Strained Cyclosilane Chemistry

MacMillan Group Meeting

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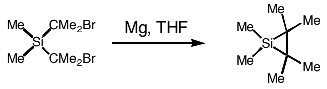
September 4, 2002

The Beginnings of Silacyclopropane Chemistry

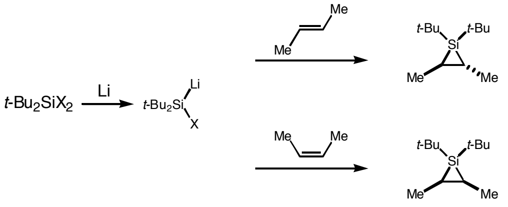
- The first simple silacyclopropane was synthesized in 1975.



76% yield

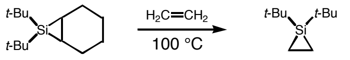
Seyferth, D.; Annarelli, D.C. *JACS* **1975**, *97*, 2273.

- Synthesis of only simple silacyclopropanes (un-, mono-, and di-substituted) was known.



65 - 70% yield

Boudjouk, P.; ... *ACIEE*, **1988**, *27*, 1355.

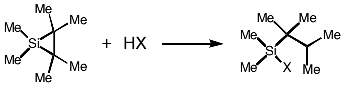


85% yield

Boudjouk, P.; Black, E.; Kumarathasan, R. *Organometallics*, **1991**, *10*, 2095.

The Beginnings of Silacyclopropane Chemistry

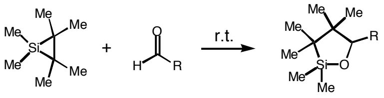
- Silacyclopropanes can be opened by a variety of nucleophiles.

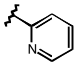
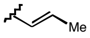
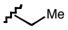


X = OH, OR, NR_2, O_2R, SnR_3

Seyferth, D.; ... *J. Organometallic Chem.*, **1982**, *225*, 177.

- Silacyclopropanes ring expand on reaction with aldehydes.

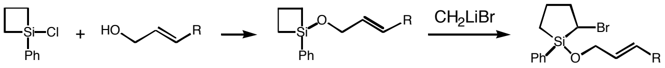


R	**yield (%)**
Ph	52
	65
	95
	40 (required UV irradiation)

Seyferth, D.; Duncan, D.P.; Shannon, M.L. *Organometallics*, **1984**, *3*, 579.

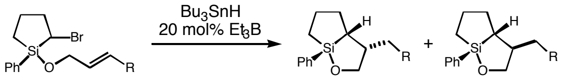
Carbenoid Insertions into Silacyclobutanes

- Lithium carbenoids (CH_2LiBr and CH_2LiI) will insert into silacyclobutanes.



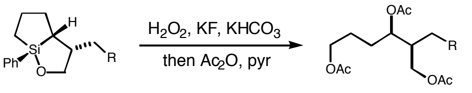
R = H or 1° alkyl ≥73% yield ≥41% yield

- 1-Bromosilacyclopentanes (and 1-Iodosilacyclopentanes) will undergo radical intramolecular *exo*-cyclizations.



6 - 2 : 1 d.r.
(*Z*-alkenes give poorest d.r.)

- Products can be oxidatively opened to the corresponding triols.

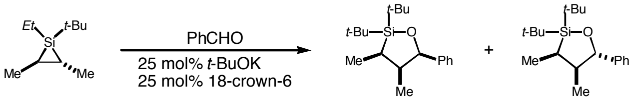


32 - 72% yield (2 steps)
(lowest yield from terminal olefin)

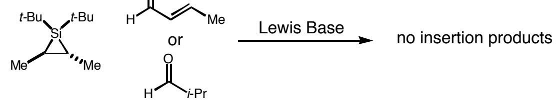
... ; Utimoto, K. *Tetrahedron*, **1993**, *49*, 8487.
... : Utimoto, K. *Bull. Chem. Soc. Jpn.*, **1995**, *68*, 625.

Aldehyde Insertions into Silacyclopropanes

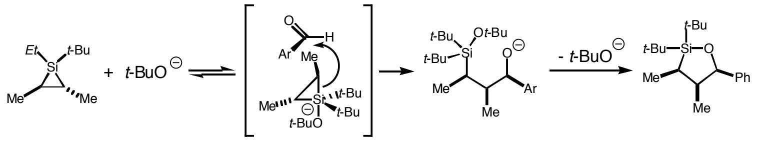
- Only non-enolizable aldehydes insert.



54% yield, 86 : 14 d.r.
(73% yield, 70 : 30 for *cis*-silacyclosilane)



- Reaction is believed to procede through a pentacooordinate silcon intermediate.

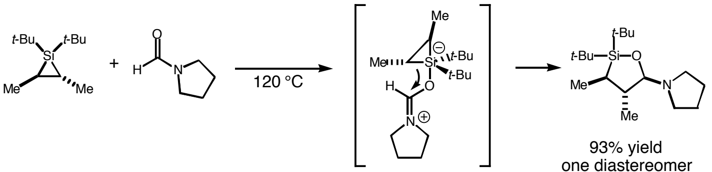


- Product shows 1,3-syn for both cis- and trans-silacyclopropanes
- Selectivity independent of Lewis base catalyst

... Woerpel K.A. *JOC* **1997**, *62*, 4737.
Takeyama, Y.; Oshima, K.; Utimoto, K. *TL*, **1990**, *31*, 6059.

