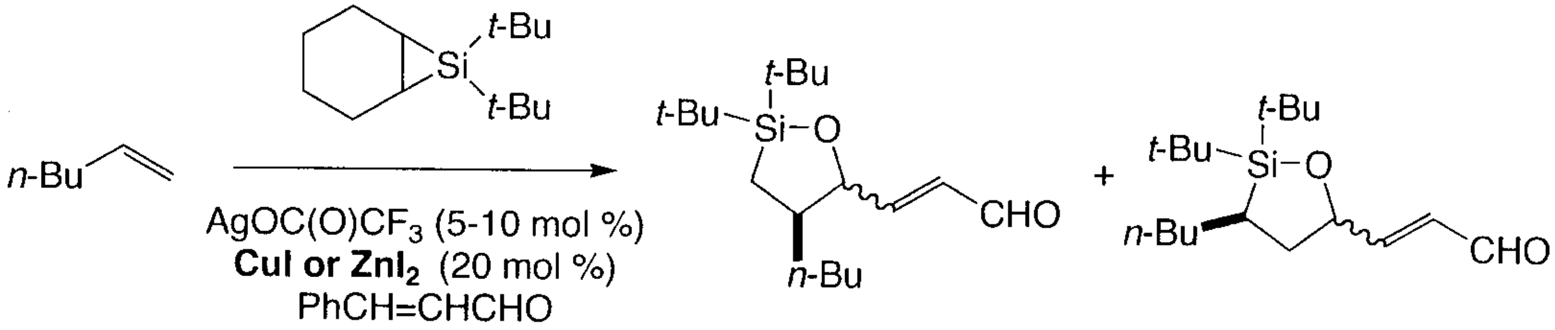
Metal-Catalyzed Di-*tert*-butylsilylene Transfer: Synthesis and Reactivity of Silacyclopropanes

Cirakovic, J.; Driver, T. G.; Woerpel, K. A.

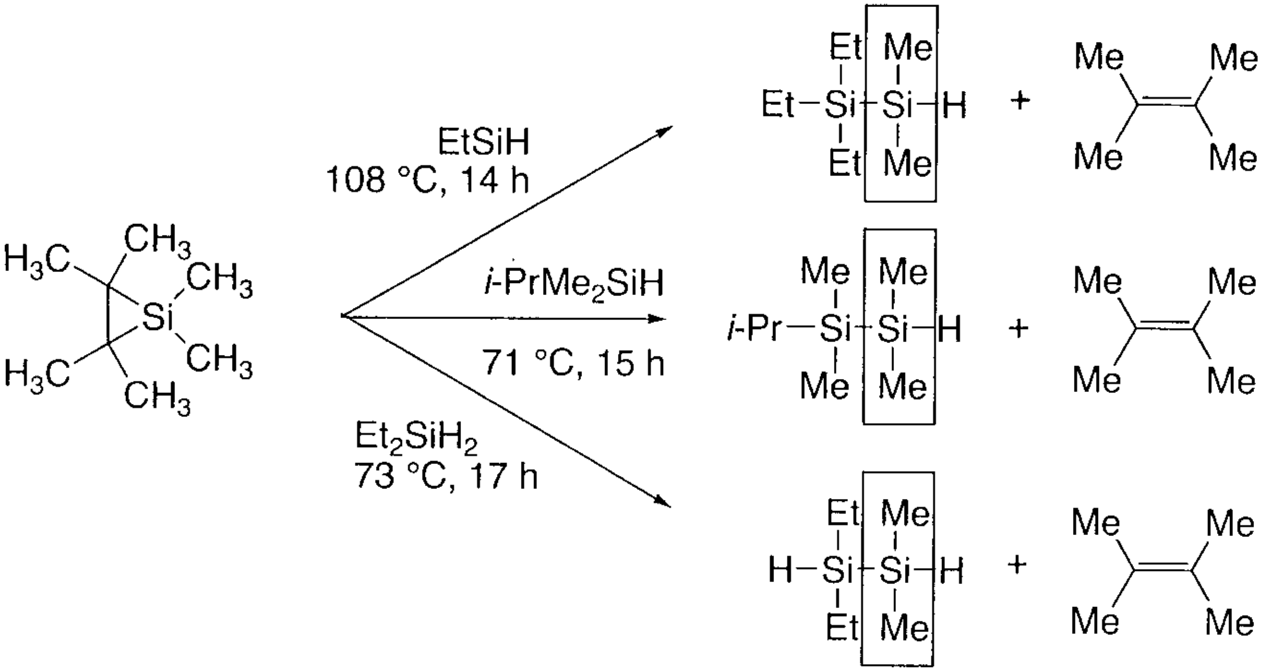
JOC, ASAP (Release date: Feb. 10, 2004)



