Regiochemical Control in the Intramolecular Addition of Allylstannanes and Allylsilanes to 2,3-Epoxy Ethers: Preparation of Functionalized Oxepanes

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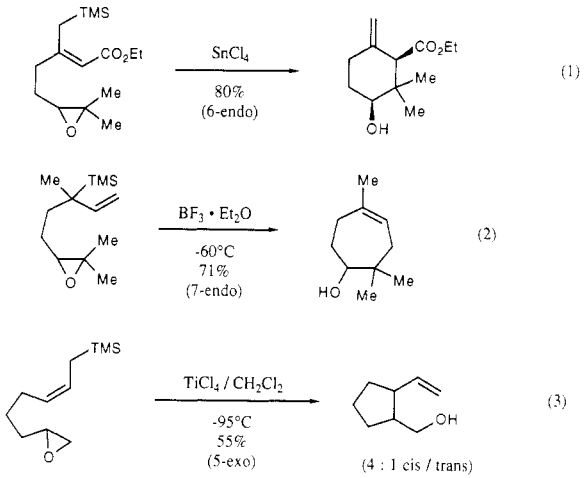
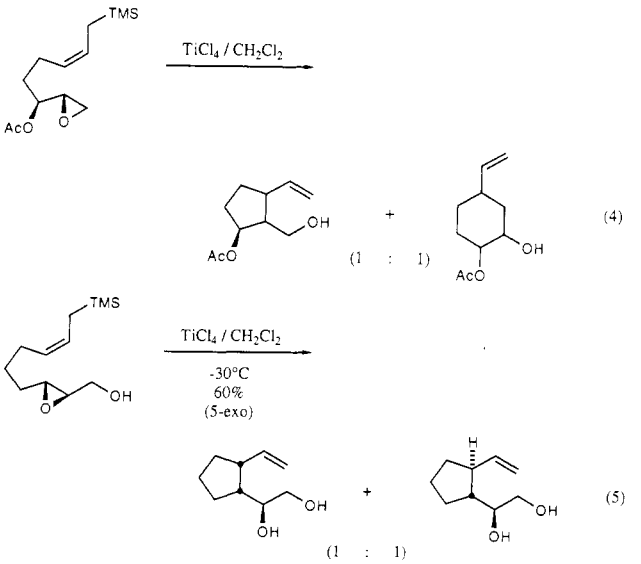
Lewis acid directed intramolecular additions of allylstannanes and allylsilanes to 2,3-epoxy ether substrates are described. Excellent regiocontrol and diastereoselectivity is achieved by titanium(IV) chloride promoted cyclization of substituted epoxy ether substrates. Cyclizations occur in high yields, providing direct routes to functionalized oxepanes.

In many cases, the attenuated reactivity of allylstannanes and allylsilanes toward carbon electrophiles provides distinct advantages over the reactivity of more classical alkali and alkaline earth organometallic nucleophiles.[2] These advantages are most recently illustrated by methodologies that exploit the high stereoselectivities intrinsic to allylstannane and allylsilane addition reactions. Equally powerful are the benefits arising from the unique chemoselectivities that these allylmetallics possess.[3] In addition to permitting unprecedented functional group discrimination in intermolecular addition reactions, this high chemoselectivity makes allylstannane and allylsilane species ideal precursors for intramolecular carbon–carbon bond-forming processes. Intermediates containing both allylmetallic nucleophile and carbon electrophile *in unprotected form* can often be prepared, purified, and characterized by standard laboratory methods. Lewis acids or fluoride ions serve as mild catalysts to trigger intramolecular reaction between the latent nucleophile and electrophilic partner in these substrates. In many instances, the high stereoselectivities observed in intramolecular addition reactions are magnified in their intramolecular variants.[4]

The emergence of the Sharpless asymmetric epoxidation reaction[5] places epoxides among the most attractive electrophiles for Lewis acid promoted reactions with allylsilanes and allylstannanes. We became particularly intrigued with the possibility of using epoxides as substrates for regiocontrolled and stereocontrolled intramolecular addition reactions. While such cyclizations are not unprecedented,[6] a general strategy for taming the ambident nature of epoxide electrophiles toward intramolecular allylstannane and allylsilane addition has not been reported. Isolated examples provide useful insight into factors responsible for regiochemical control in such processes. It is quite clear that stabilization of incipient positive charge in these Lewis acid mediated processes can override the entropic and stereoelectronic elements so important in purely nucleophilic processes.[7] In systems unbiased by oxygen substitution, carbon–carbon bond formation takes place at the most highly substituted epoxide center under Lewis acid catalysis (eq 1–3).[6d-f] As



might be anticipated, electron-withdrawing functional groups positioned to destabilize developing carbocationic character greatly influence regiochemistry in otherwise identical cyclizations (eq 4 and 5).[6f] These results, as well



(1) Alfred P. Sloan Foundation Fellow, 1987–1991.

(2) (a) Weber, W. P. *Silicon Reagents for Organic Synthesis*; Springer-Verlag: Berlin, 1983. (b) Colvin, E. W. *Silicon in Organic Synthesis*; Butterworths: London, 1981.

(3) For a review, see: Chan, T. H.; Fleming, I. *Synthesis* **1979**, 761.

(4) For recent examples see: (a) Anwar, S.; Davis, A. P. *Tetrahedron* **1988**, *44*, 3761. (b) Klaver, W. J.; Moolenaar, M. J.; Hiemstra, H.; Speckamp, W. N. *Tetrahedron* **1988**, *44*, 3805. (c) Schinzer, D.; Allagiannis, C.; Wichmann, S. *Tetrahedron* **1988**, *44*, 3851. (d) Molander, G. A.; Andrews, S. A. *Tetrahedron* **1988**, *44*, 3869. (e) Reetz, M. T.; Jung A.; Bolm, C. *Tetrahedron* **1988**, *44*, 3889.

(5) (a) Rossiter, B. E. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic: New York, 1985; Vol. 5. (b) Gao, Y.; Hanson, R. M.; Klunder, J. M.; Ko, S. Y.; Masamune, H.; Sharpless, K. B. *J. Am. Chem. Soc.* **1987**, *109*, 5765.

(6) (a) Cutting, I.; Parsons, P. J. *J. Chem. Soc., Chem. Commun.* **1983**, 1435. (b) Armstrong, R. J.; Weiler, L. *Can. J. Chem.* **1983**, *61*, 214. (c) Tan, T. S.; Mather, A. N.; Proctor, G.; Davidson, A. H. *J. Chem. Soc., Chem. Commun.* **1984**, 585. (d) Wang, D.; Chan, T.-H. *J. Chem. Soc., Chem. Commun.* **1984**, 1273. (e) Armstrong, R. J.; Weiler, L. *Can. J. Chem.* **1986**, *64*, 584. (f) Proctor, G.; Russell, A. T.; Murphy, P. J.; Tan, T. S.; Mather, A. N. *Tetrahedron* **1988**, *44*, 3953.

