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

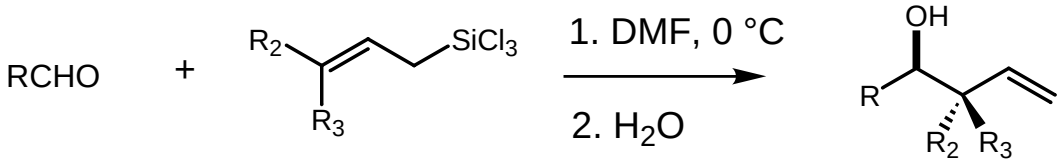
Karl Scheidt
Evans Group Friday Seminar
March 9, 2001

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

Genreal Reaction:

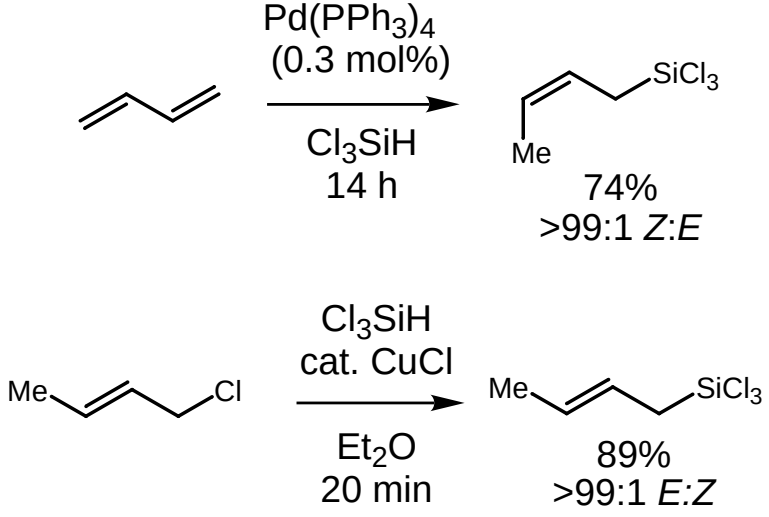


1:1 CH_2Cl_2/DMF as solvent provides product in 97% yield in 4h

RCHO = PhCHO, cinnamaldehyde, hydrocinnamaldehyde, cyclohexanecarboxaldehyde

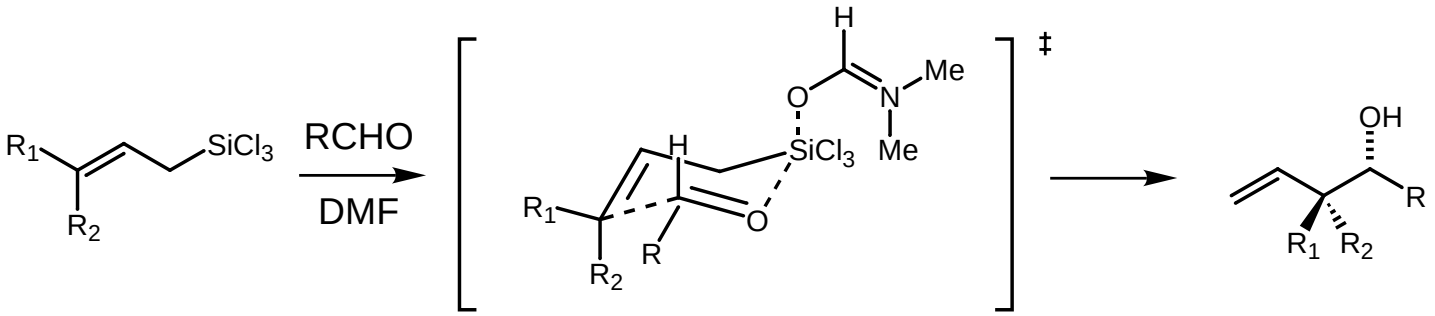
^{29}Si NMR Chemical Shifts of (*Z*)-Crotyltrichlorosilane in Various Solvents

solvent	chemical shift (ppm)
$CDCl_3$	+8.0
CD_3CN	+8.6
C_6D_6	+7.9
THF-d_8	+8.5
DMF-d_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

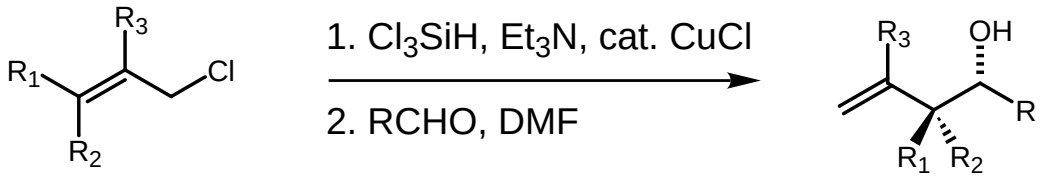


E crotyltrichlorosilane gives >99:1 anti product

Z crotyltricholorsilane gives >99:1 syn product

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

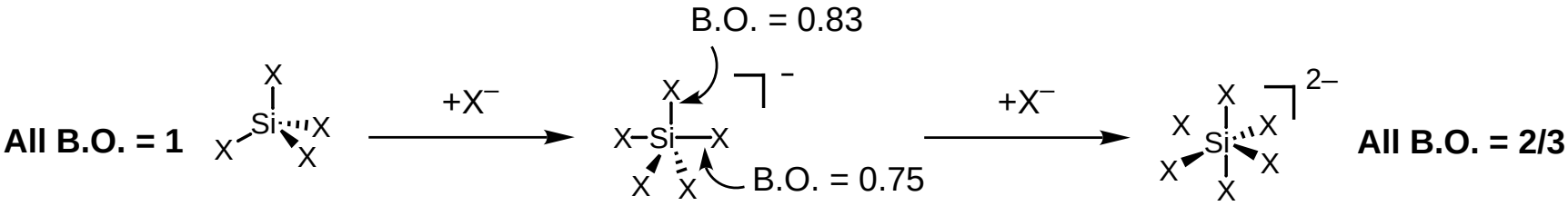
One-Pot Procedure from Allylic chloride:



>80% yields
>95:5 dr

Why are pentacoordinate compounds more electrophilic?

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



Formal charges:
X = 0
Si = 0

Formal charges:
X_{ax} = –0.25,
X_{eq} = –0.17,
Si = 0

Formal charges:
X = –0.33
Si = 0

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_3F	+1.10	–0.15(H), –0.67(F)
$SiH_3F_2^-$	+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)

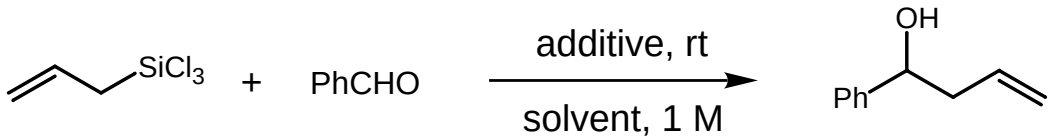
This phenomenon is termed the "spillover effect", and is widely seen in donor-acceptor complexes.

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:

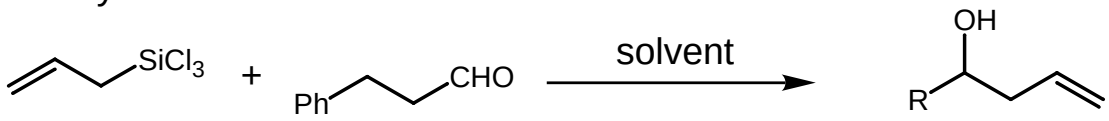


entry	additive (equiv)	solvent	$t_{1/2}$ (min)	conversion (time)	yield
1	DMF (1)	C_6D_6	nd	83 (70 h)	nd
2	HMPA (1)	C_6D_6	18	nd	77
3	HMPA (1)	$CDCl_3$	nd	63 (4 min)	85
4	HMPA (1)	CD_3CN	nd	63 (4 min)	86
5	HMPA (0.1)	C_6D_6	529	60 (46 h)	nd
6	HMPA (0.1)	THF-d_8	350	80 (124 h)	nd

HMPA superior to DMF →

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

In contrast to Kobayashi's observations:

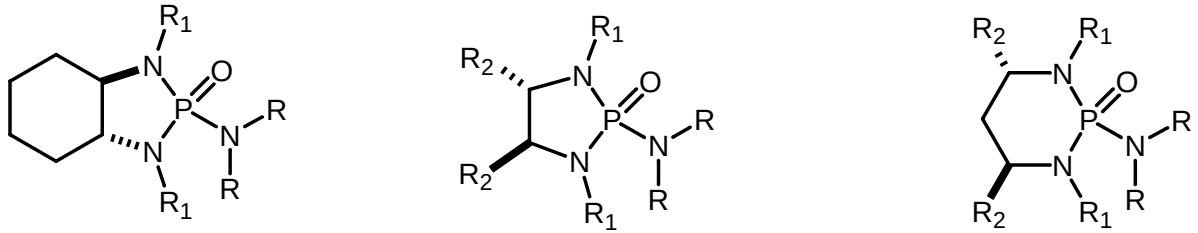


DMF: 2 h, 90% yield
HMPA: 3 h, 28% yield

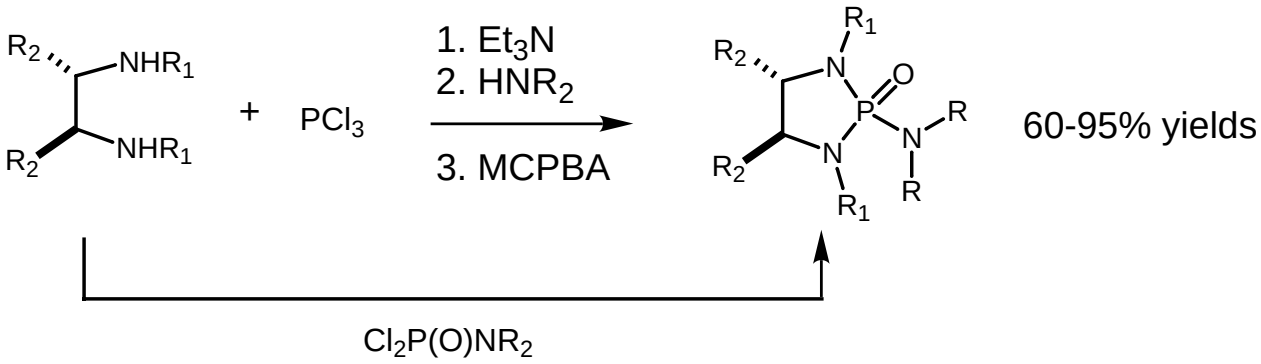
Denmark, S. E.; Coe, D. M.; Pratt, N. E.; Griedel, B. D. *J. Org. Chem.* **1994**, *59*, 6161-6163.

Development of Asymmetric Allylation: Synthesis of Chiral Phosphoramides

Catalyst structures screened be Denmark:



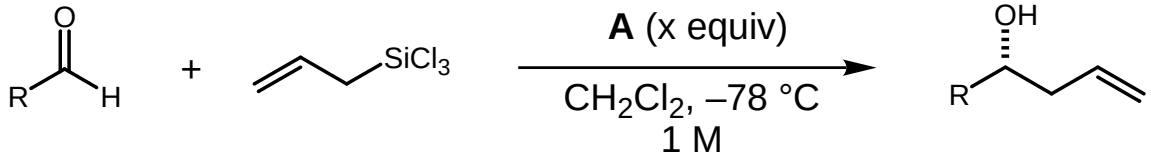
General synthesis of chiral phosphoramides:

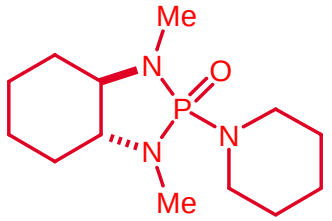


Syntheses of chiral phosphoramides: Denmark et al. *J. Org. Chem.* **1999**, *64*, 1958-1967. Hanessian et al. *J. Am. Chem. Soc.* **1984**, *106*, 5754-5757; Normant et al. *Synthesis* **1988**, 255-257.

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

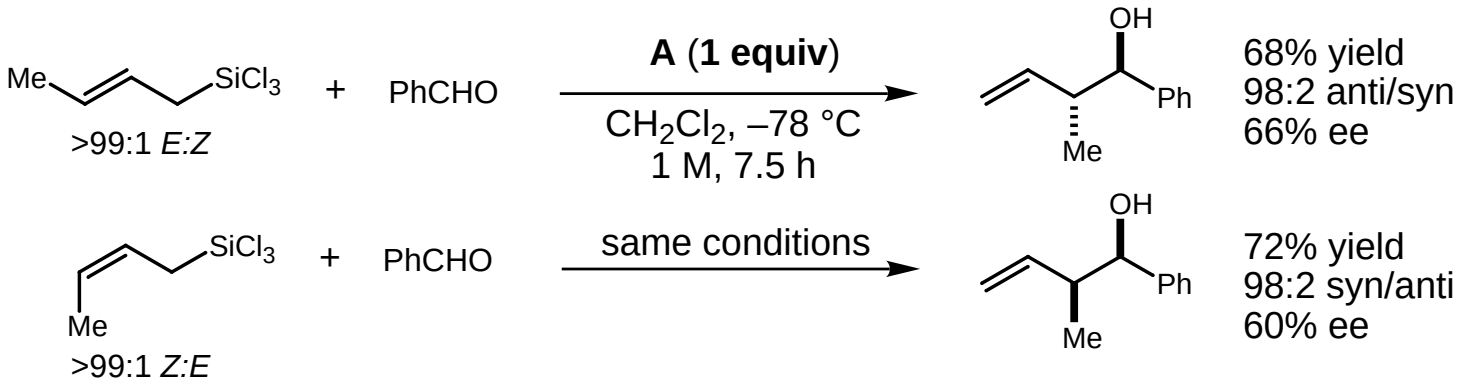
Asymmetric Allylation with Chiral Phosphoramides





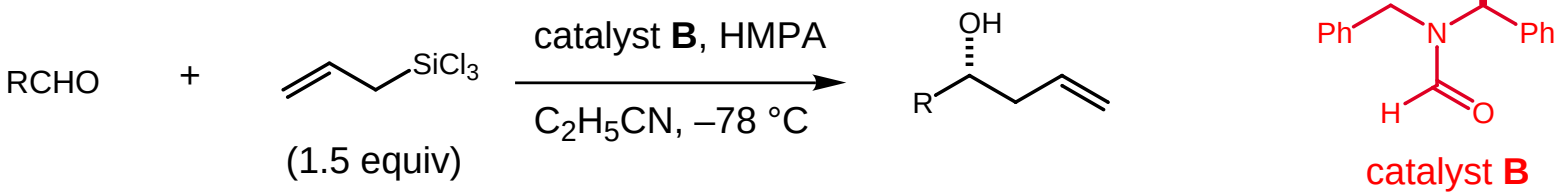
A

entry	R	equiv **A**	time	yield	% ee (config)
1	Ph	1.0	6 h	81	60 (*R*)
2	Ph	0.5	24 h	78	57 (*R*)
3	Ph	0.1	24 h	40	53 (*R*)
4	2-MeC_6H_4	1.0	6 h	81	65 (*R*)
5	4-NO_2-C_6H_4	1.0	6 h	76	21 (*R*)
6	4-$MeOC_6H_4$	1.0	6 h	80	50 (*R*)
7	4-NMe_2-C_6H_4	1.0	6 h	69	33 (*R*)
8	(*E*)-PhCH=CH	1.0	6 h	67	38 (*R*)



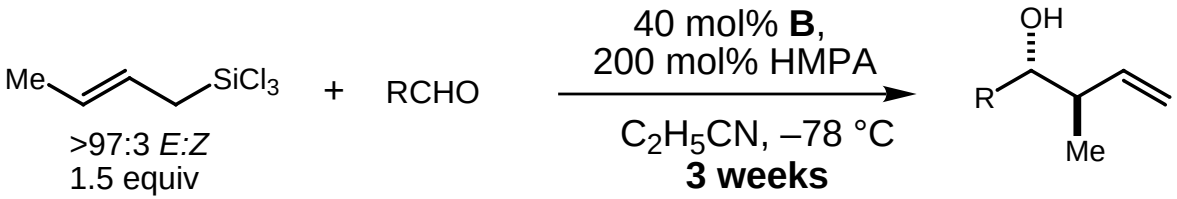
Denmark, S. E.; Coe, D. M.; Pratt, N. E.; Griedel, B. D. *J. Org. Chem.* **1994**, *59*, 6161-6163.