17a
(1,2-isomer)

17b
(1,3-isomer)

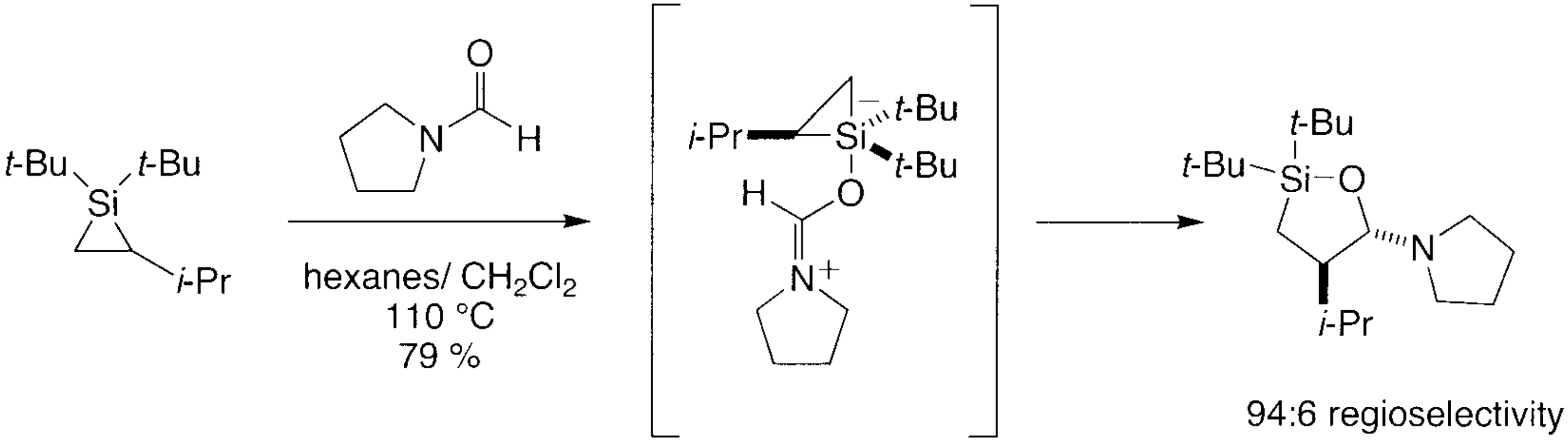
Silylenes: The Beginning



- "It should be recognized that the scope of the application of hexamethylsilirane will be limited by the extremely high reactivity of the silacyclopropane ring system toward many classes of compounds."

Seyferth, D. and Annarelli, D. C. *JACS*, **1975**, *97*, 7162-7163.

Silacyclopropane Insertions: Thermally mediated

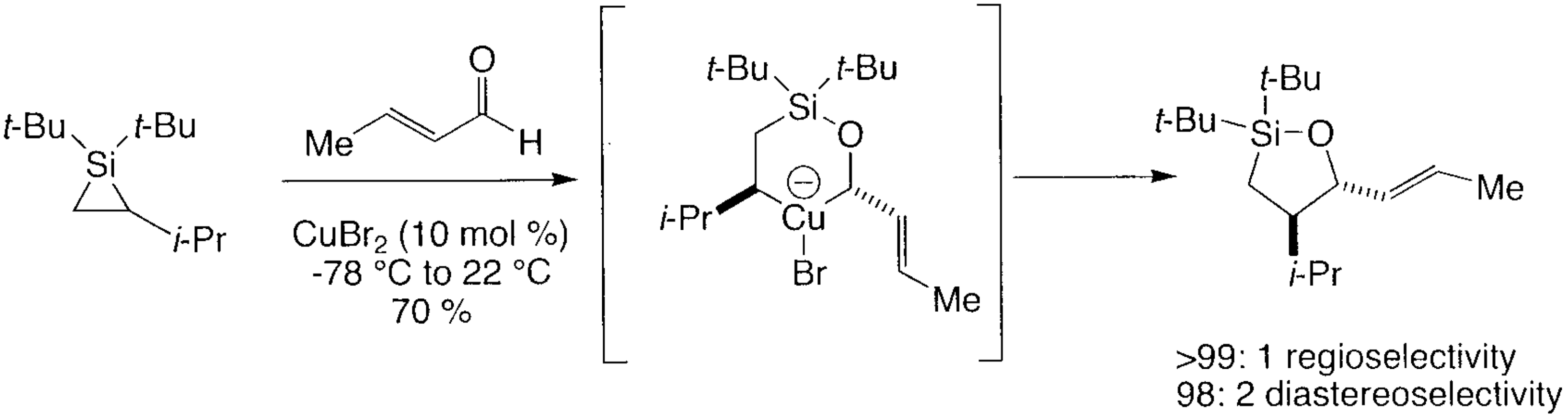


94:6 regioselectivity

- Regioselectivity is rationalized based on the equatorially-positioned isopropyl being less sterically crowded than an apically-positioned isopropyl.
- Thermally mediated process is limited to amide insertion.
- Vigorous reaction conditions represent a limitation.

