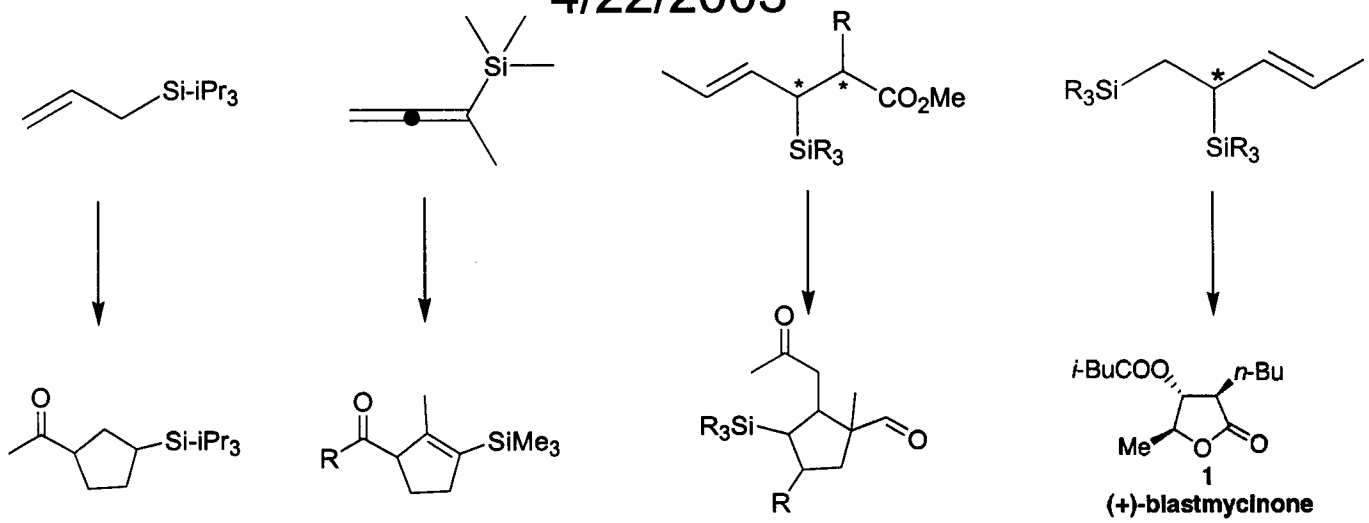
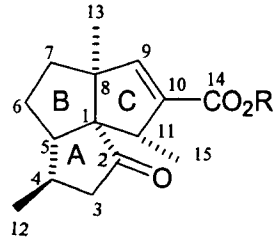
Silicon Assisted [3+2] Cycloadditions

Adam M. Kiefer

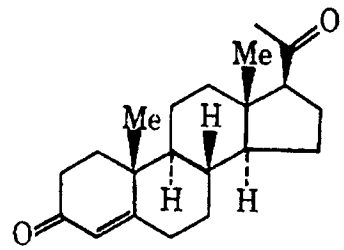
4/22/2003

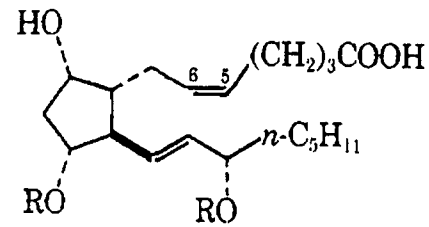


Total Synthesis Drives New Methodology



2 R=H
3 R=CH_3

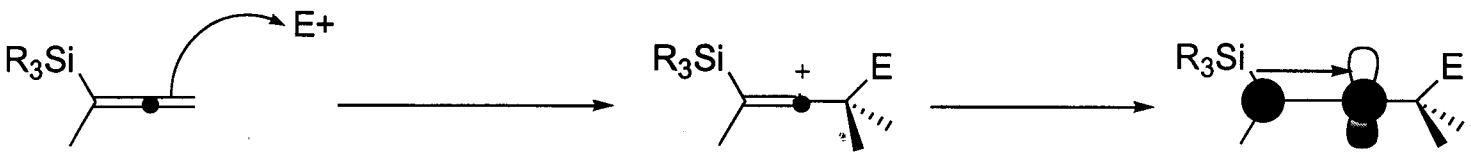




- Discovery of biologically active natural products such as the polyquinanes, steroids, and prostaglandins has prompted many new synthetic methodologies
- By the early 1980's, much research had gone into the development of new methods to form 5-membered rings
- There was no synthetic equivalent of the Diels-Alder type reaction for the formation of 5-membered carbocyles
- In 1981 Danheiser presented a novel silicon assisted [3+2] cyclization to form cyclopentenes
- This initial discovery has led to the development of many new silicon assisted cyclizations employing silicon, all of which rely on Silicon's ability to stabilize beta cations

Dragojlovic, V. *Molecules* **2000**, 5, 674
Johnson, W. et al. *J. Am. Chem. Soc*, **1964**, *93*, 4332
Corey, E.J. et al. *J. Am. Chem. Soc*, **1969, 91, 5675**

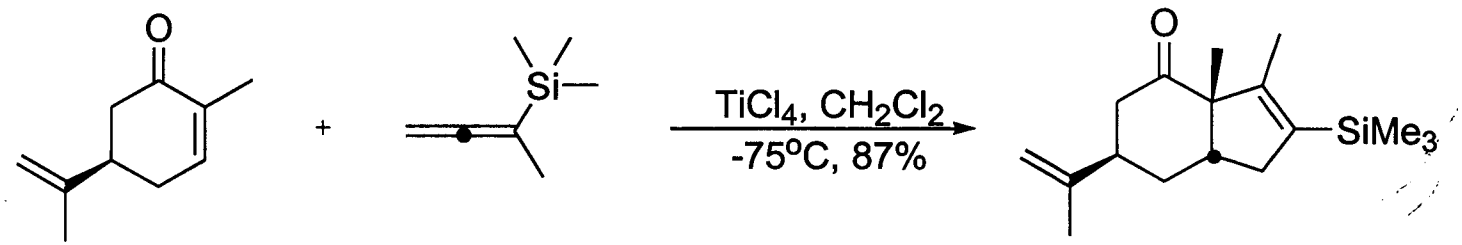
The Beta Effect



- Silicon is a slightly electropositive atom
- Si-C bond stabilizes formed carbocation via hyperconjugation
- Molecular calculations by Jorgensen show the beta carbocation to be stabilized by 38 Kcal/mol (9Kcal/mol for methyl substituent)
- Likewise a Vinyl cation is shown to be stabilized by 29 Kcal/mol (8 Kcal/mol for methyl)

Jorgenson, W. et al. *JACS.* **1985, *107*,1496**

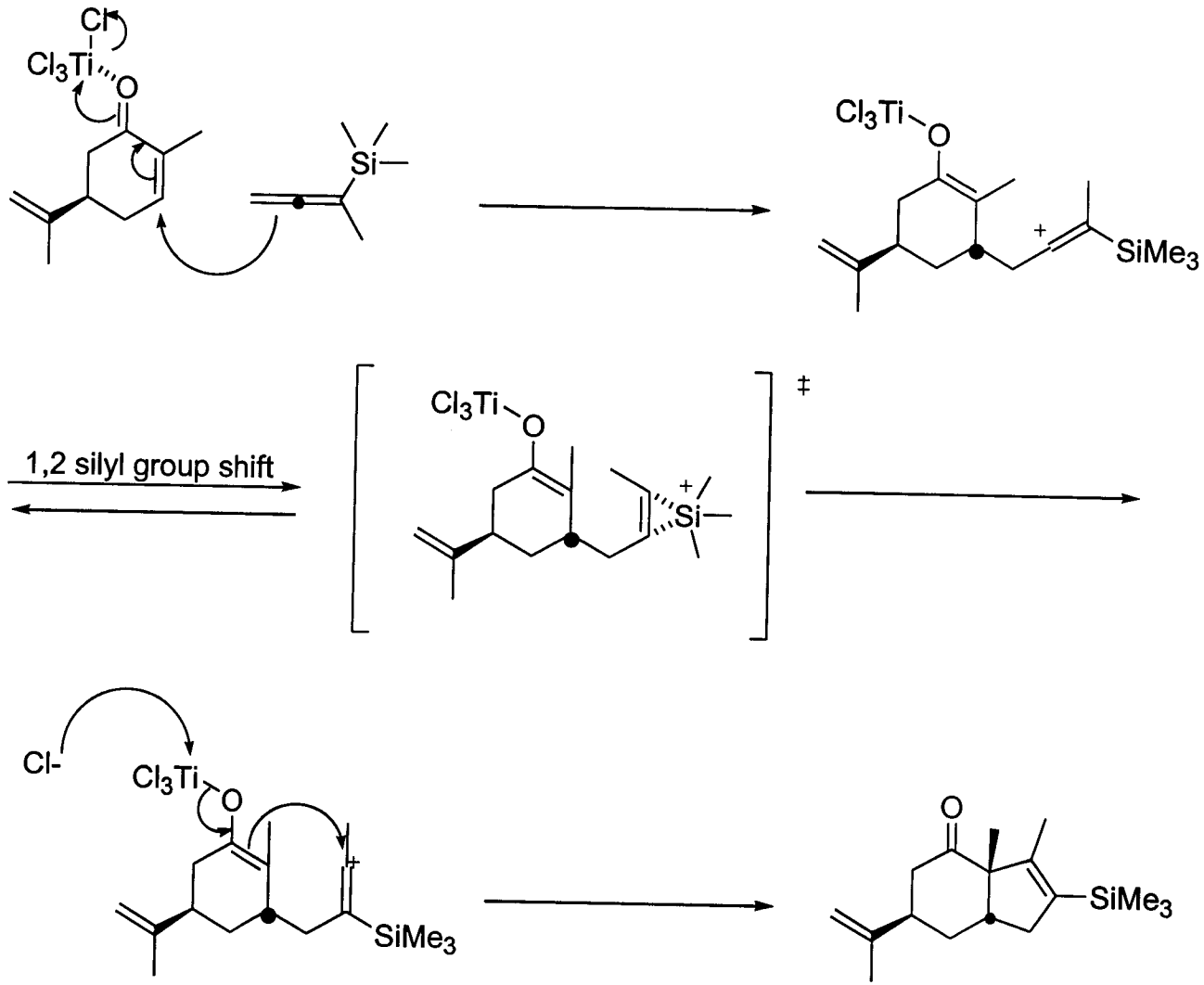
Danheiser Annulation



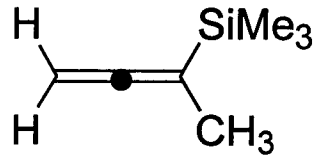
- [3+2] annulation of an α,β unsaturated ketone and a trimethylsilyl allene
- Reaction promoted by 1.5 eq $TiCl_4$
- Relies on trimethylsilyl moiety to stabilize β carbo-cation, as well as a rearrangement which leads to regioselective formation of the olefin