Asymmetric Allylation with Chiral Formamides



entry	R	**B** (mol%)	HMPA (mol%)	time (**weeks**)	yield (%)	% ee (config)
1	cyclopentyl	20	100	2	72	91
2	$PhCH_2CH_2$	20	100	3	84	95 (*S*)
3	$(C_2H_5)_2CH$	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

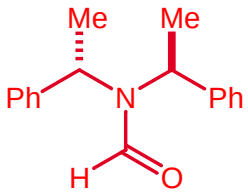
catalyst recovered in >95% by chromatography



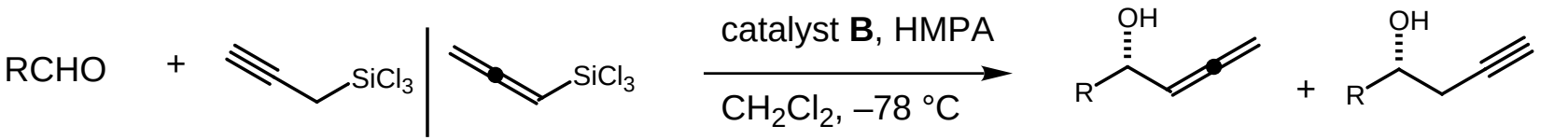
R = cyclohexyl: 92% yield, >99:1 anti/syn, 98% ee
R = $PhCH_2CH_2$: 97% yield, >99:1 anti/syn, 94% ee

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

Asymmetric Allenylation with Chiral Formamides



catalyst **B**



(3:1)

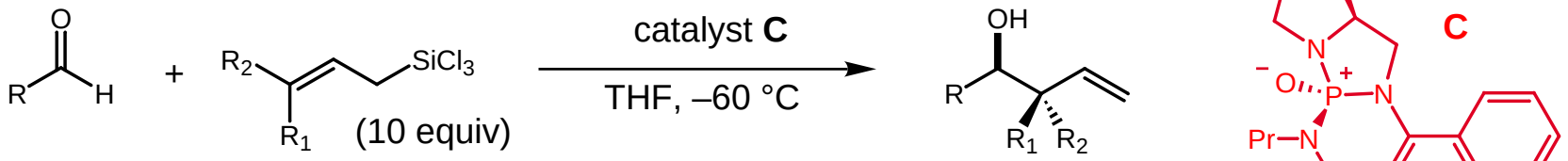
(1.5 equiv)

1 + **2**

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	$PhCH_2CH_2$	20	100	14	71	99/1	79
5	$(C_2H_5)_2CH$	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.

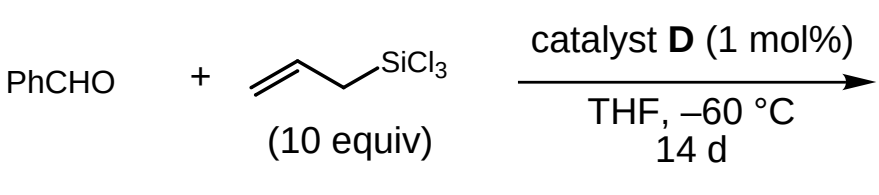
Catalytic Asymmetric Allylation with Chiral Phosphoramides

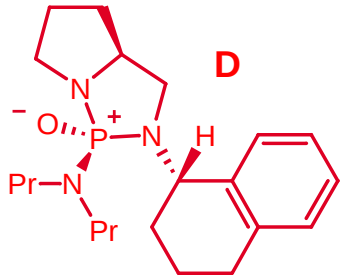


3 $R_1 = R_2 = H$
(*Z*)-**4** R_1 = Me, $R_2 = H$
(*E*)-**4** $R_1 = H$, R_2 = Me

entry	R	mol% **C**	silane	time (h)	yield (%)	syn/anti	% ee (config)
1	Ph	10	**3**	168	83	–	88 (*S*)[a]
2	2-MeC_6H_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_6H_4	20	(*Z*)-**4**	120	78	99/1	83
6	4-*t*-BuC_6H_4	20	(*Z*)-**4**	120	72	95/5	82

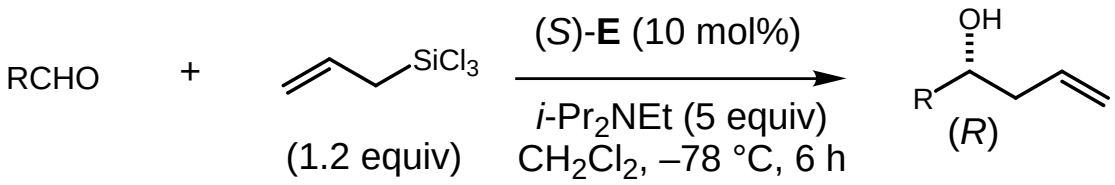
[a] Reaction run @ –78 °C

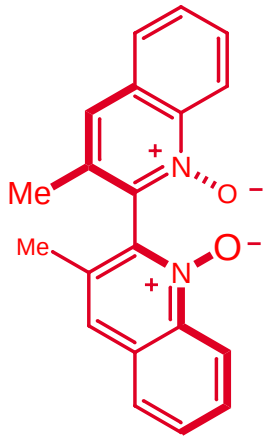




Iseki et al. *Tetrahedron Lett.* **1996**, *37*, 5149-5150.
Iseki et al. *Tetrahedron* **1997**, *53*, 3513-3526.

Catalytic Asymmetric Allylation with Pyridine N-Oxides





(*S*)-**E**

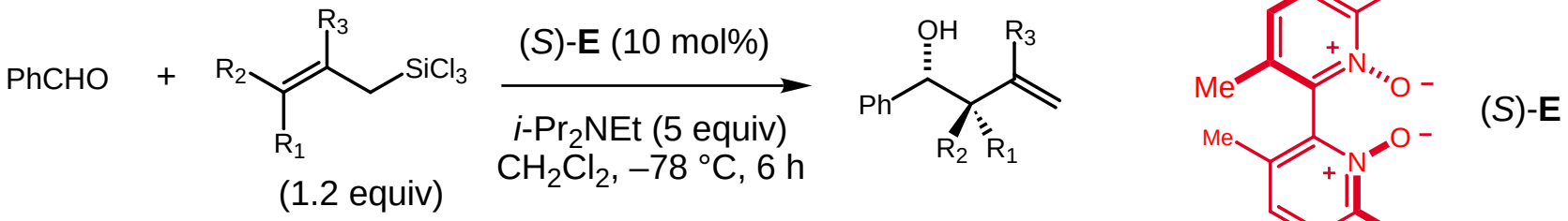
entry	R	yield (%)	ee%
1	Ph	85	88
2	4-$MeOC_6H_4$	91	92
3	4-CF_3-C_6H_4	71	71
4	2-MeC_6H_4	70	90
5	1-naphthyl	68	88
6	(*E*)-$C_7H_{15}CH$=CH	74	81
7	(*E*)-PhCH=CH	87	80
8	$PhCH_2CH_2$	30	7[a]
9	*c*-Hex	27	28[a]

[a] Provided (*S*)-homoallylic alcohol

i-Pr_2NEt only amine that accelerates productive reaction- most likely promotes turnover since it does not influence enantioselection.

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

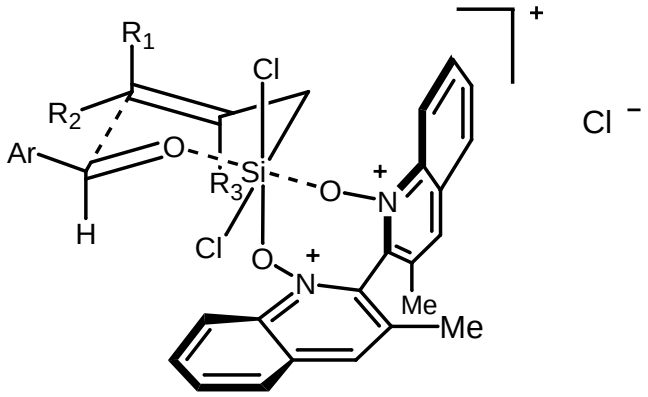
Catalytic Asymmetric Allylation with Pyridine N-Oxides



(*S*)-**E**

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

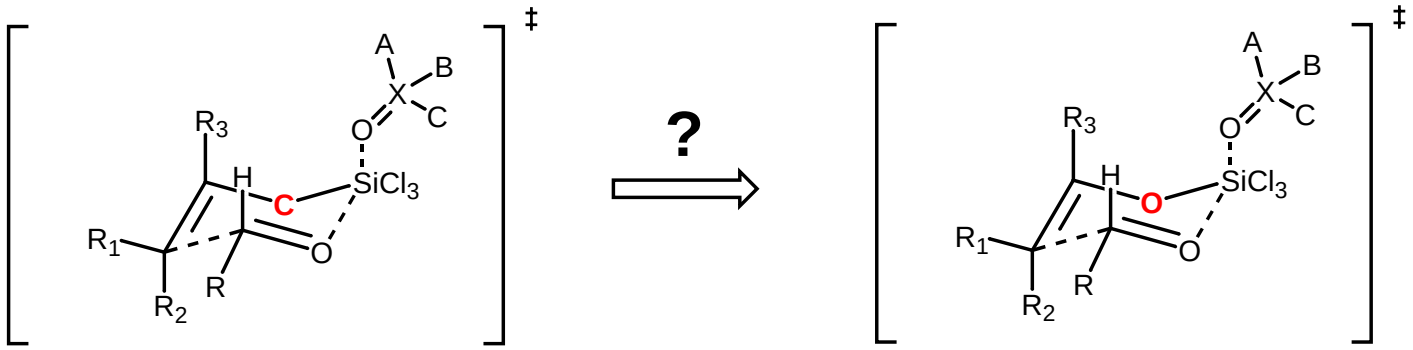
proposed transition state



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

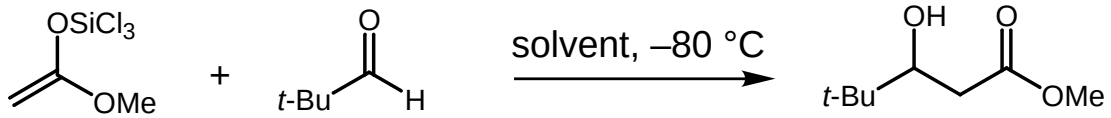
"Inventing" a New Type of Aldol Reaction

"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.

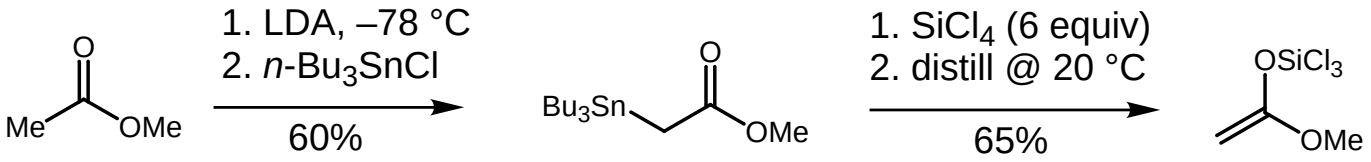


entry	solvent	promoter (equiv)	conversion	time (min)
1	toluene-d_8	none	18	120
2	CD_2Cl_2	none	50	120
3	THF-d_8	none	69	120
4	CD_2Cl_2	HMPA (0.1)	100	<3

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

Trichlorosilyl Enolates: Preparation

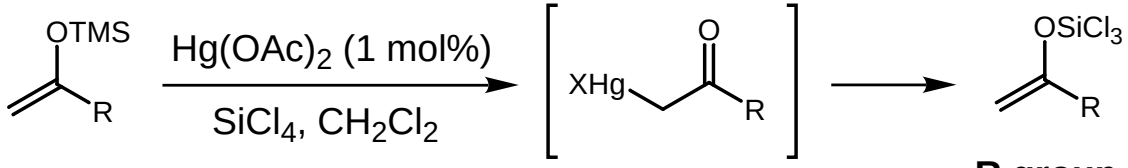
1st generation synthesis:



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:



>60% yield for most substrates

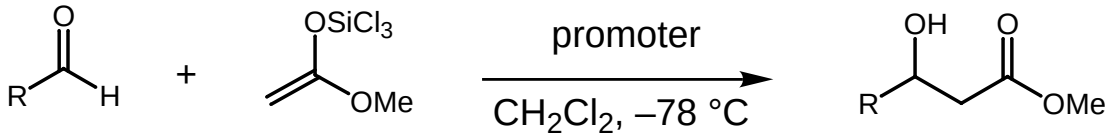
Denmark et al. *J. Org. Chem.* **1998**, *63*, 9517-9523.

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

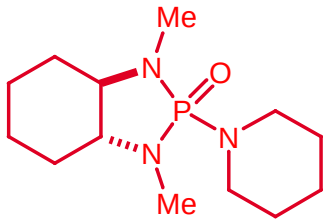
R group

i-Pr
n-Bu
i-Bu
t-Bu
TBSO-CH_2
$CH_2C{\equiv}H$
Ph

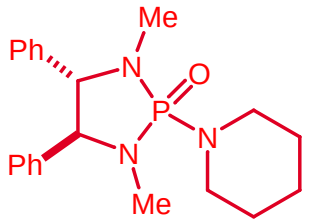
Asymmetric Aldol Reaction with Trichlorosilyl Enolates



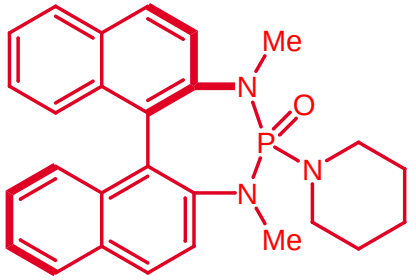
entry	RCHO	promoter (equiv)	config	ee%	yield
1	PhCHO	**A** (0.1)	(*R*)	20	88
2	PhCHO	**F** (0.1)	(*S*)	33	87
3	PhCHO	**G** (0.1)	(*S*)	23	91
4	PhCHO	**F** (1.0)	(*S*)	**53**	84
5	*t*-BuCHO	**A** (0.1)	(*R*)	26	76
6	*t*-BuCHO	**F** (0.1)	(*S*)	40	78
7	*t*-BuCHO	**G** (0.1)	(*S*)	49	75
8	*t*-BuCHO	**G** (1.0)	(*S*)	**62**	77



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



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

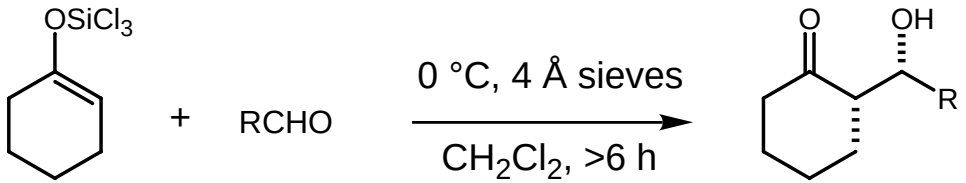


(*R*)-**G**

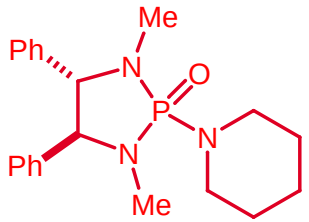
Denmark, S. E.; Winter, S. B. D.; Su, X.; Wong, K.-T. *J. Am. Chem. Soc.* **1996**, *118*, 7404-7405.