Franz, A. K.; Woerpel, K. A.
Acc. Chem. Res. **2000**, *33*, 813-820.

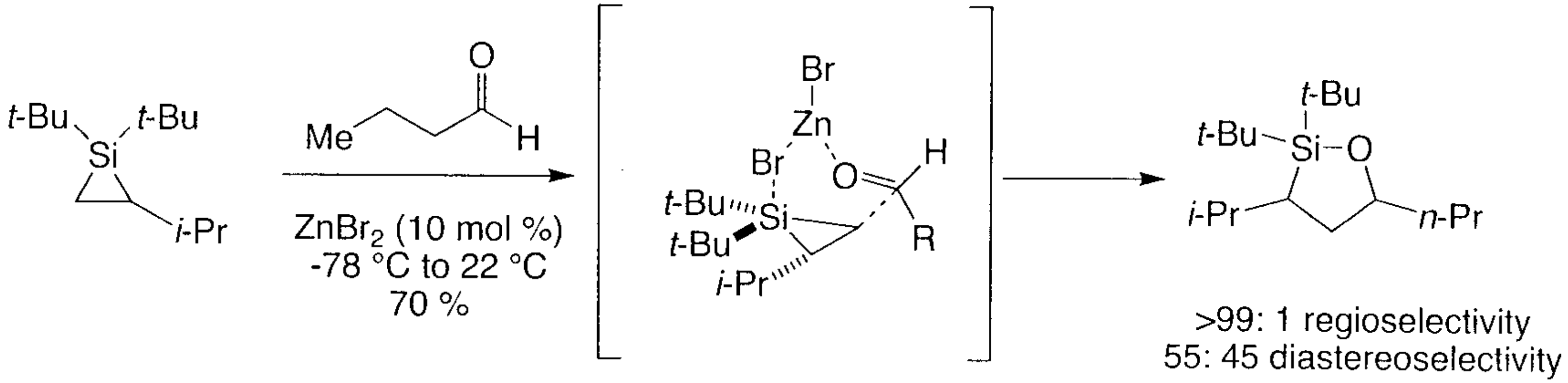
Silacyclopropane Insertions: Copper mediated



- The use of $CuBr_2$ results in the 1,2-regioisomer via insertion into the more substituted Si-C bond.
- Unsaturated aldehydes, esters (especially formate esters) and amides give the insertion product.
- Saturated aldehydes are unreactive.

Franz, A. K.; Woerpel, K. A.
Acc. Chem. Res. **2000**, *33*, 813-820.

Silacyclopropane Insertions: Zinc mediated



>99: 1 regioselectivity
55: 45 diastereoselectivity

- The use of $ZnBr_2$ results in the 1,3-regioisomer via insertion into the less substituted Si-C bond.
- Saturated and unsaturated aldehydes, esters (especially formate esters) and amides give the insertion product.

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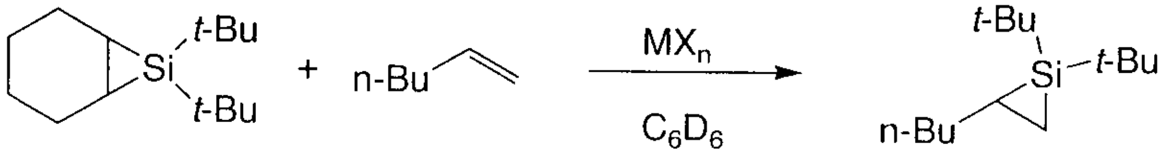
Acc. Chem. Res. **2000**, *33*, 813-820.

Catalysts Screened for Silylene Transfer



entry	catalyst (10 mol %)	temp, °C	time	% transfer[a,b]
1	none	130	36 h	100
2	$Zn(OTf)_2$	55	12 h	95
3	$CeCl_3$	25	15 h	69
4	CuF_2	25	18 h	70
5	AgI	25	30 min	80
6	$Cu(OTf)_2$	25	17 min	100
7	$Cu(OTf)_2$	0	2 h	100
8	$Cu(OTf)_2 \cdot PhH$	0	2 h	100
9	AgOTf	−27	2 h	100
10	$AgOC(O)CF_3$	−27	2 h	100

[a] As determined by ^{1}H MMR spectroscopic analysis of the reaction mixture. [b] Reaction took place in a sealed NMR tube with C_6D_6 as a solvent.