(7) (a) Parker, R. E.; Isaacs, N. S. *Chem. Rev.* **1959**, *59*, 737. (b) Stork, G.; Cohen, J. F. *J. Am. Chem. Soc.* **1974**, *96*, 5270. (c) Baldwin, J. E. *J. Chem. Soc., Chem. Commun.* **1976**, 734. (d) Cooke, M. P.; Houpis, I. N. *Tetrahedron Lett.* **1985**, *26*, 3643.

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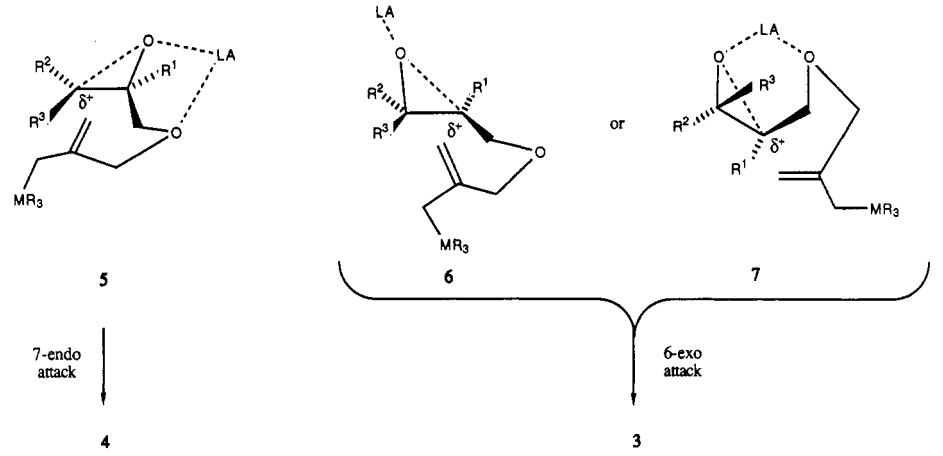
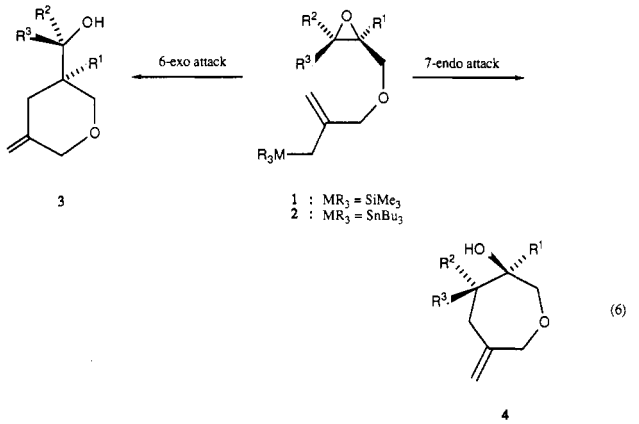
Scheme I



as reports describing regioselective intermolecular additions to epoxides[8] and recent annulation processes developed in our own laboratories,[9] suggested that proper choice of substrate and Lewis acid would provide a means of directing intramolecular epoxide cyclizations.

Results and Discussion

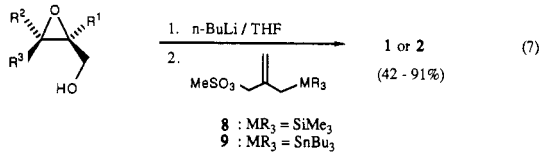
To explore the feasibility of directed intramolecular epoxide cyclization, we targeted a series of 2,3-epoxy ether substrates that could be ultimately derived from epoxy alcohols (**1**, **2**). Such substrates are susceptible to two distinct cyclization pathways. 6-Exo attack of the allylmetallic on the epoxide would lead to substituted pyran **3**, while 7-endo attack would provide oxepane **4** (eq 6).



We envisioned that regiocontrol of such substrates could be obtained by a combination of stereoelectronic factors. Our initial goal was to find a Lewis acid system that would maximize the influence of the electron-withdrawing ether moiety in our substrates. In such a system, polarization of the epoxide carbon–oxygen bond in the transition structure leading to 6-exo attack (**6** or **7**) would be disfavored due to the relative inability of that carbon center to stabilize a transient partial positive charge (Scheme I).

Secondly, we believed by employing a bidentate Lewis acid, 6-exo attack could be further disfavored by chelation between the ether oxygen and the oxygen of the epoxide. Chelated transition structure **7** leading to 6-exo attack would be unable to obtain the requisite colinear relationship[7] between the incoming nucleophilic center and the polarized epoxide oxygen–carbon bond, and therefore would be higher in energy than the corresponding transition structure leading to 7-endo attack (**5**), which has no such geometric constraint. Similar factors have been implicated in regioselective ring opening reactions of epoxy alcohols by external nucleophiles promoted by $Ti(O\textit{i}\text{-}Pr)_4$,[8] as well as in our previous annulation studies.[9]

Substrates required to test these postulates were observed by deprotonation of the substituted 2,3-epoxy alcohols with *n*-butyllithium, followed by alkylation of the resulting alkoxide with the appropriate allylic mesylate (**8** or **9**) (eq 7).[10] Attempts to use analogous sodium or potassium alkoxides in this etherification reaction invariably gave lower yields of the desired products, with desilylated or destannylated ethers being the major reaction byproducts. We were pleased to find that both series of substrates could generally be purified by silica gel chromatography without significant loss of material.



As a control, we initially examined cyclization of epoxysilane substrates with boron trifluoride diethyl etherate, a strong, nonchelating Lewis acid (Table I, entries 1–7). Regiochemistry of cyclization under these conditions was dominated by the substitution pattern about the epoxide. In each case the major cyclized product proved to be that arising from attack at the most highly substituted center, resulting in mixtures of regioisomeric products (**3** and **4**). Each regioisomer of unsymmetrically substituted substrates (entries 1, 3, 5–7) consisted of a single detectable diastereomer. Regiochemical and stereochemical assignments were based on spectroscopic evidence and were consistent with expected values.

It should be noted that −15 °C proved to be the optimal temperature for these cyclizations. Initiating the reactions at colder temperatures led to formation of unidentified cyclic byproducts, possibly arising from rearrangement of the epoxide prior to cyclization. Warmer reaction temperatures led to less regioselective reactions. Also note the

(8) (a) Caron, M.; Sharpless, K. B. *J. Org. Chem.* **1985**, *50*, 1557. (b) Chong, J. M.; Sharpless, K. B. *J. Org. Chem.* **1985**, *50*, 1560. (c) Maruoka, K.; Sano, H.; Yamamoto, H. *Chem. Lett.* **1985**, 599. (d) Dai, L.; Lou, B.; Zhang, Y.; Guo, G. *Tetrahedron Lett.* **1986**, *27*, 4343. (e) Riego, J.; Costa, A.; Saa, J. M. *Chem. Lett.* **1986**, 1565. (f) Kirshenbaum, K. S.; Sharpless, K. B. *Chem. Lett.* **1987**, 11.

