Frontiers of Chemistry Series:
Recent Uses of Silicon in Organic Synthesis

Tom Graham
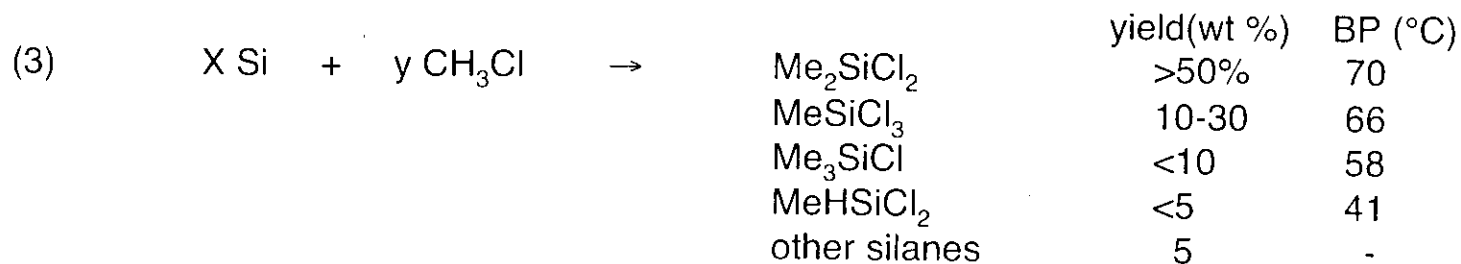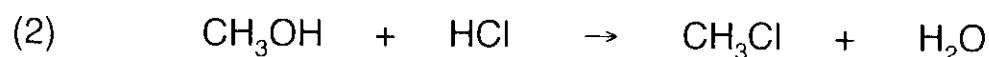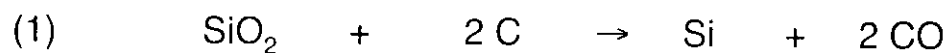
Outline

- Introduction
  - Why Silicon?
  - The Source of Silicon
  - The Environmental Fate of Silicon
- Stoichimetric
  - Passive Si (i.e. protecting groups, silicon tethers, etc.) will not be discussed.
  - Active Si (i.e. change in the silicon coordination sphere occurs during the reaction)
    - Polyketide synthesis
      - Silicon-centered allylation reagents
      - Tandem Silylformylation-allylation (crotylation) / aldol-allylation (crotylation)
      - Silacyclopropanes
      - Silacyclopentane oxides
    - Cross coupling reactions
      - Silacyclobutanes / Siloxanes
      - Hypervalent silanes
    - Allylic alkylations

- Catalytic
  - Lewis base activated Lewis acids.
  - Other chiral, silicon-centered Lewis acids.

2

Why Silicon?

- Silicon is one of the most abundant elements in the earth's crust.

- Occurs as Si(IV) (SiO_2) but is readily reduced to Si (0).

- A variety of Si derivatives are available.

- Relatively safe, non-toxic and environmentally degradable.

- Hyper-valency allows access to the penta- and hexacoordinate complexes which are reminiscent of the transition metals.

- Chemoselective methods exist for the introduction and removal.

3

The Source of Silicon

(1) SiO_2 + $2\,C$ → Si + $2\,CO$

(2) CH_3OH + HCl → CH_3Cl + H_2O

(3) $X\,Si$ + $y\,CH_3Cl$ →

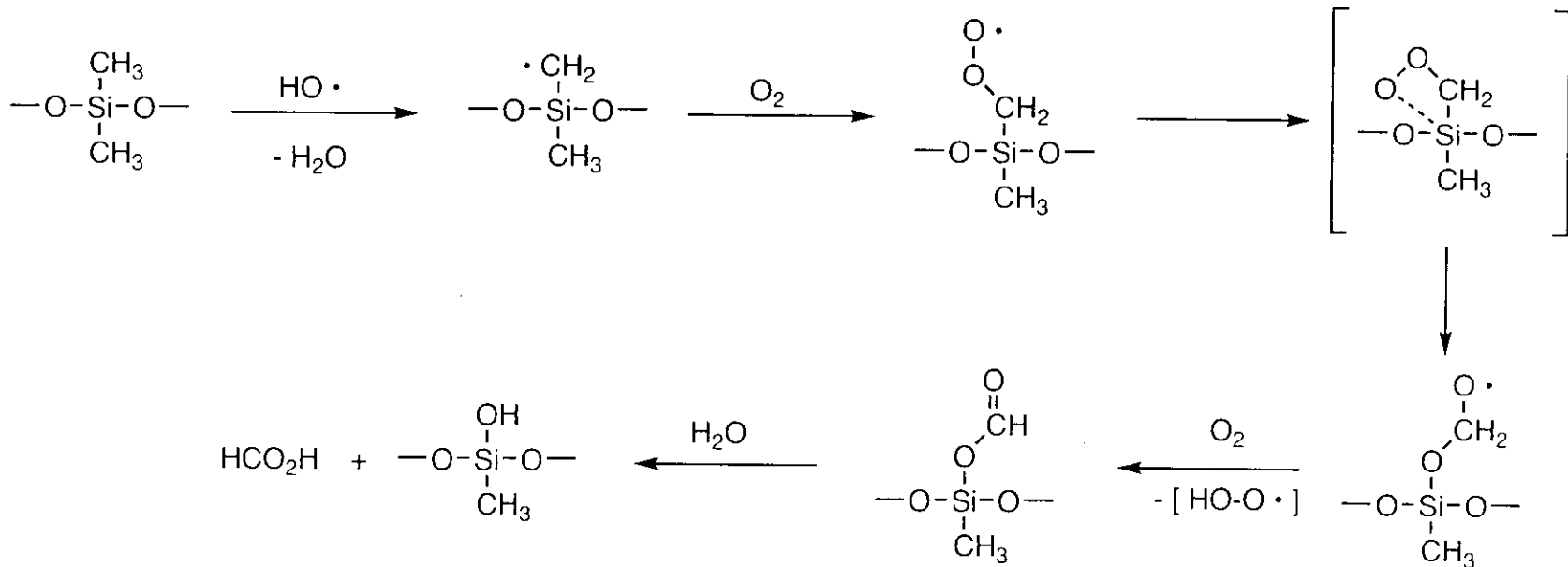|	yield(wt %)	BP (°C)
Me_2SiCl_2	>50%	70
$MeSiCl_3$	10-30	66
Me_3SiCl	<10	58
$MeHSiCl_2$	<5	41
other silanes	5	-

Equation (3) is referred to as the Rochow Direct process:

• occurs at a pressure of 1 to 5 bars and the yield 85-90%

• Copper catalyst is used in a fluidized bed of silicon metal powder. The mechanism is not completely understood.

• > 500,000 tons / year

4

The Environmental Fate of Silicon

- Low MW (<450) units are volatile and are degraded in the atmosphere.

- Half lives for the hydrolysis of high MW (450-450,000) PDMS (polydimethylsiloxane) polymers is 4-28 days depending on the soil type.

- " the data indicate organosilicons derived from dimethylsiloxanes do not pose a risk to the environment."

5

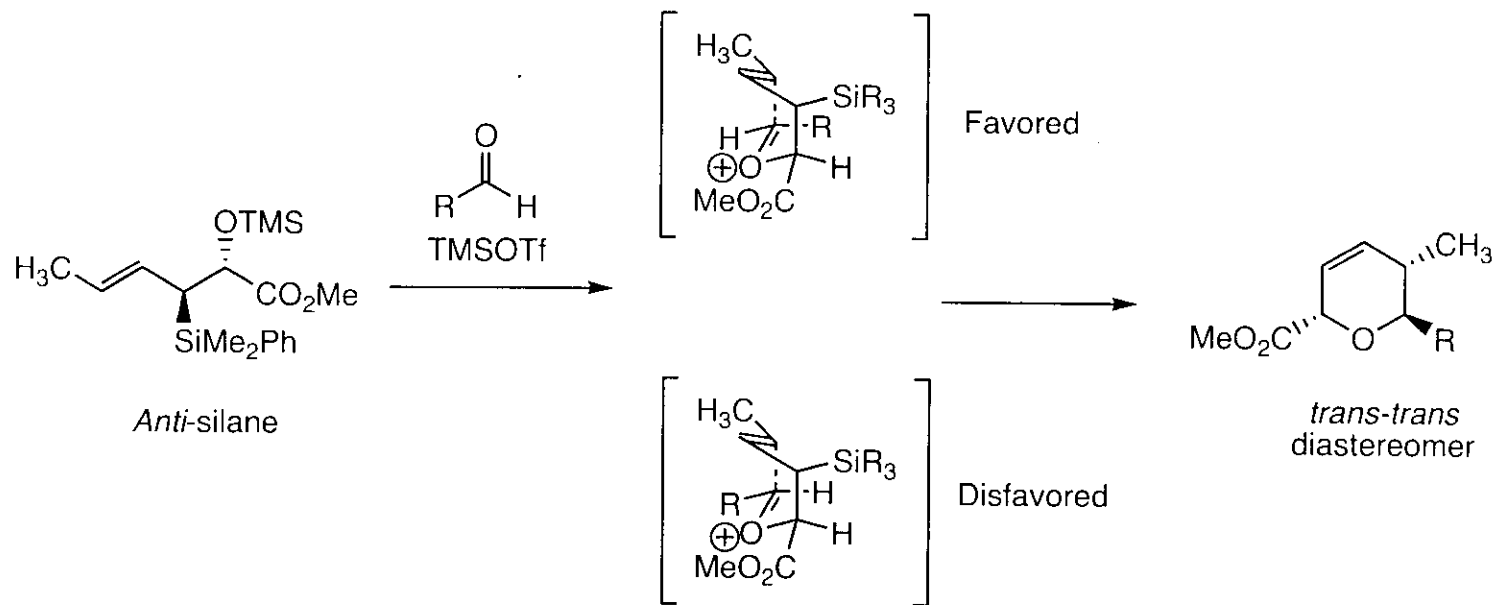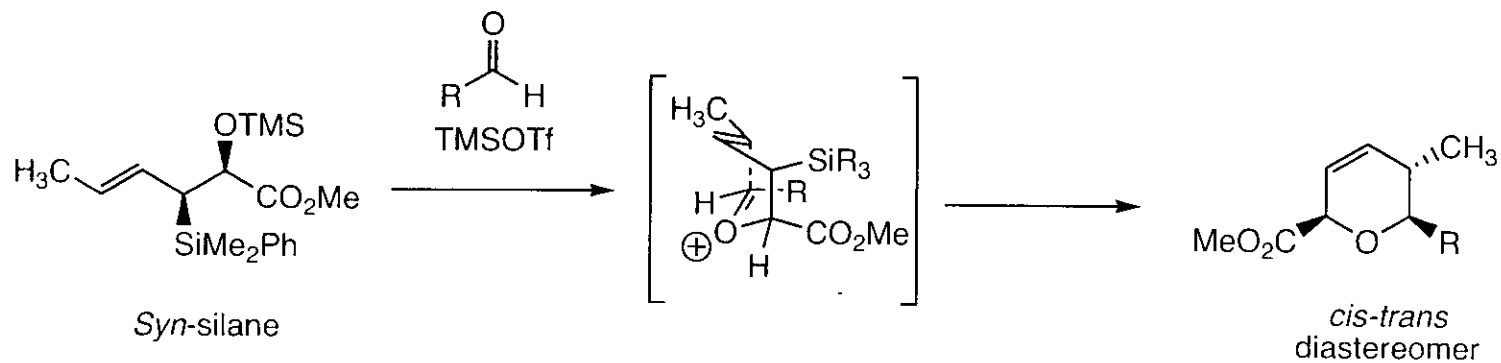# Double-Stereodifferentiating Crotylation Reactions
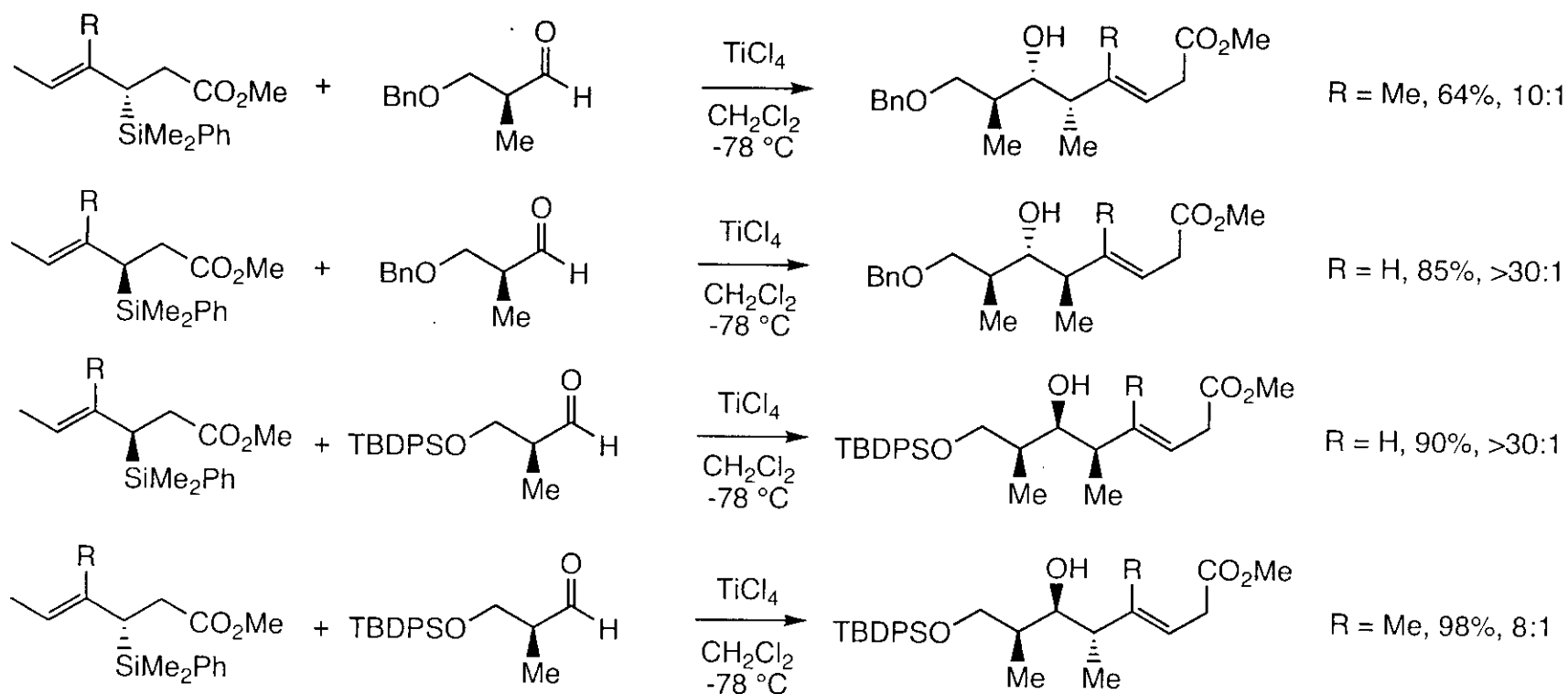
- Silane controls the absolute stereochemistry at the methyl stereocenter.
- Addition to the aldehyde can be Felkin or Cram chelate and controls the hydroxyl stereocenter.
- Open transition state.
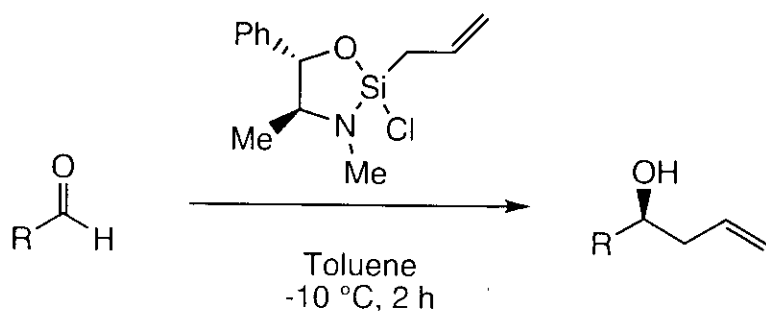
6

Jain, N. F.; Takenaka, N.; Panek, J. S. *J. Am. Chem. Soc.* **1996**, *118*, 12475-12476.

Dihydropyrans from Chiral Crotylsilanes

Syn-silane

cis-trans
diastereomer

Anti-silane

Favored

Disfavored

trans-trans
diastereomer

7   Huang, H.; Panek, J. S. *J. Am. Chem. Soc.* **2000**, *122*, 9836-9837.

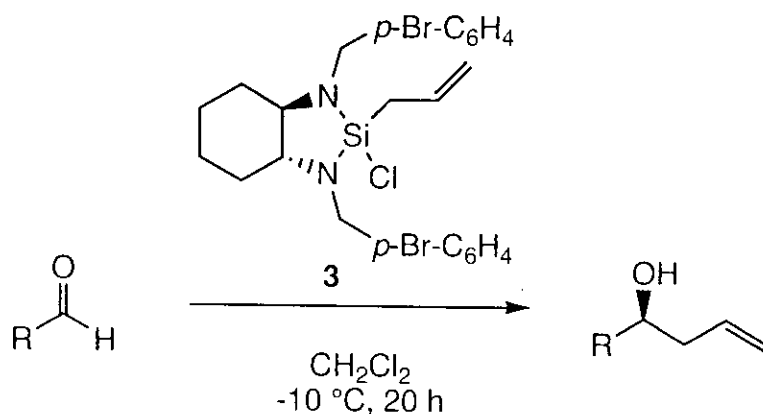# Silicon Centered Allylation Reagents:
First Generation

• Six membered ring and acyclic silacyles did not give product.

