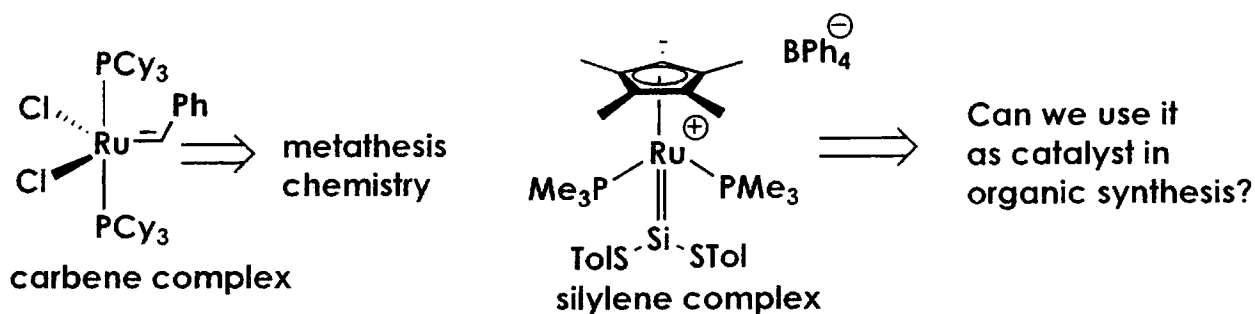
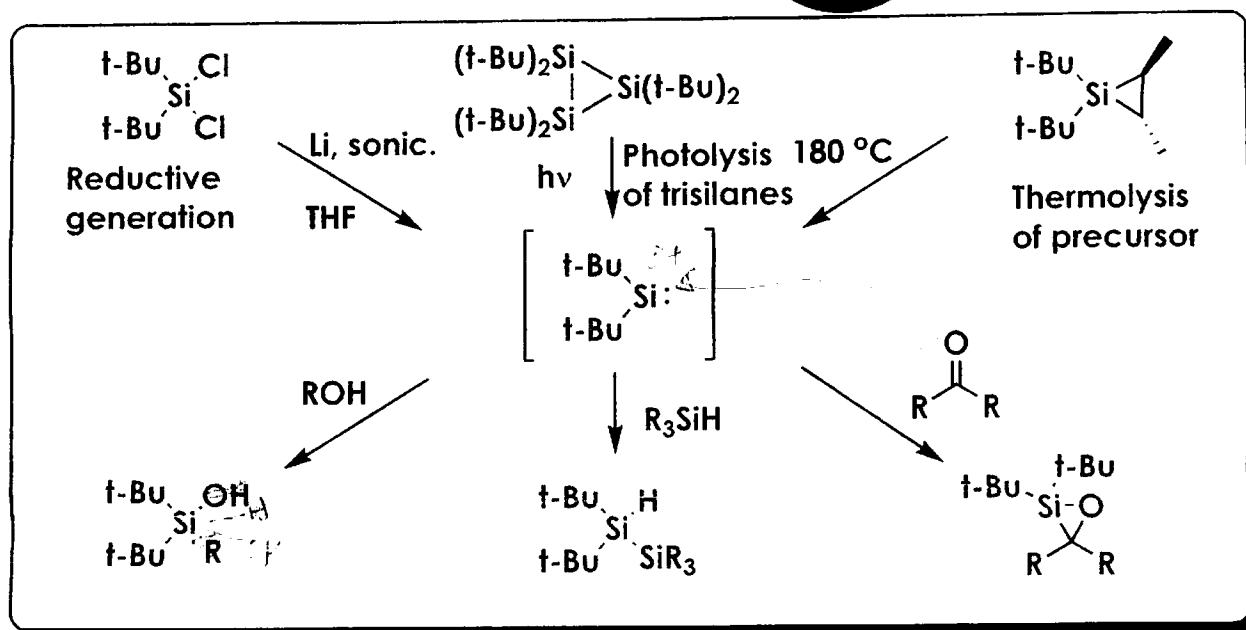
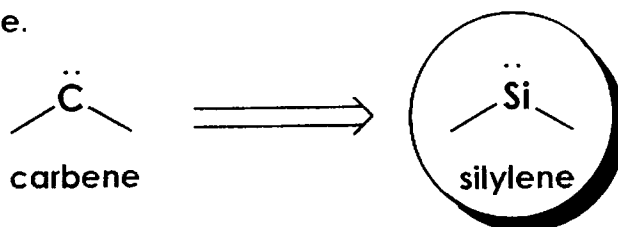


Silylenes in Organic Synthesis

Silicon reagents have been developed in organic synthesis (protective group, Mukaiyama aldol reaction, allylation, etc.), but highly reactive silicon reagents have not been used for organic synthesis.

Among such kind of reagents, silylenes are silicon analogue of carbenes. Although carbenes have been widely used in organic chemistry, application of silylenes in organic synthesis is rare.