(9) Molander, G. A.; Shubert, D. C. *J. Am. Chem. Soc.* **1987**, *109*, 576.

(10) (a) Trost, B. M.; Vincent, J. E. *J. Am. Chem. Soc.* **1980**, *102*, 5680. (b) Trost, B. M.; Chan, D. M. T.; Nanninga, T. N. *Org. Synth.* **1984**, *62*, 58.

Table I. Boron Trifluoride Diethyl Etherate Promoted Cyclization of Substituted 2,3-Epoxypropyl 2-[(Trimethylsilyl)methyl]-2-propenyl Ether (1) and Substituted 2,3-Epoxypropyl 2-[(Tributylstannyl)methyl]-2-propenyl Ether Substates (2)

entry	substrate	MR_3	R^1	R^2	R^3	ratio (3:4)	% isolated yield (3 + 4)
1	**1a**	$SiMe_3$	H	*n*-Pr	H	1:1.2	77
2	**1b**	$SiMe_3$	Me	H	H	7:1	63
3	**1c**	$SiMe_3$	H	H	*n*-Pr	1:1.2	78
4	**1d**	$SiMe_3$	H	Me	Me	1:7	73
5	**1e**	$SiMe_3$	H	Ph	H	1:9	82
6	**1j**	$SiMe_3$	H	Me	$(CH_2)_2CH{=}C(CH_3)_2$	1:7	63
7	**1k**	$SiMe_3$	H	$(CH_2)_2CH{=}C(CH_3)_2$	Me	1:7	65
8	**2a**	$SnBu_3$	H	*n*-Pr	H	1.1:1	86
9	**2b**	$SnBu_3$	Me	H	H	1.1:1	72
10	**2c**	$SnBu_3$	H	H	*n*-Pr	1.1:1	82
11	**2d**	$SnBu_3$	H	Me	Me	1.2:1	66
12	**2e**	$SnBu_3$	H	Ph	H	1:1.4	89

Table II. Titanium Tetrachloride Promoted Cyclization of Substituted 2,3-Epoxypropyl 2-[(Trimethylsilyl)methyl]-2-propenyl Ether (1) and Substituted 2,3-Epoxypropyl 2-[(Tributylstannyl)methyl]-2-propenyl Ether Substrates (2)

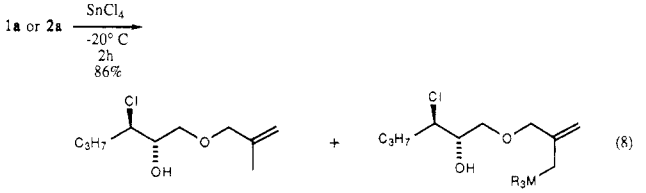
entry	substrate	MR_3	R^1	R^2	R^3	% isolated yield (4)
1	**1a**	$SiMe_3$	H	*n*-Pr	H	95
2	**1b**	$SiMe_3$	Me	H	H	75
3	**1c**	$SiMe_3$	H	H	*n*-Pr	92
4	**1d**	$SiMe_3$	H	Me	Me	68
5	**1e**	$SiMe_3$	H	Ph	H	83
6	**1f**	$SiMe_3$	H	H	H	48
7	**2a**	$SnBu_3$	H	*n*-Pr	H	100
8	**2b**	$SnBu_3$	Me	H	H	74
9	**2c**	$SnBu_3$	H	H	*n*-Pr	100
10	**2d**	$SnBu_3$	H	Me	Me	86
11	**2e**	$SnBu_3$	H	Ph	H	89
12	**2f**	$SnBu_3$	H	H	H	84
13	**2g**	$SnBu_3$	Et	Et	H	82
14	**2h**	$SnBu_3$	Et	H	Et	69
15	**2i**	$SnBu_3$	Et	Et	Et	74

low yields of the desired cyclized products in substrates derived from geraniol and nerol epoxides (entries 6 and 7). In these instances, interference of the remote olefin functionality introduced unidentified byproducts.

We were somewhat surprised to find that analogous allylstannane substrates (**2a–e**) were considerably less regioselective under identical reaction conditions, providing nearly equal amounts of regioisomers in the cases we examined (Table I, entries 8–12). We attribute this observation to the increased nucleophilicity of the allylstannanes relative to the corresponding allylsilanes, which presumably leads to an earlier transition state that is less discriminating toward stabilization of developing positive charge.

We were also interested in observing the cyclization process brought about by direct nucleophilic attack at the epoxide, i.e., reactions taking place without Lewis acid activation of the epoxide. We had hoped that such studies would reveal any inherent geometric preferences of our substrates for endo or exo attack. Unfortunately, our effort to achieve such cyclization by treatment of allylsilane substrates with fluoride ion or by transmetalation of allylstannane substrates to the corresponding allyllithium species were largely unsuccessful.

For our next step, we concentrated on selection and optimization of an appropriate Lewis acid system. We chose **1a** and **2a** as model compounds and subjected these to a variety of reaction protocols with the goal of increasing both regioselectivity and yield of cyclized products. These model compounds proved surprisingly unreactive to a number of the Lewis acid systems. For example, starting material could be recovered nearly quantitatively from toluene solutions containing excess titanium(IV) isopropoxide heated at reflux for several hours.[11] A second category of Lewis acid systems (tin(IV) chloride, aluminum chloride, zinc chloride, and diisopropoxy titanium(IV) chloride) gave predominantly mixtures of chlorohydrin products **10** and **11** (eq 8).[12]



(8)

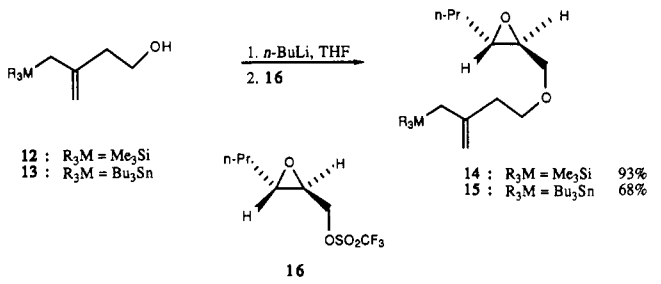
10 11

In fact, of the Lewis acids studied only titanium(IV) chloride proved generally useful for the desired transformations. Treatment of either **1a** or **2a** with dilute titanium(IV) chloride at 0 °C provided not only high yields of cyclized products, but was successful in directing the regiochemistry of addition to provide only products arising from 7-endo attack, thereby generating **4a** free of the exo regioisomer **3a** (Table II). The process was also completely diastereoselective; no detectable amount of the opposite diastereomer was evident in GC analysis of the crude reaction mixture. It is interesting to note that the regioselectivity observed in the titanium(IV) chloride promoted cyclization is highly dependent on the mode of reagent addition. Addition of titanium(IV) chloride to the substrate results in a relatively low yield of cyclized products, containing both isomers **3a** and **4a**, while slow addition of the substrate to a dilute solution of titanium-

(11) Magnesium bromide, zinc bromide, and titanium tetraethoxide were also largely unreactive.