• Reagent is prepared in large quantities in a single step from commercially available starting materials.

• Reagent is a solid that is stable upon storage.

• Simplified work-up and purification (1N HCl / EtOAc) gives products in > 90% purity.
　　(1) no IPC-OH as occurs with boron centered IPC reagents.
　　(2) No metals.

entry[a]	aldehyde	product	yield(%)[b]	ee(%)[c]
1[d]			80	81
2[d]			59	78
3			84	88
4			79[e]	87
5			70	87
6[d]			80[e]	96
7			85	88
8			71	89

[a] Reactions run with silane 3 (1.5 mmol) and aldehyde (1.0 mmol) in toluene (5 mL) at −10 °C for 2 h. [b] Isolated yield. [c] Determined by chiral HPLC analysis or by the Mosher ester method. [d] Reaction time = 24 h. [e] Due to product volatility, an alternative workup and purification was employed. See the Supporting Information.

8

Kinnaird, J. W. A.; Ng, P. Y.; Kubota, K.; Wang, X; Leighton, J. L. *J. Am. Chem. Soc.* **2002**, *124*, 7920-7921.

Silicon Centered Allylation Reagents: Second Generation

- Yields and ee's for aliphatic aldehydes are good to excellent.

- Aromatic and conjugated aldehydes require longer reaction times and give lower yields.

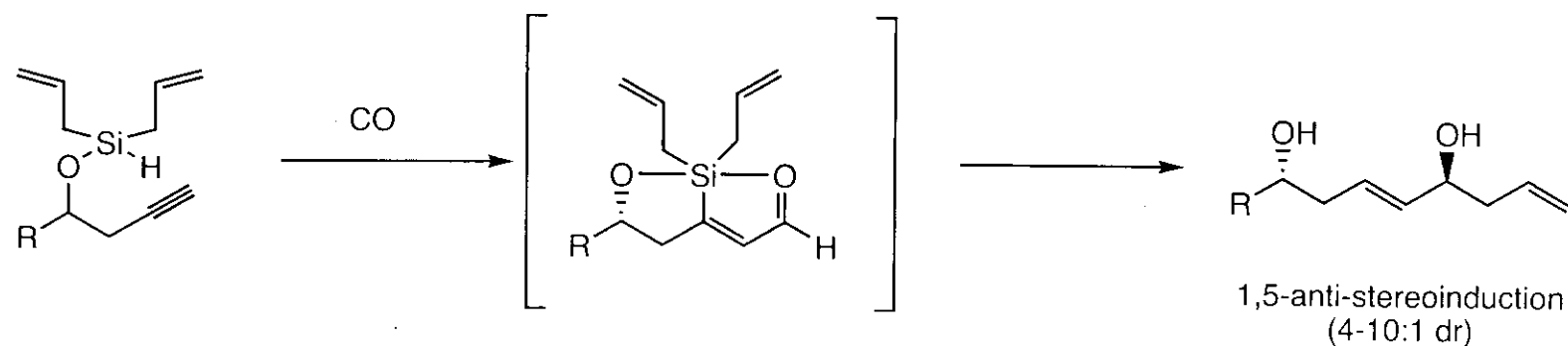- Ligand is expensive and stoichiometric but it can be recovered.

Entry[a]	R	Yield [%][b]	ee [%][c]
1	PhCH₂CH₂	90	98
2	(CH₃)₂CHCH₂	80[d]	96
3	cHex	93	96
4	PhCH₂OCH₂	67	97
5	PhCH₂OCH₂CH₂	87	98
6	tBuMe₂SiOCH₂	61	98

[a] Reactions run with silane 3 (1.0 equiv) and aldehyde (1.0 equiv) in CH₂Cl₂ at −10 °C for 20 h. [b] Yield of isolated product. [c] Determined by chiral HPLC analysis or by the Mosher ester method. See the Supporting Information. [d] Because of product volatility, an alternative workup and purification was employed. See the Supporting Information.

Entry[a]	R	Yield [%][b]	ee [%][c]
1	Ph	69	98
2[d]	p-MeOC₆H₄	62	96
3	p-CF₃C₆H₄	66	96
4[e]	(E)-PhCH=CH	75	96
5[e]	(E)-nPrCH=CH	71[f]	95

[a] Reactions run with silane 3 (1.0 equiv) and aldehyde (1.0 equiv) in CH₂Cl₂ at −10 °C for 20 h. [b] Yield of isolated product. [c] Determined by chiral HPLC analysis or by the Mosher ester method. See the Supporting Information. [d] Reaction run for 60 h. [e] Reaction run at 8 °C for 72 h. [f] Because of product volatility, an alternative workup and purification was employed. See the Supporting Information.

9

Kubota, K.; Leighton, J. L.
Angew. Chem. Int. Ed. **2003**, *42*, 946-948.

Tandem Silylformylation - Allylsilylation:
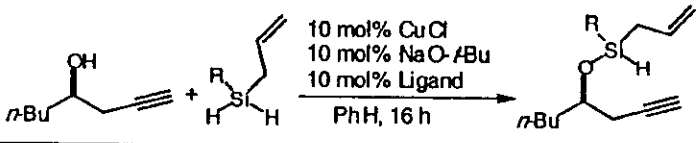## the key experiment

1,5-anti-stereoinduction
(4-10:1 dr)

Zacuto, M. J.; O'Malley, S. J.; Leighton, J. L.
J. Am. Chem. Soc. **2002**, *124*, 7890.

(1:1 dr)

1:1 dr
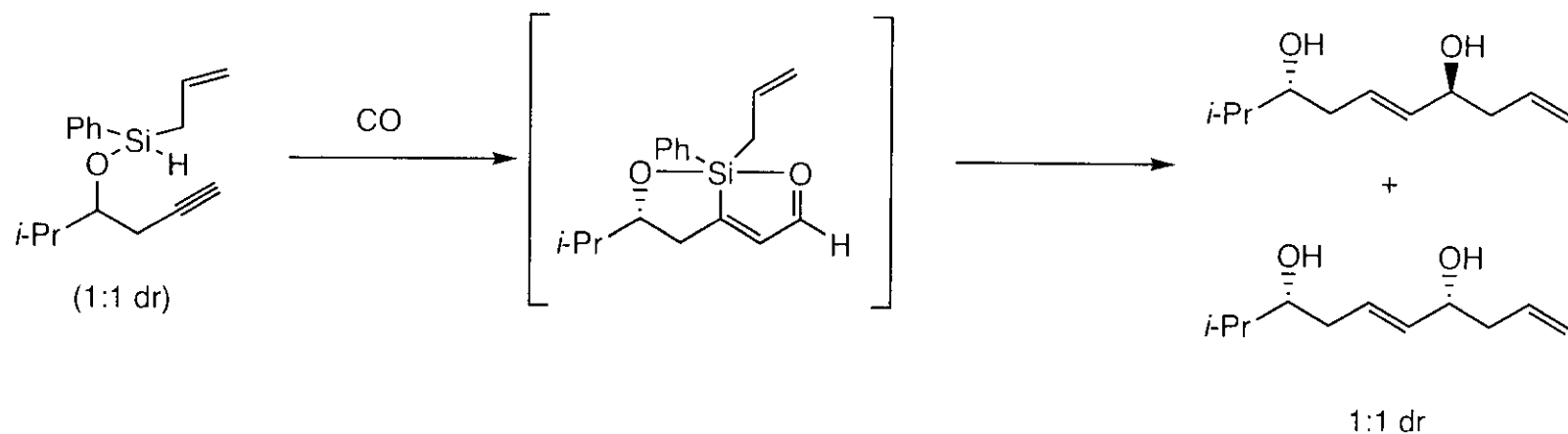
O'Malley, S. J.; Leighton, J. L.
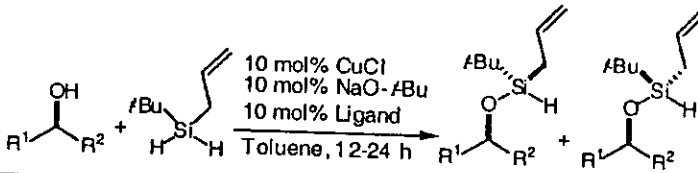*Angew. Chem. , Int. Ed.* **2001**, *40*, 2915

10

Access to Chiral Silanes

Table 1. Identification of Effective Chiral Phosphine Ligands

entry	R	ligand	conv. (%)[a]	dr[b]
1	Ph	(R)-BINAP	2	58:42
2	Ph	(R)-(S)-JOSIPHOS	2	54:46
3	Ph	(R,R)-BDPP	2	58:42
4	$2,6\text{-Me}_2\text{C}_6\text{H}_3$	(R)-BINAP	47	61:39
5	$2,6\text{-Me}_2\text{C}_6\text{H}_3$	(R)-(S)-JOSIPHOS	84	59:41
6	$2,6\text{-Me}_2\text{C}_6\text{H}_3$	(R,R)-BDPP	99	47:53
7	t-Bu	(R)-BINAP	58	80:20
8	t-Bu	(R)-(S)-JOSIPHOS	23	77:23
9	t-Bu	(R,R)-BDPP	75	80:20

[a] Conversion of alcohol measured by GC versus an internal standard.
[b] Diastereomeric ratio measured by ^{1}H NMR or GC analysis.

Table 2. Catalytic Asymmetric Silane Alcoholysis

entry	R¹	R²	ligand	yield (%)[a]	dr[b]
1	n-Pr	CH_2CCH	(R,R)-BDPP	75	80:20
2	n-Pr	CH_2CCH	(S,S)-BDPP	89	20:80
3	CH_2CCH	i-Pr	(R,R)-BDPP	91	82:18
4	CH_2CCH	i-Pr	(S,S)-BDPP	93	36:64
5[c]	Ph	CH_2CCH	(R,R)-BDPP	83	90:10
6[c]	Ph	CH_2CCH	(S,S)-BDPP	82	12:88
7[c]	Et	Ph	(R,R)-BDPP	99	78:22
8[c]	Et	Ph	(S,S)-BDPP	99	12:88

[a] Isolated yield of the mixture of diastereomers. [b] Diastereomeric ratio measured by ^{1}H NMR or GC analysis. [c] Reaction run at -15 °C for 16 h.

Chiral Silanes: access to 1,5-*syn* and 1,5-*anti*-stereoinduction

1) ((PhO)₃P)₂Rh-(CH₃COCH₃)₂·BF₄
(10 mol %)
CO, PhH, 60 °C

2) *n*-Bu₄N⁺F⁻, THF
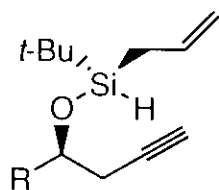
1 R = *n*-Pr, 80:20 *dr*
2 R = Ph, 90:10 *dr*
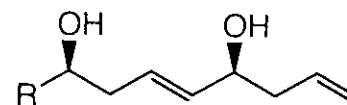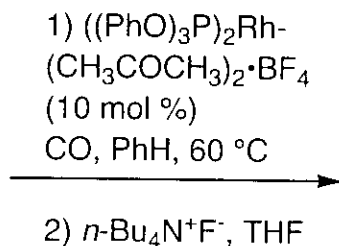
3 R = *n*-Pr, 55 %; 78:22 *dr*
4 R = Ph, 38%; 90:10 *dr*

1) ((PhO)₃P)₂Rh-(CH₃COCH₃)₂·BF₄
(10 mol %)
CO, PhH, 60 °C

2) *n*-Bu₄N⁺F⁻, THF
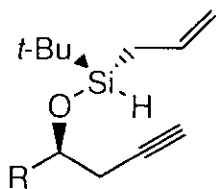
5 R = *n*-Pr, 80:20 *dr*
6 R = Ph, 88:12 *dr*
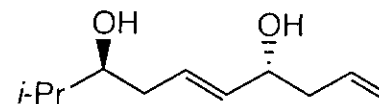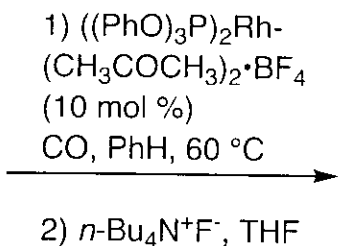
7 R = *n*-Pr, 44 %; 79:21 *dr*
8 R = Ph, 43%; 88:12*dr*

Schmidt, D. R.; O'Malley, S. J.; Leighton, J. L. *J. Am. Chem. Soc.* **2003**, *125*, 1190-1191.

12

Polyketides: The Dolabelides

Dolabelide A, R = Ac
Dolabelide B, R = H

Boron-mediated aldol

Tandem silylformylation-crotylation

13

Schmidt, D. R.; Park, P. K.; Leighton, J. L *Org. Lett.* **2003**, *5*, 3535-3537.
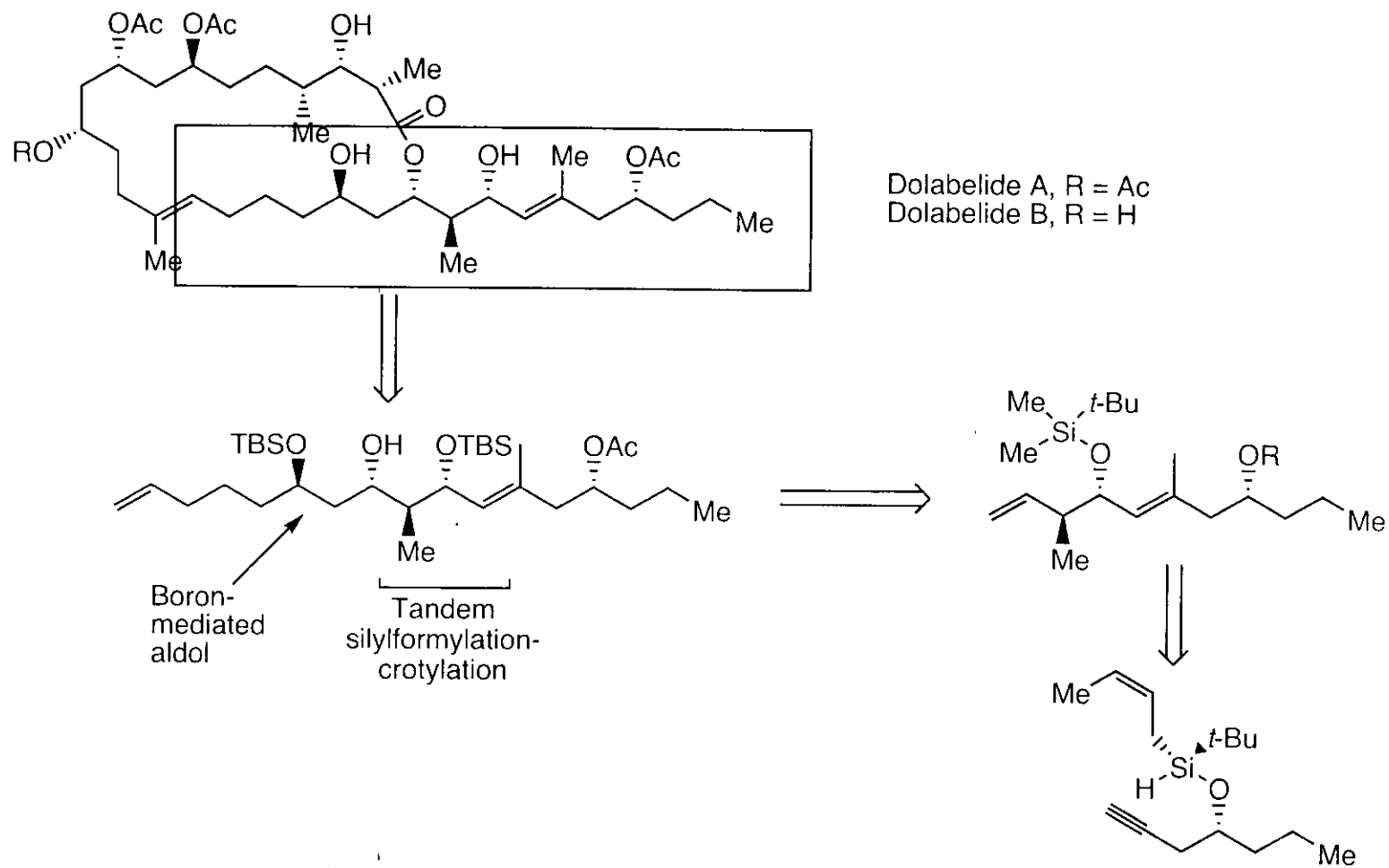
Dolabelides: Tandem Silylformylation - Crotylation

Reagents (step 1): CuCl (4 mol %), NaO-t-Bu (4 mol %), (R,R)-BDPP (4 mol %), Ph-H, 12 h, 95%, 4 : 1 dr

(R,R)-BDPP =

Reagents (step 2): [Rh(acetone)$_2$-(P(OPh)$_3$)$_2$]BF$_4$, CO, Ph-H, 60 °C, Tandem Silylformylation - Crotylation

