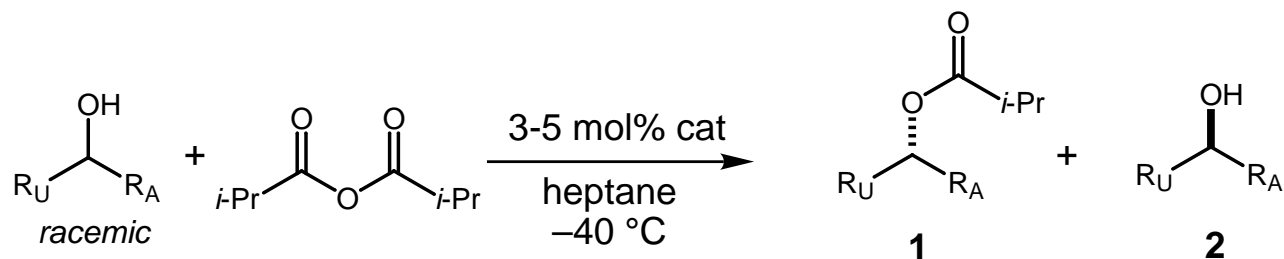
Recall:



Problem: Reaction is not general— new chiral phosphine needed



Acylation Catalyzed by Chiral Phosphines



Ar = 3,5-*t*-BuPh

catalyst

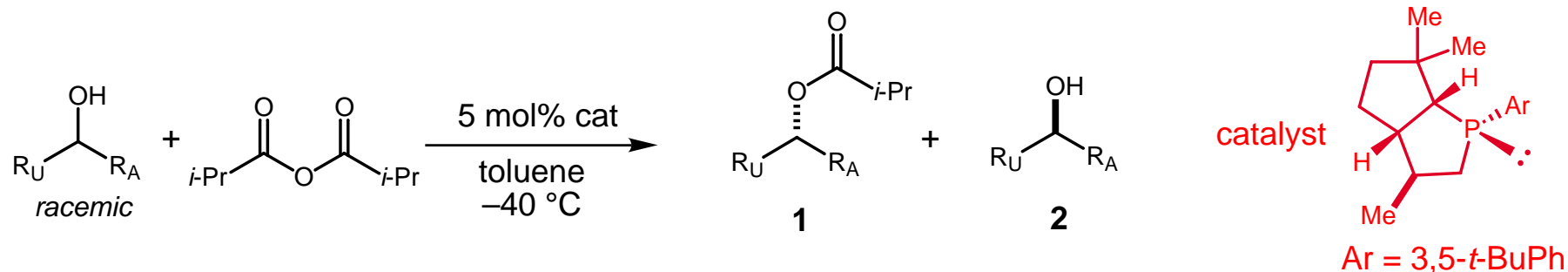
entry	R _U	R _A	time (h)	conv. (%)	%ee product (1)	s
1	Ph	Me	4	29	93	42
2	1-cC ₆ H ₉ ^a	Me	14	50	88	49
3	Ph	<i>n</i> -Bu	8	51	89	57
4	Ph	<i>i</i> -Bu	7	42	88	31
5	Ph	<i>i</i> -Pr	42	47	95	100
6	Ph	<i>t</i> -Bu	65	46	93	67
7	2-MePh	Me	4	50	95	145
8	α-naphthyl ^b	Me	7	30	97	99
9	mesityl ^b	Me	16	44	99	369 ^c

^a 1-cyclohexenyl, ^b reaction run in toluene, ^c s = 389 in duplicate run

"The data in table underestimate catalyst reactivity because no special precautions were taken to exclude oxygen."

Vedejs, E.; Daugulis, O. *J. Am. Chem. Soc.* **1999**, *121*, 5813-5814.

Acylation Catalyzed by Chiral Phosphines

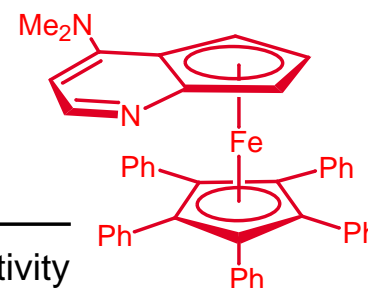
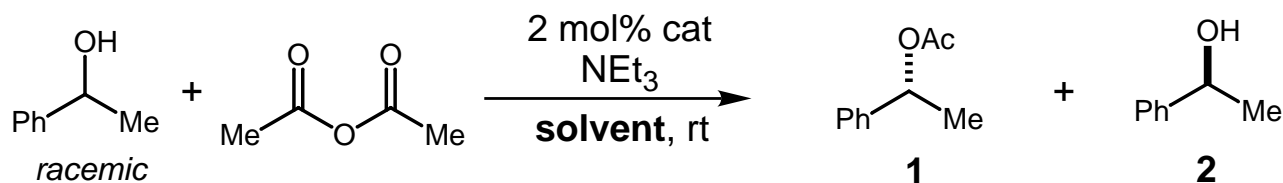


alcohol	time (h)	conv. (%)	%ee (2/1)	s	alcohol	time (h)	conv. (%)	%ee (S.M./prod)	s
 Ar = 4-Cl-Ph	12	55	78/63	10		14	50	89/88	52
	27	45	67/82	21		7	53	90/81	34*
	41	48	42/45	4		72	53	96/86	55*
	19	48	66/72	12		46	67	99/49	25*

* = rxn in heptane

Vedejs, E.; MacKay, J. *Org. Lett.* **2001**, 3, 535-536.