(12) Spawn, C. L.; Drtina, G. J.; Wiemer, D. F. *Synthesis* **1986**, *4*, 315.

Scheme II



16

(IV) chloride results in the near quantitative yields of **4a** reported. Effects due to the mode of addition in other Lewis acid promoted reactions of allylstannanes and allylsilanes have been pointed out previously.[4d,13] The slightly lower yield in the cyclization of **1a** relative to **2a** can be attributed to competing formation of chlorohydrin **10** for the less reactive allylsilane substrate.

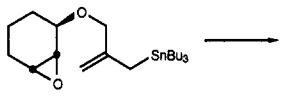
We next sought to define the generality of this process by subjecting a series of allylsilane (**1a–f**) and allylstannane substrates (**2a–i**) to the optimized $TiCl_4$ reaction conditions (Table II). The process proved most general, particularly for the allylstannane substrate series (entries 7–15). Oxepanes **4** could be generated in high yields regardless of the substitution pattern about the epoxide. For substrates unsymmetrically substituted at the 3-position, again complete diastereoselectivity was observed for the cyclization process. As with the model compounds, the allylsilane cyclizations proceeded in slightly lower yield due to competing chlorohydrin formation (entries 1–6).

Encouraged by these results, we sought to prepare the homologous allylsilane and allylstannane substrates, **14** and **15**, with hopes of expanding the scope of this methodology to include the preparation of the eight-membered rings.[14] Requisite substrates were successfully prepared by alkylation of the lithium alkoxides generated from either 3-[(trimethylsilyl)methyl]-3-buten-1-ol (**12**) or the analogous tributylstannane **13**. Because we found such alkoxides to be labile toward Brook type rearrangement at temperatures above 0 °C, it was necessary to employ highly reactive 2,3-epoxy triflate **16** as the alkylating agent in the reaction (Scheme II).

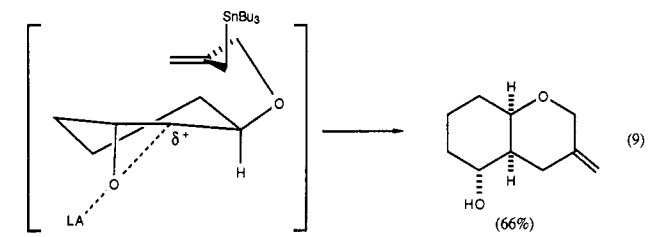
Unfortunately, subjection of allylsilane **14** to either the $BF_3{\cdot}OEt_2$ or the $TiCl_4$ reaction protocols gave no cyclized products. We were similarly unsuccessful in cyclizing corresponding allylstannane **15** utilizing $TiCl_4$, while treatment of this substrate with $BF_3{\cdot}OEt_2$ provided only the product arising from 7-exo attack as well as an unidentified rearrangement product in a combined yield of only 40%. Apparently, chlorohydrin formation or epoxide rearrangement successfully compete with the entropically disfavored cyclization in these cases.

Regiocontrol was also greatly affected when geometric constraints were imposed on the system which prevented 7-endo attack on the epoxide moiety. This was demonstrated in the attempted cyclization of cyclohexene oxide substrates **17** and **20**. These substrates were readily prepared from isomerically pure *cis*- or *trans*-2,3-epoxycyclohexanol and methyl 2-[(tributylstannyl)methyl]-2-propenylmethanesulfonate **9**, using the general epoxy-alcohol alkylation procedure described above.

Reaction of trans isomer **17** under *either* chelating or nonchelating Lewis acidic conditions gave bicyclic alcohol **19** as the only cyclized product. The rigid nature of the cyclic substrate permits only backside attack of the epoxide by the allylmetallic from the exo face as shown in transition structure **18** (eq 9). For a 7-endo epoxide ring opening process, the incoming allylstannane nucleophile cannot achieve the requisite colinear relationship with the oxygen carbon bond of the Lewis acid complexed epoxide.[7] Di-

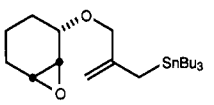


17



18 19 (9)

astereomeric *cis*-allylstannane **20** gave no cyclized products under *either* chelating or nonchelating Lewis acid promoting reaction conditions. This is presumably due to the inability of the allylstannane to approach the backside of either epoxide carbon in a proper orientation from either of the limiting conformations as shown in transition structures **21a** or **21b** (eq 10).



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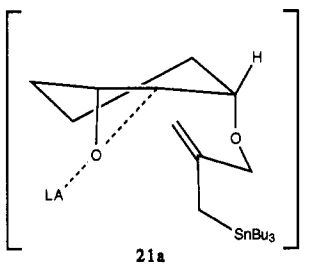
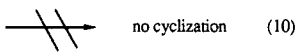
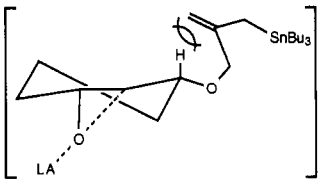


21a



(10)



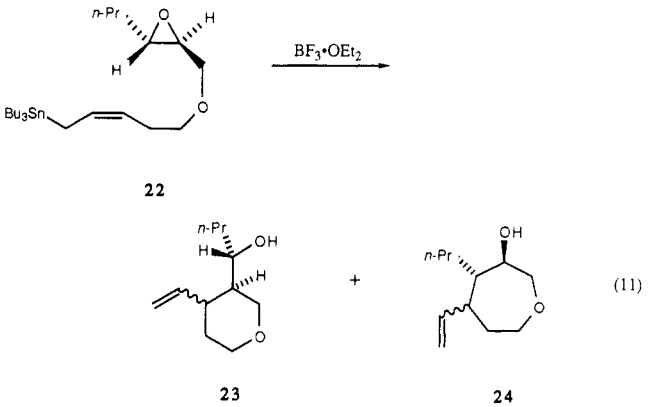
21b

We also attempted to expand our methodology to an analogous linear allylstannane **22**. Treatment of **22** with boron trifluoride diethyl etherate resulted in a 1:1 mixture of regioisomeric products, **23** and **24**, in a combined yield

(13) Keck, G. E.; Abbott, D. E.; Boden, E. P.; Enholm, E. J. *Tetrahedron Lett.* **1984**, *25*, 3927.