- Silver salts gave the best rate enhancement (lowest temperature and shortest time with 100% transfer).
- Control experiments indicate that the silylene transfer is irreversible between monosubstituted olefins (i.e. *n*-butylsilacyclopropane to allylbenzene does not occur)

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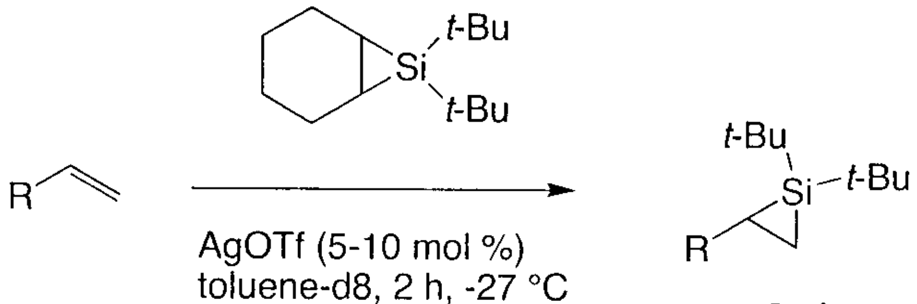
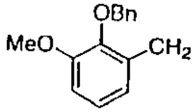
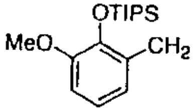
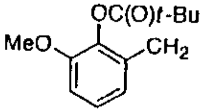
Scope: Monosubstituted Olefins



AgOTf (5-10 mol %)
toluene-d8, 2 h, -27 °C
then TMEDA

2a-j

entry	R[a]	product	% yield[b]
1	n-Bu	**2a**	90
2[c]	i-Pr	**2b**	99
3	t-Bu	**2c**	96
4	Bn	**2d**	90
5	TIPSO—$(CH_2)_2$	**2e**	82
6	BnO—$(CH_2)_2$	**2f**	71
7	t-Bu(O)CO—$(CH_2)_2$	**2g**	67
8		**2h**	61
9		**2i**	72
10		**2j**	83

[a] 1.3 equiv of alkene was used. [b] As determined by ^1H NMR spectroscopic analysis of the product mixture relative to an internal $PhSi(CH_3)_3$ standard. [c] An excess of alkene was used (ca. 10 equiv).

- not affected by sterics
- aryl, benzyl and silyl ethers are tolerated
- pivaloyl esters are tolerated

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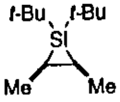
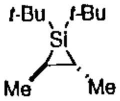
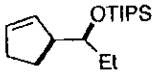
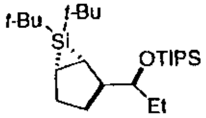
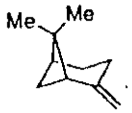
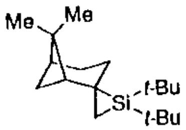
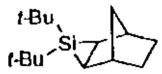
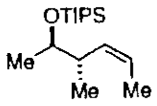
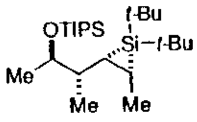
Scope: Disubstituted Alkenes

entry	alkene[a]	product	% yield[b]
1	*cis*-2-butene[c]	 **3**	99
2	*trans*-2-butene[c]	 **4**	92
3	 **5**	 **6**	85[d]
4	 **7**	 **8**	72[d]
5	 **9**	 **10**	90[d]
6	 **11**	 **12**	79[e]

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[a] 1.3 equiv of alkene were used. [b] As determined by ^1H NMR spectroscopic analysis of the product mixture relative to an internal $PhSi(CH_3)_3$ or 1,3-dimethoxybenzene standard. [c] An excess of alkene was used (ca. 10 equiv). [d] One diastereomer was visible by ^1H NMR and ^{29}Si NMR spectroscopy (dr ≥ 95:5). [e] dr = 89:11, as determined by ^{29}Si NMR spectroscopy.

- Stereospecific (entries 1 and 2)
- Diastereoselective (entries 3-5)
- Improvement in diasteroselectivity when compared to thermal or *t*-Bu_2SiCl_2 / Li methods (*JAC*S, **2002**, *124*, 6524-6525).

