SYNTHESIS OF α-ALLYNYL AND α-ALLYLSILANE AMINO ACIDS BY THE CLAISEN REARRANGEMENT

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Abstract

The enolate Claisen rearrangements of (*E*)-1-(alkylsilyl)-1-propen-3-ol-[*N*-PG]-glycinate and (*E*)-1-(alkylsilyl)-1-buten-3-ol-[*N*-PG]-glycinate esters were investigated (PG = protecting group). Several different variants of the Claisen rearrangement were evaluated; the formation of the *syn* stereoisomer was favored in all cases. The product was obtained in good to excellent yield (85–92%). The diastereoselectivity of the reaction varied from 2:1 to 29:1 (*syn:anti*) depending on reaction conditions. In the case of the Ireland-Claisen variant, the relationship between enolate trap (R_3SiCl, R_2SiCl_2 and Cl_3SiH) and diastereoselectivity was investigated, showing that chlorotrimethylsilane gave the best results in both selectivity and product yield. The size of the silyl group on the ester was also found to affect the diastereoselectivity slightly, in the sense that bulkier silanes improved reaction selectivity except in the case of aryl-substituted silanes. The Claisen rearrangement of 1-(alkylsilyl)-1-propyn-3-ol-[*N*-Boc]-glycinate ester and 1-(alkylsilyl)-1-butyn-3-ol-[*N*-Boc]-glycinate ester led to the formation of the unusual α-(3,5-bis(silyl)allenyl)-amino acid derivatives in moderate to good yield (30 to 85%) and high stereoselectivity (9:1 to 22:1). The amount of base (3.5 eq.) and enolate trap (3.5 eq.) employed in this reaction was found to be crucial for a high yield of the product.

Diastereoselective additions of methyl-2-(*N*-PG)-3-(trimethylsilyl)-(*E*)-pent-4-enoate and methyl-2-(*N*-PG)-3-(trimethylsilyl)-(*E*)-hex-4-enoate to aromatic acetals in the presence of Lewis acids were investigated. Reaction conditions were examined in detail. $TiCl_4$ was found to be most effective in promoting the addition. Among the aromatic acetals examined, 2-bromo-benzaldehyde dimethyl acetal gave the best selectivity (> 99% d.e.) and the best product yield (89%). The reaction of benzaldehyde dimethyl acetal resulted in modest selectivity (6:1) and yield (77%). $BF_3.OEt_2$

promoted the addition reaction to give moderate yield and selectivity. The reaction of $BF_3.OEt_2$ was found to be slower and required longer reaction times, to achieve high yield, than $TiCl_4$.

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LIST OF ABBREVIATIONS AND SYMBOLS

Bz	Phenylcarbonyl; Benzoyl
Boc	*tert*-Butylcarbonyl
bs	Broad singlet (^{1}H NMR)
t-$BuMe_2Si$	*tert*-Butyldimethylsilyl
Cbz	Carbobenzyloxy
^{13}C NMR	Carbon Nuclear Magnetic Resonance Spectroscopy
CI	Chemical Ionization Mass Spectrometry
DCC	Dicyclohexylcarbodiimide
d	Doublet (^{1}H NMR)
dd	Doublet of doublets (^{1}H NMR)
de	Diastereoselectivity
DCM	Dichloromethane
i-$PrMe_2Si$	Dimethylisopropylsilyl
DMAP	4-Dimethylaminopyridine
DMF	Dimethylformamide
EI	Electron Impact Mass Spectrometry
+ve ES	Positive Mode Electrospray Mass Spectrometry
-ve ES	Negative Mode Electrospray Mass Spectrometry
Et_3N	Triethyl amine
h	Hour(s)
^{1}H NMR	Proton Nuclear Magnetic Resonance Spectroscopy

HOMO	Highest occupied molecular orbital
HRMS	High-resolution mass spectrum
IR	Infrared Spectroscopy
J	Coupling Constant
L	Lowest unoccupied molecular orbital
M	Metal
m	Multiplet (^{1}H NMR)
Me	Methyl
Me_3Si	Trimethylsilyl
MeOH	Methanol
min	Minute(s)
MS	Mass Spectrometry
Ms	Methanosulfonyl
m/z	Mass to Charge Ratio of an Ion (Mass Spectrometry)
PG	Protecting group
ppm	Parts Per Million
q	Quartet (^{1}H NMR)
s	Singlet (^{1}H NMR)
TMS	Trimethylsilyl
THF	Tetrahydrofuran
t	Triplet (^{1}H NMR)
TLC	Thin Layer Chromatography

TMSCl	Chlorotrimethylsilane

Table 1.11. Crystal data and structure refinement for (103a).

Identification code		
Empirical formula	$C_{19}\ H_{40}\ N_2\ O_4\ Si$	
Formula weight	388.62	
Temperature	299(2) K	
Wavelength	0.71073 Å	
Crystal system	Triclinic	
Space group	P-1	
Unit cell dimensions	a = 10.7913(8) Å	α= 75.433(5)°.
	b = 11.49350(10) Å	β= 63.513(4)°.
	c = 11.6476(10) Å	γ = 75.315(4)°.
Volume	1234.68(14) $Å^3$	
Z	2	
Density (calculated)	1.045 Mg/m^3	
Absorption coefficient	0.117 mm-1	
F(000)	428	
Crystal size	.08 x .12 x .20 mm^3	
Theta range for data collection	1.86 to 26.50°.	
Index ranges	-12≤h≤10, -14≤k≤14, -14≤l≤6	
Reflections collected	5233	
Independent reflections	3944 [R(int) = 0.0911]	
Completeness to theta = 26.50°	77.1 %	
Absorption correction	None	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	3944 / 0 / 236	
Goodness-of-fit on F2	0.687	
Final R indices [I>2sigma(I)]	R1 = 0.0761, wR2 = 0.1861	
R indices (all data)	R1 = 0.2853, wR2 = 0.3012	
Extinction coefficient	0.015(5)	
Largest diff. peak and hole	0.349 and -0.238 $e.Å^{-3}$	

Table 1.12. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$ x 10^3)
For **(103a).** U(eq) is defined as one third of the trace of the orthogonalized Uij tensor.

	x	y	z	U(eq)
Si(1)	-5(3)	6698(2)	2319(2)	74(1)
O(1)	2194(5)	7807(5)	-2484(5)	68(2)
O(2)	3352(5)	9654(5)	368(5)	68(2)
O(3)	1412(6)	10668(6)	169(5)	69(2)
N(4)	1549(6)	8372(5)	-591(5)	52(2)
N(5)	3938(6)	11742(5)	-9421(5)	56(2)
O(6)	3789(6)	7460(6)	-1610(5)	87(2)
C(7)	1720(7)	8493(7)	530(7)	54(2)
C(8)	420(8)	8287(7)	1773(6)	59(2)
C(9)	2208(9)	9715(8)	322(6)	49(2)
C(10)	3759(8)	12831(7)	-10380(8)	65(2)
C(11)	536(10)	8626(8)	2894(7)	80(3)
C(12)	2620(9)	7849(7)	-1565(7)	58(2)
C(13)	3201(9)	7355(9)	-3699(7)	71(3)
C(14)	3241(8)	11849(8)	-7996(7)	62(2)
C(15)	4449(10)	12469(8)	-11702(7)	97(3)
C(16)	1644(8)	12211(8)	-7565(8)	93(3)
C(17)	4314(10)	13870(8)	-10282(9)	99(3)
C(18)	3639(9)	10692(8)	-7224(8)	84(3)
C(19)	4301(10)	8196(10)	-4419(8)	115(4)
C(20)	2303(9)	7472(10)	-4419(8)	111(4)
C(21)	38(11)	6065(9)	980(8)	112(4)
C(22)	-329(12)	9298(10)	3679(9)	121(4)
C(23)	3841(12)	6054(10)	-3417(10)	133(4)
C(24)	-1799(9)	6777(10)	3692(10)	128(4)
C(25)	1278(11)	5670(9)	2967(10)	124(4)

Table 1.13. Bond lengths [Å] and angles [°] for (**103a**).

Si(1)-C(21)	1.859(8)
Si(1)-C(8)	1.879(8)
Si(1)-C(25)	1.880(10)
Si(1)-C(24)	1.881(8)
O(1)-C(12)	1.354(8)
O(1)-C(13)	1.472(8)
O(2)-C(9)	1.244(8)
O(3)-C(9)	1.237(8)
N(4)-C(12)	1.344(9)
N(4)-C(7)	1.442(8)
N(5)-C(10)	1.490(9)
N(5)-C(14)	1.509(8)
O(6)-C(12)	1.209(8)
C(7)-C(8)	1.518(9)
C(7)-C(9)	1.548(10)
C(8)-C(11)	1.515(10)
C(10)-C(15)	1.497(10)
C(10)-C(17)	1.513(10)
C(11)-C(22)	1.237(11)
C(13)-C(23)	1.501(11)
C(13)-C(19)	1.527(11)
C(13)-C(20)	1.505(11)
C(14)-C(18)	1.487(10)
C(14)-C(16)	1.538(10)
C(21)-Si(1)-C(8)	112.1(4)
C(21)-Si(1)-C(25)	109.1(5)
C(8)-Si(1)-C(25)	109.9(4)
C(21)-Si(1)-C(24)	110.8(5)
C(8)-Si(1)-C(24)	106.9(4)
C(25)-Si(1)-C(24)	108.0(5)
C(12)-O(1)-C(13)	120.7(6)
C(12)-N(4)-C(7)	121.0(6)
C(10)-N(5)-C(14)	118.7(6)
N(4)-C(7)-C(8)	111.8(6)
N(4)-C(7)-C(9)	111.0(6)
C(8)-C(7)-C(9)	113.5(6)
C(7)-C(8)-C(11)	110.5(6)
C(7)-C(8)-Si(1)	116.6(5)
C(11)-C(8)-Si(1)	106.6(5)
O(3)-C(9)-O(2)	125.3(7)
O(3)-C(9)-C(7)	117.7(8)
O(2)-C(9)-C(7)	116.9(8)
N(5)-C(10)-C(15)	108.5(7)
N(5)-C(10)-C(17)	110.1(7)
C(15)-C(10)-C(17)	113.8(7)
C(22)-C(11)-C(8)	128.3(10)
O(6)-C(12)-N(4)	125.0(7)
O(6)-C(12)-O(1)	124.9(7)
N(4)-C(12)-O(1)	110.1(7)
O(1)-C(13)-C(23)	110.4(7)
O(1)-C(13)-C(19)	108.0(7)
C(23)-C(13)-C(19)	112.3(8)
O(1)-C(13)-C(20)	103.0(7)
C(23)-C(13)-C(20)	111.6(8)
C(19)-C(13)-C(20)	111.2(7)
C(18)-C(14)-N(5)	109.8(6)
C(18)-C(14)-C(16)	112.8(7)
N(5)-C(14)-C(16)	110.0(6)

Table 1.14. Anisotropic displacement parameters ($Å^2 x\ 10^3$)for **(103)**. The anisotropic displacement factor exponent takes the form: $-2\pi 2\ [\ h^2\ a^{*2} U_{11} + ... + 2\ h\ k\ a^*\ b^*\ U_{12}\ ]$

	U11	U22	U33	U23	U13	U12
Si(1)	72(2)	71(2)	78(2)	-23(1)	-19(1)	-23(2)
O(1)	58(4)	93(5)	58(3)	-36(3)	-21(3)	0(3)
O(2)	34(3)	77(4)	108(4)	-36(3)	-32(3)	-6(3)
O(3)	51(3)	59(4)	111(4)	-27(3)	-44(3)	4(3)
N(4)	34(4)	70(5)	58(4)	-28(3)	-20(3)	3(3)
N(5)	42(4)	52(5)	73(4)	-18(4)	-18(3)	-7(3)
O(6)	46(4)	134(6)	81(4)	-45(4)	-25(3)	10(4)
C(7)	43(5)	61(6)	63(5)	-17(4)	-22(4)	-12(4)
C(8)	56(5)	64(6)	57(4)	-14(4)	-23(4)	-8(4)
C(9)	44(5)	47(6)	49(4)	-17(4)	-14(4)	4(5)
C(10)	59(5)	53(6)	82(6)	-10(5)	-32(4)	-2(5)
C(11)	98(7)	78(7)	60(5)	-26(5)	-20(5)	-18(6)
C(12)	51(6)	67(7)	48(5)	-14(4)	-12(5)	-7(5)
C(13)	69(6)	89(8)	46(5)	-28(5)	-14(5)	0(6)
C(14)	67(6)	57(6)	73(5)	-23(5)	-29(5)	-13(5)
C(15)	129(9)	79(8)	70(6)	-17(5)	-37(6)	-1(6)
C(16)	56(6)	105(8)	101(7)	-54(6)	-4(5)	-3(5)
C(17)	124(9)	49(6)	132(8)	-7(5)	-60(7)	-20(6)
C(18)	84(7)	89(8)	70(5)	-14(5)	-21(5)	-16(6)
C(19)	94(8)	157(11)	72(6)	-8(7)	-16(6)	-28(8)
C(20)	94(8)	166(11)	91(6)	-76(7)	-38(6)	4(7)
C(21)	147(10)	103(8)	112(7)	-36(6)	-48(7)	-51(7)
C(22)	183(12)	110(10)	86(7)	-46(7)	-53(8)	-22(8)
C(23)	180(12)	95(10)	126(9)	-61(7)	-81(8)	55(9)
C(24)	76(7)	127(10)	149(9)	-49(7)	11(6)	-48(7)
C(25)	159(11)	82(9)	136(9)	-4(7)	-75(8)	-11(8)

Table 1.15. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$ x 10^3) for **(103a).**

	x	y	z	U(eq)
H(4A)	750	8639	-637	63
H(5A)	4865	11504	-9633	68
H(5B)	3623	11138	-9524	68
H(7A)	2479	7844	611	64
H(8A)	-383	8832	1644	71
H(10A)	2753	13086	-10165	78
H(11A)	1361	8286	3006	96
H(14A)	3589	12499	-7876	74
H(15A)	4040	11818	-11701	145
H(15B)	5435	12203	-11926	145
H(15C)	4313	13155	-12328	145
H(16A)	1210	12293	-6662	139
H(16B)	1283	11593	-7691	139
H(16C)	1442	12973	-8072	139
H(17A)	3823	14061	-9417	149
H(17B)	4173	14573	-10889	149
H(17C)	5298	13636	-10480	149
H(18A)	4641	10520	-7512	126
H(18B)	3323	10039	-7341	126
H(18C)	3210	10772	-6321	126
H(19A)	4878	8085	-3954	173
H(19B)	3842	9027	-4477	173
H(19C)	4876	8003	-5277	173
H(20A)	1639	6919	-3960	167
H(20B)	2887	7280	-5277	167
H(20C)	1810	8292	-4481	167
H(21A)	962	6030	290	168
H(21B)	-629	6577	657	168
H(21C)	-196	5259	1300	168
H(22A)	-1175	9665	3618	145
H(22B)	-132	9434	4330	145
H(23A)	4435	6015	-2987	200
H(23B)	4388	5736	-4216	200
H(23C)	3110	5580	-2865	200
H(24A)	-2476	7286	3380	191

H(24B)	-1801	7113	4369	191
H(24C)	-2036	5973	4029	191
H(25A)	2202	5611	2280	187
H(25B)	1015	4875	3301	187
H(25C)	1270	6000	3650	187

Table 1.16. Torsion angles [°] for mus1.

C(12)-N(4)-C(7)-C(8)	-142.1(7)
C(12)-N(4)-C(7)-C(9)	90.1(9)
N(4)-C(7)-C(8)-C(11)	-170.5(6)
C(9)-C(7)-C(8)-C(11)	-44.0(9)
N(4)-C(7)-C(8)-Si(1)	67.7(7)
C(9)-C(7)-C(8)-Si(1)	-165.8(6)
C(21)-Si(1)-C(8)-C(7)	-48.9(7)
C(25)-Si(1)-C(8)-C(7)	72.6(6)
C(24)-Si(1)-C(8)-C(7)	-170.5(6)
C(21)-Si(1)-C(8)-C(11)	-172.8(6)
C(25)-Si(1)-C(8)-C(11)	-51.3(7)
C(24)-Si(1)-C(8)-C(11)	65.6(7)
N(4)-C(7)-C(9)-O(3)	62.7(8)
C(8)-C(7)-C(9)-O(3)	-64.3(8)
N(4)-C(7)-C(9)-O(2)	-119.7(7)
C(8)-C(7)-C(9)-O(2)	113.4(7)
C(14)-N(5)-C(10)-C(15)	-175.6(6)
C(14)-N(5)-C(10)-C(17)	59.3(9)
C(7)-C(8)-C(11)-C(22)	129.3(10)
Si(1)-C(8)-C(11)-C(22)	-103.1(10)
C(7)-N(4)-C(12)-O(6)	-1.2(12)
C(7)-N(4)-C(12)-O(1)	178.2(6)
C(13)-O(1)-C(12)-O(6)	-5.1(12)
C(13)-O(1)-C(12)-N(4)	175.5(7)
C(12)-O(1)-C(13)-C(23)	61.1(10)
C(12)-O(1)-C(13)-C(19)	-62.1(9)
C(12)-O(1)-C(13)-C(20)	-179.7(7)
C(10)-N(5)-C(14)-C(18)	-175.9(6)
C(10)-N(5)-C(14)-C(16)	59.5(8)

Table 7. Hydrogen bonds for mus1 [Å and °].

D-H...A	d(D-H)d(H...A)	d(D...A)	<(DHA)

Table 1.17 Crystal data and structure refinement for (**103e**)

Identification code		
Empirical formula	$C_{15}H_{29}NO_4Si$	
Formula weight	315.48	
Temperature	299(2) K	
Wavelength	0.71073 Å	
Crystal system	Triclinic	
Space group	P-1	
Unit cell dimensions	a = 8.6830(8) Å	α= 97.131(2)°.
	b = 10.3930(10) Å	β= 94.114(2)°.
	c = 11.9048(12) Å	γ = 113.962(2)°.
Volume	965.25(16) Å3	
Z	2	
Density (calculated)	1.085 Mg/m^3	
Absorption coefficient	0.135 mm-1	
F(000)	344	
Crystal size	.08 x .22 x .36 mm^3	
Theta range for data collection	1.74 to 27.52°.	
Index ranges	-11≤h≤9, -13≤k≤13, -14≤l≤15	
Reflections collected	8800	
Independent reflections	4333 [R(int) = 0.0294]	
Completeness to theta = 27.52°	97.0 %	
Absorption correction	None	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	4333 / 0 / 307	
Goodness-of-fit on F2	0.986	
Final R indices [I>2sigma(I)]	R1 = 0.0455, wR2 = 0.1051	
R indices (all data)	R1 = 0.0882, wR2 = 0.1206	
Extinction coefficient	0.009(3)	
Largest diff. peak and hole	0.190 and -0.157 $e.Å^{-3}$	

Table 1.18. Atomic coordinates (x 104) and equivalent isotropic displacement parameters (Å2x 103)
for (**103e**). U(eq) is defined as one third of the trace of the orthogonalized Uij tensor.

	x	y	z	U(eq)
Si(1)	12510(1)	7778(1)	3498(1)	49(1)
O(1)	7829(2)	8352(1)	1886(1)	57(1)
O(2)	7342(2)	6344(1)	5585(1)	55(1)
N(3)	8995(2)	8111(2)	3498(1)	44(1)
O(4)	7132(2)	6128(1)	2315(1)	62(1)
C(5)	9368(2)	7394(2)	4375(2)	40(1)
O(6)	8742(2)	8714(1)	5944(1)	61(1)
C(7)	8480(2)	7584(2)	5388(2)	43(1)
C(8)	11305(2)	7977(2)	4736(2)	43(1)
C(9)	7913(2)	7411(2)	2540(2)	44(1)
C(10)	11688(2)	7312(2)	5710(2)	48(1)
C(11)	12310(2)	7966(2)	6753(2)	58(1)
C(12)	7044(3)	7870(2)	689(2)	64(1)
C(13)	11323(4)	5975(3)	2627(3)	71(1)
C(14)	14629(3)	7956(4)	4112(3)	77(1)
C(15)	12819(4)	9173(3)	2594(3)	72(1)
C(16)	6401(4)	6422(4)	6532(3)	80(1)
C(17)	12768(4)	7344(3)	7717(3)	77(1)
C(18)	5162(3)	6941(4)	613(3)	84(1)
C(19)	7981(5)	7116(4)	72(3)	99(1)
C(20)	7325(6)	9265(4)	293(4)	104(1)

Table 1.19. Bond lengths [Å] and angles [°] for (**103e**).

Si(1)-C(14)	1.857(3)	C(15)-Si(1)-C(8)	111.91(11)
Si(1)-C(15)	1.857(3)	C(13)-Si(1)-C(8)	108.92(11)
Si(1)-C(13)	1.856(2)	C(9)-O(1)-C(12)	120.60(14)
Si(1)-C(8)	1.905(2)	C(7)-O(2)-C(16)	115.93(18)
O(1)-C(9)	1.345(2)	C(9)-N(3)-C(5)	122.99(15)
O(1)-C(12)	1.467(2)	N(3)-C(5)-C(7)	109.15(14)
O(2)-C(7)	1.3292(19)	N(3)-C(5)-C(8)	110.90(13)
O(2)-C(16)	1.452(3)	C(7)-C(5)-C(8)	110.76(15)
N(3)-C(9)	1.341(2)	O(6)-C(7)-O(2)	123.45(17)
N(3)-C(5)	1.446(2)	O(6)-C(7)-C(5)	124.61(15)
O(4)-C(9)	1.2084(19)	O(2)-C(7)-C(5)	111.94(15)
C(5)-C(7)	1.512(3)	C(10)-C(8)-C(5)	110.89(13)
C(5)-C(8)	1.544(2)	C(10)-C(8)-Si(1)	111.39(13)
O(6)-C(7)	1.198(2)	C(5)-C(8)-Si(1)	113.09(13)
C(8)-C(10)	1.505(3)	O(4)-C(9)-N(3)	124.50(18)
C(10)-C(11)	1.300(3)	O(4)-C(9)-O(1)	125.84(17)
C(11)-C(17)	1.490(3)	N(3)-C(9)-O(1)	109.65(14)
C(12)-C(19)	1.509(4)	C(11)-C(10)-C(8)	125.81(19)
C(12)-C(18)	1.511(3)	C(10)-C(11)-C(17)	126.6(2)
C(12)-C(20)	1.511(4)	O(1)-C(12)-C(19)	108.3(2)
		O(1)-C(12)-C(18)	110.6(2)
C(14)-Si(1)-C(15)	108.74(15)	C(19)-C(12)-C(18)	112.8(3)
C(14)-Si(1)-C(13)	109.29(16)	O(1)-C(12)-C(20)	102.0(2)
C(15)-Si(1)-C(13)	110.15(16)	C(19)-C(12)-C(20)	112.3(3)
C(14)-Si(1)-C(8)	107.77(13)	C(18)-C(12)-C(20)	110.3(3)

Table 1.20. Anisotropic displacement parameters ($Å^2$ x 10^3) for (**103e**). The anisotropic
displacement factor exponent takes the form: $-2\pi^2 [h^2 a^{*2} U_{11} + ... + 2 h k a^* b^* U_{12}]$

	U11	U22	U33	U23	U13	U12
Si(1)	42(1)	48(1)	58(1)	14(1)	9(1)	19(1)
O(1)	68(1)	46(1)	49(1)	12(1)	-10(1)	19(1)
O(2)	57(1)	46(1)	58(1)	15(1)	19(1)	14(1)
N(3)	44(1)	34(1)	50(1)	10(1)	-4(1)	12(1)
O(4)	68(1)	43(1)	61(1)	7(1)	-13(1)	13(1)
C(5)	40(1)	32(1)	47(1)	9(1)	2(1)	13(1)
O(6)	65(1)	44(1)	70(1)	2(1)	19(1)	19(1)
C(7)	38(1)	41(1)	50(1)	13(1)	1(1)	16(1)
C(8)	39(1)	36(1)	51(1)	9(1)	-1(1)	13(1)
C(9)	41(1)	42(1)	48(1)	8(1)	1(1)	16(1)
C(10)	43(1)	41(1)	57(1)	12(1)	1(1)	15(1)
C(11)	56(1)	50(1)	62(2)	16(1)	-4(1)	17(1)
C(12)	71(1)	72(1)	42(1)	16(1)	-5(1)	22(1)
C(13)	66(2)	63(1)	80(2)	5(1)	19(1)	25(1)
C(14)	48(1)	97(2)	89(2)	17(2)	9(1)	34(1)
C(15)	79(2)	74(2)	80(2)	34(2)	35(2)	38(1)
C(16)	92(2)	74(2)	80(2)	31(2)	44(2)	30(2)
C(17)	78(2)	74(2)	69(2)	26(1)	-10(2)	22(1)
C(18)	71(2)	93(2)	74(2)	17(2)	-19(1)	24(1)
C(19)	107(2)	120(3)	60(2)	8(2)	21(2)	39(2)
C(20)	127(3)	91(2)	76(2)	42(2)	-16(2)	24(2)

Table 1.21. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$ x 10^3)
for (**103e**).

	x	y	z	U(eq)
H(1)	8934(18)	6428(17)	4089(13)	33(4)
H(2)	11660(20)	8942(19)	5019(15)	45(5)
H(3)	9420(20)	8940(20)	3580(16)	46(5)
H(4)	11470(30)	6390(20)	5570(19)	68(6)
H(5)	12460(20)	8870(20)	6920(18)	64(6)
H(6)	12650(30)	6420(30)	7520(20)	93(9)
H(7)	8480(40)	9870(30)	450(20)	103(10)
H(8)	11930(30)	5770(30)	2100(20)	87(8)
H(9)	12080(30)	7270(30)	8320(30)	95(9)
H(10)	10280(30)	5910(30)	2270(20)	95(9)
H(11)	5900(40)	7140(40)	6440(30)	130(11)
H(12)	11100(30)	5270(30)	3120(20)	90(8)
H(13)	13470(40)	9100(30)	2060(30)	113(10)
H(14)	5890(30)	5620(30)	6640(20)	97(9)
H(15)	13240(40)	10070(40)	3020(30)	138(13)
H(16)	4970(30)	6070(30)	910(20)	103(9)
H(17)	13930(40)	7920(30)	8080(30)	125(10)
H(19)	11810(50)	9110(30)	2230(30)	145(14)
H(20)	4670(40)	6710(30)	-180(30)	115(10)
H(1A)	9130(40)	7760(30)	70(30)	125(11)
H(2A)	14510(40)	7190(40)	4500(30)	134(13)
H(3A)	15140(40)	8710(30)	4660(30)	109(11)
H(4A)	7560(40)	6890(30)	-710(30)	121(11)
H(5A)	7780(40)	6150(40)	320(30)	146(14)
H(6A)	7250(40)	6860(30)	7260(30)	137(13)
H(7A)	7000(40)	9120(30)	-490(30)	130(12)
H(8A)	4630(40)	7540(40)	990(30)	139(14)
H(10A)	6640(50)	9690(40)	670(30)	135(16)
H(17A)	15360(40)	8080(30)	3590(30)	127(12)

Table 6. Torsion angles [°] for (**103a**).

Table 2.3. Crystal data and structure refinement for (**20**).

Identification code		
Empirical formula	$C_{18}H_{35}NO_4Si_2$	
Formula weight	385.65	
Temperature	173(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	P2(1)/c	
Unit cell dimensions	a = 11.255(2) Å	α= 90°.
	b = 22.070(5) Å	β= 102.420(4)°.
	c = 9.842(2) Å	γ = 90°.
Volume	2387.4(8) $Å^3$	
Z	4	
Density (calculated)	1.073 Mg/m^3	
Absorption coefficient	0.167 mm^{-1}	
F(000)	840	
Crystal size	.10 x .20 x .36 mm^3	
Theta range for data collection	1.85 to 27.50°.	
Index ranges	-13<=h<=14, -28<=k<=28, -12<=l<=12	
Reflections collected	21370	
Independent reflections	5407 [R(int) = 0.0299]	
Completeness to theta = 27.50°	98.5 %	
Absorption correction	None	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	5407 / 0 / 367	
Goodness-of-fit on F^2	1.018	
Final R indices [I>2sigma(I)]	R1 = 0.0364, wR2 = 0.0898	
R indices (all data)	R1 = 0.0521, wR2 = 0.0973	
Extinction coefficient	0.0006(6)	
Largest diff. peak and hole	0.294 and -0.255 $e.Å^{-3}$	

Table 2.4. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3)
for (**20**). U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
Si(1)	6162(1)	953(1)	9236(1)	31(1)
O(1)	4416(1)	2978(1)	8054(1)	31(1)
N(1)	6151(1)	2492(1)	8226(1)	24(1)
C(1)	2558(2)	3458(1)	7241(2)	46(1)
Si(2)	9886(1)	734(1)	7427(1)	31(1)
O(2)	5553(1)	2759(1)	10204(1)	34(1)
C(2)	3919(2)	3829(1)	9424(2)	52(1)
O(3)	9387(1)	2339(1)	9457(1)	50(1)
C(3)	2841(2)	2825(1)	9395(2)	48(1)
O(4)	8271(1)	2824(1)	7640(1)	33(1)
C(4)	3432(1)	3274(1)	8584(2)	34(1)
C(5)	5386(1)	2742(1)	8939(1)	24(1)
C(6)	7227(1)	2167(1)	8930(1)	24(1)
C(7)	8412(1)	2449(1)	8722(1)	28(1)
C(8)	9393(2)	3104(1)	7446(2)	41(1)
C(9)	7154(1)	1498(1)	8512(1)	25(1)
C(10)	4570(2)	1228(1)	8922(3)	56(1)
C(11)	6227(3)	216(1)	8360(3)	73(1)
C(12)	6732(3)	882(2)	11147(2)	72(1)
C(13)	7738(1)	1293(1)	7587(1)	27(1)
C(14)	8339(1)	1058(1)	6721(1)	29(1)
C(15)	7794(2)	1030(1)	5166(2)	42(1)
C(16)	11001(2)	1135(1)	6590(2)	57(1)
C(17)	10303(2)	828(1)	9347(2)	48(1)
C(18)	9823(2)	-87(1)	6958(2)	50(1)

Table 2.5. Bond lengths [Å] and angles [°] for (**20**).

Si(1)-C(11)	1.850(2)	C(5)-O(1)-C(4)	120.53(10)
Si(1)-C(10)	1.853(2)	C(5)-N(1)-C(6)	121.23(11)
Si(1)-C(12)	1.859(2)	C(17)-Si(2)-C(16)	110.47(11)
Si(1)-C(9)	1.8821(14)	C(17)-Si(2)-C(18)	110.30(10)
O(1)-C(5)	1.3455(16)	C(16)-Si(2)-C(18)	110.10(11)
O(1)-C(4)	1.4740(16)	C(17)-Si(2)-C(14)	110.30(8)
N(1)-C(5)	1.3420(17)	C(16)-Si(2)-C(14)	108.38(9)
N(1)-C(6)	1.4481(17)	C(18)-Si(2)-C(14)	107.23(9)
C(1)-C(4)	1.523(2)	C(7)-O(4)-C(8)	114.33(12)
Si(2)-C(17)	1.8578(18)	O(1)-C(4)-C(3)	110.23(13)
Si(2)-C(16)	1.866(2)	O(1)-C(4)-C(2)	109.95(14)
Si(2)-C(18)	1.869(2)	C(3)-C(4)-C(2)	112.96(16)
Si(2)-C(14)	1.8712(15)	O(1)-C(4)-C(1)	101.88(12)
O(2)-C(5)	1.2184(15)	C(3)-C(4)-C(1)	110.88(16)
C(2)-C(4)	1.514(3)	C(2)-C(4)-C(1)	110.38(16)
O(3)-C(7)	1.2017(18)	O(2)-C(5)-N(1)	124.79(13)
C(3)-C(4)	1.514(2)	O(2)-C(5)-O(1)	125.16(12)
O(4)-C(7)	1.3312(17)	N(1)-C(5)-O(1)	110.05(11)
O(4)-C(8)	1.4549(18)	N(1)-C(6)-C(7)	113.56(11)
C(6)-C(7)	1.5245(19)	N(1)-C(6)-C(9)	110.97(11)
C(6)-C(9)	1.531(2)	C(7)-C(6)-C(9)	110.81(11)
C(9)-C(13)	1.3127(18)	O(3)-C(7)-O(4)	122.89(13)
C(13)-C(14)	1.3052(19)	O(3)-C(7)-C(6)	123.30(13)
C(14)-C(15)	1.522(2)	O(4)-C(7)-C(6)	113.80(12)
		C(13)-C(9)-C(6)	120.83(12)
C(11)-Si(1)-C(10)	110.12(14)	C(13)-C(9)-Si(1)	117.92(11)
C(11)-Si(1)-C(12)	110.92(16)	C(6)-C(9)-Si(1)	121.17(9)
C(10)-Si(1)-C(12)	107.90(13)	C(14)-C(13)-C(9)	176.19(15)
C(11)-Si(1)-C(9)	107.46(9)	C(13)-C(14)-C(15)	121.27(14)
C(10)-Si(1)-C(9)	111.01(8)	C(13)-C(14)-Si(2)	118.74(11)
C(12)-Si(1)-C(9)	109.45(9)	C(15)-C(14)-Si(2)	119.98(11)

Table 2.6. Anisotropic displacement parameters ($Å^2 x\ 10^3$) for (**20**). The anisotropic displacement factor exponent takes the form: $-2\pi^2[\ h^2a^{*2}U^{11} + ... + 2\ h\ k\ a^*\ b^*\ U^{12}\ ]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
Si(1)	29(1)	31(1)	34(1)	3(1)	9(1)	-4(1)
O(1)	26(1)	43(1)	23(1)	3(1)	6(1)	11(1)
N(1)	25(1)	32(1)	16(1)	1(1)	3(1)	5(1)
C(1)	34(1)	56(1)	46(1)	10(1)	6(1)	18(1)
Si(2)	31(1)	37(1)	27(1)	1(1)	8(1)	7(1)
O(2)	34(1)	49(1)	19(1)	0(1)	6(1)	9(1)
C(2)	52(1)	48(1)	56(1)	-8(1)	10(1)	16(1)
O(3)	26(1)	62(1)	57(1)	23(1)	-4(1)	-4(1)
C(3)	34(1)	61(1)	52(1)	14(1)	19(1)	12(1)
O(4)	27(1)	43(1)	29(1)	6(1)	5(1)	-7(1)
C(4)	29(1)	41(1)	36(1)	4(1)	11(1)	13(1)
C(5)	24(1)	27(1)	22(1)	1(1)	5(1)	-1(1)
C(6)	23(1)	28(1)	19(1)	2(1)	4(1)	2(1)
C(7)	28(1)	28(1)	27(1)	-1(1)	4(1)	-1(1)
C(8)	34(1)	53(1)	38(1)	2(1)	11(1)	-15(1)
C(9)	23(1)	27(1)	25(1)	2(1)	4(1)	2(1)
C(10)	32(1)	61(1)	78(2)	18(1)	18(1)	-4(1)
C(11)	88(2)	36(1)	112(2)	-14(1)	57(2)	-20(1)
C(12)	68(2)	98(2)	45(1)	29(1)	1(1)	-37(2)
C(13)	25(1)	27(1)	27(1)	4(1)	2(1)	-1(1)
C(14)	31(1)	29(1)	27(1)	1(1)	8(1)	2(1)
C(15)	45(1)	52(1)	27(1)	0(1)	5(1)	12(1)
C(16)	38(1)	76(2)	61(1)	4(1)	19(1)	-7(1)
C(17)	54(1)	55(1)	32(1)	-2(1)	-1(1)	16(1)
C(18)	66(1)	42(1)	42(1)	0(1)	13(1)	18(1)

Table 2.7. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$x 10^3) for (**20**).

	x	y	z	U(eq)
H(1)	5945(14)	2457(7)	7420(18)	30(4)
H(1C)	2234(17)	3089(9)	6720(20)	48(5)
H(1B)	1889(18)	3682(9)	7462(19)	51(5)
H(1A)	2956(19)	3721(10)	6650(20)	66(6)
H(2C)	4370(20)	4087(10)	8880(20)	68(7)
H(2B)	3300(20)	4049(11)	9600(20)	76(7)
H(2A)	4450(20)	3715(10)	10210(20)	64(6)
H(3C)	3336(18)	2717(9)	10220(20)	46(5)
H(3B)	2139(19)	3010(9)	9570(20)	58(6)
H(3A)	2610(20)	2460(11)	8850(20)	69(7)
H(6)	7256(12)	2212(6)	9863(14)	16(3)
H(8B)	9753(17)	3344(9)	8250(20)	49(5)
H(8C)	9937(18)	2791(9)	7262(19)	50(5)
H(8A)	9190(18)	3368(10)	6630(20)	63(6)
H(10C)	4090(20)	903(11)	9140(20)	78(7)
H(10B)	4280(20)	1333(12)	7990(30)	91(8)
H(10A)	4540(20)	1577(14)	9510(30)	97(9)
H(11C)	5820(30)	-62(13)	8710(30)	94(9)
H(11B)	7060(30)	78(14)	8500(30)	115(11)
H(11A)	5990(30)	245(14)	7350(30)	118(12)
H(12C)	7560(30)	709(15)	11380(30)	128(12)
H(12B)	6260(30)	604(13)	11500(30)	100(9)
H(12A)	6890(30)	1261(16)	11660(30)	123(12)
H(15C)	8340(20)	1181(11)	4610(30)	82(7)
H(15B)	7040(20)	1260(10)	4920(20)	69(6)

H(15A)	7630(20)	606(11)	4860(20)	74(7)
H(16C)	11040(20)	1545(13)	6870(30)	88(9)
H(16B)	11770(30)	976(13)	6960(30)	100(9)
H(16A)	10770(20)	1098(11)	5570(30)	82(7)
H(17B)	9720(20)	612(11)	9770(20)	73(7)
H(17C)	10368(19)	1256(11)	9570(20)	67(6)
H(17A)	11060(20)	637(11)	9680(20)	79(7)
H(18C)	9340(20)	-299(10)	7470(20)	69(7)
H(18B)	9480(20)	-147(11)	5980(30)	80(7)
H(18A)	10620(30)	-274(12)	7180(30)	92(8)

Preface

Preface

α-Amino acids are important building blocks for biological systems.[1] Modified or unnatural amino acids are needed as components of drugs, peptides or proteins. They produce unusual conformations in proteins that can result in changes in binding/ enzymatic activity and (added) stability against enzymatic degradation.[2]

Non-proteinogenic amino acids are quite common in nature, and are often found in linear and cyclic peptides produced by marine organisms.[3] Many of these peptides show antibiotic activity and are therefore highly interesting from a pharmaceutical perspective. Much of the pharmacological activity of peptides is derived from the physical properties of the peptide bond.[4] However, the use of peptides as drugs is limited by problems that are associated with the properties of the amide bond itself.[5] The high polarity of this bond can lead to lower oral activity and make crossing of the blood-brain barrier inefficient.[6] Moreover, peptides are metabolically unstable towards proteolysis in the gastrointestinal tract, which can lead to loss of their original biological activity when administered orally. As result of these problems, a number of peptide modifications have been developed,[7] including the replacement of the amide bond with electronically and structurally similar groups such as the *E*-olefin isostere shown in (Figure P-1).[8]

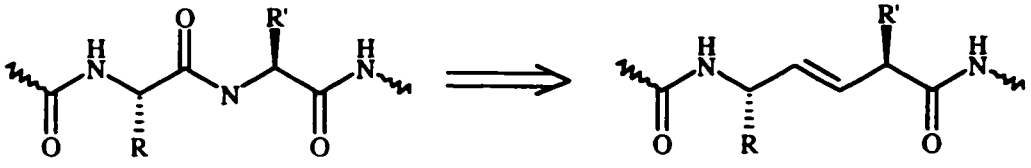


Figure P-1. *E*-olefin replacement for an amide bond in peptides.