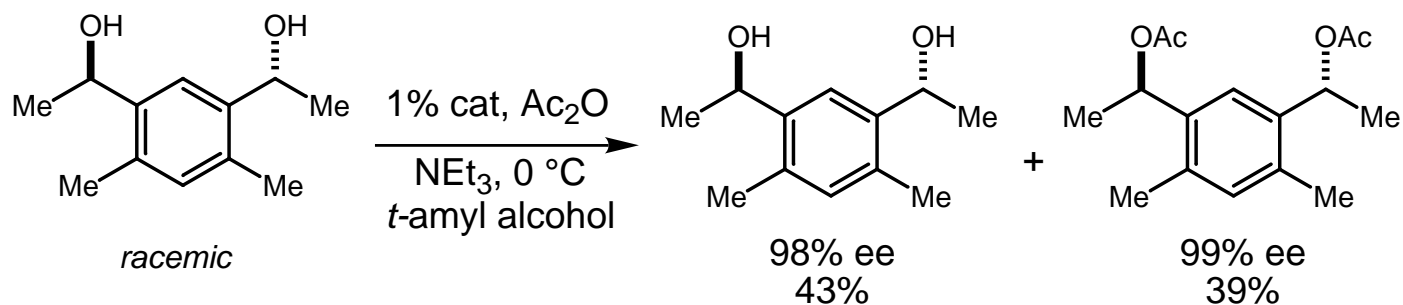
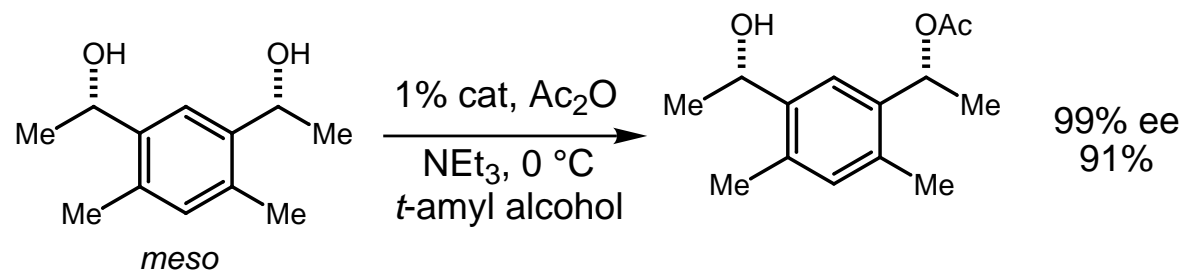
Acylation Catalyzed by Planar-Chiral DMAP Analogs



catalyst

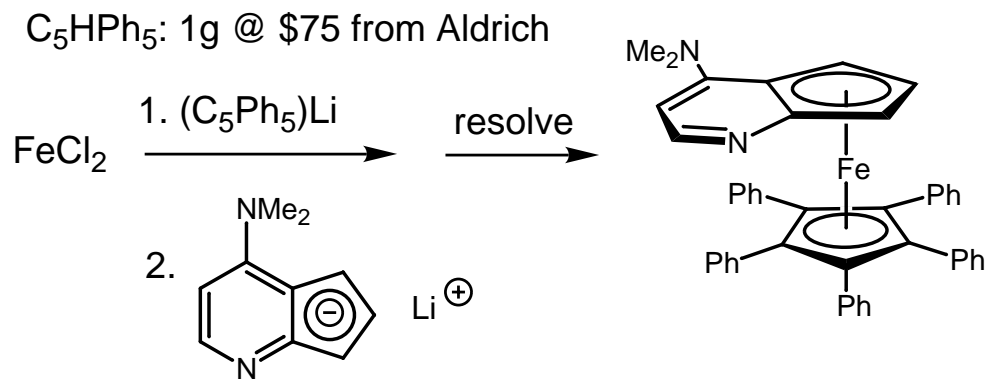
entry	solvent	% conv. after 1 h	selectivity	entry	solvent	% conv. after 1 h	selectivity
1	DMF	6	3.4	6	EtOAc	6	11
2	CH ₃ CN	10	3.6	7	toluene	13	11
3	CH ₂ Cl ₂	14	7.0	8	Et ₂ O	8	13
4	acetone	8	8.7	9	<i>t</i> -amyl alcohol	38	27 ←
5	THF	4	9.6				

Desymmetrizations:



Ruble, J. C.; Tweddell, J.; Fu, G. C. *J. Org. Chem.* **1998**, *63*,

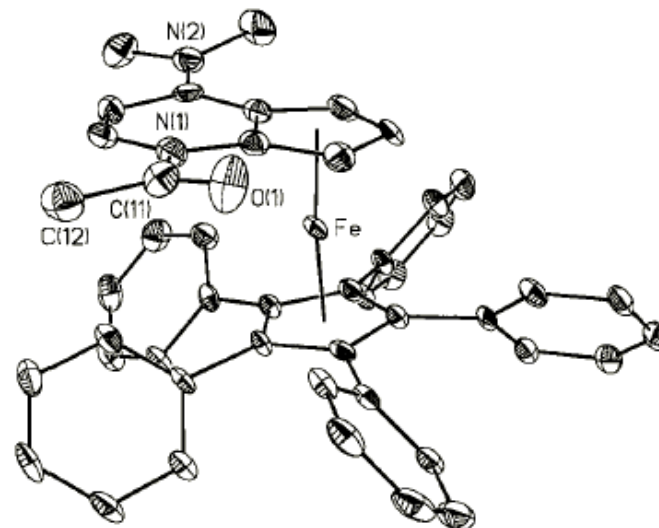
Synthesis of Planar-Chiral DMAP Analogs



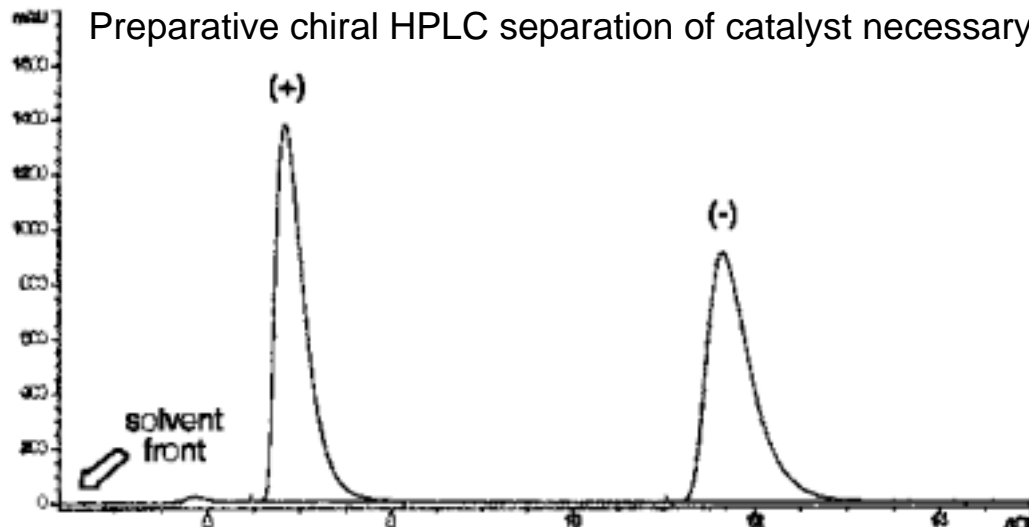
8 step synthesis (3% overall yield)

1. 1 equiv AcCl

2. $AgSbF_6$



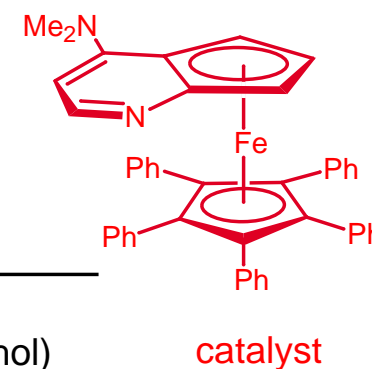
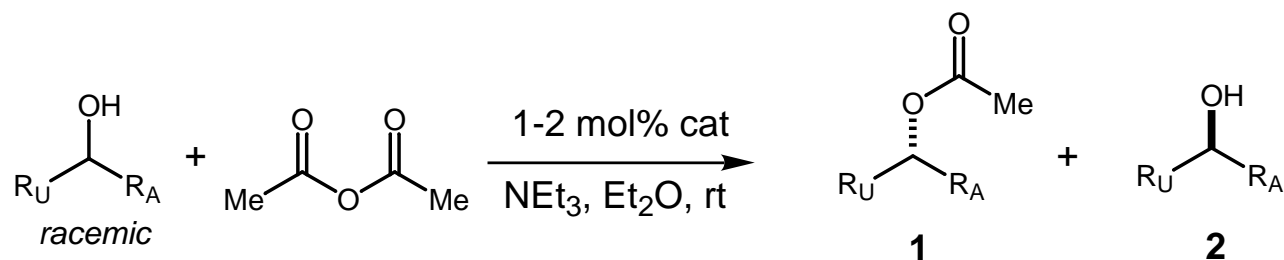
Preparative chiral HPLC separation of catalyst necessary



Catalyst prep: Ruble, J. C.; Fu, G. C. *J. Org. Chem.* **1996**, *61*, 7230-7231.

X-ray: Tao, B.; Ruble, J. C.; Hoic, D. A.; Fu, G. C. *J. Am. Chem. Soc.* **1999**, *121*, 5091-5092.

Acylation Catalyzed by Planar-Chiral DMAP Analogs



entry	R_U	R_A	%ee of 2	conversion (%)	selectivity ($\text{Et}_2\text{O}/t$ -amyl alcohol)
1	Ph	Me	95	62	14/43
2	Ph	Et	99	62	20/59
3	Ph	<i>i</i> -Pr	98	55	36/87
4	Ph	<i>t</i> -Bu	92	51	52/95
5	Ph	CH_2Cl	99	69	12/32

6	4-F-Ph	Me	99	64	18
7	4-OMe-Ph	Me	95	60	15

8	1-naphthyl	Me	99	63	22/65
9	cinnamyl	Me	99	67	14
10	α -Me-cinnamyl	Me	99	61	22

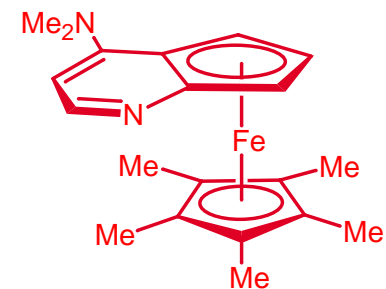
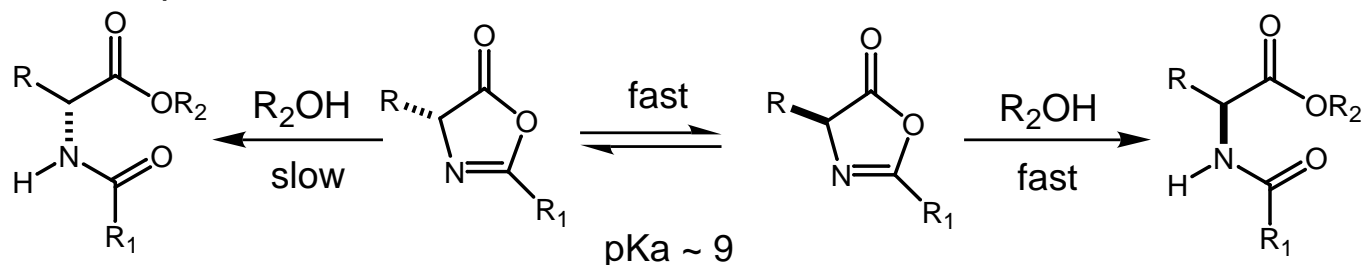
For a review on DMAP, see: Steglich et al. *Angew. Chem., Int. Ed. Engl.* **1978**, 17, 569-593

For a resolution of 2° alcohols using stoichiometric amounts of a chiral DMAP analog, see: Vedejs, E.; Chen, X. *J. Am. Soc. Chem.* **1996**, 118, 1809-1810 (s values 48-11 reported).