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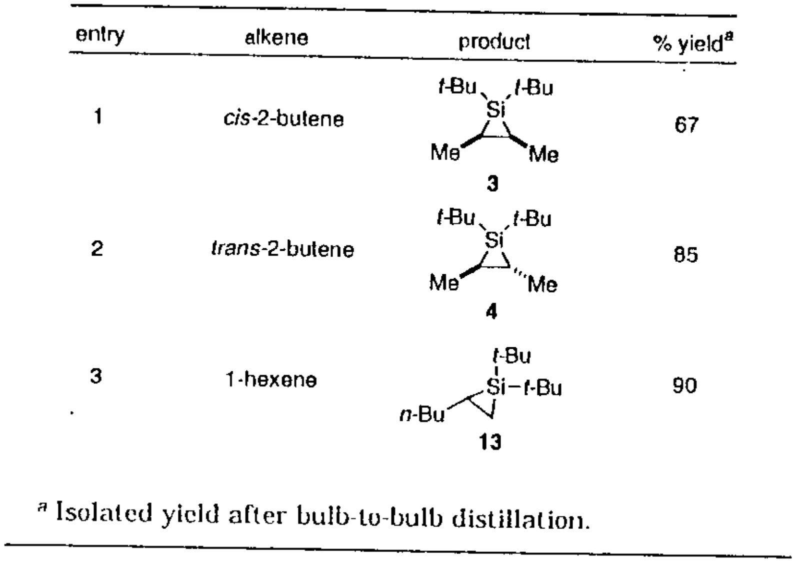
Isolation of Silacyclopropanes



entry	alkene	product	% yield[a]
1	*cis*-2-butene	**3**	67
2	*trans*-2-butene	**4**	85
3	1-hexene	**13**	90

[a] Isolated yield after bulb-to-bulb distillation.

- Silver salts (10 mol %) are implicated in the initial isolation problems.
- The catalyst loading was decreased to 5 mol %.
- Crude reaction mixture was schlenk filtered then distilled to afford pure silacyclopropanes.

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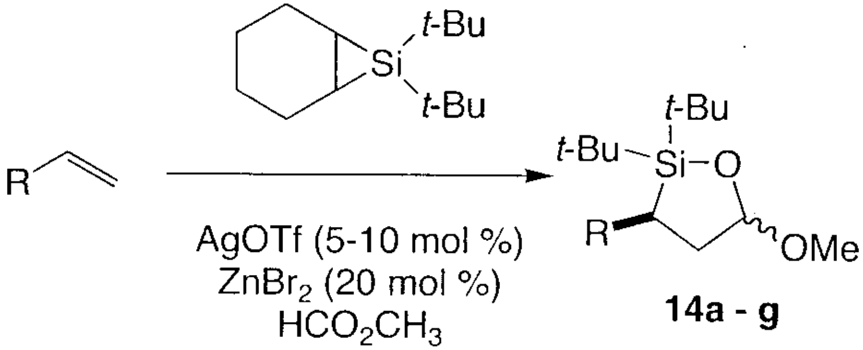
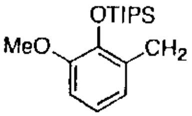
In situ Preparation of Silacyclopropanes and Methyl Formate Insertion



14a - g

entry	R	regioselectivity[a]	d.r.[a]	product	% yield[b]
1	*n*-Bu	>99:1	76:24	**14a**	87
2	*i*-Pr	>99:1	70:30	**14b**	92
3	*t*-Bu	74:26	major, 70:30 minor, 91:9	**14c**	75
4	Bn	97:3	major, 70:30	**14d**	80
5	$BnO(CH_2)_2$	>99:1	64:36	**14e**	61
6	$TIPSO(CH_2)_2$	96:4	70:30	**14f**	61
7		>99:1	70:30	**14g**	82

[a] As determined by ^1H NMR spectroscopic analysis of the unpurified product mixture. [b] Isolated yield over two steps after purification by flash chromatography.

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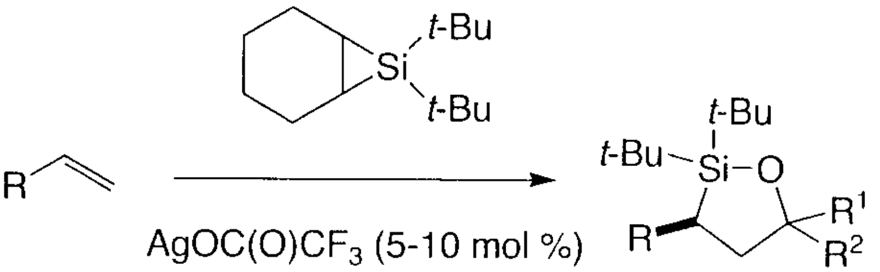
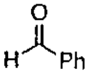
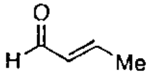
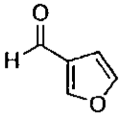
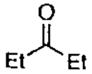
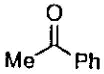
One-Flask Silylene Transfer, Carbonyl Insertion



$AgOC(O)CF_3$ (5-10 mol %)
$ZnBr_2$ or ZnI_2
R_1R_2CO

15a - e

15a, R^1 = Ph, R^2 = H
15b, R^1 = CH=CHMe, R^2 = H
15c, R^1 = 3-furanyl, R^2 = H
15d, R^1, R^2 = Et
15e, R^1 = Me, R^2 = Ph

entry	R	MX_n	R^1R^2CO	d.r.	% yield[b]
1	n-Bu	$ZnBr_2$		65:35	73
2	$PhCH_2$	ZnI_2		64:36	78
3	$PhCH_2$	ZnI_2		65:35	80
4	$PhCH_2$	ZnI_2		--	57
5	$PhCH_2$	ZnI_2		55:45	71

[a] 20 mol % of MX_n used. [b] Isolated yield over two steps after purification by flash chromatography.