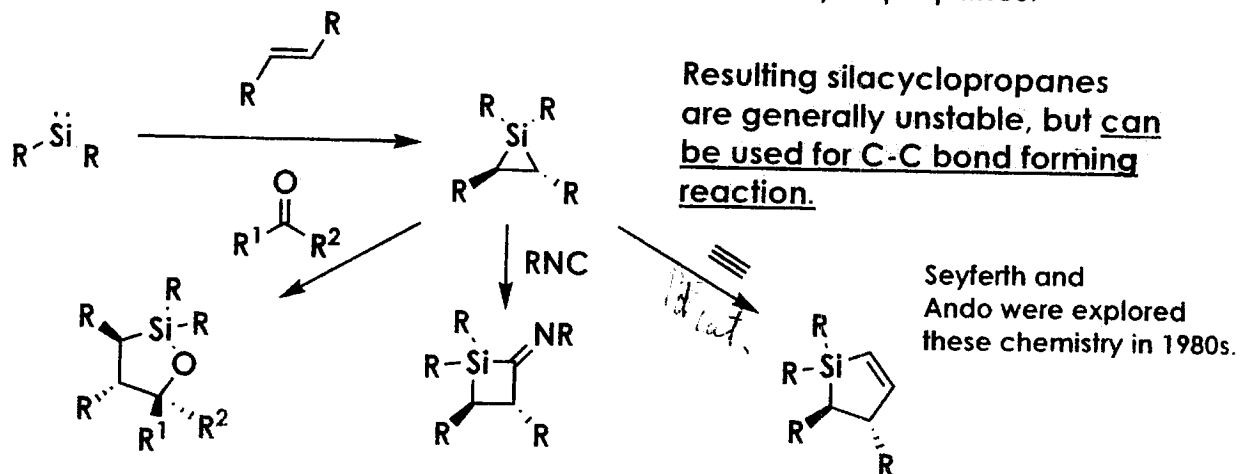


Contents

1. Ag catalyzed silylene transfer (Woerpel's work)
 - 1-1. Ag catalyzed silylene transfer
 - 1-2. Reactions with carbonyl compounds
 - 1-3. Total synthesis of (+)-5-epi-acetomycin
2. Silylene complex (Tilley's work)
 - 2-1. Preparation of silylene complex
 - 2-2. Novel hydrosilylation

1. Ag catalyzed silylene transfer

Silylenes are known to react with olefins to form silacyclopropanes.



1-1. Ag catalyzed silylene transfer

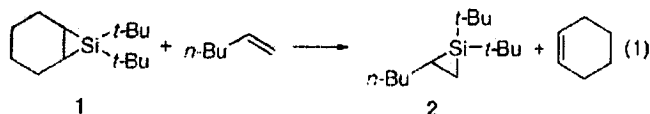
As stated above, silylenes are generated under harsh conditions, so the substrate of silacyclopropanation has been limited.

Woerpel et. al. reported Ag catalyzed silylene transfer condition which is milder than classical conditions and enable to use various alkenes as substrate.

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

JACS 2002, 124, 9370

TABLE 1. Catalyst Screening for the Silylene Transfer (Eq 1)



entry	catalyst (10 mol %)	temp. °C	time	% transfer ^a
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 -PhH	0	2 h	100
9	AgOTf	27	2 h	100
10	AgOCIO ₂ CF ₃	27	2 h	100

Several metal salts could accelerate the silylene transfer, and the most effective catalyst was AgOTf.

Catalyst loading can be reduced to as little as 1 mol %.

^a As determined by ¹H NMR spectroscopic analysis of the reaction mixture. ^b Reaction took place in a sealed NMR tube with C₆D₆ as a solvent.

Various substrates can tolerate under this condition.

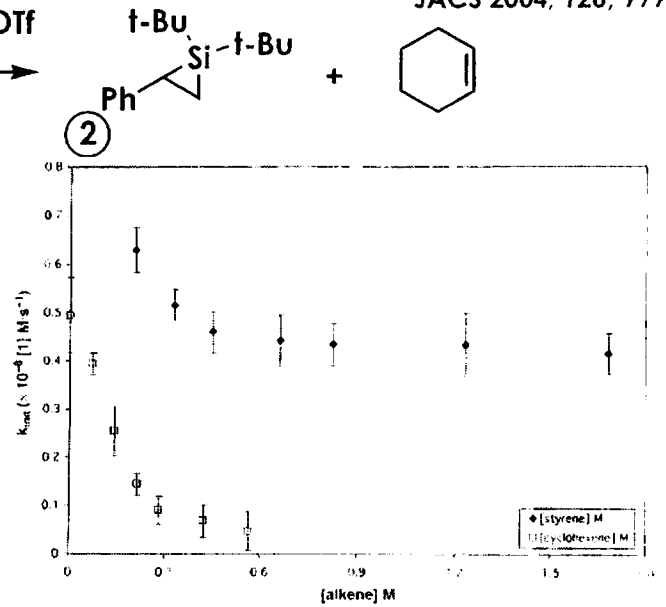
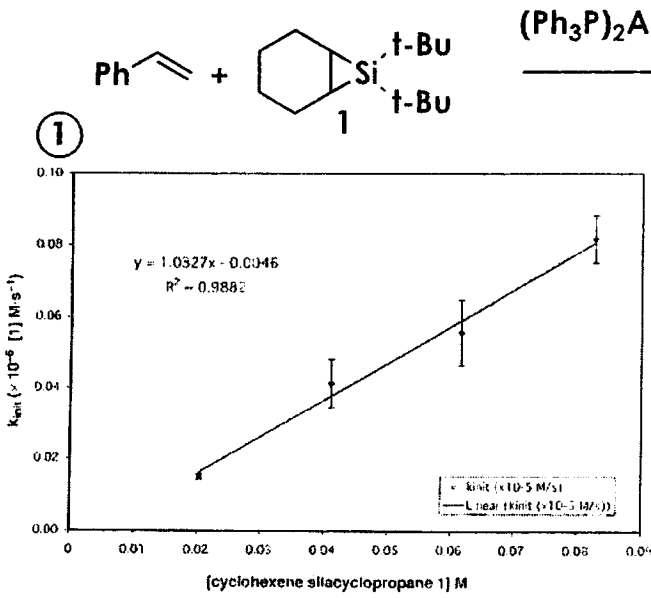
And the reaction proceeds stereospecifically and diastereoselectively.