Aldol Reactions with Trichlorosilyl Enolsilanes

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

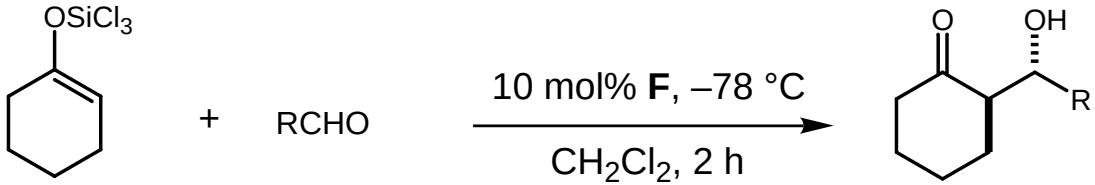


>80% yield



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

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



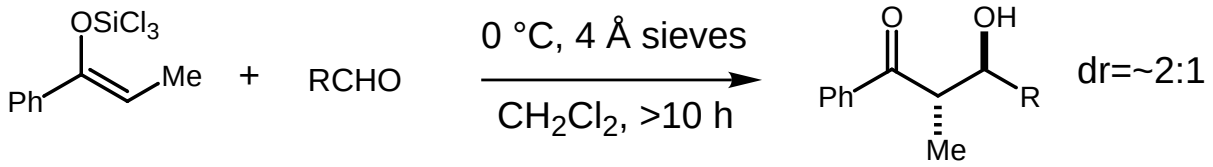
entry	R	syn/anti[a]	ee% (anti)	yield
1	Ph	1:61	93	95
2	1-naphthyl	<1:99	97	94
3	(*E*)-PhCH=CH	<1:99	88	94
4	(*E*)-PhCH=C(Me)	<1:99	92	98
5	PhC≡C-	1:5.3	82	90

[a] Determined by ^{1}H NMR (400 MHz) analysis (?)

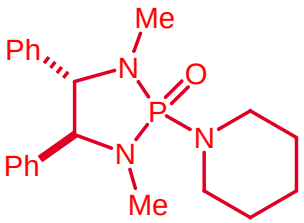
Denmark, S. E.; Wong, K.-T.; Stavenger, R. A. *J. Am. Chem. Soc.* **1997**, *119*, 2333-2334.

Aldol Reactions with PropiophenoneTrichlorosilyl Enolsilanes

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

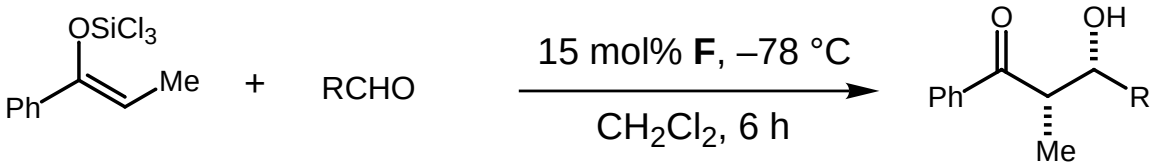


dr=~2:1



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

*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	(*E*)-PhCH=CH	9.4:1	92	97
5	(*E*)-MeCH=CH	7:1	91	94
6	PhC≡C	1:3.5	58	92

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

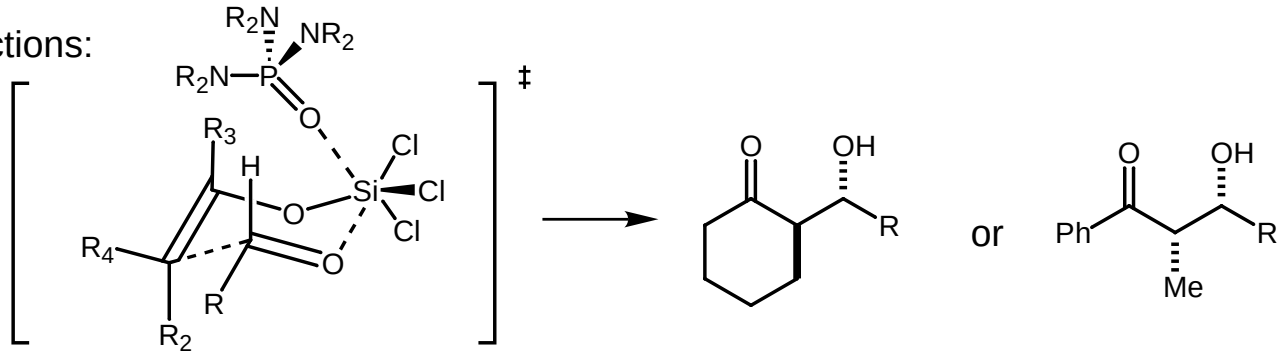
Denmark, S. E.; Wong, K.-T.; Stavenger, R. A. *J. Am. Chem. Soc.* **1997**, *119*, 2333-2334.

Early Analysis of Trichlorosilyl Enolate Aldol Reactions

Uncatalyzed reactions:

boat-like transition states predominate– pentacoordinate siliconates invoked

Catalyzed reactions:



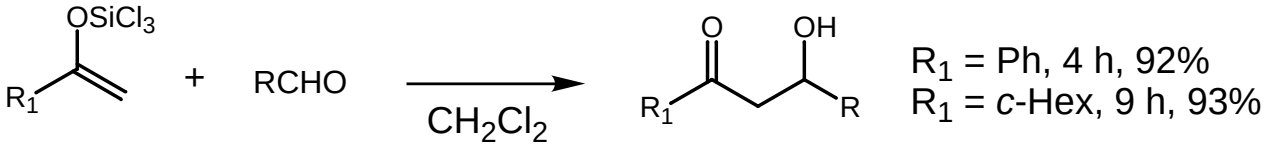
chair-like transition states predominate– octahedral siliconates invoked

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

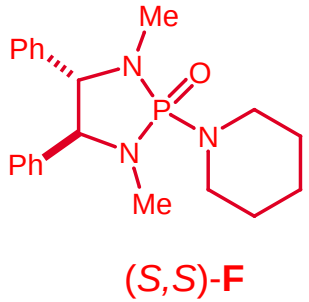
Denmark et al. *J. Am. Chem. Soc.* **1997**, *119*, 2333-2334.

Lewis Base-Catalyzed Methyl Ketone Aldol Reactions

Uncatalyzed reaction:

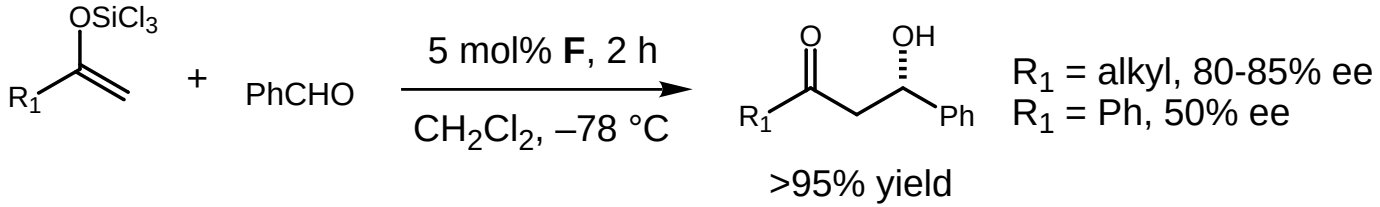


R_1 = Ph, 4 h, 92%
R_1 = *c*-Hex, 9 h, 93%



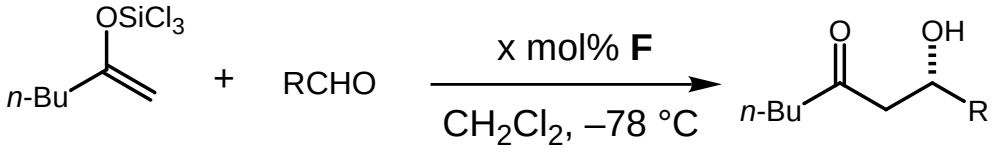
(*S,S*)-**F**

Catalyzed reaction:



R_1 = alkyl, 80-85% ee
R_1 = Ph, 50% ee

>95% yield

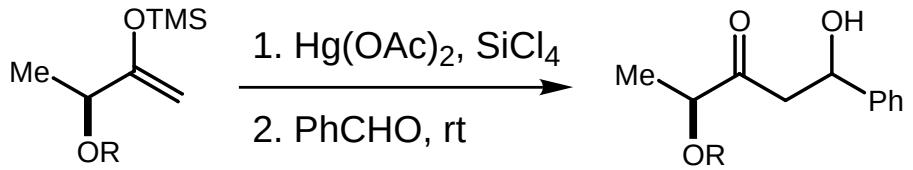


	entry	RCHO	mol% **F**	time (h)	%ee	yield
	1	cinnamaldehyde	5	2	84	94
	2	α-Me-cinnamaldehyde	5	2	92	95
	3	1-naphthaldehyde	5	2	86	92
	4	4-Ph-PhCHO	5	2	86	95
enolizable →	5	*c*-hexCHO	10	6	90	79
	6	*t*-BuCHO	10	6	92	81

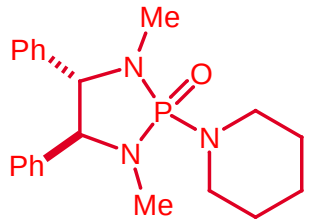
Denmark, S. E.; Stavenger, R. A.; Wong, K.-T. *J. Am. Chem. Soc.* **1998**, *63*, 918-919.

Lewis Base-Catalyzed Methyl Ketone Aldol Reactions

Uncatalyzed reaction:

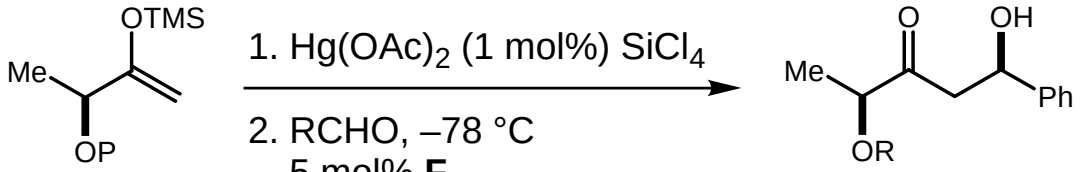


entry	R	$Hg(OAc)_2$ (mol%)	syn/anti	yield
1	TBS	0.25	1/1.2	82
2	Piv	0.5	1/2.4	71
3	Bn	0.5	1/3.4	75



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

Catalyzed reaction:

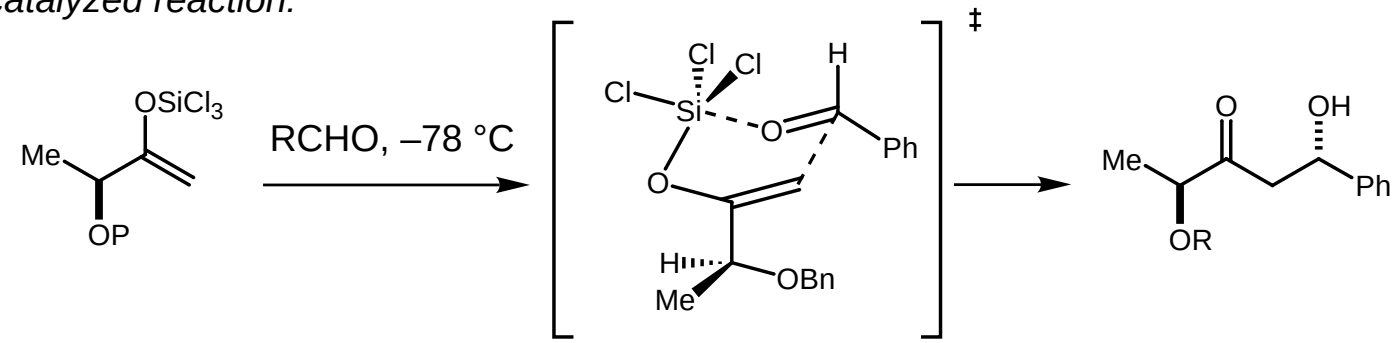


	entry	P	R	catalyst	syn/anti	yield
mismatched	1	TBS	Ph	(*S,S*)-**F**	1.5/1	85
	2	Piv	Ph	(*S,S*)-**F**	3.4/1	78
	3	Bn	Ph	(*S,S*)-**F**	1/1.1	78
matched	4	TBS	Ph	(*R,R*)-**F**	73/1	85
	5	Piv	Ph	(*R,R*)-**F**	20/1	78
	6	Bn	Ph	(*R,R*)-**F**	11/1	77
	7	TBS	(*E*)-MeCH=CH	(*R,R*)-**F**	6.2/1	81

Denmark, S. E.; Stavenger, R. A. *J. Am. Chem. Soc.* **1998**, *63*, 9524-9527.