1,5-syn stereoinduction

1) MeLi (quench), Et$_2$O, 56% 4:1 dr

2) TES-Cl, Et$_3$N, CH$_2$Cl$_2$, -20 °C, 74% (as a single diastereomer)

n-BuLi, THF, 1,4-Brook "like" Rearrangement

CuBr·DMS, DMPU then MeI

14

Schmidt, D. R.; Park, P. K.; Leighton, J. L *Org. Lett.* **2003**, *5*, 3535-3537.
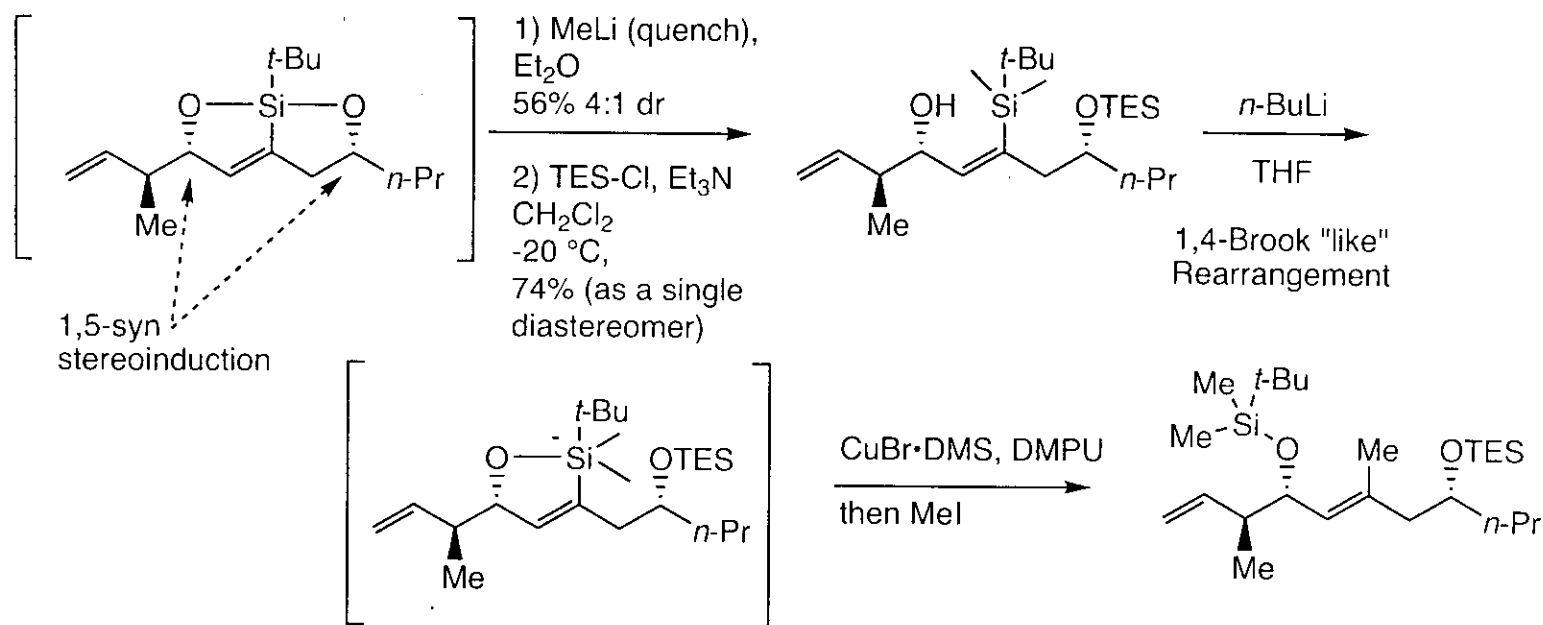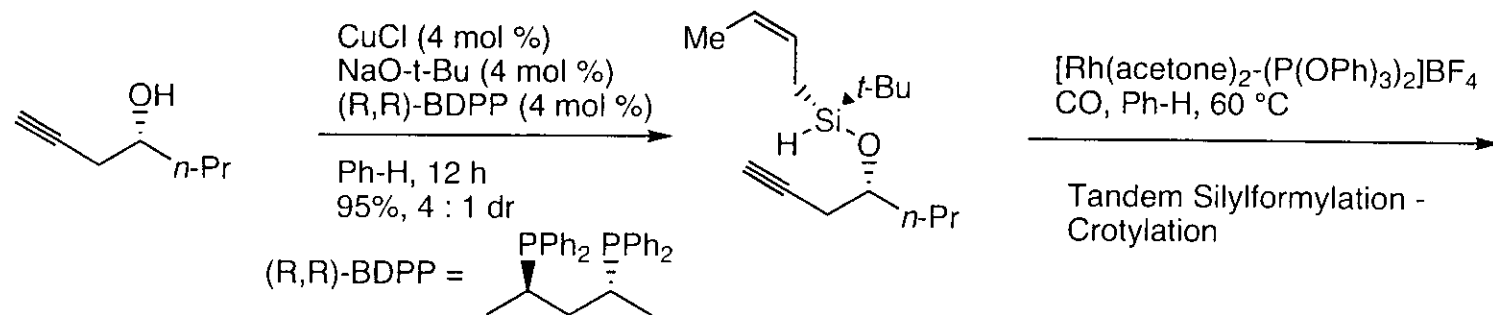
Dolabelides: Fragment Elaboration

1) PdCl$_2$, CuCl, O$_2$
DMF, THF, H$_2$O

2) Ac$_2$O, Pyr
78% 2 steps
3) (+)-(Ipc)$_2$BCl, Et$_3$N

1) Me$_4$NBH(OAc)$_3$
AcOH, CH$_3$CN, -20°C
>10:1 dr

2) TBS-Cl, Imidazole
62%, 3 steps

15

Schmidt, D. R.; Park, P. K.; Leighton, J. L *Org. Lett.* **2003**, *5*, 3535-3537.
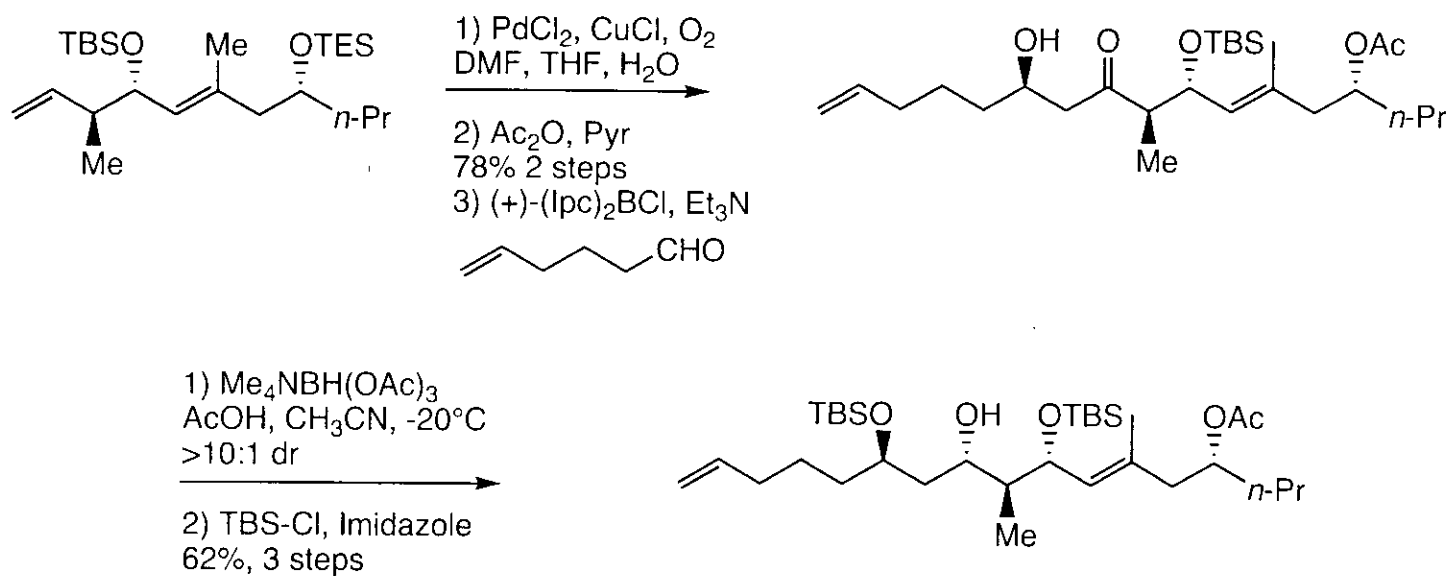
Tandem Aldol-Allylation(Crotylation)

R = Ph or Cy

Toluene
40 °C, 24 h

R = Ph; 60 %; 11:1 *dr*
R = Cy; 59 %; 12:1 *dr*

+

29%
18%

Toluene
40 °C, 24 h

52 % major
82% (66:23:8:3 *dr*)

Toluene
40 °C, 24 h

51% major
81% (65:24:7:4 *dr*)

16

Wang, X.; Meng, Q.; Nation, A. J.; Leighton, J. L. *J. Am. Chem. Soc.* **2002**, *124*, 10672-10673.

Silacyclopropanes

1) AgOTf (<5 mol %),
   Toluene, -27 °C

2) ZnBr$_2$ (20 mol %)
   HCO$_2$CH$_3$,
   -78 °C to 22 °C
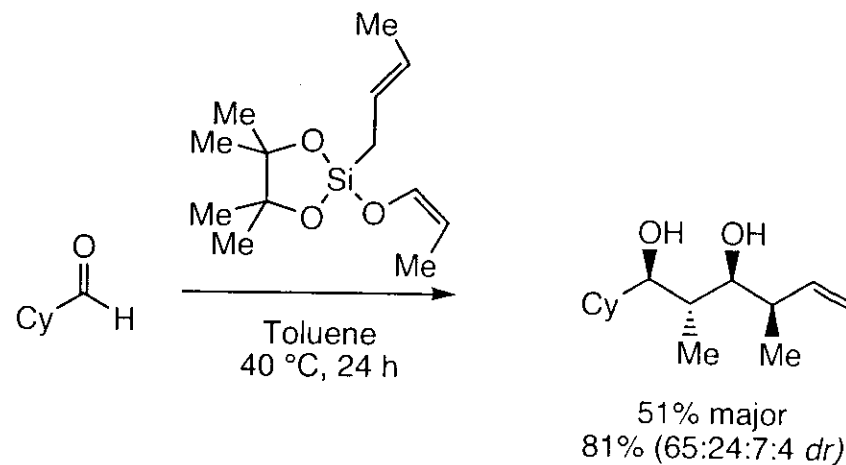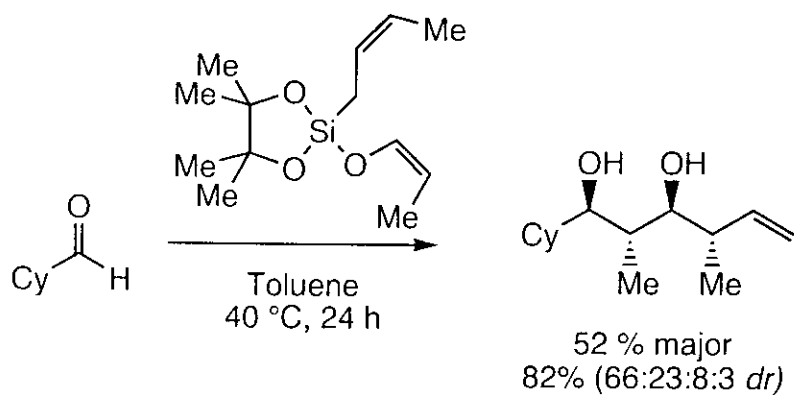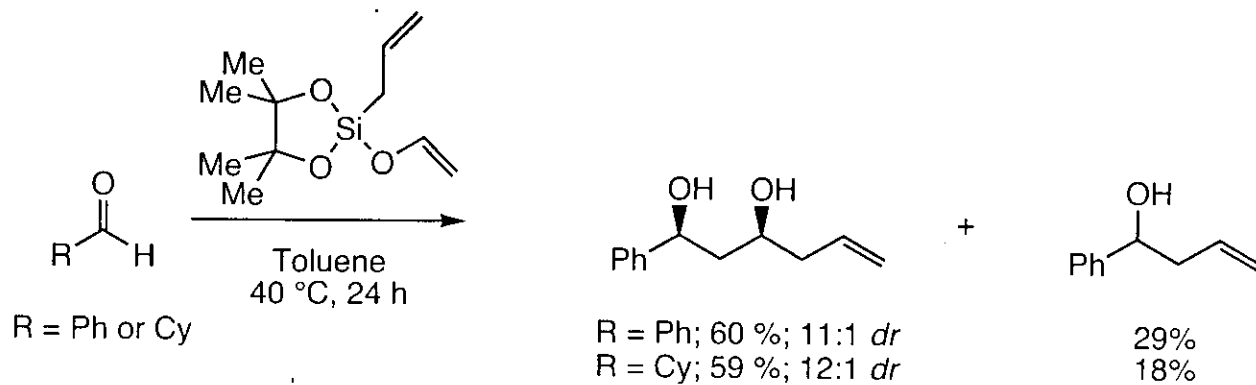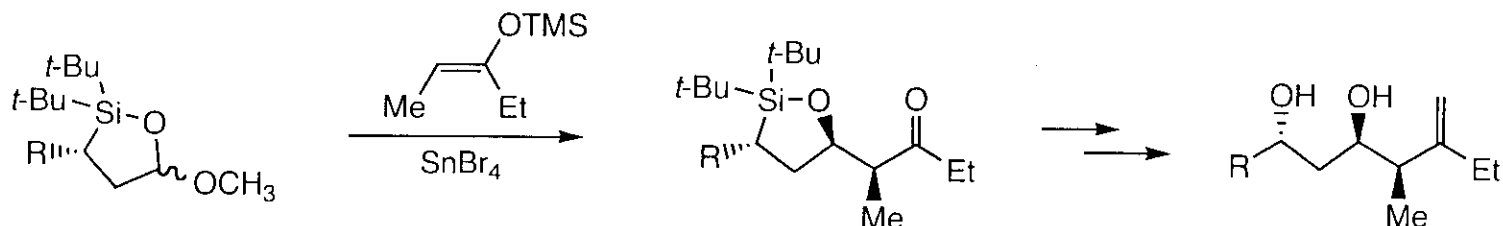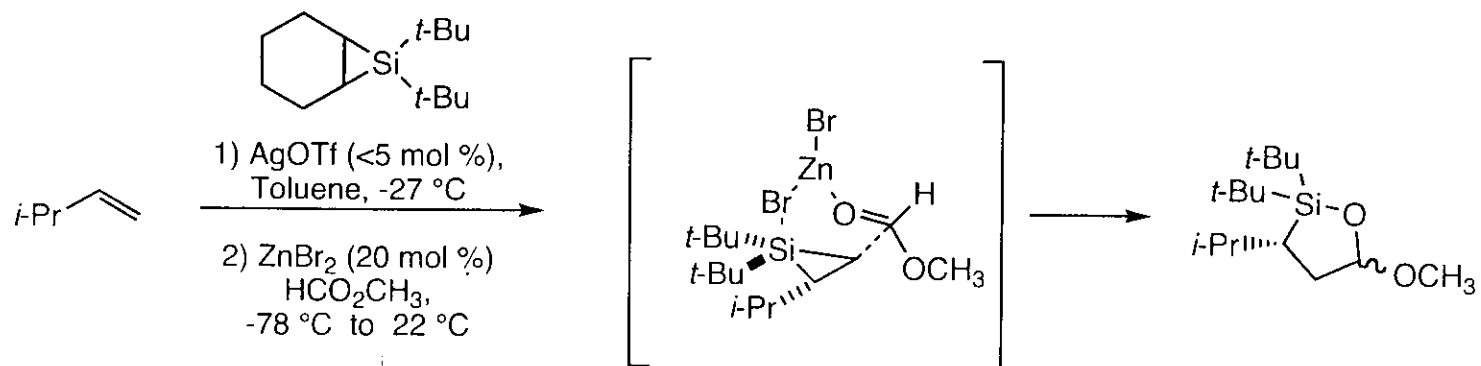
- Cu salts insert into the <u>more</u> substituted C-Si bond (unsaturated aldehydes).
- Zn salts insert into the <u>less</u> substituted C-Si bond.
- Generally not regarded as a useful alternative to other existing technologies.
- Refer to previous "Current Literature" for more details.

Cirakovic, J.; Driver, T. G.; Woerpel, K. A. *J. Org. Chem.* **2004**, ASAP (DOI: jo0355505);
Driver, T. G.; Woerpel, K. A. *J. Am. Chem. Soc.* **2003**, *125*, 10659-10663.