(14) Various alkenylsilane and allylsilane systems have been utilized previously in the generation of eight-membered rings. (a) Overman, L. E.; Castaneda, A.; Blumenkopf, T. A. *J. Am. Chem. Soc.* **1986**, *108*, 1303. (b) Overman, L. E.; Blumenkopf, T. A.; Castaneda, A.; Thompson, T. A. *J. Am. Chem. Soc.* **1986**, *108*, 3516. (c) Schreiber, S. L.; Sammakia, T.; Crowe, W. E. *J. Am. Chem. Soc.* **1986**, *108*, 3128.

of 63% (eq 11). Each regioisomer consisted of a 1:1 mixture of diastereomers, presumably at the ethylene center.[15]



(11)

Subjection of **22** to the standard titanium(IV) chloride reaction protocol gave only chlorohydrin products. At this time it is not clear why the attempted cyclization of this substrate differs from our earlier, successful examples.[4d]

Conclusions

Regioselectivity in the intramolecular addition of allylsilanes and allylstannanes to 2,3-epoxy ethers can be effectively controlled using titanium(IV) chloride, a strong, chelating Lewis acid. While a prototypical strong, nonchelating Lewis acid, boron trifluoride diethyl etherate, gave either low regioselectivity or regioselectivity dependent on the substitution about the epoxide, titanium(IV) chloride selectively catalyzed exclusive endo epoxide attack, providing high yields of substituted oxepane ring systems. Endo cyclization proceeded not only to the exclusion of exo processes, but also proceeded with strict inversion about the epoxide center, providing single diastereomers of cyclized products for unsymmetrically substituted examples.

The constraints of this control mechanism were defined in the attempted cyclization of homologous allylsilane and allylstannane substrates, in which failure to generate the corresponding eight-membered ring systems was attributed to entropic factors. The normally preferred 7-endo cyclization could be overridden by geometric constraints of the system as demonstrated by the attempted cyclization of cyclohexene oxide substrates.

Efforts continue in our laboratory to utilize allylsilane and allylstannane intermediates in regiocontrolled and stereocontrolled cyclization processes.

Experimental Section

^{1}H NMR spectra were recorded at 200, 250, or 300 MHz. ^{13}C NMR spectra were recorded at 50 or 62.5 MHz. Low-resolution and exact mass spectra were recorded on a VG-7070 EQ-HF mass spectrometer employing perfluorokerosene as internal standard and using a 70-eV ionization potential. Gas–liquid chromatographic analyses were conducted utilizing a 25 m × 320 μm 5% phenyl SE-54 fused silica capillary column. Flash chromatography was carried out by utilizing standard procedures.[16]

Reagents. Dichloromethane was stirred over concentrated H_2SO_4 overnight, washed with water and saturated potassium carbonate, fractionally distilled from calcium hydride under argon, and stored in a brown bottle over 4-Å molecular sieves. Titanium(IV) chloride was distilled prior to use and stored in a Teflon-stopcocked bottle under argon. Boron trifluoride diethyl etherate was distilled from calcium hydride and stored under argon. All reactions were conducted under an inert argon atmosphere, employing standard bench-top techniques for handling of air-sensitive materials.[17]

Preparation of Substituted 2,3-Epoxypropyl 2-[(Trimethylsilyl)methyl]-2-propenyl Ether and Substituted 2,3-Epoxypropyl 2-[(Tributylstannyl)methyl]-2-propenyl Ether Substrates. General Procedure. To a solution of (2*R**,3*S**)-2,3-epoxyhexan-1-ol (2.27 mmol) in dry THF (4.5 mL) at −78 °C was added dropwise a stock solution of *n*-butyllithium in hexanes (1.6 M, 2.3 mmol). The resulting solution was allowed to warm to room temperature over several min. To the reaction was added methyl 2-[(tributylstannyl)methyl]-2-propenesulfonate (2.3 mmol). The reaction flask was fitted with a condenser and heated at reflux for 16 h. The mixture was then cooled to room temperature and partitioned between ether (20 mL) and water (20 mL). The aqueous portion was further extracted with ether (3 × 10 mL), and the combined organic extracts were washed with brine (10 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo. Flash chromatography of the residue (5% EtOAc in hexanes on silica gel) provided **(2*R**,3*R**)-2,3-epoxyhexyl 2-[(tributylstannyl)methyl]-2-propenyl ether (2a)** as a clear, colorless liquid (900 mg, 1.96 mmol), 86%. ^{1}H NMR ($CDCl_3$): δ 4.69 (dt, *J* = 1.3, 1.9 Hz, 1 H), 4.64 (m, 1 H), 3.84 (m, 2 H), 3.58 (dd, *J* = 3.6, 11.4 Hz, 1 H), 3.40 (dd, *J* = 5.5, 11.4 Hz, 1 H), 2.89 (ddd, *J* = 2.3, 3.6, 5.6 Hz, 1 H), 2.80 (ddd, *J* = 2.3, 5.6, 5.8 Hz, 1 H), 1.80–1.20 (m, 22 H), 1.72 (s, 2 H), 1.01 (t, *J* = 7.1 Hz, 3 H), 0.95 (t, *J* = 7.2 Hz, 9 H). ^{13}C NMR ($CDCl_3$): δ 149.22, 128.23, 76.73, 74.23, 66.34, 62.95, 42.32, 38.59 (3 C), 33.22, 26.08 (3 C), 24.72 (3 C), 20.12, 18.79 (3 C), 17.44. FT-IR (neat): 2995, 1605, 1470, 1435, 1335, 1280, 1100, 1010, 870 cm^{-1}. Exact mass calcd for $C_{22}H_{44}O_2Sn$ 459.2375, found 459.2322.

Cyclization of Substituted 2,3-Epoxypropyl 2-[(Trimethylsilyl)methyl]-2-propenyl Ether and Substituted 2,3-Epoxypropyl 2-[(Tributylstannyl)methyl]-2-propenyl Ether Substrates with Boron Trifluoride Diethyl Etherate. General Procedure. To a solution of boron trifluoride diethyl etherate (2.4 mmol) in CH_2Cl_2 (6 mL) at −15 °C was added dropwise a solution of **(2*R**,3*R**)-2,3-epoxyhexyl 2-[(tributylstannyl)methyl]-2-propenyl ether (2a)** as a clear, colorless liquid (275 mg, 0.598 mmol) in CH_2Cl_2 (6 mL). The resulting solution was maintained at −15 °C for 2 h and then was quenched by rapid addition of pH 7 phosphate buffer (5 mL). The reaction was transferred into a separatory funnel with the aid of ether (5 mL), and the resulting layers were separated. The aqueous portion was further extracted with ether (5 × 5 mL), and the combined organic layers were washed with brine (5 mL), dried over Na_2SO_4, filtered, and concentrated. Chromatography (25% EtOAc in hexanes on silica) provided tetrahydropyran (**3a**) and oxepane (**4a**) as a clear, colorless liquid (combined 72.9 mg, 0.461 mmol) in 77% yield. **(3*R**)-3-[(1*S**)-1-Hydroxybutyl]-5-methylenetetrahydropyran (3a).** ^{1}H NMR ($CDCl_3$): δ 4.81 (m, 2 H), 4.08 (d, *J* = 12.2 Hz, 1 H), 3.90 (d, *J* = 12.2 Hz, 1 H), 3.84 (ddd, *J* = 1.3, 4.0, 11.2 Hz, 1 H), 3.60 (m, 1 H), 3.51 (dd, *J* = 8.9, 11.2 Hz, 1 H), 2.44 (dd, *J* = 4.9, 13.0 Hz, 1 H), 2.26 (dd, *J* = 9.8, 13.0 Hz, 1 H), 2.14–2.29 (m, 6 H), 0.94 (t, *J* = 7.2 Hz, 3 H). ^{13}C NMR ($CDCl_3$): δ 143.09, 110.05, 72.53, 72.17, 70.26, 42.88, 36.87, 32.23, 18.87, 14.04. FT-IR (neat): 3440, 2995, 1605, 1420, 1380, 1110, 990, 850 cm^{-1}. Exact mass calcd for $C_{10}H_{18}O_2$ 170.1307, found 170.1307.