- completely regioselective
- diastereoselectivity was low
- $ZnBr_2$ and ZnI_2 equally effective
- Aliphatic aldehydes required less than 1 mol % AgOTf for the insertion.

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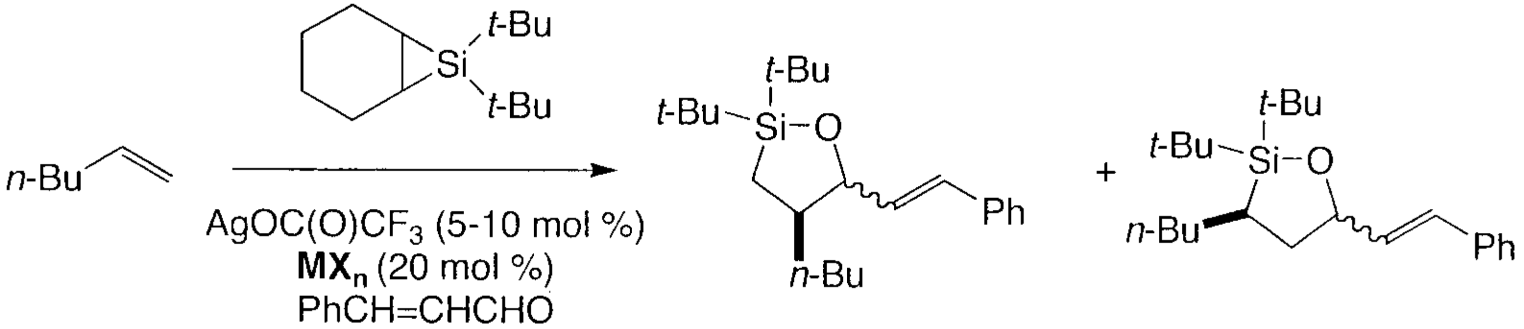
Regioselectivity Depends on the Metal Halide Additive



17a
(1,2-isomer)

17b
(1,3-isomer)

entry	MX_n	**17a:17b**	1,2 dr	1,3 dr	% yield[b]
1	CuI	96:4	82:18		85
2	ZnI_2	1:99		76:24	92

[a] 20 mol% of MXn used. [b] Isolated yield over two steps after purification by flash chromatography.

- CuI gives insertion into the more substituted Si - C bond (1,2-isomer)
- ZnI_2 gives insertion into the less substitutes Si - C bond (1,3 isomer)
- dr and yields are similar

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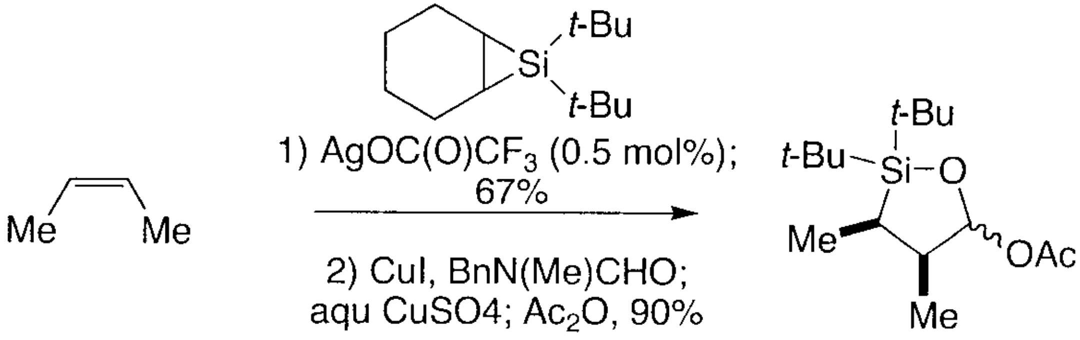
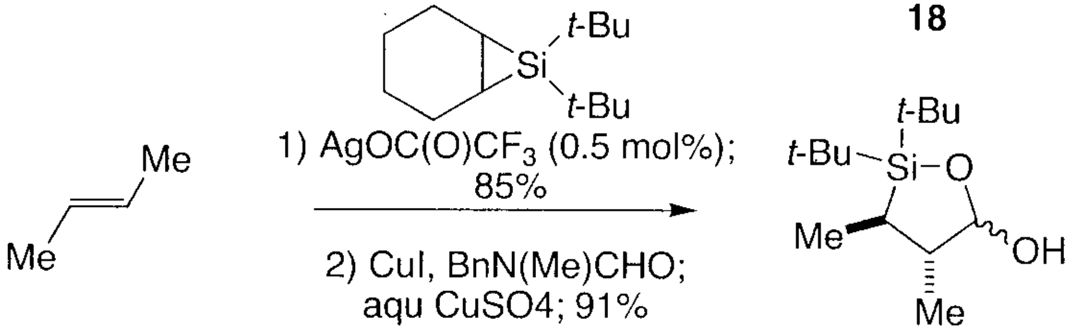
Disubstituted Silacyclopropanes