Another way to change the properties of peptides is via side chain modification. Seebach and co-workers, for example, developed an elegant synthesis for the introduction of different alkyl side chains onto a given peptide.[9] This methodology allows an extremely economical modification of sarcosine subunits of linear and cyclic peptides.[9]

An important and very different class of non-proteinogenic α-amino acids is that based on allylglycines. Many of these compounds have been reported to act as irreversible mechanism-based inhibitors of pyridoxal phosphate-dependent enzymes (**Figure P-2**). Both isomers of allylglycine were reported to be convulsants due to their inhibition of brain glutamate decarboxylase *in vitro* (**Figure P-2**).[10]

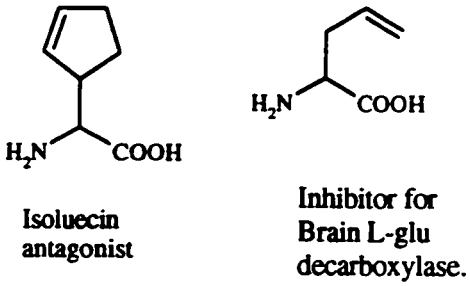
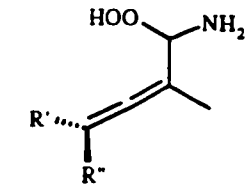


Figure P-2: γ,δ-unsaturated amino acids

The first synthesis of allylic amino acids by Claisen rearrangement was described in 1975 by Steglich and co-workers.[11] The reaction proceeds via an oxazole intermediate and is especially suitable for the synthesis of α-alkylated allylic amino acids. In 1982, the Ireland-Claisen rerrangement of glycine allylic esters was studied by Bartlett and co-workers.[12]

α-Allenic-α-amino acids (**Figure P-3**) are another class of biologically interesting molecules. They are implicated in the inhibition of vitamin B6 decarboxylases, and α-

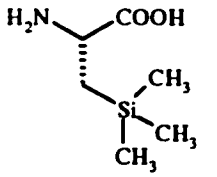
allenyl DOPA is known to inactivate porcine kidney aromatic group amino acid decarboxylase.[13]



Vitamin B decarboxylase inhibitor

Figure P-3: α-allenylamino acid

An unusual class of unnatural amino acids are those which contain a silicon functionality. Trialkylsilyl chains are known to be relatively chemically inert, bulky and to have hydrophobic properties.[14] For these reasons, they can be used as suitable substitutes for natural lipophilic amino acids, or as replacements for more polar amino acids in naturally occurring peptides.[15] Incorporation of such amino acids could lead to enhancements in biological activity and proteolytic stability of the modified peptides. One of the main reasons silicon has been incorporated into amino acids is to promote a higher solubility of silicon-containing peptides in lipid tissue, owing to the aforementioned nature of silyl groups. A number of silicon-modified amino acids have been reported recently, including the α-silyl amino acid analogue of leucine.[16] Enzymatically synthesized trimethylsilylalanine and *para*-trimethylsilylphenylalanine have also been reported.[17] One of the most interesting reported uses of such compounds is the exploitation of β-trimethylsilylalanine as a bioisostere for phenylalanine, where it acts as a stable renin inhibitor; all the peptides that had incorporated β-trimethylsilylalanine were found to be resistant toward proteolytic digestion by α-chymotrypsin (**Figure P-4**).[18]



(trimethylsilyl)alanin
Renin inhibitor

Figure P-4: Renin inhibitor

In addition to their normal association with hydrophobicity, silyl groups play an important role in organic synthesis for the assembly of sophisticated molecules.[19] Allylsilanes, vinylsilanes and alkynylsilanes are among the silicon-based reagents widely used in organic synthesis.[19]

At the outset of this thesis research, we envisioned that the combination of allenyl- and allyl-silanes with amino acids would offer a variety of interesting opportunities. First, the presence of the allylsilane group offers the possibility of further elaboration of the amino acid side chain. Second, the compounds and their derivatives may have interesting biological properties in their own right. Finally, their diastereoselective synthesis was an interesting challenge.

In this thesis, we first provide a background on the mechanistic and synthetic characteristics of the Claisen rearrangement, upon which much of this thesis depends. In Chapter 1 the stereoselective synthesis of a series of α-silylallyl amino acids is described. Chapter 2 outlines the synthesis and characterization of related α-bis(silyl)allenyl amino acids. In the final chapter, Chapter 3 is described the elaboration of these compounds using classic organosilane chemistry, particularly Lewis-acid mediated electrophilic substitution of allylsilanes with carbonyls. A brief introduction of allylsilane chemistry and properties will be given followed by a discussion of the observed results.

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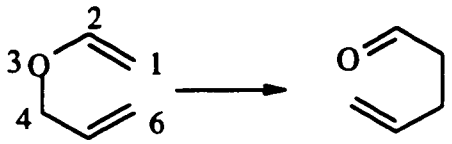
CHAPTER 1

The Claisen rearrangement of vinylsilane glycinate esters

1.1. Introduction

The Claisen rearrangement has become one of the most powerful reactions in organic synthesis for stereoselective carbon-carbon bond formation.[1] Claisen reported in 1912[2] the thermal rearrangement of allyl vinyl ether (**1**) into a homoallylic carbonyl compound (**2**) by a concerted intramolecular process (**Scheme 1.1**). In the reaction, one bond breaks and another forms, coupled with the concomitant migration of the double bonds, to give a new alkene and a new carbonyl functionality, which are important functional groups in organic synthesis. This has placed the Claisen rearrangement in a unique and important position in organic synthesis.



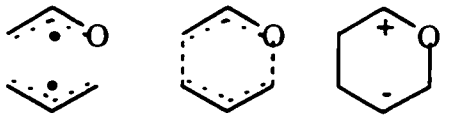
(1) (2)

Scheme 1.1:Rearrangement of allyl vinyl ether

1.2.1.Mechanism

The Claisen rearrangement belongs to a group of unimolecular reactions that do not show detectable intermediates, and are thus referred to as concerted pericyclic reactions.[1] Claisen rearrangements are highly exothermic, with a characteristic negative entropy ($\Delta S^{\ddagger}$ -10 to -15 cal mol^{-1} K^{-1}) and a negative volume of activation.[3] This suggests that the transition state is highly ordered. In the reaction, one σ bond

breaks and another forms. In a concerted[4] process, both of these events would occur simultaneously through a pericyclic transition state that has partial aromatic stabilization.[5] There are, however, still some disagreements about the nature of the transition state of the reaction. Secondary deuterium kinetic isotope studies by Gajewski and coworkers[6] indicate an early transition state, where bond breaking is more advanced than bond making. This, and other work, suggests that a spectrum of mechanisms may be operative in the reaction.[1]



(3) (4) (5)

Figure 1.1: Transition state of the rearrangement of allyl vinyl ether

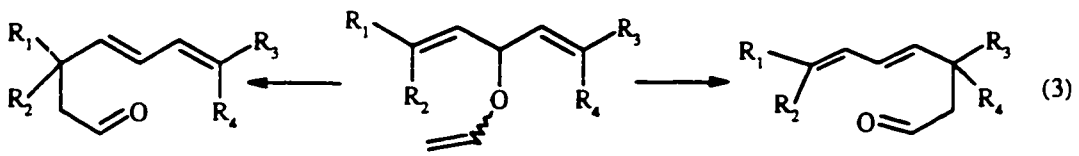
Evidence has been presented that suggests that a cyano group at positions C2 or C4 promotes the rearrangement by a factor of 10^2; NC^--substitution also has smaller effects at the other positions.[7] A donor substituent, for example trimethylsilyloxy, at C2 is strongly accelerating.[8] Based on these facts, the relevant transition state could range in character from a 1,4-diradical to two nearly independent allyl radicals as pointed out by Doering *et al.*[9] That is, the mechanism could be stepwise, rather than one of the concerted mechanisms noted above. In the first scenario, bond breaking would occur first to yield two allyl radicals as intermediates in an oxallyl radical-allyl radical pair (3); in the second case bond making would occur first to yield an

intermediate 2-oxacyclohexane-1,4-diyl (**4**) or dipole (**5**) (**Figure 1.1**).[10] Stabilization of the transition state ($TS^{\ddagger}$) by resonance interactions is therefore clearly an important factor.

1.2.2. Kinetics

The influence of donor and acceptor substituents on the rate of the Claisen and other sigmatropic rearrangements has been widely investigated.[11] Carpenter *et al.* developed a theoretical model, based on Hückel molecular orbital (HMO) calculations, to evaluate the effect of electron-withdrawing and donating substituents on the reaction rate.[7] Their model prediction was in agreement with experimental results associated with the accelerating effects of donor substituents at C1 and both donor and acceptor substituents at positions C2 and C4 of the Claisen system.[12] Acceptor substituents at C1 and C6 and donor groups at C5 and C6 are predicted to decelerate the reaction. Evidence for the relative reactivity of olefins from competitive rearrangements has shown that substituent at the C6 position controls the rate of rearrangement of bis(allyl)vinyl ether (**7**) in the order: allyl > (*E*)-propenyl > (*Z*)-propenyl > 2-methylpropenyl (Table 1.1).[13]

Table 1. 1 :Substituent effect on reaction rate.



(6) (7) (8) (3)

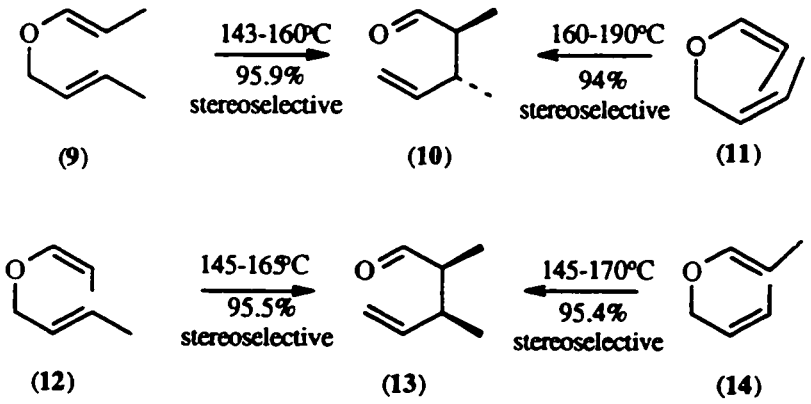
R_1	R_2	R_3	R_4	Yield **6:8**
H	H	Me	H	66:33
H	H	H	Me	95:5
Me	H	H	Me	78:22
H	H	Me	Me	100:0

Wilcox and coworkers[8] used simple alkyl groups to show that when the C5 substituent is changed from hydrogen to a methyl group, the reaction rate is reduced. However, further substitution at C5 from methyl to ethyl, *n*-propyl, *i*-propyl, and neopentyl, provides a continual increase in rate. They observed that the rate increases occurs in the order of increasing steric influence as measured by Taft's steric parameter.[14] These results indicate that the electronic and steric effects of the alkyl substituents are working in opposing directions.[15]

1.2.3. Stereocontrol

The Claisen rearrangement and its variants are a powerful means to effect stereocontrolled C-C bond formation. The highly ordered transition state effectively guarantees a reliable transfer of stereochemistry from starting materials to products.

Naturally, the geometry of the vinyl ether bond (**Scheme 1.2**) and the conformation of the transition state are important parameters in this process. The former issue is strongly dependent on the Claisen variant that is employed, whereas the transition state geometry is controlled by both steric and electronic features of the Claisen system. Substitution on the carbon chain is possible in every position of the framework, and can change the stereochemical outcome of the rearrangement product.



Scheme 1.2: Stereochemistry of 1, 4-substituted allyl vinyl ether rearrangement

The (*E*,*E*)-isomer (**9**) is found to rearrange nine times faster than the (*Z*,*Z*)-isomer (**11**), while the two (*E*,*Z*)-isomers (**12, 14**) are intermediate in reaction rate (**Scheme 1.2**). The data reveal that the most favorable stereochemistry for rearrangement is the (*E*,*E*)-isomer (**9**), wherein both the methyl groups can be equatorially disposed in the transition state.

1.2.4. Transition State Structures

Doering and Roth suggested that the transition state of the Claisen rearrangement could exist in geometries analogous to those of the chair and boat conformers of the

cyclohexane ring.[16] They were able to show that the chair transition state is favored. They estimated from heat of reactions a difference in free energy of activation of $\Delta\Delta G^{\ddagger}$ ~ 5.7 kcal mol^{-1} between the chair and the boat conformers. According to the Woodward-Hoffmann rules,[17] five different concerted transition states are possible for the Claisen rearrangement: chair, boat, twist, cross and plane. Only the chair and the boat have to be considered (**Figure 1.2**), as twist, cross, and plane are antarafacial (and forbidden) processes that require highly elevated temperatures.[18] In the boatlike transition state, an anti bonding interaction between LUMO and HOMO makes it an unfavorable pathway. To correctly predict the product stereochemistry, however, it is crucial to know the preference for a chair or boat-like transition state in the rearrangement. The transition state geometry is controlled both by steric and electronic features of the Claisen system.

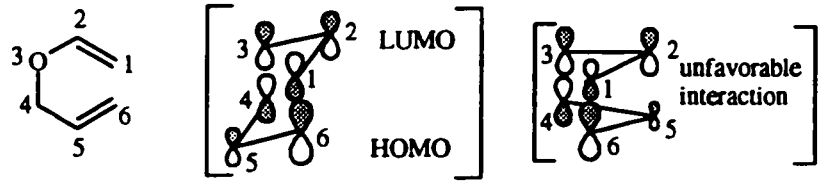
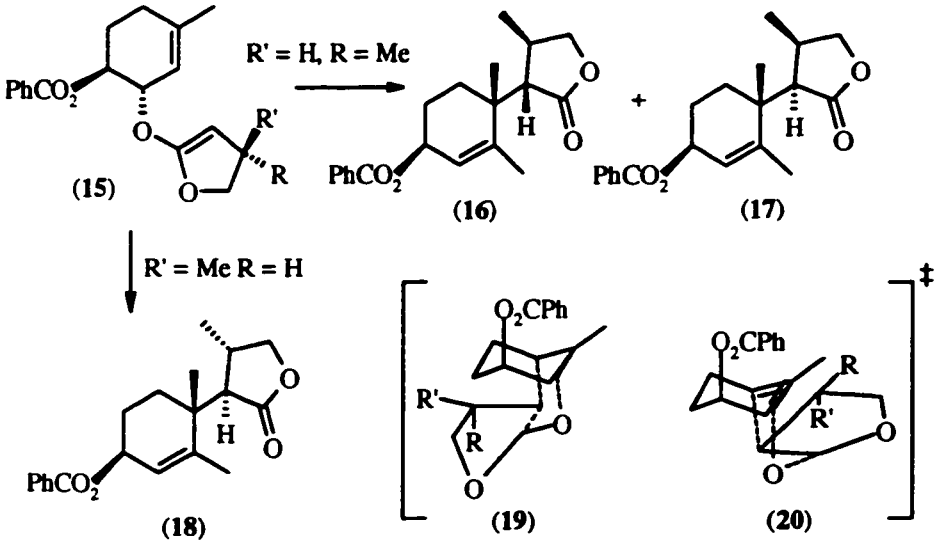


Figure 1. 2 : Molecular orbital depiction of the Claisen rearrangement

Schmid and co-workers determined that greater than 95% of the rearrangement proceeds through a chair-like transition state ($\Delta\Delta G^{\ddagger}$ 2.5 – 3.0 kcal) rather than boat-like transition state.[11] The negative entropy of activation observed ($\Delta S^{\ddagger}$ = -10 to -15 cal mol^{-1} K^{-1}) is consistent with the high degree of order in the transition state.[10]

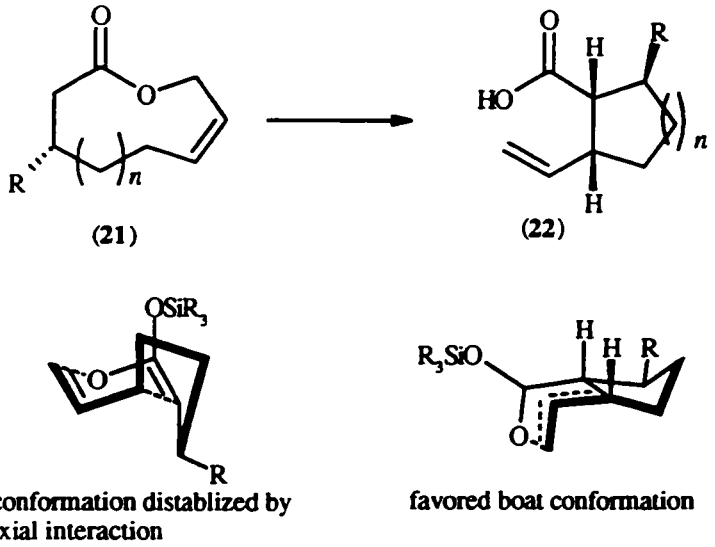
There is a well established preference for chair-like transition states in acyclic systems. In some acyclic systems, however, conformational constraints can override the inherent preference for chair-like transition states leading to the partial involvement of boat-like transition state structures. Lythgoe and coworkers have shown that properly placed substituents in the Claisen rearrangement of (**15**) can preferentially lead to the stabilization of different transition states.[19] The rearrangement of (**15a**), where R' = H, R = Me, leads to a 70:30 mixture of diastereoisomers (**16**) and (**17**), respectively, via the chair-like transition state (**19**). In contrast (**15b**), where R' = Me, R = H, gives exclusively (**18**). Steric hindrance between the methyl group and the cyclohexane ring in (**15b**) leads to a clear preference for the boat-like transition state (**20**).zz



Scheme 1. 3: Substituent effect on the transition state

In cyclic systems, it is possible for the reaction to take place exclusively via the alternative boat conformation by relief of ring strain (**Scheme 1.4**).[20] In most

instances, one can predict the correct stereochemical configuration of the reaction product on the basis of the chair transition state that minimizes steric interactions between the substituents. Thus, the Claisen rearrangement provides a means of introducing functionality in a stereo- and regio-specific manner while at the same time fixing the geometry about the newly formed carbon-carbon double bond.



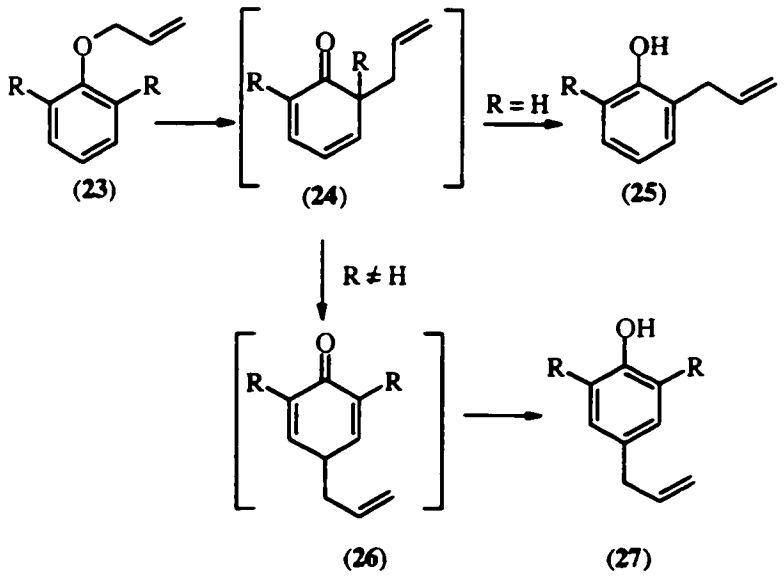
Scheme 1.4: Stereochemistry of cyclic systems

1.3.1. Neutral and Acidic Claisen Rearrangements

In the years following its discovery, the Claisen rearrangement did not gain widespread use in organic synthesis. The traditional Claisen rearrangement often requires temperatures too high for the survival of sensitive functional groups, which limited its applicability in organic synthesis. However, it gained its popularity in the early 1960's due to introduction of more versatile variants.

1.3.2. Aromatic Claisen Rearrangement

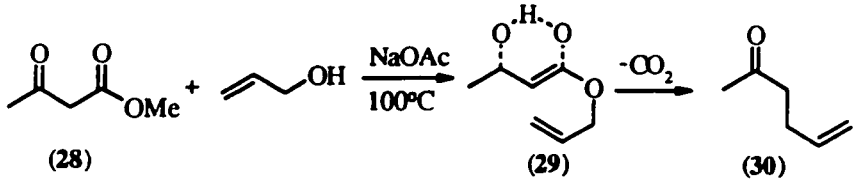
The rearrangements of allyl phenyl ethers (**23**) to *ortho*-allyl phenols (**25**) were the first Claisen rearrangements to be thoroughly studied.[21] The reaction proceeds through a cyclohexadienone (**24**) that enolizes to the stable phenol (**25**). The end of the chain remote from the oxygen becomes attached to the *ortho*- or *para*-position of the aromatic ring, depending on substitution pattern of the ring (Scheme 1-5). The rearrangement requires temperatures in the range of 150 °C to 225 °C. Applications of this reaction include the synthesis of flavenes and dihydrocoumarins.[22]



Scheme 1.5: Aromatic Claisen rearrangement

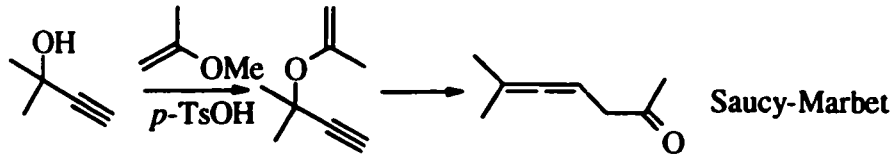
1.3.3. The Carroll Rearrangement

In 1940, Carroll reported the rearrangement of β-keto esters (**29**) obtained from the condensation of allylic alcohols with acetoacetic esters (**28**). The rearrangement is followed by loss of the MeO group and leads to the formation of the diketoallyl ester, which in the presence of 2 equivalents of base rearranges to the ketone (**30**).[23]



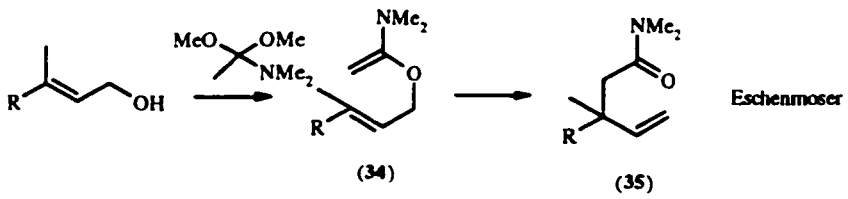
(28) (29) (30)

In 1967, Saucy and Marbet demonstrated the acid-catalyzed reaction of tertiary, propargylic alcohols with isopropenyl methyl ether to give ether (**32**), which upon heating underwent rearrangement to produce β-ketoallene (**33**) in high yields.[24]



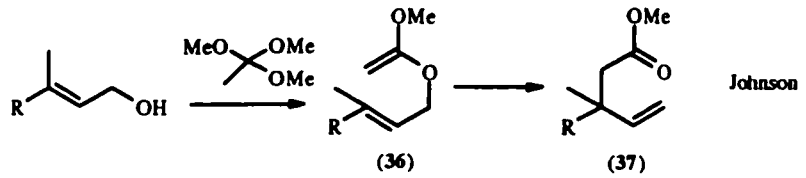
(31) (32) (33)

Eschenmoser and coworkers reported in 1964 a Claisen variant that greatly facilitated the stereoselective synthesis of γ,δ-unsaturated amides.[25] The reaction is carried out by heating an allylic alcohol and an amide acetal such as dimethylacetamide dimethyl acetal. The reaction occurs by exchange of the allylic alcohol for one of the alkoxy groups of the amide acetal, followed by elimination to (**34**) and rearrangement to produce (**35**).



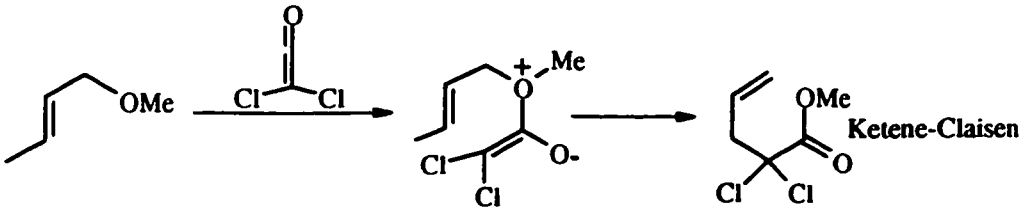
(34) (35)

Somewhat later, Johnson *et al.* reported a reaction that is closely related to the Eschenmoser-Claisen rearrangement.[26] The acid-catalyzed exchange of orthoacetals with allylic alcohols produced a mixed orthoester as an intermediate, which then underwent sequential elimination to (**36**) and rearrangement to (**37**), allowing carboalkoxymethyl groups to be introduced at the γ-position of allylic alcohols.



(36) (37)

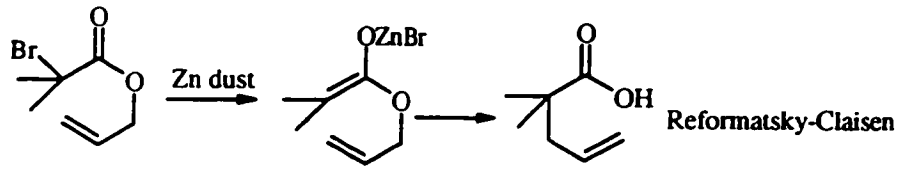
In 1978, Bellus and Malherbe reported a novel ketene version of the Claisen rearrangement.[27] Treatment of an allylic ether with dichloroketene prepared *in situ* resulted in the formation of a 1,3-dipolar allyl vinyl ether, which subsequently underwent rearrangement to give (**43**). This process works well also with allylic sulfides and selenides.



(41) (42) (43)

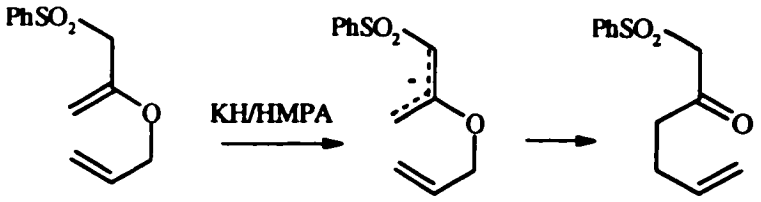
1.4.1. Anionic Claisen Rearrangements

Various anionic versions of the Claisen rearrangement are also known. For example, a Reformatsky-Claisen type reaction involving the reaction of Zn with an α-bromoester (**38**) results in the formation of a zinc-enolate (**39**), which rearranges to give carboxylic acid (**40**).[28]



(38) (39) (40)

More recently, in 1982, Denmark and Harmata demonstrated the first example of a carbanion-accelerated Claisen rearrangement.[29] Treatment of (**44**) with 1.5 eq. of KH in refluxing HMPA produced rearranged product (**46**) in 78% yield.



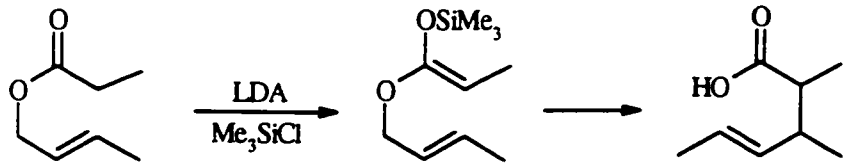
(44) (45) (46) (8)

Carbanion-accelerated Claisen

1.5.1. The Ireland-Claisen Rearrangement

In 1972, Ireland and his co-workers introduced an important improvement to the Claisen rearrangement,[30] which has since received widespread use in organic synthesis. The enolization of (**47**) with a lithium dialkylamide base, followed by silylation with

TMSCl, generated reactive silyl ketene acetals (**48**) at -78 °C. These underwent the Claisen rearrangement efficiently at ambient temperatures to afford (**49**). The rate enhancement observed by Ireland is due to the reduced free energy of activation for the rearrangement of about 9 kcal mol^{-1} relative to allyl vinyl ether (**1**).[8] The Me_3SiO substituent stabilizes the π–bond of the oxyvinyl intermediate species (**48**).

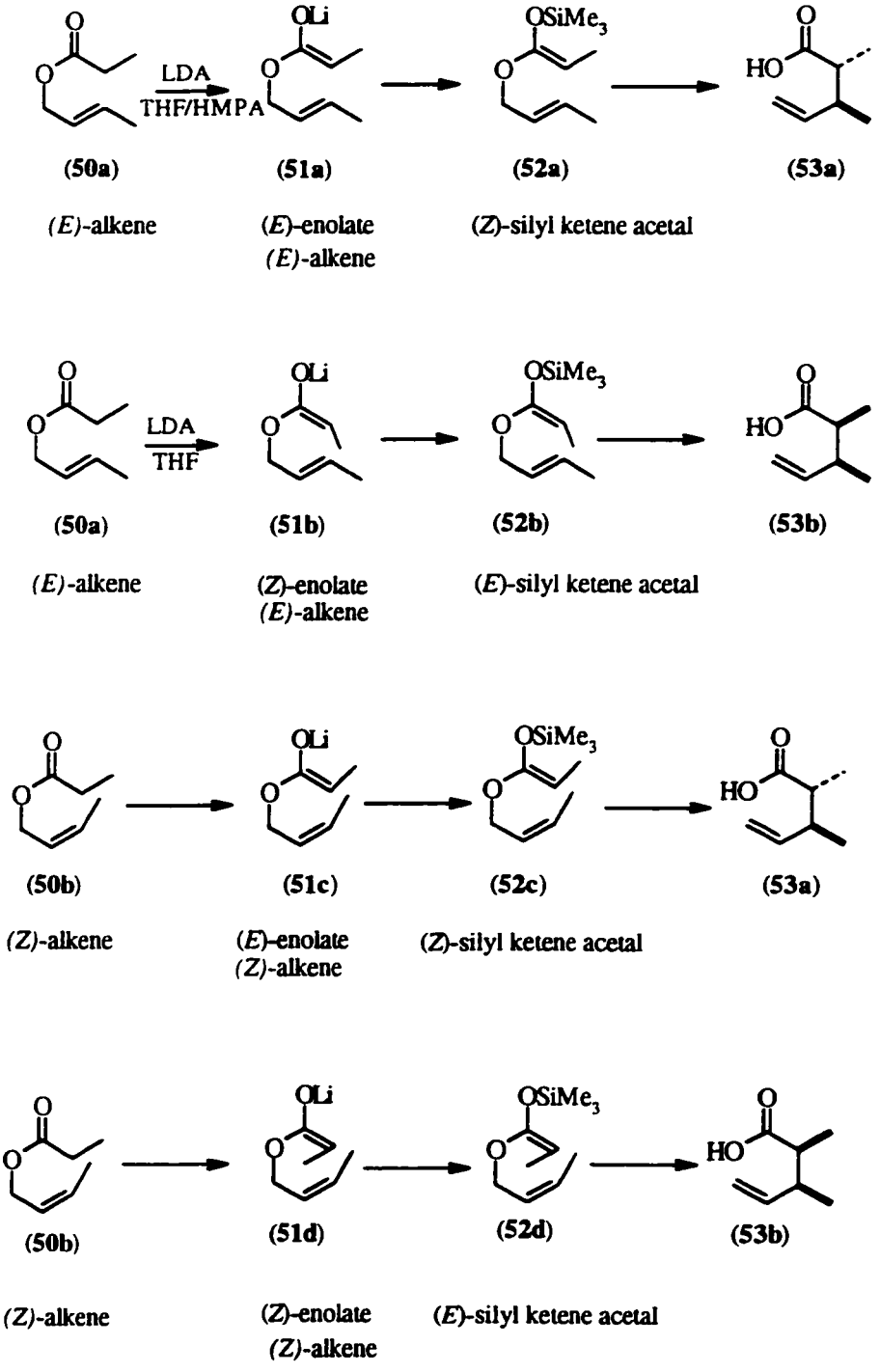


(**47**) (**48**) (**49**)

Several factors contribute to the versatility of the Ireland ester enolate Claisen rearrangement. Among these are: the ability to use a stoichiometric combination of the alcohol and the acid components; the relatively low temperature of the pericyclic process that allows for the assembly of complex, highly functionalized structures; and, through the efficient control of ketene acetal geometry, the highly reliable and predictable transfer of stereochemistry from starting material to product.