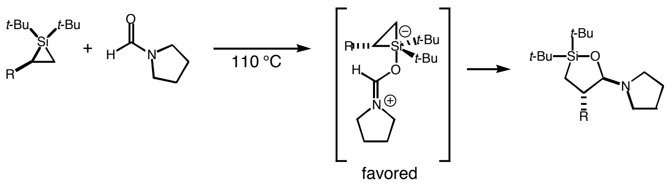
Amide Carbonyl Insertions into Silacyclopropanes

- Formamides do not insert into cis-silacyclopropanes.



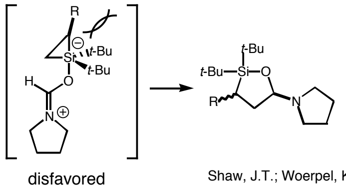
93% yield
one diastereomer

- Reaction is believed to procede through a pentacooordinate silcon intermediate.



R = Me 60 : 40, 63% yield R = *i*-Pr 94 : 6, 79% yield

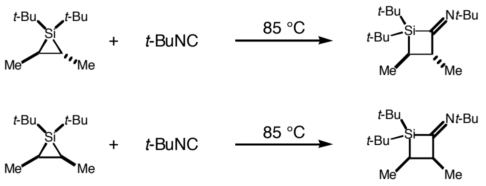
- Amides are more reactive than other carbonyls due to their increased Lewis basicity.



Shaw, J.T.; Woerpel, K.A. *JOC* **1997**, *62*, 442.

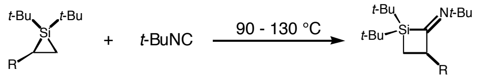
Isocyanide Insertions into Silacyclopropanes

- Isocyanides perform similar chemistry to formamides, but with higher reactivity and selectivity.
- Reaction is believed to procede through the intermediates proposed for formamide insertion.



99% yield
>20 : 1 d.r.

98% yield
>20 : 1 d.r.



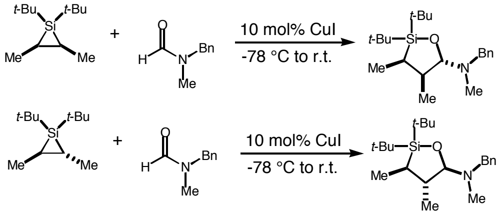
R	yield	regioselectivity
n-Bu	94%	>95 : 5
i-Pr	98%	92 : 8
t-Bu	97%	86 : 14

- Decrease in selectivity with increasing steric bulk is believed to be due to unfavorable interactions between the R group and the coordinated isocyanide.

Nguyen, P.T.; Palmer, W.S.; Woerpel, K.A. *JOC* **1999**, *64*, 1843.

Metal-Catalyzed Insertions into Silacyclopropanes

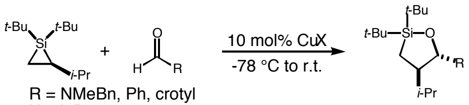
- Reactions occur at significantly lower temperatures.



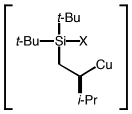
72% yield
93 : 7 selectivity

74% yield
>95 : 5 selectivity

- The copper-catalyzed insertion of formamides and stabilized aldehydes is believed to go through a transmetalation.

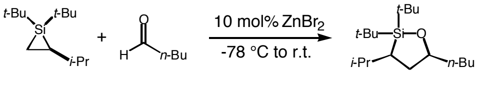


74 - 82% yield
91 : 9 d.r. or better

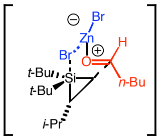


R = NMeBn, Ph, crotyl
X = I, Br_2

- Zinc is believed to catalyze the insertion of alkyl aldehydes through cooridination/activation.



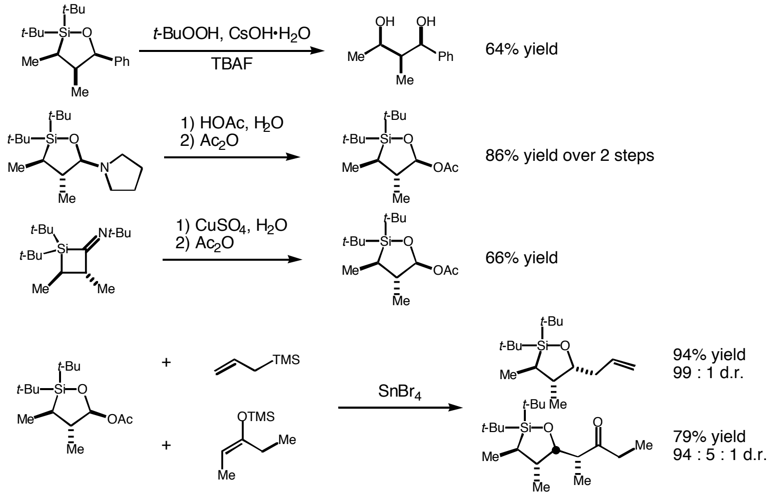
70% yield
55 : 45 d.r.
>99 : 1
regioselectivity



Nguyen, P.T.; Palmer, W.S.; Woerpel, K.A. *JOC* **1999**, *64*, 1843.
Franz, A.K.; Woerpel, K.A. *Chem. Rev.* **2000**, *33*, 813.