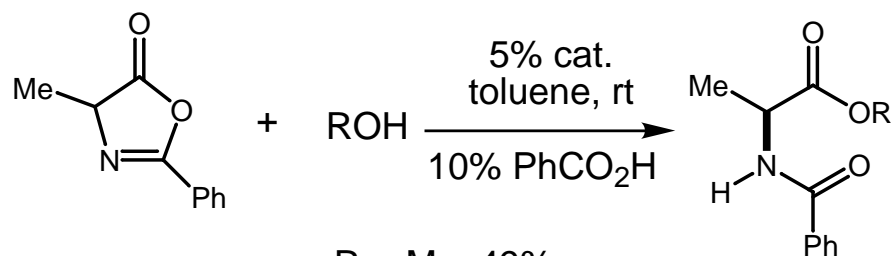
Ruble, J. C.; Latham, H. A.; Fu, G. C. *J. Am. Chem. Soc.* **1997**, 119, 1492-1493.

Dynamic Kinetic Resolutions of Azlactones with DMAP Analogs

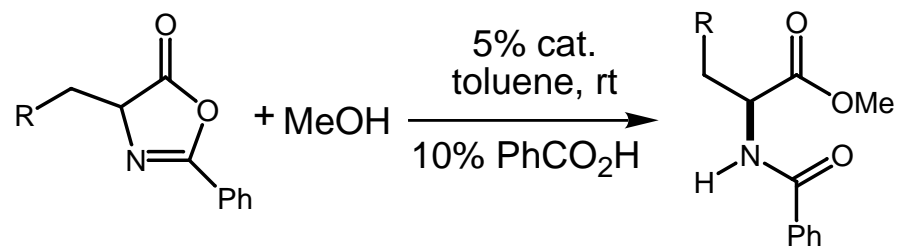
The concept



catalyst



R = Me, 49% ee
Et, 53% ee
i-Pr, 78% ee



entry	R	%ee	yield (%)
1	H	54	98
2	Me	44	94
3	CH=CH ₂	61	94
4	<i>i</i> -Pr	55	95
5	<i>c</i> -Hex	54	93
6	Ph	56	94
7	CH ₂ SMe	50	94

Solvent study identified toluene as optimal solvent

Reaction with *i*-PrOH too slow ($t_{1/2} \sim 1$ week)

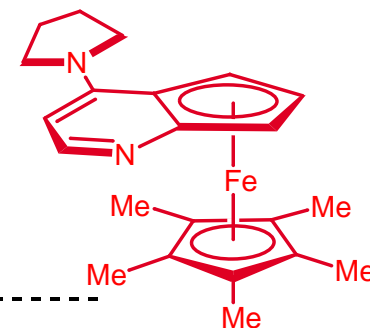
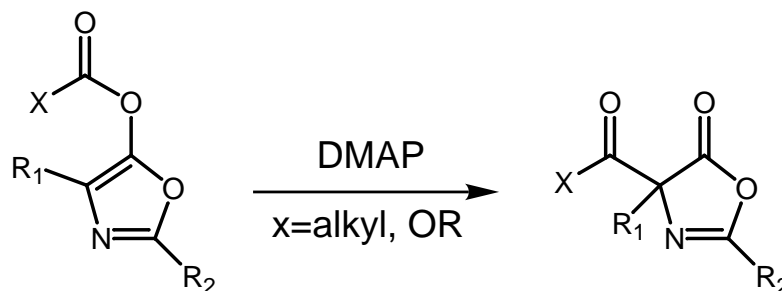
"We inadvertently discovered that the presence of benzoic acid leads to ring opening... at a faster rate."

Liang, J.; Ruble, J. C.; Fu, G. C. *J. Org. Chem.* **1998**, 63, 3154-3155.

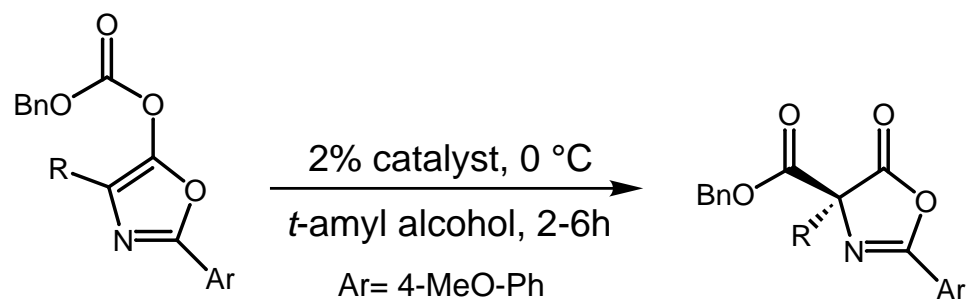
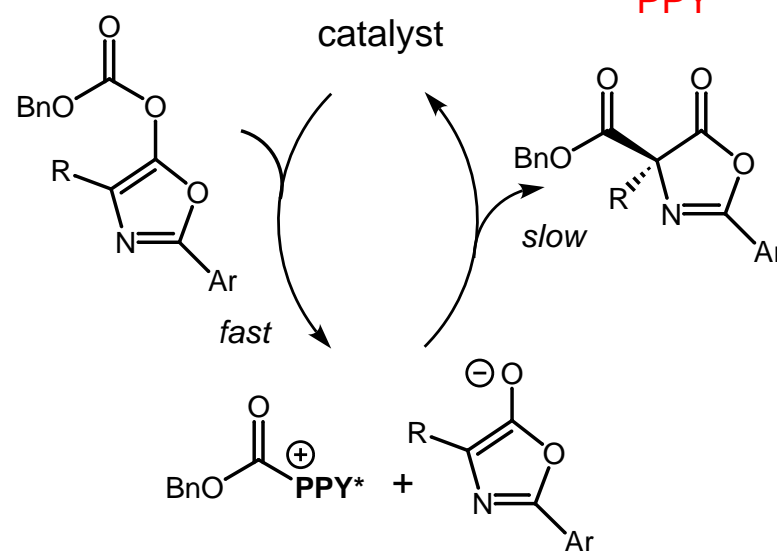
For a review on dynamic kinetic resolutions, see: Stecher, H.; Faber, K. *Synthesis* **1997**, 1-69.