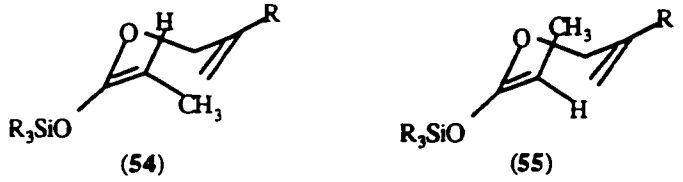
The geometry of the silyl ketene acetal can be controlled during the ester enolization process by varying the solvent system.[36] For instance, enolization of (**50a**), where the allylic double bond has the (*E*)-configuration, leads preferentially to (*E*)-enolate (**51a**) with THF as the solvent, while the use of 23% HMPA/THF favors the formation of the (*Z*)-enolate (**51b**). Regardless of the allylic bond configuration (*Z* or *E*), the stereochemistry is retained on silylation to give the (*Z*)-silylketene acetal and the (*E*)-

silylketene acetal, respectively, which after rearrangement give predominantly the *anti* and *syn* isomers, accordingly (**Scheme 1.6**).[31] Similarly, in the (*Z*)-allyl compound (**50b**), either the (*E*) or the (*Z*)-enolate could be produced through proper choice of solvent and reaction conditions (**Scheme 1.6**).



Scheme 1.6: Ireland-Claisen rearrangement

A number of steric effects on the rate of rearrangement have been observed that can be accommodated by a chair-like transition state model. The (*E*)-silyl enol ethers rearrange somewhat more slowly than the corresponding (*Z*)-isomers (**54**) (**Figure 1**). This effect is interpreted as resulting from the pseudoaxial placement of the methyl group in the transition state for rearrangement of the (*E*)-isomer (**55**). The size of the substituent R also influences the rate, with the rate increasing somewhat for both stereoisomers as R becomes larger. It is proposed that steric interactions with R are relieved as the C-O bond stretches. The rate acceleration would reflect the higher ground state energy resulting from these steric interactions.



(**54**) (**55**)

Z-isomer *E*-isomer

Figure 1.3: Proposed transition state for the silyl enol ether rearrangement

1.5.2. Reaction Conditions

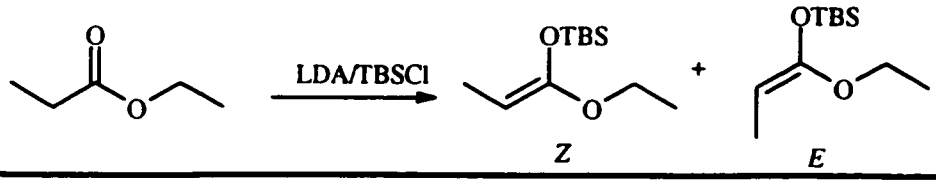
There are three crucial structural elements that determine the diastereoselectivity of the ester enolate Claisen rearrangement: the chair or boat-like nature of the transition state, the geometry about the vinylic double bond, and the geometry about the allylic double bond. A change in any one of these elements results in a reversal of diastereoselectivity if the other two elements remain unchanged. Studies by Ireland

showed that the configuration of the enolate can be controlled by proper choice of reactions and solvent (**Table 1.2**).[36]

Deprotonation of crotyl ester **(50a)** with LDA in THF leads to selective formation of the kinetically favored (*Z*)-ester enolate **(51b)**, to give upon silylation the (*E*)-silylketene acetal **(52b)** (**Scheme 1.6**).[32] After rearrangement at -65 °C and mild hydrolysis of the silyl ester, an 87:13 ratio of mixed γ, δ-unsaturated acids **(53b)** and **(53a)** is isolated in 79% yield (scheme 1-6). These two products can be obtained in 19:81 ratio by using 23% HMPA/THF as a solvent system for the generation of the thermodynamically favored (*Z*)-silylketene acetal **(52a)** via the corresponding (*E*)-lithium enolate **(51a, Scheme 1.6)**.[33]

A systematic variation of reaction parameters such as solvent and ester:base ratio for ethyl propionate showed that the stereoselectivity of the formation of the (*E*)-lithium enolate and thus of the entire rearrangement can be significantly increased by a change in the reaction solvent from 23% HMPA/THF to 45% DMPU/THF (**Table 1.2**, entry 12 and 14).[36]

Table 1.2: Effect of ester to base ratio and solvent on stereoselectivity in silylketene acetal formation from ethyl propionate with LDA.[36]

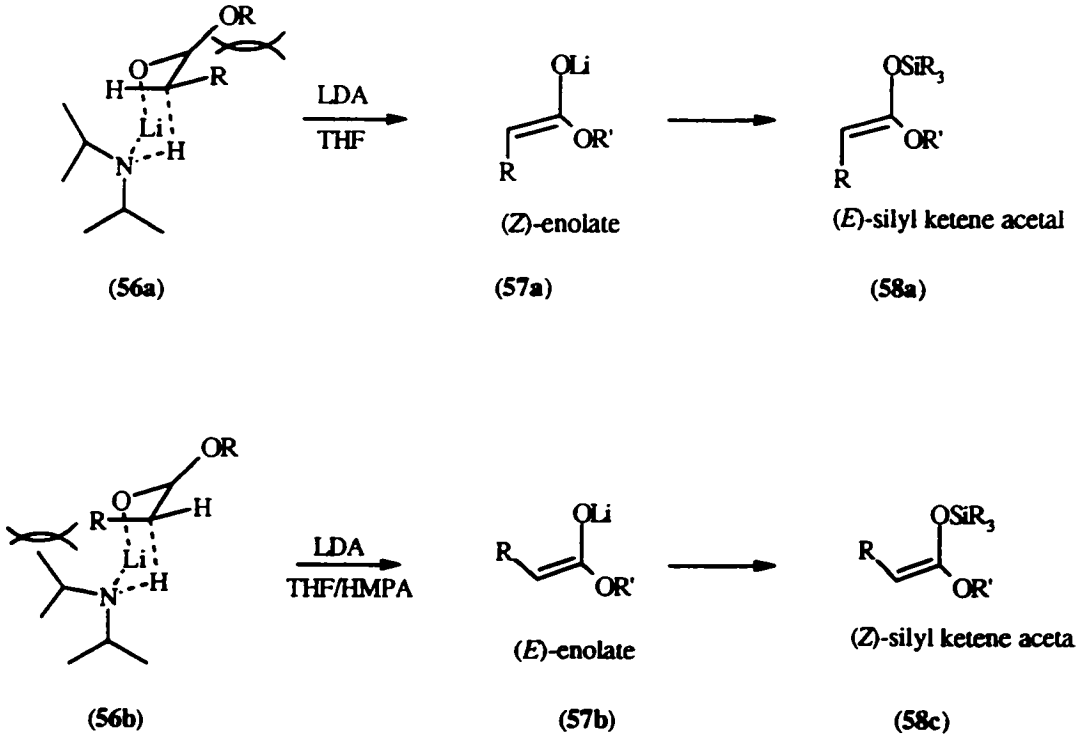


Z *E*

Entry	Solvent	Ester:base	*Z*:*E*	Yield (%)
1	THF	1.4:1	1:1	5
2	THF	1.2:1	20:80	35
3	THF	1:1	6:94	90
4	THF	0.6:1	6:94	90
5	THF/30% DMPU	1.2:1	67:33	70
6	THF/30% DMPU	0.95:1	68:32	90
7	THF/30% DMPU	0.8:1	60:40	85
8	THF/30% DMPU	0.5:1	60:40	95
9	THF/30% DMPU	1.05:1	98:2	70
12	THF/45% DMPU	0.8:1	93:7	80
13	THF/45% DMPU	0.5:1	84:16	90
14	THF/23% HMPA	1.2:1	93:7	85
15	THF/23% HMPA	1:1	85:15	65
16	THF/23% HMPA	0.8:1	59:41	80
17	THF/23% HMPA	0.6:1	55:45	40

The preferred formation of the kinetically favored (*E*)-silylketene acetal with amide bases in THF can be rationalized by the acyclic transition state model (**56a**) (**Scheme 1.7**) that enables a close interaction between Li^+ cation, carbonyl oxygen and base. The presence of additives such as HMPA or DMPU results in a greater degree of solvation

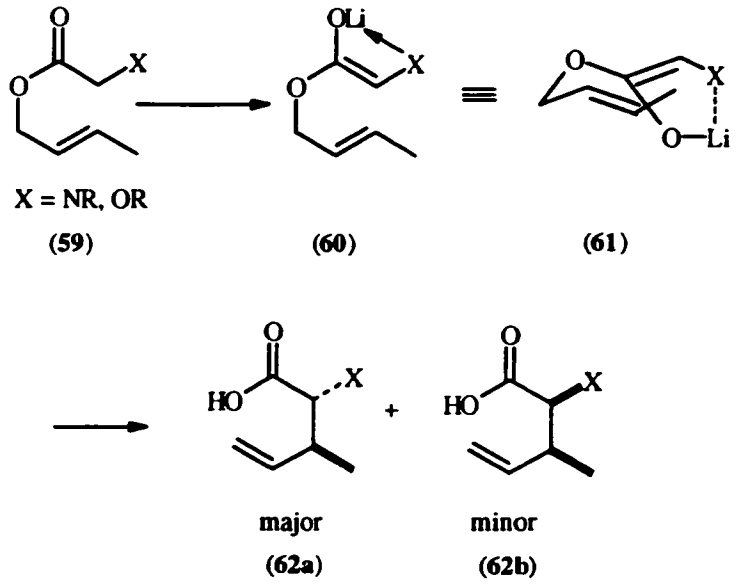
of the lithium cation and a weakened Li^+-carbonyl oxygen interaction (**56b**). The association between base and ester is thus diminished and the 1,3-diaxial strain in the transition state (**56b**) is reduced, whereas transition state (**56a**) is still destabilized by $A^{1,3}$-strain.



Scheme 1.7: Solvent effect on silyl enol ether configuration

Enolization experiments by Corey *et al.* employed hindered bulky bases such as lithium *tert*-octylbutyl amide (LOBA), which led to a higher selectivity for the (*E*)-enolate (Li enolate) when compared to LDA. Thus, they concluded that the stereochemical outcome in the presence of HMPA was not a kinetic effect, but was due to simple equilibration to the more thermodynamically stable (*Z*)-enolate.[34] These results were supported by similar observations by Rathke.[35] However, Ireland argues that Corey's

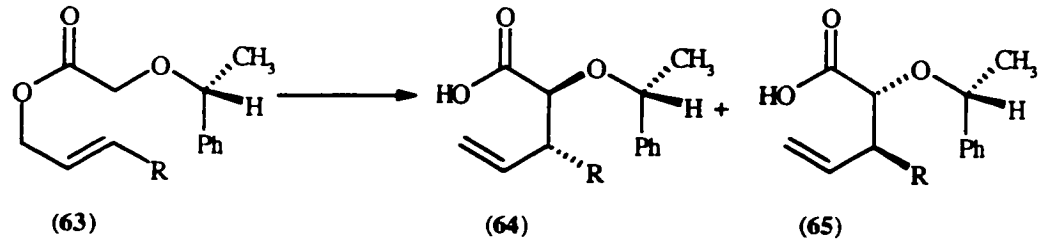
experiments are based on ketone enolates and are not directly applicable to ester enolates. Further studies of the enolization of ethyl propionate were made by Ireland. In THF, a decrease in the ester to base ratio from 1:1 to 0.6:1 did not change the selectivity or yield (**Table 1.2**, entry 3 and 4). However, an increase in that ratio from 1:1 to 1.4:1 drastically reduced the yield from 90% to 5% (**Table 1.2**, entry 3 and 1). A decrease in the ester to base ratio (0.6:1) in the mixed solvent system lowered the (*Z*)-selectivity and decreased the yield (**Table 1-2**, entry 17). Conversely, a slight increase in the ester to base ratio led to an increase in (*Z*)-selectivity, accompanied by a drop in yield (entry 2).[36] From these experiments, the (*E*)-silyl ketene (kinetic enolate) is favored in THF, while the (*Z*)-silyl ketene acetal (thermodynamic enolate) preferentially forms in THF/HMPA. In the case of α-heteroatom-substituted esters, preferential formation of the (*Z*)-enolate (Li enolate) has been shown by Bartlett,[37] Fujisawa,[38] Burke,[39] Panek,[40] and Kazmaier (Scheme 1-8).[41]



Scheme 1.8: Enolization of α-heteroatom substituted esters

1.5.3. The Asymmetric Claisen Rearrangement

There are two new chiral centers produced in the rearrangement. Their relationship is determined by the chair-like transition state and depends on the geometry of the double bonds of the starting material (*vida supra*). When optically pure starting material is used, the stereochemistry is efficiently transferred to the product.[42] There are two ways to prepare enantiopure materials: by the use of external chiral reagents or the use of chiral substrates. Kallmerten *et al.* reported an auxiliary-directed, asymmetric Claisen rearrangement using chiral alcohols.[43] The allylic α-alkoxy ester (**63**) underwent rearrangement after deprotonation with KHMDS and subsequent silylation with TMSCl leading to α–alkoxy-γ,δ-unsaturated acids (**64**)/(**65**) in good yield, and complete *syn* diastereoselectivity in yields of 50-80%.

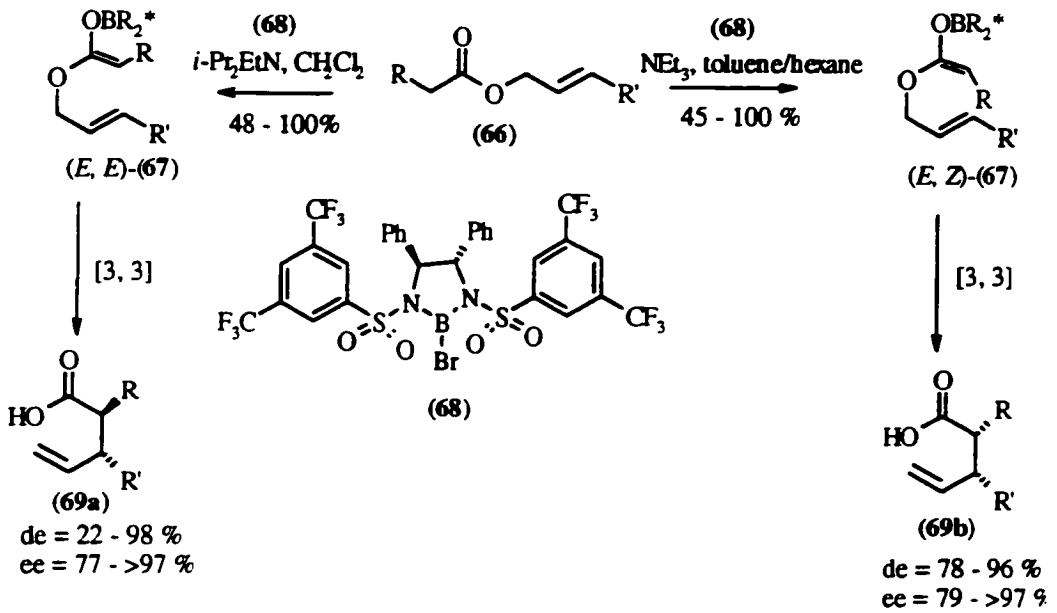


(63) (64) (65)

R = Me; 50% de, R = Ph; 72% de

Scheme 1.9: Chiral auxiliary directed Claisen rearrangement

Corey and his coworkers reported the first asymmetric enantioselective version of the Ireland-Claisen rearrangement using a chiral boron reagent.[44] The rearrangement of various allylic propionate and butyrate esters generally succeeded with good yields and excellent diastereo- and enantioselectivities (**Scheme 1.10**).

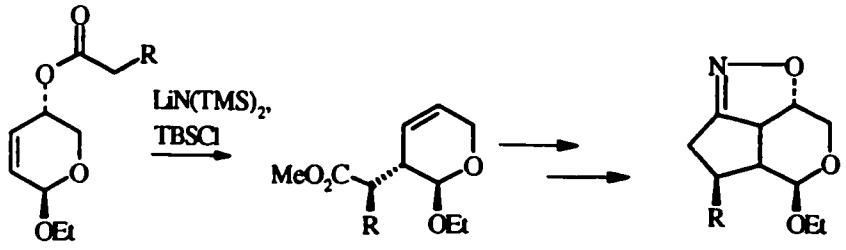


Scheme 1.10: Enantioselective Claisen rearrangement via chiral boron reagent

The achiral allylic esters (**66**) were converted with the enantiopure boron reagent (**68**) to (*E,E*-**67**) or (*E,Z*-**67**), respectively, depending on conditions. The enolates underwent rearrangement at ambient temperature leading to γ,δ-unsaturated acids (**69a**) and (**69b**), respectively.

1.5.4. Applications of the Ireland Claisen Rearrangement.

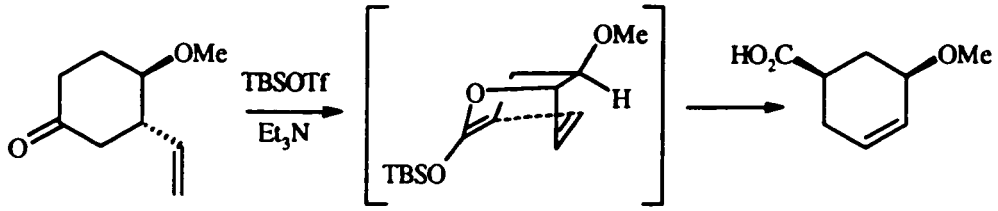
The Claisen rearrangement has been used for crucial C-C bond formation steps in the synthesis of many natural products and biologically important molecules include steroids,[45] macrocycles,[46] polyether antibiotics,[48] amino acids,[47] C-glycosides,[48] terpenes,[49] iridoids,[50] stannanes,[51] and silanes.[52] Curran and co-workers, for example, have used the Ireland-Claisen rearrangement in a stereoselective synthesis of iridoid agylcones (**72**) (**Scheme 1.11**).[53] Iridoids are important intermediates in the biosynthesis of many alkaloids. In addition, many of them possess biological activity such as antimicrobial effects. Treatment of ester (**70**) with $LiN(TMS)_2$ and TBSCl and subsequent rearrangement proceeds with reasonable selectivity through a chair-like transition state to give (**71**) and its diastereomer in a 5:1 ratio.



(**70**) (**71**) (**72**)

Scheme 1.11: Stereoselective synthesis of iridoid agylcone

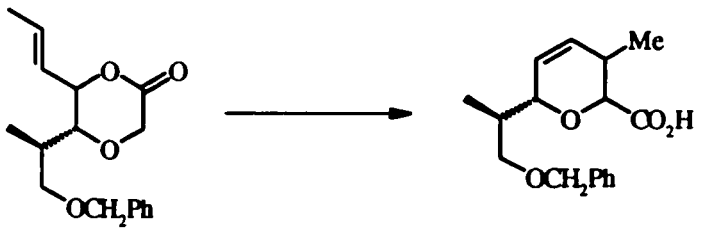
Schreiber and Smith applied the Ireland-Claisen rearrangement in the enantioselective synthesis of the cyclohexyl moiety of FK-506,[54] an antibiotic macrolide with potent immunosuppressive activities. The rearrangement from (**73**) to (**75**) proceeded in 71% overall yield via the boat transition state (**74**).



(**73**) (**74**) (**75**)

Scheme 1.12: Enantioselective synthesis of cyclohexyl moiety of the FK-506

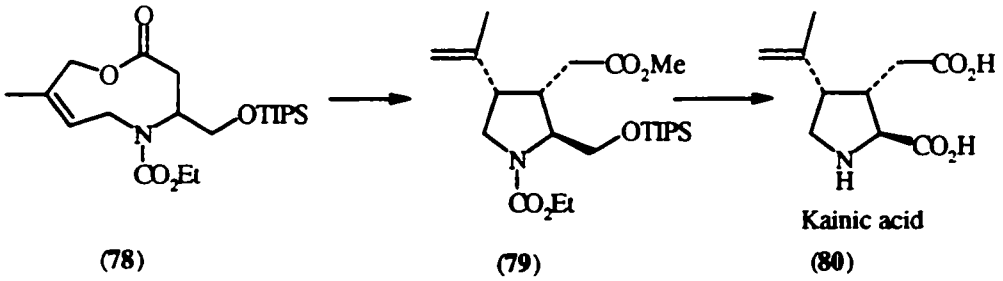
Burke and coworkers have used the Ireland-Claisen rearrangement to prepare the hydropyran subunit (**77**) of macrodiolide and macrotriolide ionophores. The rearrangement of (**76**) led to the product (**77**) in 76% yield.[55]



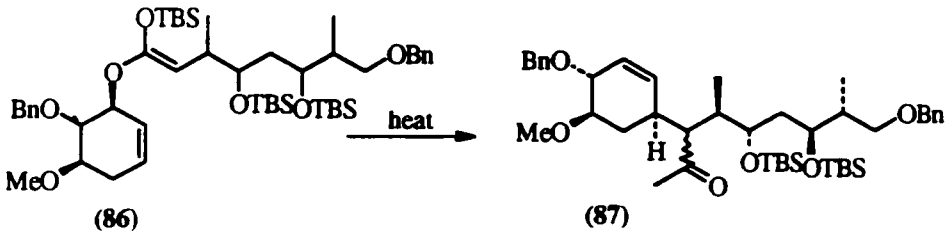
(**76**) (**77**)

Scheme 1.13: Enantioselective synthesis of hydropyran

Knight and co-workers have demonstrated the efficiency of the Ireland-Claisen rearrangement in the total synthesis of (-)-α-Kainic acid.[56] Their strategy involved ring contraction of lactone (**78**) to pyrrolidinedicarboxylic acid (**79**) in 55% overall yield, which upon further modifications led to the enantioselective synthesis of the target molecule.[57] Danishefsky[58] has used the Ireland-Claisen rearrangement to incorporate the C28-C49 unit of Rapamycin, an antibiotic with immunosuppressive activities (**Scheme 1.15**).



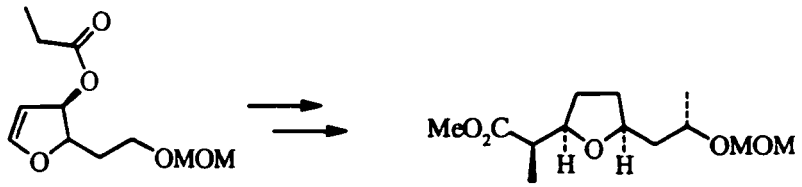
Scheme 1.14: Synthesis of (-)-α-Kainic acid



Scheme 1.15: Synthesis of rapamycin subunit

Ireland[59] has applied the rearrangement in the synthesis of nonactic acid. Enolization of propionate ester (**83**), followed by trapping and rearrangement, provided the product

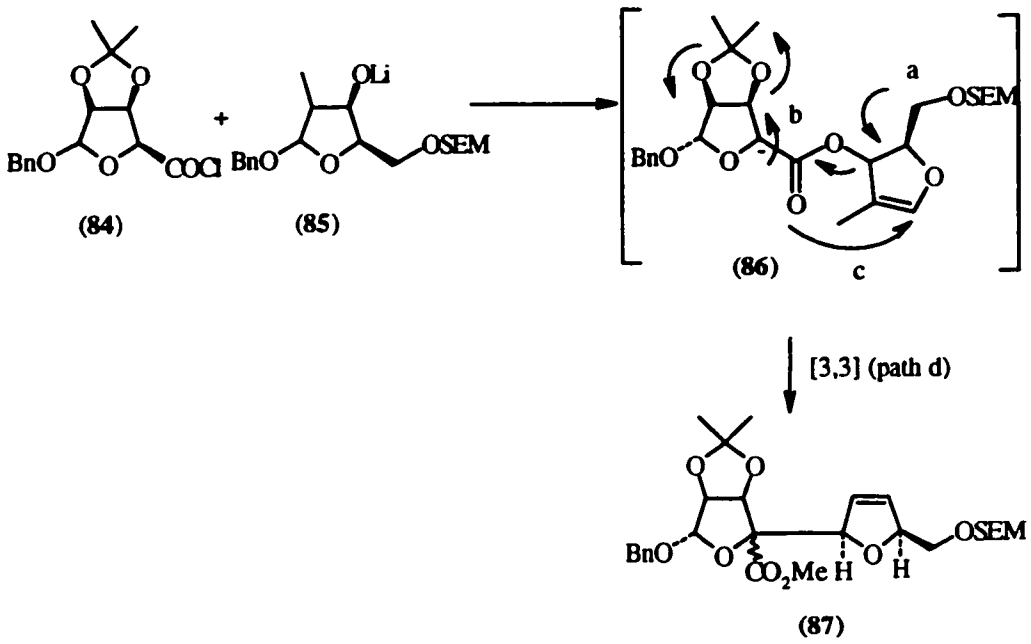
through the boat transition state pathway (**Scheme 1.16**). Such a structure is common in many polyether ionophore antibiotics.



(**83**) (-)-nonactic acid

Scheme 1.16: Synthesis of (-)-nonactic acid

Ireland, again, has used the Claisen rearrangement to effectively join the monensin c/d ring system (**87**).[60] Ester (**86**) is extremely sensitive to fragmentation (path a), β-elimination (path b) and rearrangement (path c). The rearrangement was effected by mixing of the furanoid acid chloride (**84**) and lithium alcoholate (**85**), followed by ester enolization in a solution of premixed LDA and TMS-Cl at -100 °C, which provided the corresponding silyl ketene acetal. Warming to ambient temperature followed by methyl ester formation then led to tricycle (**87**) in an excellent yield (**Scheme 1.17**).



Scheme 1.17: Synthesis of monensin subunit

1.6.1. Research Proposal

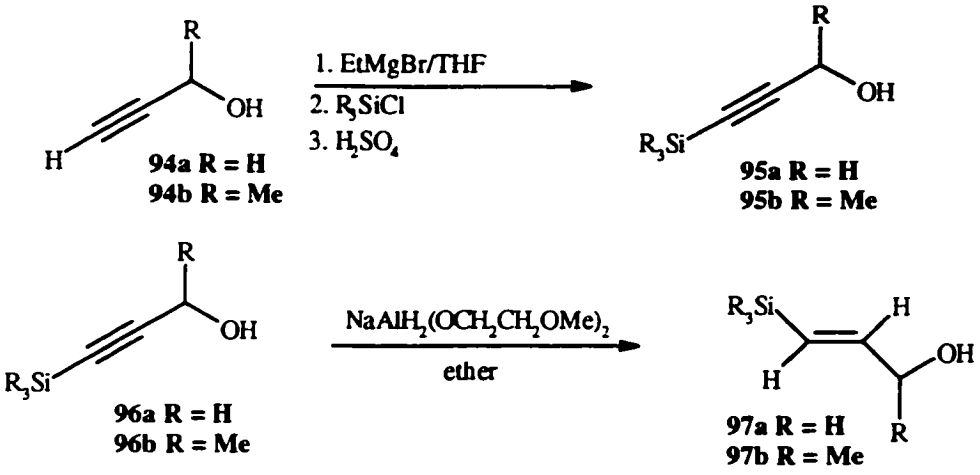
The Ireland-Claisen rearrangement occupies a prominent position among the available procedures for acyclic carbon-carbon bond formation in a stereochemically-defined manner.[61] The importance of functionalized peptides and amino acids prompted us to seek a novel way of introducing functionality into amino acid side chains. γ,δ-Unsaturated amino acids have become the subject of intense investigation due to their biological activity.[62] We sought to synthesize allylsilane-containing amino acids not only for the potential bioactivity of such compounds, but also because of the potential for further functionalization at the allylic position, taking advantage of well-documented allylsilane chemistry.[63] We surmised that the combination of the stereocontrol of the Claisen rearrangement to give allylsilanes, described by Panek[64] and others for non-amino acids, might provide a new, generic entry to unnatural amino acids. To this end, we have investigated methods to facilitate the rearrangement of (*E*)-1-silylpropen-3-ol and (*E*)-1-silylbuten-3-ol glycinate esters to α-allylsilane-amino acids.

1.7. 1. Results and Discussion

Synthesis of (*E*)-3-(trimethylsilyl)propen-1-ol and (*E*)-4-(trimethylsilyl)buten-2-ol glycinate esters.

The stereochemical integrity of the Claisen rearrangement is one of its most important attributes. The geometry of the double bond is an important stereocontrol element for the rearrangement; when the enolate adopts the (*Z*)-configuration, the (*Z*)-alkene leads to the *anti* isomer, while the (*E*)-alkene leads to the *syn* product. (*E*)-1-Silylpropen-3-ol (**97a**) and (*E*)-1-silylbuten-3-ol (**97b**) can be prepared according to literature procedures.[65] Treatment of either propargyl alcohol or 3-butyn-2-ol with 2.7 equivalents of EtMgBr results in the removal of both the methynyl and alcohol protons (**Scheme 1.18**). Addition of excess chlorotrialkyl(aryl)silane (2.7 equiv.) results in the silylation of both sites. Work-up under acidic conditions (1.4 M H_2SO_4) leads to the removal of the silyl group from oxygen, and gives the desired product (**95**) in moderate to excellent yield depending on the size of the silyl group (**Table 1.3**). Reduction of the triple bond with sodium bis(methoxyethoxy)aluminum hydride leads to the exclusive formation of the (*E*)-vinylsilane allylic alcohol (**97**) in good yield.

Alternative methods for the synthesis of vinylsilanes, such as hydrosilylation of the triple bond of a propargyl ester, were not successful, as mixtures of (*Z*) and (*E*) products were recovered. The configuration of the double bond was determined by the ^{1}H NMR coupling constants and the presence of a single isomer (*E*) was confirmed by GC, which showed only one signal (**Table 1.3**).



Scheme 1.18: Synthesis of (*E*)-vinylsilane alcohol.

Table 1.3 Preparation of the (*E*)-vinylsilane alcohols.

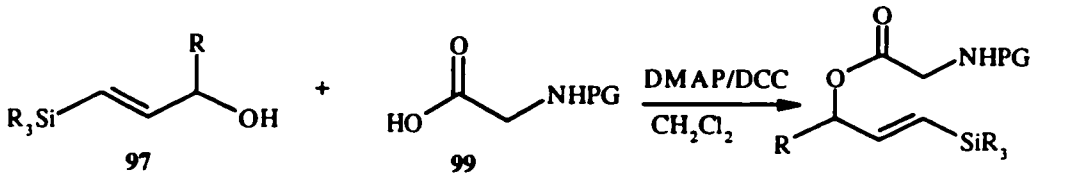
Alcohol	R_3Si	Yield[a] (95)	Yield[a] (97)	*E*/*Z*[b]
94a	Me_3Si	92	77	100:1
	Me_2Ph	70	65	"
	t-$BuMe_2$	54	58	"
	Me_2CHMe_2Si	84	71	"
94b	Me_3Si	95	72	"
	Me_2CHMe_2Si	82	68	"

[a]Isolated yield. [b]determined by GC and ^1H NMR.

1.7. 2. Synthesis of Vinylsilane Glycinate Esters

The silylated allyl glycinate esters used as substrates for the ester enolate Claisen rearrangement were prepared by the esterification of the *N*-protected amino acid (**99**) with the appropriate alcohol. Addition of DCC at 0 °C to a solution of the alcohol and DMAP in CH_2Cl_2 or DMF, depending on protecting group of the amino acid, followed

by addition of amino acid resulted in formation of the esters (**100a-f**) in high yield (**Table 1.4**).



PG = protecting group

100a R $_3$Si = Me $_3$Si, R = H
100b R $_3$Si = *i*-PrMe$_2$Si, R = H
100c R $_3$Si = Me $_2$PhSi, R = H
100d R $_3$Si = *t*-BuMe$_2$Si, R = H
100e R $_3$Si = Me $_3$Si, R = Me
100f R $_3$Si = *i*-PrMe$_2$Si, R= Me

Scheme 1.19: Synthesis of (*E*)-vinylsilane glycinate esters

Table 1.4 Summary of the esterification conditions.

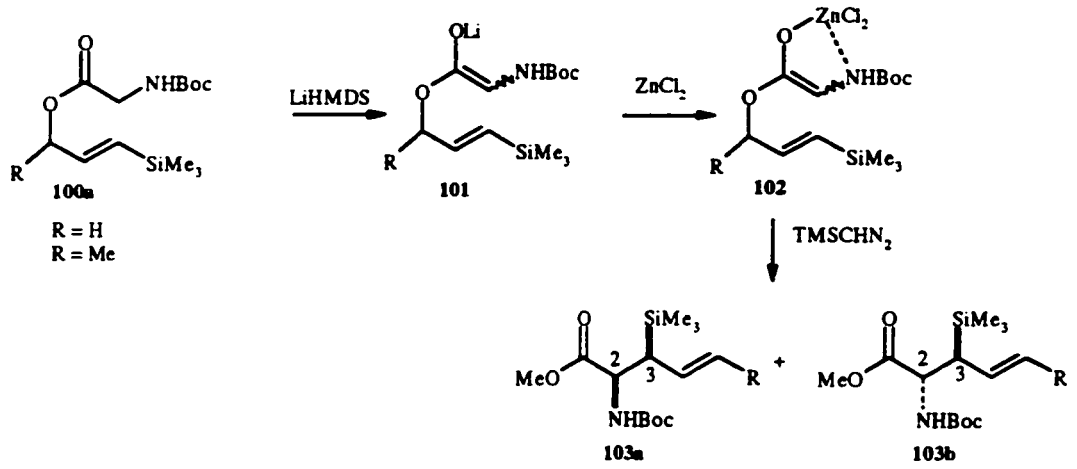
Alcohol	R_3Si	R	Solvent	PG	Yield of Ester
97a	Me_3Si	H	CH_2Cl_2	Boc	87
97b	Me_2CHMe_2Si	H	CH_2Cl_2		83
97c	Me_2PhSi	H	CH_2Cl_2		81
97d	*t*-$BuMe_2Si$	H	CH_2Cl_2		77
	Me_3Si	H	DMF		60
97e	Me_3Si	Me	CH_2Cl_2	Boc	82
"	"	"	DMF	Bz	74
"	"	"	DMF	Cbz	76
97f	Me_2CHMe_2Si	Me	CH_2Cl_2	Boc	80

1.7. 3. The Enolate Claisen Rearrangement of *E*-1-Silyl-vinylsilane Glycinate Esters (100a-f).