alkene ^a	product	% yield ^b			
<i>cis</i> -2-butene ^c		99			72 ^d dr > 95: 5
<i>trans</i> -2-butene ^c		92			90 ^d dr > 95: 5
		85 ^d dr > 95: 5			79 ^d dr = 89: 11

① Mechanistic study

To clarify the mechanism of silver catalyzed silylene transfer reaction, they conducted several studies including kinetic studies.

Driver, T. G.; Woerpel, K. A.
JACS 2004, 126, 9993



kinetic order is one in cyclohexene silacyclopropane 1

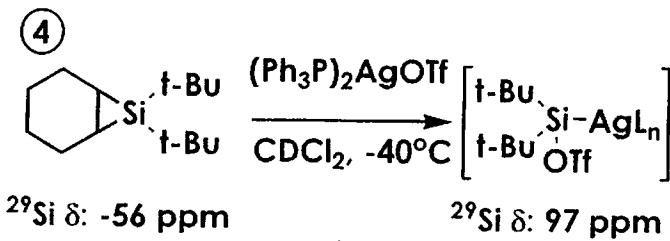
inverse saturation behavior was observed for both styrene and cyclohexene

dissociation of alkene must precede reaction of catalyst with 1

③ ligand effect on reaction rate

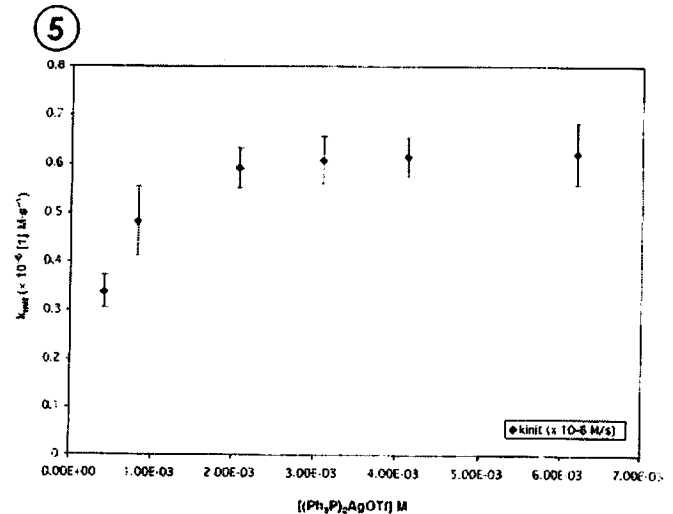
$(C_6F_5)_3P \gg Ph_3P \gg (MeOC_6H_4)_3P \gg Cy_3P \gg t-Bu_3P$

ligand must initially dissociate



downfield shift is consistent with isolated metal silylene complex
observed two doublets implies $^{107}Ag-^{29}Si$ and $^{109}Ag-^{29}Si$ coupling

formation of silylsilver complex was supported

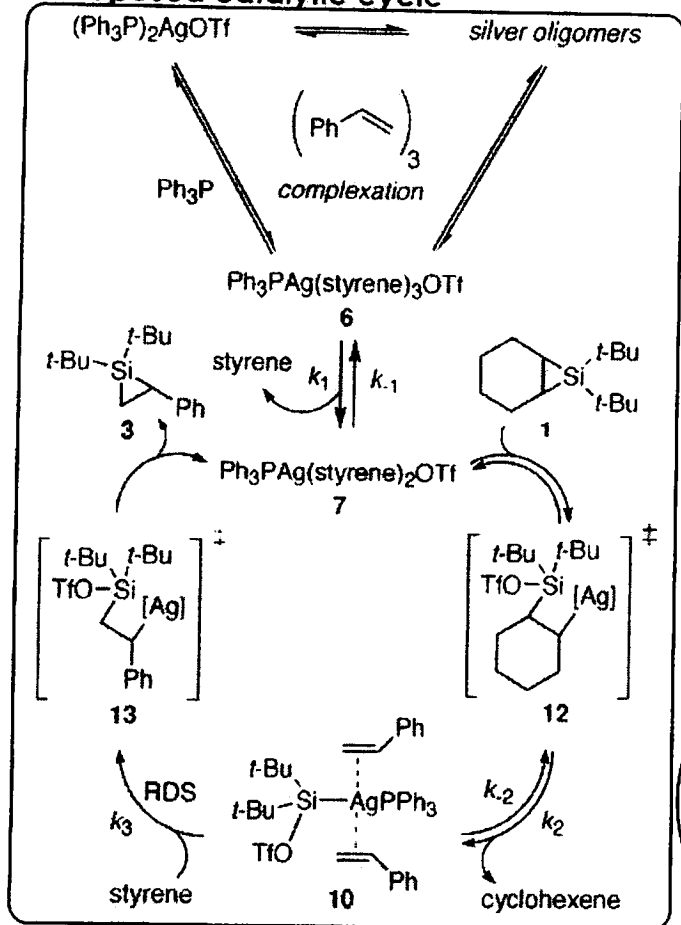


saturation behavior occurred

reversible step must precede participation of a catalyst in the mechanism

Considering all these results, they proposed catalytic cycle shown in next page. 3/8