Rearrangements of O-Acylated Azlactones

Steglich 1970:



Proposed Mechanism

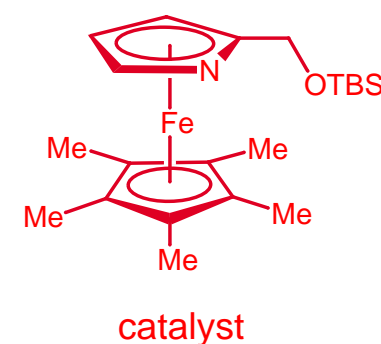
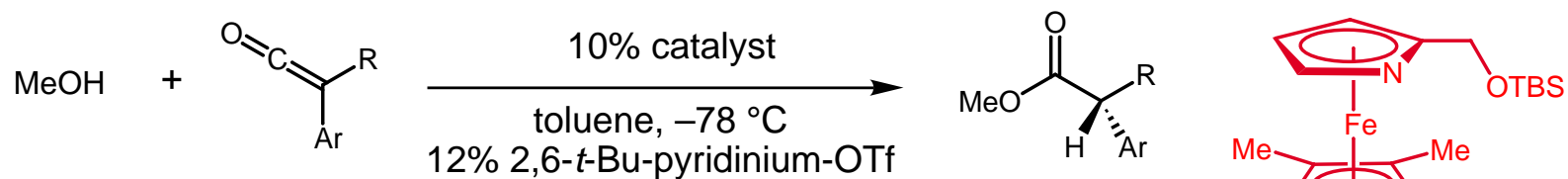


entry	R	%ee	yield (%)
1	Me	91	94
2	Et	90	93
3	CH ₂ Ph	90	93
4	allyl	91	93
5	CH ₂ CHMe ₂	92	95
6	CH ₂ CH ₂ SMe	88	94

resting state

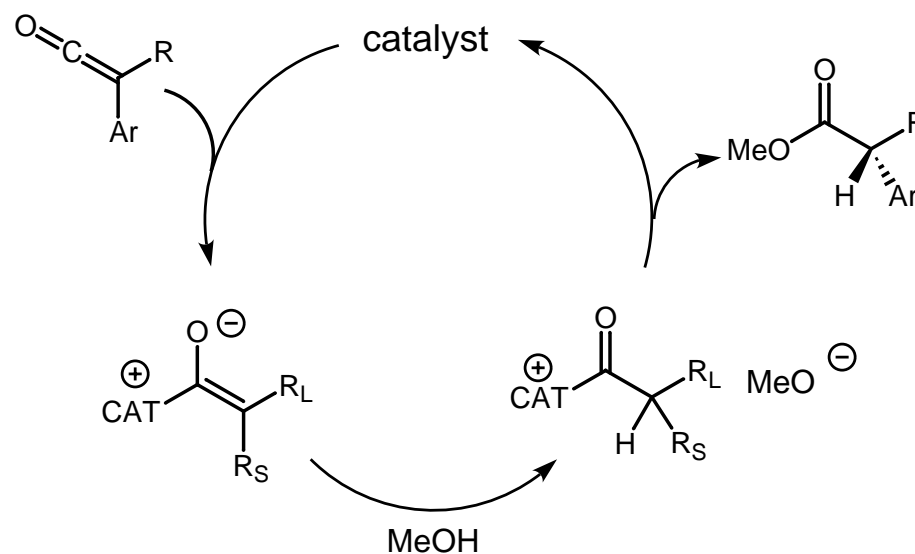
zero order in substrate
Crossover experiments provide
evidence of ion pair

Enantioselective Additions of Alcohols to Ketenes



entry	substrate	%ee	yield (%)
1	R = Me 	77	87
2	R = Et 	68	92
3		77	88
4		74	97

Proposed mechanism:

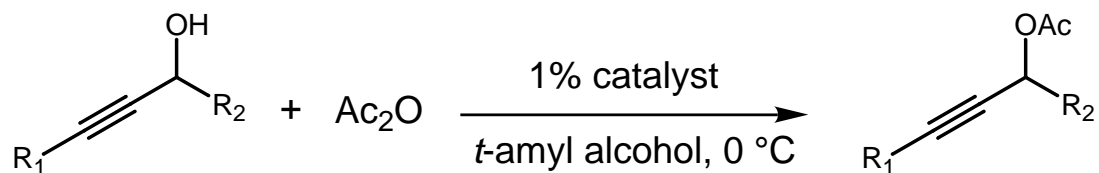


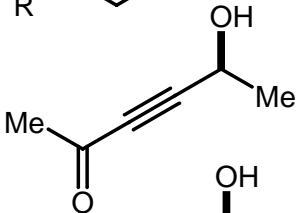
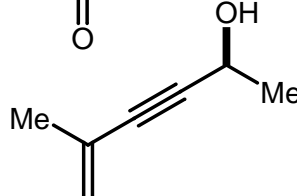
no nonlinear effects

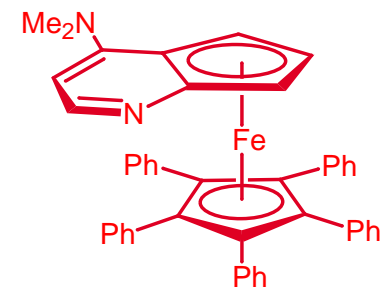
reaction has KIE of 3.2
(MeOH vs. MeOD)

Hodous, B. L.; Ruble, J. C.; Fu, G. C. *J. Am. Chem. Soc.* **1999**, 121, 2637-2638.

Kinetic Resolutions of Propargylic Alcohols



entry	unreacted ROH (major enantiomer)	s (%ee of unreacted ROH)
1	R = Me	20 (96%ee @ 58% conv.)
2	Et	18 (94%ee @ 58% conv.)
3	<i>i</i> -Pr	11 (93%ee @ 63% conv.)
4	<i>t</i> -Bu	3.8 (95%ee @ 86% conv.)
5	R = OMe	14 (94%ee @ 60% conv.)
6	CF ₃	10 (99%ee @ 71% conv.)
7	F	13 (97%ee @ 65% conv.)
8		12 (95%ee @ 64% conv.)
9		7.9 (95%ee @ 69% conv.)