We examined the rearrangement of *N*-protected allylic glycinates (**100a-f**) and have observed in each case the diastereoselective formation of the α-amino acid. The enolate Claisen rearrangement of *E*-allylic glycinates afforded the *syn* isomer as the major product, while the *Z*-allylic glycinate gave the *anti* product, depending on the enolization conditions used. Our initial studies involved the investigation of a series of reaction protocols to establish the scope and limitation of the rearrangement. In the following section, we discuss the relationship between reaction conditions and degree of stereochemical control.

1.7. 4. Chelate Enolate Claisen Rearrangement of (100a) and (100e).

Initially, we studied the use of a zinc-chelated enolate for the rearrangement.[66] Kazmaier *et al.* reported higher yields and better diastereoselectivity in the rearrangement of glycinate esters in the presence of chelating salts such as $ZnCl_2$. With the amino acid derivatives under consideration, both $ZnCl_2$ and $MgBr_2$ led to an enhanced diastereoselectivity, but in both cases the yields were much lower than the traditional Ireland-Claisen procedure (**Table 1.5**).[67]



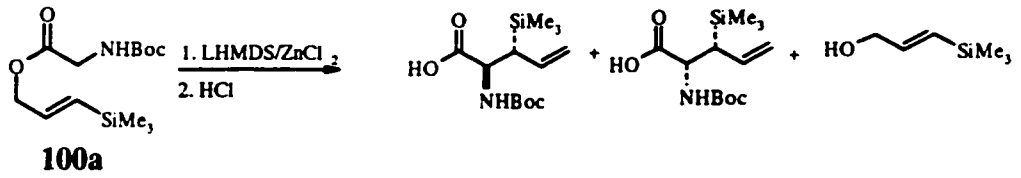
Scheme 1.20: Chelate-enolate Claisen rearrangement

The addition of LHMDS to a solution of allyl glycinate derivative (**100a**) at -78 °C, followed by addition of $ZnCl_2$ after 10 minutes, resulted in a clear yellow solution. The reaction was monitored by TLC and the formation of the product was observed after 4 hours, at which point the reaction temperature had reached -20 °C. The reaction mixture was allowed to warm up to room temperature overnight; work-up under acidic conditions resulted in the formation of products (**103a**), and (**103b**) in a *syn:anti* ratio of 25:1 (entry 1, **Table 1.5**).

Table 1.5 Summary of the chelate-Claisen conditions.

entry	Condition	R_3Si	Temp. °C	R	Time (h)	(Yield), *syn:anti* ratio
1	LHMDS/$ZnCl_2$	Me_3Si	-78 to rt		24	(30) 25:1
2	LHMDS/$ZnCl_2$	Me_3Si	-78 to 5	H	10	(50) 25:1
3	LDA/$ZnCl_2$	Me_3Si		Me		(57) 28:1
4	LDA/$MgBr_2$	Me_3Si		Me		(46) one isomer

Unfortunately, a substantial amount of starting ester decomposition was associated with this procedure and the combined chemical yield of the two isomeric amino acids was only 30% (**Scheme 1.21**). The yield of the product was improved to 50% when the reaction time was reduced to 10 hours instead of 24 hours, and the reaction was worked-up at 5 °C. However, the diastereoselectivity was unaffected (entry 2, **Table 1.5**). Similar reaction conditions were used for the rearrangement of (**100e**): addition of LDA to a solution of the ester followed by addition of $ZnCl_2$ led to formation of the product in a *syn:anti* ratio of 28:1 and 57% yield (entry 3, **Table 1.5**). When $MgBr_2$ was employed as the enolate trap, a better selectivity was obtained: only the *syn*-isomer was observed by GC. Unfortunately, the product yield was relatively low at 46%.



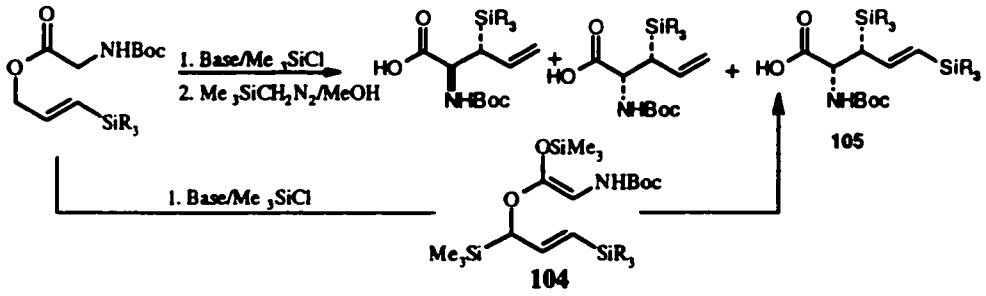
Scheme 1.21: Rearrangement of 100a

Next, we examined the Ireland-Claisen rearrangement of a series of glycinate esters with different silyl substituents and amine protecting groups. In general, good diastereoselectivity (19:1) and high yield (80%, entry 2) were observed by using the standard Ireland-Claisen rearrangement conditions (sequential addition of the ester to LHMDS and quenching with chlorotrimethylsilane).[61] Although the products were formed in moderate to excellent (3:1 > 22:1) diastereoselectivity and a good yield (62 - 79%), both the stereoselectivity and the yield improved when the reverse addition of the base to the ester was employed (29:1, 85%) (entry 1, **Table 1.6**). The product carboxylic acids were converted to the corresponding methyl esters, to facilitate characterization by treatment with trimethylsilyldiazomethane in methanol. The major isomer in each case was purified by flash chromatography.

1.7. 5. Influence of Base and Trapping agent on the Ireland-Claisen Rearrangement

To determine the role of the reaction conditions on diastereoselectivity in the ester enolate Claisen rearrangement of silylated, allyl amino acid esters (**100a-100f**), we examined the influence of the base/ester ratio in the enolization process and the enolate trap on the rearrangement of (**100a**) and have reported our preliminary results.[67] Initially, we employed standard reaction conditions involving addition of the ester to a

solution of LHMDS or LDA at -78 °C, followed by addition of the electrophile. This led to the rearrangement products in low yield (60%). Attempts to increase the yield by increasing the quantity of base used in the enolization process led to severely diminished yields. In the case of (**100a**), for example, excess base led to the formation of compound (**105**) in only 20% yield (entry 2, **Table 1.6**), which results from deprotonation of (**100a**) at the allylic position followed by silylation to give (**104**) and rearrangement as shown below; addition of Et_3N to the reaction mixture enhanced the reaction yield (**Scheme 1.22**). Reducing the amount of base to 2.5 equivalents in the enolization process (entry 1, **Table 1.7**) eliminated the formation of (**105**). Compounds such as (**105**) are not common side products in the Ireland-Claisen rearrangement. The more common side product results from silylation of the enolate carbon, a process that was not observed in our reactions.



Scheme 1.22: Mechanism for formation of 105

The combination of excess base (3.5 equiv.), prolonged reaction times and higher temperatures (60 °C, reflux) not only led to the formation of (**105**), but also resulted in the decomposition of the enolate intermediate via β–elimination,[68] which produced a

substantial amount of allylic alcohol, as observed by ^{1}H NMR analysis of the crude reaction mixture. Elimination of the allylic ether moiety apparently competes in certain cases with the rearrangement products.[69]

In all cases, the best results were obtained when 2.5 equivalents of base, either LDA or LHMDS, was employed: there is no significant difference in terms of yield and product diastereoselectivity between these two bases. LDA give slightly higher yields when combined with Et_3N. Addition of freshly prepared LDA to a THF solution of the ester at -78 °C, followed by immediate addition of chlorosilane, gave the silyl ketene acetal. This compound undergoes rearrangement at about -20 °C to the corresponding silyl ester, which was cleaved to the carboxylic acid during acidic work-up. For the purpose of purification and analysis, the crude products of the rearrangements were esterified by the treatment of trimethylsilyldiazomethane in methanol. The methyl ester was isolated in moderate to excellent yield (55–92%), depending on enolate trap. The product yield was significantly enhanced by the addition of Et_3N into the mixture two minutes after the chlorosilane addition. Attempts to use more electrophilic dichloro- or trichlorosilanes or bulkier monochlorosilanes which could improve the product diastereoselectivity, by encouraging chelation or introducing steric congestion in the transition state, respectively, were not successful and led to both diminished yields and diastereoselectivities (entries 4,5,6, **Table 1.6**).

Table 1.6 Summary of the Claisen rearrangement of (100a).

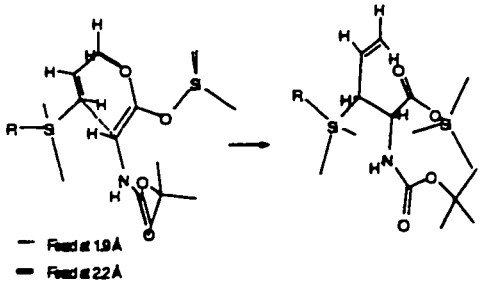
Entry	Conditions	(103) (yield) *syn/anti* ratio	Yield (105)
1	LDA (2.5 eq.)/Me_3SiCl (3 eq.)/Et_3N	(85) 29:1	
2	LDA (3.5 eq.)/Me_3SiCl (3.5 eq.)	(50)	20
3	LDA (2.5 eq.) /*t*-$BuMe_2SiCl$	(55) 5:1	
4	LDA/Ph_2SiCl_2	(42) 3:1	
5	LDA/Cl_3SiH	(40) 5:1	
6	LDA/$PhSiCl_3$	(34) 3:1	
7	LHMDS/Me_3SiCl	(79) 19:1	
8	inverse addition	(82) 29:1	
9	DMAP/TMSCl	9:1	
10	$PhMe_2SiCl$/ Et_3N	15:1	
11	*t*-$BuMe_2SiCl$/ Et_3N	(28) 2.6:1	

1.7. 6. Effect of the Silyl Group on Diastereoselectivity

The effect of different silyl groups on the starting ester (Me_3Si, *i*-$PrMe_2Si$, Me_2PhSi, *t*-$BuMe_2Si$) was studied to see if such groups could influence the diastereoinduction. It was expected that greater steric bulk on the silane would lead to an enhanced diastereoselectivity due to reduced degrees of freedom in the transition state of the Claisen rearrangement. In all the reaction conditions tested, the reactions of **(100a)** and **(100d)** showed the best stereoselectivity and gave the best chemical yields. In general, the use of other silyl groups led either to an erosion in yield or selectivity or both. As the size of the silyl group increased there was a dramatic decrease in reaction yield following the trend Me_3Si > *i*-$PrMe_2Si$ > Me_2Ph > *t*-$BuMe_2$ **(Table 1.7)**. Although there is a slight decrease in diastereoselectivity with increasing silyl group

size, the trend does not hold for the aromatic-containing silyl group (Me_2PhSi), which gave the lowest selectivity.

Simple molecular modelling[70] of the transition state (lengthening of the C-O bond, shortening of the =C···C= distance, dotted line, 1.9 Å, bold line 2.2 Å) following the work of Houk,[71] showed that in the first instance the silyl group is somewhat remote from the reaction center and secondly, the large group can avoid the reaction center by simple rotation (**Scheme 1.23**).



Scheme 1.23: Substituent effect on TS‡.

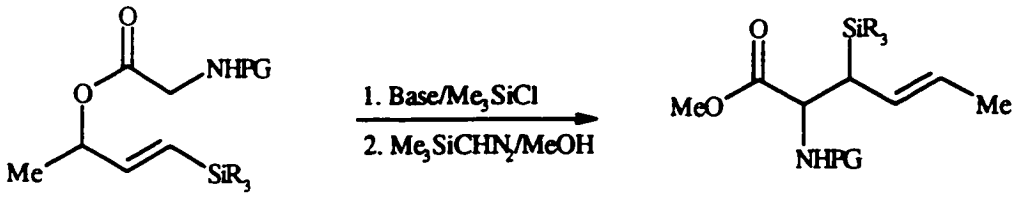
This suggests that size may not be the only significant factor on the diastereoselectivity of the reaction, given that *t*-$BuMe_2Si$ (16:1) and *i*-$PrMe_2Si$ (22:1) show comparable selectivities.

Table 1.7 Effect of the silyl group on the stereoselectivity of the rearrangement.

Entry	Compound	Conditions	R_3Si	*syn/anti* ratio
1	100c	Me_3SiCl/ Et_3N	$PhMe_2Si$	(62) 5.5:1
2	100d	Me_3SiCl/ Et_3N	*t*-$BuMe_2Si$	(40) 16:1
3	100b	Me_3SiCl/ Et_3N	*i*-$PrMe_2Si$	(66) 22:1

1.7. 7. Rearrangement of 100e

The optimized reaction conditions for compound (**100a**) were used for the rearrangement of (**100e**) and (**100f, Scheme 1.24**). In general, a notable increase in diastereoselectivity and reaction yield resulted from introduction of an α-methyl substituent into the allylic system (**100e-f**).



100e
PG = Boc, Bz, Cbz

R = Me103e PG = Boc

Scheme 1.24: Rearrangement of 100e

We examined the solvent effect on diastereoselectivity in the rearrangement of compounds (**100e**) and (**100f**). The rearrangement of (**100e**) in a THF / 23% HMPA mixture did not result in a reversal of stereochemistry: the product methyl ester was isolated in a *syn:anti* ratio of 23:1. However, compound (**100f**) showed almost no selectivity giving a 2:1 *syn:anti* ratio when a mixed solvent system was used THF/23

%HMPA, (entry 4, **Table 1.8**). The combination of LHMDS and bulky enolate trap (*t*-$BuMe_2SiCl$) did not lead to the formation of the rearranged product.

Table 1.8 Summary of the rearrangement conditions of 100e-f.

Entry	Compound	Conditions	R_3Si	*syn/anti* ratio	Yield
1	**100e**	A (reverse)	Me_3Si	One isomer	92
2		B (experimental section)		46:1	65
3		C (experimental section)			50
4		THF/HMPA(23%)		23:1	72
5	**100f**	THF/HMPA(23%)	*i*-$PrMe_2Si$	2:1	65
6		(reverse addition)		25:1	78

1.7. 7. Influence of the Amine Protecting Group on the Rearrangement

In order to establish the influence of the protecting group on the rearrangement and to ensure facile deprotection for future synthetic operations, we examined the rearrangement of Boc, Bz and Cbz-protected ester (**100e**). The *tert*-butoxycarbonyl (Boc) protected allyl glycinate derivative was superior in terms of both chemical yield and diastereoselectivity when compared to the other two protecting groups carbobenzoxy (Cbz) and benzoyl (Bz) (**Table 1.9**). Cbz and Bz-protected esters rearranged in comparable yield. Cbz was slightly more *syn:anti* selective than the Bz derivative (entry 3, **Table 1.9**). Bartlett and co-workers have observed similar results.[72] When more than three equivalents of base were employed in the enolization

process, deprotection of the Boc group was observed when the reaction was allowed to warm up to room temperature.

Table 1.9. Effect on rearrangement by amino protecting groups.

Entry	Condition	Protecting Group	Yield	Ratio (*syn/anti*)
1	LDA/TMSCl/Et_3N	Boc	92	32:1
2	LDA/TMSCl	Bz	71	9:1
3	LDA/TMSCl	Cbz	80	12:1

1.7. 8. Characterization: Assignment of the Stereochemistry

Proof of stereochemistry for methyl α-allylsilaneglycinates was obtained by two independent means. The diastereomeric ratio was determined by GC and ^{1}H NMR analysis. The major isomer of compound (**100a**), as the diisopropyl ammonium salt, and compound (**100b**), as the methyl ester, were submitted for X-ray crystallographic analysis. These results were correlated with the *J* coupling constants of the C2 and C3 protons (**Table 1.10**).[73] For the remaining examples, stereochemical assignment was based on ^{1}H NMR chemical shifts of the C3 methine proton, which distinguishes the *syn* and *anti* diastereomers (**Table 1.10**). In most cases, the vicinal coupling constants for the 2,3-*syn* diastereomer (zig-zag conformation as shown in **Figure 1.4**) are larger than for those of the 2,3-*anti* counterpart, and show a downfield shift relative to that of the *anti* isomer. The resonance of the C2 methine proton is not useful for stereoselectivity determination as it overlaps with the signals of the vinylic protons.

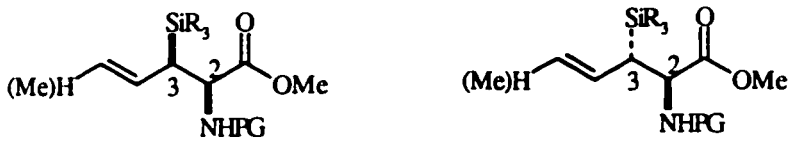
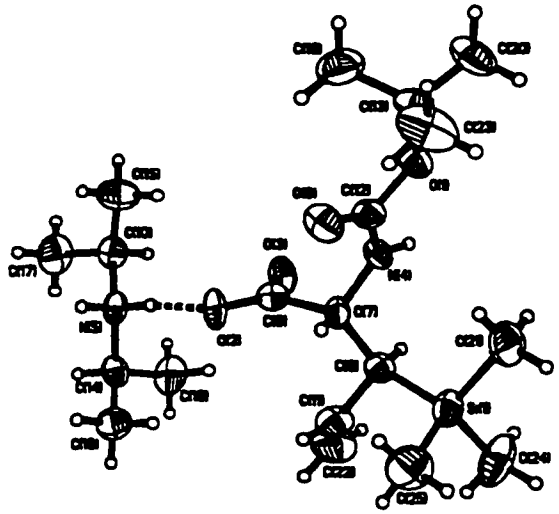


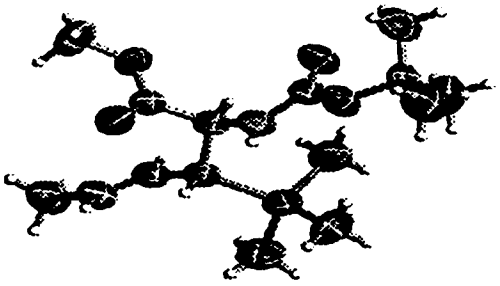
Figure 1-4: Zigzag conformation of 103a.

Table 1.10 $^3J_{2,3}$ and Chemical shift value for C2 and C3 ^{1}H.

Compound	SiR_3	PG	δ		$J_{2,3}$	
(Me)H			*syn*	*anti*	*syn*	*anti*
103a	Me_3Si	Boc	1.95	2.03	5.86	4.59
103b	*i*-$PrMe_2Si$		2.01		5.99	
103c	Me_2PhSi		2.18	2.29	6.37	5.28
103d	*t*-$BuMe_2Si$		2.16	2.41	6.87	4.40
(Me)H						
103l	Me_3Si	Boc	1.83		5.65	
103h	Me_3Si	Cbz	1.81		5.34	
103e	Me_3Si	Bz	1.98	2.07	5.37	5.16
103f	$Me_2CHSiMe_2$	Boc	1.88	1.79	6.94	5.33
103k	Me_3Si	Bz	2.10	2.17	5.36	5.60



Scheme 1.25 Crystal structure of diisopropyl ammonium salt of (103a)

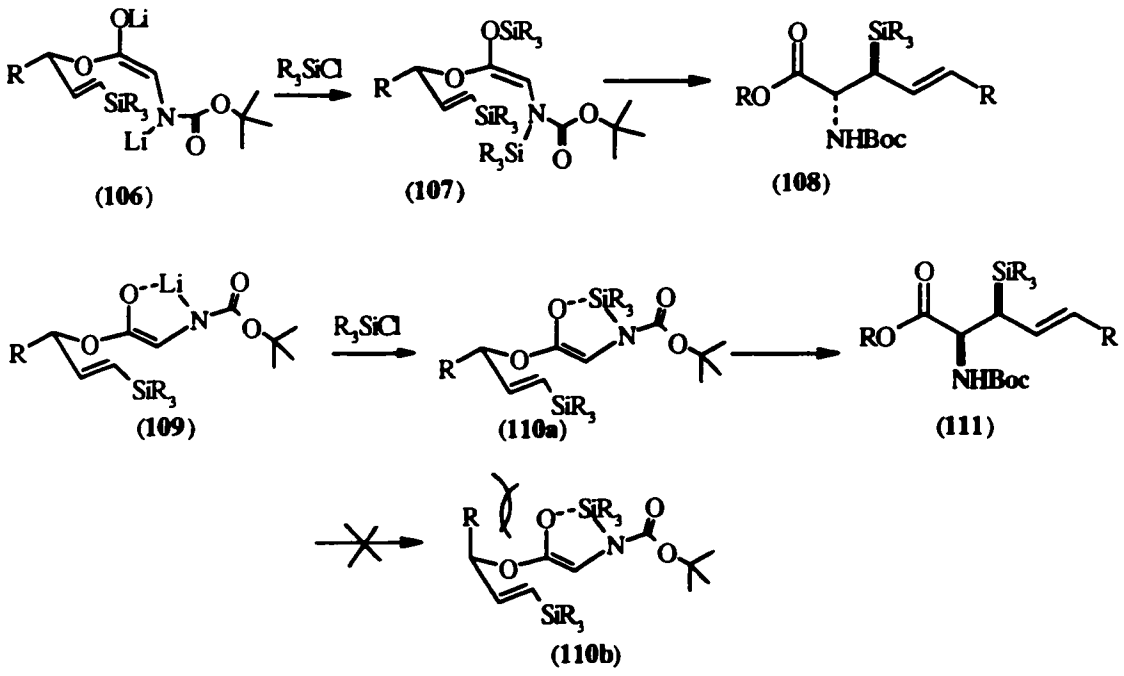


Scheme 1.26 Crystal structure of (103e)

The stereochemical outcome of the reaction can be explained by a comparison of the relevant transition states for the rearrangement. In general, a chair-like transition state is favored over the boat-like transition state.[74] The *syn* selectivity in the Claisen rearrangement product, when the starting ester contains α-heteroatom substituents such as nitrogen and oxygen, has been attributed to the formation of five-membered chelates, which give the *syn* isomer as the major product (**110**).[75] This is evident from our results of the rearrangement of the Boc-protected glycinate esters (**100a-f**). In all cases, the *syn* isomer was the major product using either set of reaction conditions; Ireland-Claisen and chelate-Claisen rearrangements. The low diastereoselectivity observed in the Cbz and Bz-protected glycinate esters may have its origin in the presence of the aromatic ring in the protecting groups. It is conceivable that the ring affects the nucleophilicity of the nitrogen atom, thus reducing its ability to coordinate to the silicon center, preventing chelation. It is well known that certain amines coordinate to tetravalent silicon centers to produce hypervalent silane species.[76] This Si-N interaction could be an additional stereocontrol element in the rearrangement. It is also possible that the aromatic rings of the protecting groups adopt a conformation that prevents chelation.

The involvement of a single predominant transition state under all the experimental conditions is indicated by the relationship between the allylic alcohol geometry (*E*-olefin) in the starting ester and the nature of the major *syn* diastereomer in the product. However, in the case of the Ireland-Claisen rearrangement the possibility of different

transition states, where there are two independent Li atoms involved, one on the oxygen and one on nitrogen (**106**), cannot be ruled out (**Scheme 1.27**). The observed diastereoselectivity is consistent with the expectation that the enolate geometry capable of supporting a cyclic chelate predominates. The chair-like transition state with the Me group in pseudoequatorial position (**110a**) is energetically favored over the transition state with the methyl group in a pseudoaxial position (**110b**) in the α-methyl substituted series (**100e**) and (**100f**), resulting in exclusive formation of the (*E*)-isomer of the newly formed double bond (**111**).



Scheme 1.27: Proposed transition state of the rearrangement of (100a-f)

1.7. 9. Conclusion

In the Ireland-Claisen rearrangement of vinylsilane glycinate esters, chlorotrimethylsilane was found to give the best yields and diastereoselectivities, which were comparable to those obtained when $ZnCl_2$ and other chelating salts are utilized. Enhancements of the diastereoselectivity by $ZnCl_2$ and $MgBr_2$ support the involvement of chelation in the transition state of the rearrangement; the diminished yield in these cases is probably due to decomposition of the enolate intermediate. The expectation that dichlorosilanes would work in a similar manner to $MgBr_2$ to encourage chleation and drive the rearrangement was not realized. Both the diastereoselectivity and chemical yield was found to depend on the electrophile as well as the presence of base additives such as Et_3N, and other reaction conditions.

1.8.1. EXPERIMENTAL

^{1}H and ^{13}C NMR spectra were recorded on Bruker AC-200 spectrometer with $CDCl_3$ or C_6D_6 as an internal standard. IR spectra were recorded on a Biorad spectrometer. Electron impact (EI) and chemical ionization (CI, NH_3) mass spectra were recorded at 70 eV with a source temperature of 200 °C on a VG Instruments analytical ZAB-R mass spectrometer equipped with a VG 11-250 data system. Gas chromatographic (GC) analyses were carried out using a Hewlett-Packard 5890A gas chromatograph equipped with a conventional heated injector, a flame ionization detector, a Hewlett-Packard 3393A integrator, and a DB-1 megabore capillary column (30m x 0.54mm Chromatographic Specialties, Inc.). Mass spectra and GC/MS analyses were recorded on a Hewlett-Packard 5890II gas chromatograph equipped with a HP-5971A mass selective detector and a DB-5 fused silica capillary column (30m x 0.25mm; Chromatographic Specialties, Inc.).

All reactions were performed with dry glassware under an atmosphere of anhydrous nitrogen. The following reagents were purchased from Aldrich and used without further purification: *N*-protected glycine, $ZnCl_2$, $MgBr_2$. Triethylamine and hexamethylphosphoramide (HMPA) were distilled from CaH_2. Diisopropylamine was distilled from NaOH. Propargyl alcohol and 3-butyn-2-ol were distilled from flame-dried glass wear prior to use. Tetrahydrofuran (THF) was distilled from sodium benzophenone ketyl under nitrogen just before use. TLC plates used for determining

reaction progress were aluminium sheets precoated with SiO_2 60 F_{254} as purchased from E. Merck, Darmstadt.

General procedure for the synthesis of silylated alcohols

1-(Trimethylsilyl)-1-propyn-3-ol (95a).

A three-neck, round-bottomed flask equipped with a magnetic stirring bar and dry nitrogen inlet, was fitted with a reflux condenser, a thermometer, and a septum. The apparatus was flushed with nitrogen and then charged with magnesium turnings (12.2 g, 50 mmol) and dry THF (50 mL). To the stirred suspension was added drop-wise bromoethane (37.3 mL, 50 mmol) over 1 h (via a syringe) maintaining the temperature at 37 - 47 °C. After complete addition, the gray suspension was heated at 50 °C for 1 h and then cooled to 5 °C on ice. A solution of propargyl alcohol (10.47 mL, 18.50 mmol) in THF (20 mL) was cautiously added drop-wise to the gray suspension over 1 h, maintaining the temperature at 10 °C. The gray suspension became very viscous, preventing movement of the stirring bar. Therefore, an additional 60 mL of THF was added: the solution remained heterogeneous. The reaction mixture was stirred overnight. The resultant solution was cooled to 5 °C on ice and 1.0 equivalent of chlorotrimethylsilane (6.35 mL, 50 mmol) was added dropwise over 1 h maintaining the temperature at 25 °C or less by external cooling with ice. After complete addition, the mixture was heated to reflux for 2 h with an oil bath. The suspension was cooled to 20 °C and then aqueous sulfuric acid (300 mL of a 1.4 M solution) was cautiously added over 1 h so that the temperature remained below 40 °C. The resulting solution

was stirred for 5 min. The organic layer was extracted with ether (3 x 100 mL), the ether layer was washed with 2 x 100 mL of water. The combined organic extracts were dried over $MgSO_4$ and solvent removed *in vacuo*. The yellow-brown residue was purified by short path distillation to afford colorless oil (21.5 g, 16.8 mmol, 90% yield).

^1H NMR (200 MHz, $CDCl_3$) δ 4.23 (s, 2H, C-1); 1.97 (s, 1H, OH); 0.14 (s, 9H, $(CH_3)_3Si$); ^{13}C NMR (50 MHz, $CDCl_3$) δ; IR ν_{max} 3331 (br, O-H), 2961, 2866, 2177, 1446, 1413, 1252, 1045, 983, 844, 761.

Synthesis of (*E*)-1-(Trimethylsilyl)-1-propen-3-ol (97a).

A two-neck, 500 mL round-bottomed flask fitted with a thermometer, septum, nitrogen inlet, and magnetic stirring bar was charged with sodium bis(2-methoxyethoxy)aluminum hydride (SMEAH, 47 mL of a 3.4 M solution, 160 mmol) and ether (65 mL). The SMEAH solution was cooled to 0 °C on ice and then treated dropwise from a syringe with a solution of 3-trimethylsilyl-2-propyn-1-ol (12.78 g,100 mmol) in ether (60 mL) over 30 min maintaining the temperature at 5 °C or less. After complete addition, the ice bath was removed. The reaction was complete within 1 h. The mixture was cooled to 0 °C and then quenched by the addition of aqueous sulfuric acid (200 mL of a 3.6 M solution). The organic layer was extracted with ether (2 x 100 mL). The organic extract was dried over anhydrous $MgSO_4$ and solvent was removed *in vacuo*. The yellow oil was purified on SiO_2 with 20-25% ethyl acetate/pentane to afford a colorless oil (9.1 g, 70 mmol, 70%).

^{1}H NMR (200 MHz, $CDCl_3$) δ 6.12 (dt, 1H, *J* = 4, 18 Hz); 5.86 (d, 1 H, *J* = 18 Hz); 4.12 (dd, 2 H, *J* = 4, 6 Hz); 0.18 (s, 9 H, $(CH_3)_3Si$); ^{13}C NMR (50 MHz, $CDCl_3$) δ 144.8, 129,2, 65.1, -1.45.

General Procedure for the Synthesis of Silylated Vinyl Glycinates.

An oven dried 250 mL round-bottomed flask equipped with a magnetic stir bar was charged with allylic alcohol (2.6 g, 20 mmol) and DMAP (0.20 g, 2.0 mmol). The flask was sealed with a rubber septum and dry CH_2Cl_2 (20 mL) was added. The resulting clear solution was allowed to stir for 15 min at room temperature. DCC (4.1 g, 20 mmol) in CH_2Cl_2 (10 mL) was added via syringe. The mixture was allowed to stir at 0 °C for 15 min before the *N*-protected glycine (20 mmol) in CH_2Cl_2 (10 mL) was added via syringe. The mixture was allowed to warm up to room temperature overnight. The precipitated urea was filtered off and the resulting clear yellow solution was washed with sat. $NaHCO_3$. After drying with $MgSO_4$, the solvent was removed *in vacuo*.

(*E*)-1-(Trimethylsilyl)-1-propen-3-yl [*N*-(*tert*-butoxycarbonyl)]glycinate (100a).

Purification on silica gel (ethyl acetate/pentane 1:4) afforded a colorless oil (5.0 g, 17.4 mmol, 87%). ^{1}H NMR (200 MHz, $CDCl_3$) δ 5.98-5.86 (m, 2H), 4.99 (br, 1 H), 4.63 (d, 2H, *J* = 3.9 Hz), 3.92 (d, 2H, *J* = 6.5 Hz), 1.42 (s, 9H), 0.06 (s, 9H); ^{13}C NMR (50.32 MHz, $CDCl_3$) δ 169.99, 155.58, 138.47, 134.19, 79.96, 67.50, 42.43, 28.28, -1.55; IR (neat) ν_{max} 3376, 2967, 1763, 1701, 1625, 1519, 1509, 1166; CIMS

(NH_3 gas) m/z, (relative intensity %), 305 ($M + NH_4^+$), 288 (M^+), 249(3), 232(14), 188(2), 176(30), 144(29), 130(5), 90 (40), 73(85), 57 (100); HRMS (M^+ +1) calculated for $C_{13}H_{25}O_4NSi$: 288.165, found: 288.163

(*E*)-1-(Dimethylphenylsilyl)-1-propen-3-ol [*N*-(*tert*-butoxycarbonyl)]glycinate (100c).

Purification on silica gel (ethyl acetate/pentane 1:4) afforded a colorless oil (5.90 g, 17 mmol, 81%); ^1H NMR (200 MHz, $CDCl_3$) δ 7.48 (m, 2H), 7.34 (m, 3H), 6.10 (dt, J = 3.4, 18.8 Hz, 1H), 5.94 (d, J = 18.8 Hz,1H), 5.06 (bs, 1H), 4.68 (b, J = 2.1 Hz, 2H), 3.93 (d, J = 3.4 Hz, 2H), 1.43 (s, 9H), 0.32 (s, 6H); ^{13}C NMR (50.32 MHz, $CDCl_3$) δ 169.97, 155.65, 140.31, 137.80, 133.73, 131.68, 129.11, 127.78, 79.93, 67.24, 42.37, 28.24, -2.86; IR ν_{max} 3380, 2977, 1719, 1167; CIMS (NH_3 gas) m/z, (relative intensity %) 350 (M + H, 12)$^+$, 278 (5), 216 (23), 176 (45), 57 (100).

(*E*)-1-(*tert*-Butyldimethylsilyl)-1-propen-3-yl [*N*-(*tert*-butoxycarbonyl)]glycinate (100d).

Purification on silica gel (ethyl acetate/pentane 1:4) afforded a colorless oil, R_f = 0.68; (20 % ethyl acetate/pentane). (5.89 g, 18 mmol, 77%); ^1H NMR (200 MHz, $CDCl_3$) δ 6.01 (td, J = 3.2, 12.5 Hz, 1H), 5.86 (d, 1H, J = 12.5 Hz), 5.14 (bs, 1H), 4.60 (d, J = 4.2 Hz, 2H), 3.87 (d, J = 3.2 Hz, 2H), 1.38 (s, 9H), 0.80 (s, 9H), -0.38 (s, 6H).; ^{13}C NMR (50.32 MHz, $CDCl_3$) δ 169.97, 155.68, 139.85, 131.27, 79.78, 67.47, 42.32, 27.75, 26.33, 16.25, -6.41: IR ν_{max} 3385, 2955, 2931, 1755, 1722, 1514; EIMS m/z, (relative intensity %) 330 (M + H, 11)$^+$, 289 (5), 274 (20), 216 (40), 116 (4), 73 (60), 57 (100).

(*E*)-1-(Dimethylisopropylsilyl)-1-propen-3-yl [*N*-(tert-butoxycarbonyl)]glycinate (100b).