Elaboration of Ring-Expanded Silacyclopropanes

- These oxidation conditions work for hindered silanes.



64% yield

86% yield over 2 steps

66% yield

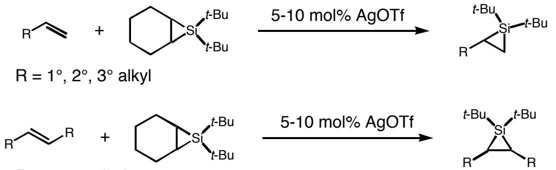
94% yield
99 : 1 d.r.

79% yield
94 : 5 : 1 d.r.

Smitrovich, J.H.; Woerpel, K.A. *JOC*, **1996**, *61*, 6044.
Shaw, J.T.; Woerpel, K.A. *JOC*, **1997**, *67*, 442.
Nguyen, P.T.; Palmer, W.S.; Woerpel, K.A. *JOC*, **1999**, *64*, 1843.
Franz, A.K.; Woerpel, K.A. *Acc. Chem. Res.* **2000**, *33*, 813.
Bear, T.J.; Shaw, J.T.; Woerpel, K.A. *JOC*, **2002**, *67*, 2056.

A New synthesis of Silacyclopropanes

- Silver-catalyzed silyl transfer is a mild way to form mono- and disubstituted silacyclopropanes.



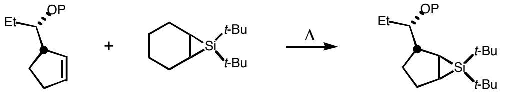
R = 1°, 2°, 3° alkyl

61 - 99% conversion

R = 1°, 2° alkyl
cis, trans, and α,α-disubstituted

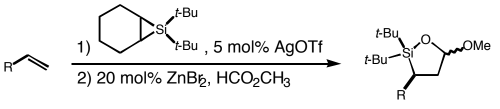
72 - 99% conversion
complete transfer of double bond geometry

- Silyl transfer is highly diastereoselectiveand allows access to more complex substrates.



P = TIPS: 97% yield, 96 ; 4 d.r.
P = BN: 93% yield, 88 : 12 d.r.

- One-pot silacyclopropanation-insertion is possible

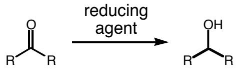


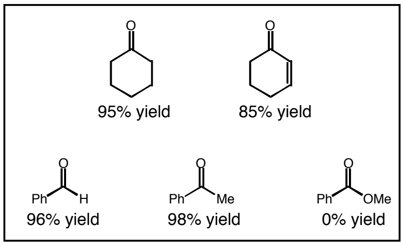
61 - 92% yield
d.r. no better than 76 : 24

Driver, T.G.; Franz, A.K.; Woerpel, K.A. *JACS*, **2002**, *124*, 6524.
Cirakovic, J.; Driver, T.G.; Woerpel, K.A. *JACS*, **2002**, *124*, 9370.

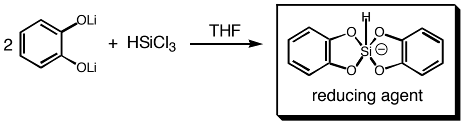
Strained Cyclosilanes are Stronger Reducing Agents than Typical Silanes

- ■ Unstrained silanes do not perform this reduction.





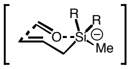
- ■ The reducing agent was formed *in situ*.



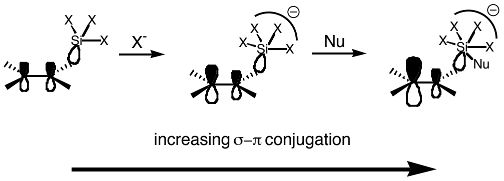
Kira, M.; Sato, K.; Sakurai, H. *JOC*, **1987**, *52*, 948.

Increasing Coordination of Silicon Increases Reactivity

- ■ Allylations of aldehydes by strained cyclosilanes are believed to go through a cyclic transition state.



- ■ Pentacoordinate silicon is formally negatively charged, but the charge is delocalized into electronegative ligands, thereby increasing the Lewis acidity of the silicon.

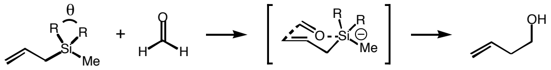


- ■ Coordination of electron rich ligands to the silicon increases the σ–π conjugation. (^{13}C NMR evidence)

Sakurai, H. *Synlett*, **1989**, 1.

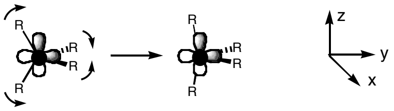
Ligand Bond Angle is Directly Related to Reactivity

- Activation energies calculated for the addition of allylsilane to formaldehyde show a strong relationship to C-Si-C bond angle.