18



19

- At 5 mol % AgOTf, no 2,3-disubstituted products were formed with any carbonyl compounds.
- Higher yields were obtained when the silacyclopropane was isolated in the first step.
- Speculated that excess AgOTf accelerates the decomposition.

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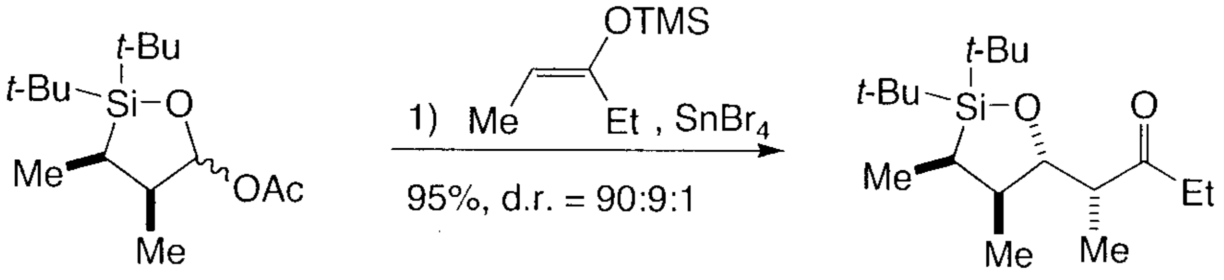
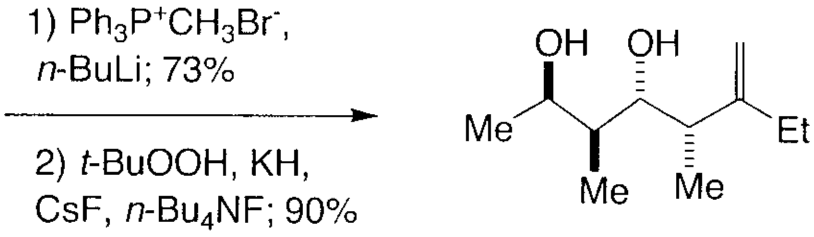
Synthetic Utility: Example # 1



18 **20**

20



21

- 4 contiguous stereocenters set in 6 steps, 38% overall yield.

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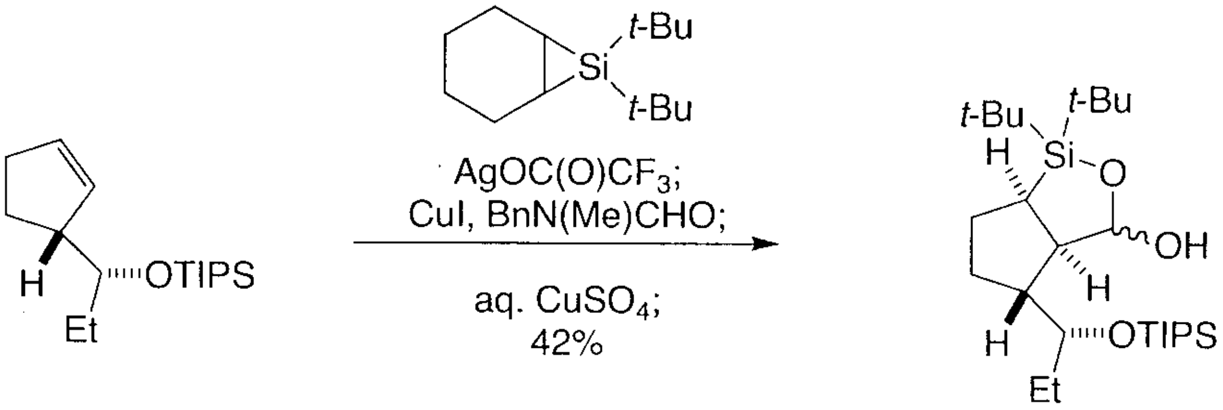
Synthetic Utility: Example # 2