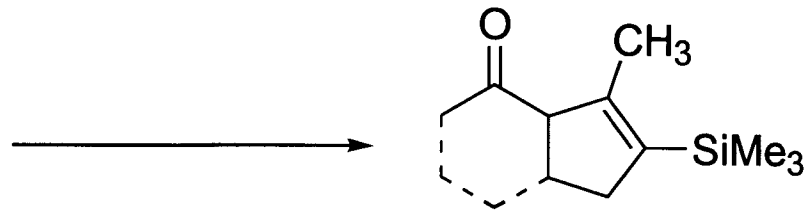
Danheiser, R.L. et al. *JACS,* **1981**, *103,* 1604

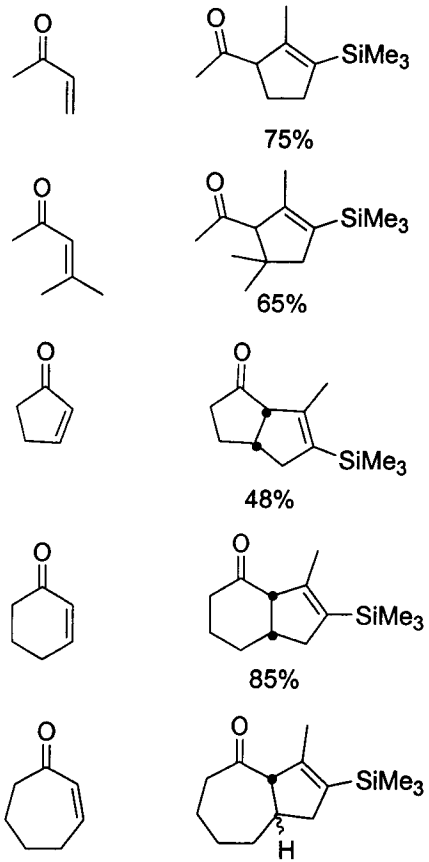
Proposed Mechanism for Danheiser Annulation

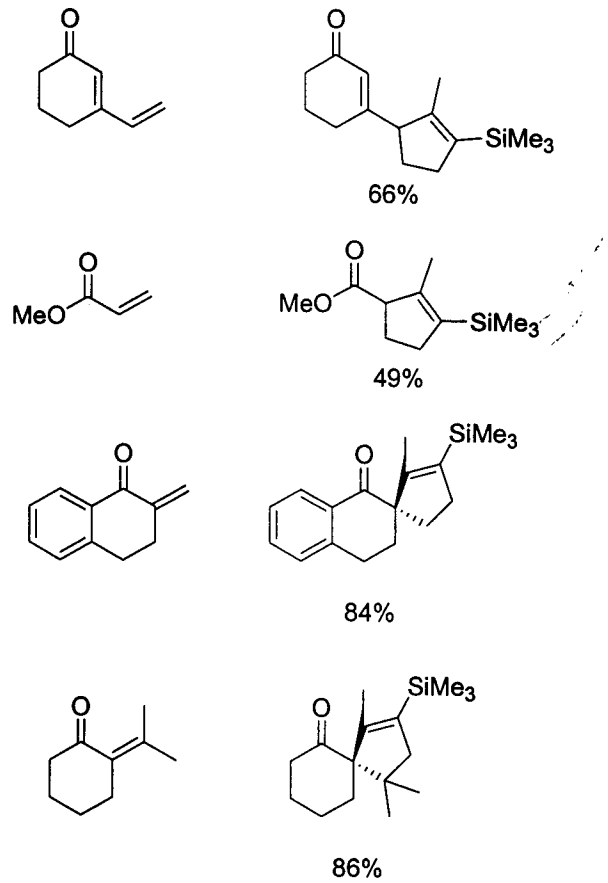


Reactive Substrates: Allenophiles

a,ß unsaturated ketone + 

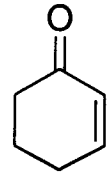
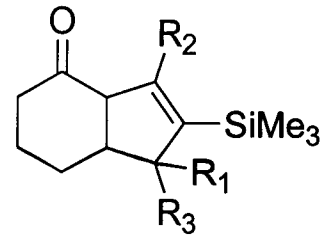


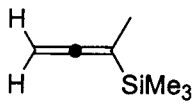


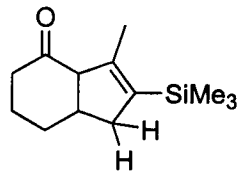


Danheiser, R.L. et al. *JACS,* **1981**, *103,* 1604
Danheiser, R.L. et al. *Tetrahedron,* **1983**, 39, 935

Reactive Substrates: Allenes

Trimethylsilyl allene +  $\xrightarrow[-75\ ^{o}C]{TiCl_4,\ CH_2Cl_2}$ 





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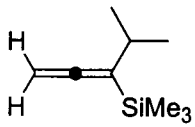
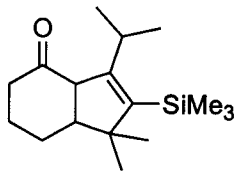
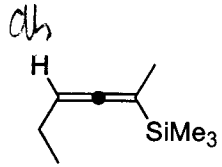
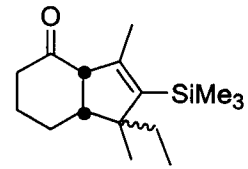


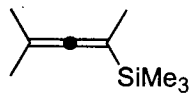


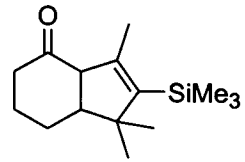
81% - 85%





79% (95-5, exo:endo)





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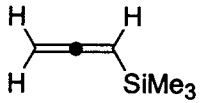
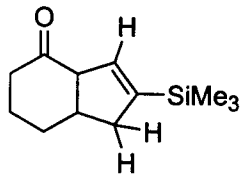
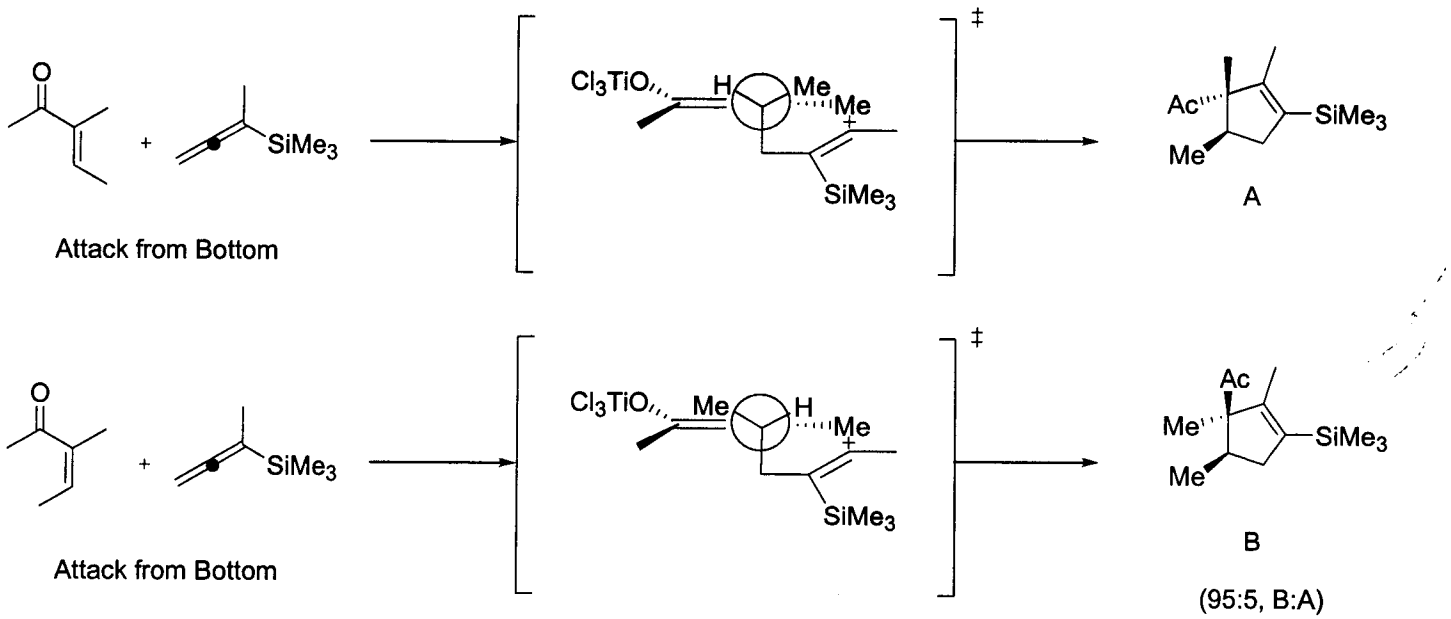




17% - 19%

Danheiser, R.L. et al. *JACS,* **1981**, *103,* 1604
Danheiser, R.L. et al. *Tetrahedron,* **1983**, 39, 935

Stereochemical Consequences…



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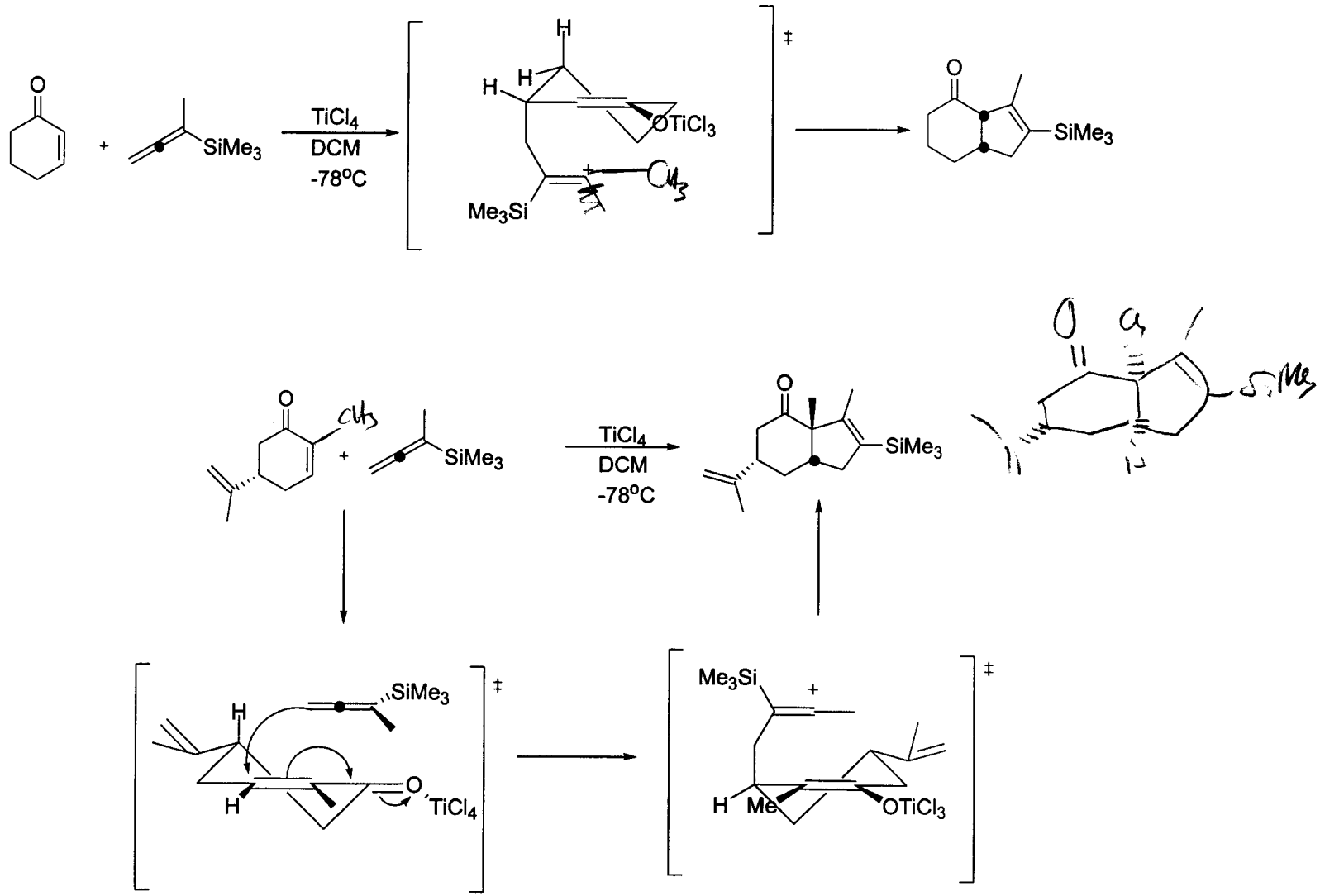
Danheiser, R.L. et al. *Tetrahedron,* **1983**, 39, 935