***trans*-3-Hydroxy-4-propyl-6-methyleneoxepane (4a).** ^{1}H NMR ($CDCl_3$): δ 4.88 (dd, *J* = 1.6, 3.3 Hz, 1 H), 4.69 (m, 1 H), 4.24 (dt, *J* = 1.7, 14.3 Hz, 1 H), 4.11 (dt, *J* = 1.1, 14.3 Hz, 1 H), 3.60 (ddd, *J* = 0.9, 3.2, 13.3 Hz, 1 H), 3.4 (m, 1 H), 2.41 (d, *J* = 8.3 Hz, 1 H), 2.10 (dd, *J* = 6.8, 13.3 Hz, 1 H), 1.7–1.4 (m, 7 H), 0.90 (t, *J* = 7.2 Hz, 3 H). ^{13}C NMR ($CDCl_3$): δ 141.65, 118.96, 75.29, 70.81, 70.17, 45.91, 40.42, 32.25, 19.84, 19.43. FT-IR (neat): 3510, 2990, 1595, 1320, 1290, 1010, 890 cm^{-1}. Exact mass calcd for $C_{10}H_{18}O_2$ 170.1307, found 170.1314.

Cyclization of Substituted 2,3-Epoxypropyl 2-[(Trimethylsilyl)methyl]-2-propenyl Ether and Substituted 2,3-Epoxypropyl 2-[(Tributylstannyl)methyl]-2-propenyl Ether Substrates with Titanium(IV) Chloride. General Procedure. To a solution of **2a** (224 mg, 0.487 mmol) in CH_2Cl_2 (4.9 mL) at 0 °C was added dropwise a stock solution of titanium(IV) chloride

(15) Recently reported cyclizations of similar systems are also nondiastereoselective. See ref 6f.

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in CH_2Cl_2 (0.10 M, 0.49 mmol). The resulting solution was maintained at 0 °C for 15 min and then was quenched by rapid addition of saturated K_2CO_3 (5 mL). The reaction was transferred into a separatory funnel with the aid of ether (5 mL), and the layers were separated. The aqueous portion was further extracted with ether (5 × 5 mL), and the combined organic layers were washed with brine (5 mL), dried over Na_2SO_4, filtered, and concentrated. Chromatography (25% EtOAc in hexanes on silica) provided oxepane **4a** (82.9 mg, 0.487 mmol) as a clear, colorless liquid in 100% yield. Gas–liquid chromatographic analysis of the purified material indicated a chemical purity of 98%.

Cyclization of 2,3-Epoxy-2-methylpropyl 2-[(Tributylstannyl)methyl]-2-propenyl Ether (2b) with Titanium(IV) Chloride. By use of the general procedure described above, **2b** (249 mg, 0.578 mmol) was cyclized over 15 min to provide **3-hydroxy-3-methyl-6-methyleneoxepane (4b)** as a clear, colorless liquid (87.2 mg, 0.428 mmol, 74%), isolated by flash chromatography (30% EtOAc in hexanes on silica gel). Gas–liquid chromatographic analysis of the purified material indicated a chemical purity of 96%. ^{1}H NMR ($CDCl_3$): δ 5.01 (b s, 1 H), 4.94 (b s, 1 H), 4.01 (d, J = 10.1 Hz, 1 H), 3.96 (d, J = 10.1 Hz, 1 H), 3.68 (d, J = 11.3 Hz, 1 H), 3.43 (d, J = 11.3 Hz, 1 H), 2.36–1.84 (m, 4 H), 2.21 (b s, 1 H), 1.23 (s, 3 H). ^{13}C NMR ($CDCl_3$): δ 141.82, 116.29, 75.23, 74.28, 73.69, 40.38, 28.06, 18.26. FT-IR (neat): 3480, 2995, 1605, 1235, 1100, 990 cm^{-1}. Exact mass calcd for $C_8H_{14}O_2$ 142.0994, found 142.1003.

Cyclization of (2*R,3*S**)-2,3-Epoxyhexyl 2-[(Tributylstannyl)methyl]-2-propenyl Ether (2c) with Titanium(IV) Chloride.** By use of the general procedure described above, **2c** (284 mg, 0.620 mmol) was cyclized over 15 min to provide ***cis*-3-hydroxy-4-propyl-6-methyleneoxepane (4c)** as a clear, colorless liquid (105 mg, 0.620 mmol, 100%), isolated by flash chromatography (25% EtOAc in hexanes on silica gel). Gas–liquid chromatographic analysis of the purified material indicated a chemical purity of 96%. ^{1}H NMR ($CDCl_3$): δ 4.93 (m, 1 H), 4.73 (b s, 1 H), 4.20 (d, J = 13.9 Hz, 1 H), 4.12 (d, J = 13.9 Hz, 1 H), 3.79 (dd, J = 3.3, 13.2 Hz, 1 H), 3.68 (dd, J = 1.3, 13.2 Hz, 1 H), 3.43 (ddd, J = 1.3, 3.3, 5.6 Hz, 1 H), 2.44 (dd, J = 8.2, 12.1 Hz, 1 H), 2.36 (b s, 1 H), 2.24 (dd, J = 3.0, 12.1 Hz, 1 H), 2.05–1.35 (m, 5 H), 0.88 (t, J = 7.2 Hz, 3 H). ^{13}C NMR ($CDCl_3$): δ 143.21, 114.11, 75.13, 71.01, 69.02, 44.34, 40.42, 33.35, 24.84, 18.16. FT-IR (neat): 3500, 2995, 1600, 1345, 1295, 1000, 870 cm^{-1}. Exact mass calcd for $C_{10}H_{18}O_2$ 170.1307, found 170.1323.