17

Silacyclopentene Oxides:
A Strategy for Polyol Synthesis
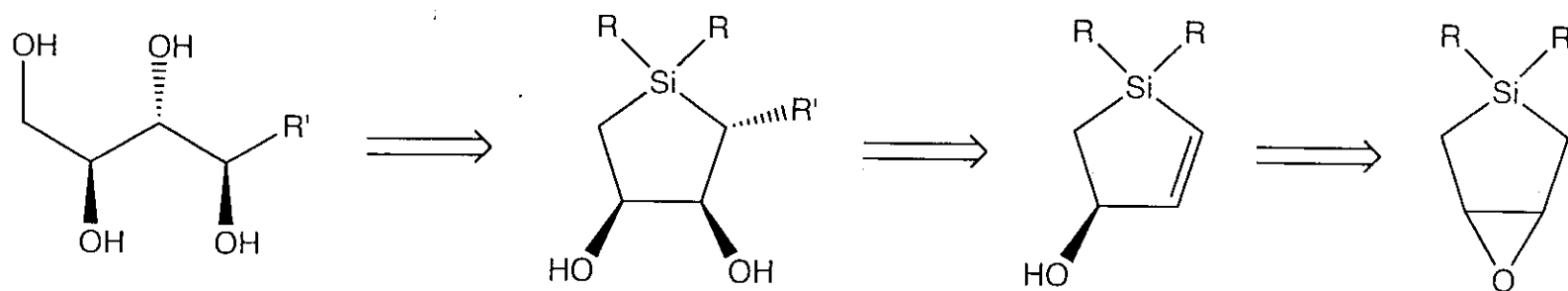
Liu, D.; Kozmin, S. A. *Angew. Chem. Int. Ed.* **2001**, *40*, 4757-4759

18

Silacyclopentene Oxides

Mg, THF

Ph$_2$SiCl$_2$
82%

MCPBA

CH$_2$Cl$_2$
98%

Preparative scale
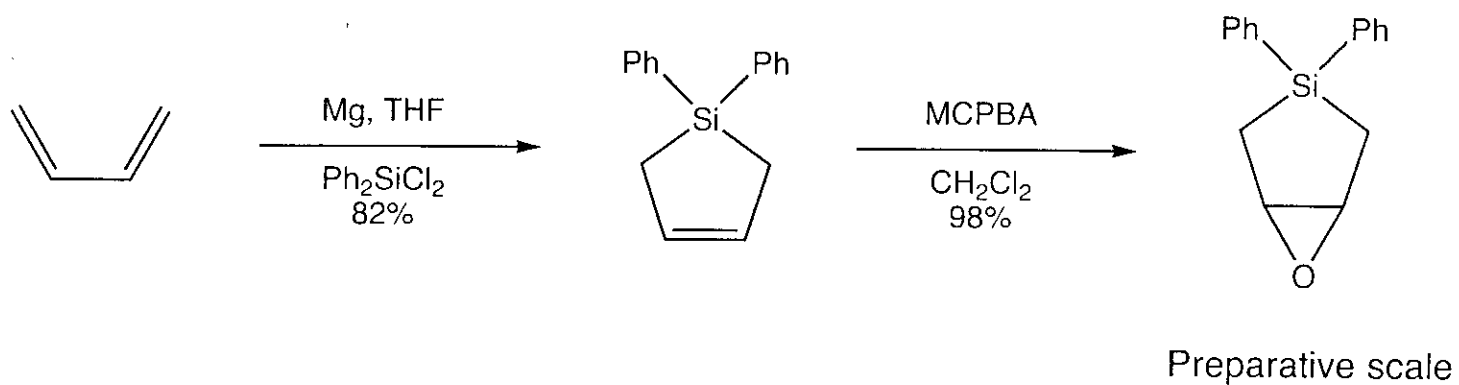
Richter, W. J. *Synthesis* **1982**, 1102.
Mignani, S. et. al. *Syn. Commun.* **1995**, *25*, 3855.
Manuel, G. et. al. *J. Organomet. Chem*, **1993**, *447*, 167.

19

Stereoselective Rearrangements
of Silacyclopentene Oxides

LDA (200 mol %)
THF-DBU, -78 °C to 0 °C

5 mol % ligand: 72 % yield, 91 % ee
10 mol % ligand: 78% yield, 93% ee
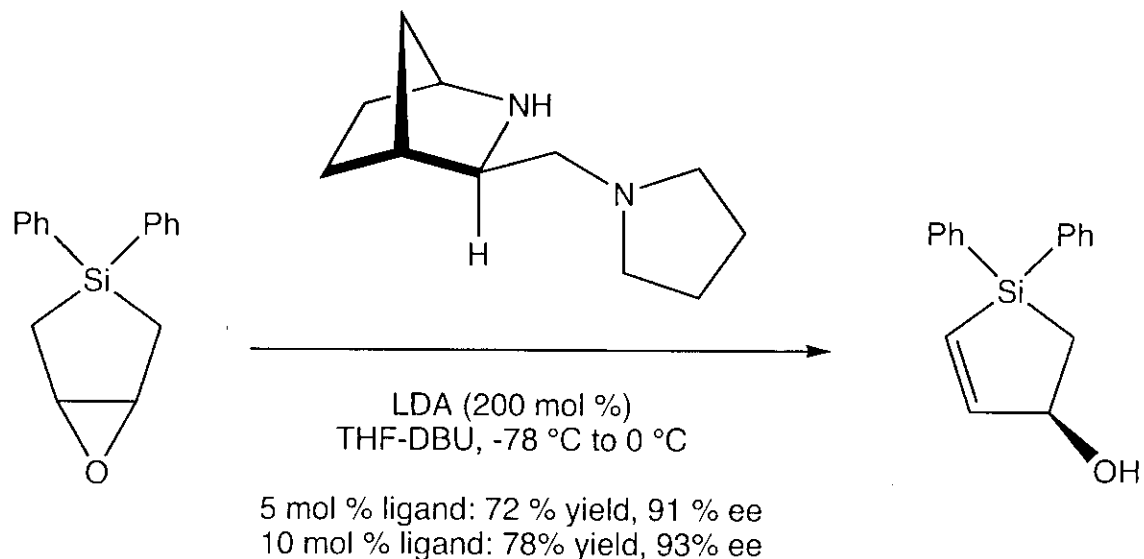
- Silicon atom is expected to be beneficial because:
    - α-Si-carbanion stabilization
    - silicon substituents can be varied to maximize selectivity and reaction rate.

- A variety of chiral diamine and amino-alcohol ligands were tested with diphenyl, methyl/napthyl, and diisopropyl substituted silacyclopentene oxides.

- Bicyclic amide (shown above) (150 mol %) and diphenyl silane gave the best ee (95%).

20

Liu, D.; Kozmin, S. A. *Angew. Chem. Int. Ed.* **2001**, *40*, 4757-4759

Epoxidation / Cuprate Addition Sequence
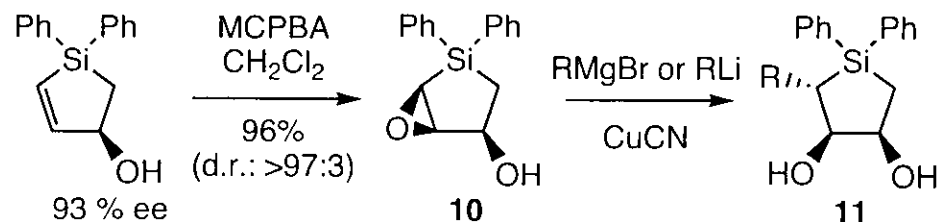
Entry	R	11	Yield [%][b]	d.r.
1	∿∿∕	(−)-11a	91[c]	> 97:3
2	∿∿∕	(−)-11a	72[d]	> 97:3
3	⋋∕	(−)-11b	78[c]	> 97:3
4	∿∕	(−)-11c	92[c]	> 97:3
5	∕∿∕	(−)-11d	87[c]	> 97:3
6	Ph∿∕	(−)-11e	92[c]	> 97:3
7	Ph∕∿∕	(−)-11f	86[c]	> 97:3
8	TMS∿∕	(−)-11g	91[d]	> 97:3
9	H∿∕ (LiAlH₄)	(−)-11f	64[e]	> 97:3

[a] For detailed experimental procedures and compound characterization, see Supporting Information. [b] Refers to the yield of spectroscopically pure product isolated after silica gel chromatography. [c] Organocuprate was generated from the corresponding Grignard reagent. [d] Organo-cuprate was generated from the corresponding organolithium reagent. [e] Reduction was carried out on the methoxymethyl(MOM)-protected alcohol (−)-10 to prevent formation of the *meso* product.

21

Oxidative Cleavage of the Cyclic Silanes
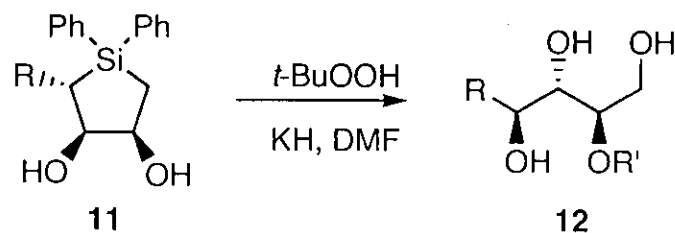
Entry	Silane	R	R′	12	Yield [%][b]
1	(−)-11a		H	(−)-12a	78
2	(+)-11b		H	(−)-12b	76
3	(+)-11c		H	(−)-12c	79
4	(−)-11f	Ph	H	(−)-12d	70
5	(−)-11h	H	MOM	(−)-12e	74

[a] For detailed experimental procedures and compound characterization, see Supporting Information. [b] Refers to the yield of spectroscopically pure product isolated after silica gel chromatography.

Liu, D.; Kozmin, S. A. *Angew. Chem. Int. Ed.* **2001**, *40*, 4757-4759.
Smitrovich, J. H.; Woerpel, K. A. *J. Org. Chem.* **1996**, *61*, 6044.

22

(-)-Pinolidoxin: Retrosynthesis

Liu, D. Kozmin, S. A. *Org. Lett.* **2002**, *4*, 3005-3007.
Isolation and biological activity: Evidente, A. et. al. *Phytochemistry* **1993**, *34*, 999.

23
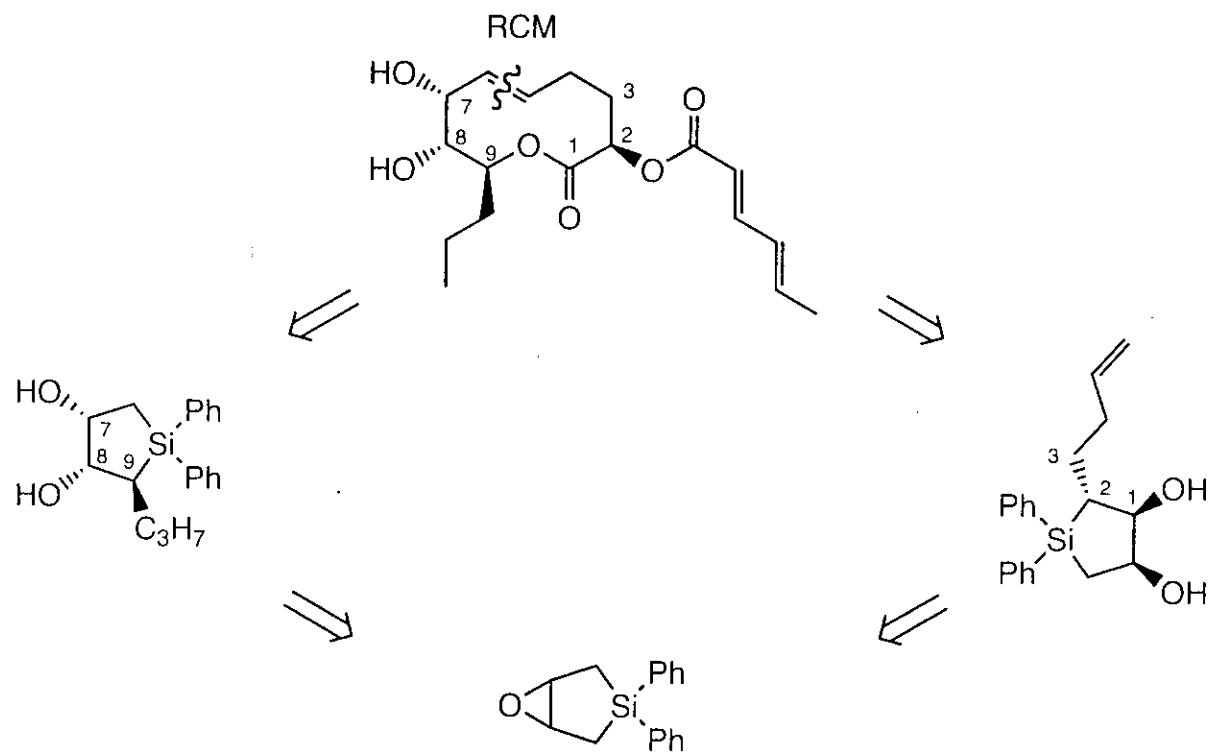
(-)-Pinolidoxin: Fragment Synthesis

Top scheme:

Ph Ph Si / OH

1) MCPBA, CH₂Cl₂
2) n-PrMgBr, CuCN, THF

92%

Ph Ph Si / HO OH

1) Me₂C(OMe)₂, PPTS, MeOH

2) t-BuOOH, KH DMF
74%

OH OH / O O

1) TES-Cl, Et₃N
2) Swern, 81% (2 steps)

3) Ph₃P=CH₂
4) TBAF, THF
76% (2 steps)

OH / O O

Bottom scheme:

Ph Ph Si / OH

1) MCPBA, CH₂Cl₂
2) 3-butenylMgBr, CuCN, THF

82%

Ph Ph Si / HO OH

1) Me₂C(OMe)₂, PPTS, MeOH

2) t-BuOOH, KH DMF
66%

OH OH / O O

1) Sorbic acid DCC, DMAP, 88%

2) TFA, THF
3) Pb(OAc)₄
4) NaClO₂
58% (3 steps)

HO₂C O

24

Liu, D. Kozmin, S. A. *Org. Lett.* **2002**, *4*, 3005-3007.

(-)-Pinolidoxin: Fragment Coupling and Macrocyclization

2,4,6-trichlorobenzoyl
chloride, Et$_3$N, DMAP

PhH
82%

1) TFA, THF, H$_2$O, 81%
2) Grubbs II Catalyst, 62%
trans:cis $\rightleftharpoons$ 67:33

with the acetonide in place
cis:trans = >95:5

(-)-Pinolidoxin

25

Liu, D. Kozmin, S. A. *Org. Lett.* **2002**, *4*, 3005-3007.
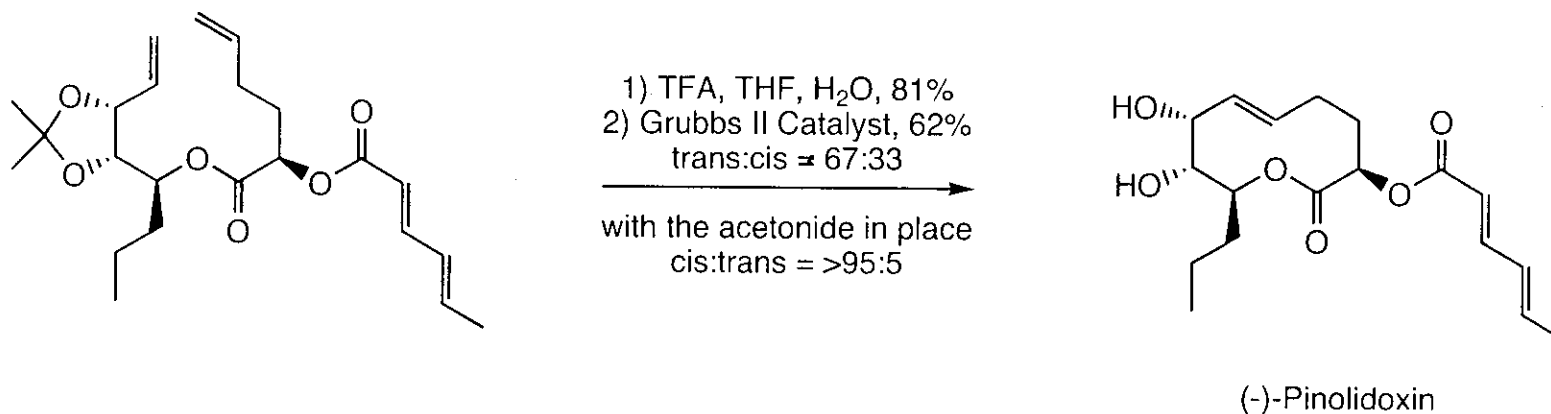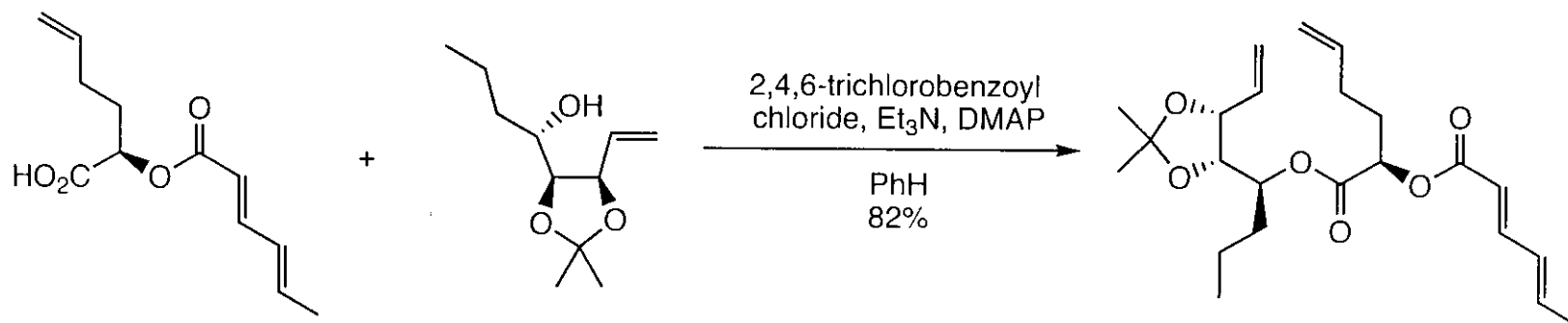
Cross Coupling of Organosilanes via a Pentacoordinate Intermediate

SiX_3 = $SiMe_2(OEt)$; 95 %
SiX_3 = $SiMe(OEt)_2$; 96 %
SiX_3 = $SiMe(OEt)_3$; 54 %
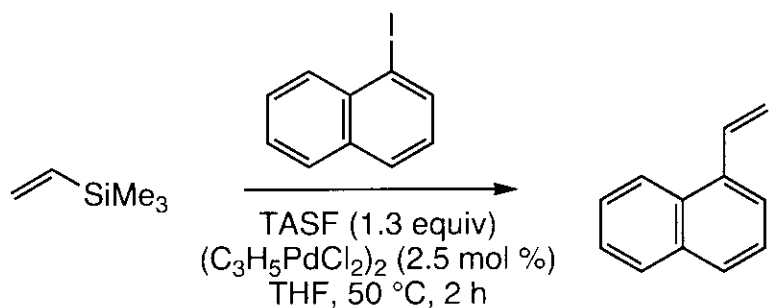
- 23 examples given with yields 67 - 100%.
- vinyl, allylic and alkynyl silanes were used.
- HMPA and $P(OEt)_3$ added in some cases.