R, R	θ	activation energy (kcal/mol)
$(CH_2)_3$	78 (actual)	30.5
Me, Me	70 (fixed)	26.5
Me, Me	80 (fixed)	30.4
Me, Me	90 (fixed)	34.5
Me, Me	100 (fixed)	38.6
Me, Me	110.2 (actual)	40.4

- As the ligand bond angle decreases, the $3p_x$ orbital becomes less occupied and more available for attack by the incoming nucleophile. This reduces the activation energy of the reaction.

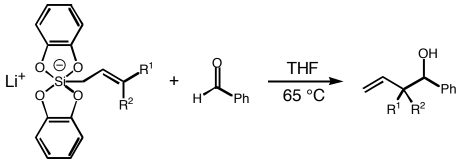


- The attack of the nucleophile on the allyl silacyclobutane relieves ring strain on forming the pentacoordinate intermediate.

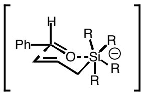
Omoto, K.; Sawada, Y.; Fujimoto, H. *JACS*, **1996**, *118*, 1750.

Catechol-Derived Allyl Cyclosilanes React Without Need for a Catalyst

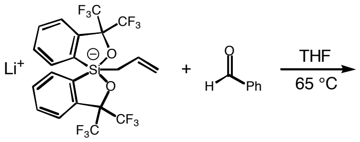
- Transfer of stereochemistry from crotylsilane to product supports a cyclic transition state.



R^1	R^2	yield (%)
H	H	91
Me	Me	87
Me	H (88 : 12)	82 (*anti* 88 : 12)
H	Me (79 : 21)	91 (*syn* 78 : 22)



- Lack of reactivity of a hexacoordinate allyl silane indicates that the aldehyde must coordinate to the silicon to react. ^{13}C NMR indicates the γ-carbon is more nucleophilic than the pentacoordinate allyl silane.

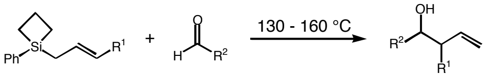


no reaction

Kira, M.; Sato, K.; Hakurai, H. *JACS*, **1988**, *110*, 4599.

Silacyclobutane Sakurai Chemistry

- Allylic silacyclobutane will add to aldehydes at elevated temperatures.



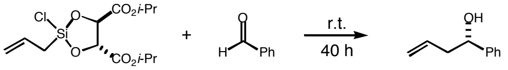
R^1	R^2	yield (%)	*anti : syn*
n-Pr (*E*)	Ph	68	95 : 5
n-Pr (*E*)	*n*-hex	59	90 : 10
n-Pr (*E*)	*c*-hex	44	>99 : 1
n-Pr (*Z*)	Ph	66	5 : 95
n-Pr (*Z*)	*n*-hex	60	20 : 80
Ph (*E*)	Ph	63	92 : 8
Ph (*E*)	*n*-hex	72	97 : 3
Ph (*E*)	*c*-hex	57	>99 : 1

- Transfer of allyl stereochemistry indicates a cyclic transition state.

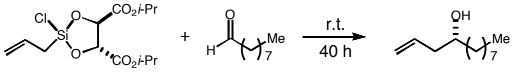
Matsumoto, K.; Oshima, K.; Utimoto, K. *JOC*, **1994**, *59*, 7152.

Enantioselective Sakurai

- Substitution of the chloride with an alkyl group reduces enantioselectivity.

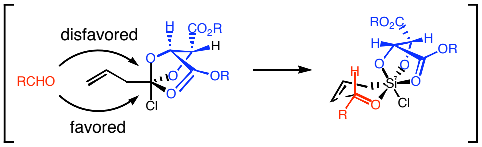


r.t.: 93% yield, 47% ee
-40 °C: 73% yield, 60% ee



-40 °C: 76% yield, 80% ee

- Reaction of the *E*- and *Z*-crotylsilanes proceeded with high diastereoselectivity (*anti* and *syn* products, respectively), supporting the cyclic transition state.

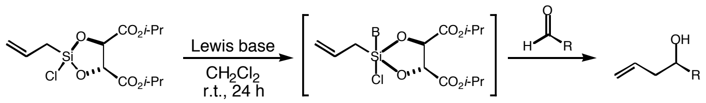


- Favored reaction path is proposed to aviod steric interaction with the free ester of the ligand.

Zhang, L.C.; Sakurai, H.; Kria, M. *Chem. Let.* **1997**, 129.

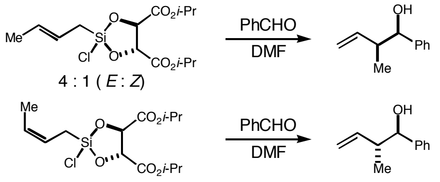
Another Enantioselective Sakurai

- Wang proposes the necessity of base activation.