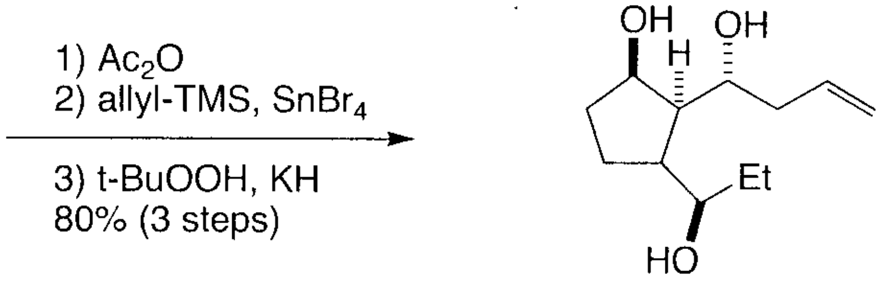
5



$AgOC(O)CF_3$;
CuI, BnN(Me)CHO;
aq. $CuSO_4$;
42%

22

22



1) Ac_2O
2) allyl-TMS, $SnBr_4$
3) t-BuOOH, KH
80% (3 steps)

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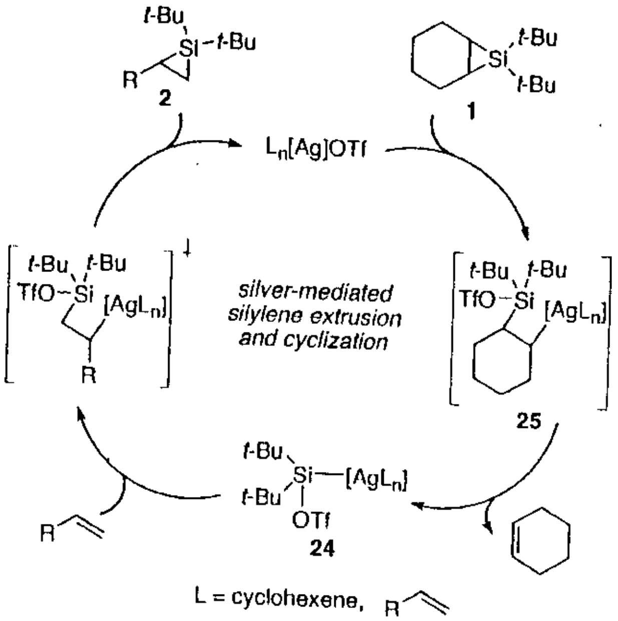
The Proposed Catalytic Cycle for Silylene Transfer



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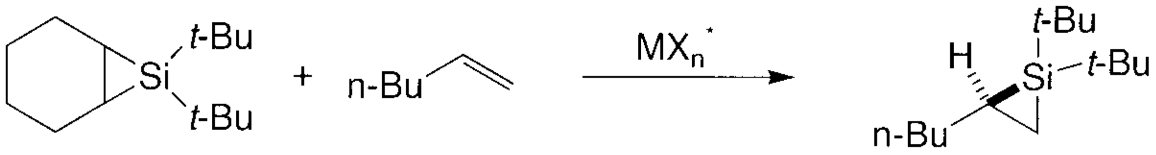
Conclusions:

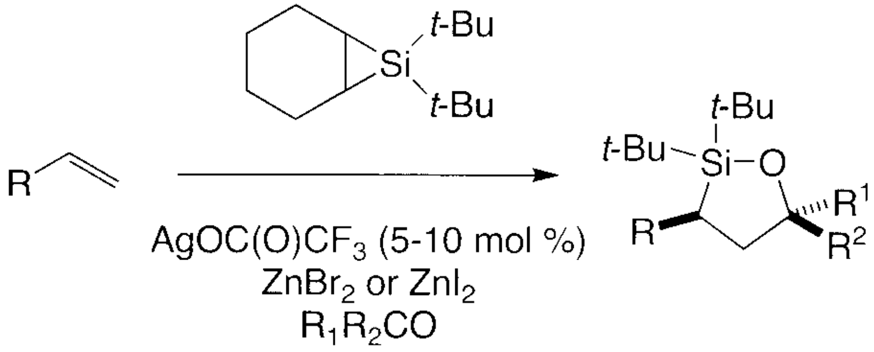
- A mild and efficient method for silacyclopropane synthesis was presented.
- The lower temperature results in better diastereoselectivity and improved substrate compatibility.
- Low catalyst loading (0.5 mol %)
- Method has broad-scope (mono- and disubstituted olefins) and offers access to a diverse set of oxasilacyclopentanes.

Future Directions:

- If a silver-stabilized silylene is an intermediate, then can stereoselectivity be induced via ligands on the silver (or other metals)?



- Can the diastereoselectivity be improved?



- Are there other sources of silylenes that are more "user-friendly"?