Hatanaka, Y.; Hiyama, T.
J. Org. Chem. **1988**, *53*, 918-920.
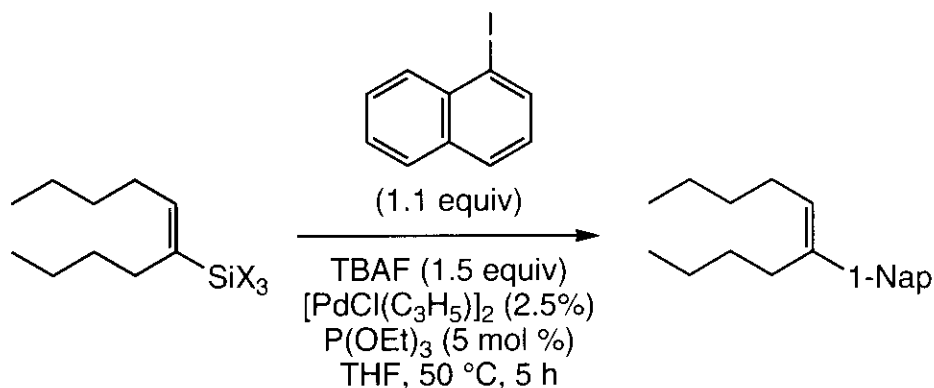
- 13 examples given with yields 45 - 96%.
- alkenyltrialkoxysilanes more reactive than alkenyl trifluorosilanes (inert).
- alkenyl bromides also coupled with longer reaction times.

Tamao, K.; Kobayashi, K.; Ito, Y.
Tetrahedron Lett. **1989**, *30*, 6051-6054.

26

Cross-Coupling Reactions of Silacyclobutanes?
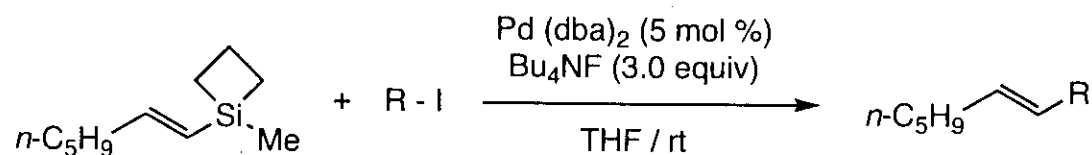
- Aryl iodides (electron poor and electron rich) generally couple in less than 1 h with yields > 90%.

- Vinyl iodides usually couple in less than 2 h with yields 65-95%.

- Premixing the silacyclobutane and TBAF was required to limit formation of reduction byproducts.

- A significant exotherm was observed when silacyclobutane and TBAF were mixed.

Denmark, S. E.; Choi, J. Y. *J. Am. Chem. Soc.* **1999**, *121*, 5821-5822.

27

The Fate of the Silacyclobutane

1) Bu$_4$NF (1.0 equiv)
   THF / rt

2) separation on SiO$_2$

n-C$_5$H$_{11}$ ... Si-OH   42 %

+   45 %

2: X = OH
6: X = OSi(Me)$_2$C$_7$H$_{13}$
7: X = F
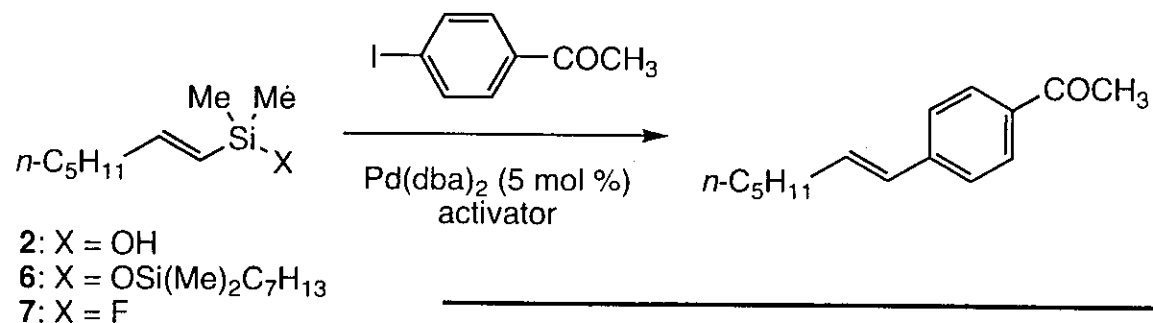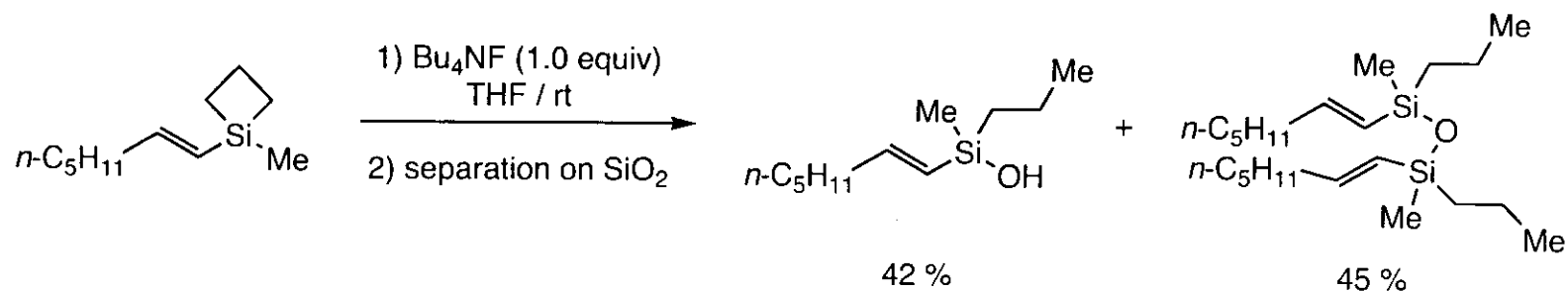
Pd(dba)$_2$ (5 mol %)
activator

		yield, % (time)		
	no activator	TBAF[a]	TBAF[b]	TBAOH[b]
2	NR	82 (1 h)	79 (10 min)	75 (3 h)
6	NR	82 (1 h)	82 (10 min)	78 (3h)
7	NR	79 (1 h)	78 (10 min)	22 (24 h)

[a] 1 equiv. [b] 2 equiv.

28

Denmark, S. E.; Wehrli, D.; Choi, J. Y. *Org. Lett.* **2000**, *2*, 2491-2494.
Denmark, S. E.; Sweis, R. F.; Wehrli, D. *J. Am. Chem. Soc.* ASAP, 2004.

Fluoride Promoted Cross Coupling

Low [TBAF] Regime
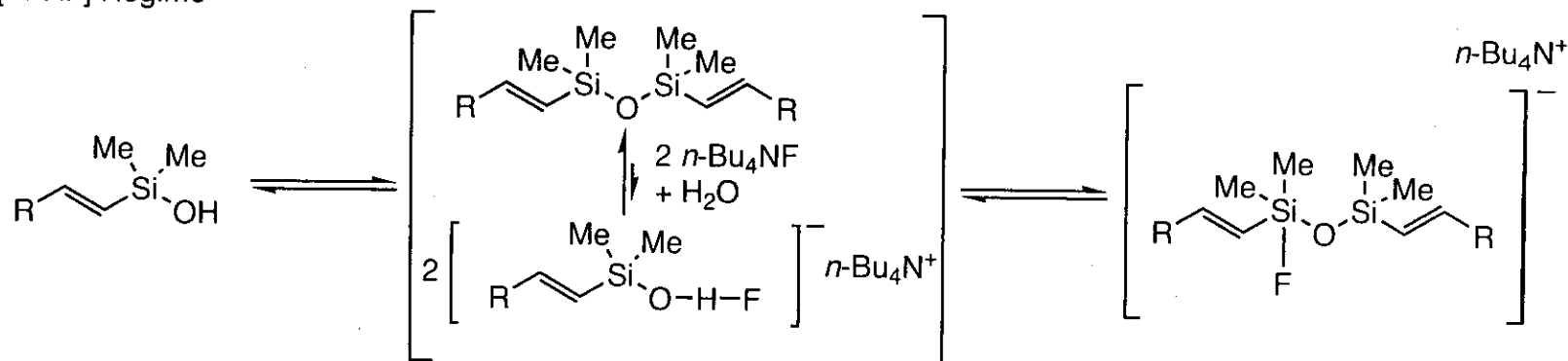
High [TBAF] Regime
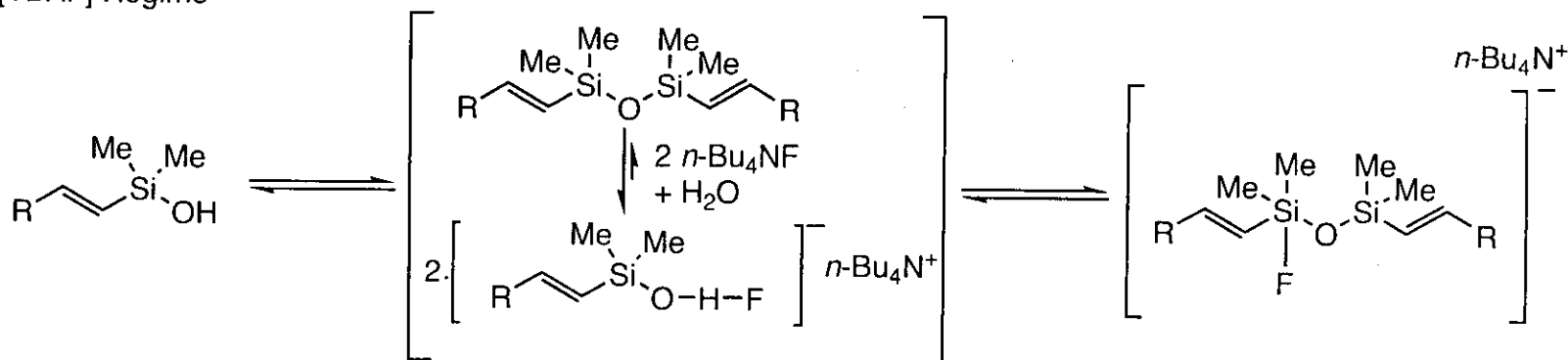
- The rate is second order in silanol and first order in disiloxane.
- The transmetallation is the turn-over limiting step.
- The rate dependence on [TBAF] is first order for low [TBAF] and inverse first order for high [TBAF].

29

Denmark, S. E.; Sweis, R. F. *J. Am. Chem. Soc.* ASAP, 2004.

(+)-Brasilenyne: Retrosynthesis

intramolecular
cross coupling

ring-closing
metathesis

(+)-Brasilenyne

OPMB

OPMB

L-malic acid

Denmark, S. E.; Yang, S. *J. Am. Chem. Soc.* **2002**, *124*, 15196-15197.

30
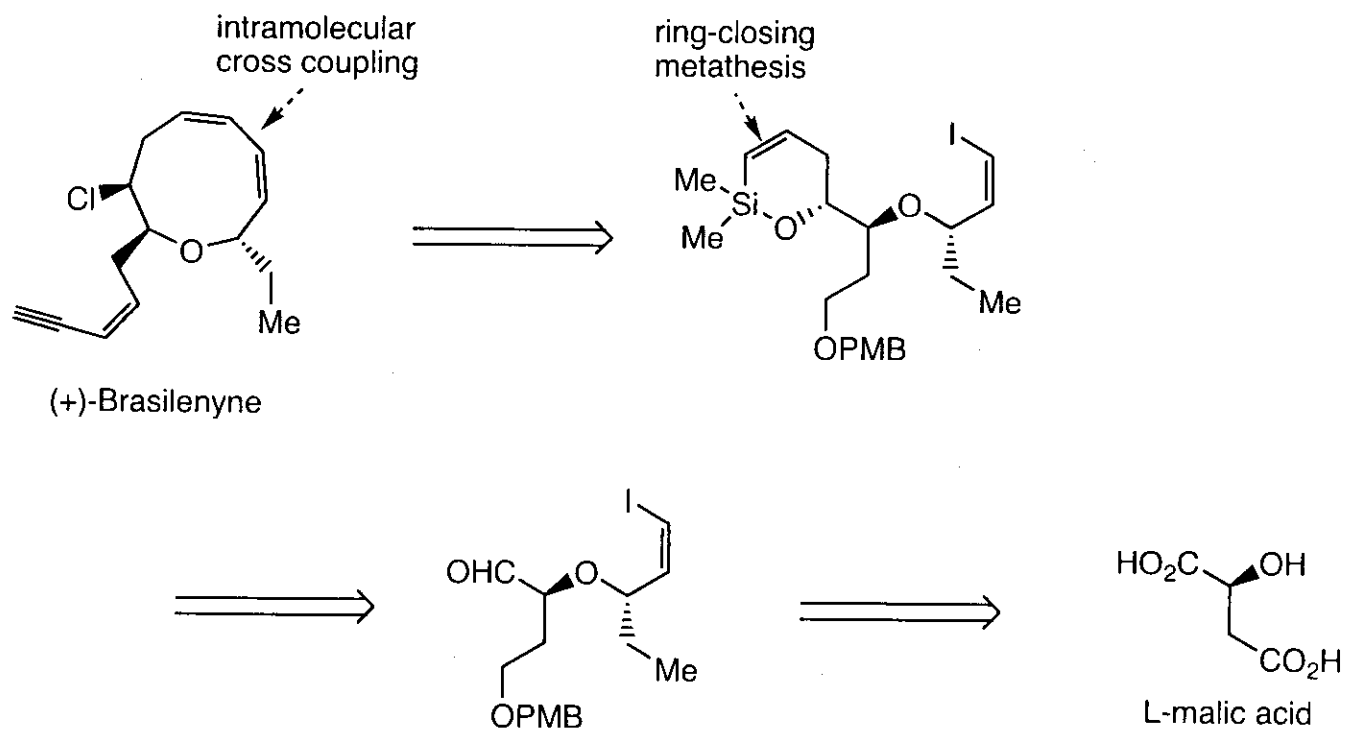
(+)-Brasilenyne: Synthesis of the Key Intermediate

1) Propanal, BF₃·OEt₂; 85%
2) BH₃·THF, THF; 82%

3) TBS-Cl, pyr., CH₂Cl₂; 85%

cis:trans = 7:3

L-malic acid

1) bis(TMS)acetylene
TiCl₄, CH₂Cl₂ then
p-TSA, Ph-H; 86%

2) NIS, AgNO₃; 95%
3) KO₂CN=NCO₂K
AcOH; 80%

1) Me(OMe)NH·HCl, AlMe₃
CH₂Cl₂; 93%

2) PMB-Cl, Ag₂O
CH₂Cl₂; 82%
3) DiBAl-H, CH₂Cl₂; 82%

allylB(ᶦIpc)₂, Et₂O
-100 °C; 89%

"Mg²⁺ salt free"
(>97:3 dr)

Denmark, S. E.; Yang, S. *J. Am. Chem. Soc.* **2002**, *124*, 15196-15197.