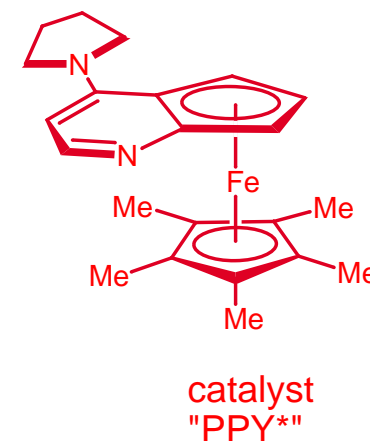
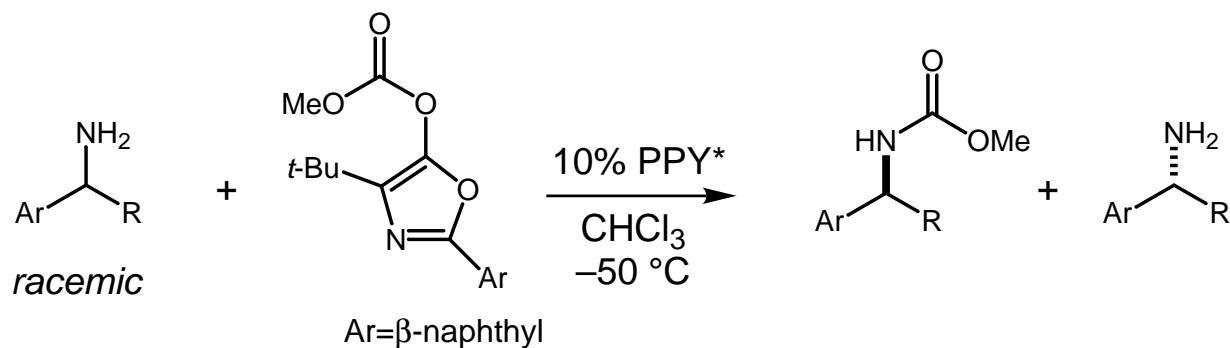
catalyst

acetic anhydride optimal
anhydride

added R₃N works, but
omission of base gives
highest s value

Tao, B.; Ruble, J. C.; Hoic, D. A.; Fu, G. C. *J. Am. Chem. Soc.* **1999**, 121, 5091-5092.

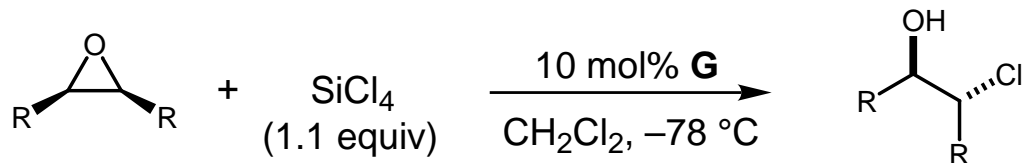
Kinetic Resolutions of Amines



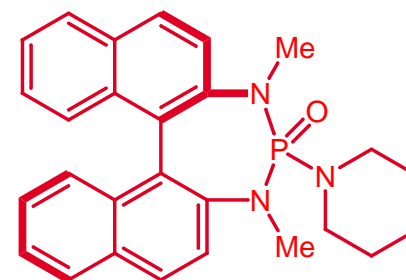
entry	amine	s	entry	amine	s
1		12	5		13
2		27	6		22
3		16	7		16
4		11	8		11

Aria, S.; Bellemin-Lapponnaz, S.; Fu, G. C. *Angew. Chem., Int. Ed. Engl.* **2001**, *40*, 234-236.

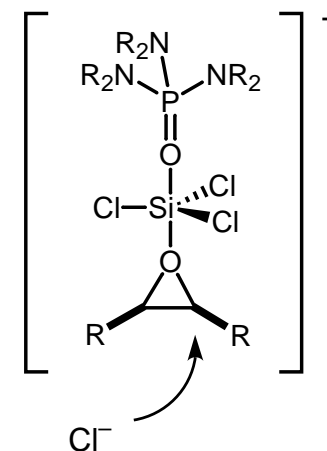
Asymmetric Ring Opening of meso-Epoxides



entry	substrate	time (h)	%ee	yield (%)
1		0.3	6	87
2		0.3	50	90
3		132	0	95
4		3	84	94
5		4	71	95



(R)-G

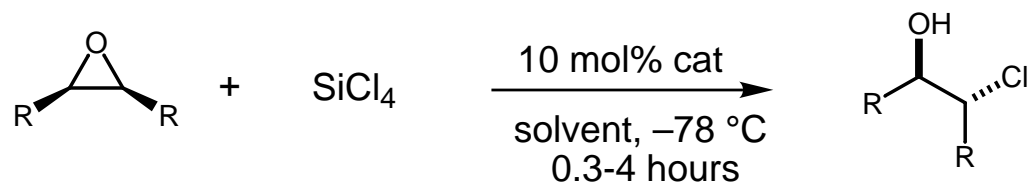


proposed transition state

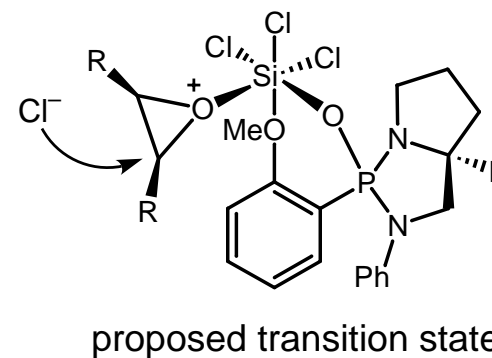
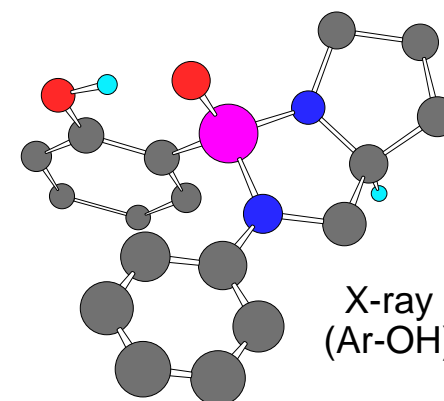
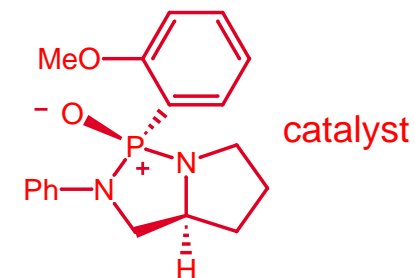
"The origin of asymmetric induction is obscure at this time."