Stereochemical Consequences



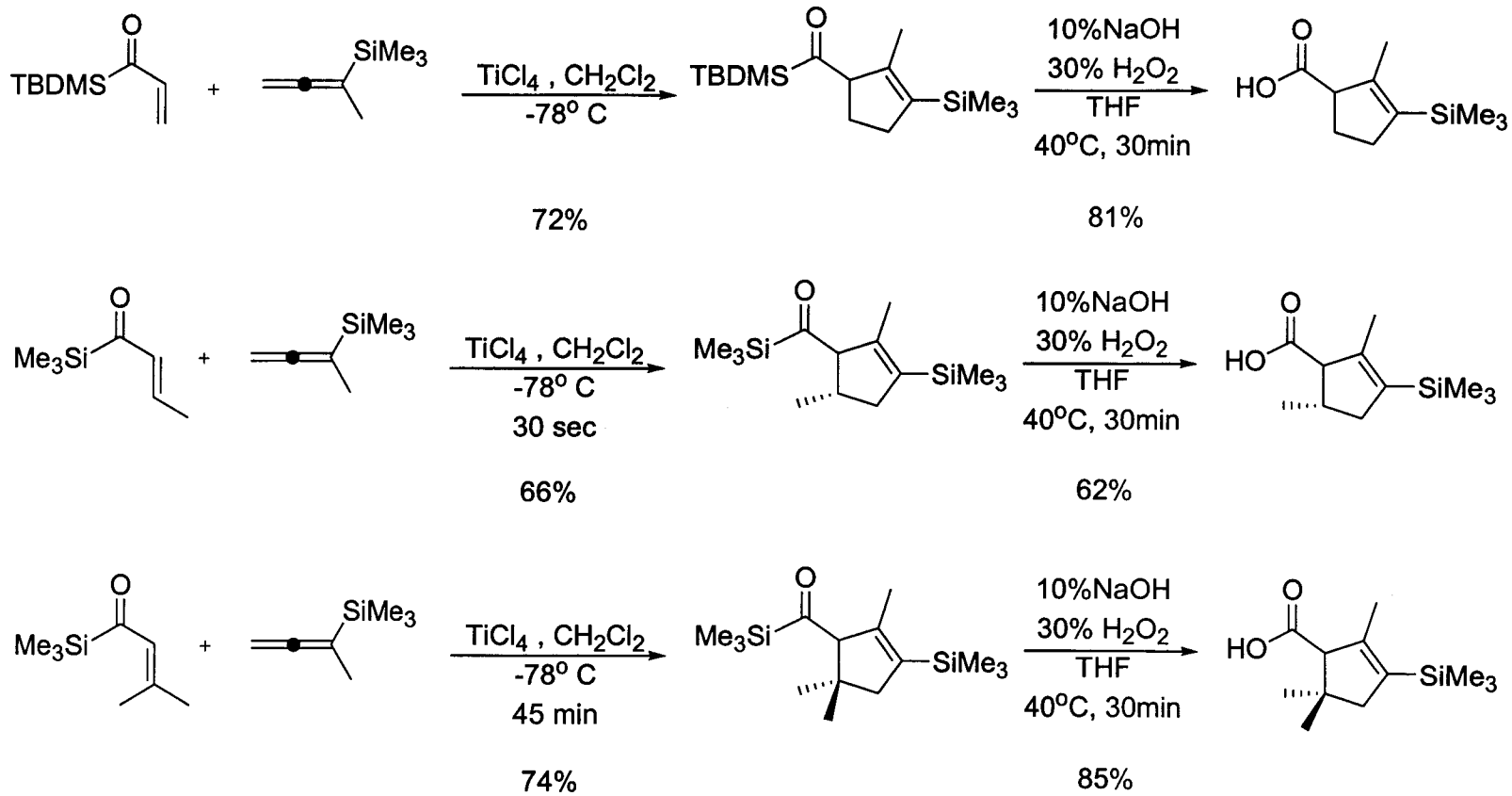
Danheiser, R.L. et al. *JACS,* **1981**, *103,* 1604
Danheiser, R.L. et al. *Tetrahedron,* **1983**, 39, 935

Limitations of the Danheiser Annulation

- Works Primarily with α,β unsaturated ketones
- Does not work with α,β unsaturated aldehydes, methacrolein under reaction conditions yields a "complex mixture of products"
- Does not work with nitroolefins
- Reaction of α,β unsaturated esters is considerably slow in comparison to the reaction of α,β unsaturated ketones (13.5 hrs : 1 hr)
- ~~β, β disubstituted allenes are unreactive at -78 ° C, but do react within reasonable times~~.
- Highly sterically encumbered ketones, such as isophorone, are unreactive
- Substitution at the α position of the allene is a necessity, due to the relative instability of the terminal vinyl cation

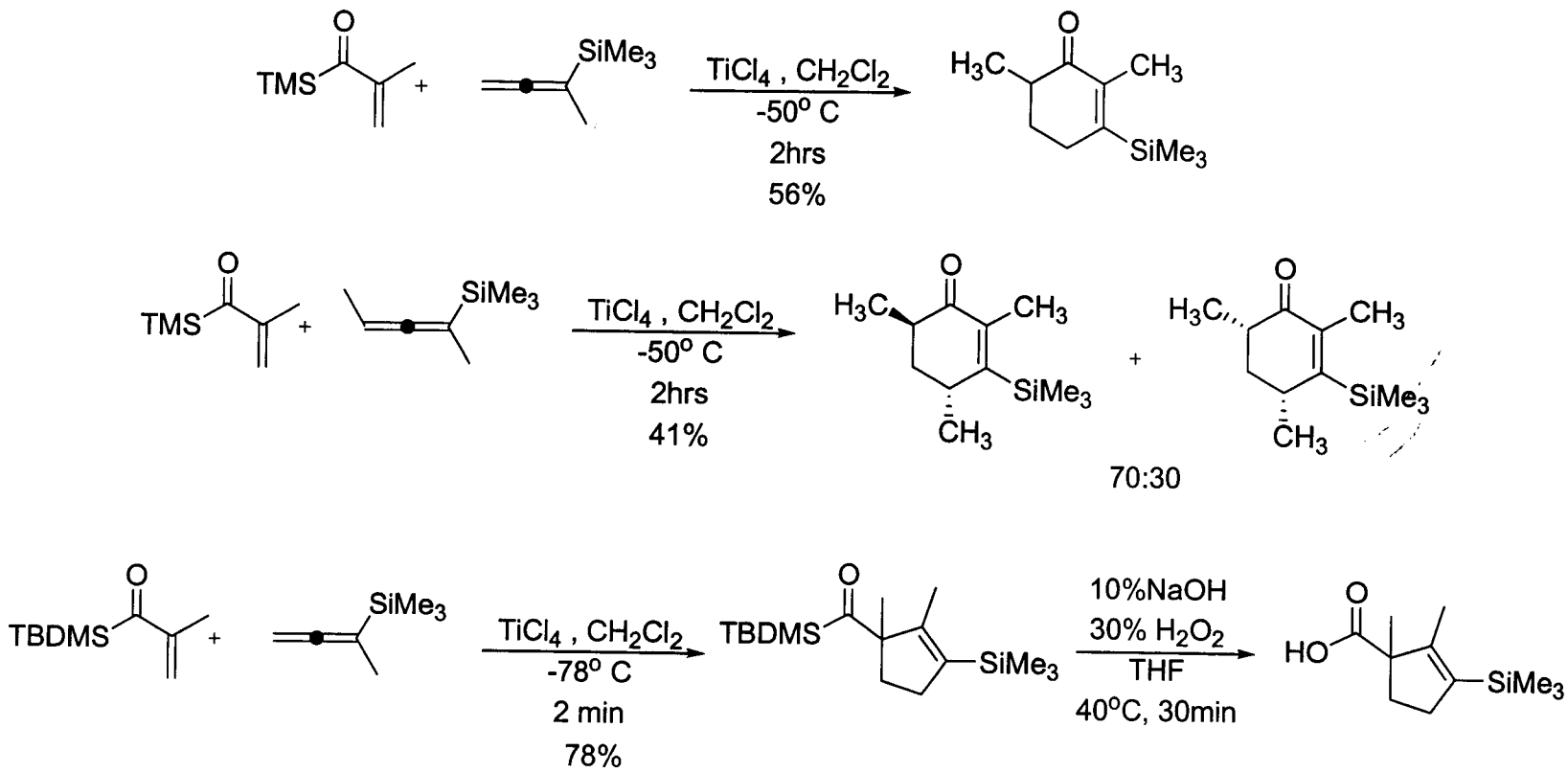
Danheiser, R.L. et al. *JACS,* **1981**, *103,* 1604
Danheiser, R.L. et al. *Tetrahedron,* **1983**, 39, 935