Purification on silica gel (ethyl acetate/pentane 1:4) afforded a colorless oil, (6.57 g, 21 mmol, 83%); ^{1}H NMR (200 MHz, $CDCl_3$) δ 6.01 (dt, *J* = 4.5, 18.8 Hz, 1H), 5.84 (d, *J* = 18.8 Hz, 1H), 5.09 (b, H), 4.61 (d, *J* = 4.5 Hz, 2H), 3.88 (d, *J* = 5.5 Hz, 2H), 1.39 (s, 9H), 0.89 (s, 3H), 0.86 (s, 3H), 0.72 (m, 1H), -0.30 (s, 6H); ^{13}C NMR (50.32 MHz, $CDCl_3$) δ 169.97, 155.64, 139.46, 131.93, 79.83, 67.52, 42.37, 28.22, 17.37, 13.33, -5.55; IR ν_{max} 3379, 2955, 1721, 1167; CIMS (NH_3 gas), (relative intensity %) m/z 330 (3), 291 (5), 230 (81), 176 (100), 74 (58), 58 (29), 42 (12).

(*E*)-1-(Trimethylsilyl)-1-propen-3-yl [*N*-(Benzoyl)]glycinate (100g).

The crude product was purified by column chromatography on silica gel eluting with ethyl acetate/pentane (1:4), to give **100g**; R_f = 0.38 (30 % ethyl acetate/pentane), (5.2 g, 18 mmol, 60%).

^{1}H NMR (200 MHz, $CDCl_3$) δ 7.36-7.22 (m, 5H), 7.19 (b, 1H), 5.94 (dt, *J* = 4.3, 18.8 Hz, 1H), 5.84 (d, *J* = 18.9 Hz, 1H), 4.54 (d, *J* = 4.3 Hz, 2H), 4.10 (d, *J* = 5.3 Hz, 2H), 0.04 (s, 9H); ^{13}C NMR δ (50.32 MHz, $CDCl_3$) δ 169.72, 167.66, 138.46, 134.11,133.66, 131.59, 128.41, 127.11, 67.52, 41.74, -1.58; IR ν_{max} 3343., 2957, 1751, 1651, 1539; CIMS (NH_3 gas), (relative intensity %) m/z 292 (M + H, 10)$^+$, 276 (5), 236 (8), 206 (19), 162 (41), 105 (21), 73 (100).

(*E*)-1-(Trimethylsilyl)-1-propen-3-yl [*N*-(Benzyloxycarbony)]glycinate] (100h).

The crude product was purified by column chromatography on silica gel eluting with ethyl acetate/pentane (1:4), to give **100g**; R_f= 0.52 (30% ethyl acetate/pentane), (6.42, g, 20 mmol, 65%);

^{1}H NMR (200 MHz, $CDCl_3$) δ 7.26 (s, 5H), 5.99 (dt, *J* = 4.3, 18.8, Hz, 1H), 5.89 (d, *J* = 18.8 Hz, 1H), 5.33 (bs, 1H), 5.06 (s, 2H), 4.60 (d, *J* = 4.2 Hz, 2H), 3.94 (d, *J* = 5.4 Hz, 2H), 0.02 (s, 9H); ^{13}C NMR (50.32 MHz, $CDCl_3$) δ 169.68, 156.27, 138.427, 136.26, 134.37, 128.50, 128.14, 128.06, 67.63, 67.06, 42.76; -1.53; IR ν_{max} 3360, 2956, 1777, 1529, 1249, 1193; CIMS m/z, (relative intensity %) 339 $(M + H)^+$ (6), 322 (25), 278 (22), 131 (12), 91 (100).

(*E*)-1-(Trimethylsilyl)-1-buten-3-yl [*N*-(Benzyloxycarbonyl)]glycinate] (100e).

The crude product was purified by column chromatography on silica gel eluting with ethyl acetate/pentane (1:4), to give **100e** (8.71, g, 26 mmol, 76%), as a colorless oil. ^{1}H NMR δ 7.32-7.24 (5H, Ar), 5.96 (dd, 1H, *J* = 4.8, 18. 8 Hz), 5.83 (d, 1H, *J* = 18.8 Hz), 5.38-5.09 (m, 1H), 3.94 (d, 2H, *J* = 5.4 Hz), 1.28 (d, 3H, *J* = 6.47 Hz), 0.49 (s, 9H). ^{13}C NMR (50.32 MHz, $CDCl_3$) δ 169.13, 156.20, 143.81, 136.24, 131.33, 128.41, 128.04, 127.95, 73.59, 66.92, 42.89, 19.67, -1.57; CIMS (NH_3) m/z, (relative intensity %) 353 $(M + NH_4^+$, 10), 336 (20), 291 (18), 268 (42), 227 (6), 210 (40), 108 (28), 91 (45), 73;

(*E*)-1-(Trimethylsilyl)-1-buten-3-yl [*N*-(*tert*-butoxycarbonyl)glycinate] (100e).

The rude product was purified by column chromatography on silica gel eluting with ethylacetate/pentane (1:4), to give **100e** (9.0, g, 30 mmol, 82%), as a colorless oil.

^{1}H NMR (200 MHz, $CDCl_3$) δ 5.91 (dd, J = 4.34, 18.88 Hz, 1H), 5.77 (d, J = 18.88 Hz, 1H), 5.31 (m, 1H), 5.18 (bs, 1H), 3.84 (d, J = 5.52 Hz, 2H), 1.37 (s, 9H), 1.24 (d, J = 6.5 Hz, 3H), 0.01 (s, 9H); ^{13}C NMR (50.32 MHz, $CDCl_3$) δ 169.49, 155.61, 143.86, 131.09, 79.70, 73.35, 42.52, 28.19, 19.66, -1.57; IR ν_{max} 3375, 2959, 2980, 1753, 1721, 1518, 1170; CIMS (NH_3 gas), (relative intensity %) m/z, 214 (8), 120 (42), 73 (100), 57 (71).

(*E*)-1-(Dimethylisopropylsilyl)-1-buten-3-yl [*N*-(*tert*-butoxycarbonyl)glycinate] (100f).

The crude product was purified by column chromatography on silica gel eluting with ethyl acetate/pentane (1:4), to give **100f**; R_f = 0.68 (7.2 g, 22 mmol, 80%), as a colorless oil.

^{1}H NMR (200 MHz, $CDCl_3$) δ 5.98 (dd, 5.0, J = 18.83 Hz, 1H), 5.82 (d, J = 18.9 Hz, 1H), 5.41-5.33 (m, 1H), 5.02 (b, 1H), 3.90 (d, J = 3.4 Hz, 2H), 1.44 (s, 9H), 1.30 (d, J = 6.5Hz, 3H), 0.92 (d, J = 7.12 Hz, 6H), 0.81-0.72 (m, 1H), 0.01 (s, 6H); ^{13}C NMR (50.32 MHz, $CDCl_3$) δ 169.79, 155.93, 145.24, 129.39, 80.13, 73.91, 42.91, 28.54, 20.12, 17.67, 13.68, -5.22; IR ν_{max} 3377, 280, 1722, 1514, 1250, 1171; EIMS m/z (relative intensity %) 330 (M + H, 22)$^+$, 274 (11), 230 (95), 176 (78), 73 (30), 57 (100); CIMS (M + NH_4^+) 347.

Conditions for the ester enolate Claisen rearrangement.

In a typical experiment, freshly distilled diisopropylamine (0.35 mL, 2.5 mmol) was added to *n*-butyllithium (1.5 mL of a 1.6 M solution in hexane, 2.5 mmol) at 0 °C. The reaction mixture was stirred for 10 min at 0 °C, the cooling bath was removed and the reaction was stirred for a further 15 min at room temperature.

Method A: the silylated allylic ester (1 mmol) was added to a freshly prepared lithium diisopropylamide solution (2.5 mmol) in THF (5 mL). Chlorotrimethylsilane (0.38 mL 3 mmol) was added after 3 minutes. The resulting yellow solution was diluted with ethyl acetate and hydrolyzed with 1 N hydrochloric acid. The aqueous layer was extracted with ethyl acetate (2 x 5 mL), the combined organic layers were dried over $MgSO_4$, and the solvent was removed *in vacuo*.

Method B: To a solution of potassium hexamethyldisilazide in anhydrous THF (25 mL) at -78 °C was added chlorotrimethylsilane. After 5 min, a solution of the ester in THF (2 mL) was added dropwise. The solution was then allowed to warm up to room temperature overnight, mixed with 1N HCl and stirred for 10 min. The mixture was extracted twice with sat. $NaHCO_3$ solution.

Method C: A solution of lithium hexamethyldisilazide in hexanes (1.0 M, 3.3 mL, 3.3 mmol) in anhydrous THF (2 mL) at -78 °C was added to the ester (0.37 g, 1.3 mmol). After 3 min, TMSCl (0.49 mL, 0.39 mmol) was added, followed by addition of Et_3N

(0.54 mL, 0.39 mmol). The solution was stirred for 10 min, and the cooling bath was removed. The solution was diluted with ethyl acetate (2 mL), and 1N HCl solution (4 mL), and stirred vigorously for 10 min. The aqueous layer was extracted with ethyl acetate (2 x 5 mL). The combined organic layers were dried over $MgSO_4$, and the solvent was removed *in vacuo*.

Method D: A freshly prepared lithium diisopropylamide solution (2.5 mmol) in THF (5 mL) was added to a stirred mixture of silylated allyl ester (1 mmol) and $MgBr_2$ or $ZnCl_2$ (0.20 g and 0.15 g, respectively, 1.1 mmol) in dry THF (2 mL) at -78 °C. The mixture was allowed to warm up to room temperature overnight. The resulting yellow solution was diluted with ethyl acetate and hydrolyzed with 1 N hydrochloric acid.

(*E*)-Methyl 2-(*tert*-butyloxycarbonyl)-3-(trimethylsilyl)pent-4-enoate (103a)

Crude product was purified by column chromatography on silica gel eluting with (25% ethyl acetate/pentane) to give **103a**, (0.35 g, 1.1 mmol, 85%), as a colorless oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ 5.55 (m, 1H), 5.12 (s, 1H), 4.97 (dd, 2H, J = 16.8, 10.7 Hz), 4.37 (m, 1H), 3.65 (s, 3H), 1.91 (dd, 1H, J = 8.6, 16.0 Hz), 1.38 (s, 9H), 0.03 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.68, 154.98, 134.05, 116.79, 79.86, 53.75, 51.77, 39.75, 28.30, -2.54; IR ν_{max} 3443, 2957, 1741, 1251; CIMS (NH_3 gas) *m/z* 318 (5), ($M + NH_4^+$), 302 (5.3), 246 (14), 202 (3.7), 186 (27), 112 (92), 73 (94), 57 (100); calculated for $C_{14}H_{28}NO_4Si$ 302.1788, found 302.1775.

(*E*)-Methyl 2-(*tert*-butyloxycarbonyl)-3-(dimethylphenylsilyl)pent-4-enoate (103c)

The crude product was purified by column chromatography on silica gel eluting with (25% ethyl acetate/pentane), to give **103c**, (0.62 g, 0.25 mmol, 65%), as a colorless oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.50 (d, 2H, *J* = 3.4 Hz), 7.19 (m, 3H), 5.59 (m, 1H), 5.02 (dd, 1H, *J* = 1.6, 10.1, Hz), 4.90 (b, 1H), 4.90 (dd, 1 H, *J* = 1.2, 16.9, Hz), 4.37 (bm, 1H), 3.53 (s, 3H), 2.18 (dd, 1H, *J* = 6.4 10.3, Hz), 0.98 (s, 3H), 0.04 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.54, 154.87, 137.01, 134.07, 129.24, 127.78, 117.04, 79.78, 54.01, 51.64, 39.40, 28.30, -3.85, -4.19; IR ν_{max} 3441, 2984, 1742, 1373, 1242; EIMS. 364 (M + H, 32)$^+$, 308 (26), 264 (54), 230 (100), 186 (15), 170 (66), 135 (142), 81 (17), 69 (9). HRMS calculated for $C_{17}H_{33}NO_4Si$: 364.1589, found: 364.1944.

(*E*)-Methyl 2-(*tert*-butyloxycarbonyl)-3-(*tert*-butyldimethylsilyl)pent-4-enoate (103d)

The crude product was purified by column chromatography on silica gel eluting with (25% ethyl acetate/pentane), to give **103d**, (0.14g, 0.40 mmol, 40%), as a colorless oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ 5.60 (m, 1H), 5.32 (b, 1H), 4.77 (m, 3H), 3.25 (s, 1H), 2.16 (dd, 1H, *J* = 6.9 16.8, Hz), 1.42 (s, 9H), 0.899 (s, 9H), 0.12 (s, 3H), 0.01 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.11, 155.11, 135.81, 117.59, 79.44, 54.60, 51.17, 37.16, 27.46, 27.28, 18.56, -6.80, -7.79; IR ν_{max} 3444, 2957, 1718, 1491, 1366; EIMS 344 (M + H)$^+$, 287 (2), 270 (3), 230 (32), 170 (21), 154 (16), 118 (44),

81 (53), 73 (100), 57 (89), 41 (33). HRMS calculated for $C_{17}H_{34}O_4NSi$: 344.1762 (M + H)$^+$, found: 344.2257.

(*E*)-Methyl 2-(*N*-phenylcarbonyl)-3-(trimethylsilyl)hex-4-enoate (103l).

The crude product was purified by column chromatography on silica gel eluting with (25% ethyl acetate/pentane), to give **103l**, (0.22g, 0.71 mmol, 71%), as a colorless oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.29 (m, 5H), 5.33 (m, 1H), 5.23 (m, 1H), 5.06 (m, 2H), 4.37 (bm, 1H), 3.65 (s, 1H), 1.80 (dd, 1H, J = 5.4, 10.7 Hz), 1.61 (dd, 3H, 1.2, 6.3 Hz), -0.03 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.20, 166.39, 133.90, 131.50, 128.44, 128.15, 127.89, 126.88, 125.95, 52.85, 51.78, 37.92, 17.99, -2.52; IR ν_{max} 3351, 2955, 1744, 1652, 1526, 1249;

(*E*)-Methyl 2-(*N*-carbobenzyloxy)-3-(trimethylsilyl)hex-4-enoate (103h).

The crude product was purified by column chromatography on silica gel eluting with (25% ethyl acetate/pentane, R_f = 0.71), to give **103h**, (0.36 g, 1.0 mmol, 80%), as a colorless oil.

^{1}H NMR (300MHz, $CDCl_3$) δ 7.25 (m, 5H), 5.36 (m, 2H), 5.08 (m, 3H), 4.35 (b, 1H), 3.64 (s, 3H), 1.81 (dd, 1H, J = 5.4, 10.6 Hz), 1.61 (dd, 3H, J = 1.4, 6.4 Hz), 0.05 (s, 9H); ^{13} C NMR (75 MHz, $CDCl_3$) δ 172.29, 155.48, 136.29, 128.41, 128.18, 128.07, 125.67, 66.83, 54.29, 51.73, 38.03, 33.56, 29.60, 16.40, -2.54; IR ν_{max} 3351, 2955,

1726, 1503, 1250, 842; EIMS, 350 (M^+, 4), 290 (3), 258 (5), 199 (3), 91 (100), 73 (51).

(*E*)-Methyl 2-(*N-tert*-butylcarbonyl)-3-(trimethylsilyl)hex-4-enoate (103e).

The crude product was purified by column chromatography on silica gel eluting with (25% ethyl acetate/pentane, $R_f = 0.83$), to give **103e**, (0.43 g, 1.4 mmol, 92%), as a colorless oil.

^{1}H NMR (75 MHz, $CDCl_3$) δ 5.39 (m, 1H), 5.17 (m, 1H), 5.02 (b, 1H), 4.35 (b, 1H), 3.70 (s, 3H), 1.83 (dd, 1H, J = 5.7, 10.6 Hz), 1.67 (d, 3H, J = 6.34 Hz), 1.43 (s, 9H), 0.05 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.49, 155.61, 143.85, 131.09, 79.70, 73.35, 42.52, 28.20, 19.66, -1.57; IR ν_{max} 3439, 2980, 1710, 1497, 1250, 842; HRMS, calculated for $C_{15}H_{29}NO_4Si$ 316.1668, found: 316.1638; EIMS 316 (M + H, 2)$^+$, 198 (6), 156 (5), 134 (21), 111 (82), 95, 73 (80), 57 (100).

(*E*)-Methyl 2-(*N-tert*-butylcarbonyl)-3-(dimethylisopropylsilyl)hex-4-enoate (103f).

The crude product was purified by column chromatography on silica gel eluting with (25% ethyl acetate/pentane, $R_f = 0.81$), to give **103h**, (0.41 g, 1.2 mmol, 78%), as a colourless oil;

^{1}H NMR (300 MHz, $CDCl_3$) δ 5.38-2.24 (m, 1H), 5.17-5.08 (m, 1H), 5.02-4.49 (m, 1H), 4.26 (b, 1H), 3.61 (s, 3H), 1.88 (dd, 1H, J = 6.0, 10.8 Hz), 1.60 (d, 3H, J = 5.1 Hz), 1.36 (s, 9H), 0.86 (s, 6H); ^{13}C NMR NMR (75 MHz, $CDCl_3$) δ 172.79, 154.94, 127.72, 126.36, 79.70, 53.93, 51.59, 35.71, 28.27, 17.62, 17.47, 12.00, -6.64; EIMS,

344 (M + H, 6)$^+$, 288 (22), 270 (7), 244 (24), 126 (43), 95 (100), 73 (70), 57 (100); HRMS, calculated for $C_{17}H_{34}NO_4Si$ 344.224 (M^+ + H), found 344.225.

Methyl 2-(*N*-phenylcarbonyl)-3-(trimethylsilyl)pent-4-enoate 103k

Crude product was purified by column chromatography on silica gel eluting with (25% ethyl acetate/pentane, R_f = 0.71), to give (0.16 g, 0.51 mmol, 47%) of product, as a colorless oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ 6.71 (d, 1H, *J* = 7.8 Hz), 5.64 (1H, m), 5.07 (dd, 1H, *J* = 1.9, 10.1, Hz), 4.99 (dd, 1H, *J* = 1.5, 16.7 Hz), 4.91 (dd, 1H, *J* = 5.4, 8.1 Hz), 2.10 (dd, 1H, *J* = 5.4, 11.0, Hz); ^{13}C NMR (50.32 MHz, $CDCl_3$) 172.30, 166.68, 134.14, 131.85, 128.71, 127.12, 117.43, 65.61, 52.88, 41.98, 39.92, -2.39; IR ν_{max} 3437, 3020, 2958, 1742, 1161, 1518, 1486, 1216.

1.9. References

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Chapter 2

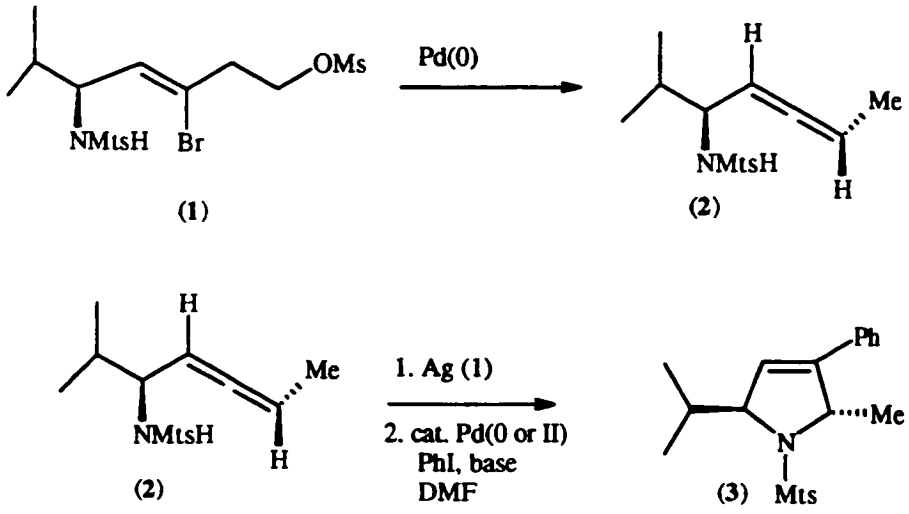
Synthesis of α-(3,5-bis(silyl)allenyl)-amino acid derivatives

Abstract

Propargylsilane glycinate ester (**19**) undergoes [3,3]-sigmatropic rearrangement in the presence of excess lithium diisopropylamide and excess trialkylchlorosilane (3.5 equivalents of each) to give α-(3,5-bis(silyl)allenyl)-amino acid derivatives in moderate to good yield (30 to 85%) and in high diastereoselectivity (9:1 to 22:1) depending on the enolate trap; the stereochemical outcome of the product was deduced from single crystal X-ray crystallographic analysis of compound (**20**).

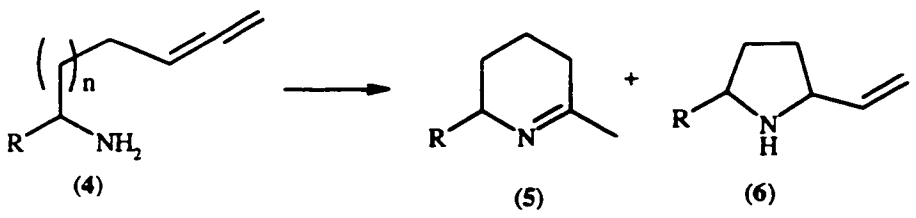
2. 1. Introduction

α-Aminoallenes are important for medicinal chemistry. Such molecules are known to exhibit biological activity in their own right, and they are also versatile intermediates for the synthesis of three-,[1] four-,[2] five-,[3] and six-membered azacycles,[4] as demonstrated by different groups. Ibuka *et al.*[1] have developed synthetic strategies for the preparation of aminoallenes and further showed that the Pd (0 or II)-catalyzed intramolecular cyclization of aminoallene (**2**) led to substituted pyrrolines (**3**) in high yield and with good enantioselectivity.



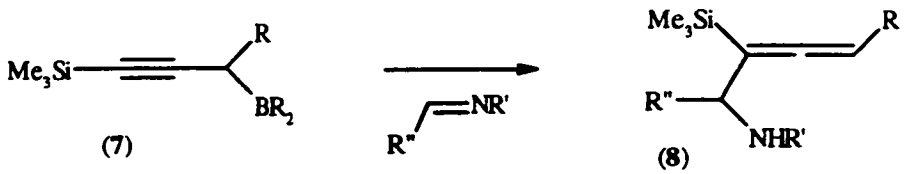
Scheme 2. 1: Synthesis of aminoallenes.

Marks *et al.* reported the catalytic hydroamination/cyclization of aminoallenes mediated by organolanthanides to access important 5- and 6-azacycles present in natural products (Scheme 2. 2).[4]



Scheme 2. 2: Cyclization reaction of aminoallenes

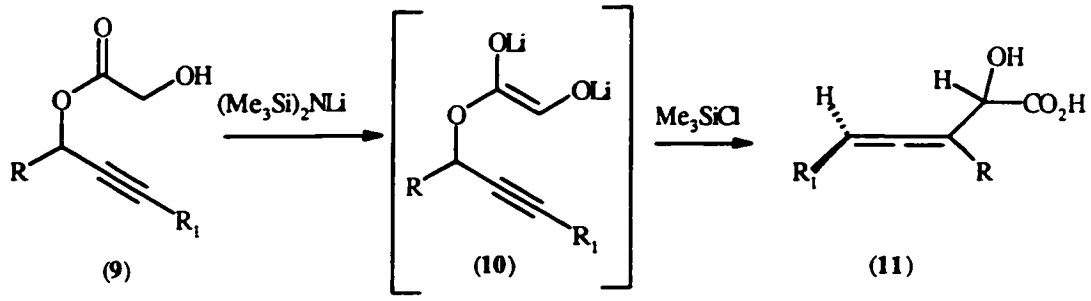
In general, allenic structures are prepared by the reactions of metals with propargylic species.[5] Nikam and Wang reported the addition of a boron reagent to C=N bonds: the reaction of imines with an organoborane derived from 1-trimethylsilyl-1-alkynes led to the formation of α-aminoallene product (**8**) (Scheme 2. 3).[6]



Scheme 2. 3: Synthesis of α-silylallene-amines

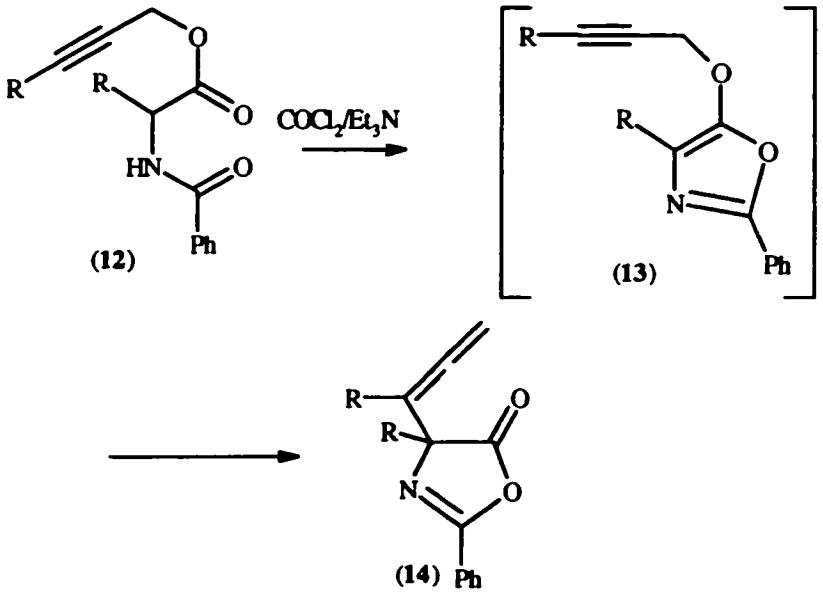
In connection with our program for the synthesis of silicon-containing γ,δ-unsaturated amino acids and functionalized allenylsilanes, we surmised that allenylsilane-containing amino acids could be synthesized via the Claisen rearrangement.

Fujisawa and co-workers previously reported the ester enolate Claisen rearrangement of propargylic glycolate esters (**Scheme 2. 4**).[7]



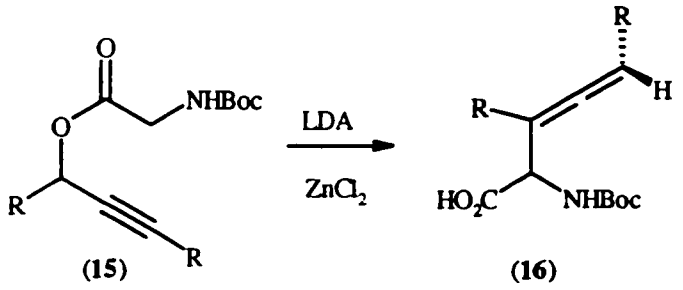
Scheme 2. 4: Claisen rearrangement of propargyl glycolates

Steglich *et al.* reported an alternative method for allene synthesis mediated by oxazolones.[8] Treatment of propargylic esters (**12**) of *N*-benzoylamino acids with a dehydrating agent resulted in the formation of allenic oxazolones (**14**) via a propargyloxyoxazole intermediate (**13**).[8] However, this procedure is limited to amino protecting groups that are capable of forming oxazolones (Scheme 2. 5).



Scheme 2. 5: [3, 3]-sigmatropic rearrangement of propargyloxyoxazole.

Kazmaier and co-workers have recently reported a variation of the ester Claisen rearrangement that they developed using $ZnCl_2$ and other chelating metal salts. Deprotonation of *N*-protected propargyl glycinate with LDA at -78 °C and subsequent addition of metal salts such as $ZnCl_2$ led to the formation of α-alleneamino acids in good yield and with high diastereoselectivity (**Scheme 2. 6**).[9]



(15) (16)

Scheme 2. 6: Chelate-enolate Claisen rearrangement of propargyl glycinate

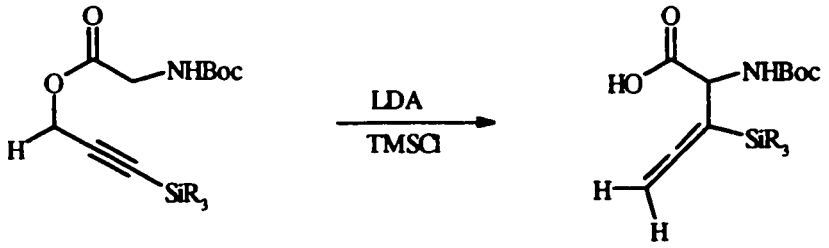
Prior to our study, Castelhano and co-workers[10] successfully synthesized α-allenicamino acids via the oxazolone method (**Scheme 2. 5**). However, they were unable to obtain an appreciable yield via the Ireland-Claisen rearrangement of the propargylic glycinate esters. Other groups also reported a lack of success in the Ireland-Claisen rearrangement of propargylic esters.[11] The major problem of the reaction is the competitive deprotonation of the propargylic proton. These results discouraged us from using the Ireland-Claisen procedure for translocation of the three-carbon residue from the ester oxygen to the α-position, which is accompanied by the conversion of the propargyl to the allenyl functionality. The orthoester Claisen rearrangement is usually the preferred method for the [3, 3]-sigmatropic rearrangement of propargylic esters.[11]

Having demonstrated, the efficient preparation of α-allylsilylamino acids by the Claisen rearrangement in Chapter one it was of interest to establish if the same levels of

geometric and diastereoselectivity could be achieved in the synthesis of α-silylallenylamino acids.

2. 2. Results and Discussion

The starting esters, necessary for the Claisen rearrangement, are accessible from the condensation of *N*-protected amino acid and the corresponding alcohol using DCC and DMAP.[12] In order to avoid the problems noted above with the Ireland-Claisen rearrangement, we employed the method of Kazmaier to effect the rearrangement of propargyl glycinate ester (**17**) to give the terminal allenyl amino acid (**18**). The reaction was carried by addition of ester (**17**) to a freshly prepared solution of LDA, followed by the addition of $MgBr_2$ in THF solution. Progress of the reaction was monitored by TLC; only starting material was observed after 10 hours at -78 °C. When the reaction mixture was allowed to warm up to room temperature overnight, a lower product yield was obtained due to competing deprotection of the Boc group.



$R_3Si = Me_3Si$ **17a**
$R_3Si = i\text{-}PrMe_2Si$ **17b**

$R_3Si = Me_3Si$ **18a**
$R_3Si = i\text{-}PrMe_2Si$ **18b**

Scheme 2. 7: Claisen rearrangement of (17a) and (17b)

We were not able to achieve reproducible results in the chelate-Claisen rearrangement of (**17**). However, we were encouraged by the results of Fujisawa *et al.*[7] for the

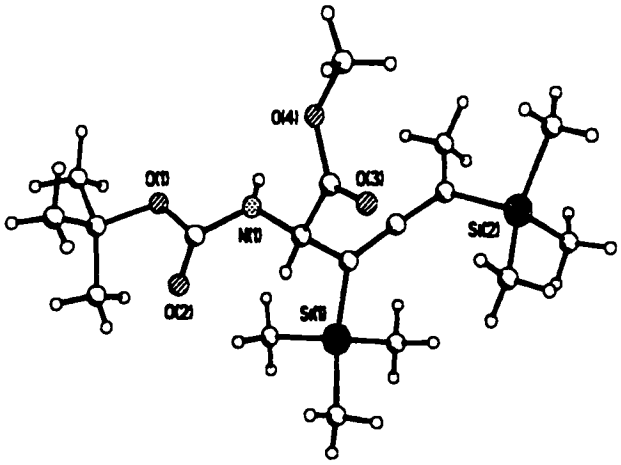
rearrangement of propargyl glycolate esters (**Scheme 2. 4**). We therefore next employed the Ireland-Claisen rearrangement of (**17a**) with different bases and reaction conditions in the hope that rearrangement could be effected by these parameters. Treatment of ester (**17a**) with 2.5 equivalents of freshly prepared LDA in THF at -78 °C followed by the addition of chlorotrimethylsilane to quench the dianion, after 24 hours, gave a mixture of products that included 10% of desired product **18a**, and 30% of recovered starting ester (**Table 2.1**). Increasing the amount of base used, from 2.5 to 3 equiv., at -78 °C, then warming up to room temperature after five hours gave a mixture of products. Analysis of the crude ^{1}H NMR showed similar product mixtures as before, although there was less starting material present. With the rearrangement of (**17b**), results were somewhat more positive and we were able to isolate product (**18b**) in a very low yield (**Scheme 2. 7**).

Table 2. 1: summary of the rearrangement of (17a).

Condition	R_3Si	Product
LDA/ $MgBr_2$	Me_3Si	No product
LDA/ TMSCl	Me_3Si	10%
LDA/ TMSCl	*i*-$PrMe_2Si$	30%

Different results were obtained when the α-methyl-substituted propargyl glycinate ester (**19**) was subjected to the Ireland-Claisen rearrangement (sequential addition of the ester to LDA and quenching with trialkylchlorosilane at -78 °C); the formation of one major product was observed. The carboxylic acid product was converted to its methyl ester with trimethylsilyldiazomethane in MeOH. ^{1}H NMR analysis of the crude product showed one

set of signals in addition to unreacted starting material. However, GC analysis of the crude reaction mixture showed a 36:3 ratio of two diastereoisomeric products. Chromatographic isolation of the major isomer and ^{1}H NMR analysis showed the presence of two different TMS groups, which was confirmed by mass spectrometric analysis. However, we were unable to assign the relative stereochemistry and structure of the product from ^{1}H and ^{13}C NMR data alone. Fortunately, colorless crystals were obtained after recrystallization of the major isomer from hexane solution, one of which was submitted for a single crystal X-ray analysis to permit the identification of the product bis(trimethylsilyl)allenyl amino acid with the *syn*-configuration (**20**).[13]



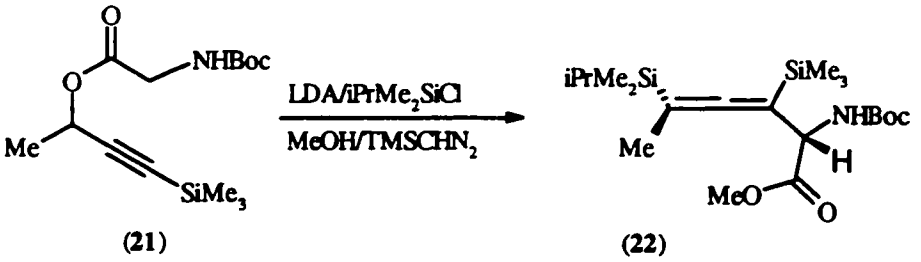
Scheme 2. 8: Crystal structure of (20)

The yield of (**20**) was further improved to 85% by increasing the amount of base and enolate trap used in the enolization process up to 4 equiv. of LDA and an excess amount of chlorosilane (4 equiv.).

(19) (20)

Scheme 2. 9: Ireland-Claisen rearrangement of (19)

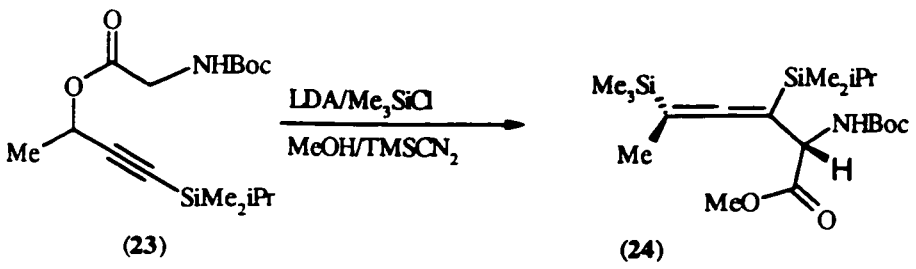
When bulkier chlorosilanes such as *t*-$BuMe_2SiCl_2$ and $PhMe_2SiCl$ were used as trapping agents, either to follow the rearrangement or synthesize the bis(silyl)allene analogues of (**20**), only unreacted ester was recovered. Prolonged reaction times at room temperatures led to the formation of an intractable mixture of products. However, when Me_2*i*-PrSiCl was used as the trapping agent, the bissilylated product (**22**) was isolated in good yield (72%) and with excellent diastereoselectivity (22:1 **Scheme 2. 10**).