① Proposed catalytic cycle



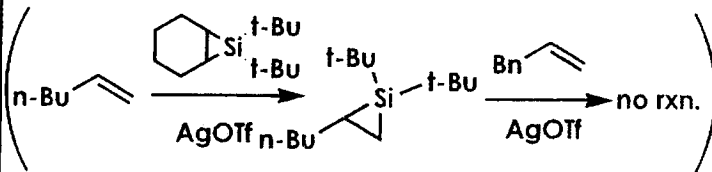
Points

catalytically inactive silver oligomers dissociates to monomeric species 6 (saturation behavior of the catalyst)

dissociation of styrene prior to transmetalation (inverse saturation behavior of styrene)

silysilver complex formation via β -silyl elimination of 12 (observation of complex 10, silver catalyst should participate in silylene extrusion step)

irreversible electrophilic cyclization of silysilver complex with styrene

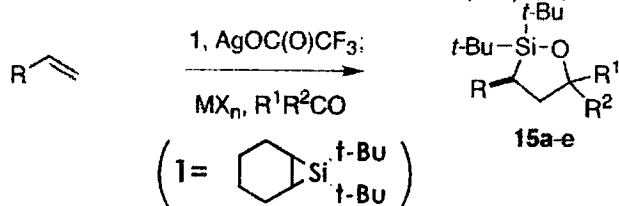


1-2. Reactions with carbonyl compounds

Although various silacyclopropanes are useful for C-C bond forming reaction, isolation is difficult and it reduces the utility.

Woerpel has developed one pot procedure from alkene.

Cirakovic, J.; Driver, T. G.; Woerpel, K. A.
JOC 2004, 69, 4007

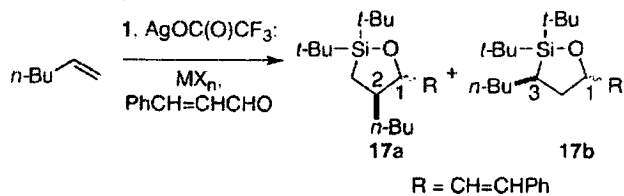


Carbonyl insertion proceeds highly regioselective manner, but diastereoselectivity is low.

entry	R	MX_n	$\text{R}^1\text{R}^2\text{CO}$	d.r.	% yield ^b
1	n-Bu	ZnBr_2	$\text{H}-\text{C}(=\text{O})-\text{Ph}$	65:35	73
2	PhCH_2	ZnI_2	$\text{H}-\text{C}(=\text{O})-\text{CH}=\text{CH}-\text{Me}$	64:36	78
3	PhCH_2	ZnI_2	$\text{H}-\text{C}(=\text{O})-\text{furan}$	65:35	80
4	PhCH_2	ZnI_2	$\text{Et}-\text{C}(=\text{O})-\text{Et}$...	57
5	PhCH_2	ZnI_2	$\text{Me}-\text{C}(=\text{O})-\text{Ph}$	55:45	71

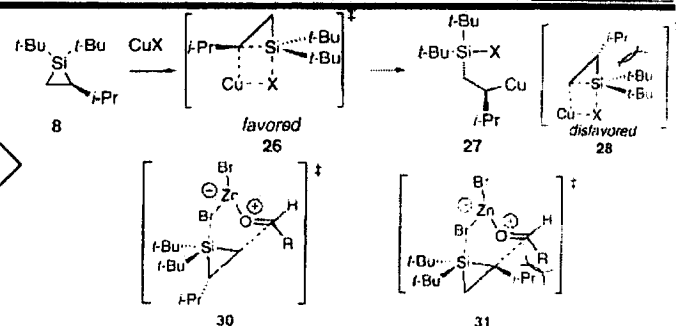
^a 20 mol % of MX_n used. ^b Isolated yield over two steps after purification by flash chromatography.

interesting inversion of regioselectivity using Zn salt or Cu salt



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

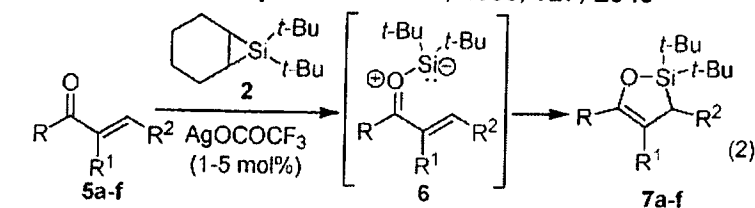
^a 20 mol% of MX_n used. ^b Isolated yield over two steps after purification by flash chromatography.



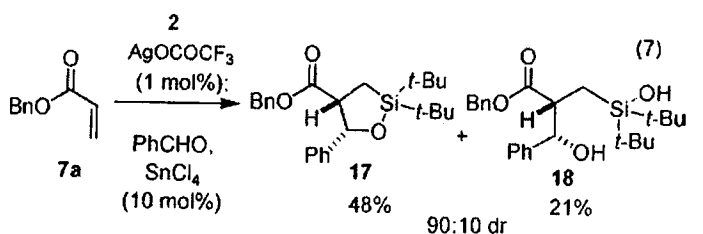
activation type is different

Silylene transfer to α,β -unsaturated carbonyl compounds gave synthetically useful compounds.