31
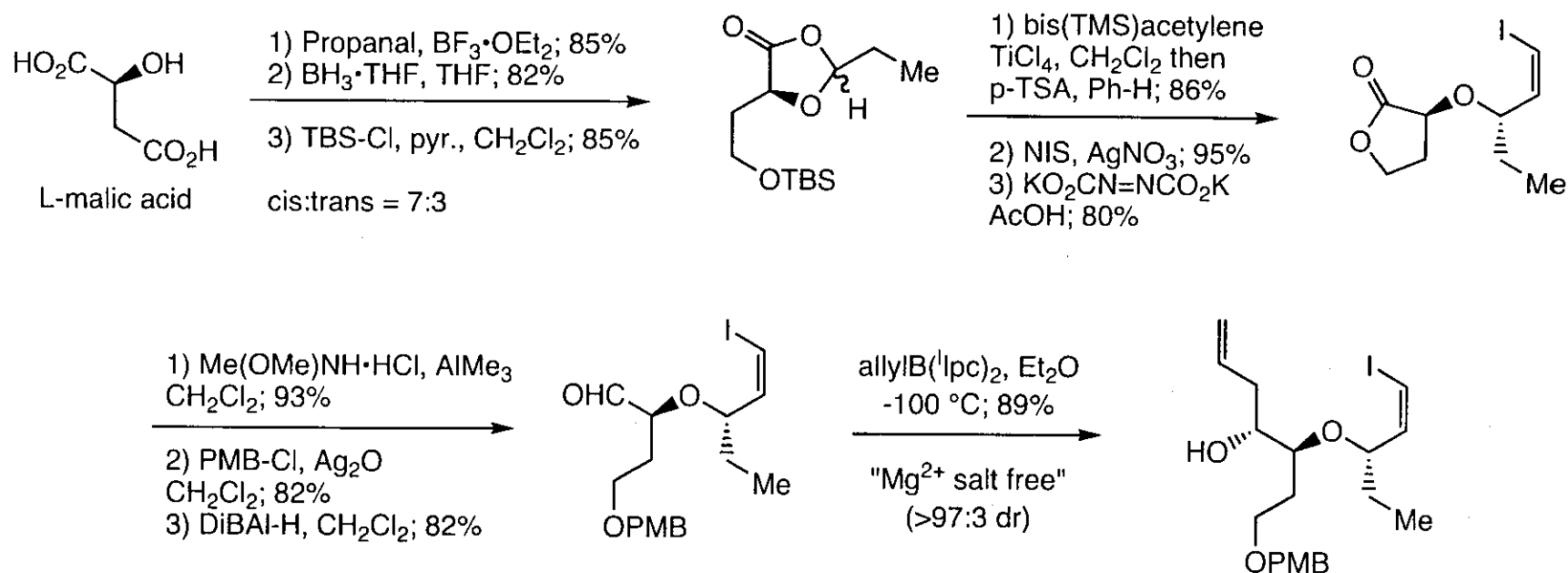
(+)-Brasilenyne: Key Cyclization and Completion
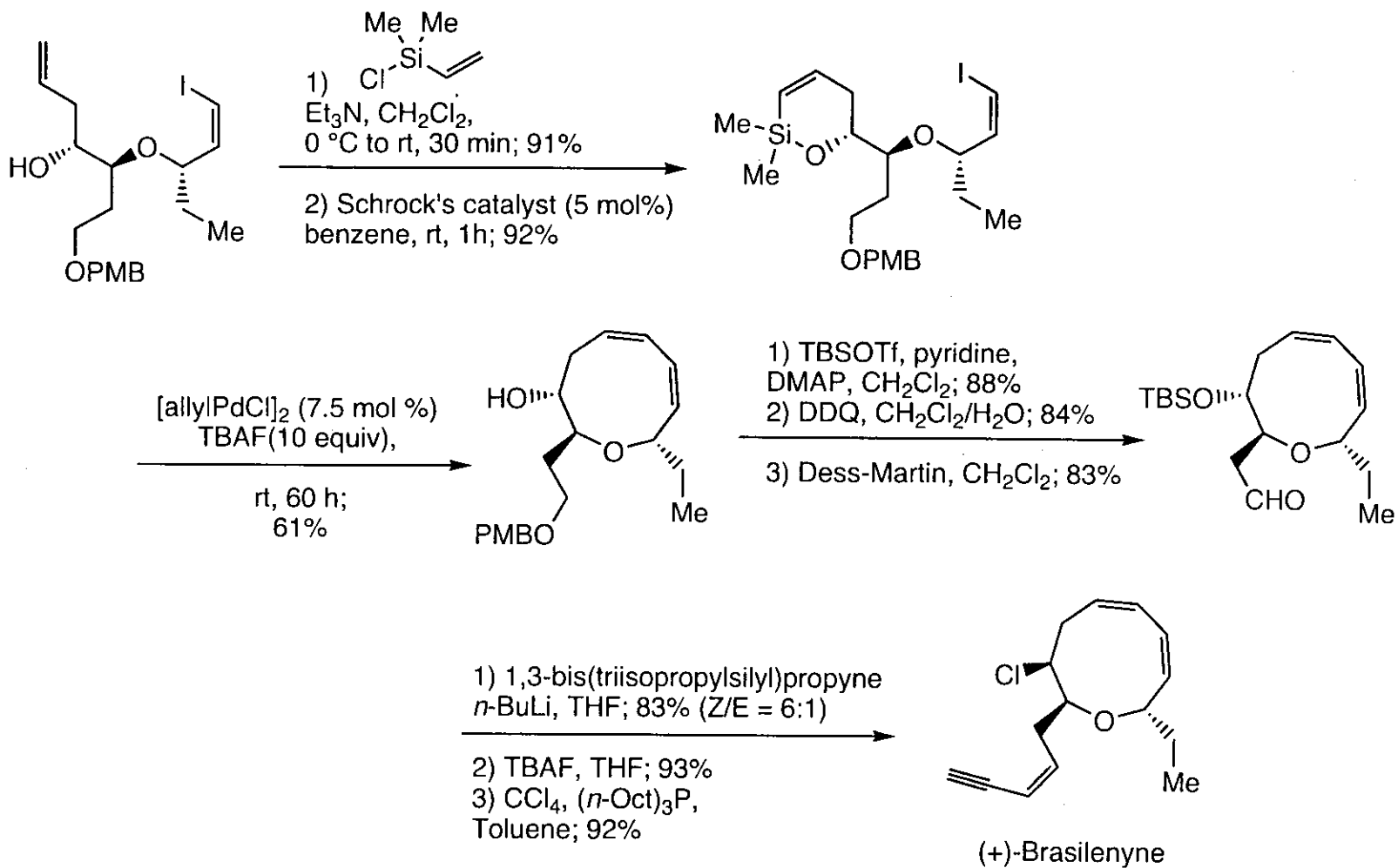
1) Me Si Me, Cl, ⟨vinyl⟩
Et₃N, CH₂Cl₂,
0 °C to rt, 30 min; 91%

2) Schrock's catalyst (5 mol%)
benzene, rt, 1h; 92%

[allylPdCl]₂ (7.5 mol %)
TBAF(10 equiv),

rt, 60 h;
61%

1) TBSOTf, pyridine,
DMAP, CH₂Cl₂; 88%
2) DDQ, CH₂Cl₂/H₂O; 84%

3) Dess-Martin, CH₂Cl₂; 83%

1) 1,3-bis(triisopropylsilyl)propyne
n-BuLi, THF; 83% (Z/E = 6:1)

2) TBAF, THF; 93%
3) CCl₄, (n-Oct)₃P,
Toluene; 92%

(+)-Brasilenyne

Denmark, S. E.; Yang, S. *J. Am. Chem. Soc.* **2002**, *124*, 15196-15197.

32

Fluoride-Free Cross Coupling of Organosilanes
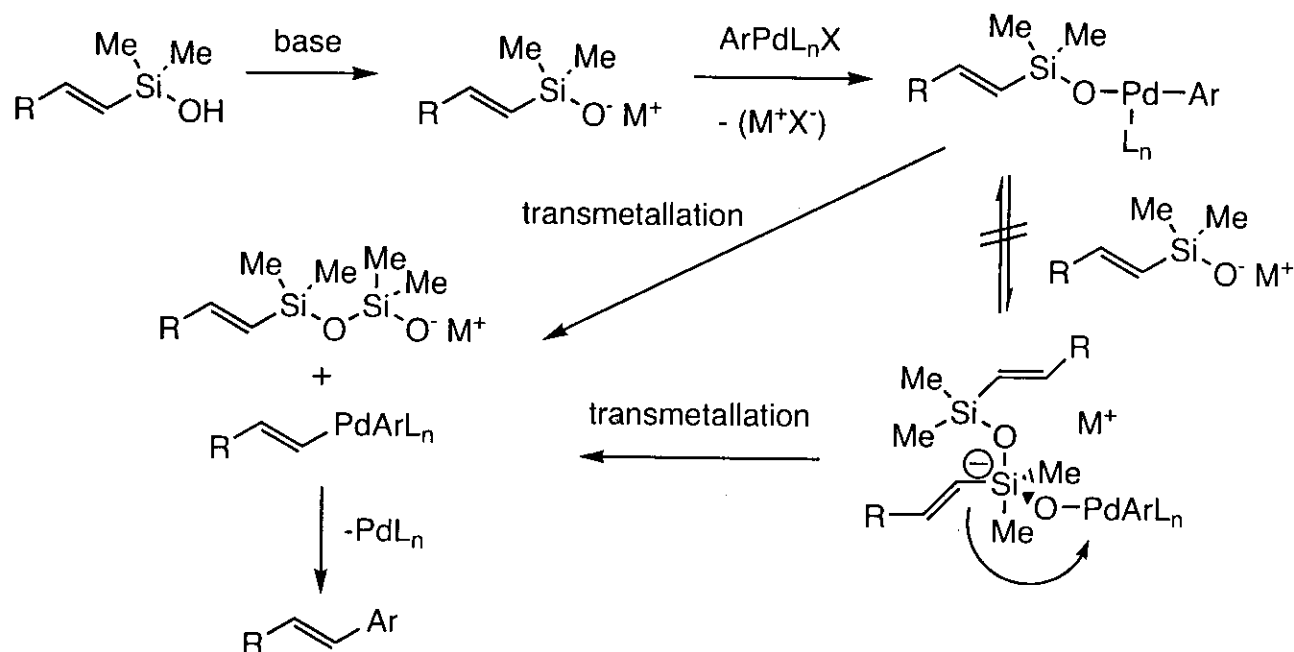
- When compared to TBAF, other activators may be less expensive and provide for easier purifications.
- Hydride reagents lead to reduction of the aryl iodide.
- The use of K⁺O*t*-Bu⁻ gave less reduction, but resulted in extended reaction times (3 h).
- KOTMS (2.0 equiv) gave good yields and rates.
- Recent results suggest that a pentavalent Si is <u>not</u> involved as a key intermediate prior to transmetallation.

Denmark, S. E.; Sweis, R. F. *J. Am. Chem. Soc.* **2001**, *123*, 6439-6440.
Denmark, S. E.; Sweis, R. F. *J. Am. Chem. Soc.* ASAP, 2004.

33

Fluoride-Free Cross Coupling of Organosilanes

$$R^1\text{-CH=C(R^2)-SiMe_2OH} \quad (\mathbf{1}) \quad + \quad Ar\text{-}I \quad \xrightarrow[\text{DME / rt}]{\substack{K^+\,{}^-OSiMe_3\ (2.0\ \text{equiv}) \\ Pd(dba)_2\ (5\ \text{mol}\%)}} \quad R^1\text{-CH=C(R^2)-Ar} \quad (\mathbf{2})$$
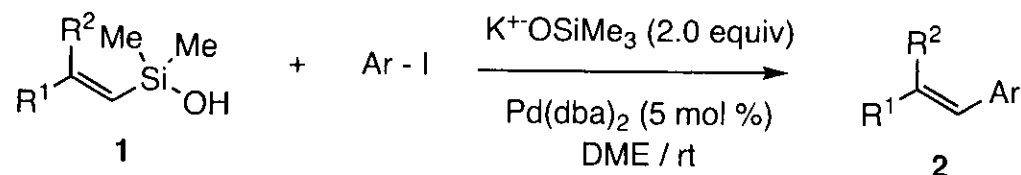
| entry	silane	R^1	R^2	aryl	time, h	product	yield, %	ratio, E/Z[b]
1	(E)-$\mathbf{1}$	n-C_5H_{11}	H	1-naphthyl	2	(E)-$\mathbf{2a}$	93[c]	97.9/2.1
2	(Z)-$\mathbf{1}$	H	n-C_5H_{11}	1-naphthyl	9	(Z)-$\mathbf{2a}$	88[c]	2.8/97.2
3	(E)-$\mathbf{1}$	n-C_5H_{11}	H	phenyl	0.5	(E)-$\mathbf{2b}$	91[c]	99.3/0.7
4	(Z)-$\mathbf{1}$	H	n-C_5H_{11}	phenyl	7.5	(Z)-$\mathbf{2b}$	86[c]	1.8/98.2
5	(E)-$\mathbf{1}$	n-C_5H_{11}	H	4-$(CH_3CO)C_6H_4$	9	(E)-$\mathbf{2c}$	82[c]	98.8/1.2
6	(Z)-$\mathbf{1}$	H	n-C_5H_{11}	4-$(CH_3CO)C_6H_4$	13	(Z)-$\mathbf{2c}$	83[c]	2.9/97.1
7	(E)-$\mathbf{1}$	n-C_5H_{11}	H	4-$(CH_3O)C_6H_4$	1	(E)-$\mathbf{2d}$	88[c]	99.3/0.7[d]
8	(Z)-$\mathbf{1}$	H	n-C_5H_{11}	4-$(CH_3O)C_6H_4$	9.5	(Z)-$\mathbf{2d}$	91[c]	1.1/98.9[e]
9	(E)-$\mathbf{1}$	n-C_5H_{11}	H	4-$(NO_2)C_6H_4$	0.25	(E)-$\mathbf{2e}$	95[f]	98.5/1.5
10	(Z)-$\mathbf{1}$	H	n-C_5H_{11}	4-$(NO_2)C_6H_4$	0.25	(Z)-$\mathbf{2e}$	85[f]	3.8/96.2
11	(E)-$\mathbf{1}$	n-C_5H_{11}	H	4-$(EtO_2C)C_6H_4$	0.25	(E)-$\mathbf{2f}$	85[f]	99.8/0.2
12	(Z)-$\mathbf{1}$	H	n-C_5H_{11}	4-$(EtO_2C)C_6H_4$	0.25	(Z)-$\mathbf{2f}$	83[f]	0.7/99.3
13	(E)-$\mathbf{1}$	n-C_5H_{11}	H	2-$(TBSOCH_2)C_6H_4$	9	(E)-$\mathbf{2g}$	80[f]	99.5/0.5
14	(Z)-$\mathbf{1}$	H	n-C_5H_{11}	2-$(TBSOCH_2)C_6H_4$	14.5	(Z)-$\mathbf{2g}$	76[f]	2.0/98.0[g]

[a] Reactions employed 1.1 equiv of $\mathbf{1}$. [b] Determined by GC analysis. [c] Yield of chromatographed, distilled products. [d] Accompanied by 3.8% cine-rearranged product. [e] Accompanied by 6.2% cine-rearranged product. [f] Yield of analytically pure material. [g] at 50 °C.

34

Access to Trisubstituted Olefins
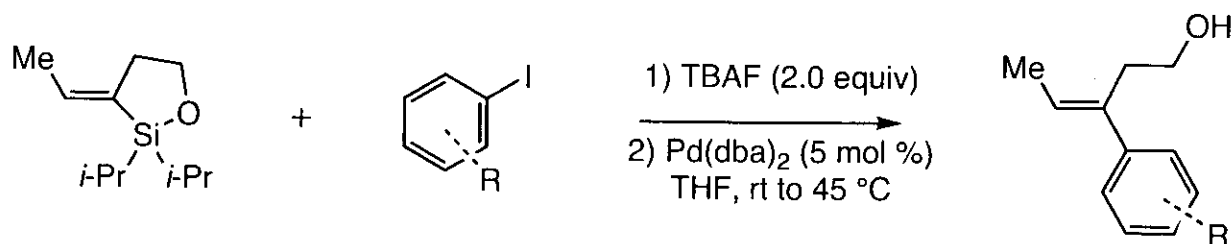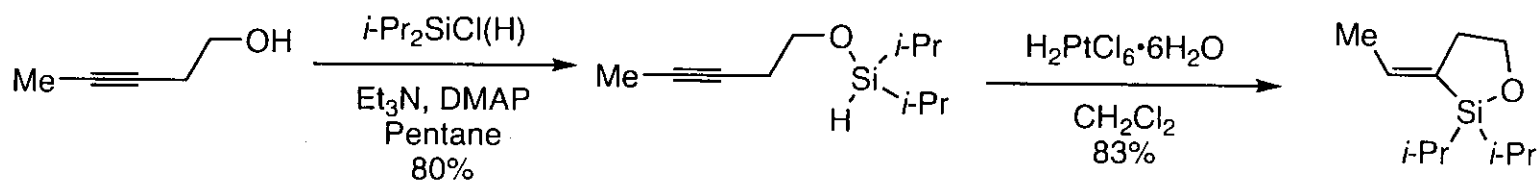
entry	R	time, h/temperature, °C	product	yield,[b] %
1	H	6.66/rt	3a	88
2	2-Me	6.83/rt	3b	74
3	2-MeO	10.0/35	3c	74
4	2-NO$_2$	23/35	3d	56
5	3-HOCH$_2$	6.0/rt	3e	81
6	4-CH$_3$O	6.50/rt	3f	72
7	4-MeCO	6.0/rt	3g	70
8	4-NO$_2$	6.25/rt	3h	67[c]
9	4-CN	46/45	3i	70
10	4-COOEt	16/45	3j	86

[a] Reaction conditions: 1.1 equiv of **2a**, 2.0 equiv of TBAF, and 5 mol % of Pd(dba)$_2$ were employed for 1.0 equiv of iodide in THF at rt. The iodide was added in portions as specified (see Supporting Information). [b] Yields of analytically pure materials. [c] Isomeric ratio 95.2/4.8 by capillary GC analysis.

Denmark, S. E.; Pan, W. *Org. Lett.* **2001**, *3*, 61-64.
Anti-intramolecular hydrosilylation with Ru:
Denmark, S. E.; Pan, W. *Org. Lett.* **2002**, *4*, 4163-4166.