Cyclization of 2,3-Epoxy-3-methylbutyl 2-[(Tributylstannyl)methyl]-2-propenyl Ether (2d) with Titanium(IV) Chloride. By use of the general procedure described above, **2d** (259 mg, 0.582 mmol) was cyclized over 15 min to provide **3-hydroxy-4,4-dimethyl-6-methyleneoxepane (4d)** as a clear, colorless liquid (78.3 mg, 0.501 mmol, 86%), isolated by flash chromatography (30% EtOAc in hexanes on silica gel). Gas–liquid chromatographic analysis of the purified material indicated a chemical purity of 95%. ^{1}H NMR ($CDCl_3$): δ 4.93 (dd, J = 1.5, 3.5 Hz, 1 H), 4.83 (b s, 1 H), 4.29 (dt, J = 1.5, 14.2 Hz, 1 H), 4.15 (dt, J = 3.5, 14.2 Hz, 1 H), 3.61 (dd, J = 4.9, 12.6 Hz, 1 H), 3.50 (dd, J = 1.1, 12.6 Hz, 1 H), 3.17 (ddd, J = 1.1, 4.9, 9.3 Hz, 1 H), 2.36 (d, J = 13.1 Hz, 1 H), 1.87 (d, J = 13.1 Hz, 1 H) 1.72 (b s, 1 H), 1.13 (s, 3 H), 0.95 (s, 3 H). ^{13}C NMR ($CDCl_3$): δ 140.58, 121.11, 77.13, 72.31, 72.02, 43.34, 30.14, 23.33, 20.26. FT-IR (neat): 3470, 2990, 1605, 1400, 1005, 870 cm^{-1}. Exact mass calcd for $C_9H_{16}O_2$ 156.1150, found 156.1133.

Cyclization of (2*R,3*R**)-2,3-Epoxy-3-phenylpropyl 2-[(Tributylstannyl)methyl]-2-propenyl Ether (2e) with Titanium(IV) Chloride.** Using the general procedure described above, **2e** (350 mg, 0.709 mmol) was cyclized over 5 min to provide ***trans*-3-hydroxy-4-phenyl-6-methyleneoxepane (4e)** as a clear, colorless liquid (128 mg, 0.631 mmol, 89%), isolated by flash chromatography (18% EtOAc in hexanes on silica gel). ^{1}H NMR ($CDCl_3$): δ 7.35–7.15 (m, 5 H), 4.99 (s, 1 H), 4.93 (s, 1 H), 4.37 (d, J = 14.2 Hz, 1 H), 4.18 (d, J = 14.2 Hz, 1 H), 3.99 (dd, J = 3.7, 12.0 Hz, 1 H), 3.82 (m, 1 H), 3.39 (dd, J = 9.6, 12.0 Hz, 1 H), 2.60 (dd, J = 6.7, 11.7 Hz, 1 H), 2.52 (dd, J = 6.7, 6.9 Hz, 1 H), 2.41 (d, J = 11.7 Hz, 1 H), 1.46 (d, J = 3.2 Hz, 1 H). ^{13}C NMR ($CDCl_3$): δ 144.22, 140.51, 128.76 (2 C), 128.31 (2 C), 127.06, 115.28, 74.68, 69.58, 68.24, 53.30, 40.11. FT-IR (neat): 3550, 2995, 2880, 1610, 1435, 1345, 1270, 1020, 990, 870 cm^{-1}. Exact mass calcd for $C_{13}H_{14}O$ (M − 18) 186.1045, found 186.1073.

Cyclization of 2,3-Epoxypropyl 2-[(Tributylstannyl)methyl]-2-propenyl Ether (2f) with Titanium(IV) Chloride. By use of the general procedure described above, **2f** (229 mg, 0.549 mmol) was cyclized over 15 min to provide **3-hydroxy-6-methyleneoxepane (4f)** as a clear, colorless liquid (92.3 mg, 0.461 mmol, 84%), isolated by flash chromatography (33% EtOAc in hexanes on silica gel). Gas–liquid chromatographic analysis of the purified material indicated a chemical purity of 99%. ^{1}H NMR ($CDCl_3$): δ 4.91 (m, 2 H), 4.37 (d, J = 13.2 Hz, 1 H), 4.18 (d, J = 13.2 Hz, 1 H), 3.99 (dd, J = 1.3, 11.0 Hz, 1 H), 3.42 (m, 1 H), 3.39 (dd, J = 9.6, 11.0 Hz, 1 H), 2.34–2.03 (m, 4 H), 1.34 (d, J = 2.7 Hz, 1 H). ^{13}C NMR ($CDCl_3$): δ 139.245, 120.89, 76.13, 73.17, 74.55, 40.55, 21.83. FT-IR ($CHCl_3$): 3510, 2970, 1605, 1300, 1280, 1000 cm^{-1}. Exact mass calcd for $C_7H_{13}O_2$ (M + 1) 129.0916, found 129.0899.

Cyclization of (2R*,3*R)-2-Ethyl-2,3-epoxypentyl 2-[(Tributylstannyl)methyl]-2-propenyl Ether (2g) with Titanium(IV) chloride.** By use of the general procedure described above, **2g** (217 mg, 0.561 mmol) was cyclized over 25 min to provide **(3*R**,4*S**)-3,4-diethyl-3-hydroxy-6-methyleneoxepane (4g)** as a clear, colorless liquid (84.8 mg, 0.460 mmol, 82%), isolated by flash chromatography (18% EtOAc in hexanes on silica gel). ^{1}H NMR ($CDCl_3$): δ 4.94 (b s, 1 H), 4.88 (b s, 1 H), 4.69 (d, J = 10.2 Hz, 1 H), 4.23 (d, J = 10.2 Hz, 1 H), 3.69 (d, J = 11.4 Hz, 1 H), 3.39 (d, J = 11.4 Hz, 1 H), 2.35 (s, 1 H), 2.13–1.58 (m, 7 H), 1.05 (t, J = 7.1 Hz, 3 H), 0.92 (t, J = 7.2 Hz, 3 H). ^{13}C NMR ($CDCl_3$): δ 144.89, 118.93, 76.13, 74.01, 73.98, 43.57, 40.42, 25.15, 24.84, 19.85, 19.23. FT-IR (neat): 3450, 2995, 1595, 1475, 1425, 1385, 1270, 1030, 880 cm^{-1}. Exact mass calcd for $C_{11}H_{20}O_2$ 184.1545, found 184.1526.