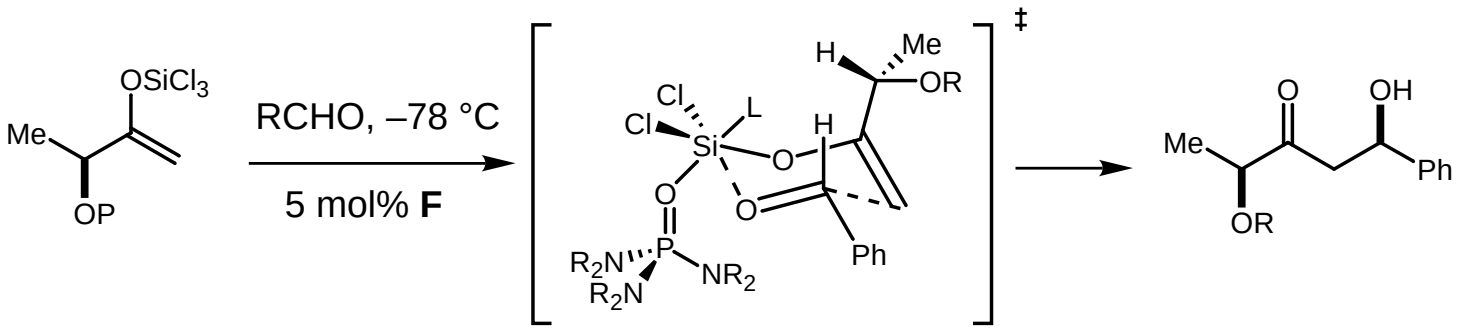
Methyl Ketone Aldol Reactions: Rationale

Uncatalyzed reaction:



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

Catalyzed reaction:



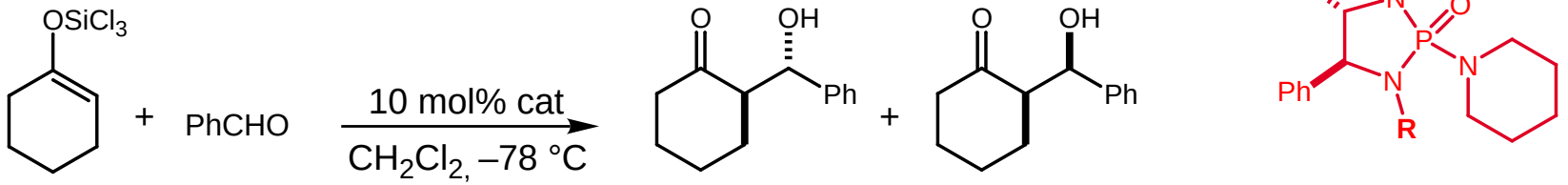
minimization of oxygen dipoles

Model does not account for matched and mismatched cases.

Denmark, S. E.; Stavenger, R. A. *J. Am. Chem. Soc.* **1998**, *63*, 9524-9527

Mechanistic Insights on Trichlorosilyl Enolate Aldols

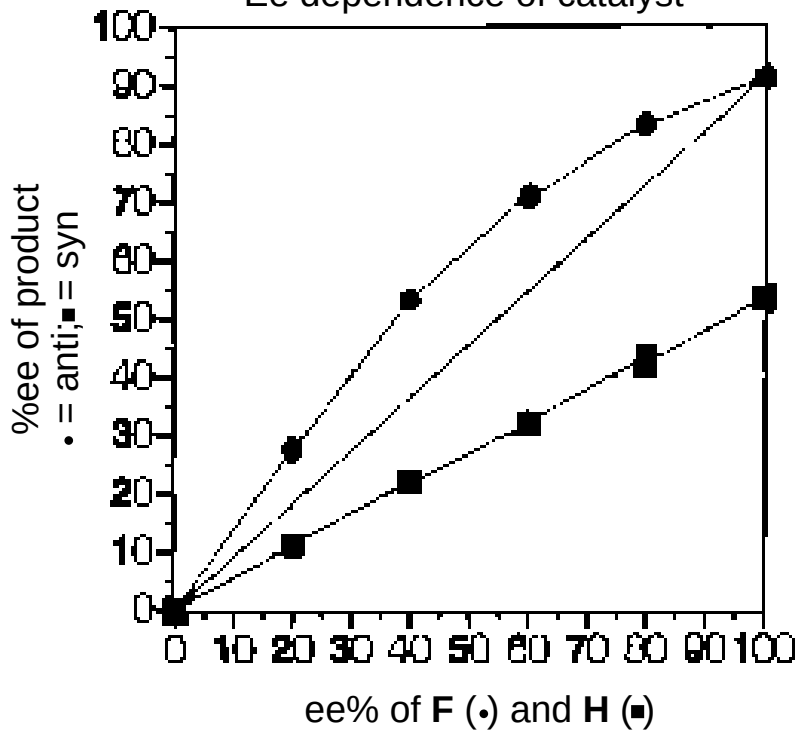
Intriguing switch of diastereoselectivity



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

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

Ee dependence of catalyst

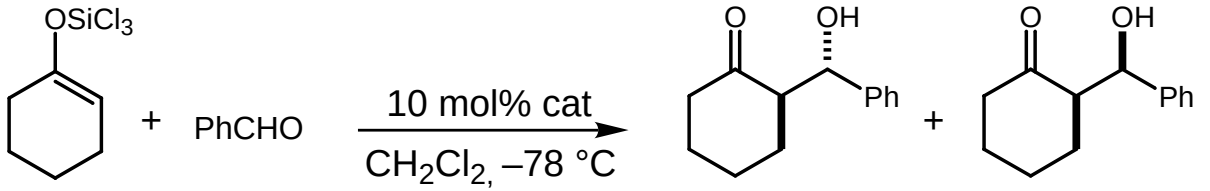


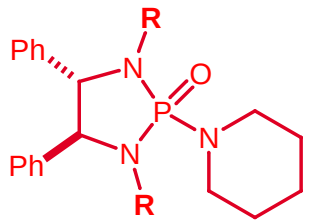
Anti diastereomer favored with less hindered catalysts as well as at higher loadings of achiral **F** analog

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



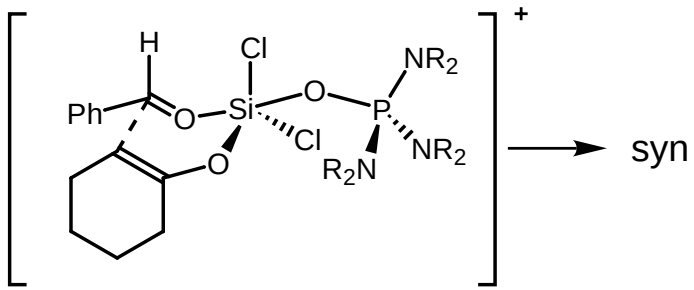


(*S,S*) **F,** R = Me
(*S,S*) **H**, R = Ph

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

Positive nonlinear dependence on catalyst **F**

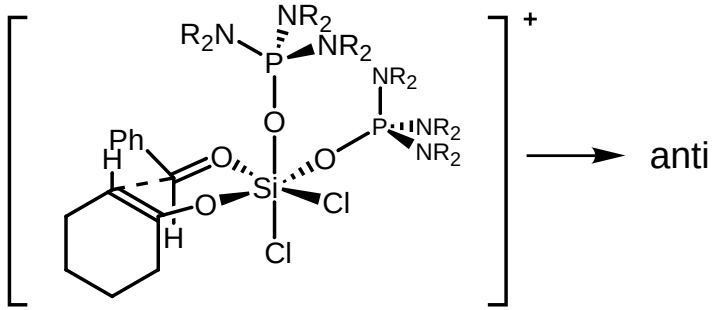
Magnitude of nonlinear effect not catalyst concentration dependent– no reservoir effect



syn

cationic trigonal bipyramidal

Favored for bulky catalyst **H**



anti

cationic octahedral

Favored for smaller catalyst **F**

Bu_4NCl inhibits the reaction– inhibits ionization of enolsilane-catalyst complex

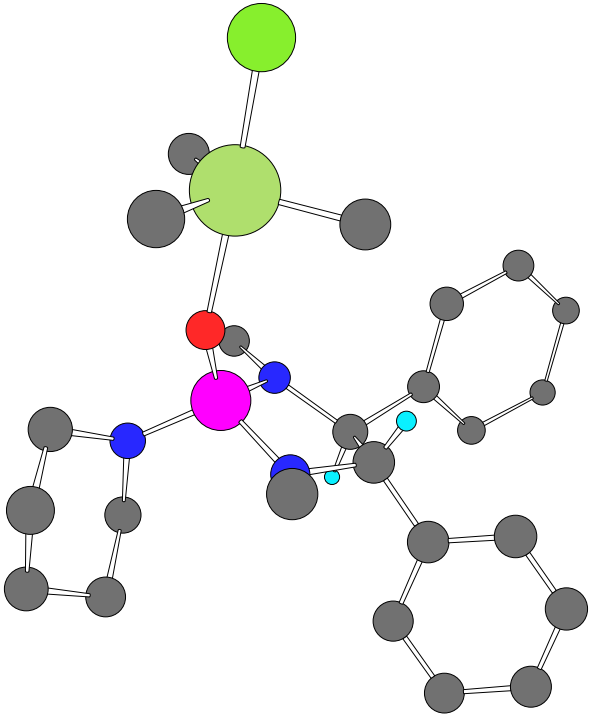
Bu_4NOTf accelerates the reaction by increasing the ionic strength of the medium

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.

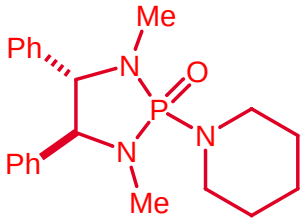
Structural Insights of Trichlorosilyl Enolate Aldols

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



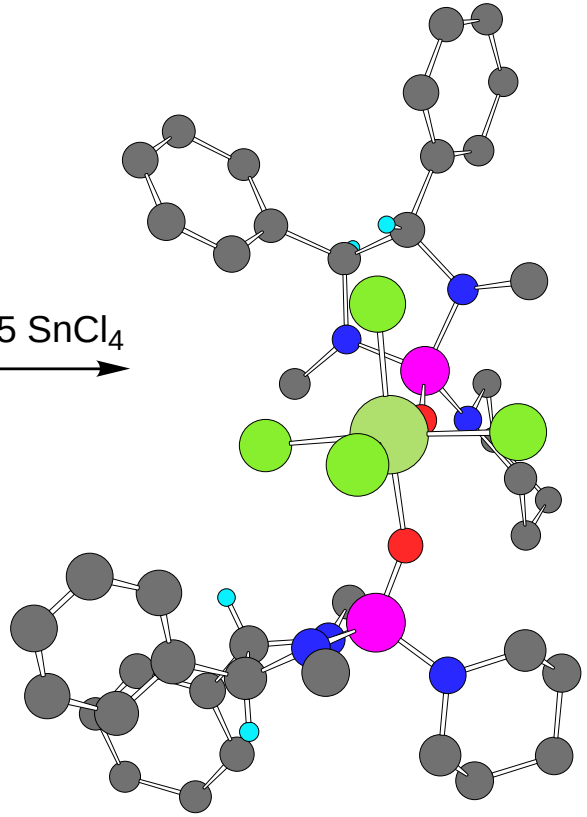
trigonal bipyramidal geometry

$SnMe_3Cl$ ←



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

→ $0.5\ SnCl_4$

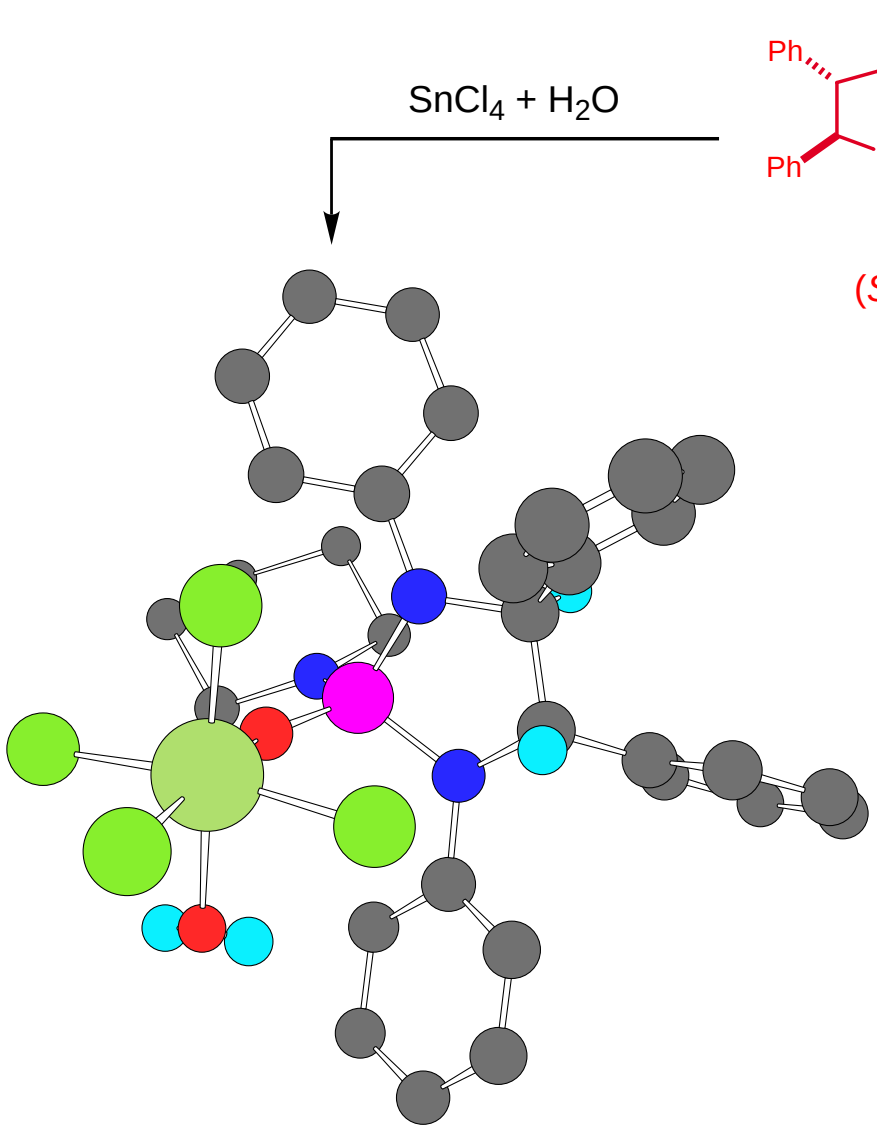


octahedral geometry

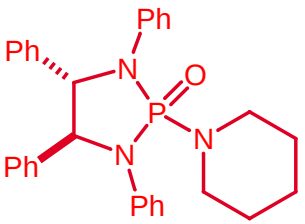
P–O–Sn not linear
piperdine N almost sp_2

Denmark, S. E.; Su, X. *Tetrahedron* **1999**, *55*, 8727-8738.