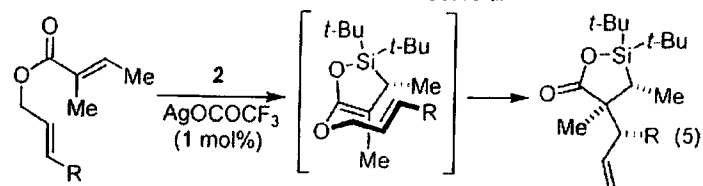
Calad, S. A.; Woerpel, K. A. *JACS*, 2005, 127, 2046



Silylsilver complex was attacked by more nucleophilic carbonyl to form silacarbonyl ylide, then ring closure occurred to give oxasilacyclopentenone.



Cyclized product of ester has keten silyl acetal moiety which can undergo Mukaiyama Aldol reaction in the presence of Lewis acid in one pot.



Silylene transfer/ Ireland-Claisen rearr. sequence can construct quaternary carbon center in high diastereoselectivity.

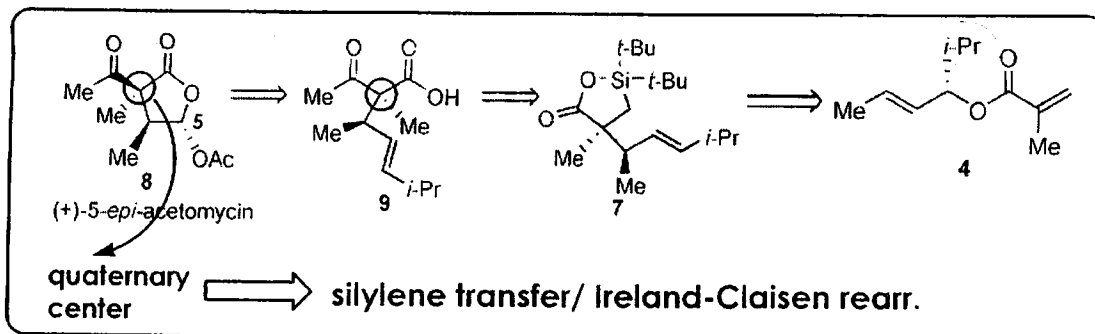
13a, R = Ph
13b, R = Me

15a, 96%, 97:3 dr
15b, 95%, one isomer

1-3. Synthesis of (+)-5-epi-Acetomycin

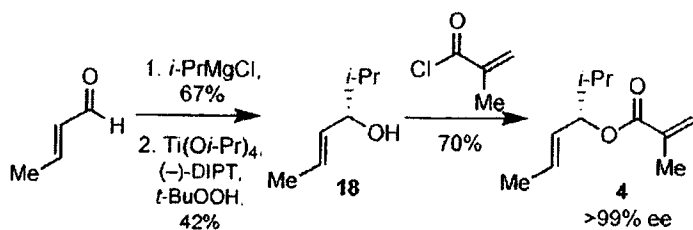
They afforded enantioselective synthesis of 5-epi-Acetomycin using their silylene transfer/ Ireland-Claisen rearr. reaction.

retrosynthetic analysis



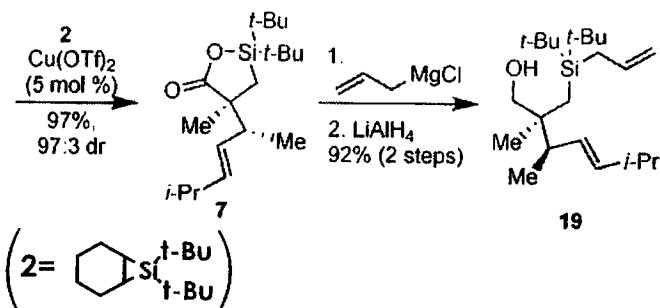
Scheme 5. Chiral Induction and Chirality Transfer

Points

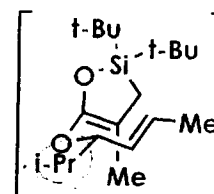


Chiral induction using kinetic resolution.

Cu salt was optimal for this substrate. (product inhibition was seen upon scale-up of silver catalyzed reaction.)

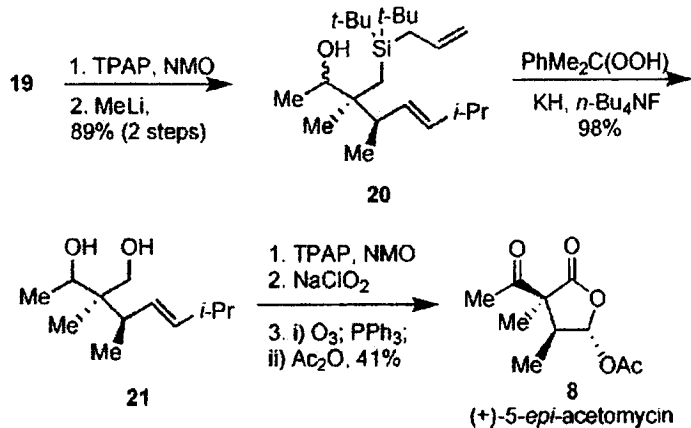


Transition state of Ireland-Claisen rearr. (i-Pr group positioned at equatorial)



Silalactone was opened by nucleophilic addition to silicon center.