(21) (22)

Scheme 2. 10: Ireland-Claisen rearrangement of (21)

Similar reaction conditions as for (**19**) were used for the rearrangement of (**23**). The product (**24**) was isolated in 78% yield with 9:1 diastereoselectivity. Both compounds (**22**) and (**24**) have identical NMR and GC retention times (**Table 2. 2**).



(23) (24)

Scheme 2. 11: Ireland-Claisen rearrangement of (23)

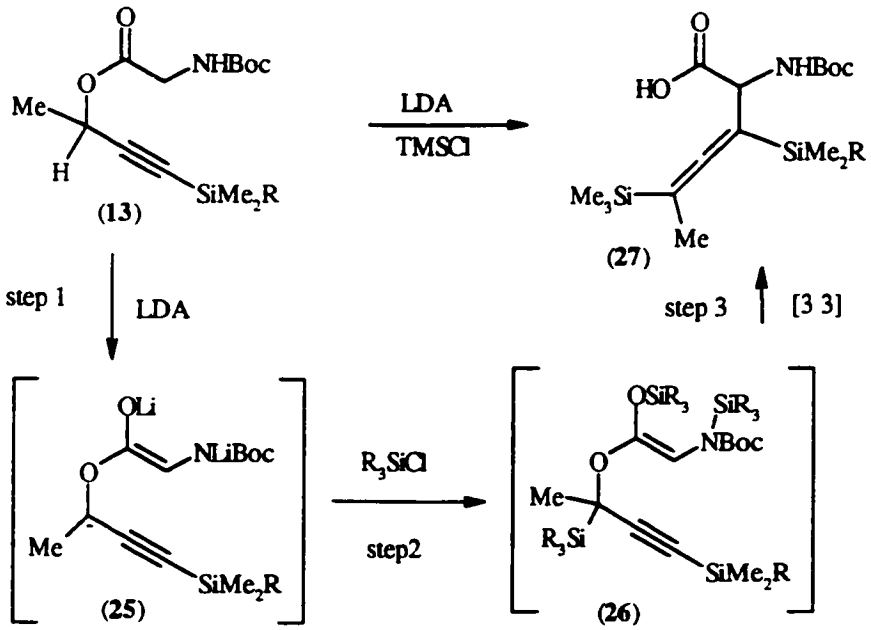
All attempts to perform the Ireland-Claisen rearrangement on Cbz- and Bz-protected glycinate esters meet with failure. Mostly, starting material was recovered or the yield of the product was very low.

Table 2. 2: summary of the rearrangement of (19), (23).

Condition	R_3Si	(yield) *syn:anti*
LDA (2.5 eq)/TMSCl	Me_3Si	Complex mixture
LDA (2.5 eq)/*i*-$PrMe_2SiCl$	Me_3Si	(72%) 22:1
LDA (2.5 eq)/ TMSCl	*i*-$PrMe_2SiCl$	Complex mixture
LDA (3.5 eq)/ TMSCl	Me_3Si	(85%) 36:3
LDA/*t*-$BuMe_2SiCl$	Me_3Si	No product
LDA/$Me_2PhSiCl$	Me_3Si	No product
LDA (3.5 eq)/ TMSCl	*i*-$PrMe_2SiCl$	(78%) 9:1

The formation of bis(silyl)allene-amino acids (**20**), (**22**) and (**24**) can be explained in two different scenarios; i) excess LDA leads to the formation of trianion (**25**); trapping of the anions with chlorotrialkylsilane leads to the formation of (**26**), which undergoes

sigmatropic rearrangement to give final product (**27**), or ii) the rearrangement takes places first and then excess LDA deprotonates the allene product to produce an allenyl anion that subsequently reacts with trialkylchlorosilane to produce the final bis(silyl)allene product (Scheme 2. 12). The second scenario is unlikely, since there is no rearranged product observed when 2 equiv. of base are used or when bulky chlorosilanes are used; these experiments were designed to reduce silylation at the α-position. Both the enolization and the silylation of the α-position take place at low temperature; it was not possible to observe formation of the silylated product (**26**) and its disappearance by TLC.

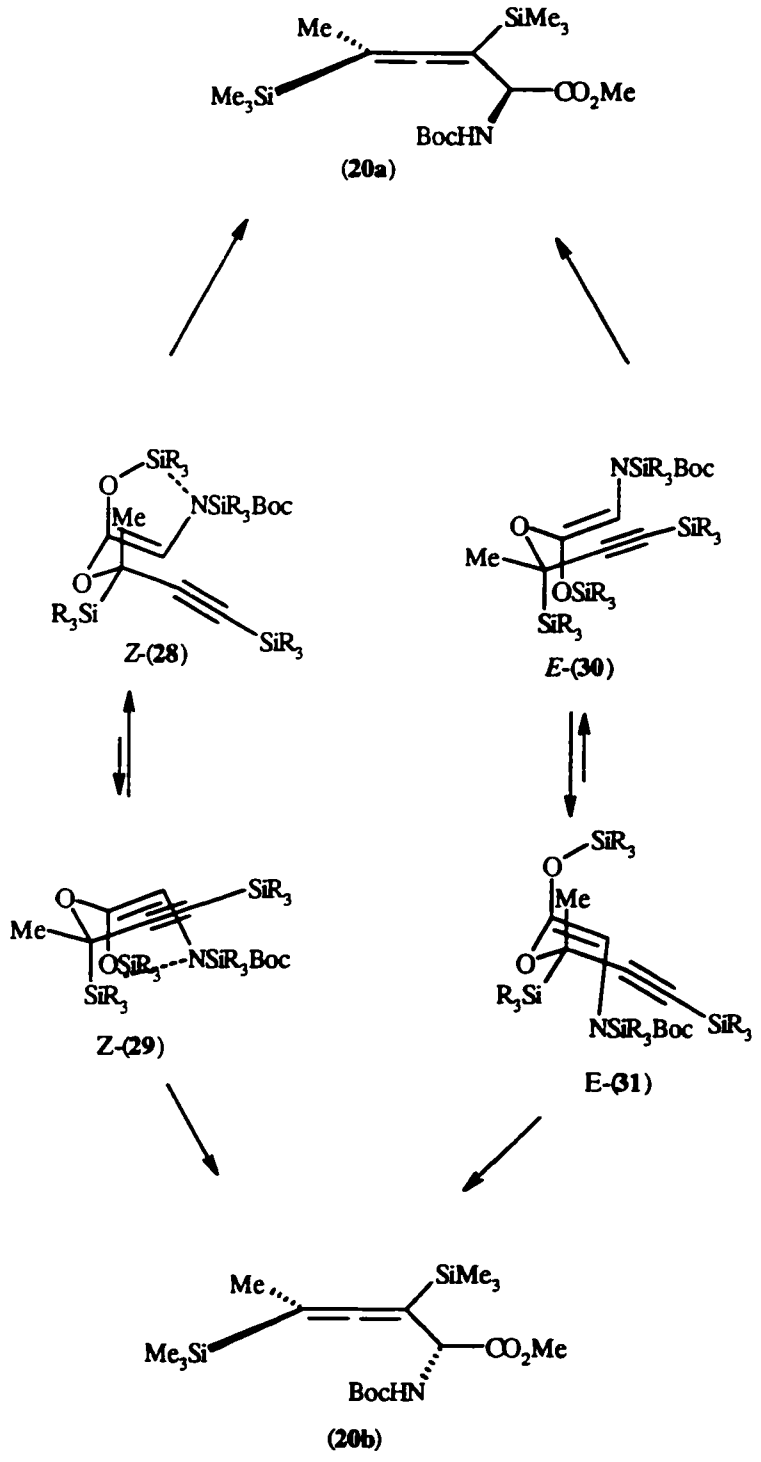


Scheme 2. 12: Possible mechanism of formation of α-(3,5-bis(trimethylsilyl)allenyl)-amino acid (20)

Stereochemistry

The observed high *syn* diastereoselectivity of the product can be explained by comparison of the possible transition states for the rearrangement. The chair-like transition state is

favored over the boat-like transition state, and the stereoselectivity is dependent on the configuration of the enolate double bond.[14] Assuming that rearrangement takes place after silylation at the α position, the silyl group, being the most sterically demanding among the substituents, will adopt a pseudoequatorial position (**Scheme 2. 13**). Of the two (*Z*)-silylketene acetal transition states (**28**) and (**29**), structure (**28**) where the R_3Si group is equatorially disposed, provides the least steric interaction among the substituents. By contrast, structures (**30**) and (**31**) suffer severe 1,3-diaxial interactions between the bulky R_3Si group and the silyl ether subunit.[11]



Scheme 2. 13: Proposed transition state structure

It is well established that α-heteroatom-substituted ester enolate rearrangements lead preferentially to the formation of the (*Z*)-silyl ketene acetal.[15] Thus, transition state (**28**) should give the least steric interaction. The results in Table 2 show that diastereoselectivity increases as the size of R_3Si increases. Conformations (**29**) and (**30**) bring R_3Si and $OSiR_3$ into closer proximity than do conformations (**28**) and (**31**). Thus, increasing the size of the trapping agent from Me_3Si to *i*-$PrMe_2Si$ is expected to favor (**28**) over (**29**) and (**31**) over (**30**); these structures favor the formation of the *syn* isomer as the major product (**20a**). Fujisawa proposed an alternative transition state for the rearrangement of propargyl glycolate ester involving a boat-like transition state (**32**) that minimizes the 1,3-diaxial interaction between $OSiR_3$ and Me groups (**33**). However, it compromises the chelation. In an extreme case, such a model could favor the formation of (*E*)-silyl ketene acetal over the (*Z*)-silylketene acetal (**Figure 2. 1**).[7]

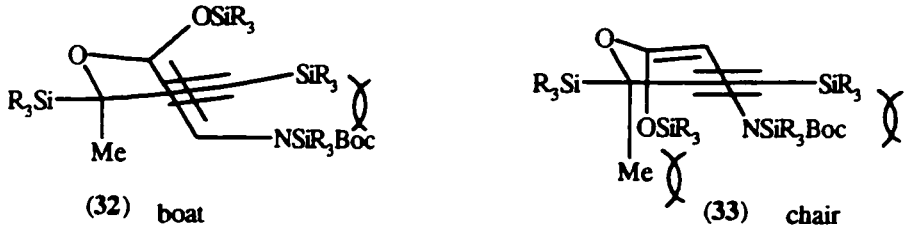


Figure 2. 1: Proposed transition state of the Claisen rearrangement

2. 3. Conclusion

Neither the chelate-Claisen rearrangement nor the Ireland-Claisen rearrangement led to reasonable yields or reproducible results in the synthesis of α-(silylallenyl)-amino acids. However, unusual α-(bis(silyl)allenyl)- amino acid derivatives were synthesized in

excellent yield and good diastereoselectivity, taking advantage of the highly organized transition state of the Claisen rearrangement of propargyl glycinates.

2.5. EXPERIMENTAL

^{1}H and ^{13}C NMR spectra were recorded on Bruker AV-200, 300 and 500 MHz spectrometers with $CDCl_3$ as an internal standard. IR spectra were recorded on a Biorad spectrometer. Electron impact (EI) and chemical ionization (CI, NH_3) mass spectra were recorded at 70 eV with a source temperature of 200 °C on a VG Instrument analytical ZAB-R mass spectrometer equipped with a VG 11-250 data system. Gas chromatographic (GC) analyses were carried out using a Hewlett-Packard 5890A gas chromatograph equipped with a conventional heated injector, a flame ionization detector, a Hewlett-Packard 3393A integrator, and a DB-1 megabore capillary column (30 m x 0.54 mm, Chromatographic Specialities, Inc.).

All the syntheses were performed with dry glassware under an atmosphere of anhydrous nitrogen. The following reagents were purchased from Aldrich and were used without further purification: chlorotrimethylsilane, *tert*-butylchlorodimethylsilane, chloroisopropyldimethylsilane, chlorodimethylphenylsilane, *tert*-butoxycarbonyl glycine. Propargyl alcohol and 3-butyn-2-ol were purchased from Aldrich and distilled immediately before use. Silica gel was purchased from Silicycle. Tetrahydrofuran (THF) was distilled from sodium/benzophenone immediately before use. Dichloromethane was distilled from phosphorus pentoxide before use.

General procedure for the synthesis of alcohols

A three-neck, round-bottomed flask equipped with a magnetic stirring bar, and dry nitrogen inlet, was fitted with a reflux condenser, a thermometer, and a septum. The apparatus was flushed with nitrogen and then charged with magnesium turnings (5 g, 20 mmol) and dry THF (30 mL). To the stirred suspension was added drop-wise bromoethane (2.54 mL, 20 mmol) over 30 min. (via a syringe) maintaining the temperature at 37 - 47 °C. After complete addition, the gray suspension was heated at 50 °C for 1 h and then cooled to 5 °C on ice. A solution of propargyl alcohol (or substituted propargylic alcohols, 7.4 mmol) in THF (10 mL) was cautiously added drop-wise to the gray suspension over 20 min maintaining the temperature at approximately 10 °C. The reaction mixture was stirred overnight. The resultant solution was cooled to 5 °C on ice and chlorotrimethylsilane (2.54 mL, 20 mmol) was added dropwise over 1 h maintaining the temperature at 25 °C or less by external cooling with ice. After complete addition, the mixture was heated to reflux for 2 h with an oil bath. The suspension was cooled to 20 °C and then aqueous sulfuric acid (200 mL of a 1.4 M solution) was cautiously added over 45 min so that the temperature remained below 40 °C. The resulting solution was stirred for 5 min. The organic layer was extracted with ether (2 x 100 mL); the ether layer was washed with water (2 x 100 mL). The combined organic extracts were dried over $MgSO_4$ and solvent removed *in vacuo*. The yellow-brown residue was purified by short path distillation to afford a colorless oil.

1-Trimethylsilyl-1-propyn-3-ol.

(2.25g, 17mmol, 88%); ^{1}H NMR (200 MHz, $CDCl_3$) δ 4.23 (s, 2H); 1.97 (s, 1H, OH); 0.14 (s, 9H, $(CH_3)_3Si$); ^{13}C NMR (50 MHz, $CDCl_3$) δ; IR ν_{max} 3331 (b, -OH), 2961, 2866, 2177, 1446, 1413, 1252, 1045, 983, 844, 761.

1-Trimethylsilylbutyn-3-ol

(2.55g, 18 mmol, 90%);^{1}H NMR (200 MHz, $CDCl_3$) δ 4.38 (q, J = 6.58 Hz, 1H), 3.79 (s, 1H), 1.30 (d, J = 6.67 Hz, 3H), 0.025 (s, 9H, $Si(CH_3)_3$); ^{13}C NMR 107.90, 87.53, 58.07, 24.02, -0.36.

1-Dimethylisopropylsilylbutyn-3-ol

(1.61g, 16 mmol, 80%); ^{1}H NMR δ (200 MHz, $CDCl_3$) δ 4.51 (q, J = 6.57 Hz, 1H), 2.08 (s, 1H), 1.44 (d, J = 6.60 Hz, 3H), 0.98 (d, J = 6.60 Hz, 6H), 0.90 (m, 1H), 0.093 (s, 6H, $Si(CH_3)_3$); ^{13}C (50 MHz, $CDCl_3$) δ 108.50, 86.92, 58.86, 24.47, 16.94, 13.91, -3.78.

General procedure for the synthesis of propargyl glycinate esters.

An oven dried 250 mL round-bottomed flask equipped with a magnetic stirring bar was charged with silylated propargyl alcohol (20 mmol) and dimethylaminopyridine DMAP (0.24 g, 2.0 mmol). The flask was sealed with a rubber septum and dry dichloromethane CH_2Cl_2 (20 mL) was added. The resulting clear solution was allowed to stir for 15 min at room temperature. DCC (4.1 g, 20 mmol) in CH_2Cl_2 (10 mL) was added via syringe. The mixture was allowed to stir at 0 °C for 15 min before *N*-protected glycine (20 mmol) in CH_2Cl_2 (10 mL) was added via syringe. The mixture was allowed to warm up to room temperature overnight. The precipitated urea was filtered off and the resulting clear

yellow solution was washed with saturated $NaHCO_3$. After drying with $MgSO_4$, the solvent was removed *in vacuo*. The crude product was purified by flash chromatography.

1-(Trimethylsilyl)propyn (*N*-Boc)glycinate ester (17a)

The product was purified on silica gel (1:5 EtOAc/pentane) to yield (15 mmol, 4.33g, 75%) of the ester (**17a**).

^{1}H NMR (200 MHz, $CDCl_3$) δ 5.08 (b, 1H), 4.66 (s, 2H), 3.86 (d, J = 5.5 Hz), 1.37 (s, 9H), 0.095 (s, 9H); ^{13}C NMR δ (50 MHz, $CDCl_3$) δ 169.88, 155.87, 98.47, 92.82, 80.18, 53.55, 42.50, 28.44, -0.21; IR ν_{max} 3384, 2943, 1722, 1517; EIMS 286 $(M + H)^+$, 214 (10), 111 (41), 91 (30), 73 (100), 59 (5).

1-Dimethylisopropylsilylproyn (*N*-Boc)glycinate ester (17b).

The product was purified on silica gel (1:5 EtOAc/hexanes) to yield (14 mmol, 4.38 g, 80%) of the ester (**17b**).

^{1}H NMR (200 MHz, $CDCl_3$) δ 5.00 (bs, 1H), 4.75 (s, 2H), 3.94 (d, J = 4.2 Hz, 2H), 1.44 (s, 9H), 0.98 (d, J = 7.1 Hz, 6H), 0.88-0.766 (m, 1H), 0.11 (s, 9H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 169.66, 155.58, 98.81, 91.32, 80.10, 53.44, 42.37, 28.27, 17.16, 13.64, -4.11; IR ν_{max} 3385, 2943, 1722, 1522; CIMS (NH_3) 331 $(M + NH_4^+)$, 314 (12), 275 (2), 258 (20), 214 (100), 170 (40), 93 (40), 76 (3).

3-(Trimethylsilyl)butyn-2-ol (*N*-Boc)glycinate ester (21).

The product was purified on silica gel (1:6 EtOAc/pentane) to yield (15 mmol, 4.66 g, 82 %) of the ester.

^{1}H NMR (200 MHz, $CDCl_3$) δ 5.49 (q, J = 6.4, 1H), 4.62 (b, 1H), 3.99 (bd, 2H), 1.41(s, 9H), 0.03 (s, 9H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 169.20, 155.67, 102.82, 90.18, 80.0,

61.68, 42.54, 28.28, 21.45, -0.31. IR ν_{max} 3379, 2935, 2120, 1722; CIMS 317 (M + NH_4^+), 261 (8), 244 (2), 200 (5), 192 (5), 148 (3), 192 (20), 73 (46), 57 (100).

1-(Dimethylisopropylsilyl)butyn-3-yl (*N*-Boc)glycinate ester (23).

The product was purified on silica gel (1:5 EtOAc/pentane) to yield (13 mmol, 4.25 g, 78%) of the ester. ^{1}H NMR (200 MHz, $CDCl_3$) δ 5.48 (q, J = 6.6 Hz, 1H), 5.01 (b, 1H), 3.88 d, J = 5.2 Hz, 1H), 1.44 (s, 9H), 0.93 (d, J = 6.7 Hz, 6 H), 0.90 (m, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 169.36, 155.80, 103.64, 88.80, 80.07, 61.80, 42.62, 28.40, 21.65, 17.31, 13.82, -3.93; IR ν_{max}3384, 2943, 1722.

General Procedure for the propargyl glycinate rearrangement

General preparation of lithium diisopropylamide: In a typical experiment freshly distilled diisopropylamine (12 mmol, 1.72 mL) was added to *n*-BuLi (7.50 mL of a 1.6 M solutions in hexanes, 12 mmol) in THF (2.0 mL) at 0 °C. The reaction mixture was stirred for 10 min at 0 °C, the cooling bath was removed and the reaction was stirred for a further 15 min at room temperature.

A solution of lithium diisopropylamide (1.3 M) was cooled at -78 °C, and a solution of the ester (1.0 g, 3.5 mmol) in THF (1.0 mL) was added via syringe dropwise. After 3 min, trialkylchlorosilane (1.55 mL, 12.25 mmol) was added. The solution was stirred for 6 h, and the cooling bath was removed. The solution was diluted with ethyl acetate (2 mL), and saturated $NaHCO_3$ solution (4 mL), and the mixture was stirred vigorously for 10 min. The aqueous layer was extracted with ethyl acetate (2 x 5 mL), combined organic layers were dried over $MgSO_4$, and the solvent was removed *in vacuo*.

Methyl-2-(*N*-Boc)-3,5-bis(trimethylsilyl)-3,4-hexadienoate (20).

The product was purified on silica gel (1:5 EtOAc/pentane) to yield (2.84 mmol, 1.1 g, 85%) of the ester . ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.93 (d, *J* = 7.9 Hz, 1H), 4.57 (d, *J* = 8.7 Hz, 1H), 3.59 (s, 3H), 1.57 (s, 3H), 1.34 (s, 9H), 0.04 (s, 9H), -0.03 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 205.39, 172.16, 155.06, 89.10, 87.90, 79.96, 53.19, 52.0, 28.56, 14.60, -0.77, -1.74; IR ν_{max}, 3444, 2960, 1913, 1711; HRMS, m/z: found 385.21044, (required 385.21034); R_f = 0.7 (20% ethyl acetate/pentane).

Methyl-2 (*N*-Boc)-3-(dimethylisopropylsilyl)-5-(trimethylsilyl)-3,4-dienohexanoic acid (24) and **Methyl 2-(*N*-Boc)-3-(trimethylsilyl)-5-(dimethylisopropylsilyl)-3,4-dienehexanoate (22).**

The product was purified on silica gel (1:5 EtOAc/pentane) to yield (2.79 mmol, 1.2 g, 78%) of the ester

^{1}H NMR (300 MHz,$CDCl_3$) ^{1}H NMR δ 4.96 (d, *J* = 8.1 Hz, 1H), 4.54 (d, *J* = 8.6 Hz), 3.58 (s, 3H), 1.57 (s, 3H), 1.33 (s, 9H), 0.63 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.90, 154.94, 88.57, 86.02, 79.71, 53.09, 51.70, 28.28, 17.44, 14.55, 13.22, -2.00, -4.87, -5.28; IR ν_{max} 3448, 2957, 1913, 1747; EIMS (relative intensity %) 414 $(M+H)^+$, 371 (13), 343 (2), 315 (9), 165 (6), 118 (20), 73 (100).

2-(*N*-Boc)-3-(dimethylisopropylsilyl)-5-(trimethylsilyl)-3,4-dienopentanoic acid (18b).

^{1}H NMR (300 MHz, $CDCl_3$) δ 5.29 (s, 1H), 4.99 (bs, 1H), 3.94 (s, 1H), 3.92 (s, 1H), 1.45 (s, 9H), 0.98, (d, 6H), 0.7-0.8 (m, 1H), 0.14 (s, 9H), 0.09 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 206.05, 172.06, 154.97, 88.73, 86.21, 79.87, 53.28, 51.88, 28.45, 17.64, 14.72,

13.49, -1.82, -5.10; IR ν_{max} 3440, 2951, 1910, 1749; CIMS m/z, (relative intensity %) 358 $(M + H)^+$ (3), 319 (22), 248 (12), 200 (17), 90 (100), 73 (78), 57 (13), 41 (21).

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Chapter 3.

Lewis acid-mediated addition of α-allylsilane amino acid derivatives to aromatic acetals.

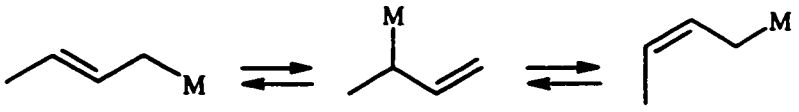
Abstract

Diastereoselective addition of methyl 2-(*N*-PG)-3-(trimethylsilyl)-(*E*)-pent-4-enoate (**72**) and methyl 2-(*N*-PG)-3-(trimethylsilyl)-(*E*)-hex-4-enoate (**77a-c**) to aromatic acetals in the presence of Lewis acids is described. Reaction conditions were examined in detail. $TiCl_4$ was found to be the most effective Lewis acid for promoting the addition. At least 1 mol eq. of $TiCl_4$ was required to achieve high yield, whereas up to 2 eq. of $BF_3.OEt_2$ were required for high yield. Remarkable selectivity (> 99% d.e) and high yield (up to 89%) were obtained with halo-substituted aromatic acetals.

Introduction

3. 1. Allylsilanes.

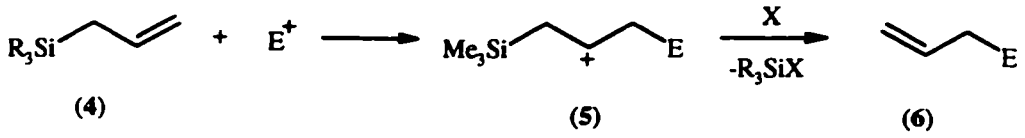
Allylmetal reagents (M = Li, MgL, ZnL, CdL, BL_n, AlL_n, TiL_n, ZrL_n, CrL_n, etc.) add to a variety of electrophiles.[1] The reaction has proven to be one of the most important procedures in carbon-carbon bond forming reactions. But these reagents undergo a rapid 1,3-shift of the metal group at modest temperatures, affecting their regioselectivity in the addition process (**Scheme 3. 1**).[2]



(2) (1) (3)

Scheme 3. 1: 1,3-shift of the metal group.

Allylsilanes add to electrophiles but, in contrast to allylmetals, are thermally stable and relatively inert to water and basic conditions.[3] Their utility is derived from the high yield, excellent regioselectivity, stereoselectivity, and mild conditions under which the reaction can be performed.[2] The mechanism of the electrophile substitution reaction of allylsilanes involves attack of the electrophile on the π bond of the allylsilane (**4**) at the terminal carbon of the allylic group to generate cationic intermediate (**5**). A nucleophile (X^-) then displaces the silyl group with the formation of an alkene (**6, Scheme 3. 2**).[4] The ease and regioselectivity of the reaction of allylsilanes with electrophiles can be understood by the fact that cation (**5**) is stabilized by hyperconjugative overlap of the Si-C bonding orbital with the empty *p* orbital (silicon β-effect).[5]

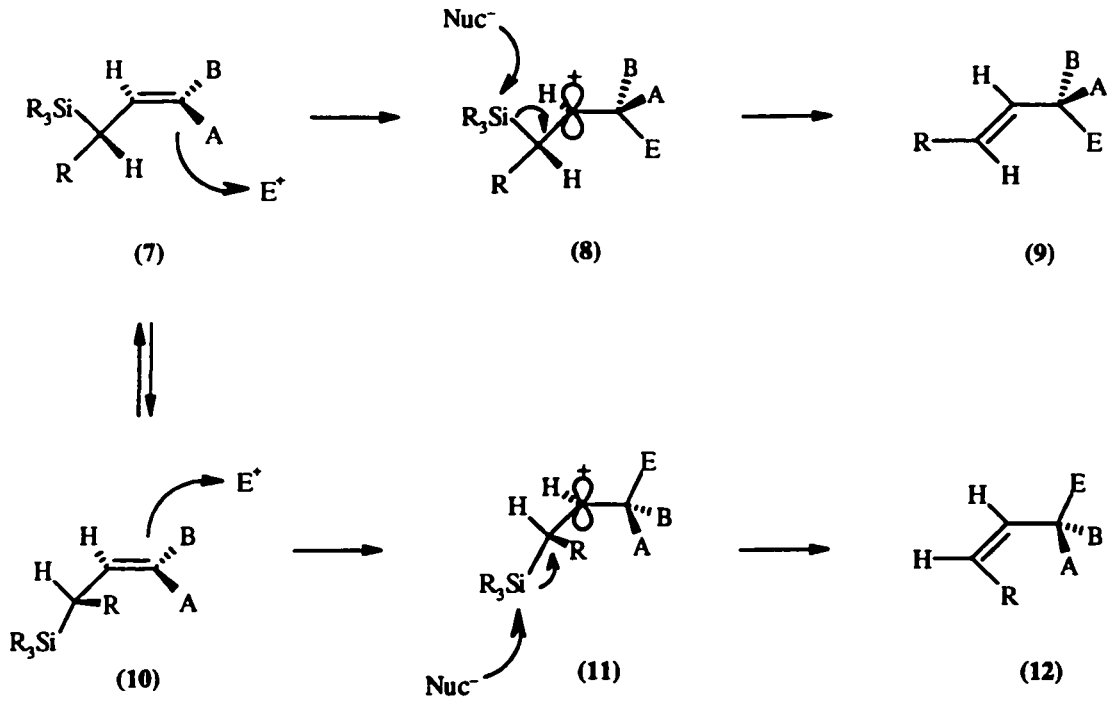


(4) (5) (6)

Scheme 3. 2: Electrophilic substitution reaction of Allylsilanes.

3. 2 The Stereochemistry of Reactions of allylsilanes

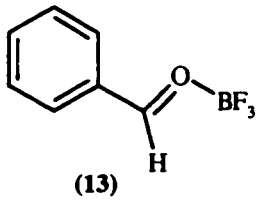
The reaction of allylsilanes substituted at the α–position with electrophiles leads predominantly to product with (*E*)-double bond geometry. This remarkable stereoselectivity follows from the probable conformation of the allylsilane.[6] The preferred conformation **(7, Scheme 3. 3)** has the small substituent H more or less eclipsing the double bond. The bulky silyl group encourages attack by the electrophile to the opposite face of the π-system, with the result that the double bond produced in the product **(9)** is generally *trans*, and the overall reaction is stereoselectively *anti*.[7] However, there have been cases where the *cis* double bond was observed in the product, particularly when electrophiles with bulky substituents are employed. A substantial proportion of the reaction can take place in the alternative conformation **(10)**; if the R group is not large, it can adopt the conformation such that it is eclipsed with the double bond.[8]



Scheme 3. 3: Stereochemistry of electrophilic substitution of an allylsilane.

3. 3. Lewis acid-carbonyl complexes.

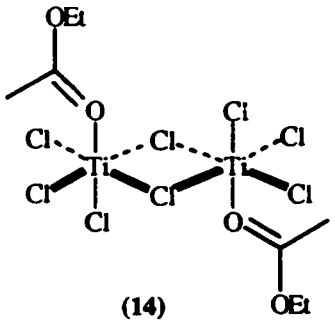
The addition of allylsilanes to carbonyls is activated by variety of Lewis acids. The role of the Lewis acid is to improve the electrophilicity of the carbonyl through complexation.[9] This interaction could be a σ-bonding complex or a π-system complex.[10] The most common Lewis acids employed in the reaction of allylsilanes with carbonyls are $AlCl_3$, BF_3, $BF_3.OEt_2$, $TiCl_4$, $SnCl_4$, etc. The interaction between Lewis acids and carbonyls is important, and it has been investigated for many years. Both theoretical and experimental evidence has been provided for the existence and the nature of Lewis acid-carbonyl complexes.[11] In 1986, Reetz published the first X-ray structure of an aldehyde-Lewis acid complex. He also showed that in the BF_3-benzaldehyde complex, BF_3 is complexed *anti* to the phenyl ring of the aldehyde.[12]



(13)

Figure 3. 1: BF_3OEt_2/aldehyde complex.

Unlike BF_3, $TiCl_4$ can form 1:1 complexes with carbonyl compounds through a dimeric structure involving bridging chlorine atoms (**Figure 3. 2**).[13]



(14)

Figure 3. 2: $TiCl_4$/carbonyl complex.

Lewis acids also activate acetals towards addition of allylsilanes.[14] Low temperature ^{13}C NMR studies by Denmark *et al.*[15] have established the formation of 1:1 Lewis acid-acetal complexes (**15**) using $BF_3.OEt_2$ as the Lewis acid, where only one methoxy group complexes with $BF_3.OEt_2$. In the case of $SnCl_4$, two different complexes were reported depending on the amount of $SnCl_4$ used. One-half an equivalent of $SnCl_4$ induced the formation of the 2:1 complex (**16**), in which a single methoxy group of each acetal is complexed to the tin atom. However upon addition of 1 equivalent of $SnCl_4$, complex

(17) was formed in which both methoxy groups of the acetal are complexed (**Figure 3. 3**).

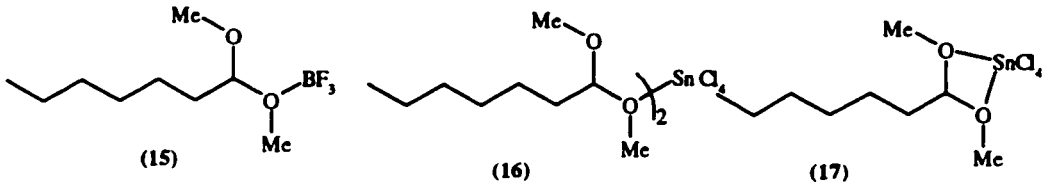
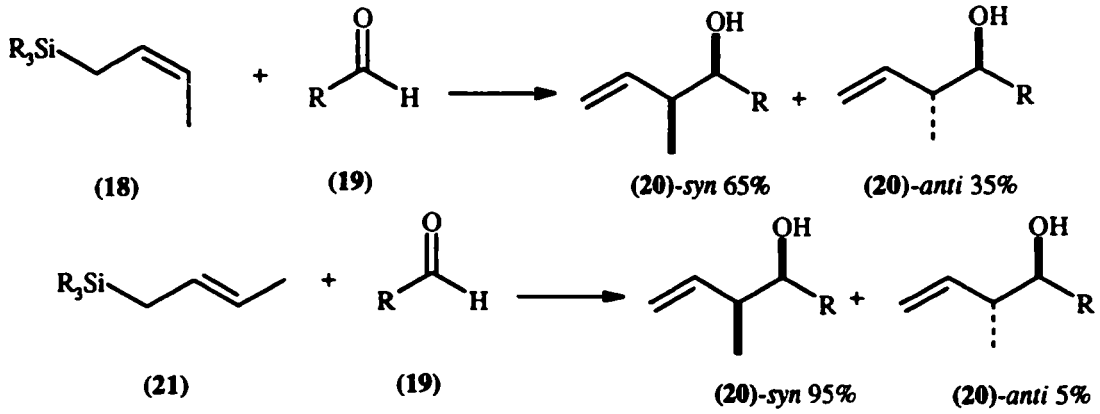


Figure 3. 3: $SnCl_4$/acetal complexes.

3. 4. Lewis acid-mediated reactions of allylsilanes with carbonyls

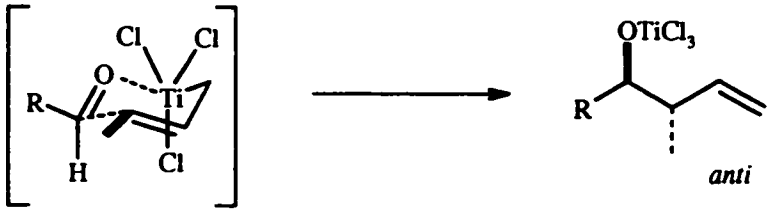
Allylsilanes, monosubstituted at the δ-position (crotylsilanes) add to carbonyls to give *syn* product as the major stereoisomer.[3] The (*E*)-crotylsilanes are highly selective in the *syn* sense (>95:5). In contrast, the (*Z*)-crotylsilanes are less selective (60-70:40-30 *syn:anti*, **Scheme 3. 4**).[16]



Scheme 3. 4: Stereochemistry of allylsilane addition to aldehydes.