Structural Insights on Trichlorosilyl Enolate Aldols

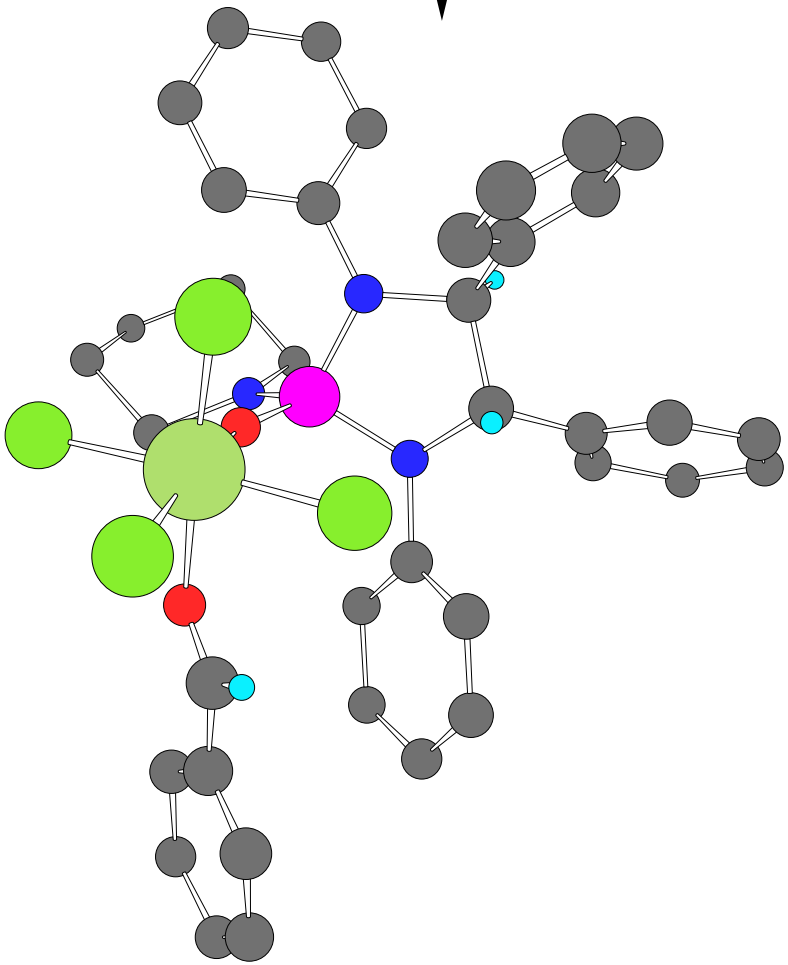


$SnCl_4 + H_2O$



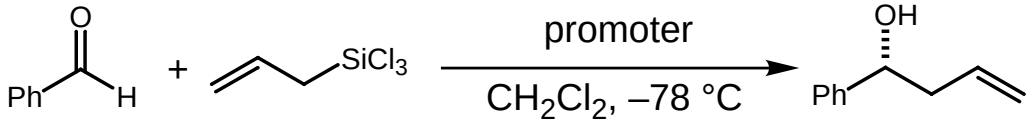
(*S*,*S*) **H**

$SnCl_4 + PhCHO$



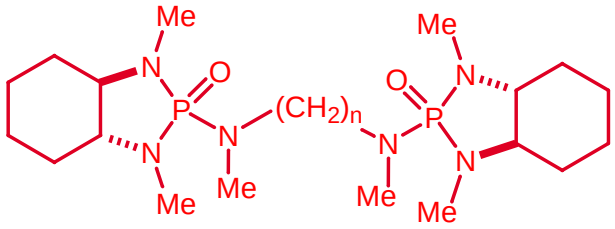
Denmark, S. E.; Su, X. *Tetrahedron* **1999**, *55*, 8727-8738.

Allyltrichlorosilane Additions Revisited: New and Improved

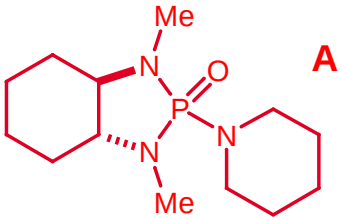


	entry	promoter	tether (n)	equiv	yield (%)	%ee
Denmark 1994	1	**A**	–	1.0	81	60
	2	**A**	–	0.1	49	53
	3	**I**	2	0.5	60	0
	4	**I**	3	0.5	72	35
	5	**I**	4	0.5	82	17
	6	**I**	4	0.1	52	10
	7	**I**	5	0.5	78	65
	8	**I**	**5**	**0.1**	**54**	**72**
	9	**I**	6	0.5	75	46
	10	**J**	–	0.1	49	80
	11	**J**[a]	–	0.1	67	80
	12	**J**[a]	–	0.5	76	80
	13	**J**[a]	–	0.05	43	79

[a] 5.0 equiv of *i*-Pr_2NEt added for turnover

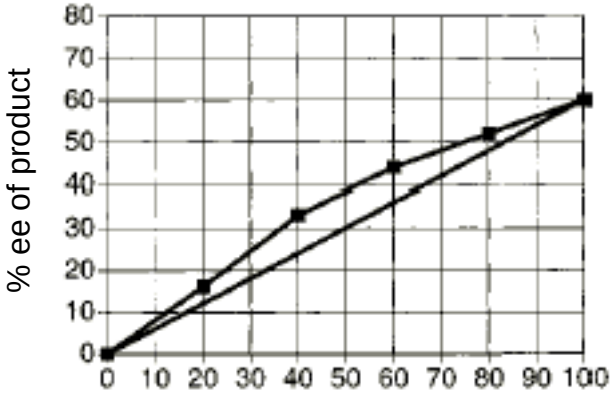


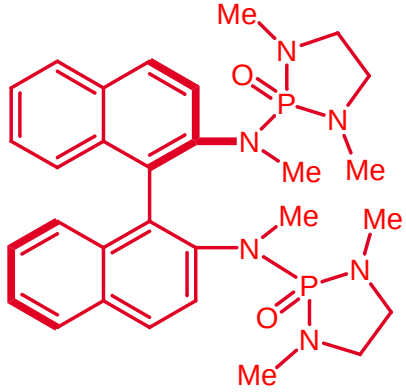
I



A

Positive nonlinear effect observed





J

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 = selectivity
c = conversion

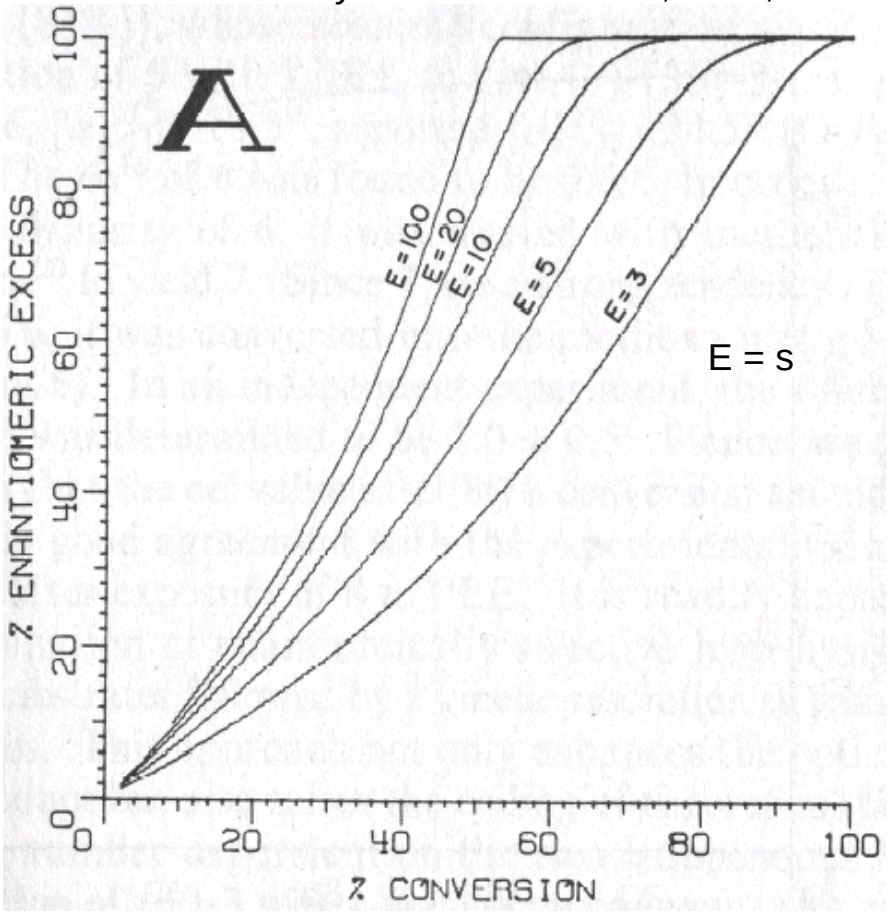
$$c = 1 - \frac{A + B}{A_0 + B_0}$$

ee = %ee of recovered substrate

A_0 = initial amt. of fast-reacting enantiomer
B_0 = intial amt. of slow-reacting enantiomer

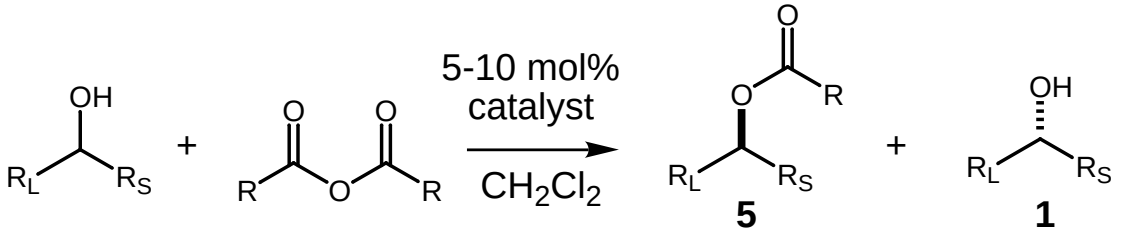
A = amt. of fast-reacting enantiomer @ time T
B = amt. of slow-reacting enantiomer @ time T

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



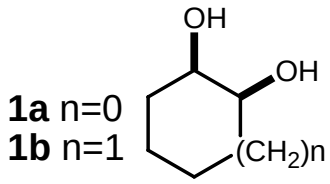
For an excellent analysis of kinetic resolution, see: Sih et al. *J. Am. Chem. Soc.* **1982**, *104*, 7294-7299.
For a review of kinetic resolutions, see: Kagan, H. B.; Fiaud, J. C. *Top. Stereochem.* **1998**, *18*, 249-330.

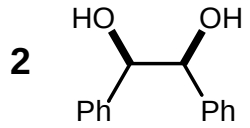
Enantioselective Acylations Catalyzed by Chiral Phosphines



entry	substrate	catalyst	anhydride	%ee **5** (conv.)	selectivity (s)
1	**1b**	**3**	Ac_2O	9 (40)	1.2
2	**1b**	**4**	Ac_2O	11 (60)	1.3
3	**1b**	**6a**	Ac_2O	65 (66)	4.5
4	**1b**	**6b**	Ac_2O	42 (80)	2.6
5	**1a**	**6a**	Ac_2O	52 (10)	3.2
6	**2**	**3**	Ac_2O	50 (40)	2.9
7	**2**	**6a**	Ac_2O	27 (22)	1.2
8	**2**	**4**	Bz_2O	22 (31)	1.6
9	**2**	**6a**	Bz_2O	68 (84)	5.5
10	**2**	**6b**	Bz_2O	58 (70)	4.7
11	PhCH(OH)*t*Bu	**6a**	3-$ClBz_2O$	81 (25)	12-15

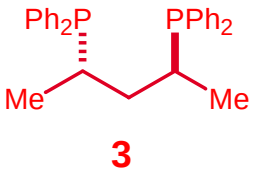
meso substrates

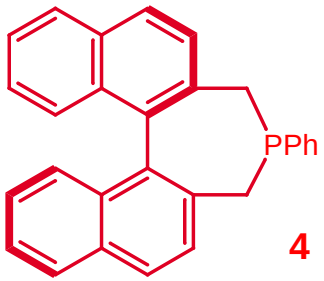


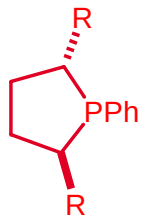


perdeuterated Ac_2O give monoacetate without loss of deuterium: no ketene mechanism operative

chiral phosphines:





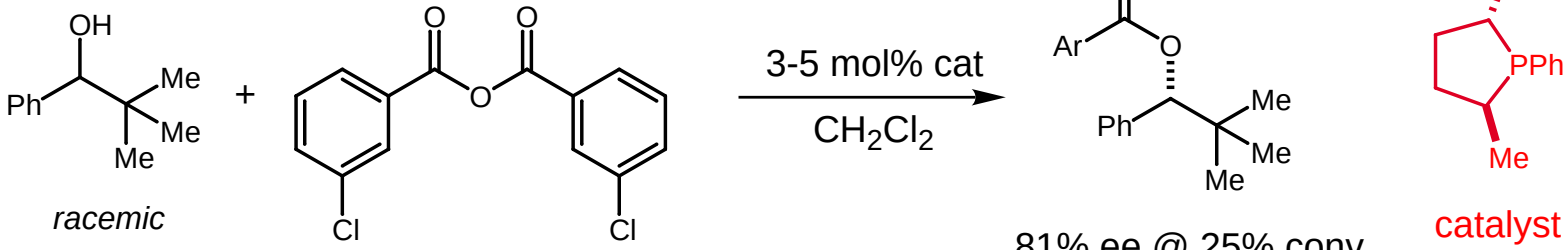


6a, R = Me
6b, R = Et

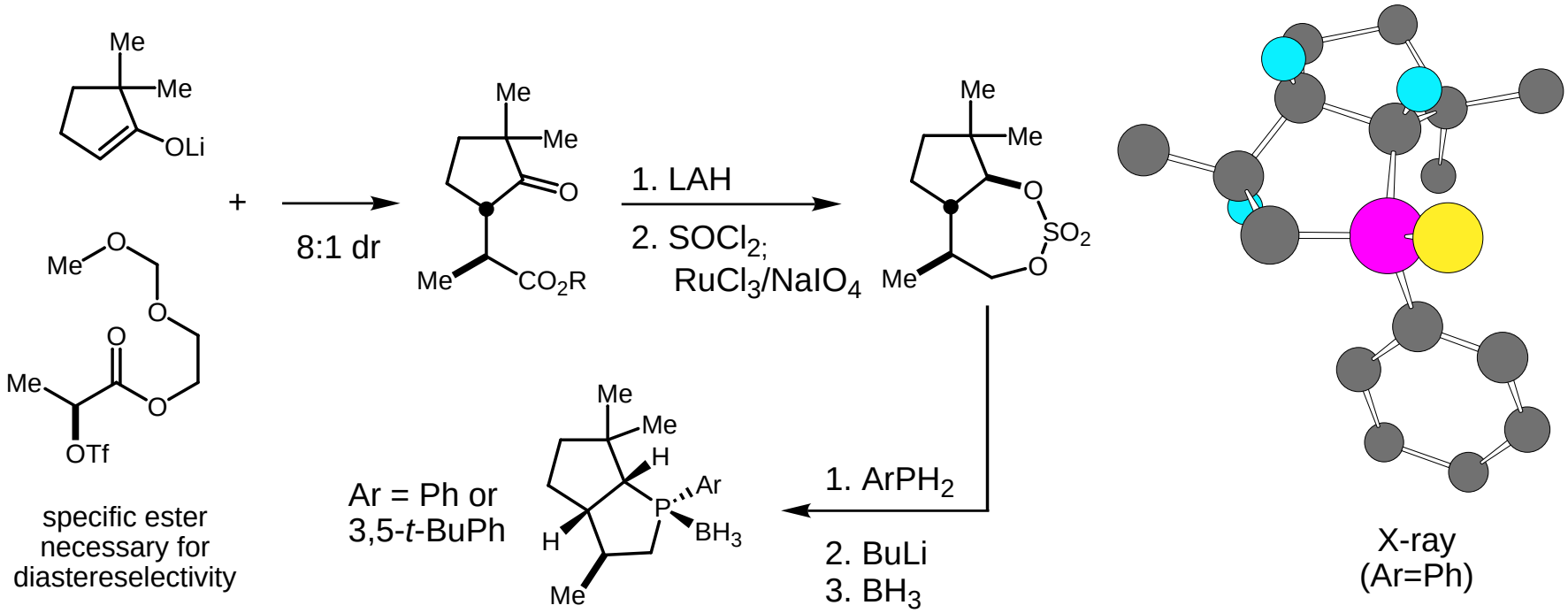
Vedejs, E.; Daugulis, O.; Diver, T. S. *J. Org. Chem.* **1996**, *61*, 430-431.