Scheme 6. Synthesis of (+)-5-*epi*-Acetomycin



Si group was used to introduce oxygen by Tamao oxidation.

This Tamao oxidation condition was based on their report. The features of this condition are strong base and applicability toward hindered silicon groups.

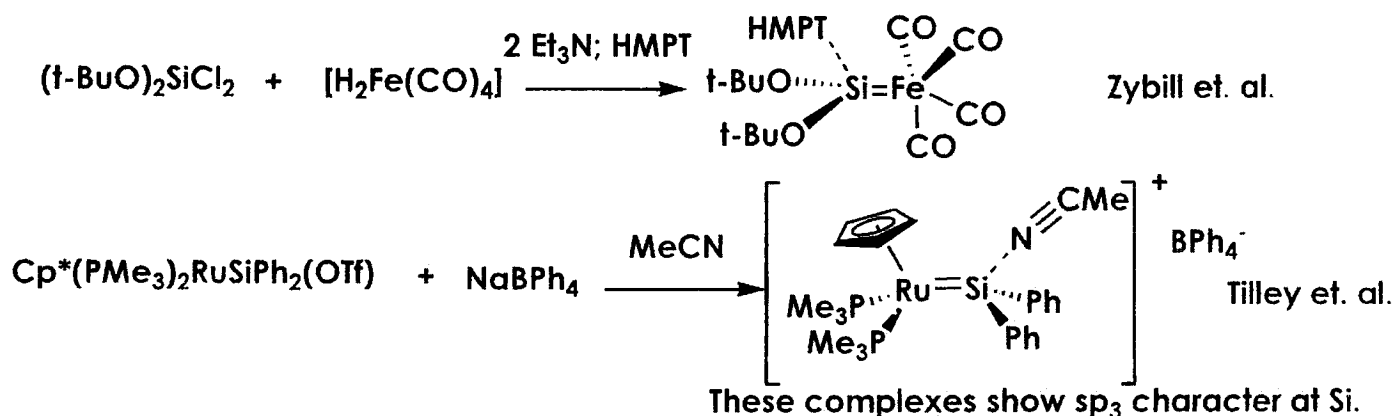
β -Keto acid was prone to decarboxylation at rt.

(huddled quickly under 0°C)

2. Silylene complex

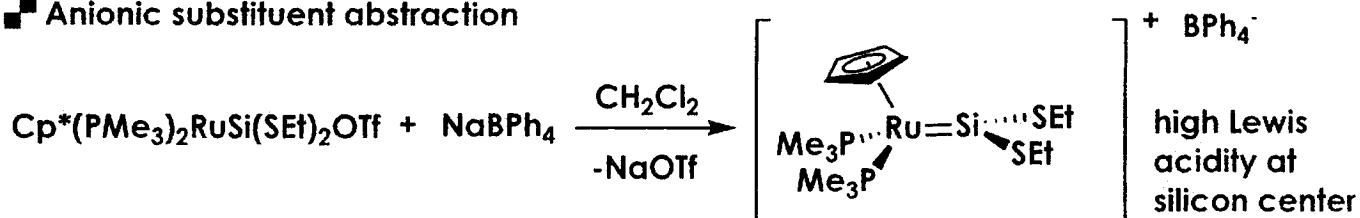
2-1. Preparation of silylene complex

Base-stabilized silylene complexes were prepared by two groups in 1987.

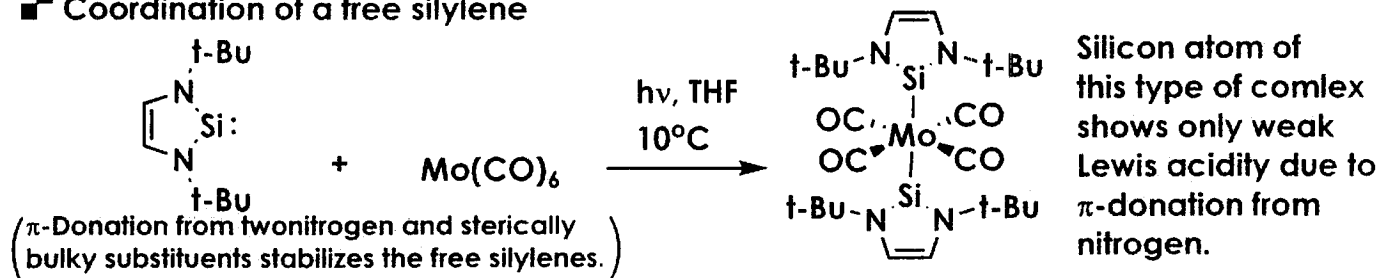


Three reliable preparation methods of base-free silylene complex have been developed.