3.4. 1. Mechanism of Lewis acid-promoted allylsilane addition to carbonyl compounds.

Carbonyls are the most utilized electrophiles in allylsilane reactions. Lewis acids promote this reaction in a regio- and stereoselective manner. This reaction has become the method of choice for the synthesis of homoallylic alcohols, which are useful intermediates in organic synthesis.[3] The range of Lewis acids used is wide, but titanium tetrachloride and boron trifluoride etherate are the most common.[17] Typically, the reaction takes place somewhere between -78 °C and 0 °C in dichloromethane solution, and either a catalytic or, more frequently, a stoichiometric proportion of Lewis acid is used. The reaction of crotylsilanes with aldehydes and ketones results in the formation of two new chiral centers, which leads to four isomeric products; the *syn* isomer is the dominant product from the reaction as shown above (**Scheme 3. 4**). However, the traditional Zimmerman-Traxler model, rationalized for the allylmetal reagent addition to electrophiles, cannot account for the observed selectivity (**Scheme 3. 5**).[18]

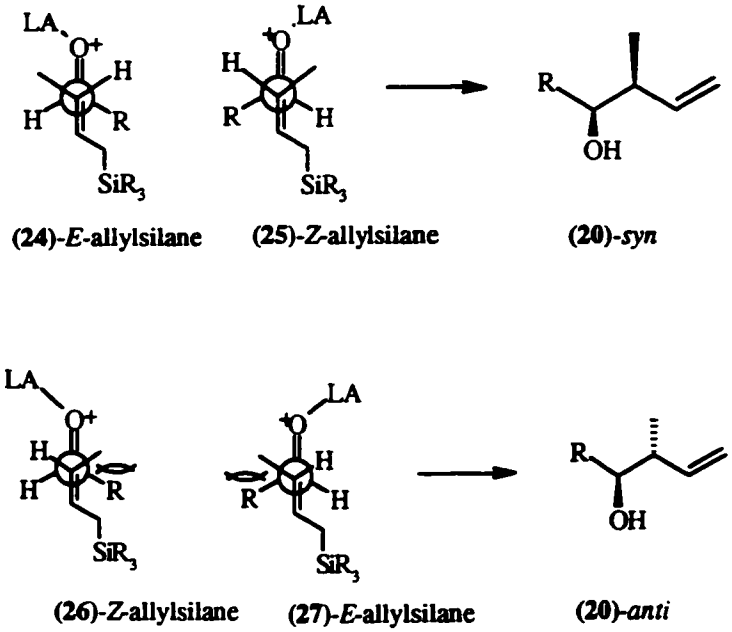


(22) (23)

Scheme 3. 5: Zimmerman-Traxler Model.

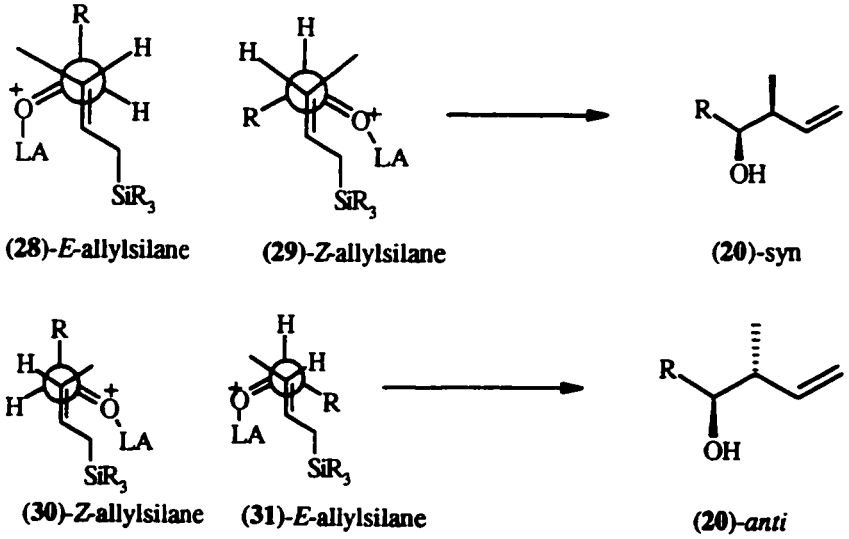
The high *syn* selectivities observed in these reactions are determined by the preferred orientation of the reactive double bonds (allylsilane double bond and carbonyl double bond) in the transition state structures.

The relative stereochemical outcome of these reactions has been interpreted through the use of two related transition state models. These models use very different orientations of the reacting double bonds to explain the stereoselectivity. Yamamoto[19] suggested an open transition state model referred to as an antiperiplanar transition state, where the participating π–bonds are oriented at 180° to each other. During the reaction, the allylsilane and the carbonyl group are in an *anti* relationship to each other and are also coplanar. Transition states **(24, 25)** lead to the *syn* diastereomer. On the other hand, transition states **(26)** and **(27)** lead to the anti diastereomer. Comparing these model transition states, **(24)** and **(25)** are favored due to diminished steric interactions between the aldehyde substituent and the vinylmethyl group. The destabilizing interactions created by these substituents which places them in a gauche orientation are greatest for transition states **(26)** and **(27, Scheme 3. 6)**.



Scheme 3. 6: Antiperiplanar transition state model.

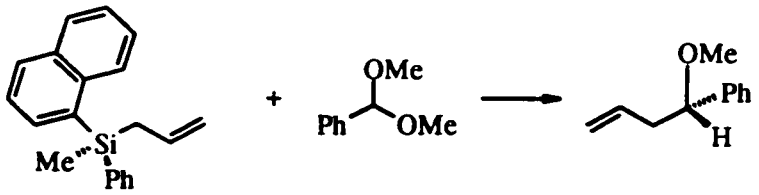
Denmark[20] has rationalized the stereoselectivities in these reactions by an alternative transition state model referred as synclinal geometry, which places the reacting π-bonds at an angle of approximately 30° to each other. Again, transition states (**28** and **29**) leading to the *syn* diastereomer, are more favored than transition states (**30** and **31**) leading to the *anti* diastereomer (**Scheme 3. 7**). In this model the size of the Lewis acid attached to the oxygen atom helps to determine the most favorable transition state geometry. Both models predict the *syn* isomer as the major product. A theoretical model developed by Houk and co-workers calculated that the relative energy differences between the synclinal and the antiperiplanar models are negligible.[21]



Scheme 3. 7: Synclinal transition state model.

3.4. 2. Intermolecular addition of chiral allylsilanes to aldehydes

There are two approaches for introducing chirality on allylsilane: using a silicon-centered chiral allylsilane, or a carbon-centered chiral allylsilane.[22] A synthetic procedure for preparation of optically active silicon-centered allylsilanes was first developed by Sommer and others.[23] Paquette and Hathaway reported the Lewis acid-mediated reaction of allylmethyl-α-naphthylphenylsilane **(32)** with a number of carbonyl compounds; their attempts with aldehydes were not successful. However, under $BF_3.OEt_2/CH_2Cl_2$ conditions the reaction of **(32)** with benzaldehyde dimethyl acetal **(33)** gave the homoallylic methyl ether **(34)** in modest yield with a low level of stereoselectivity (3.9-5.5% ee).[24] This may be a consequence of the open transition state typical of Lewis acid-promoted allylsilane additions, where the chiral center is located distal from the carbon where new C-C bond formation takes place, or to a prior racemization of the chiral silicon species.[4]

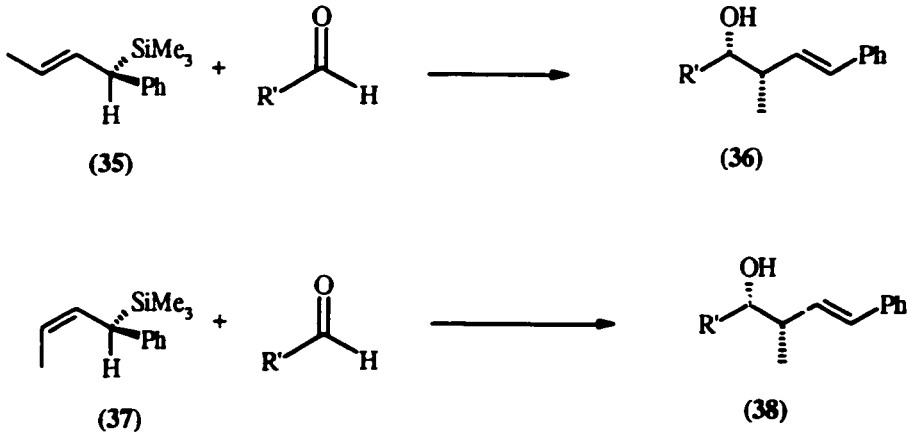


(32) **(33)** **(34)**

Scheme 3. 8: Optically active allylsilane addition to acetals.

In contrast to the dismal enantioinduction observed with silicon-centered chiral allylsilanes, Kumada and coworkers reported excellent enantioselectivities when carbon-centered chiral allylsilanes were employed **(Scheme 3. 9)**.[25] They studied the reaction of optically pure *E/Z*-crotylsilanes **(35)** and **(37)** with several aldehydes. Their experiments

demonstrated that the reaction took place with remarkable retention of optical activity and high *anti* selectivity of the transition state leading to the *syn* isomer as the major product from both allylsilanes, regardless of the geometry of the double bond. Other studies have similarly shown that the reaction proceeds with antiperiplanar stereoselectivity. The mechanistic rationalization suggests that the incoming electrophile attacks the double bond on the surface opposite to the silyl group leading to the *syn* isomer as the major isomer (**Table 3. 1**).



Scheme 3. 9: Optically active allylsilane addition to aldehydes.

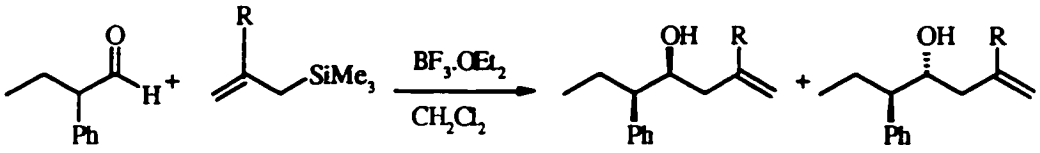
Table 3. 1: Addition of optically active allylsilanes (*R*)-(*E*)-(35) and (*R*)-(*Z*)-(37) to achiral aldehydes

allylsilane	R'CHO	*syn:anti*	*syn:anti*	Yield (%)
(*R*)-(*E*)(35)	*t*-BuCHO	>99:1		47
(*R*)-(*Z*)(37)	*t*-BuCHO		>99:1	27
(*R*)-(*E*)(35)	*i*-PrCHO	>95:5		67
(*R*)-(*Z*)(37)	*i*-PrCHO		>65:35	61
(*R*)-(*E*)(35)	*t*-BuCHO	>99:1		44
(*R*)-(*Z*)(37)	*t*-BuCHO		>99:1	10

The antiperiplanar model (**Scheme 3. 6**) proposed by Yamamoto[1] accounts in a better way for the results than the synclinal transition state model (**Scheme 3. 7**).[26]

3.4. 3. Reaction with chiral aldehydes.

When the aldehyde contains a stereocenter, diastereofacial selectivity on the carbonyl group is possible. Heathcock *et al.* reported that addition of allylsilane **(40)** to 2-phenylpropionaldehyde **(39)** in the presence of $BF_3.OEt_2$ afforded homoallylic alcohol **(41)** with modest selectivities **(Scheme 3. 10)**.[27]

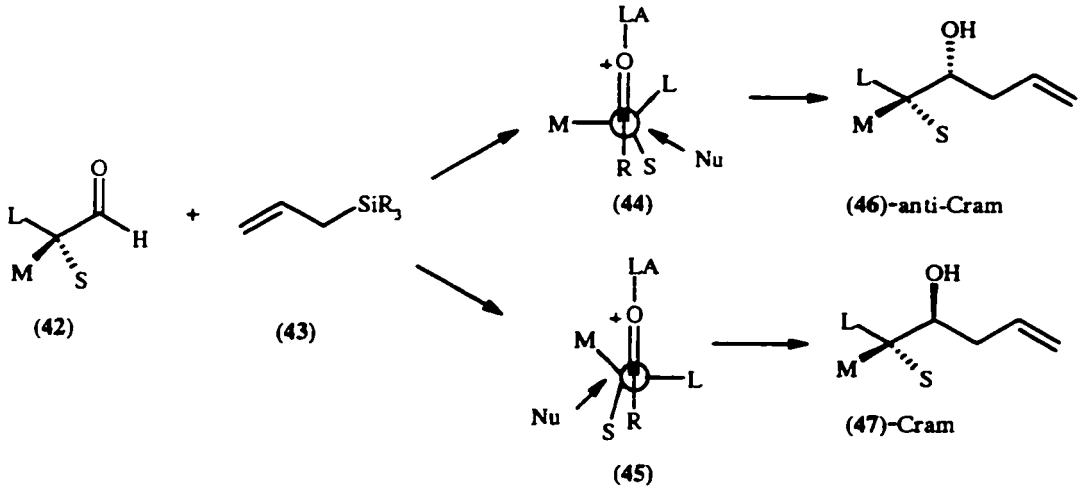


(39) **(40)** **(41)**-*syn*, major **(41)**-*anti*, minor

R = H	2	:	1
R = Me	7	:	1

Scheme 3. 10: Allylsilane addition to chiral aldehydes.

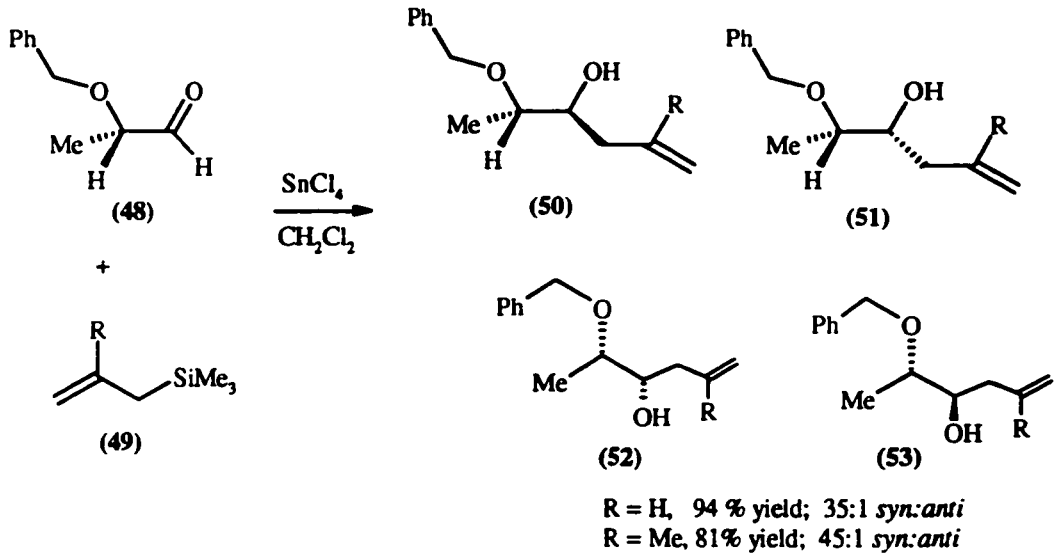
The diastereoselectivity of these additions can be predicted by the Felkin-Anh model for diastereoselectivity resulting from nucleophilic addition to the carbonyl group. It makes the assumption that nucleophilic attack takes place from a direction approaching the smallest substituent (S), when the large substituent (L) is oriented opposite to the plane of the carbonyl group, leading to the Cram product **(Scheme 3. 11)**. The addition of allyltrimethylsilane to 2-methylbutanal (L = Et, M = Me, S = H) with $BF_3.OEt_2$ was reported to take place without selectivity, because the stereo differentiation, provided by the competition between the methyl and ethyl groups, is not larger.[28] However, in these reactions bulkier Lewis acids are found to induce a moderate *syn*-selectivity in accordance with the Felkin-Anh model.[29]



Scheme 3. 11: Stereoselectivity of addition of allylsilane to chiral aldehydes.

3.4. 4. Chelation controlled reaction with aldehydes bearing Lewis bases.

When the stereocenter has an ether group α- or β- to the carbonyl group, very high diastereoselectivity is observed, due to the formation of a ring made up by chelation of the Lewis acid between the ether oxygen and the carbonyl oxygen. The allylsilane attacks from the less hindered side of a ring. Lewis acids like boron trifluoride, with only one coordination site, have different and usually rather lower diastereoselectivities than multidentate Lewis acids. The choice of Lewis acid can invert the selectivity in favorable cases, with titanium tetrachloride giving the product of chelation control and boron trifluoride the product in the normal Cram sense.

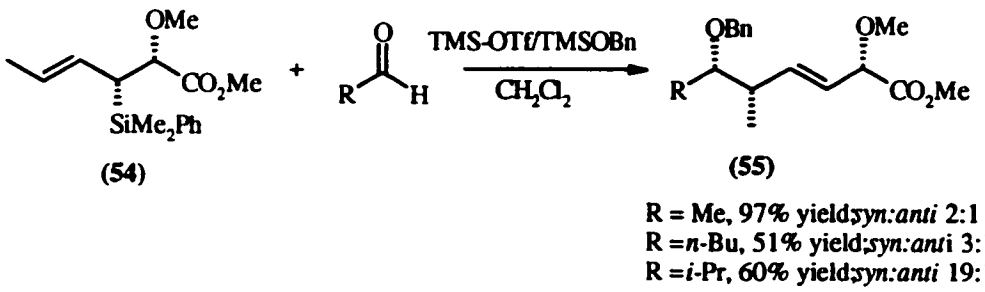


Scheme 3. 12: Chelation control with Lewis acid-bearing aldehydes.

Heathcock *et al.* reported that good to excellent *syn* selectivity could be obtained in the reactions between (**48**) and (**49**) mediated by $SnCl_4$ (**Scheme 3. 12**).[27]

3.4. 5. Chelation control with Lewis base-bearing allylsilanes

Functionalized allylsilanes bearing ligands with a lone pair of electrons can potentially coordinate to Lewis acids and promote stereoselectivity. Panek studied the diastereoselectivity of the addition of optically active β-methoxy-substituted crotylsilane (**54**) derivatives to aldehydes.[30] The reaction is catalyzed by trimethylsilyl triflate (TMS-OTf) to generate oxonium ions, which then react with the crotylsilane to give the *syn* product (**55**).[31]

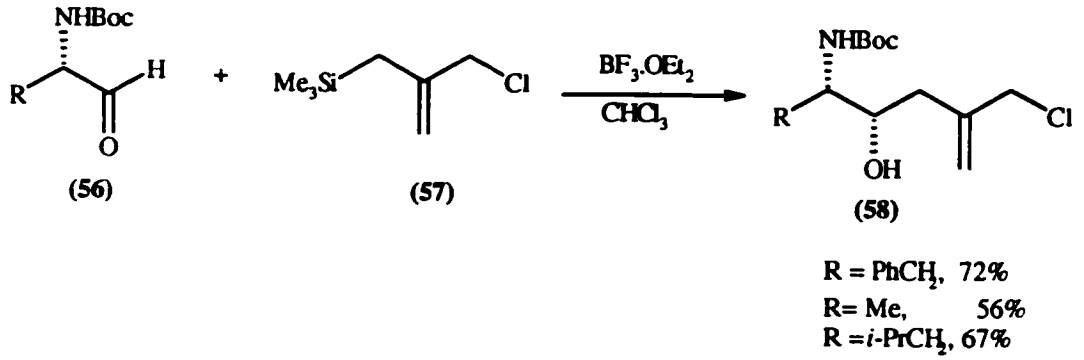


Scheme 3. 13: Chelation control with Lewis acid-bearing allylsilanes.

These studies showed that the addition takes place on the *Re* face of the aldehydes, leading to the *syn* isomer as the major product. An antiperiplanar transition state can account for such selectivity. The diastereofacial selectivity increases as a function of the size of the alkyl R group (**Scheme 3. 13**).[32]

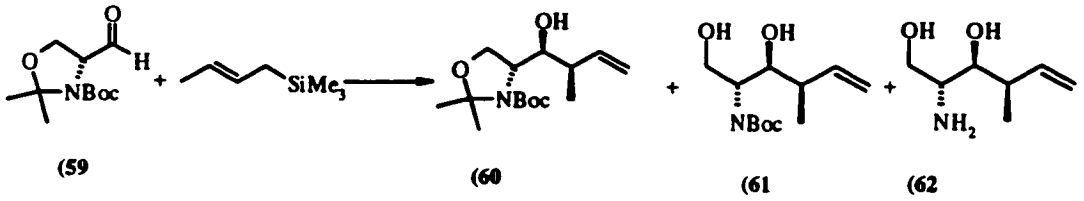
3.4. 6. Intermolecular addition of allylsilanes to α-aminoaldehydes

Modified amino acids are important for medicinal chemistry; they are used for development of new drugs.[33] Taddei *et al.* reported that *N*-Boc amino aldehydes (**56**) derived from naturally occurring α-amino acids, react with 2-chloromethyl-3-trimethylsilyl-1-propene (**57**) in the presence of $BF_3.OEt_2$ to give amino alcohols (**58**), resulting in key intermediates for the preparation of hydroxyethylene dipeptide isosteres.[34] In all cases only the *syn* isomer was observed.



Scheme 3. 14: Lewis acid-mediated addition of allylsilanes to α-amino-aldehydes.

The same group also achieved the preparation of γ-branched amino acids via the addition reaction of crotylsilane to acetonides of *D*-serine aldehydes (**59**) in the presence of $TiCl_4$. They obtained the expected product (**60**) with high *syn* selectivity, accompanied by ring opening products (**61**) and (**62**) depending on the amount of $TiCl_4$ employed (**Scheme 3. 15**).[35]

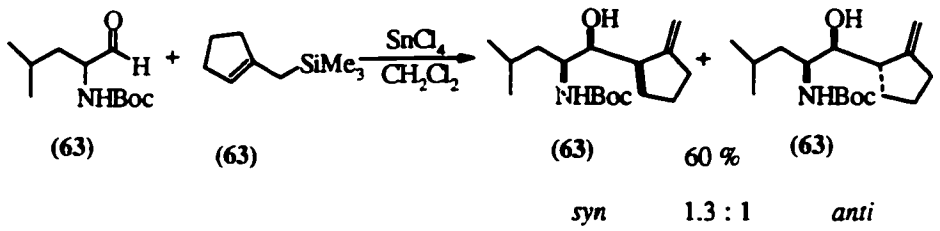


$TiCl_4$					
1 eq.(2h)	8	:	2	:	0
1eq. (8h)	5	:	3	:	2
2 eq.(2h)	1	:	7	:	2

Scheme 3. 15: Lewis acid-mediated addition of allylsilanes to α-amino-aldehydes

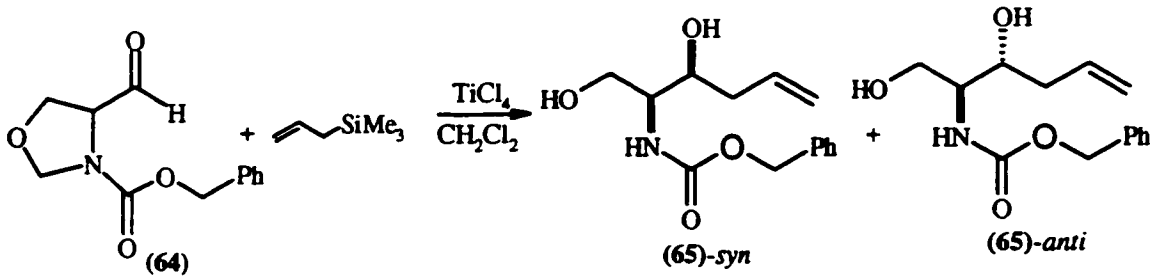
The $SnCl_4$-promoted addition of allyltrimethylsilane to α-aminoaldehydes is controlled by α-chelation and therefore leads predominantly to *syn*-alcohols.[36] These alcohols can subsequently be converted into various hydroxyethylene dipeptide isosteres.

In contrast, the addition of cyclopentenylmethyltrimethylsilane to Boc-leucinal occurred with only low diastereoselectivity (**Scheme 3. 16**).[37]



Scheme 3. 16: Lewis acid-mediated addition of allylsilanes to α-amino-aldehydes

Kiyooka noticed a dramatic change in diastereoselectivity depending upon the quantity of $TiCl_4$ used during the addition of allyltrimethylsilane to chiral α–*N*-(carbobenzyloxy)amino aldehydes (**64**, Scheme 3.17).[38]



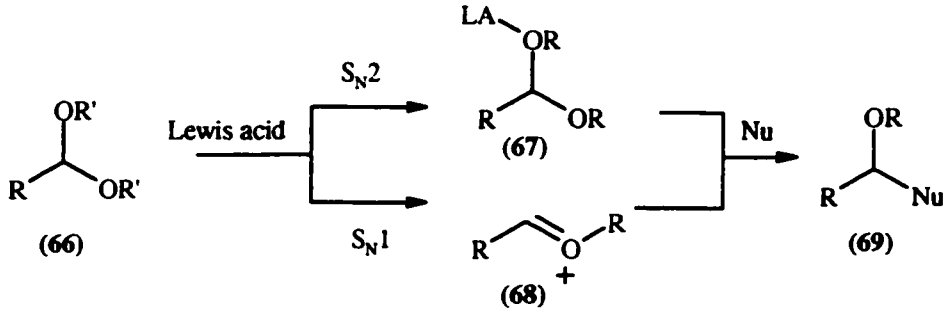
$TiCl_4$			
0.4	7	:	1
0.5	8	:	1
0.8	1	:	9
1.0	1	:	20
1.2	1	:	1

Scheme 3. 17: Diastereoselectivity dependence on quantity of Lewis acid.

3. 5. Lewis acid promoted reactions of allylsilanes with acetals.

Sakurai and Hosomi reported that allylsilanes underwent reaction with various acetals in the presence of $TiCl_4$ to afford the corresponding homoallylic ethers.[14] Unlike the reaction of allylsilanes with aldehydes, the mechanism of this reaction could proceed via

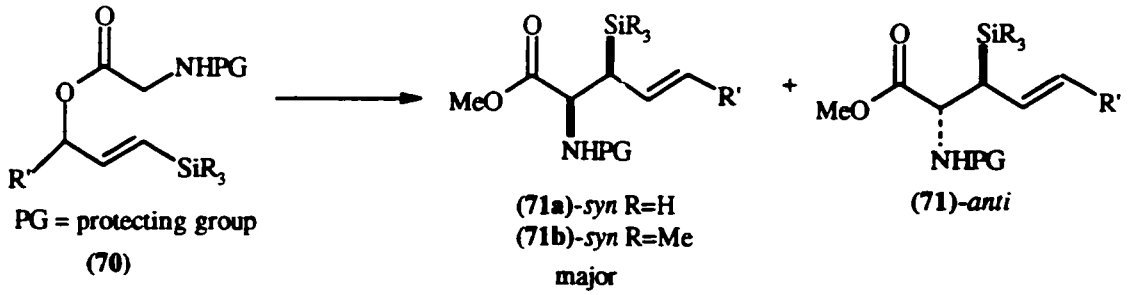
either of two different pathways: direct nucleophilic substitution of Lewis acid-acetal complex (**67**), an S_N2 mechanism, or prior formation of oxocarbenium ion (**68**) which then undergoes nucleophilic attack, an S_N1 mechanism.



Scheme 3. 18: Mechanism of nucleophilic addition to acetals.

3. 6. Results and Discussion.

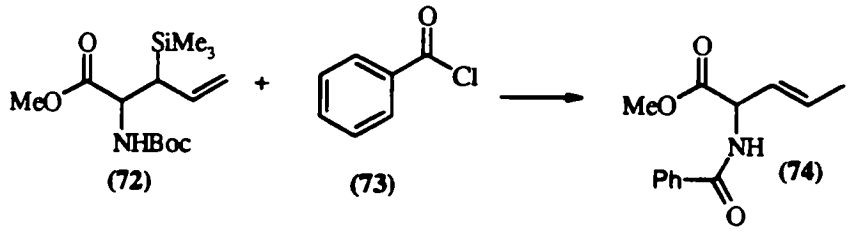
Lewis acid-mediated reactions of allylsilanes with carbonyl electrophiles have been well documented and a variety of reaction conditions are available for optimum yield and selectivity.[39] It was our interest to examine the use of α-silylallyl amino acids for further synthetic transformation. The starting α-allylsilane amino acid derivatives were synthesized via Claisen rearrangement as shown in **(Scheme 3. 19)** and outlined in Chapter 1.



Scheme 3. 19: Ireland-Claisen rearrangement of (70)

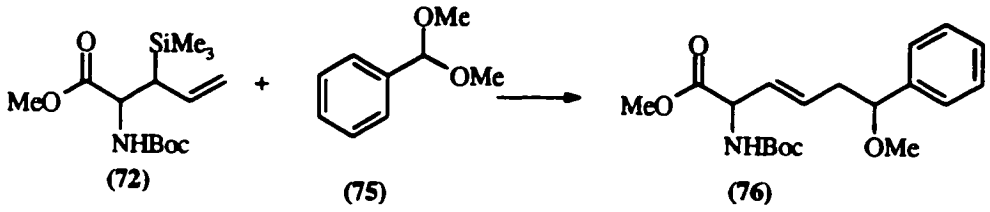
We tested the reactivity of methyl 2-(*N*-PG)-3-(trimethylsilyl)-(*E*)-pent-4-enoate (R = H, *syn*-**71a**) and methyl 2-(*N*-PG)-3-(trimethylsilyl)-(*E*)-hex-4-enoate (R = Me, *syn*-**71b**) against series of electrophiles. Initially, we attempted the reaction of **(72)** with benzaldehyde under different reaction conditions and Lewis acids. We expected to obtain homoallylic alcohols with some level of diastereoselectivity. This reaction did not lead to the expected product, only starting material was recovered after 6 hours at low temperature. Excess Lewis acid ($TiCl_4$, $SnCl_4$) and high temperatures (0 °C – rt) led to the formation of a complex mixture of products. Next, we switched to more reactive electrophiles. Treatment of a mixture of allylsilane and benzoyl chloride with 2 mol.

equivalents of $TiCl_4$ at -78 °C did not show product after 3 hours by TLC. When the reaction temperature was raised from -78 °C to 0 °C, a second spot showed on the TLC, and this product increased with temperature and time. After work-up of the reaction, the crude ^1H NMR analysis showed no appreciable product. After chromatographic isolation, the second product was identified to be **(74)**. This arises from deprotection of the amine, and addition of the amine to benzoyl chloride, and is accompanied by protodesilylation during the reaction work-up.



Scheme 3. 20: Lewis acid-mediated addition of (72) to acid chlorides.

However, when we attempted the reaction of **(72)** with aromatic acetals, we were able to observe some product **(76)**. In order to establish the scope and applicability of the reaction, the reaction of allylsilane amino acids **(72)** and benzaldehyde dimethyl acetal **(75)** was tested in the presence of different Lewis acids and reaction protocols **(Scheme 3.21)**.



Scheme 3. 21: Lewis acid-mediated addition of (72) to acid acetals

Table 3. 2: Reaction of (72) with benzaldehyde dimethyl acetal

Entry	Procedure	Lewis acid	Time (temperature)	Yield %
1	A	$BF_3.OEt_2$ (1 eq.)	10h (-78 °C → rt)	20
2		$BF_3.OEt_2$ (1.5 eq.)	7h (-78 °C)	40
3	B	$BF_3.OEt_2$ (2 eq.)	10h (-78 °C)	66
4		$BF_3.OEt_2$ (0.5 eq.)		No product
5	A	$TiCl_4$ (2 eq.)	(-78 °C (10 min.) → rt)	25
6		$TiCl_4$ (1.2 eq.)	24h (-78 → rt)	51
7	B	$TiCl_4$ (1.2 eq)	7h (-78 °C)	70
8	B	$TiCl_4$ (1.2 eq)	15h (-78 °C)	78
9		$TiCl_4$ (4 eq.)	24h (-78 → rt)	30
10	A	$TiCl_4$ (1 eq.)	24h (-78 °C → rt)	48
11		$TiCl_4$ (0.5 eq.)	24h (-78 °C → rt)	No product
12		$ZnCl_2$ (1 eq.)	10h (-78 °C)	No product

3.6. 1. $BF_3.OEt_2$ and $TiCl_4$-mediated reaction of (72) and benzaldehyde dimethyl acetal

Selection of an appropriate Lewis acid was an important consideration for these processes. We proceeded by employing the simplest aromatic acetal, benzaldehyde dimethyl acetal, as a model compound and set out to examine the effect of various Lewis acids on the condensation process. Our initial studies involved the reaction of allylsilane (**72**) and benzaldehyde dimethyl acetal with $TiCl_4$ under procedure A: treatment of 1:1 molar ratio of allylsilane (**72**) and acetal with 2 equivalents of $TiCl_4$ at -78 °C for 10 minutes (entry 5, **Table 3. 2**). The reaction was allowed to warm up to room temperature overnight, followed by quenching with saturated sodium bicarbonate, and led to the formation of the product in low yield (25 %), which was accompanied by deprotected starting material. In order to overcome the problem of deprotection of the amine, less reactive Lewis acids were examined. To this end we employed $BF_3.OEt_2$, which is a weaker Lewis acid than $TiCl_4$.[17] The reaction was carried out at -78 °C (procedure A) and

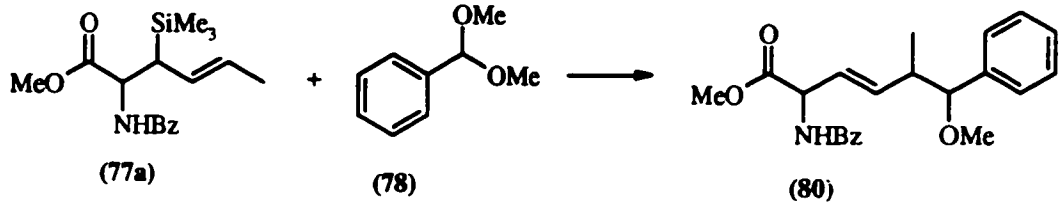
monitored by TLC; after two hours a small amount of product was observed. The reaction was kept at -78 °C for 3 hours, then allowed to warm up to ambient temperature. After 10 hours the reaction was worked up and 20% of product was isolated along with 30 % of starting material (entry 1, **Table 3. 2**). The yield of the reaction was improved when the mode of mixing the reagents and temperature of the reaction were changed (procedure B); allylsilane (**72**) was slowly added to a pre-mixed solution of benzaldehyde dimethyl acetal and $BF_3.OEt_2$ in CH_2Cl_2 at -78 °C. The best results were achieved when 2 eq. of $BF_3.OEt_2$ was employed (entry 3, **Table 3. 2**). In most of the reactions, stoichiometric quantities of $BF_3.OEt_2$ and acetal were required to achieve significant yields (50%).