Base	R	yield (%)	ee (%)
Et$_3$N	Ph	72	27
Et$_3$N	*n*-octyl	69	44
DMF	Ph	52	52
DMF	*n*-octyl	71	71
HMPA	Ph	21	21
HMPA	*n*-octyl	15	15

- Evidence from crotylations supports a closed chair transition state with a hexcoordinate silicon.



4 : 1 (*E* : *Z*)

72% yield, 4 : 1 d.r.

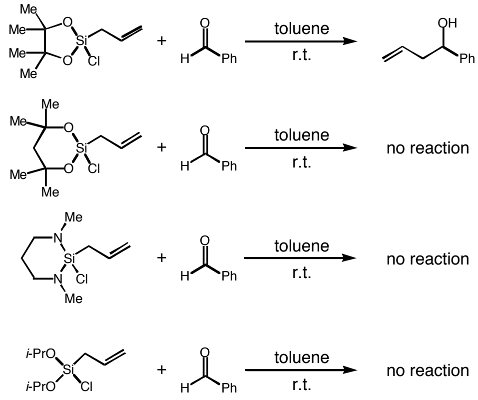
100% *Z*

76% yield, one diastereomer

Wang, D.; ... *Tetrahedron: Asymmetry*, **1999**, *10*, 327.

The Most Recent Enantioselective Sakurai Reaction

- Activation of the silicon by a Lewis base (leading to a hexacoordinate transition state) is not necessary for reactivity.



52% yield (unoptimized)

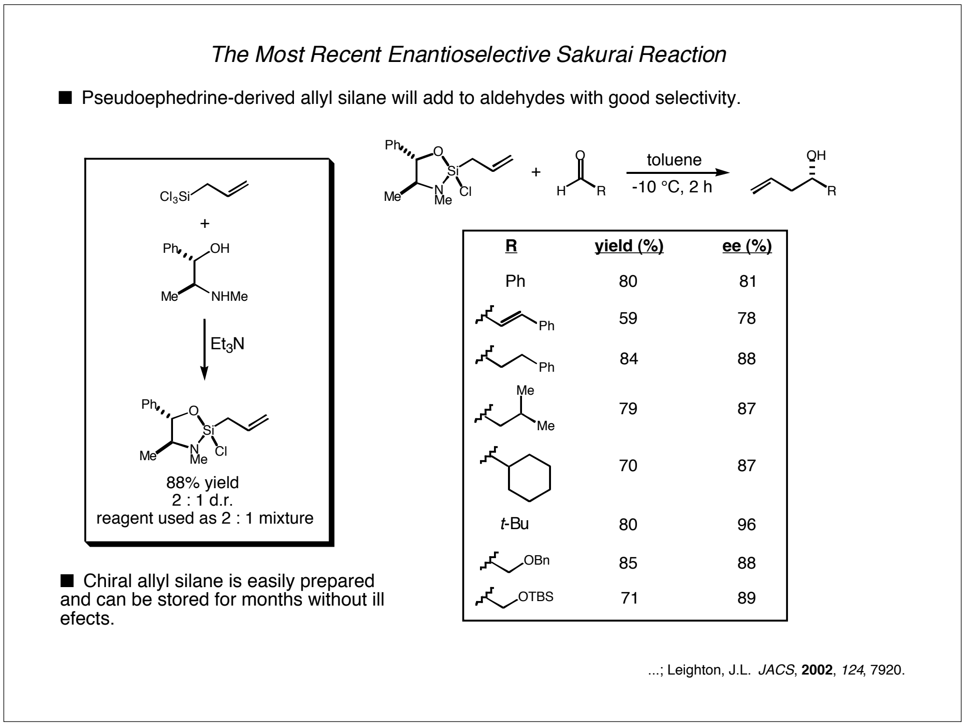
no reaction

no reaction

no reaction

- Ring strain activates the allyl silane for addition to the aldehyde.

...; Leighton, J.L. *JACS*, **2002**, *124*, 7920.



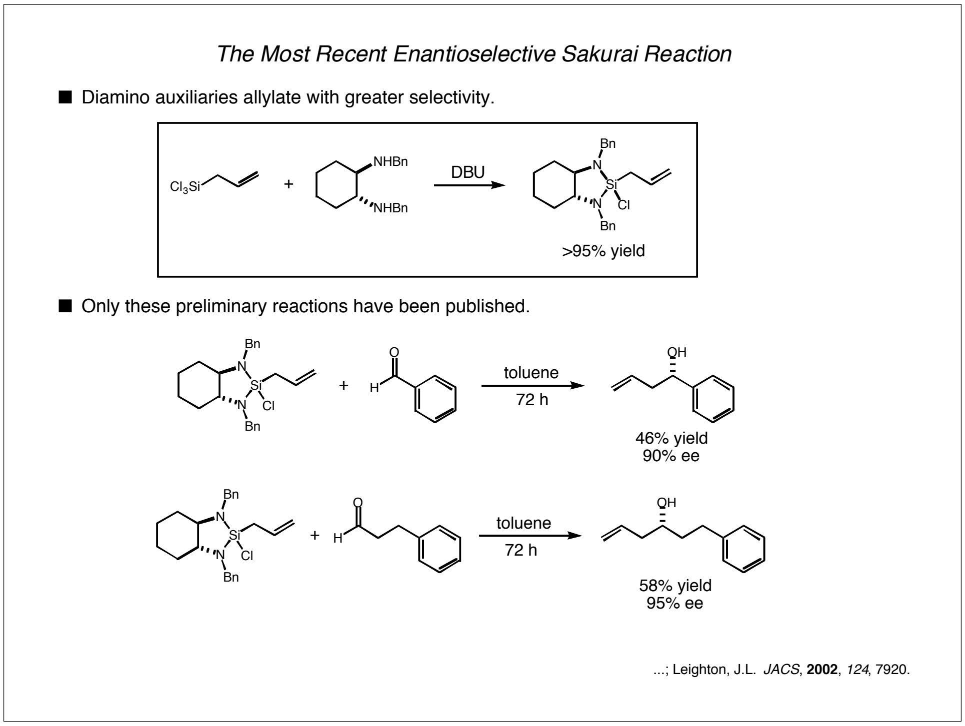
The Most Recent Enantioselective Sakurai Reaction