Improved Chiral Phosphine for Kinetic Resolutions

Recall:

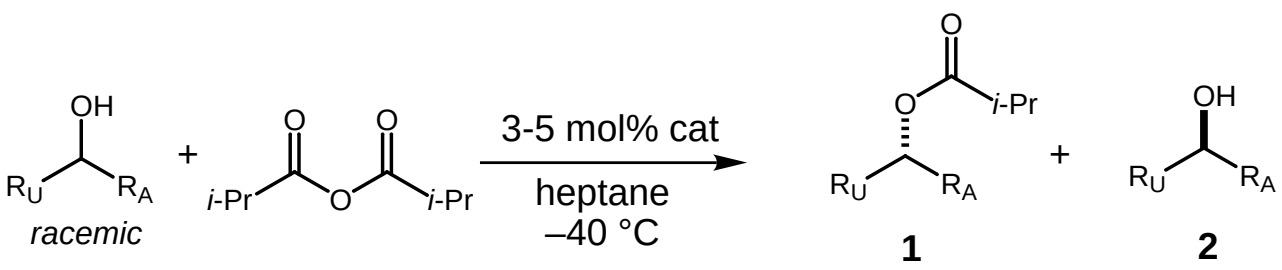


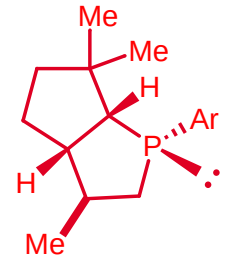
Problem: Reaction is not general– new chiral phosphine needed



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

Acylations Catalyzed by Chiral Phosphines





Ar = 3,5-*t*-BuPh

catalyst

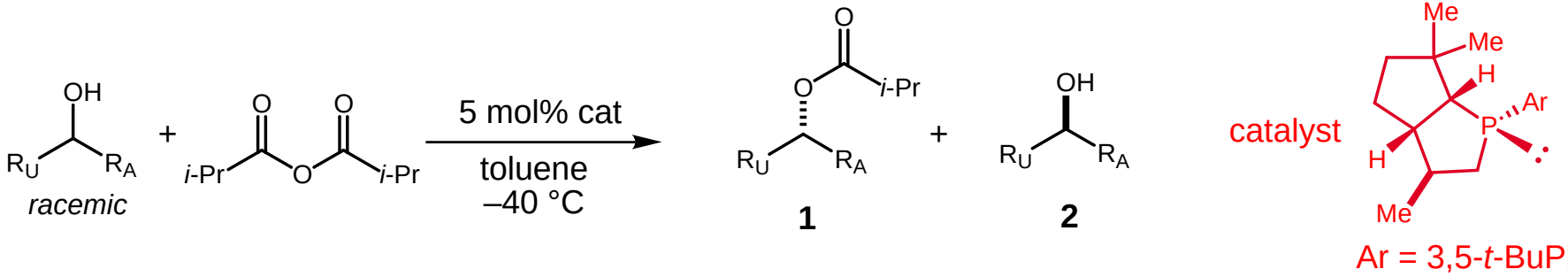
entry	R_U	R_A	time (h)	conv. (%)	%ee product (**1**)	*s*
1	Ph	Me	4	29	93	42
2	1-cC_6H_9[a]	Me	14	50	88	49
3	Ph	*n*-Bu	8	51	89	57
4	Ph	*i*-Bu	7	42	88	31
5	Ph	*i*-Pr	42	47	95	100
6	Ph	*t*-Bu	65	46	93	67
7	2-MePh	Me	4	50	95	145
8	α-naphthyl[b]	Me	7	30	97	99
9	mesityl[b]	Me	16	44	99	369[c]

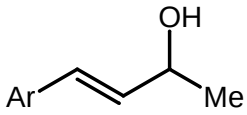
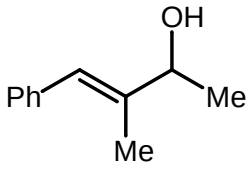
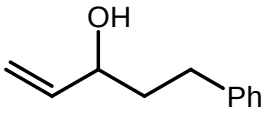
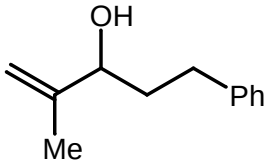
[a] 1-cyclohexenyl, [b] reaction run in toluene, [c] s = 389 in duplicate run

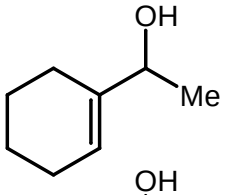
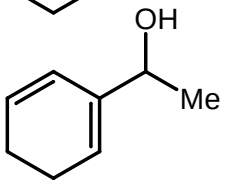
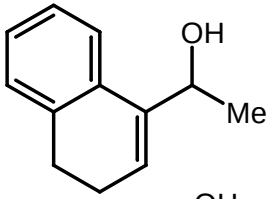
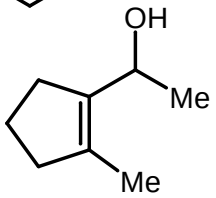
"The data in table underestimate catalyst reactivity because no special precautions were taken to exclude oxygen."

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

Acylations Catalyzed by Chiral Phosphines



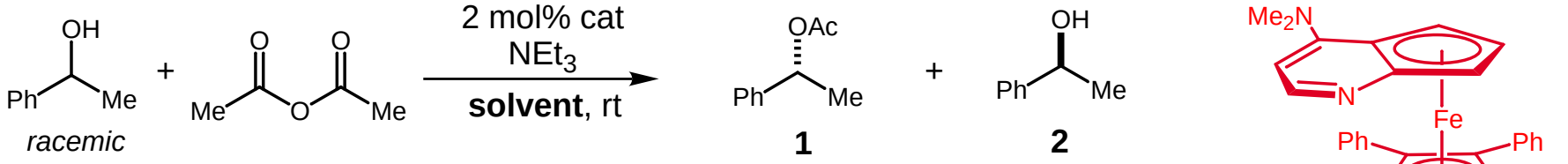
alcohol	time (h)	conv. (%)	%ee (**2**/**1**)	s
 Ar = 4-Cl-Ph	12	55	78/63	10
	27	45	67/82	21
	41	48	42/45	4
	19	48	66/72	12

alcohol	time (h)	conv. (%)	%ee (S.M./prod)	s
	14	50	89/88	52
	7	53	90/81	34*
	72	53	96/86	55*
	46	67	99/49	25*

* = rxn in heptane

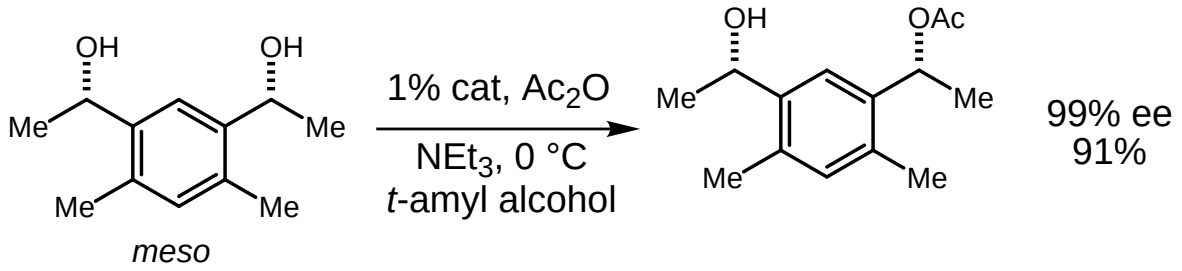
Vedejs, E.; MacKay, J. *Org. Lett.* **2001**, *3*, 535-536.

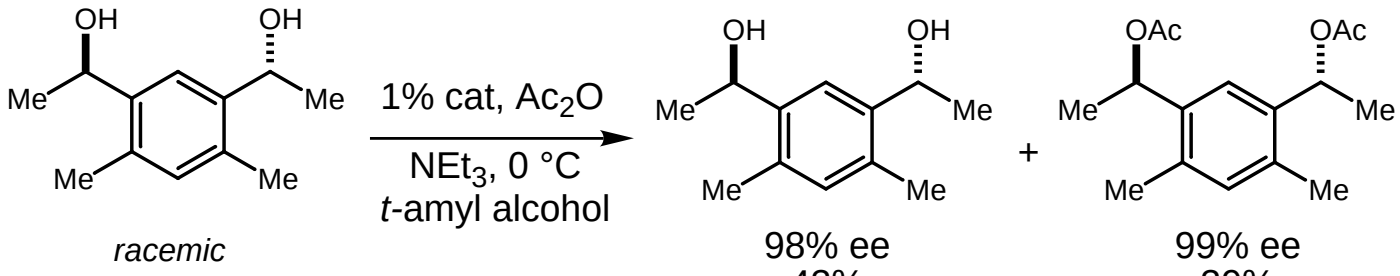
Acylations Catalyzed by Planar-Chiral DMAP Analogs



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_3CN	10	3.6	7	toluene	13	11
3	CH_2Cl_2	14	7.0	8	Et_2O	8	13
4	acetone	8	8.7	9	*t*-amyl alcohol	38	27
5	THF	4	9.6				

Desymmetrizations:

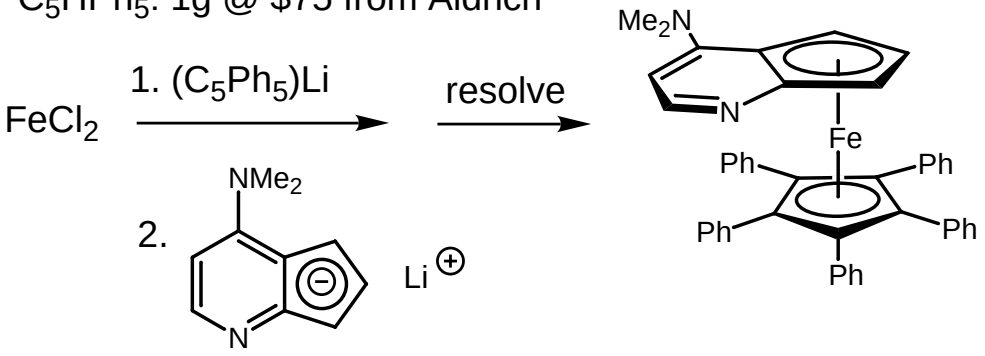




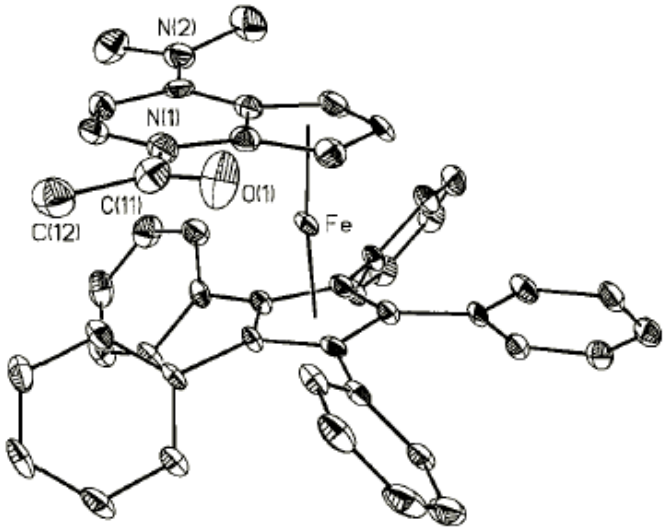
Ruble, J. C.; Tweddell, J.; Fu, G. C. *J. Org. Chem.* **1998**, *63*,

Synthesis of Planar-Chiral DMAP Analogs

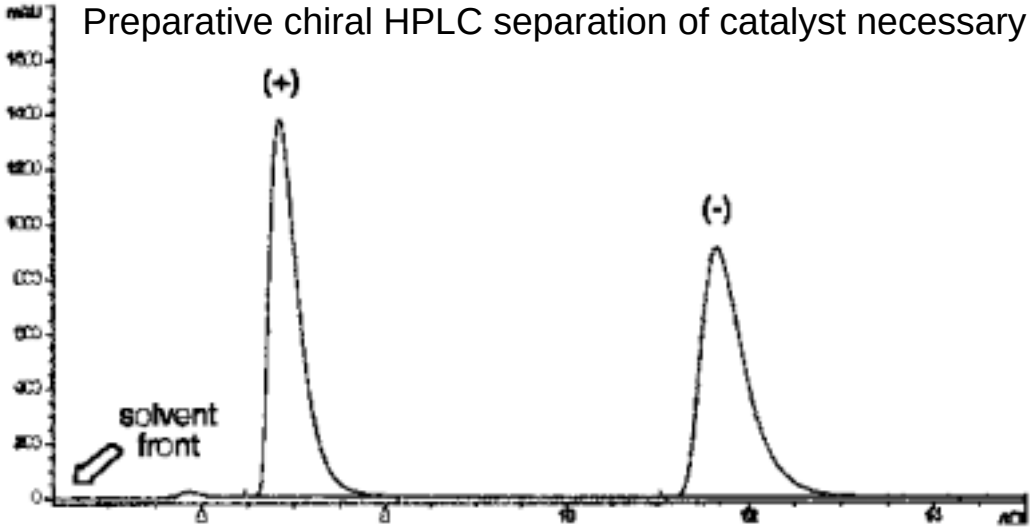
C_5HPh_5: 1g @ \$75 from Aldrich



8 step synthesis (3% overall yield)

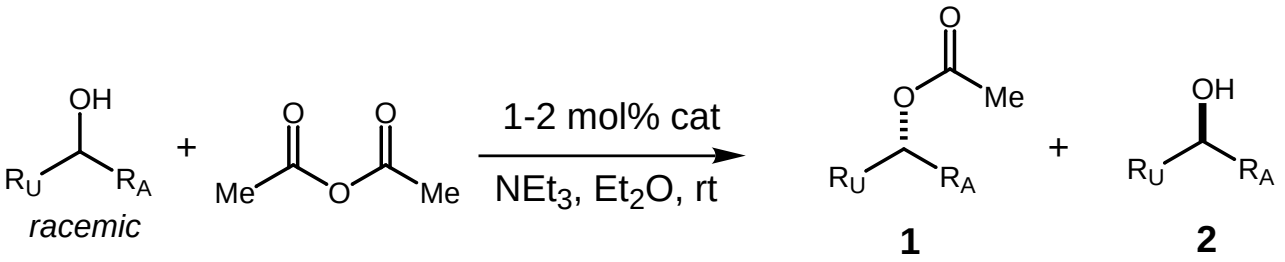


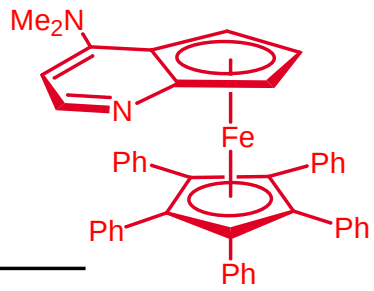
Preparative chiral HPLC separation of catalyst necessary



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.