Reaction of Allenylsilanes with Acylsilanes



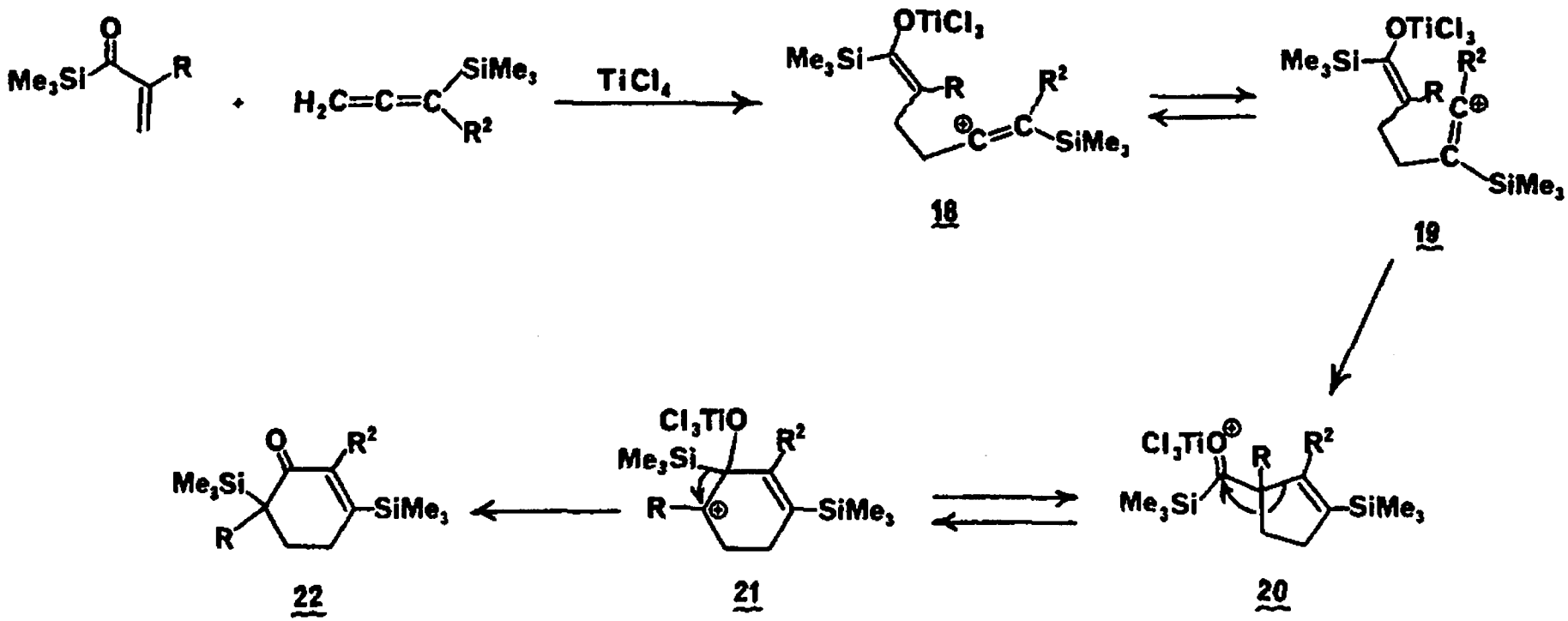
Danheiser, R.L., Fink, D. M. *Tet Lett.*, **1985**, 26, 2513

Reaction of Allenylsilanes with Acylsilanes



Danheiser, R.L., Fink, D. M. *Tet Lett.*, **1985**, 26, 2513

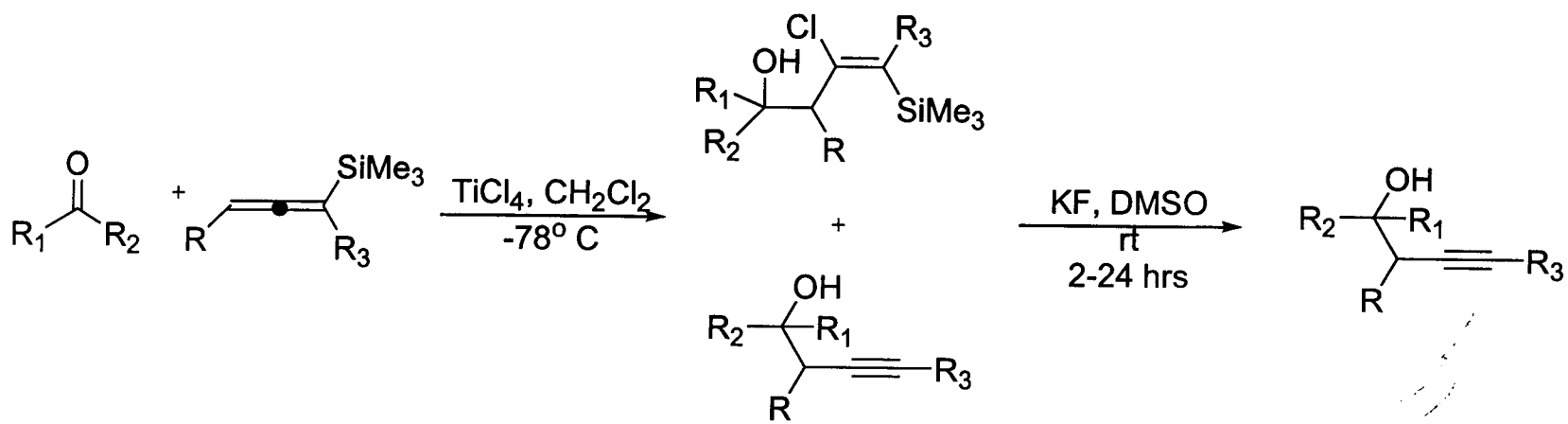
Proposed Mechanism for [3+2] Cyclopentenannulation with Acylsilanes



- Reaction pathway dependent on formation of tertiary carbocation 21
- If bulkier Silyl group is used, vinyl shift disfavored due to sterics
- Using acyl silanes, cyclopentenyl carboxylic acids and α,β unsaturated

Danheiser, R.L., Fink, D. M. *Tet Lett.*, **1985**, 26, 2513

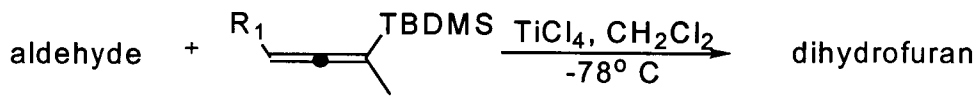
Adaptation of the Danheiser Annulation to the Synthesis of Heterocycles



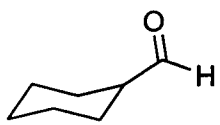
- Early studies demonstrate annulation reaction conditions with aldehydes and ketones produces homopropargyl alcohols in moderate to high yield
- Chloride anion either assists in desilylation, or is trapped by vinyl cation
- These reactions occur preferentially over cyclization to the dihydrofuran
- Solution: Increase steric bulk around the silicon to depress the rate of desilylation

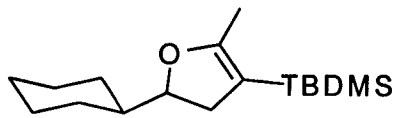
Danheiser, R.L., Carini, D.J. *JOC*, **1980**, *45*, 2513

Synthesis of Substituted Dihydrofurans and Alkaloids



R1=H





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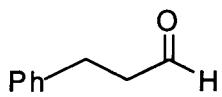

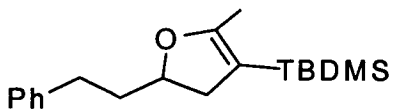

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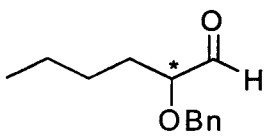

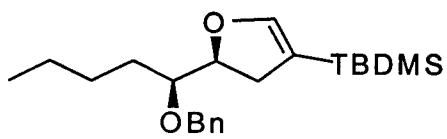

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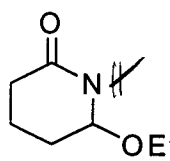

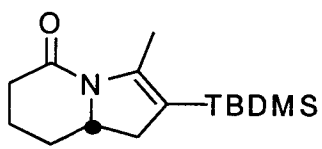

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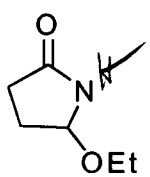

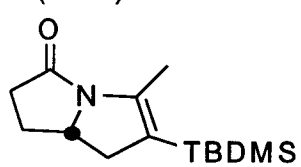

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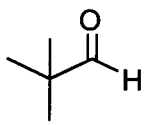
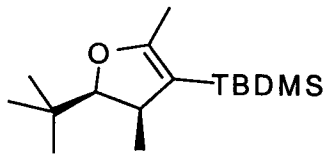
R1=Me





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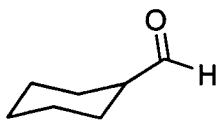
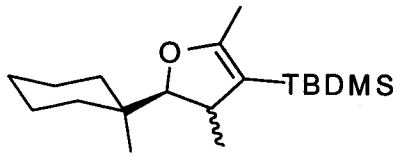
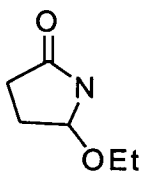
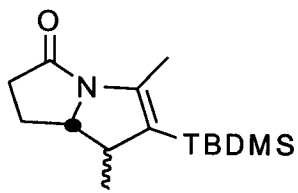




97% (7:1, cis:trans)





60% (1.2:1, cis:trans)

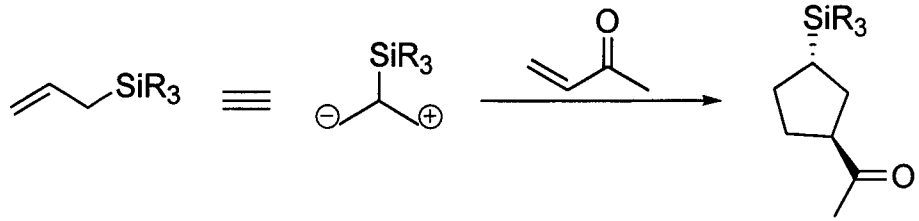
TBDMS group is difficult to functionalize!

Danheiser, R.L. et al. *JACS*, **1985**, *107*, 7233

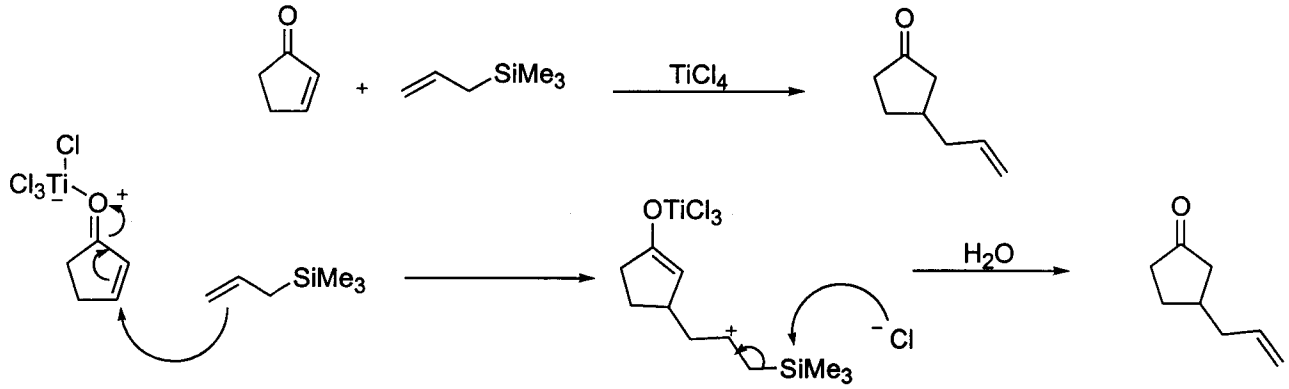
Summary of Allene Chemistry

- Excellent regiochemistry imparted by Silicon group
- Predictable stereochemistry due to constraint of the 5-membered ring (usually cis ring juncture)
- Established scope and limitations
- Chiral starting materials lead to chiral products in a predictable fashion
- Functionalization of Silicon group difficult
- Harsh conditions to cleave C-Si bond limit functionality of starting materials