35

Stilbene Derivatives from Sequential Heck / Cross Coupling Reactions
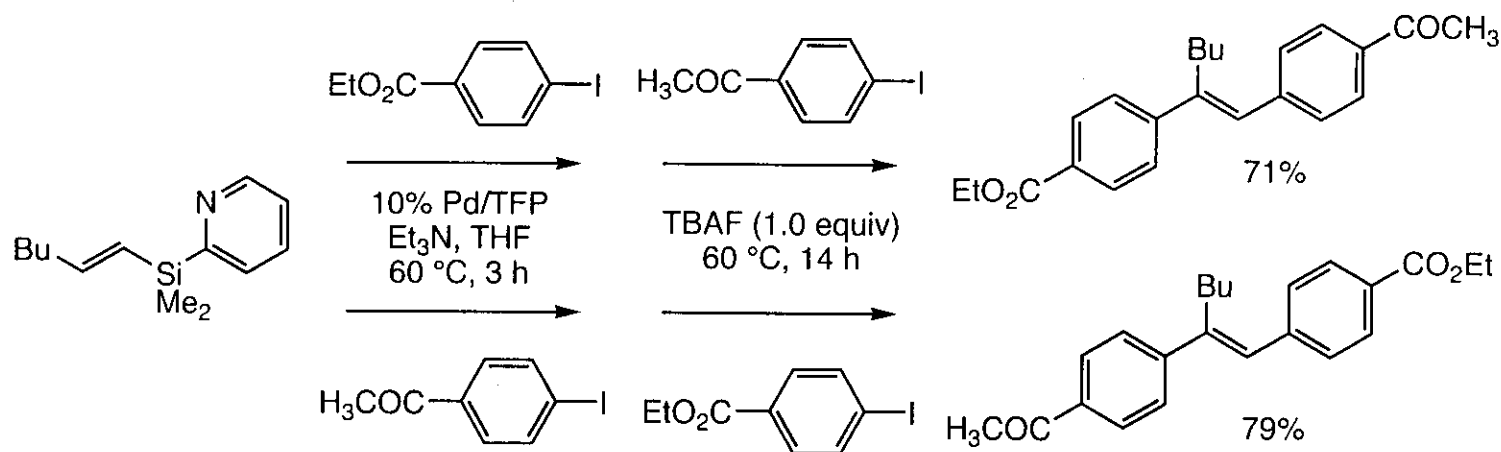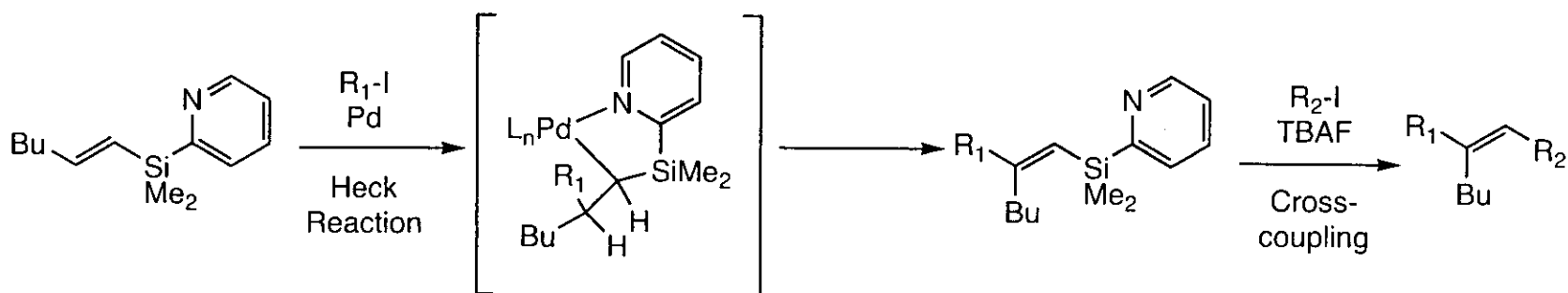
Itami, K; Nokami, T.; Yoshida, J. *J. Am. Chem. Soc.* **2001**, *123*, 5600-5601;
Itami, K; Nokami, T.; Ishimura, Y.; Mitsudo, K.; Kamei, T.; Yoshida, J.
J. Am. Chem. Soc. **2001**, *123*, 11577-11585.

36

Allylic Alkylations

PhSi(OEt)$_3$, TBAF, Pd(dba)$_2$
THF, 60 °C, 95 %

or

Ph$_3$SiF$_2^-$NBu$_4^+$
Pd(dba)$_2$, THF, reflux, 81%

Ph⌁OBz → Ph⌁Ph

Pd^0 ↓

- Pd^0 ↑

Ph⌁
|
Pd - OBz

$\ominus$ $^+$NBu$_4$

OEt
|
Ph−Si‚\OEt
| ▼OEt
F

$\ominus$ $^+$NBu$_4$

F
|
Ph−Si‚\Ph
| ▼Ph
F

Ph⌁
|
Pd - Ph

37

Correia, R.; DeShong, P. *J. Org. Chem.* **2001**, *66*, 7159-7165.

Allylic Alkylations

Reaction scheme: cyclohexenyl-OBz + ArSi(OEt)$_3$, TBAF (2.0 equiv), Pd(dba)$_2$, THF, 60 °C, 12-48 h → cyclohexenyl-Ar
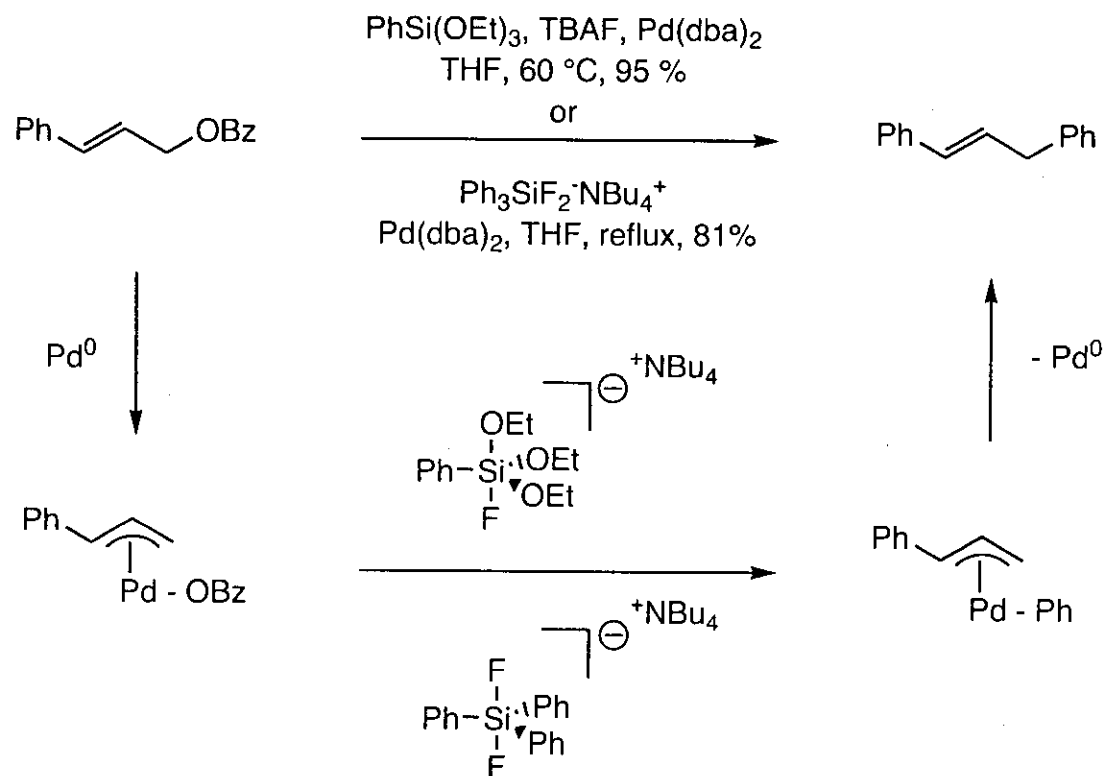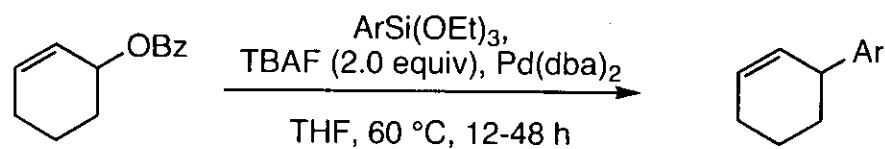
Table 1. Palladium-Catalyzed Arylation of Cyclic Allylic Benzoates

Entry	Allylic Benzoate	Siloxane	Product	Yield (%)
1	3	Me–C$_6$H$_4$–Si(OEt)$_3$ **9**	**10**	87
2	3	Me–C$_6$H$_4$–Si(OEt)$_3$ **11**	**12**	86
3	3	Me–C$_6$H$_4$–Si(OMe)$_3$ **13**	**14**	77
4	3	MeO–C$_6$H$_4$–Si(OEt)$_3$ **15**	**16**	88
5	3	MeO–C$_6$H$_4$–Si(OEt)$_3$ **17**	**18**	88
6	3	**19**	**20**	87
7	3	**21**	**22**	9^a
8	3	Cl–C$_6$H$_4$–Si(OEt)$_3$ **23**	**24**	87
9	3	Me$_2$N–C$_6$H$_4$–Si(OEt)$_3$ **25**	**26**	84
10	3	H$_2$N–C$_6$H$_4$–Si(OEt)$_3$ **27**	**28**	34^b
11	(+)-5	9	(±)-29	84
12	(+)-5	15	(±)-30	78

Correia, R.; DeShong, P. *J. Org. Chem.* **2001**, *66*, 7159-7165.

Catalytic Silanes: Lewis Base Activation of Lewis Acids
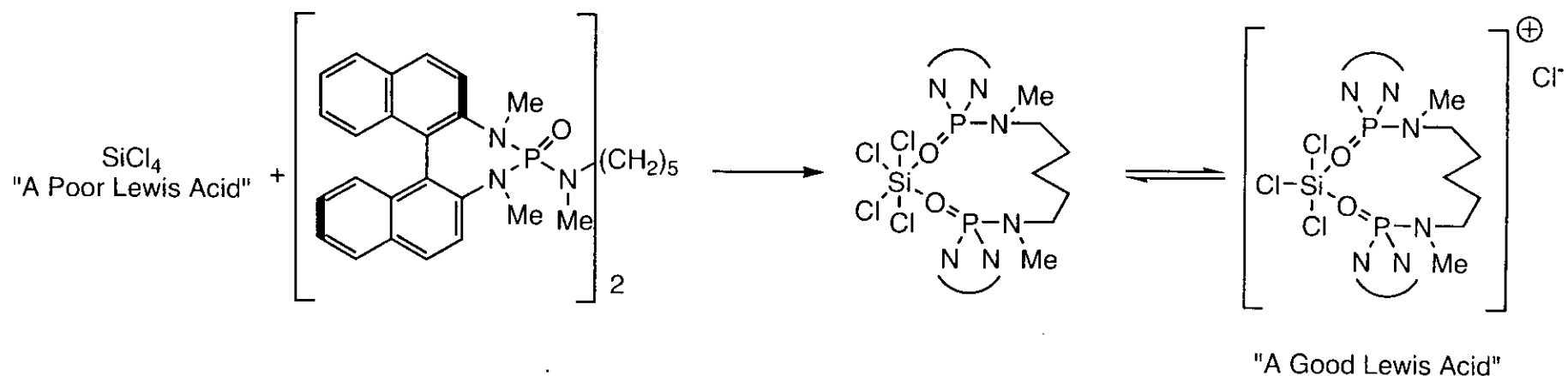
- $SiCl_4$ is a readily available, weak Lewis acid.

- Upon binding the bis-phosphoramide ligand, a change in the coordination sphere occurs ultimately leading to ionization of the complex which becomes a good Lewis acid.

- With many Lewis acids, there is a loss in Lewis acidity upon ligand binding.

Denmark, S. E.; Heemstra, Jr., J. R. *Org. Lett.* **2003**, *5*, 2303-2306;
Denmark, S. E.; Stavenger, R. A. *Acc. Chem. Res.* **2000**, *33*, 432-440.

39

Methyl Ketone Enolates in Aldol Additions

1) (R,R)-phosphoramide (5 mol%)
i-Pr$_2$NEt (10 mol %),
CH$_2$Cl$_2$, -72 °C

2) NaHCO$_3$ (aq), KF

entry	R	product	time, h	yield,[b] %	er[c]
1	(E)-PhCH=CH	(+)-13	4	97.5[c]	99.5/0.5
2	(E)-PhCH=C(CH$_3$)[d]	(+)-14	24	54,.	78.0/22.0
3	1-naphthyl	(+)-15	10	95[c]	96.0/4.0
4	2-naphthyl	(+)-16	4	92	99.5/0.5
5	4-CH$_3$OC$_6$H$_4$	(+)-17	4	97.5	99.5/0.5
6	4-CF$_3$C$_6$H$_4$	(+)-18	4	96	99.5/0.5
7	2-furyl	(+)-19	6	88	95.0/5.0
8	2-thiophenyl	(+)-20	8	79	99.0/10.0
9	PhCH$_2$CH$_2$		24	nr	nd

[a] All reactions employed 1.5 equiv of SiCl$_4$, 1.2 equiv of enolate, 10 mol % i-Pr$_2$NEt, and 5 mol % (R,R)-1 at 0.5 M in CH$_2$Cl$_2$ at −72 °C for 3 h. [b] Yield of analytically pure material. [c] Determined by CSP-SFC. [d] Reaction employed 10 mol % (R,R)-1. [e] Chromatographically homogeneous material.
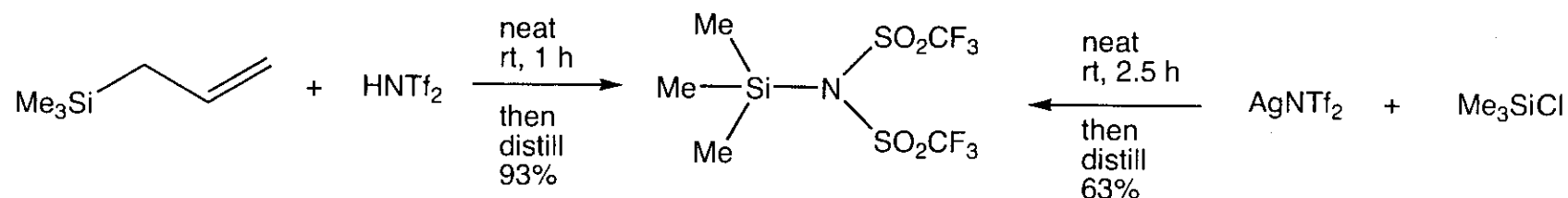
- Aryl and unsaturated aldehydes give good yields and ee's.
- α-Branching attenuated the reactivity.
- Aliphatic aldehydes were unreactive.

40

Denmark, S. E.; Heemstra, Jr., J. R. *Org. Lett.* **2003**, *5*, 2303-2306;

Another Lewis Acid:
N-trimethylsilyl-bis(trifluoromethanesulfonyl)imide

Me$_3$Si — CH$_2$—CH=CH$_2$ + HNTf$_2$

neat
rt, 1 h
then
distill
93%

Me—Si(Me)(Me)—N(SO$_2$CF$_3$)(SO$_2$CF$_3$)

neat
rt, 2.5 h
then
distill
63%

AgNTf$_2$ + Me$_3$SiCl

41

The Diels-Alder Reaction Catalyzed by TMSNTf$_2$
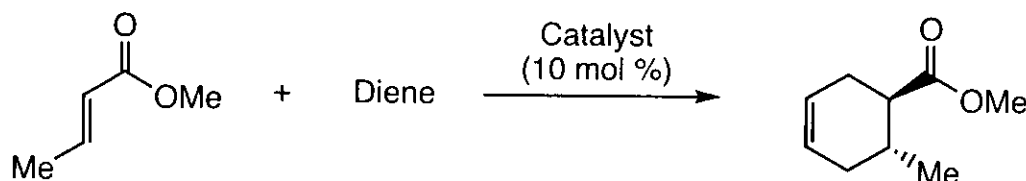
Entry	Diene	addition T°	Conditions	Catalyst	Yield (%)[a]	Endo : Exo[b]
A		0° C	0°C - 20 min	TMSOTf	< 5	13.3 : 1
				TMSNTf$_2$	83	24 : 1
B		0° C	0°C - 60 min	TMSOTf	0	-
				TMSNTf$_2$	92	49 : 1
C	(BDMSO, BDMSO)	0° C	RT - 60 min	TMSOTf	0	-
				TMSNTf$_2$	76	24 : 1
D	(TMSO, Ph)	-50° C	RT - 60 min	TMSOTf	0	-
				TMSNTf$_2$	91	≥ 99 : 1
E	(TMSO, Me, N, Ph)	0° C	0°C - 90 min	-	<5	1 : 2
				TMSOTf	<5	1 : 2
				TMSNTf$_2$	74	2 : 1

(a) total yield of pure adducts; (b) Endo/Exo ratios were determined by gas chromatography or ^{1}H NMR on the crude mixture.
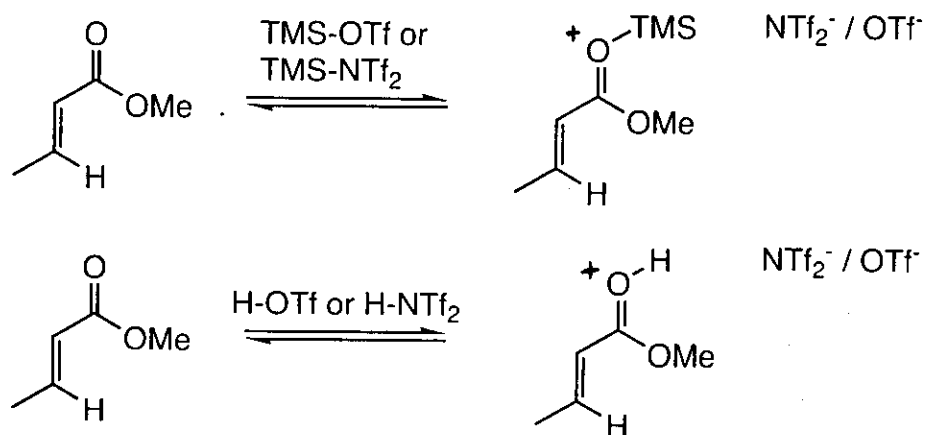
- Enhanced Lewis acidity when compared to TMSOTf

- One example of a carbonyl-ene reaction (44% yield) that did not proceed with TMSOTf

Mathieu, B.; Ghosez, L. *Tetrahedron Lett.* **1997**, *38*, 5497-5500.

How good is TMS-NTf$_2$?