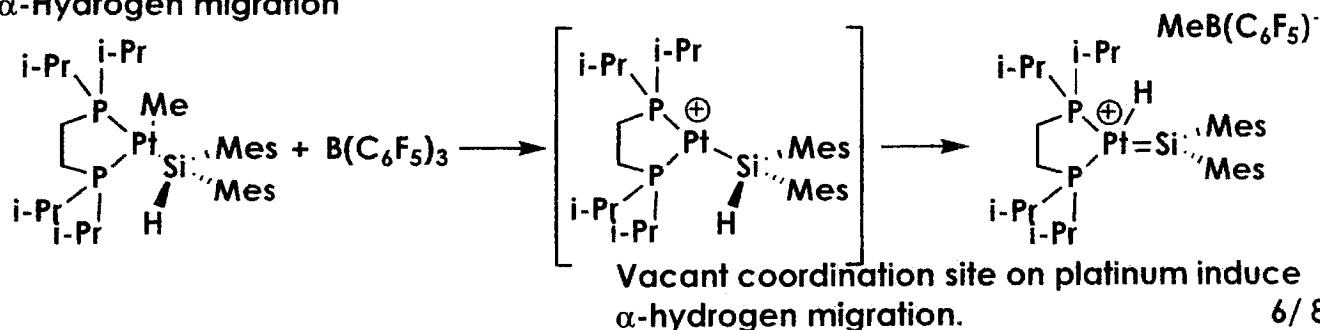
■ Anionic substituent abstraction



■ Coordination of a free silylene

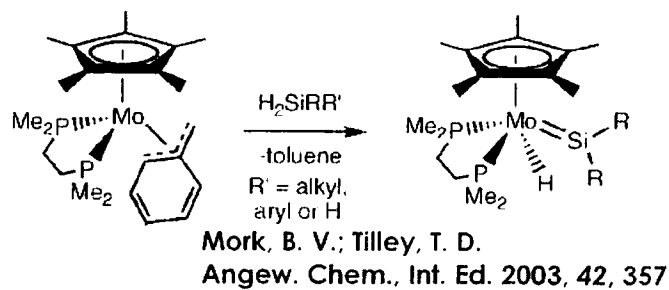
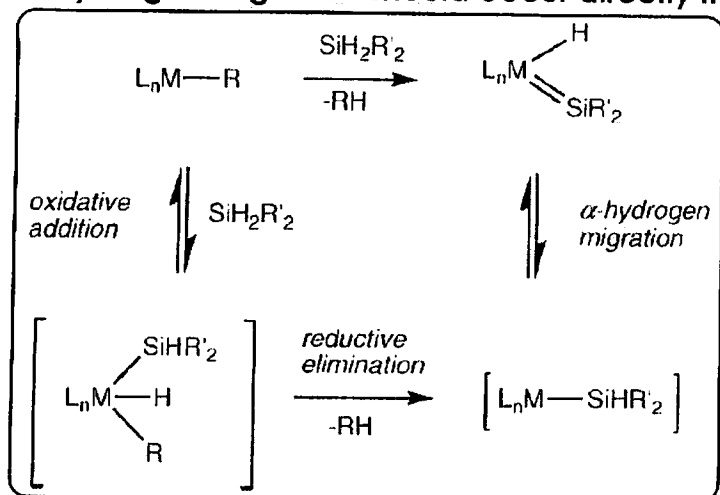


■ α -Hydrogen migration



2-2. Novel hydrosilylation

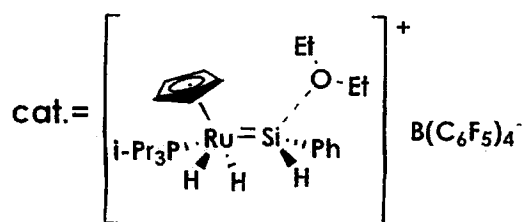
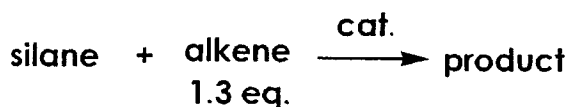
To achieve catalytic reaction using silylene complex, Si-H oxidative addition followed by α -hydrogen migration should occur directly from primary or secondary silanes.



This result showed that direct silylene complex formation from silanes is possible in the presence of a weak ligand.

Tilley et. al. realized the catalytic hydrosilylation using silylene complex.

Glaser, P. V.; Tilley, T. D. JACS, 2003, 123, 13640



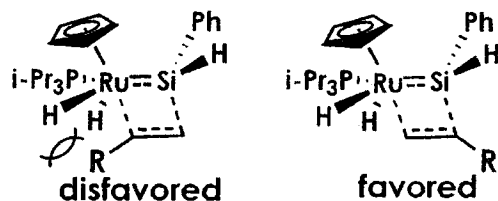
Silane	Alkene	Product	Isolated Yield (%)	Conditions: loading of 5, solvent, reaction time
PhSiH ₃	1-hexene	PhSi(H) ₂ Hex (7)	77	0.5% C ₆ H ₆ 16h
"	ethene	PhSi(H) ₂ CH ₂ CH ₃ (8)	54	5% CH ₂ Cl ₂ 3h
"	ethene-d ₄	PhSi(H) ₂ CD ₂ CD ₂ H (9)	—	5% CD ₂ Cl ₂ 3h
"	cyclohexene	PhSi(H) ₂ Cy (10)	72	2% C ₆ H ₆ 18h
"	styrene	PhSi(H) ₂ CH ₂ CH ₂ Ph (11)	94	0.5% C ₆ H ₆ 14h
"	1-methyl-cyclohexene	(±)trans-1-(PhSiH ₂)-2-Me(C ₆ H ₁₀) (12)	70	1% CH ₂ Cl ₂ 16h
HexSiH ₃	1-hexene	Hex ₂ SiH ₂ (14)	57	1% C ₆ H ₆ 18h