Acylations Catalyzed by Planar-Chiral DMAP Analogs





catalyst

entry	R_U	R_A	%ee of **2**	conversion (%)	selectivity (Et_2O/*t*-amyl alcohol)
1	Ph	Me	95	62	14/43
2	Ph	Et	99	62	20/59
3	Ph	*i*-Pr	98	55	36/87
4	Ph	*t*-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

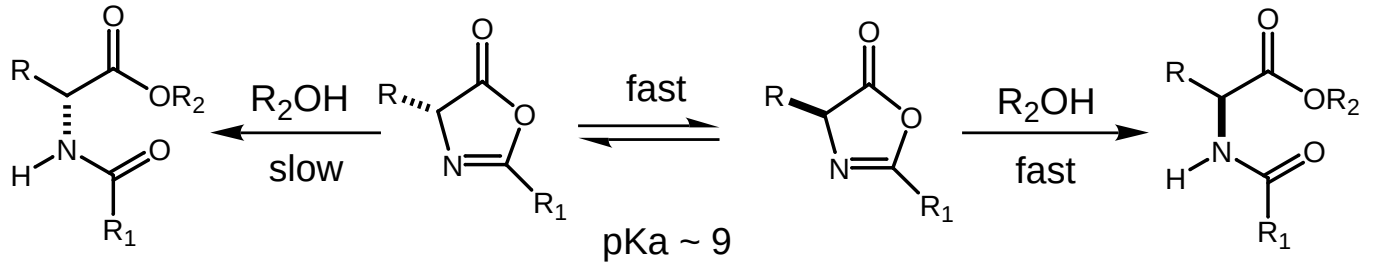
For a review on DMAP, see: Steglich et al. *Angew. Chem., Int. Ed. Engl.* **1978**, *17*, 569-593

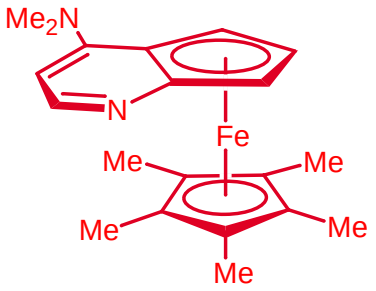
For a resolution of 2° alcohols using stoichiometric amounts of a chiral DMAP analog, see: Vedejs, E.; Chen, X. *J. Am. Soc. Chem.* **1996**, *118*, 1809-1810 (s values 48-11 reported).

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

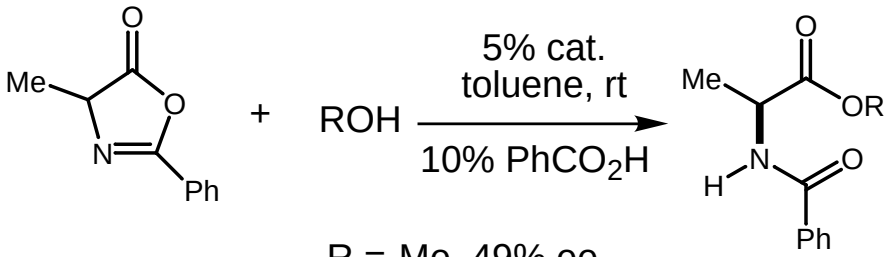
Dynamic Kinetic Resolutions of Azlactones with DMAP Analogs

The concept

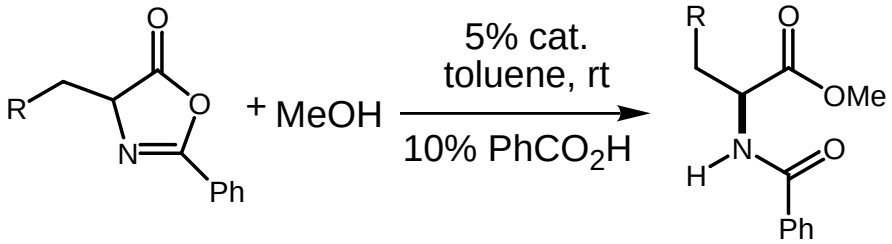




catalyst



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*-Pr	55	95
5	*c*-Hex	54	93
6	Ph	56	94
7	CH_2SMe	50	94

Solvent study identified toluene as optimal solvent

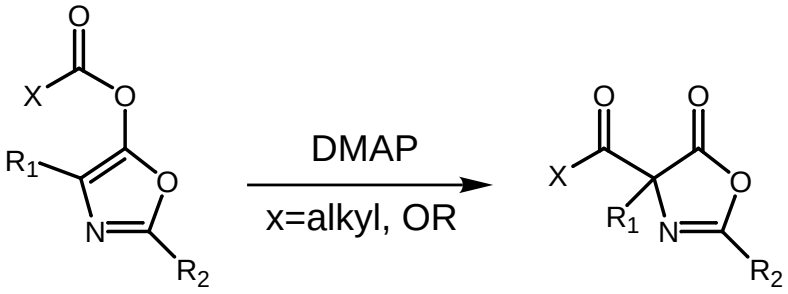
Reaction with *i*-PrOH too slow ($t_{1/2}$ ~ 1 week)

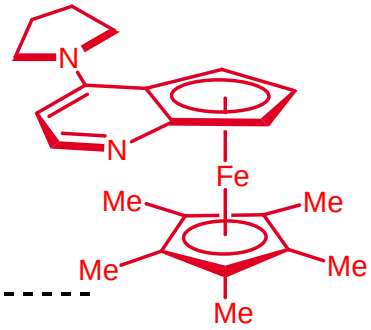
"We inadvertently discovered that the presence of benzoic acid leads to ring opening... at a faster rate."

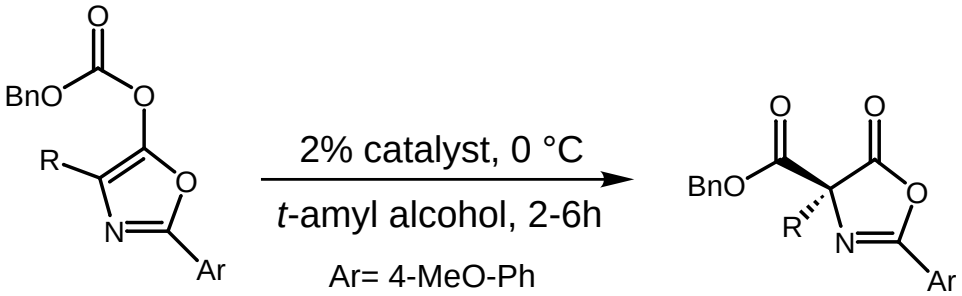
Liang, J.; Ruble, J. C.; Fu, G. C. *J. Org. Chem.* **1998**, *63*, 3154-3155.
For a review on dynamic kinetic resolutions, see: Stecher, H.; Faber, K. *Synthesis* **1997**, 1-69.

Rearrangements of O-Acylated Azlactones

Steglich 1970:

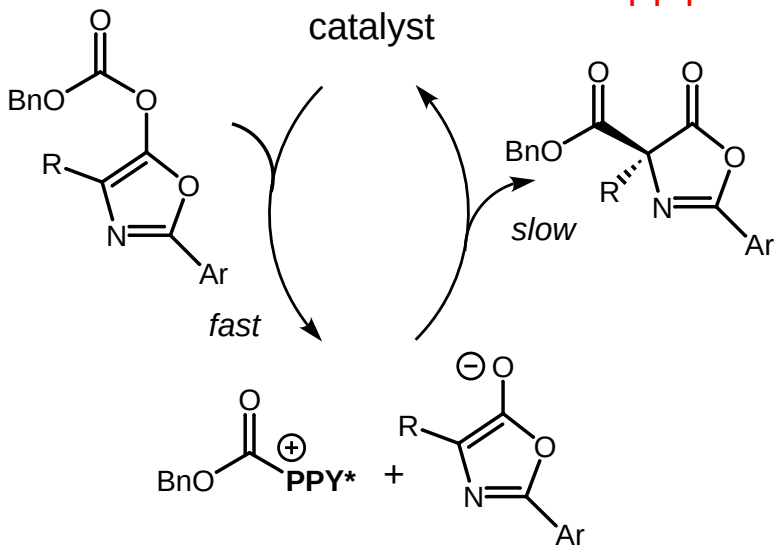






entry	R	%ee	yield (%)
1	Me	91	94
2	Et	90	93
3	CH_2Ph	90	93
4	allyl	91	93
5	CH_2CHMe_2	92	95
6	CH_2CH_2SMe	88	94

Proposed Mechanism

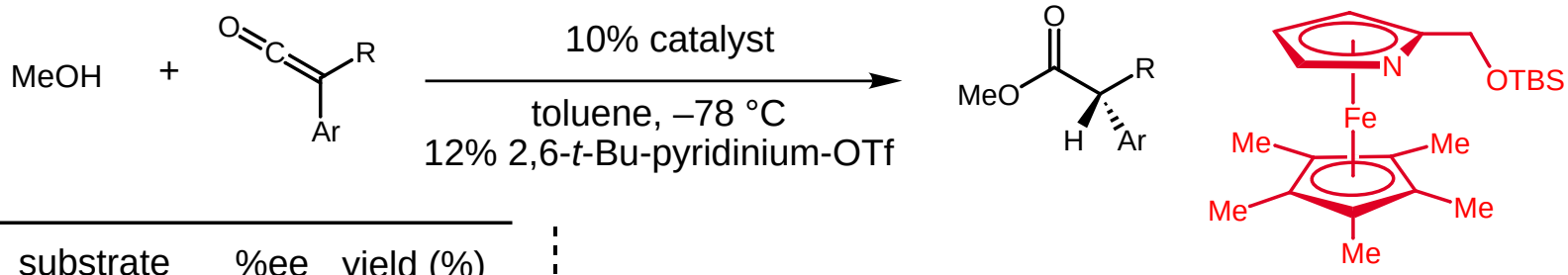


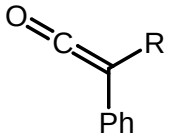
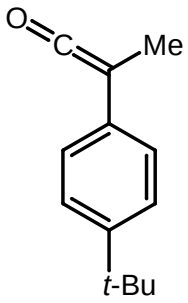
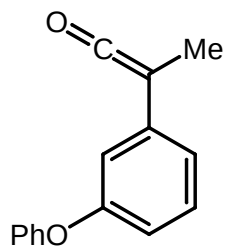
resting state

zero order in substrate
Crossover experiments provide evidence of ion pair

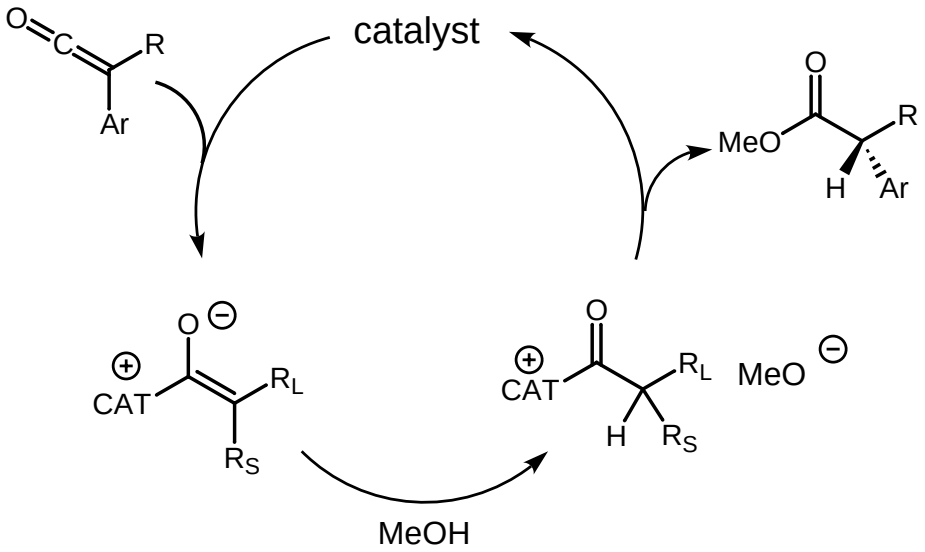
Ruble, J. C.; Fu, G. C. *J. Am. Chem. Soc.* **1998**, *120*, 11532-11533.

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:

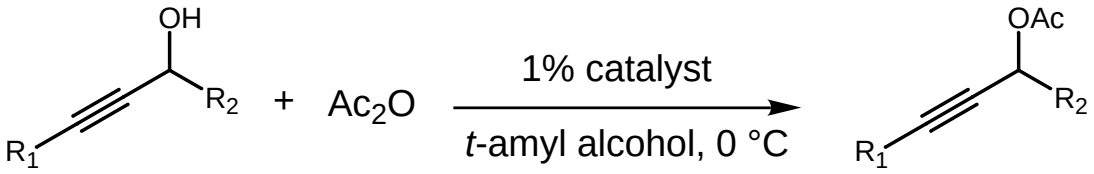


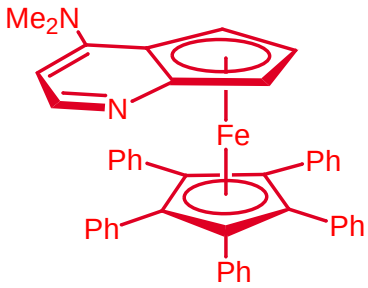
no nonlinear effects

reaction has KIE of 3.2
(MeOH vs. MeOD)

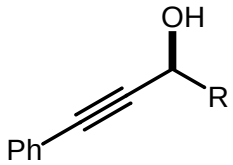
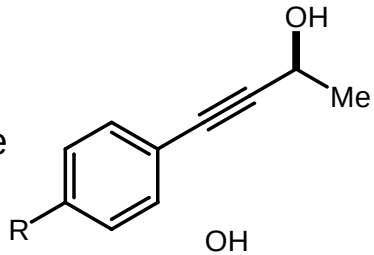
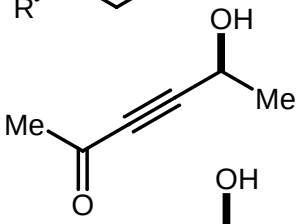
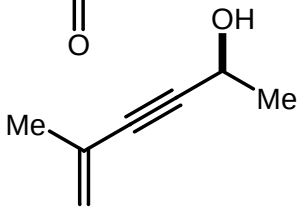
Hodous, B. L.; Ruble, J. C.; Fu, G. C. *J. Am. Chem. Soc.* **1999**, *121*, 2637-2638.

Kinetic Resolutions of Propargylic Alcohols





catalyst

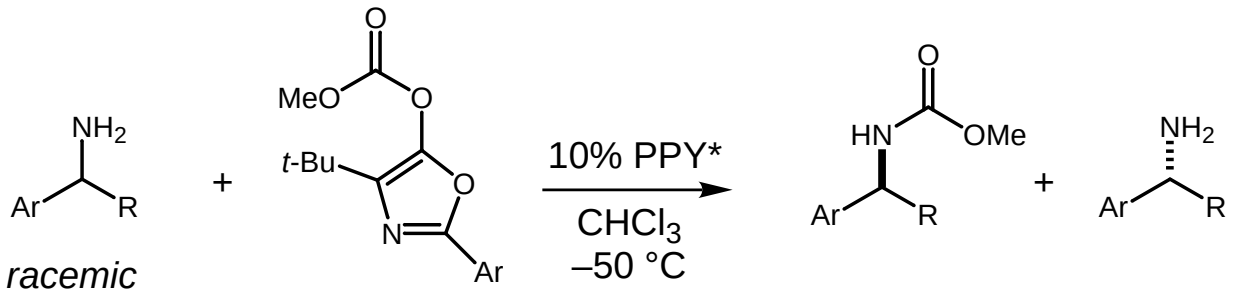
entry	unreacted ROH (major enantiomer)	s (%ee of unreacted ROH)
1 R = Me		**20** (96%ee @ 58% conv.)
2 Et		**18** (94%ee @ 58% conv.)
3 *i*-Pr		**11** (93%ee @ 63% conv.)
4 *t*-Bu		**3.8** (95%ee @ 86% conv.)
5 R = OMe		**14** (94%ee @ 60% conv.)
6 CF_3		**10** (99%ee @ 71% conv.)
7 F		**13** (97%ee @ 65% conv.)
8		**12** (95%ee @ 64% conv.)
9		**7.9** (95%ee @ 69% conv.)