Denmark, S. E.; Barsanti, P. A.; Wong, K.-T.; Stavenger, R. A. *J. Org. Chem.* **1998**, 63, 2428-2429.

Asymmetric Ring Opening of meso-Epoxydes

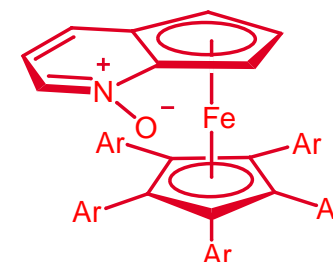
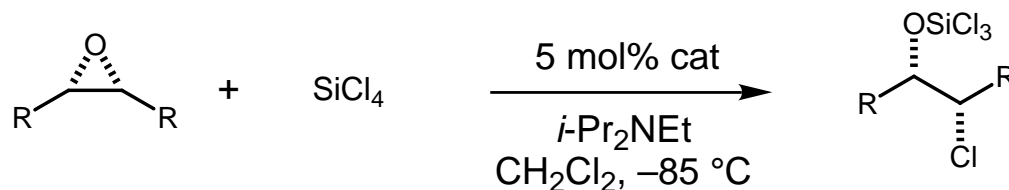


entry	substrate	solvent	%ee	yield (%)	config
1		THF	23	68	(1 <i>R</i> ,2 <i>R</i>)
2		CH ₂ Cl ₂	48	41	(1 <i>R</i> ,2 <i>R</i>)
3		CH ₂ Cl ₂	62	85	(1 <i>R</i> ,2 <i>R</i>)
4		CH ₂ Cl ₂	98	79	(1 <i>R</i> ,2 <i>R</i>)
5		CH ₂ Cl ₂	99	77	(1 <i>R</i> ,2 <i>R</i>)
6		THF	92	68	(1 <i>R</i> ,2 <i>R</i>)
7		CH ₂ Cl ₂	94	78	(2 <i>S</i> ,3 <i>S</i>)



Buono et al. *Angew. Chem. Int. Ed. Engl.* **2000**, 39, 2554-2557.

Asymmetric Ring Opening of meso-Epoxides

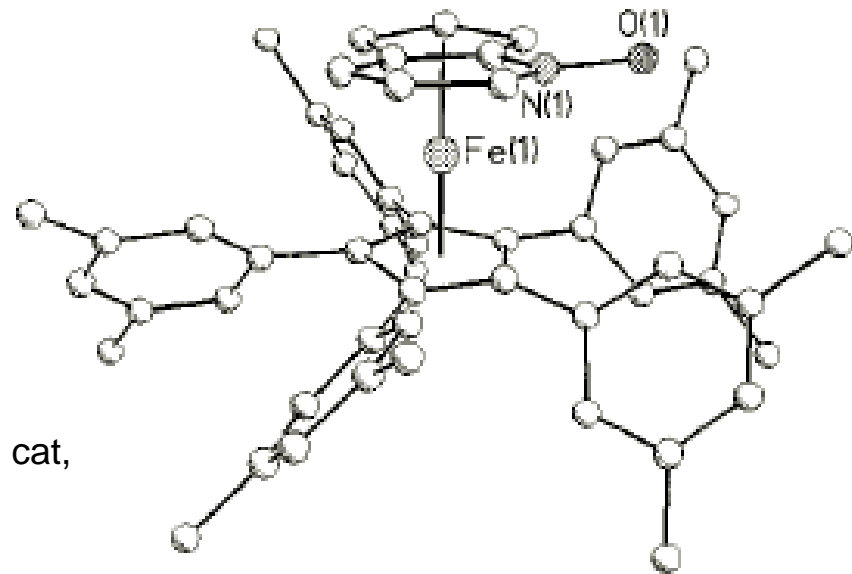


catalyst
Ar = 3,5-Me₂C₆H₃

entry	R	yield (%)	ee (%)
1	Ph	88	94
2	4-F-Ph	97	91
3	4-Me-Ph	94	93
4	4-CF ₃ -Ph	93	98
5	2-naphthyl	84	94
6	CH ₂ OBn	91	50

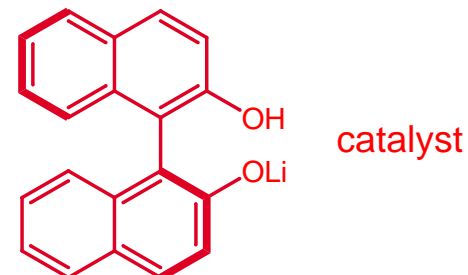
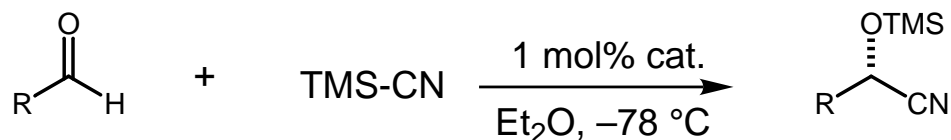
Increased steric demand of catalyst increases enantioselectivity dramatically: Ar = Ph, 60% ee vs. Ar = 3,5-Me₂C₆H₃, 94% ee for opening of *cis*-stilbene oxide

1. Positive nonlinear effect
2. Zero-order in SiCl₄ and *i*-Pr₂NEt
3. ¹H and ²⁹Si NMR show interaction between SiCl₄ and cat, but not between SiCl₄ and epoxide or *i*-Pr₂NEt

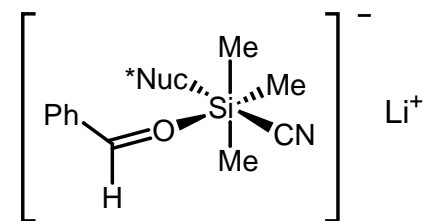


Tao, B.; Lo, M. M.-C.; Fu, G. C. *J. Am. Chem. Soc.* **2001**, 123, 353-354.