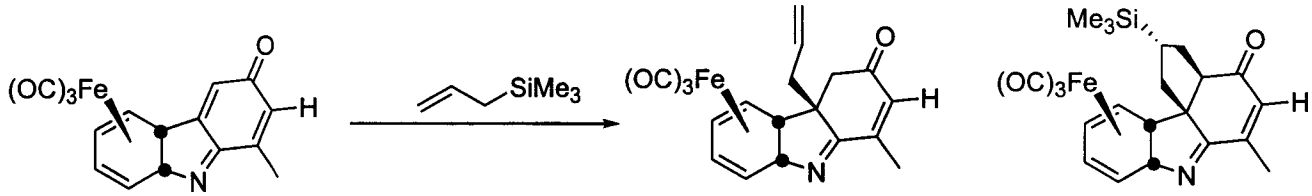
Allylsilanes as Masked 1,3 Dipoles…



Hosomi-Sakurai Reaction (Sakurai allylation)

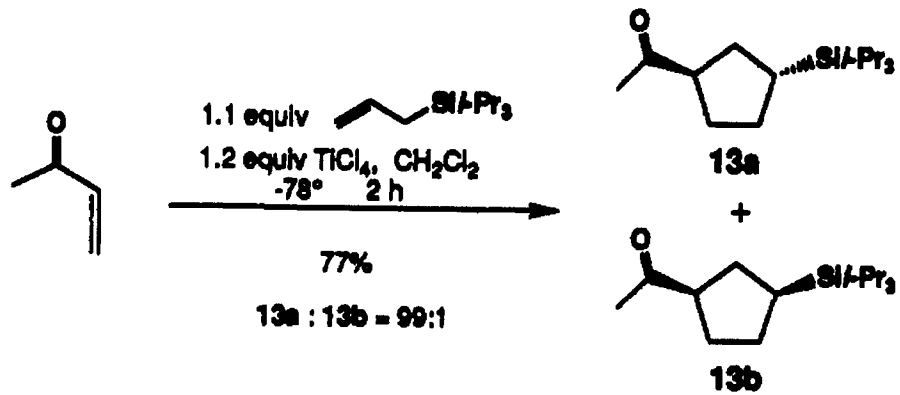


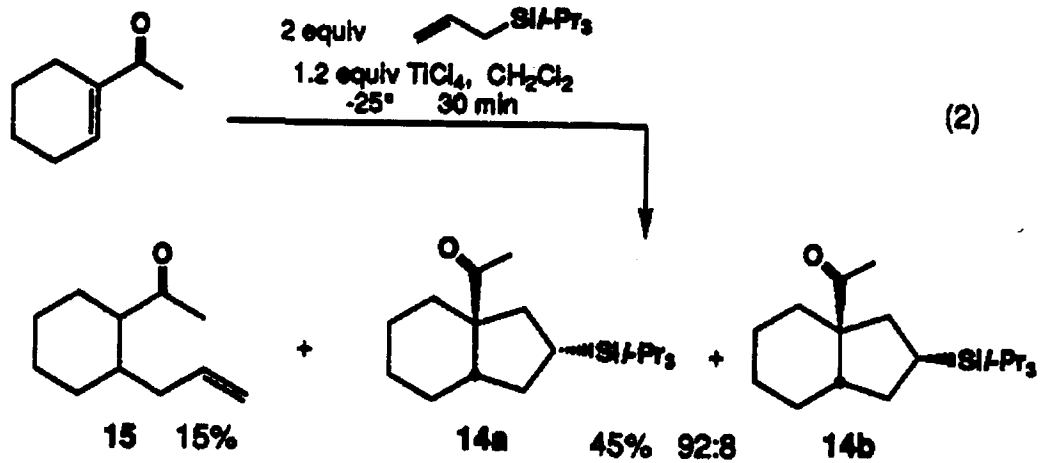
Knolker's Observation



Knolker, H. et al. *SYNLETT,* **1990,** 429

Danheiser's Contribution

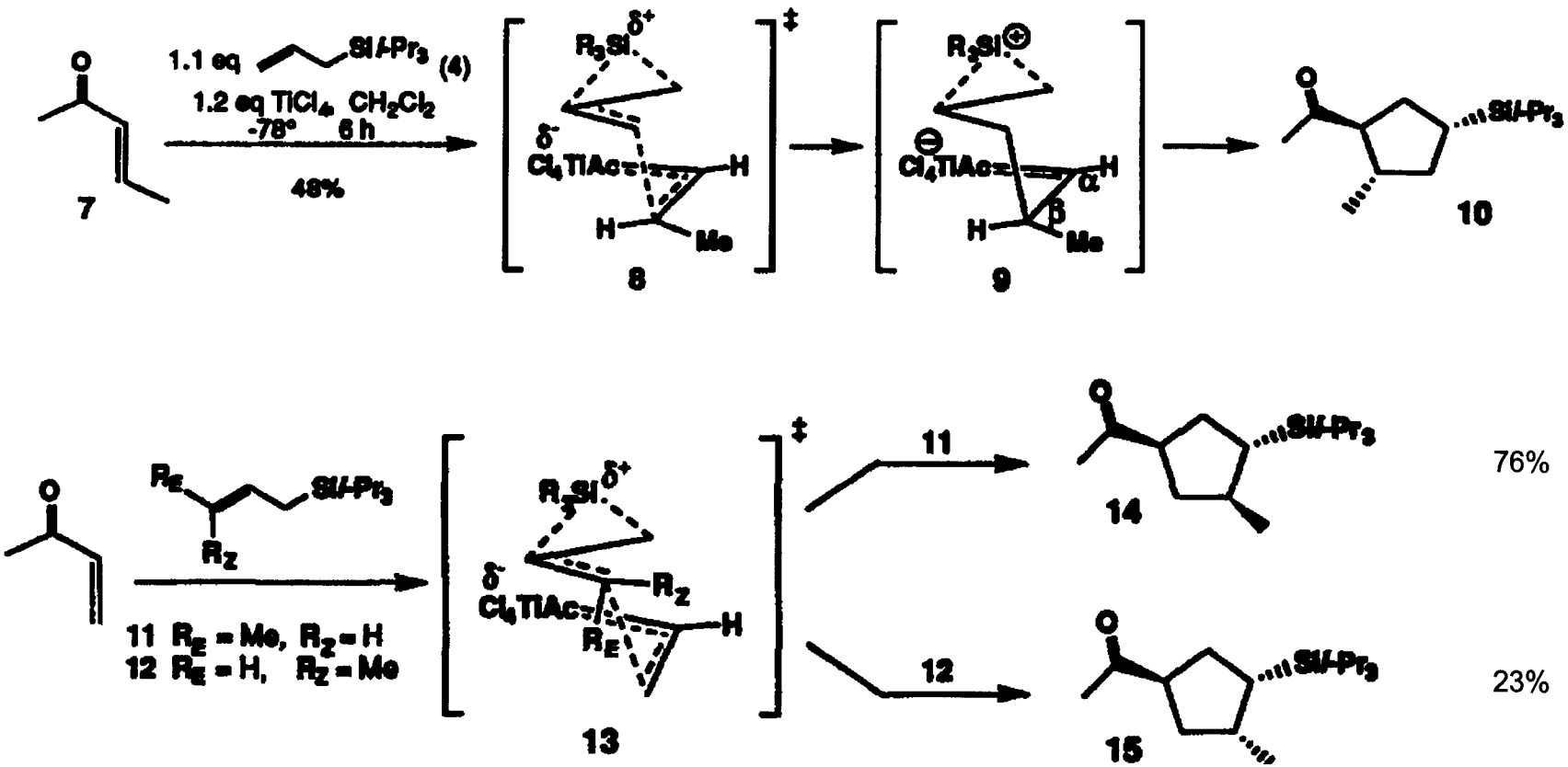




(2)

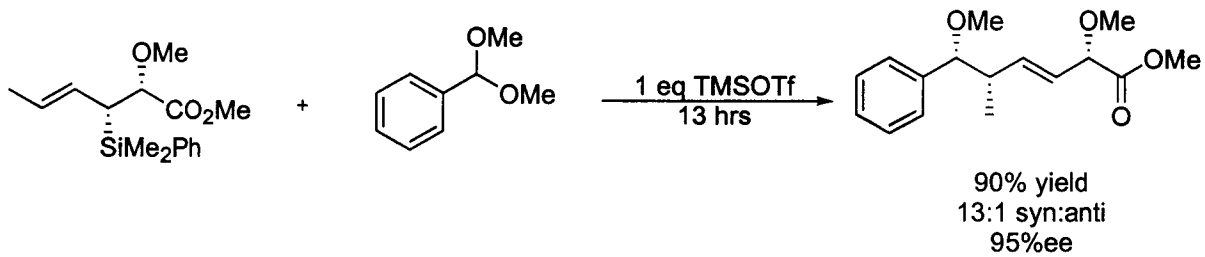
Danheiser, R.L. et al. *JOC*, **1992**, *57*, 6094

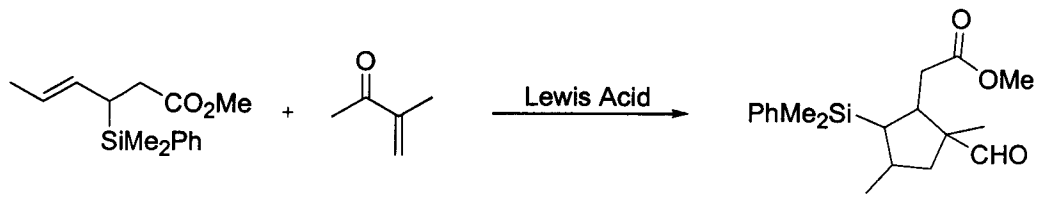
Rationalization of Stereochemistry



Danheiser, R.L. et al. *Tet. Lett.*. **1993**, *34* 3845

The Use of Chiral *E*-crotylsilanes Towards Stereoselective Synthesis of Cyclopentanes