The reaction conditions optimized for $BF_3.OEt_2$ were employed for the reaction of titanium tetrachloride and benzaldehyde dimethyl acetal. Only 1 equivalent of $TiCl_4$ was needed to effect the reaction and the desired product was obtained within 6 hours in high yield (77%). However, the reaction temperature proved to be an important factor in obtaining good yield (entry 7, Table 3. 2): higher temperatures led to the removal of the amine protecting group. Large excesses of $TiCl_4$ did not only lead to removal of the protecting group but also complicated the reaction work-up. The best result was obtained when procedure B was employed and the temperature was kept at -78 °C for 10 or more hours (78%, entry 8, **Table 3.3**). The product was purified on silica gel and fully characterized by ^1H and ^{13}C NMR. However, no diastereomeric products could be observed by NMR. Presumably, the two chiral centers at C2 and C5 are too far away from each other for diastereoselection to take place. Since this reaction did not apparently

lead to any stereoselectivity, we next evaluated the reaction of methyl-2-(*N*-PG)-3-(trimethylsilyl)-(*E*)-hex-4-enoate (**77**) with aromatic acetals.

3.6. 2. $BF_3.OEt_2$ and $TiCl_4$-mediated reaction of (77a) and aromatic acetal.

The reaction of methyl 2-(*N*-PG)-3-(trimethylsilyl)-(*E*)-hex-4-enoate (**77a-c**) with different protecting groups was examined. Compound (**77a**), derivatized with the benzoyl group (Bz), was used in the hope that Bz would be stable to the acidic conditions of the reaction. The reaction of benzaldehyde dimethyl acetal and crotylsilane was studied with two different Lewis acids, boron trifluoride etherate and titanium tetrachloride. The results are summarized in (**Table 3.3**). As shown in Table 3.3, all reactions studied gave mixtures of two diastereomers resulting from attack of the crotylsilane (**77a**) on the two diastereotopic faces of the Lewis acid coordinated acetal group.



Scheme 3. 22: Lewis acid-mediated addition of (77a) acetals

Table 3. 3: Summary of the Lewis acid mediated addition of (77a) to benzaldehyde dimethylacetal.

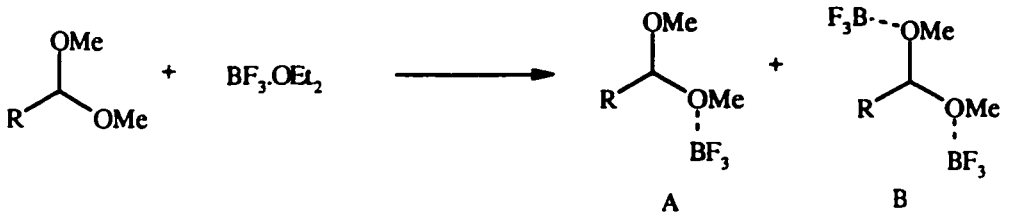
Entry	Procedure	Lewis acid	Time (temp.)	Yield	d.e.
1	B	$BF_3.OEt_2$ (2.0 eq.)	10 h (-78 °C)	70	5.8:1
2		$BF_3.OEt_2$ (0.5 eq.)	12 (-78 °C)	No product	
3		$TiCl_4$ (1.0 eq.)	6h (-78 °C)	60	6.2:1
4		$TiCl_4$ (0.5 eq.)	10 (-78 °C)	35	6.2:1
5		$TiCl_4$ (0.2 eq.)		No product	
6		$TiCl_4$ (1.2 eq.)	5h (-78 °C → rt)	68	6.2:1
7	D	$TiCl_4$ (1.2 eq.)	24h (-78 °C)	80	6.2:1

Again, the yield of the reaction depended on the quantity of the Lewis acids. In all cases higher yields were obtained when one or more equivalents of the Lewis acid was used. In general, $TiCl_4$ is the preferred Lewis acid, as it gave a better yield and, although the reaction of $BF_3.OEt_2$ is slower, there is no significant difference in the diastereoselectivity between $BF_3.OEt_2$ and $TiCl_4$.

It was reported that the $TiCl_4$-mediated addition of allylsilane to aldehydes depended on quantity of $TiCl_4$ used,[40] due to the formation of different $TiCl_4$/aldehyde complexes. It was decided to test if such a scenario would exist in our reaction. When 0.5 mol. equivalent of $TiCl_4$ was used to activate the reaction, no difference was observed on reaction stereoselectivity (entry 4, **Table 3.3**), but the yield was lower and there was substantial amount of unreacted starting material. Further reduction of the amount of $TiCl_4$ used to 0.2 eq. did not lead to any product (entry 5, **Table 3.3**): only starting material was recovered. When mixed solvents were employed, such as a CH_2Cl_2/toluene mixture at -78 °C, no reaction took place; again only unreacted starting material was recovered.

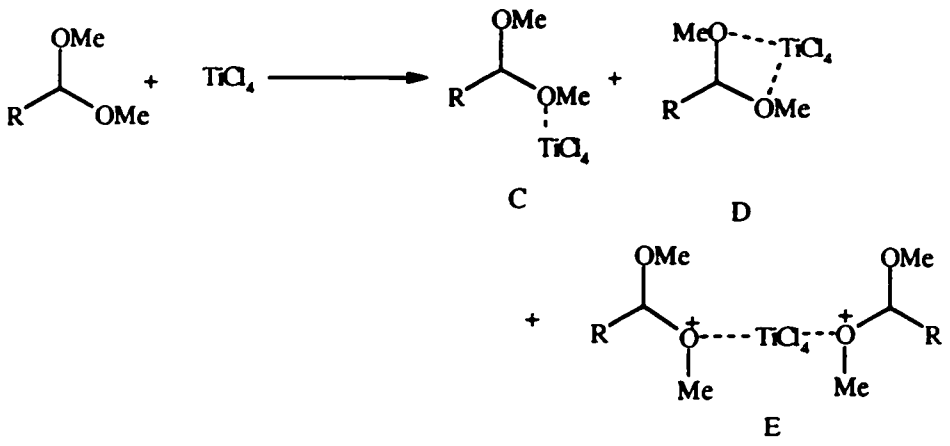
Several generalizations may be drawn from the data in **table 3.3.** First, diastereoselectivity is moderate for both Lewis acids for the reaction of crotylsilane **(77a)** and benzaldehyde dimethyl acetal. Yields are good with $TiCl_4$ (80%, entry 7), lower with $BF_3.OEt_2$ (70%, entry 1, **Table 3.3**), but depend on the mode of combining the reagents and the reaction temperature (procedure D). The yield decreases with the quantity of Lewis acid used. This suggests that the Lewis acid/acetal complexation is an important

parameter for the reaction yield and selectivity. Formation of both the 1:1 acetal/ $BF_3.OEt_2$ complex or 1:2 complex are possible (**Scheme 3. 23**).



Scheme 3. 23: $BF_3.OEt_2$/acetal complexes

In the case of $TiCl_4$, a 1:1 complex (C), 1:1 complex (D) or 2:1 complex (E) of acetal/$TiCl_4$ are possible (**Scheme 3. 24**). The existence of such complexes can affect the outcome of the stereochemistry and the yield of the product. In the case of $BF_3.OEt_2$, if complex B is the reactive intermediate, then the yield of the reaction should increase with amount of $BF_3.OEt_2$ used. This is what we observed in both the reactions of allylsilanes (**72**) and (**77a**) with benzaldehyde dimethyl acetal (entries 1, 3, **Table 3.3**). In the case of $TiCl_4$, when 0.5 equivalent of $TiCl_4$ was used, the yield was low and unreacted starting material was recovered. Further reduction of the amount of $TiCl_4$ led to an even further reduction of the yield. However, increasing the amount of $TiCl_4$ used resulted in an increase in yield (entry 7, **Table 3.3**). In both cases, there was no significant change in the reaction diastereoselectivity, in relation to the amount of Lewis acid used. These experiments suggest that 1:2 acetal/$BF_3.OEt_2$ complex B and 1:1 $TiCl_4$/acetal complex D .are formed in the $BF_3.OEt_2$ and $TiCl_4$-mediated addition of α-allylsilane amino acids to aromatic acetals, respectively.

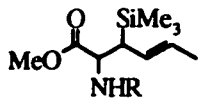
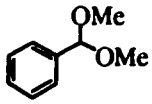
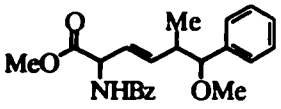
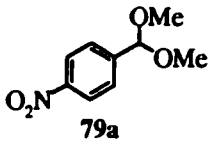
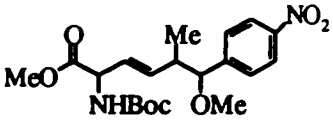
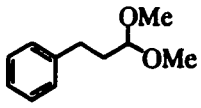
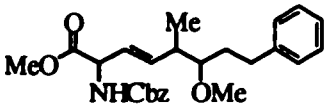
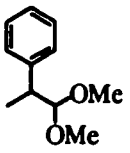
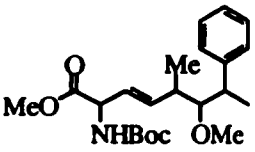


Scheme 3. 24: $TiCl_4$/acetal complexes

A summary of the experimental results describing the diastereoselective additions of α-amino allylsilanes (**77a –77d**) to a series of related aryl acetals (**75, 79a-79c**) is given in (**Scheme 3. 25**). All the reactions proceed smoothly with $TiCl_4/CH_2Cl_2$ at -78 °C to give high chemical yield and high diastereoselectivity; substituted aromatic acetals performed better than benzaldehyde dimethyl acetal. In the case of 4-NO_2-benzaldehyde dimethyl acetal, an excellent yield (80%) and diastereoselectivity (40:1) were achieved.

When an alkyl chain is placed between the aromatic ring and the acetal group (**79b**), still better yields and better selectivity were obtained than in the reaction of (**77**) with benzaldehyde dimethyl acetal.

Summary of $TiCl_4$-mediated (**77a-c**) additions to aromatic acetals.

Entry			
1	 **77a** **R= Bz**	 **75**	 77% 6:1 24h **80a**
2	**77b** **R= Boc**	 **79a**	 80% 40:1 6h **80b**
3	**77c** **R=Cbz**	 **79b**	 76% 5h **80c**
4	**77b** **R= Boc**	 **79c**	 64% 12h **80d**

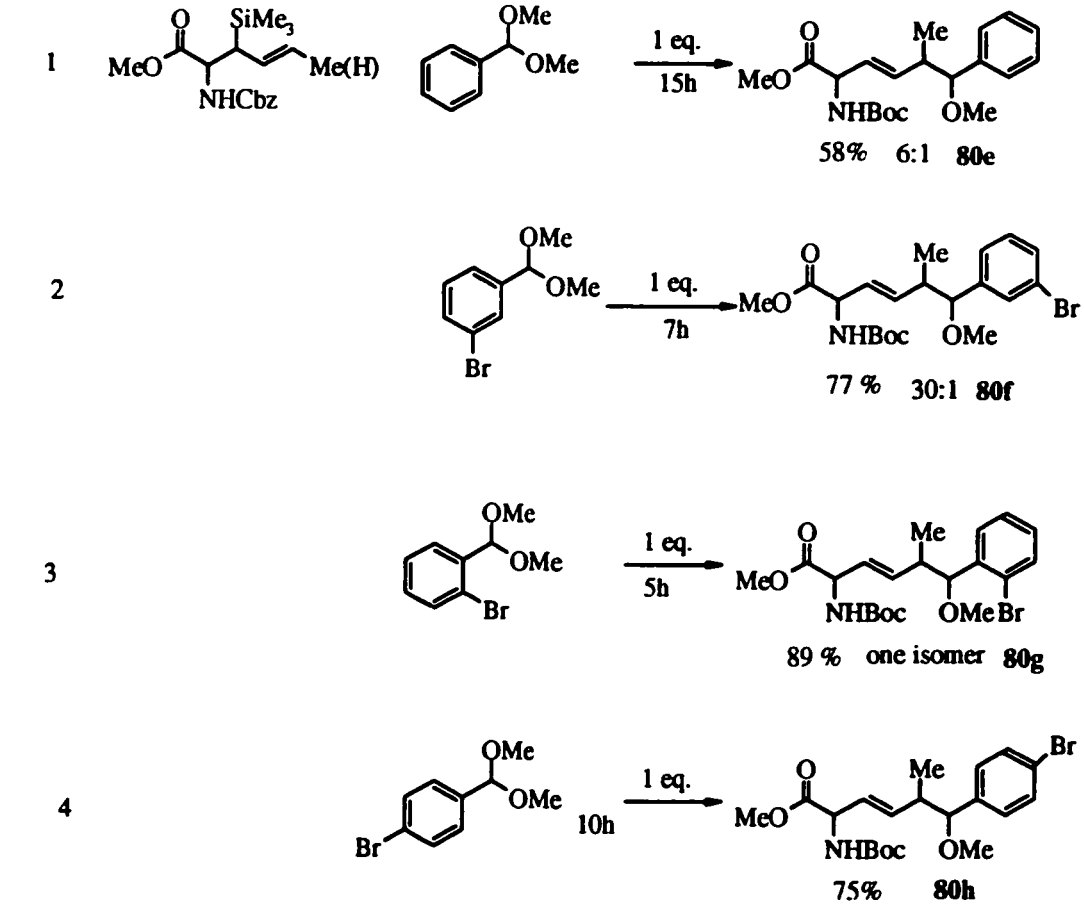
Scheme 3. 25: Lewis acid-mediated addition of (77a-c) to aromatic acetals.

The protecting group on the amino group did not play a major role in the diastereoselectivity of these reactions. The Boc group tends to come off at higher temperatures and when excess Lewis acid is employed. However, this problem could be avoided by keeping the reaction temperature at -78 °C for a longer period of time (6-12 hours).

3.6. 3. Acetal substituent effect on diastereoselectiviy.

The modest selectivity and the low yield of the reaction of benzaldehyde dimethyl acetal with allylsilanes **(72)** and **(77a)** led us to further investigate aromatic acetals with different substitution patterns, including *o*, *m*, and *p*-substituted. The reaction of 4-methoxybenzaldehyd dimethyl acetal with **(77b)** did not lead to the formation of the addition product. However, the high chemical yield and high diastereoselectivity observed in the case of 4-NO_2-benzaldehyde dimethyl acetal encouraged us to investigate other substituted aromatic acetals. Among the substituted aromatic acetals examined, halo-substituted aromatic acetals led to excellent yield and excellent diastereoselectivity. In all cases, only 1.0 equivalents of $TiCl_4$ was required to effect the reaction **(Scheme 3.26)**. A remarkable result was obtained with 2-bromobenzaldehyde dimethyl acetal: the product was formed in high yield (89 %), and only one isomer was observed by ^1H NMR (entry 3, **Scheme 3.26**).

Summary of $TiCl_4$-mediated addition of (**77b**) to halo-substituted aromatic acetals: substituent effect on diastereoselectivity and reaction yield.

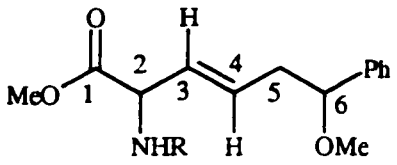


Scheme 3. 26: Substituent effect on diastereoselectivity of the reaction.

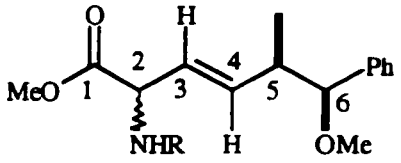
3. 7. Stereochemistry

In the reaction of crotylsilane (**77**) with aromatic acetals (**G, Figure 3. 4**) a new double bond and two new chiral centers form in a 1,2-relationship. Both the configuration of the newly formed double bond and the stereochemistry of the emerging chiral centers depend on the stereochemistry of the starting allylsilane (**77**). All the starting silanes have a *syn*

relationship at C2 and C3 (**Scheme 3.19**). The double bond of the crotylsilanes (**77a-77c**) has the (*E*)-configuration (see Chapter 1).



F



G

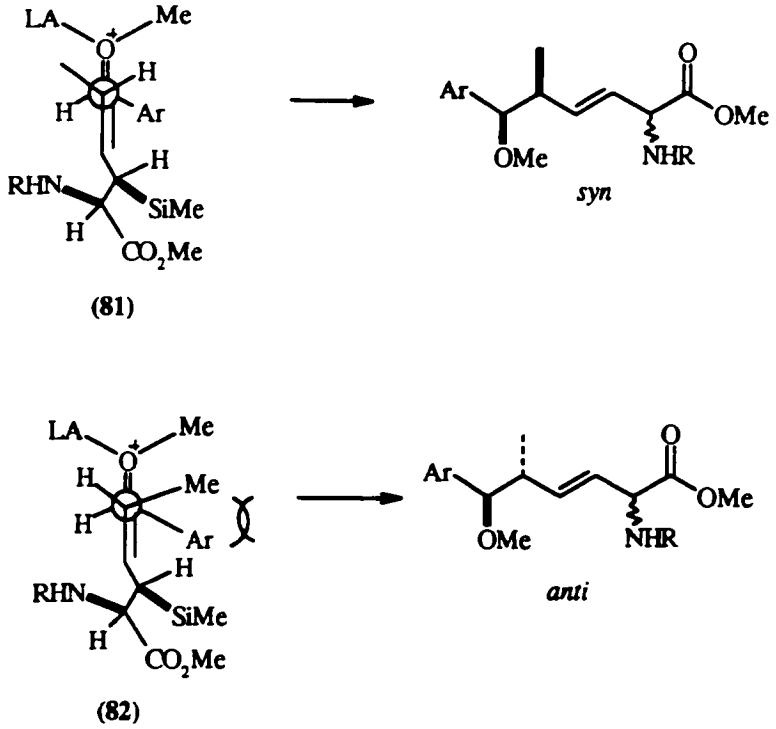
Figure 3. 4: Stereochemistry of the product.

We have tried to use both HPLC and GC to measure diastereoselectivity of the reaction. However, only one signal was observed in both cases. From the reaction of (**77a-c**) with the aromatic acetals, two sets of ^{1}H NMR signals were observed in the product (**G**). These signals are due to the two adjacent chiral centers at C5 and C6 (**G**, **Figure 3. 4**). Comparison of the chemical shift and coupling constant with those reported in the literature indicate that the *syn* isomer is the major product in all cases.[32] The double bond geometry in the product from the reaction of (**72**) and (**77a-c**), respectively, with the acetals is determined from the ^{1}H NMR coupling constant of C3 and C4, J ~ 16.0 Hz, indicative of an (*E*)-double bond.

3. 8 Mechanism

The stereochemical outcome of the reaction is a consequence of the small group (H) occupying the inside position (eclipsed with the double bond of the allylsilane) in the transition state of the reaction, when contrasted to the bulky α-amino acid group eclipsing the allylsilane double bond (**Scheme 3. 3**). Two antiperiplanar transition states among the possible transition states are shown below (**Scheme 3. 27**). Transition state

(81) minimizes the steric interaction between the aromatic ring and the MeO group assuming that one methoxy group complexes with the Lewis acid and the reaction proceeds via an S_N2 mechanism. This is consistent with the observed diastereoselectivity. The reaction of **(77b)** with 2-Br-benzaldehyde dimethyl acetal results in the formation of only one isomer as product (entry, 3, **Scheme 3. 25**), due to the close proximity of the Br-atom at the reaction center in the transition state.



Scheme 3. 27: Antiperiplanar transition state structures.

In the reaction of crotylsilanes with aromatic acetals, Sakurai and Hosomi suggested an alternative six membered transition state for the observed *syn* selectivity **(Figure 3. 5)**.[14] Between the proposed transition states, transition state **(83)** places the Me group of the silane and the Me group of the MeO in positions that minimize the 1,3-diaxial interaction, while in the transition state **(84)** the two Me groups experience severe 1,3-diaxial

interactions. The crotylsilane **(77)** has a bulky (*N*-PG) substituent at the α-position. The size of the amine group would make such a six-membered transition state **(8?** unfavorable. For simplicity, transition states **(81)** and **(82)** do not account for the possibl. interaction of the amine group with the Lewis acid.

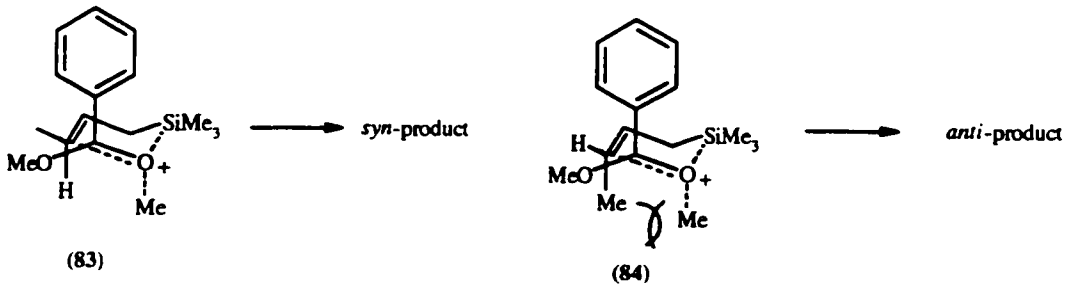


Figure 3. 5: Six-membered transition state structures

3. 9. Conclusion

In summary, we have studied the reactions of aromatic acetals with both α-allylsilanes and α-crotylsilane amino acid derivatives. Benzaldehyde dimethyl acetal shows modest diastereofacial selectivity and modest yield, consistent with antiperiplanar addition of allylsilane to the acetal. Less than 1 mol. equivalent of the Lewis acid resulted in somewhat lower yields, while an excess tended to complicate reaction workup. High reaction temperatures also decreased reaction efficiency. Excellent yield and diastereoselectivity was obtained with Br-substituted aromatic acetals.

3. 10. Experimental

^{1}H and ^{13}C NMR spectra were recorded on Bruker AV-200, 300 and 500 MHz spectrometers with $CDCl_3$ as an internal standard. IR spectra were recorded on a Biorad spectrometer. Electron impact (EI) and chemical ionization (CI, NH_3) mass spectra were recorded at 70 eV with a source temperature of 200 °C on a VG Instrument analytical ZAB-R mass spectrometer equipped with a VG 11-250 data system. Gas chromatographic (GC) analyses were carried out using a Hewlett-Packard 5890A gas chromatography equipped with a conventional heated injector, a flame ionization detector, a Hewlett-Packard 3393A integrator, and a DB-1 megabore capillary column (30m x 0.54mm Chromatographic Specialities, Inc.).

All the syntheses were performed with dry glassware under an atmosphere of anhydrous nitrogen. The following reagents were purchased from Aldrich: zinc chloride was flame heated/dried, boron trifluoride etherate and titanium tetrachloride were distilled prior to use. Silica gel was purchased from Silicycle. Dichloromethane was distilled from phosphorus pentoxide before use.

Representative experimental procedure for the $TiCl_4$-promoted reaction of methyl-2-(*N*-PG)-3-(trimethylsilyl)-(*E*)-pent-4-enoate (72) with aromatic acetals.

Procedure A: In a round-bottomed flask, benzaldehyde dimethyl acetal (0.2 g, 1.3 mmol) and allylsilane (0.39 g, 1.3 mmol) in freshly distilled CH_2Cl_2 (2 mL) solution was cooled at -78 °C. The mixture was allowed to stir for 10 min. before a solution of $TiCl_4$ (1.2 eq. 1.6 mmol) was introduced through a syringe and a needle over 10 min. The

reaction mixture was allowed to warm up to room temperature overnight. The reaction mixture was quenched with H_2O (10 mL) and extracted with EtOAc (2 x10 mL).

Procedure B: A 25 mL round-bottomed flask equipped with a magnetic stir bar and rubber septum, and charged with dry CH_2Cl_2 (3 mL), and benzaldehyde dimethyl acetal (0.15 g, 0.98 mmol) was cooled at 0 °C. To this solution, $TiCl_4$ (2.0 eq., 2 mmol) was added under N_2. The reaction mixture was warmed up to room temperature for 10 min, then cooled to -78 °C. A solution of methyl 2-(*N*-PG)-3-(trimethylsilyl)-(*E*)-pent-4-enoate (**72**) (0.29 g, 0.98 mmol) in CH_2Cl_2 (2 mL) was added dropwise over a period of 5 min. After 24 h the reaction mixture was diluted with a saturated solution of $NaHCO_3$ (5 mL) and extracted with EtOAc (2 x 5mL). The combined organic layers were dried with anhydrous $MgSO_4$, filtered and solvent was removed *in vacuo*. The product was purified by chromatography on silica gel using 25 % EtOAc: pentane as eluent.

Procedure C: A solution of the benzaldehyde dimethylacetal (0.30 g, 1 mmol) in dry methylene chloride (2 mL) was cooled to -78 °C and treated with $TiCl_4$ (1.5 mmol). The red-orange solution was stirred for 2 min, a solution of crotylsilane (0.31g, 1mmol) in CH_2Cl_2 (1 mL) was added. The reaction mixture was left stirring for 2 h at -78 °C and diluted with saturated sodium bicarbonate solution.

Procedure D: to a precooled $TiCl_4$ (1 mmol) solution (-78 °C) was added a solution of the acetal in CH_2Cl_2 (2 mL) slowly over the course of 10 min, the resulting milky orange solution was then stirred for more than 15 min in order to allow time for the coordinative interactions between the acetal and $TiCl_4$ to be completely established. When the solution

became clear yellow, allylsilane in CH_2Cl_2 (2 mL) was added over the course of 20 minutes through syringe and needle.

(*E*)-Methyl 6-(phenyl)-2-(*N*-*tert*-butoxycarbonyl)-6-methoxyhex-3-enoate (76). Purification of the crude product on SiO_2 (25% EtOAc/pentane eluant) afforded (0.34 g, 1.0 mmol, 77%); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36-7.25 (m, 5H), 5.77-5.72 (m, 1H), 5.49-5.44 (dd, 1H, *J* = 5.e, 15.2 Hz), 5.09 (bd, 1H), 4.78 (bs, 1H), 4.17-4.13 (m, 1H), 3.73, (s, 3H), 3.22 (s, 3H), 2.56-2.54 (m, 1H), 2.42-2.39 (m, 2H), 1.46 (s, 9H); ^{13}C (50.32 MHz, $CDCl_3$) δ 171.49, 154.80, 130.30, 128.27, 127.59, 126.90, 126.76, 83.31, 79.90, 56.56, 55.21, 52.27, 40.71, 28.25; IR (neat) ν_{max} 3363, 2979, 1749, 1495; CIMS (NH_3 gas) 367 ($M^+ + NH_4$), 350 $(M^+ + H)^+$, 311, 279, 250, 218, 121, 91, 57.

(*E*)-Methyl 6-(2-bromophenyl)-2-(*N*-Boc)-6-methoxy-5-methyl-hex-3-enoate (80g). Purification of the crude product on SiO_2 (30% EtOAc/pentane eluant) afforded (0.47 g, 1.1 mmol, 89%); ^{1}H (500 MHz, $CDCl_3$) δ 7.32 (m, 5H), 5.76 (dd, 1H, *J* = 7.8, 15.6 Hz), 5.36 (dd, 1H, *J* =5.7, 15.4 Hz), 5.01 (bm, 1H), 4.72 (bm, 1H), 4.45 (d, 1H, *J* = 5.61 Hz), 3.68 (s, 3H), 3.17 (s, 3H), 2.54-251 (m, 1H), 1.42 (s, 9H), 0.99 (d, *J* = 6.77 Hz, 3H); ^{13}C NMR (50.32 MHz, $CDCl_3$) δ 171.79, 154.73, 139.68, 136.26, 132.72, 128.92, 128.63, 127.49, 124.73, 124.07, 85.29, 80.05, 57.45, 55.21, 52.53, 42.43, 28.43, 14.65. IR (neat) ν_{max} 3367, 2979, 1718, 1501, 1166, 757, 733; HRMS on fragment calculated for $C_{18}H_{25}O_3NBr$ 382.1001, found 382.1017. ESMS 464 ($M + Na^+$), 482 ($M + K^+$).

(*E*)-Methyl 6-(3-bromophenyl)-2-(N-Boc)-6-methoxy-5-methyl-hex-3-enoate (80e) Purification of the crude product on SiO_2 (30% EtOAc/pentane eluant) afforded (0.34 g, 0.77 mmol, 77%); ^{1}H NMR (300, $CDCl_3$) δ 7.33-7.03 (m, 4H), 5.54 (dd, *J* = 7.7, 15.6 Hz,

1H), 5.23 (dd, J = 5.8, 15.5 Hz, 1H), 4.92 (bs, 1H), 3.82 (d, J = 6.40 Hz, 1H), 3.63 (s, 3H), 3.13 (s, 3H), 3.00 (q, J = 6.8 Hz, 1H), 1.39 (s, 9H), 0.95 (d, J = 6.8 Hz,1H); ^{13}C NMR (50.32 MHz, $CDCl_3$) δ 171.71, 154.95, 142.79, 135.80, 130.694, 130.41, 129.75, 126.24, 125.14, 122.42, 86.99, 80.09, 57.34, 55.26, 52.58, 43.18, 29.82, 28.40, 15.57; IR ν_{max} 3368, 2978, 1717; CIMS (NH_3) m/z 444 (M + NH_4^+, 7), 403 (62), 344, 199 (100).

(*E*)-Methyl 6-(4-bromophenyl)-2-(N-Boc)-6-methoxy-5-methyl-hex-3-enoate (80h).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.34 (d, J = 8.3 Hz, 2H), 6.97 (d, J = 8.3 Hz, 2H), 5.43 (dd, J = 15.5, 7.7 Hz, 1H), 5.16 (dd, J = 15.4, 5.9 Hz, 1H), 4.95 (bs, 1H), 4.60 (bs, 1H), 3.80 (d, J = 6.6 Hz, 1H), 3.59 (s, 3H), 3.09 (s, 3H), 2.39 (m, 1H), 1.40 (s, 9H), 0.93 (d, J = 6.74 Hz); ^{13}C (75 MHz, $CDCl_3$) δ 171,48, 154.79, 139.05, 135.63, 131.08, 129.17, 125.01, 121.24, 86.93, 79.95, 67.03, 57.00, 52.37, 42.95, 28.52, 15.56; IR ν_{max}3366, 2978, 1747; HRMS m/z calculated for $C_{23}H_{29}NO_5Br$ 442.1234, found: 4442.1229.

(*E*)-Methyl 6-(phenyl)-2-(*N*-Benzoyl)-6-methoxy-5-methyl-hex-3-enoate (80a).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.32 (m, 5H), 5.68 (dd, 1H, J = 7.0, 15.1 Hz), 5.40 (dd, 1H, J = 5.8, 15.2 Hz), 5.19 (bm, 1H), 3.92, (bd, 1H, J = 6.8 Hz), 3.74 (s, 3H), 3.21 (s, 3H), 2.59-2.55 (m, 1H), 1.09 (d, 3H, J = 6.7 Hz); ^{13}C NMR (50.32 MHz, $CDCl_3$) δ 171.58, 166.98, 140.08,136.76, 133.91, 128.70, 128.13, 127.66, 127.26, 124.25, 87.74, 57.14, 54.33, 52.77, 43.15, 15.81; IR (neat) ν_{max} 3435, 2940, 1742, 1661, 1282, 909, 734; CIMS (NH_3) m/z 368 (M + H, 5)$^+$, 336 (22), 121 (100), 77 (5).

(*E*)-Methyl 6-(4-nitrophenyl)-2-(*N*-Boc)-6-methoxy-5-methyl-hex-3-enoate (80b).

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.15 (d, 2H, J = 8.7 Hz), 7.35 (d, J = 8.7 Hz), 5.67-5.55 (ddd, 1H, J = 1.1, 7.7, 15.5, Hz), 5.41 (dd, 1H, J = 6.1, 15.5 Hz), 5.07 (bd, 1H, J = 16.2

Hz), 4.69 (bd, 1H, J = 6.2 Hz), 4.04 (d, 1H, J = 6.3 Hz), 3.64 (s, 1H), 3.19 (s, 3H), 2.55-2.45 (m, 3H), 1.40 (s, 9H), 0.99 (d, 3 H, J = 6.78 Hz); ^{13}C NMR (50.32 MHz, $CDCl_3$) δ 171.48,154.82,147.93, 147.49, 135.02, 128.32, 125.72, 123.31, 86.75, 80.17, 57.53, 55.25, 52.52, 43.13, 28.39, 15.57; IR ν_{max} 3383, 2935, 1715, 1524, 1348, 734; HRMS m/z calculated for $C_{20}H_{28}N_2O_6$ 409.1977, found: 409.1975 EIMS; 409 (1), 353 (5), 293 (4), 249 (5), 166 (100), 57 (71), 41 (25).

(*E*)-Methyl 8-phenyl-2-(*N*-Cbz)-6-methoxy-5-methyl-octa-3-enoate (80d).

^1H NMR (300 MHz, $CDCl_3$) δ; 7.24 (m, 5H), 7.15 (m, 5H), 5.72 (m, 1H), 5.11 (b, 1H), 4.9 (s, 2H), 4.7 (b, 1H), 3.7 (s, 3H), 3.3 (s, 3H), 3.0 (m, 1H), 2.6 (m, 2H), 1.7 (m, 2H), .99 (d, J = 6.7, 3H) ^{13}C NMR (50.32 MHz, $CDCl_3$) δ 136, 129, 128, 125, 124, 123, 84, 67, 57, 55, 52, 39, 32, 31, 15; HRMS required (426.2299), found (426,2280); IR (neat) ν_{max} 3433, 2934, 1720, 1496, 744, 700.

MSCI $(M+ NH_3)^+$, 443 (100), 426 (71), 382 (12), 350 (14), 207 (10), 108 (77), 91 (100), 52 (15).

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Chapter 4
Conclusion and future work

Conclusion

In this thesis we have shown that stereochemically defined α-amino acid derivatives could be achieved. In the first two chapters, the Claisen rearrangement of both vinylsilane and propargylsilane glycinate esters were performed in different reaction conditions. The Ireland-Claisen rearrangement of vinylsilane glycintes led to the formation of α-allylsilane amino acid derivatives in high yield and diastereoselectivity. The *syn* isomer was the major isomer in all reaction condition. The use of chelating salts such as $MgBr_2$ and $ZnCl_2$ led to enhanced diastereoselectivity of the product, but drastically lower yield was obtained in all cases.

In the rearrangement of propargylsilane glycinate esters neither the Ireland-Claisen nor the chelate-Claisen rearrangement led to the desired product in good yield. However, the Ireland-Claisen rearrangement of the propargylsilane glycinate esters led to formation of α-(bis(silyl)allenyl)-amino acid derivatives in excellent yield and good diastereoselectivity.

In chapter 3 of this thesis we have shown that allylsilanes carrying amino acid derivatives could reacted with acetals in the presence of Lewis acids. 1 eq. of $TiCl_4$ was required to obtain high yield, while at least 2 eq. of $BF_3.OEt_2$ was needed to effect the reaction.

Future Work

The work presented in thesis was limited to manipulation of racemic starting material. In the future the utilization of enantio pure material would offer opportunity for enantioinduction in the product. Testing biological activity of such molecules will be very interesting and may lead to discovery of therapeutically useful compounds.

There is potential application in the field of polymer chemistry. The procedures described in this thesis will allow incorporation of silicon polymers and peptides. Such materials could be used drug delivery and encapsulation technology.