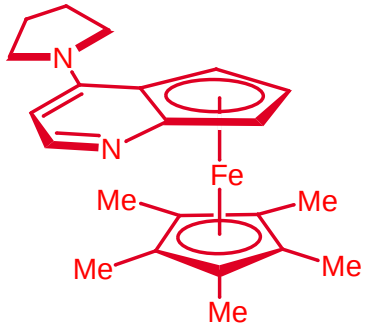
acetic anhydride optimal anhydride

added R_3N works, but omission of base gives highest s value

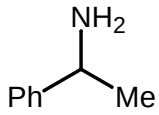
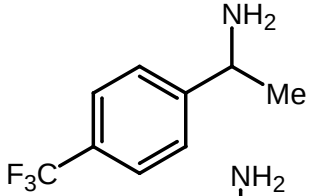
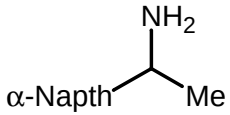
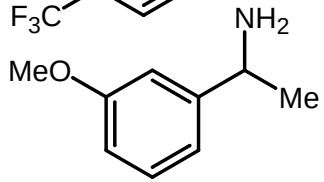
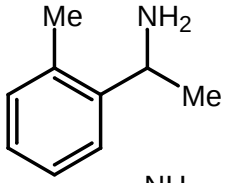
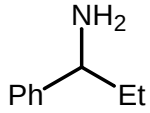
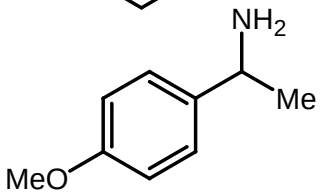
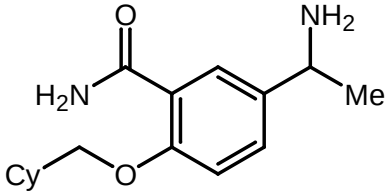
Tao, B.; Ruble, J. C.; Hoic, D. A.; Fu, G. C. *J. Am. Chem. Soc.* **1999**, *121*, 5091-5092.

Kinetic Resolutions of Amines



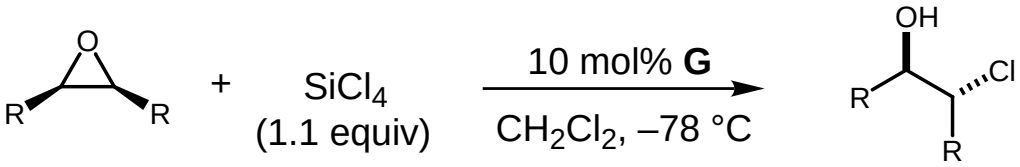


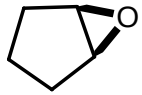
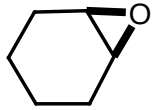
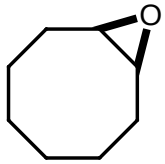
catalyst
"PPY*"

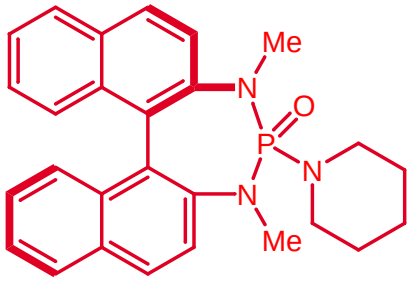
entry	amine	*s*	entry	amine	*s*
1		12	5		13
2		27	6		22
3		16	7		16
4		11	8		11

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

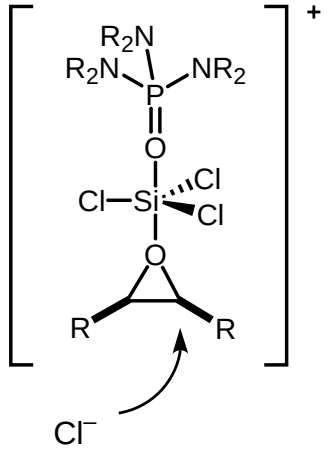
Asymmetric Ring Opening of meso-Epoxides



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**

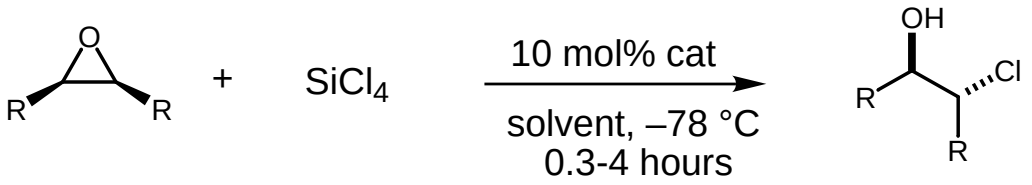


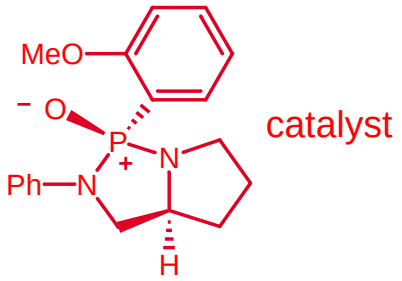
proposed transition state

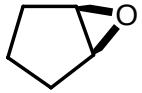
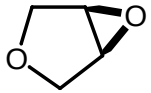
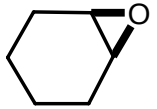
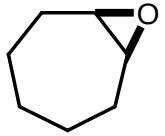
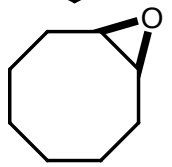
"The origin of asymmetric induction is obscure at this time."

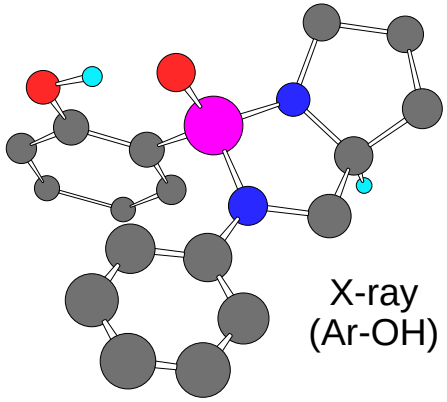
Denmark, S. E.; Barsanti, P. A., Wong, K.-T.; Stavenger, R. A. *J. Org. Chem.* **1998**, *63*, 2428-2429.

Asymmetric Ring Opening of meso-Epoxides

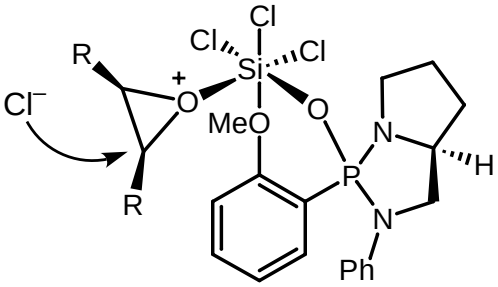




entry	substrate	solvent	%ee	yield (%)	config
1		THF	23	68	(1*R*,2*R*)
2		CH_2Cl_2	48	41	(1*R*,2*R*)
3		CH_2Cl_2	62	85	(1*R*,2*R*)
4		CH_2Cl_2	**98**	79	(1*R*,2*R*)
5		CH_2Cl_2	**99**	77	(1*R*,2*R*)
6		THF	**92**	68	(1*R*,2*R*)
7		CH_2Cl_2	**94**	78	(2*S*,3*S*)



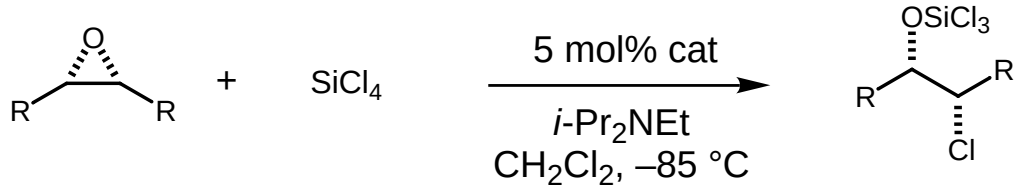
X-ray
(Ar-OH)

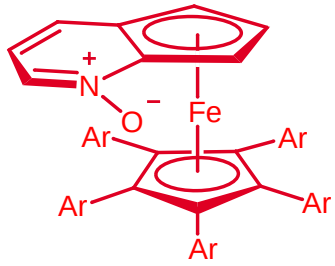


proposed transition state

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

Asymmetric Ring Opening of meso-Epoxides



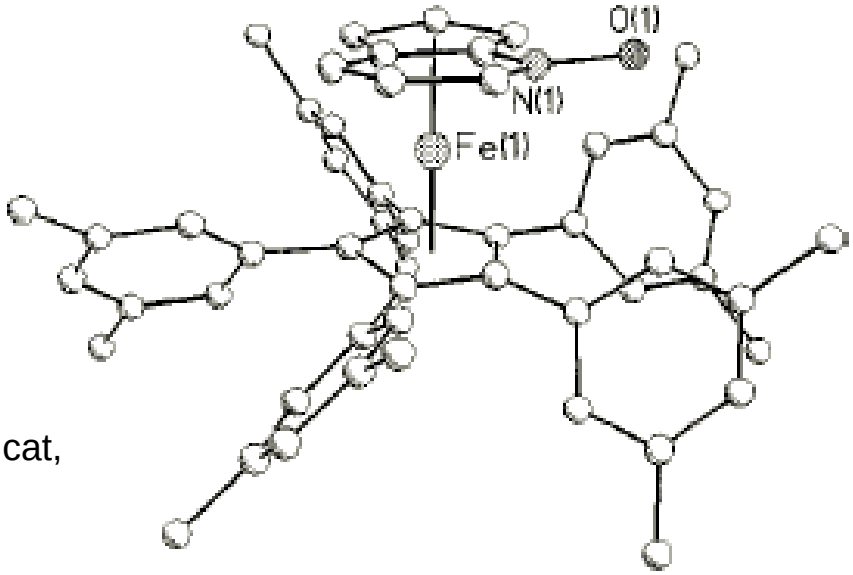


catalyst
Ar = 3,5-$Me_2C_6H_3$

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_2OBn	91	50

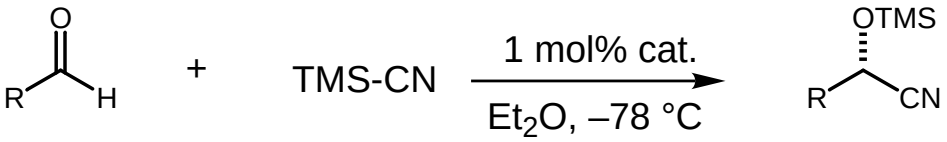
Increased steric demand of catalyst increases enantioselectivity dramatically: Ar = Ph, 60% ee vs. Ar = 3,5-$Me_2C_6H_3$, 94% ee for opening of *cis*-stilbene oxide

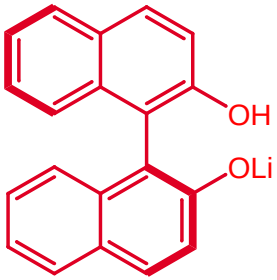
1. Positive nonlinear effect
2. Zero-order in $SiCl_4$ and *i*-Pr_2NEt
3. ^1H and ^{29}Si NMR show interaction between $SiCl_4$ and cat, but not between $SiCl_4$ and epoxide or *i*-Pr_2NEt



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

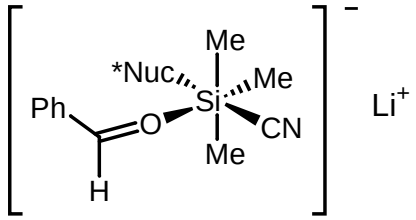
Asymmetric Addition of TMS-CN to Aldehydes





catalyst

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_3Ph	0	73	<5 min
11	2-naphthyl	6	93	24 h
12	cinnamaldehyde	8	95	3.5 h
13	*n*-hexyl	9	82	<5 min
14	*c*-hexyl	30	94	20 min
15	*t*-Bu	23	62	5 min



proposed intermediate

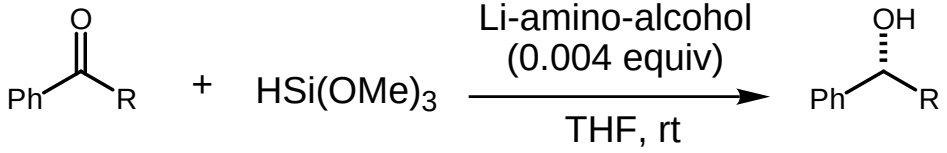
mono-lithio salt superior to di-lithio

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.

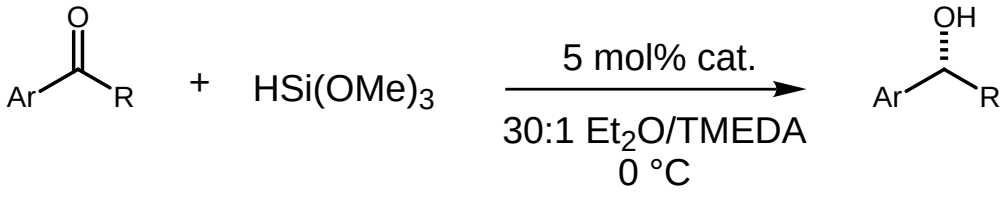
Asymmetric Catalytic Reduction of Ketones

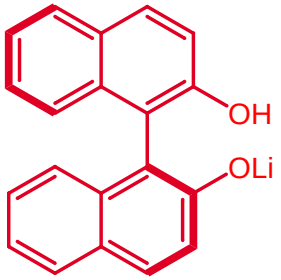


Note: *$(MeO)_3SiH$ vapors cause blindness: bp = 95 °C*

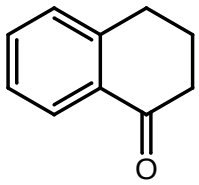
entry	R	amino-alcohol	yield (%)	%ee
1	Me	(*S*)-Phenylalaninol	75	49
2	Me	(*S*)-Prolinol	89	52
3	Et	(*S*)-Phenylalaninol	88	32

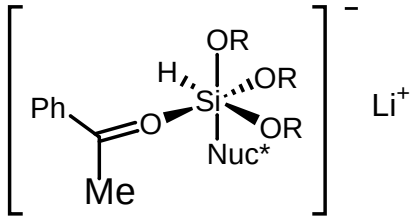
Hosomi et al. *Tetrahedron Lett.* **1988**, *29*, 89-92.





catalyst

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



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.