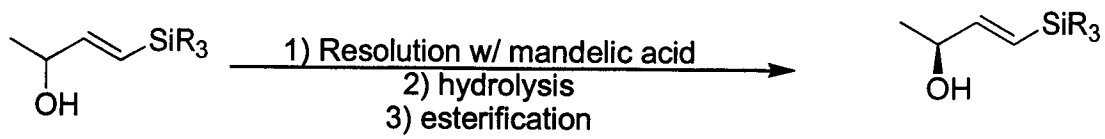


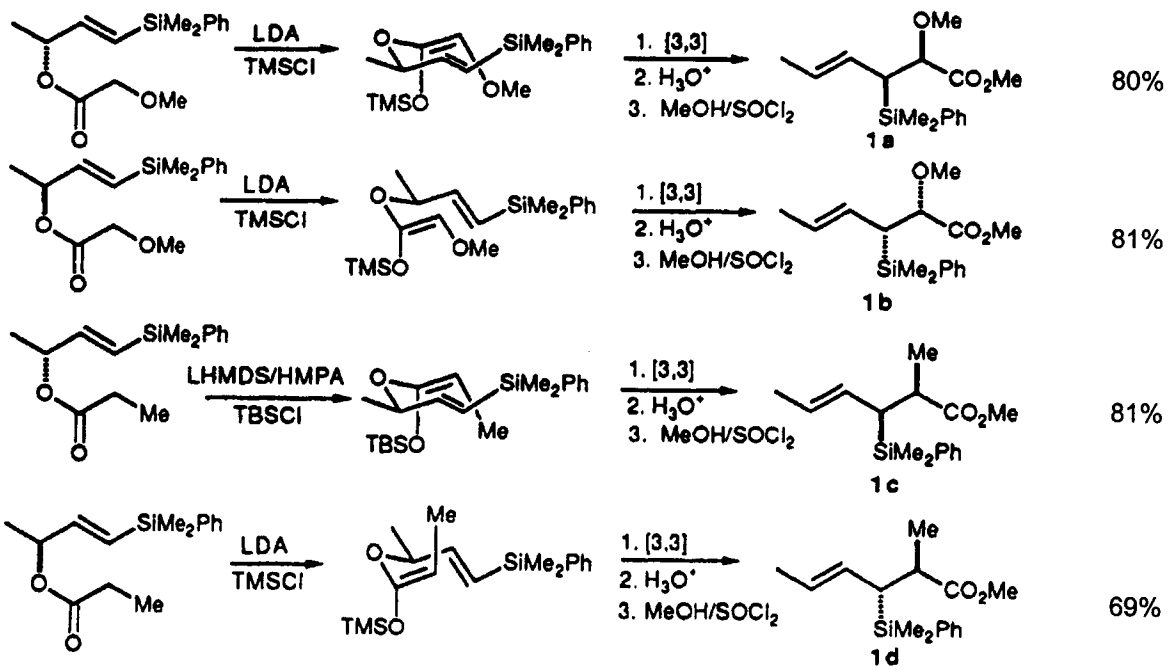


- Addition of chiral crotyl silanes to oxocarbenium ions was studied extensively by Panek
- It was concieved that addition of these nucleophiles to α,β unsaturated ketones would yield the corresponding cyclopentane in high yields and enantiopurity

Panek, J.S., Yang, M. *JACS*, **1991**, *113*, 6594

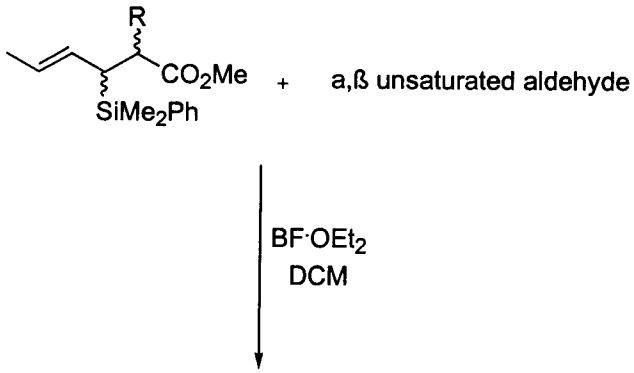
Preparation of Chiral E-crotylsilanes





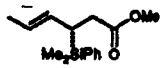
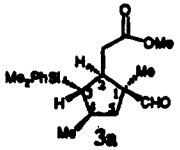
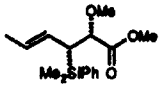
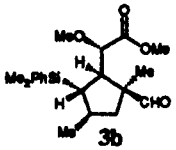
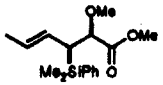
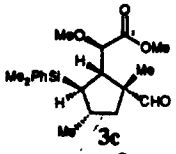
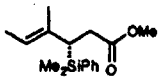
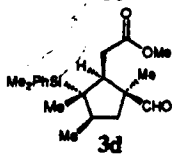
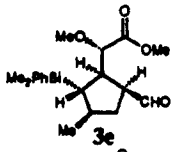
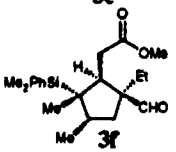
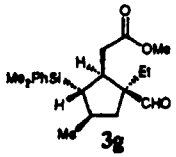
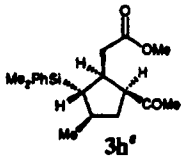
Panek, J.S., Sparks, M.A. *JOC*, **1991**, *56*, 3431

Asymmetric Synthesis of Tetrasubstituted Cyclopentanes

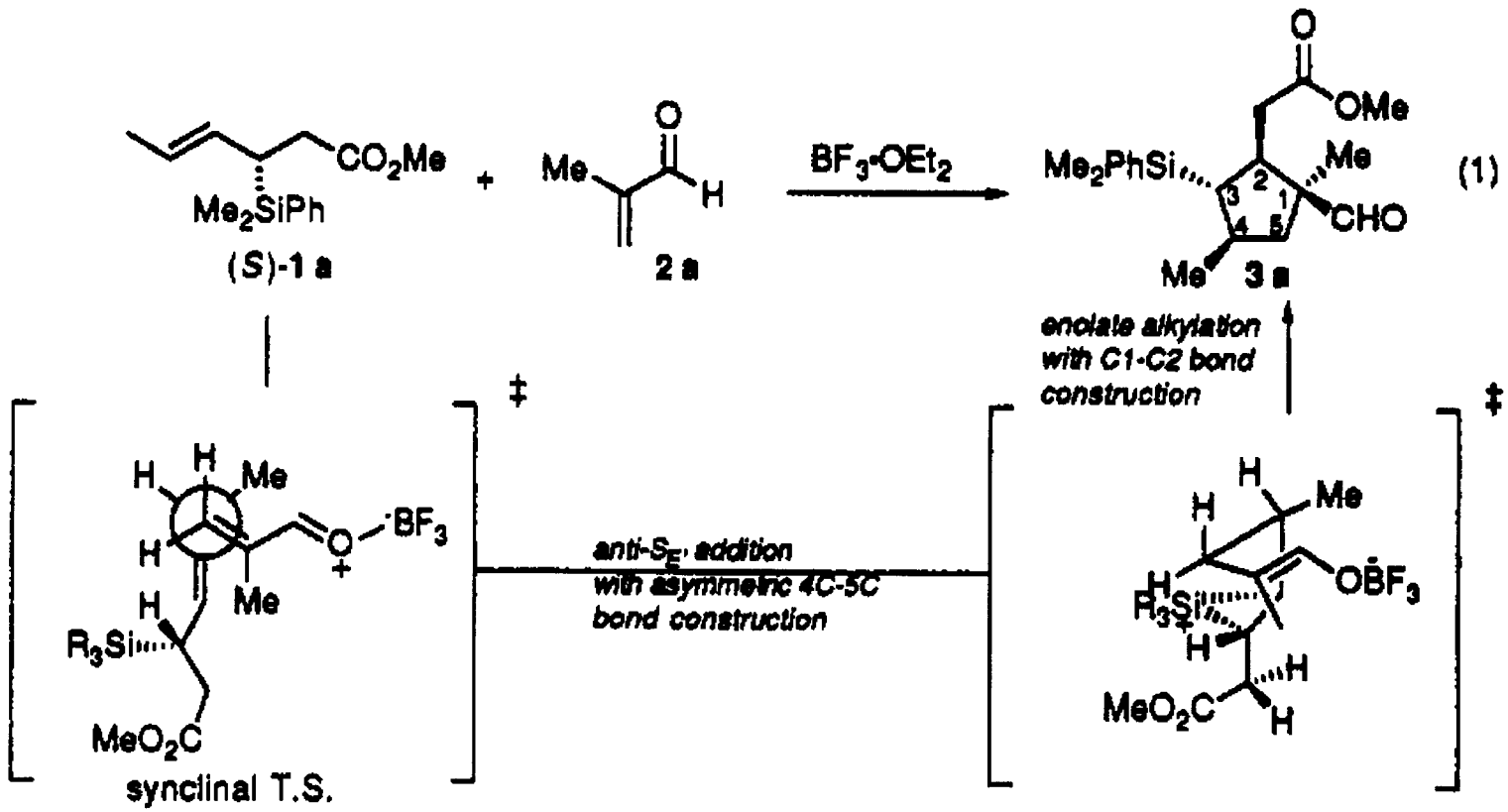


Panek, J.S., Jain, N.F. *JOC*, **1993**, *58*, 2345

Table I. Asymmetric [3 + 2] Cyclopentane Annulation

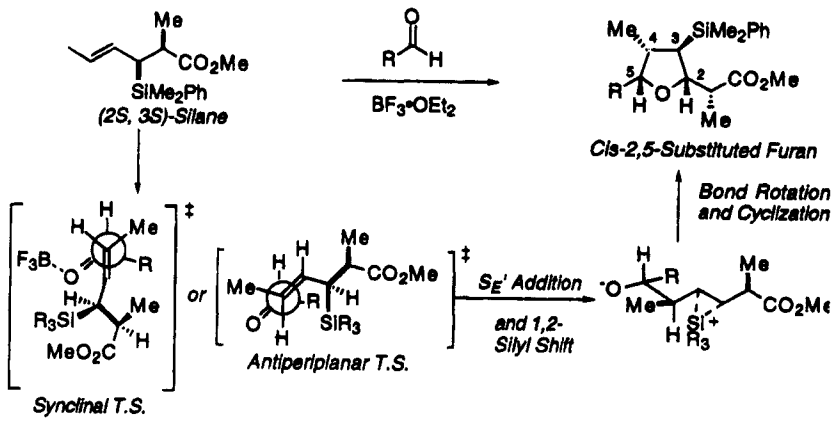
crotylsilane	α,β-unsaturated aldehyde/ketone	reaction condns[a] (T (°C)/time (h))	major diast[b]	% yield[c]
 1a	 2a	rt/8	 3a	93
 1b	2a	rt/12	 3b	73
 1c	2a	rt/12	 3c	73
 1d	2a	rt/7	 3d	65
1b	 2b	rt/5.5	 3e	62
1d	 2c	rt/7	 3f	51
1a	2c	rt/7	 3g	81
1a	 2d	−10–0/10	 3h[d]	56

Stereochemical Rationale



Masse, C.E., Panek, J.S., *CHEMREV*, **1995**, *95*, 1293

Diastereoselective Synthesis of Substituted Furans



entry	aldehydes	(E)-crotylsilane	reaction cond'ts.[a] Temp/hour	major diastereomer[b]	yield%[c]	ratio 4,5-syn/anti[d]	%de[e]
1	2a	(2S,3S)-1a	-78 °C/15h	3a	85	30:1	96
2	2a	(2R,3R)-1b	-78 °C/15h	3b	85	30:1	96
3	2a	(2R,3S)-1c	-78 °C/15h	3c	80	30:1	96
4[f]	2a	(2R,3R)-1d	-78 °C/15h	3d	68	30:1	96
5	2b	1c	-30 °C/15h	3e	65	30:1	96
6	2b	1d	-30 °C/15h	3f	50	20:1	96

Masse, C.E., Panek, J.S., *CHEMREV*, **1995**, *95*, 1293
Panek, J.S., Yang, M. *JACS*, **1991**, *113*, 9868