- Pseudoephedrine-derived allyl silane will add to aldehydes with good selectivity.

R	yield (%)	ee (%)
Ph	80	81
Ph	59	78
Ph	84	88
Me Me	79	87
	70	87
t-Bu	80	96
OBn	85	88
OTBS	71	89

- Chiral allyl silane is easily prepared and can be stored for months without ill efects.

...; Leighton, J.L. *JACS*, **2002**, *124*, 7920.



The Most Recent Enantioselective Sakurai Reaction

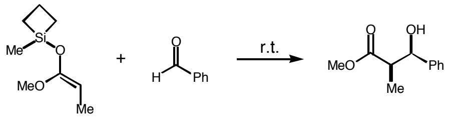
- Diamino auxiliaries allylate with greater selectivity.

- Only these preliminary reactions have been published.

...; Leighton, J.L. *JACS*, **2002**, *124*, 7920.

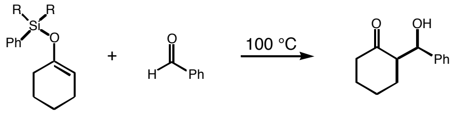
Silyl Ring Strain Accelerates Aldol Chemistry

- ■ Silacyclobutane ketene acetals show good syn selectivity.

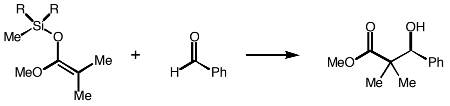


quantitative yield
19 : 1 d.r.

- ■ Silacyclobutane ketene acetals show increased reactivity.



R = Me: no reaction
R = $(CH_2)_3$: 84% yield (34 h), 7 : 1 d.r.

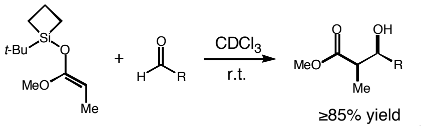


R = Me: 150 °C, 24 h, <25% yield
R = $(CH_2)_3$: 27 °C, 4 h, quantitative yield

Myers, A.G.; Kephart, S.E.; Chen, H. *JACS*, **1992**, *114*, 7922.

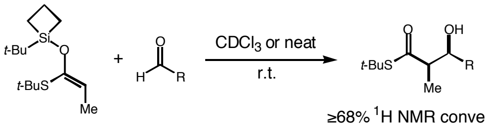
Enoxysilacyclobutane Syn-Aldol Reaction

- ■ The aldol reaction of ester, thioester, and amide silacyclobutane enolates proceeds uncatylized and with high diastereoselectivity.



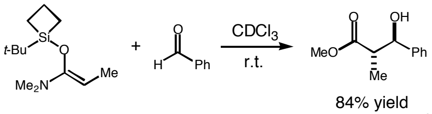
R = Ph, cinnamyl, 1° and 2° alkyl

≥85% yield
≥93 : 7 *syn* : *anti*



R = Ph, cinnamyl, 1° alkyl

≥68% ^{1}H NMR conversion
≥70 : 30 *syn* : *anti*



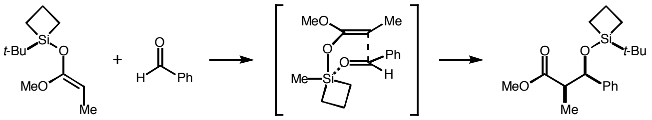
84% yield
9 : 91 *syn* : *anti*

- ■ Enoxysilacyclobutanes are not competent Mukiayama-Michael nucleophiles, favoring 1,2-addition over 1,4-addition.

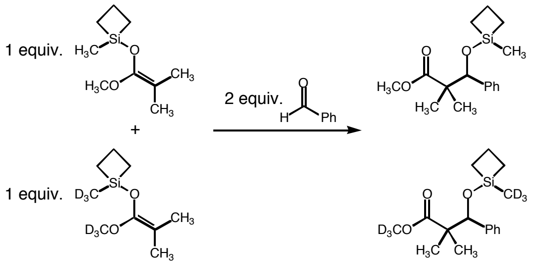
Denmark, S.E.; Griedel, B.D.; Coe, D.M. *JOC*, **1993**, *58*, 988.
Denmark, S.E.; ... *JACS*, **1994**, *116*, 7026.