① Features of this hydrosilylation

- ! anti-Markovnikov selectivity
- ! only primary silanes can participate in this reaction
- ! cis-stereochemistry of addition
- ! C₂D₄ gave only as detectable product (no H/D shuffling)

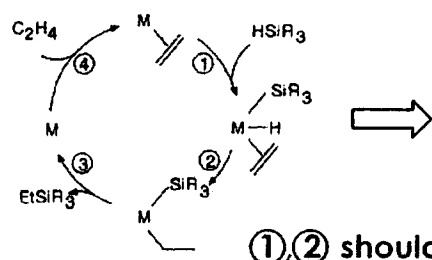
① Mechanistic consideration

(a) [2 π +2 π] cycloaddition of the Ru=Si with alkene



Observed anti-Markovnikov selectivity can't be explained.

(b) Chalk-Harrod type mechanism

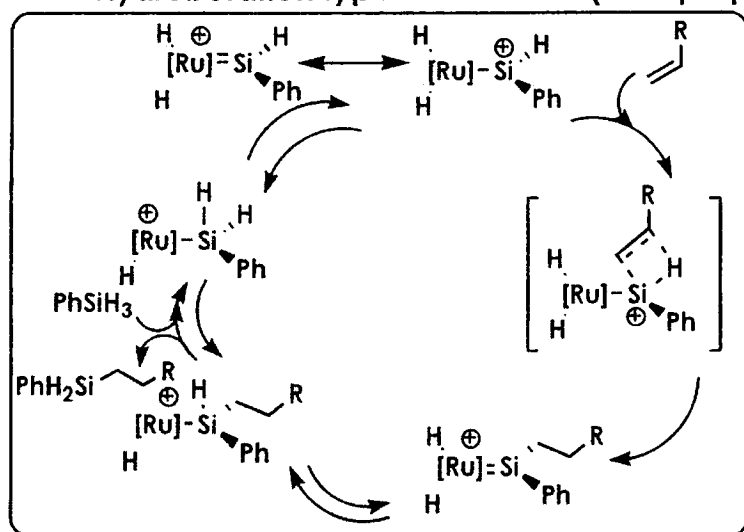


It can't explain two observation

Why secondary silanes can't participate?

H/D shuffling should be observed by following this mechanism.

c) Hydroboration type mechanism (their proposed mechanism)



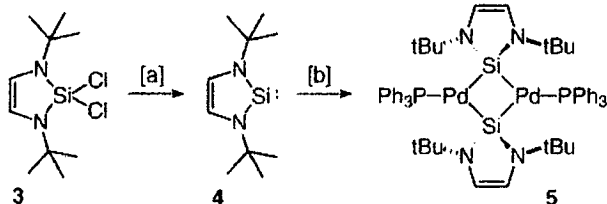
It can explain all the observation.

- ⇒ anti-Markovnikov selectivity
- ⇒ large substituents away from ruthenium center
- ⇒ primary silane selectivity
- ⇒ required for formation of a hydrogen-substituted silylene
- ⇒ cis addition
- ⇒ concerted hydrosilylation
- ⇒ no H/D shuffling
- ⇒ irreversible Si-H addition step

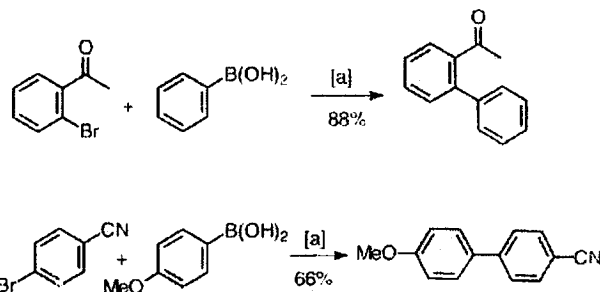
DFT calculation showed that the highest energy transition state of this process is more than 8 kcal/mol lower than that of Chalk-Harrod mechanism.

Appendix

Furstner, A.; Krause, H.; Lehmann, C. W.
Chem. Commun., 2001, 2372



Scheme 2 Reagents and conditions: [a] CsK (2.2 equiv.), THF, rt, 18 h, 67%; [b] Pd(PPh₃)₄, rt, 1 h, 50%.



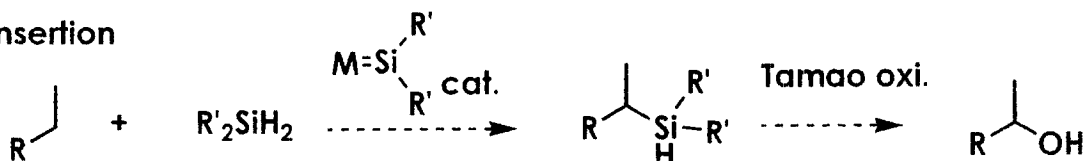
Scheme 3 Reagents and conditions: [a] complex 5 (5 mol%), DME, K₂CO₃, 80 °C.

Stable free silylene has the ability to be a ligand of cross coupling reaction like NHC ligand.

To make silylene reagent more powerful tool in organic synthesis...

Expand the application as ligand for other cross coupling reactions.

C-H insertion



Further improvement of Tamao oxidation or new conversion method of silicon moiety should be required for efficient transformation in organic synthesis.