Lewis Acid Control of Diastereoselectivity

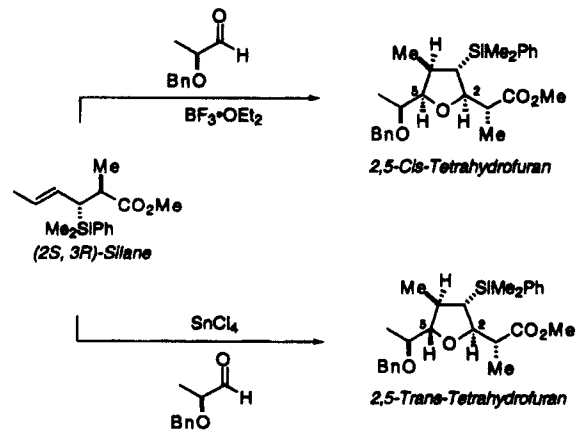
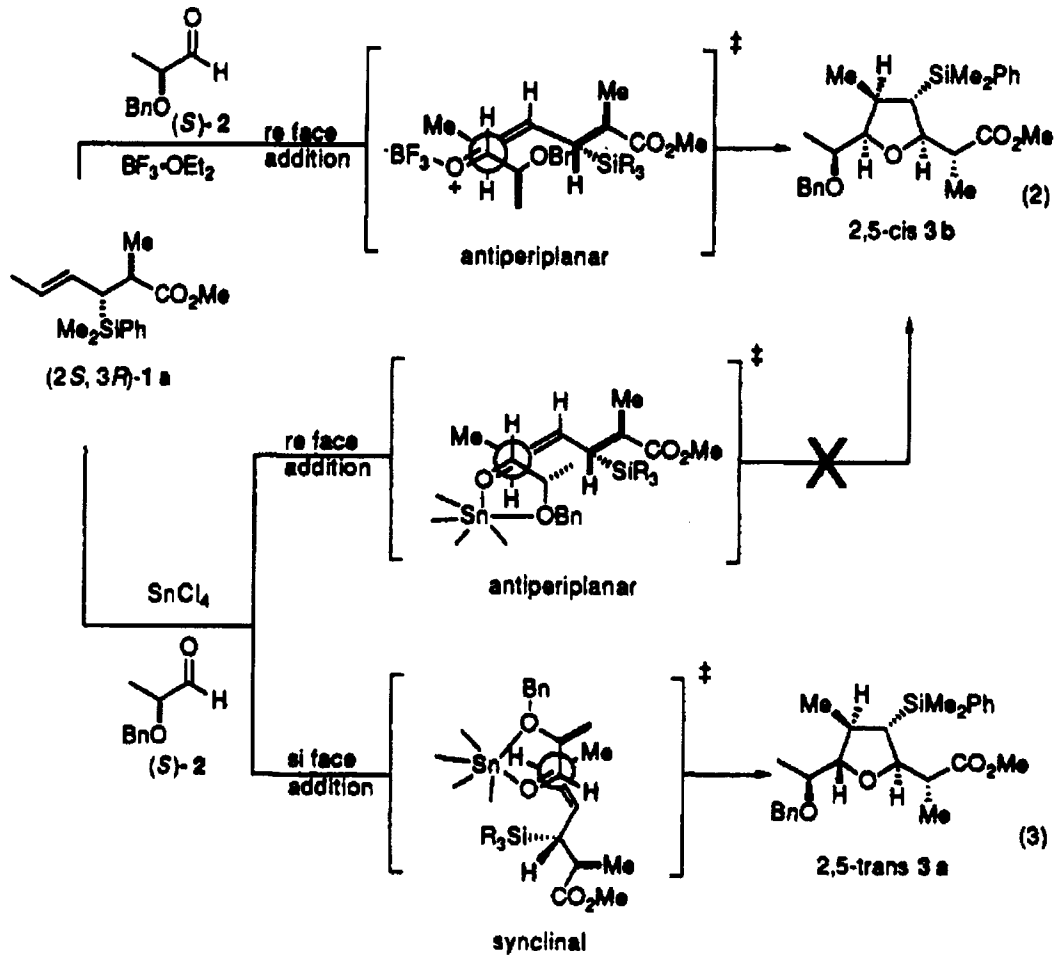


Table I. Double Asymmetric Induction in Additions of Chiral (*E*)-Crotylsilanes to (*S*)-2-(Benzyloxy)propanal

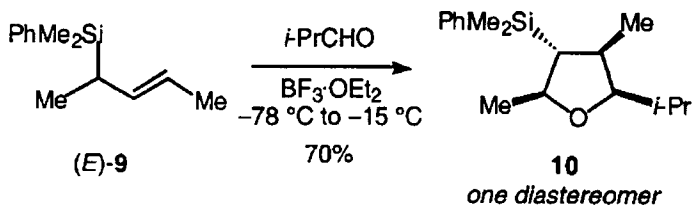
entry	aldehyde[a]	(*E*)-crotylsilane[b]	reaction condn[c] LA/temp/time	reaction products,[d] (% yield)[e] tetrahydrofuran	homoallylic alcohol	ratio anti/syn C4/C5 (furan)[f]
1.	2	(2*S*, 3*R*)-1a	$SnCl_4$ -35 °C/12h	3a (75)	4a (<5)	>40:1
2.	2	1a	$BF_3{\cdot}OEt_2$ -25 °C/12h	3b (50)	4b (<5)	40:1
3.	2	(2*R*, 3*S*)-1b	$BF_3{\cdot}OEt_2$ -25 °C/12h	3c (65)	4c (10)	>40:1
4.	2	1b	$SnCl_4$ -35 °C/12h	3c (36)	4c (38)	>40:1

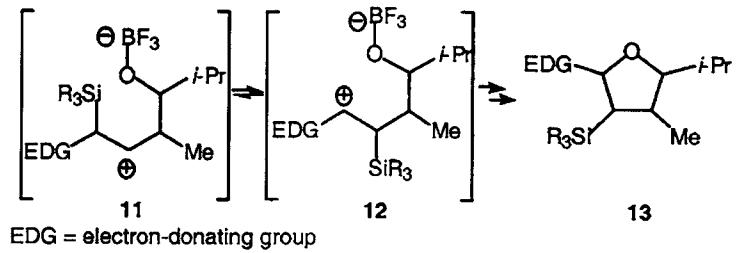
Rationalization of Diastereoselectivity



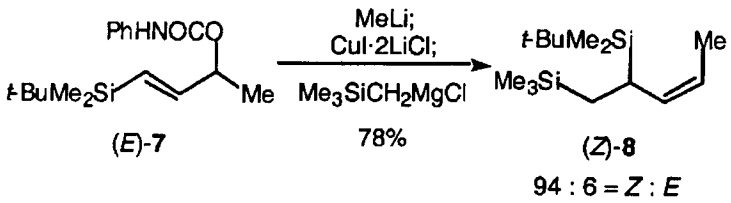
Panek, J.S. et al *JOC* **1993**, *58* 809

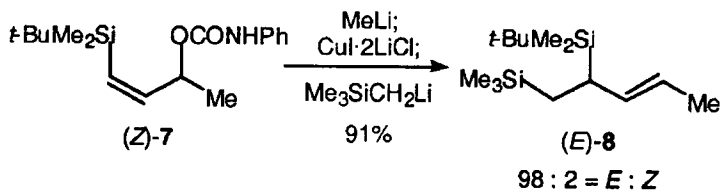
[3+2] Cyclizations via Silylmethyl Allylic Silanes





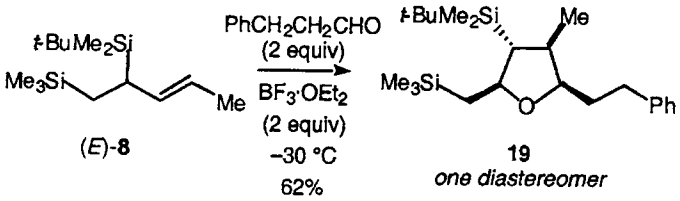
- Silylmethyl allylic silanes have rarely been used in organic synthesis
- Woerpel and coworkers recognized that, upon reaction with aldehydes, as in the case of Panek's work, a 1,2 silylmigration might occur.
- If an electron donating group, such as a methylsilyl group was attached, the cation would be doubly stabilized, pushing the reaction to proceed
- No general preparation for silylmethyl allylic silanes was known

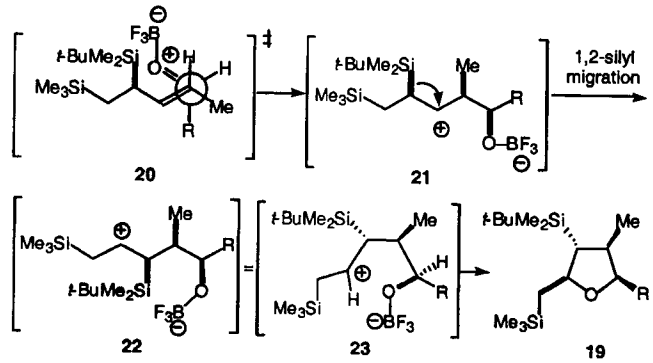


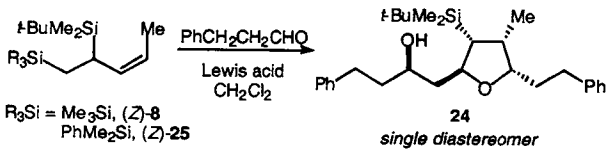


Smitrovich, J.H., Woerpel, K.A., *Synthesis*, **2002**, *18*, 2778

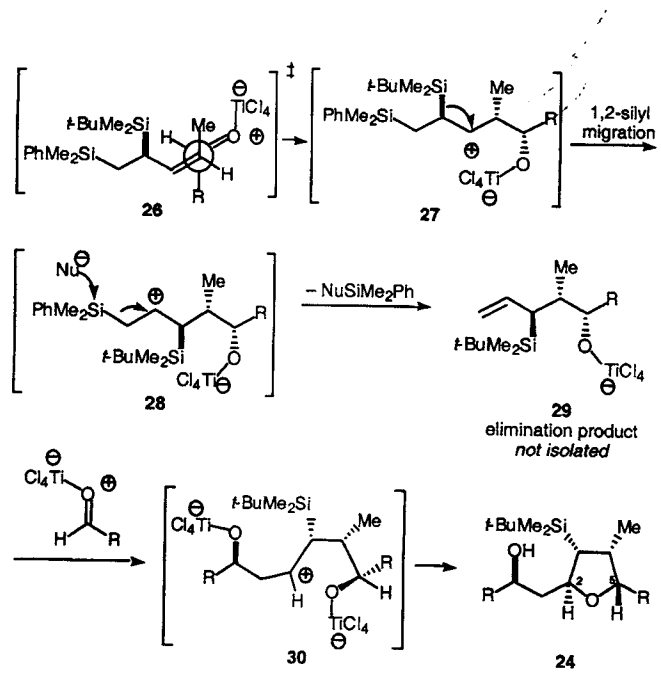
Synthesis of Substituted Tetrahydrofurans