Enoxysilacyclobutane Syn-Aldol Reaction

- High diastereoselectivity suggests a closed transition state.
- *Syn* aldol product suggests a boat transition state.
- Boat transition state is supported by computational studies.



- Deuterium-labelling crossover experiments indicate intramolecular silyl transfer, supporting a closed, cyclic transition state.

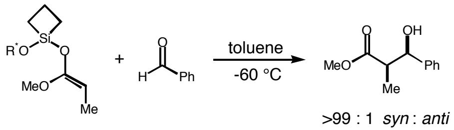


0.54% silyl crossover product detected by MS

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

Uncatalyzed, Syn-Selective Enoxysilacyclobutane Asymmetric Aldol

- Ester-derived enoxysilacyclobutanes reacted with high diastereo- and enantioselectivity, but suffered from poor yields due to C-silylation of the enolate and low *E* : *Z* ratios.

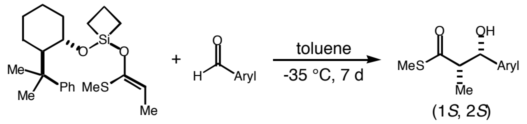


60 : 40 O : C silyl
80 : 20 *E* : *Z*

>99 : 1 *syn* : *anti*

R*	ee (%)
(-)-menthol	74
(+)-2,2-diphenylcyclopentanol	7
(+)-*endo*-borneol	11
(+)-*trans*-2-phenylcyclohexanol	63
(-)-8-phenylmenthol	95
(-)-*trans*-2-cumylcyclohexanol	97

- Thioester-derived enoxysilacyclobutanes are preferred due to higher yields, lack of C-silylation in preparation, and high *E* : *Z* ratios.



(-)-*trans*-2-cumylcyclohexanol
enoxysilacyclobutane

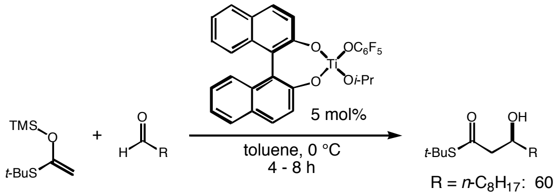
(1*S*, 2*S*)

Aryl	yield (%)	ee (%)
Ph	60	94
cinamyl	64	92
p-methoxy Ph	62	94
2-furyl	68	90
1-naphthyl	50	94
trifuloro-*p*-tolyl	45	94

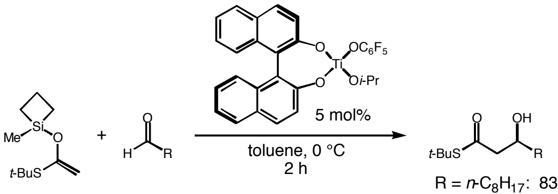
Denmark, S.E.; Griedel, B.D. *JOC*, **1994**, *59*, 5136.

Silacyclobutanes Increase the Enantioselectivity of Ti-BINOL-Catalyzed Aldol

- The use of silacyclobutyl versus trimethylsilyl enolate increases reactivity and selectivity.



R = n-C$_8$H$_{17}$: 60% yield, 91% ee
R = CH$_2$OBn: 80% yield, 96% ee

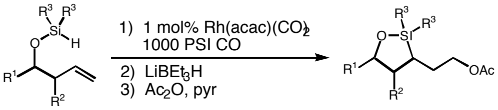


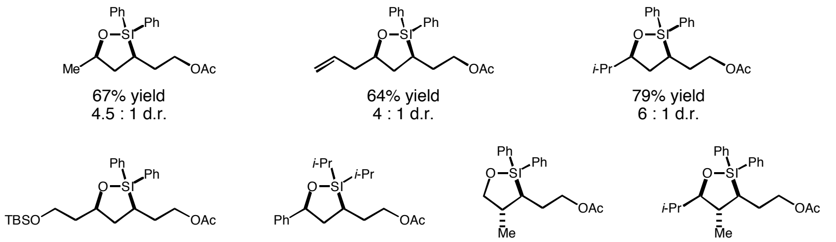
R = n-C$_8$H$_{17}$: 83% yield, 97% ee
R = CH$_2$OBn: 95% yield, 98% ee

Matsukawa, S.; Mikami, K. *Tet.: Asym.*, **1995**, *6*, 2571.

Rhodium-Catalyzed Intramolecular Silylformylation

- Isolated yields are over three steps due to the difficulty of purifying the aldehyde product.





67% yield
4.5 : 1 d.r.

64% yield
4 : 1 d.r.

79% yield
6 : 1 d.r.

60% yield
4 : 1 d.r.

54% yield
7 : 1 d.r.

10% yield
11 : 1 d.r.
(rest hydrosilylation)

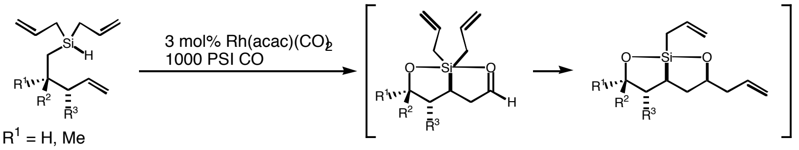
71% yield
10 : 1 d.r.