Asymmetric Addition of TMS-CN to Aldehydes



entry	R	%ee	yield (%)	time
1	Ph	56	96	5 min
2	4-Me-Ph	59	95	15 min
3	3-Me-Ph	55	93	40 min
4	2-Me-Ph	5	99	40 min
5	4-MeO-Ph	54	95	68 h
6	3-MeO-Ph	52	89	30 min
7	2-MeO-Ph	47	92	8 h
8	4-NO ₂ -Ph	–	decomp	–
9	4-Cl-Ph	43	38	2 h
10	4-CF ₃ Ph	0	73	<5 min
11	2-naphthyl	6	93	24 h
12	cinnamaldehyde	8	95	3.5 h
13	<i>n</i> -hexyl	9	82	<5 min
14	<i>c</i> -hexyl	30	94	20 min
15	<i>t</i> -Bu	23	62	5 min



proposed intermediate

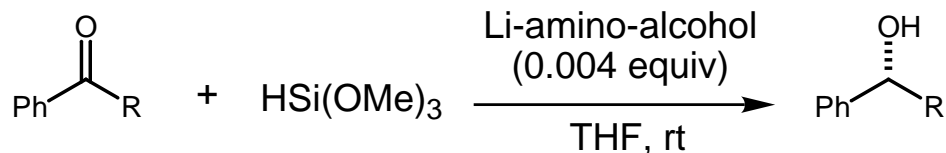
mono-lithio salt superior to di-lithio

Na, K, or Mg cation catalyzed reaction, but all were racemic

Mono-lithio salt of (*R,R*)-(-)-salen also competent catalyst, but enantioselectivity not much improved

Holmes, I. P.; Kagan, H. B. *Tetrahedron Lett.* **2000**, 41, 7453-7456.

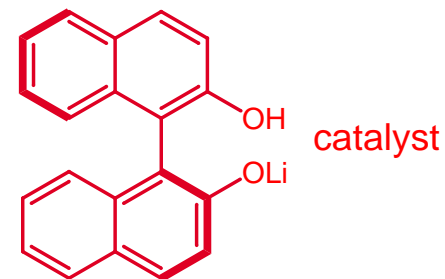
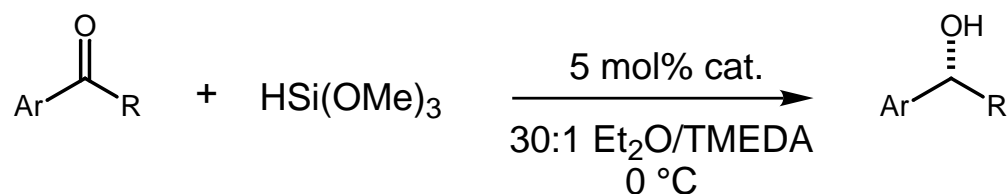
Asymmetric Catalytic Reduction of Ketones



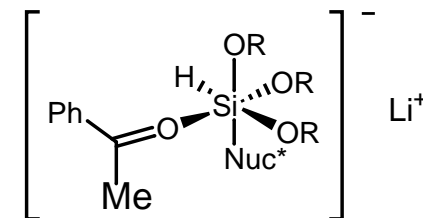
Note: $(\text{MeO})_3\text{SiH}$ vapors cause blindness: $bp = 95\text{ }^\circ\text{C}$

entry	R	amino-alcohol	yield (%)	%ee
1	Me	(S)-Phenylalaninol	75	49
2	Me	(S)-Prolinol	89	52
3	Et	(S)-Phenylalaninol	88	32

Hosomi et al. *Tetrahedron Lett.* **1988**, 29, 89-92.



entry	Ar	R	yield (%)	%ee
1	Ph	Me	80	61 (<i>R</i>)
2	1-Naphthyl	Me	67	77 (<i>R</i>)
3	Ph	<i>i</i> -Bu	60	81 (<i>R</i>)
4	(<i>E</i>)-CH=CHPh	Me	91	57 (<i>S</i>)
5		–	39	93 (<i>R</i>)



proposed intermediate

Schiffers, R.; Kagan, H. B. *Synlett* **1997**, 1175-1178.

Conclusions

Allylations with allyl and crotyl trichlorosilanes catalyzed by chiral Lewis bases provide high enantioselectivities and yields for unsaturated aldehydes.

Aldol reactions of trichloro enolsilanes and aldehydes is exceptionally sensitive to the structures of the reacting partners and to small changes in catalyst structure.

Kinetic resolutions of alcohols with chiral phosphines generally have excellent selectivity values and an increasing family of successful substrates from which to choose.

Planar-chiral DMAP analogs are good catalysts for kinetic resolutions of secondary alcohols, and amines as well as ketene additions, azlactone dynamic kinetic resolutions and the rearrangement of *O*-acylated azlactones.

Lewis base-catalyzed additions of SiCl_4 to *meso*-epoxides is highly substrate dependent, but excellent enantioselectivities have been observed.

Lewis base-catalyzed reductions have yet to be fully developed into a general reaction, but enantioselectivities are promising.

While the selectivities of the reactions presented here are excellent in some cases, there remains the challenge to improve the existing reactions through a better understanding of the fundamental transformations— the origins of asymmetric induction in many cases are not clear.