Table 3. Effect of Lewis and Brönsted acids on the chemical shifts of H^3 protons of α,β-unsaturated carbonyl compounds

LA/HA	$\Delta\delta$ H^3		
	Methylcrotonate	Crotonaldehyde	Cyclohexanone
TMSNTf$_2$	0.89	1.74	1.43
TMSOTf	~0	~0	~0
HNTf$_2$	0.11	0.46	0.2
HOTf	0.46	1.28	1.18
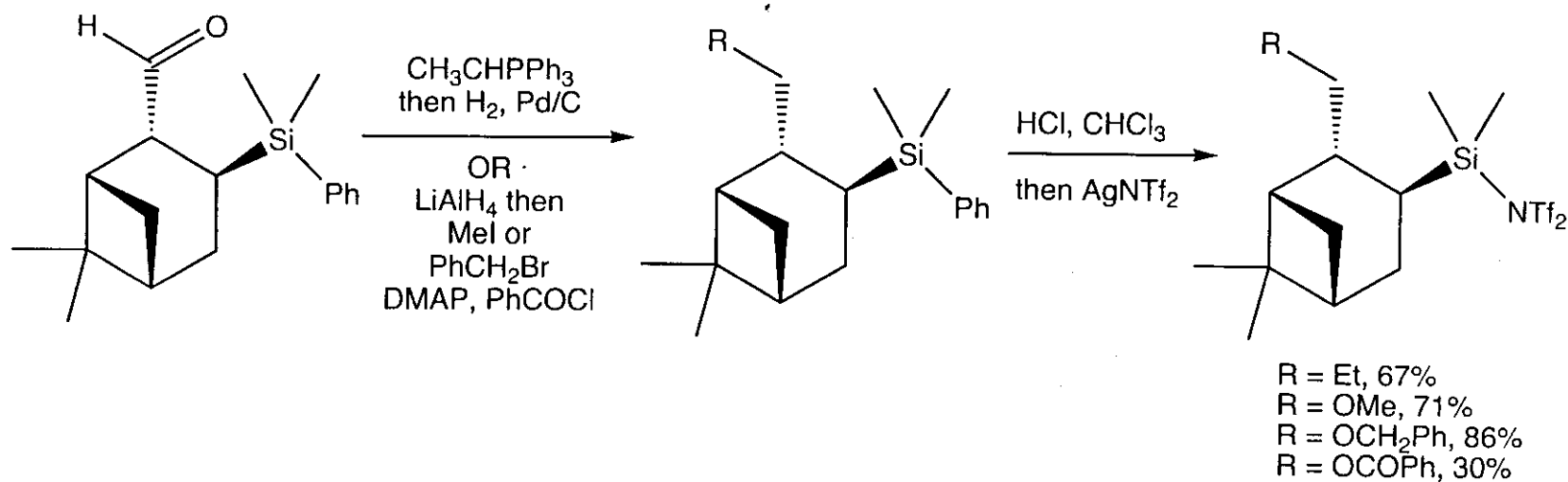
43

Mathieu, B.; Ghosez, L. *Tetrahedron* **2002**, *58*, 8219-8226.

Chiral Silicon Lewis Acids

R = Et, 67%
R = OMe, 71%
R = OCH₂Ph, 86%
R = OCOPh, 30%

44

Chiral Silicon Lewis Acids

3a, R' = Et
3b, R' = OMe
3c, R' = OCH₂Ph
3d, R' = OCOPh
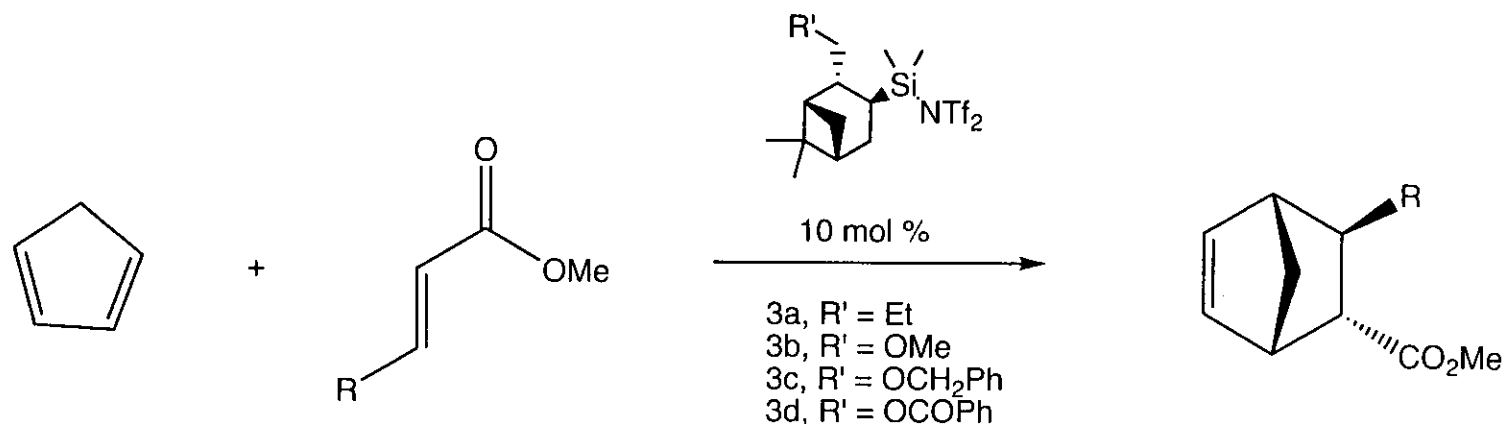
Entry	Catalyst	R	Conditions	endo:exo[b]	Yield[c] (%)	ee endo[b] (%)
1	3a	H	Toluene, −78°C. 1.5 h	99:1	83	7 (2S)
2	3b	H	Toluene, −45°C. 1.5 h[a]	99:1	98	43 (2S)
3	3b	H	Toluene, −78°C, 1.5 h	99:1	83	54 (2S)
4	3b	H	Toluene, −100°C, 1.5 h[a]	99:1	94	54 (2S)
5	3b	Me	Toluene[d]. −78°C. 8 h[a]	–	NR	–
6	3b	Me	Toluene, −45°C. 8 h[a]	97:3	93	24 (2S)
7	3c	H	Toluene, −78°C. 1.5 h	99:1	79	26 (2S)
8	3d	H	Toluene, −78°C. 1.5 h	99:1	80	13 (2S)

Highest ee ever reported for a Diels-Alder reaction catalyzed by a chiral silicon Lewis acid.

[a] Reactions were run in the presence of 10 mol% of 2,6-bis(t-butyl)-4-methylpyridine.
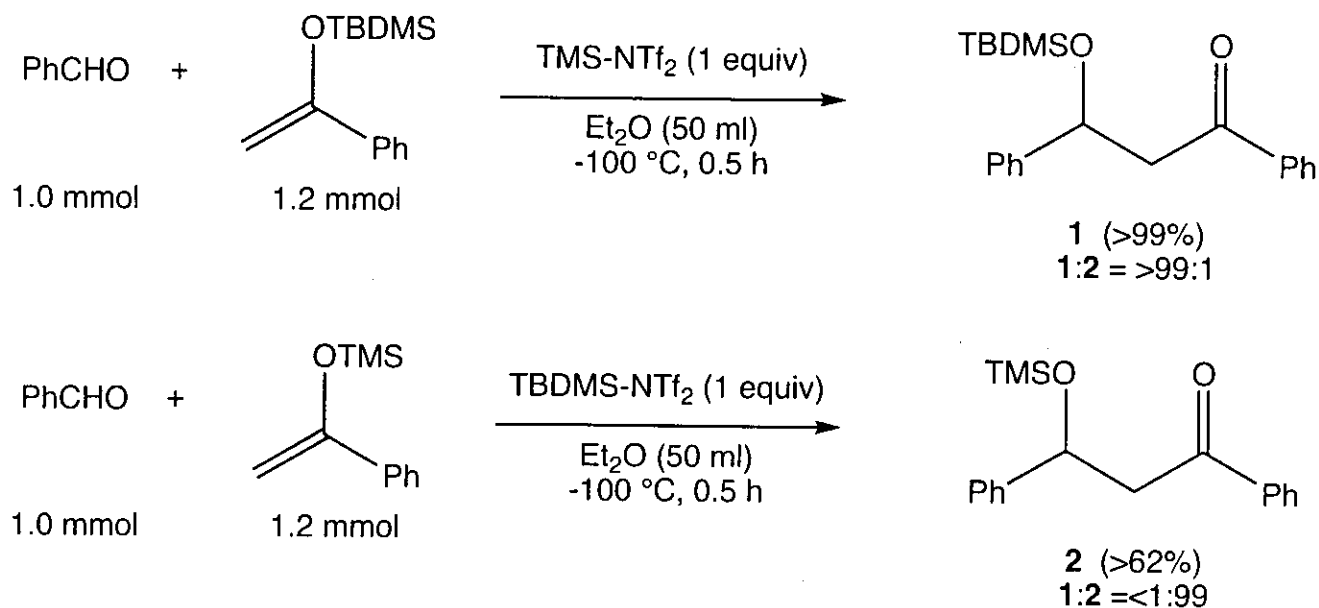[b] ee and endo:exo ratio obtained on a chirasil DEX-CB GC column.
[c] Yield of isolated compound.
[d] Ether. propiononitrile and CH₂Cl₂ were also tested without success.
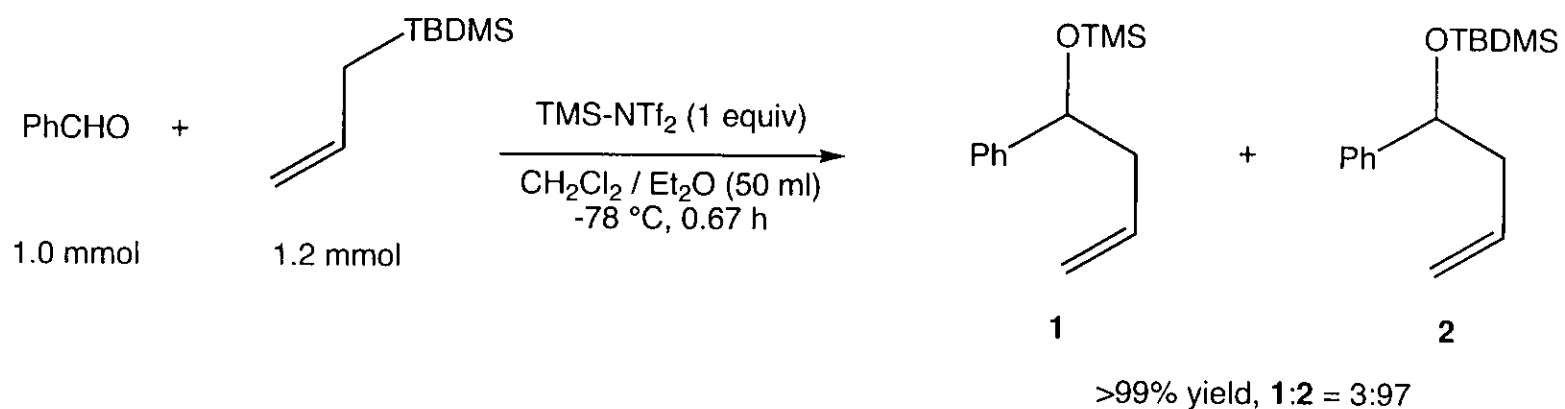
45

Does the -NTf$_2$ Ligand Dissociate?
Mukaiyama Aldol

PhCHO + [structure: OTBDMS vinyl ether with Ph]

1.0 mmol   1.2 mmol

TMS-NTf$_2$ (1 equiv)
————————————→
Et$_2$O (50 ml)
-100 °C, 0.5 h

[product structure: TBDMSO, O, Ph, Ph]

1 (>99%)
1:**2** = >99:1

PhCHO + [structure: OTMS vinyl ether with Ph]

1.0 mmol   1.2 mmol

TBDMS-NTf$_2$ (1 equiv)
————————————→
Et$_2$O (50 ml)
-100 °C, 0.5 h

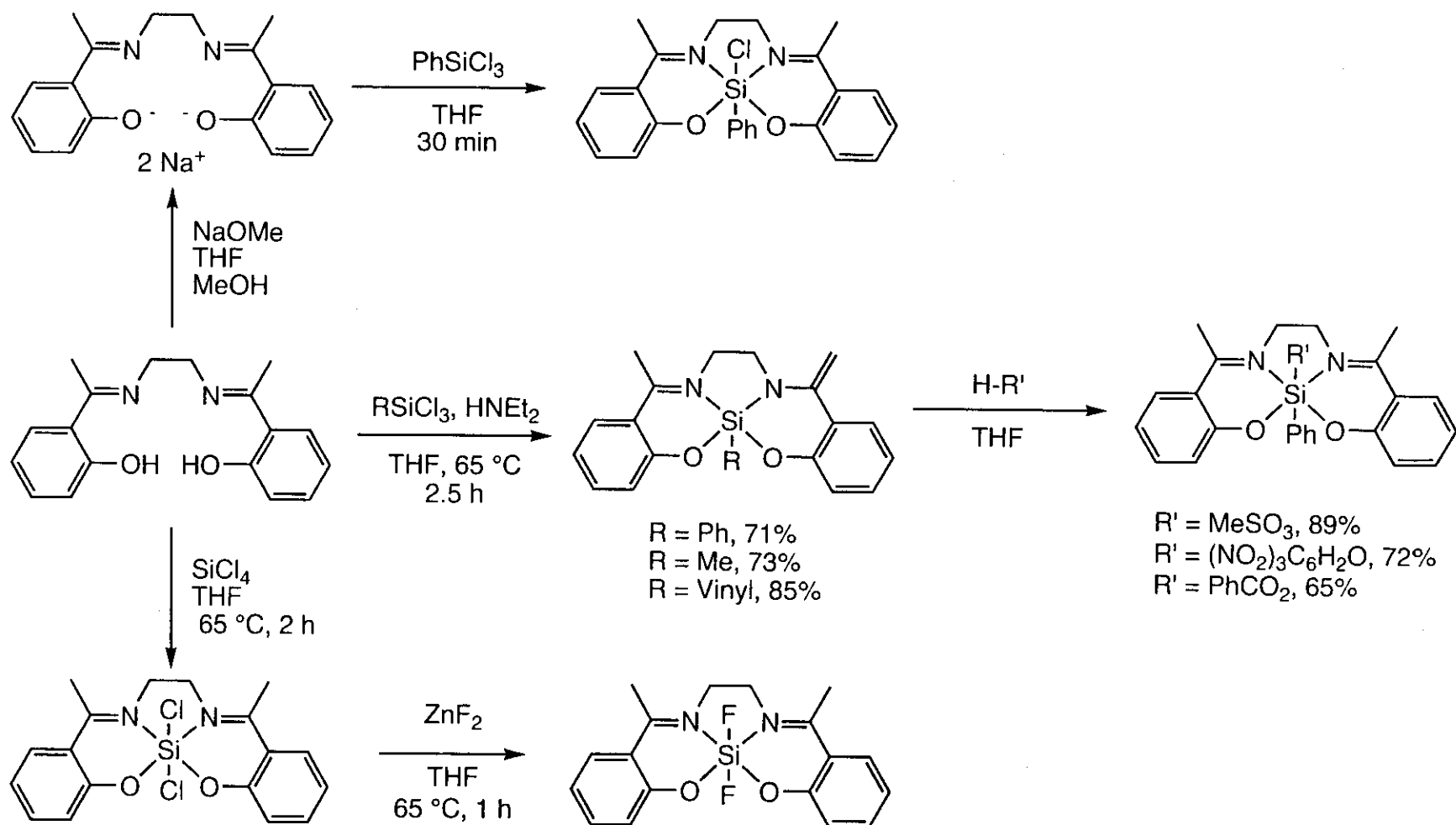[product structure: TMSO, O, Ph, Ph]

2 (>62%)
1:**2** =<1:99

- The results suggest that the NTf$_2$ ligand remains bonded to the silicon.

- +SiR$_3$ induced cascade process was not ruled out.

46   Ishihara, K.; Hiraiwa, Y.; Yamamoto, H. *Chem. Commun.* **2002**, 1564-1565.

Does the -NTf$_2$ Ligand Dissociate?
Sakurai-Hosomi allylation

PhCHO + [structure with TBDMS]

TMS-NTf$_2$ (1 equiv)

CH$_2$Cl$_2$ / Et$_2$O (50 ml)
-78 °C, 0.67 h

1.0 mmol   1.2 mmol

[product with OTMS, Ph] **1**   +   [product with OTBDMS, Ph] **2**

>99% yield, **1**:**2** = 3:97

Ishihara, K.; Hiraiwa, Y.; Yamamoto, H. *Chem. Commun.* **2002**, 1564-1565.

47

Controlling the Silicon Coordination Sphere

R = Ph, 71%
R = Me, 73%
R = Vinyl, 85%

R' = MeSO$_3$, 89%
R' = (NO$_2$)$_3$C$_6$H$_2$O, 72%
R' = PhCO$_2$, 65%

48

Wagler, J.; Böhme, U.; Roewer, G. *Angew. Chem. Int. Ed.* **2002**, *41*, 1732-1734.

Conclusions: Stoichiometric Silicon

Chiral crotylsilanes
- Proven technology that has been used for numerous polyketide constructions.
- Synthesis of the chiral silane reagent requires several steps.

Silicon centered allylation reagents
- Can be made in one step from commercially available starting materials
- Solids that are stable to storage.
- Provide products of high purity and the ligand can be recovered.

Tandem sequences
- Efficient construction of polyketide sequences.
- Requires further development to address reaction scope and/or selectivities.

Silacycles
- Silylene transfer reagents offer some promise for the use of silacyclopropanes.
- The use of silacyclopentane oxide has been demonstrated as an expedient route to highly oxygenated sequences.

Cross-coupling
- Recent advances in the understanding of silicon cross coupling reactions offer a very promising alternative to tin (Stille) and boron (Suzuki) reagents.
- Currently, flouride or base (KOTMS) are required for activation.

49

Conclusions: Catalytic Silicon

- Efforts have mainly focused on using the silicon as a Lewis acid.

- Chiral phosphoramides
    - The most advanced technology.
    - In situ generation of the catalyst has recently been demonstrated.
    - Significant information concerning the mechanism has been published.

- Other ligands have been explored but have not been demonstrated to be of significant use in organic synthesis.

50