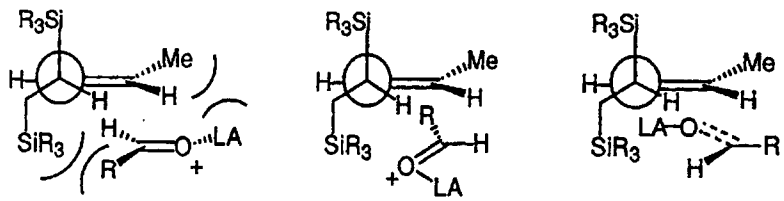


Entry	Substrate	Lewis Acid (Equiv)[a]	Temperature	Time (h)	Yield[b] (%)
1	(Z)-**8**	$BF_3{\cdot}OEt_2$ (1)	−78 °C →−33 °C	24	No reaction
2	(Z)-**8**	BF_3 OEt_2 (1)	0 °C	20	No reaction
3	(Z)-**8**	$SnBr_4$ (1)	−30 °C	20	No reaction
4	(Z)-**8**	$TiCl_4$ (1)	−30 °C	19	Complex mixture
5	(Z)-**8**	$TiCl_4$ (1)	−78 °C	3	25
6	(Z)-**8**	$TiCl_4$ (2)	−90 °C	4	41
7	(Z)-**25**	$TiCl_4$ (2)	−90 °C	4	46



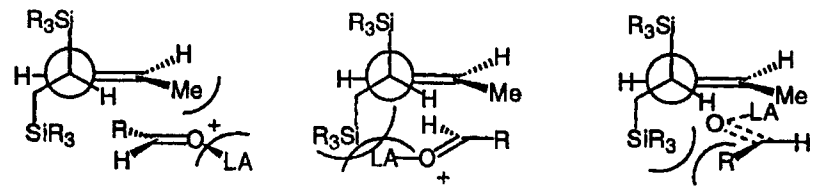
Smitrovich, J.H., Woerpel, K.A., *Synthesis*, **2002**, *18*, 2778

Difference in Reactivities Between E,Z Olefins



31 *antiperiplanar* **32** *synclinal* **33** *synclinal*

Analysis of E-Olefin TS



34 *antiperiplanar* **35** *synclinal* **36** *synclinal*

Analysis of Z-Olefin TS

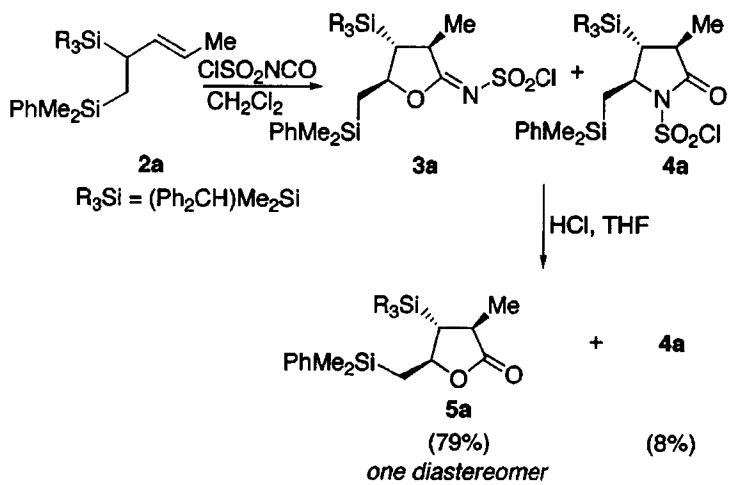
- For E-olefin there are three approaches that lead to product
- Only anti-periplanar is refuted due to sterics

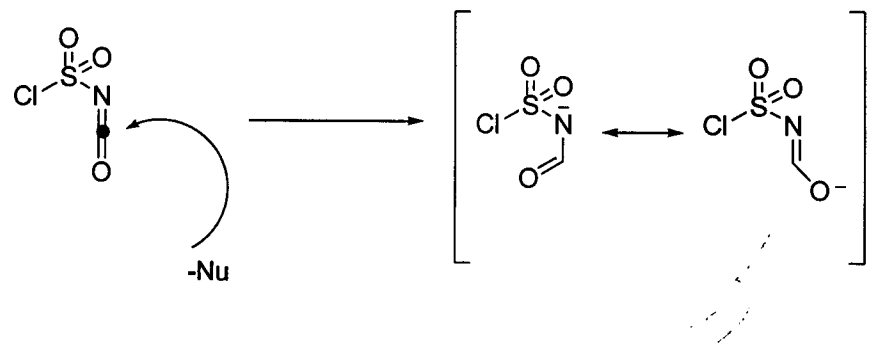
- In the case of the Z-olefin, all three transition states are disfavored by sterics

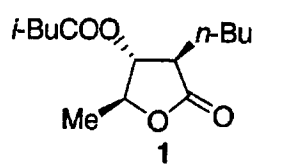
Smitrovich, J.H., Woerpel, K.A., *Synthesis*, **2002,** *18,* 2778

Diastereoselective Synthesis of Lactones

Scheme 1







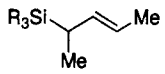
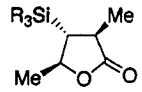
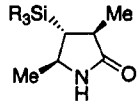
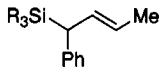
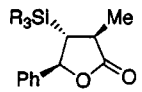
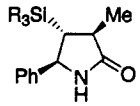
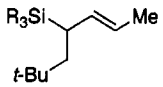
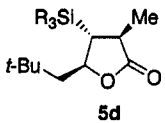
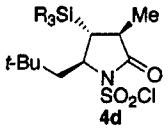
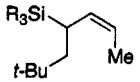
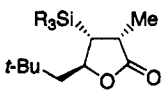
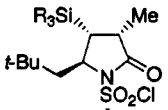
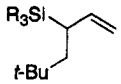
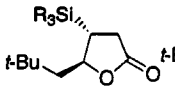
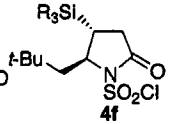
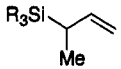
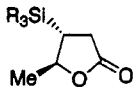
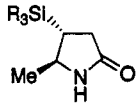
1
(+)-blastmycinone

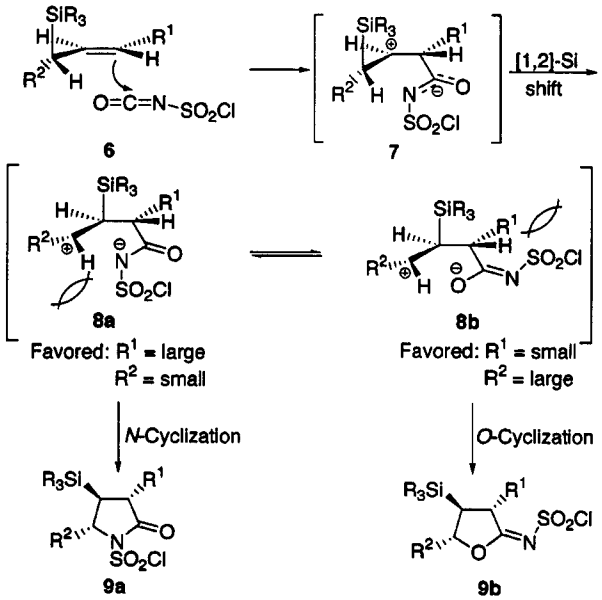
Gamma butyrolactones are found in a variety of natural products

Woerpel, K.A., Peng, Z. *Org. Lett.* **2001,** *3,* 675

Studies to Determine O,N selectivity

Table 1. Annulation Reactions of Allylic Silanes with $ClSO_2NCO$[a]

Allylic Silane 2[b]	[O]/[N][c]	Products Yields[d] (Diastereomer ratio)[e]	
 **2b** ($E:Z = 99:1$)[f]	1 : 6	 **5b** 16% (95 : 5)	 **4b** 77% (98 : 2)
 **2c** ($E:Z > 99:1$)[f]	1 : 2	 **5c** 30% (98 : 2)	 **4c** 57% (99 : 1)
 **2d**[g] ($E:Z = 98:2$)[f]	>20 : 1	 **5d** 61% (≥ 99 : 1)	 **4d** 1%
 **2e** ($E:Z = 4:96$)[f]	>20 : 1	 **5e** 81% (94 : 6)	 **4e** 3%
 **2f**	8 : 1	 **5f** 82% (≥ 96 : 4)	 **4f** 8%
 **2g**	1 : 1	 **5g** 37% (91 : 9)	 **4g** 42% (91 : 9)



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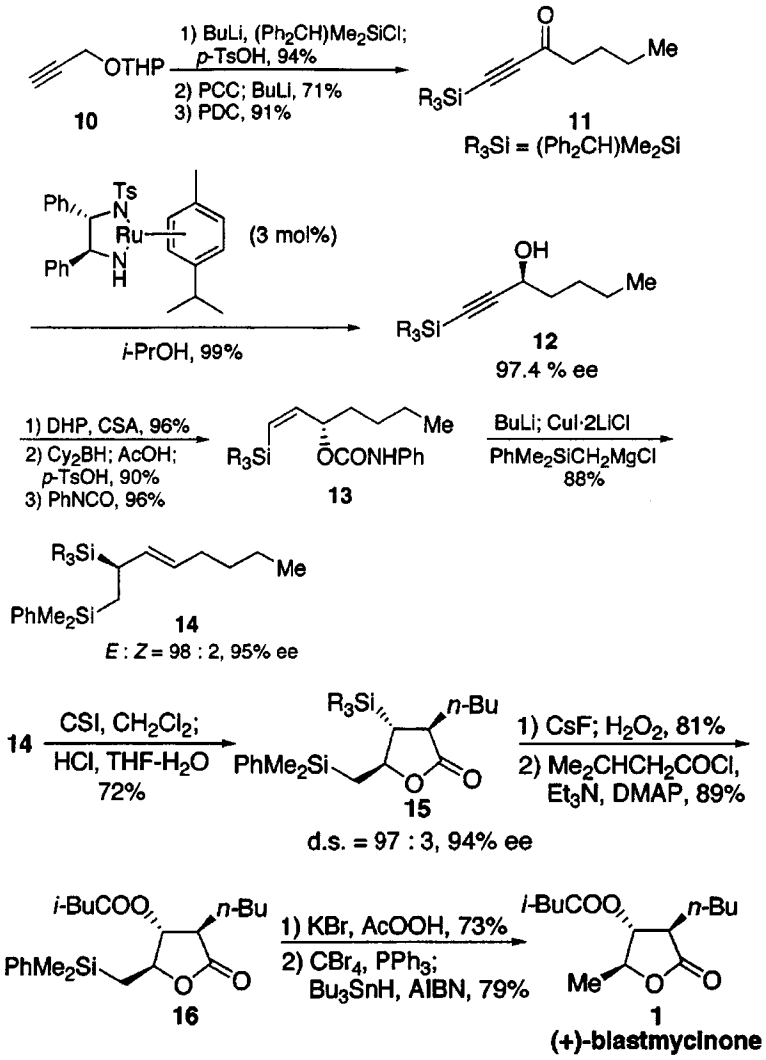
Total Synthesis of Blastomycin



- 13% yield over 13 steps
- 3 contiguous stereocenters set selectively in one step
- Methylsilyl allylsilanes are reactive starting material whose chemistry has yet to be fully explored

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Conclusion

- Silicon assisted [3+2] cyclization reactions have been carried out using allenyl, and allyl silanes
- There are predictable, diastereoselective syntheses in the literature for carbocycles as well as heterocycles
- The Danheiser annulation as well as early allyl cyclizations suffer from alkyl silyl groups that are difficult to manipulate
- Later syntheses employ activated silanes that can undergo stereoselective functionalization
- Much work has yet to be accomplished in all examples, primarily in the silyl methyl allylic silanes
- Although well studied, few total syntheses employ this methodology