- This methodology provides access to *syn* polyol fragments after oxidative removal of the silicon.

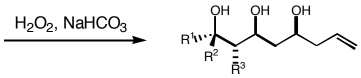
Leighton, J.L.; Chapman, E. *JACS*, **1997**, *119*, 12416.

Tandem Intramolecular Silylformylation-Allylation

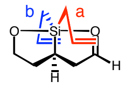
- This is the first use of oxasilacyclopentanes in an uncatalyzed bond-forming process.



R^1 = H, Me
R^2 = 1°, 2° alkyl, crotyl
R^3 = Me



45 - 65% yield
≥69 : 31 d.r.



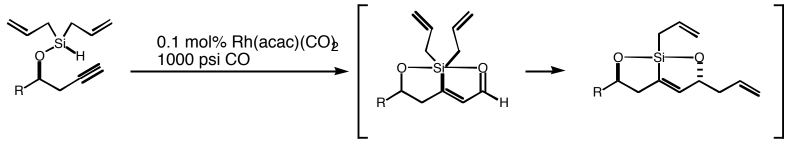
allylation by group a favored

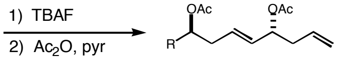
- Deuterium labeling experiments indicate an intramolecular allylation.

Leighton, J.L.; Zacuto, M.J. *JACS*, **2000**, *122*, 8587.

Tandem Intramolecular Silylformylation-Allylation shows 1,5-Asymmetric Induction

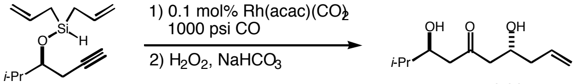
- Silylformylation of alkynes is possible under these tandem reaction conditions.



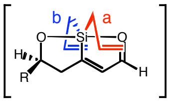


R	yield (%)	d.r.
n-Pr	68	4 : 1
$CH_2C{\equiv}CH$	63	4 : 1
CH_2CH_2OTBS	63	5 : 1
i-Pr	83	8 : 1
Ph	83	7 : 1
t-Bu	66	10 : 1

- Oxidative work-up provides access to 1,3,5-oxygenated systems.



71% yield

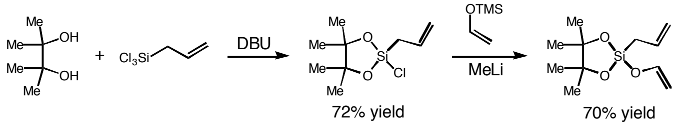


- Transfer of allyl group b is favored due to a's unfavorable steric interaction with R.

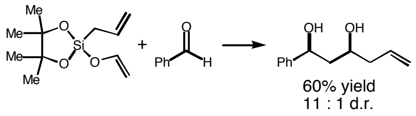
O'Malley, S.J.; Leighton, J.L. *ACIEE*, **2001**, *40*, 2915.

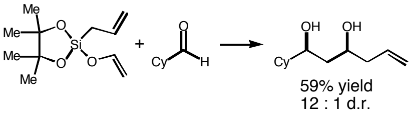
Tandem Intramolecular Aldol-Allylation

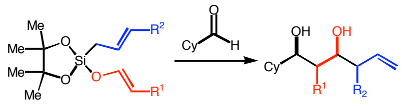
- The Lewis-acidity of ring-strained cyclosilanes is sufficient to undergo this reaction.



- The stereochemistry of the aldol reaction indicates that it proceeds through a boat transition state.







R^1	R^2	yield (%)	d.r. (major : others)
H	Me (*E*)	60	8 : 1
H	Me (*Z*)	71	10 : 1
Me (*Z*)	H	59	65 : 35
Me (*E*)	H	30	2 : 1
Me (*Z*)	Me (*Z*)	52	66 : 34
Me (*Z*)	Me (*E*)	51	65 : 35
Me (*E*)	Me (*E*)	71	86 : 14

(*Z*) stereochemistry yields*anti*
(*E*) stereochemistry yields*syn*

Wang, X.; Meng, Q.; Nation, A.J.; Leighton, J.L. *JACS*, **2002**, ASAP.

Some Interesting Lewis-Base-Catalyzed Epoxide Opening Chemistry

Denmark, S.E.; ... *JOC*, **1998**, *63*, 2428.
... ; Buono, G. *ACIEE*, **2000**, *39*, 2554. (not available online)
Reymond, S.; Brunel, J.M.; Buono, G. *Tetrahedron: Asymmetry*, **2000**, *11*, 4441.
... ; Buono, G. *Eur. J. Org. Chem.*, **2001**, 2819.
Denmark, S.E.; Wynn, T.; Jellerichs, B.G. *ACIEE*, **2001**, *40*, 2255.
Buono, G. *ACIEE*, **2001**, *40*, 4536.
Buono, G. *Eur. J. Org. Chem.*, **2002**, 218.