Cyclization of (2R*,3*S)-2-Ethyl-2,3-epoxypentyl 2-[(Tributylstannyl)methyl]-2-propenyl Ether (2h) with Titanium(IV) Chloride.** By use of the general procedure described above, **2h** (303 mg, 0.783 mmol) was cyclized over 25 min to provide **(3*R**,4*R**)-3,4-diethyl-3-hydroxy-6-methyleneoxepane (4h)** as a clear, colorless liquid (92.9 mg, 0.540 mmol, 69%), isolated by flash chromatography (18% EtOAc in hexanes on silica gel). ^{1}H NMR ($CDCl_3$): δ 4.94 (m, 2 H), 4.59 (d, J = 13.0 Hz, 1 H), 4.44 (d, J = 13.0 Hz, 1 H), 3.79 (d, J = 11.2 Hz, 1 H), 3.89 (d, J = 11.2 Hz, 1 H), 2.67 (s, 1 H), 2.20–1.45 (m, 7 H), 0.95 (t, J = 7.1 Hz, 3 H), 0.92 (t, J = 7.2 Hz, 3 H). ^{13}C NMR ($CDCl_3$): δ 143.99, 121.97, 77.03, 74.51, 74.43, 44.75, 42.40, 24.24, 23.24, 19.30 (2C). FT-IR (neat): 3470, 2995, 1600, 1469, 1375, 1230, 1000, 880 cm^{-1}. Exact mass calcd for $C_{11}H_{20}O_2$ 184.1545, found 184.1543.

Cyclization of 2,3-Diethyl-2,3-epoxypentyl 2-[(Tributylstannyl)methyl]-2-propenyl Ether (2i) with Titanium(IV) Chloride. By use of the general procedure described above, **2i** (169 mg, 0.337 mmol) was cyclized over 5 min to provide **3-hydroxy-3,4,4-triethyl-6-methyleneoxepane (4i)** as a clear, colorless liquid (53.1 mg, 0.250 mmol, 74%), isolated by flash chromatography (12% EtOAc in hexanes on silica gel). ^{1}H NMR ($CDCl_3$): δ 4.93 (b s, 1 H), 4.87 (b s, 1 H), 4.34 (d, J = 9.8 Hz, 1 H), 4.13 (d, J = 9.8 Hz, 1 H), 3.48 (d, J = 13.4 Hz, 1 H), 3.18 (d, J = 13.4 Hz, 1 H), 2.56 (d, J = 12.8 Hz, 1 H), 2.32 (d, J = 12.8 Hz, 1 H), 2.18–1.56 (m, 7 H), 1.10–0.86 (m, 9 H). ^{13}C NMR ($CDCl_3$): δ 141.05, 119.06, 76.44, 74.23, 72.08, 44.13, 41.01, 32.49, 31.00, 25.15, 24.84, 19.85, 19.23. FT-IR (neat): 3510, 2990, 1595, 1555, 1445, 1385, 1210, 1010, 890 cm^{-1}. Exact mass calcd for $C_{13}H_{22}O$ (M − 18) 194.1670, found 194.1632.

Cyclization of *trans*-1,2-Epoxy-3-[[2-[(tributylstannyl)methyl]-2-propenyl]oxy]cyclohexane (17) with Titanium(IV) Chloride. By use of the general procedure described above, **17** (128 mg, 0.298 mmol) was cyclized over 45 min to provide **19** as a clear, colorless liquid (30.7 mg, 0.197 mmol), 66%, isolated by flash chromatography (18% EtOAc in hexanes on silica gel). Gas–liquid chromatographic analysis of the purified material indicated a chemical purity of 97%. ^{1}H NMR ($CDCl_3$): δ 4.86 (b s, 1 H), 4.82 (b s, 1 H), 4.17 (d, J = 10.6 Hz, 1 H), 3.99 (d, J = 10.6 Hz, 1 H), 3.76 (m, 2 H), 2.78 (d, J = 13.9 Hz, 1 H), 2.25 (dd, J = 0.95, 13.9 Hz, 1 H), 1.99–1.19 (m, 8 H). ^{13}C NMR ($CDCl_3$): δ 142.35, 109.22, 78.22, 74.35, 71.03, 53.02, 44.27, 34.01, 28.77, 26.43. FT-IR ($CHCl_3$): 3510, 2990, 1600, 1475, 1335, 1210, 1000, 910 cm^{-1}. Exact mass calcd for $C_{10}H_{16}O_2$ 168.1150, found 168.1163.

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Registry No. **1a**, 120741-70-0; **1b**, 120741-71-1; **1c**, 120741-72-2; **1d**, 120741-73-3; **1e**, 120741-86-8; **1f**, 120741-86-8; **1j**, 120741-75-5; **1k**, 120741-76-6; **2a**, 120741-77-7; **2b**, 120741-78-8; **2c**, 120741-79-9; **2d**, 120741-80-2; **2e**, 120741-81-3; **2f**, 120741-82-4; **2g**, 120741-83-5; **2h**, 120741-84-6; **2i**, 120741-85-7; **3a**, 120741-88-0; **3b**, 120741-90-4; **3c**, 120741-92-6; **3d**, 120741-94-8; **3e**, 120741-95-9; **3j**, 120741-97-1; **3k**, 120741-99-3; **4a**, 120741-89-1; **4b**, 120741-91-5; **4c**, 120741-93-7; **4d**, 120771-34-8; **4e**, 120741-96-0; **4f**, 120741-87-9; **4g**, 120742-02-1; **4h**, 120742-03-2; **4i**, 120742-04-3; **4j**, 120741-98-2; **4k**, 120771-24-6; **17**, 120742-05-4; **19**, 120742-01-0; (2*R**,3*S**)-2,3-epoxyhexanol, 90528-63-5; methyl 2-[(tributylstannyl)methyl]-2-propenesulfonate, 120742-00-9.

Asymmetric Induction in Intramolecular Ene Reactions of Chiral 1,7-Dienes: A Diastereo- and Enantioselective Synthesis of Substituted Cyclohexanes[1]

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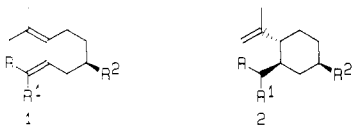
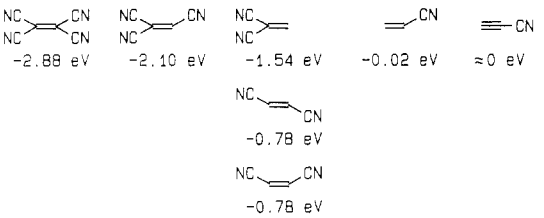
The asymmetric induction in intramolecular thermal and Lewis acid catalyzed ene reactions of chiral 1,7-dienes **9** activated by two electron-withdrawing groups on the enophile is studied. The cycloadducts resulting from intramolecular ene, sequential ene, and hetero-Diels–Alder reactions are characterized and the ratio of the diastereomers obtained is determined. Knoevenagel condensation of citronellal (**8**) with acyclic 1,3-dicarbonyl and analogous compounds **7** gave the corresponding 1,7-dienes **9**, which cyclized under thermal conditions and with $ZnBr_2$ to the trans-substituted ene products **15** and **16**, the hetero-Diels–Alder products **17** and **18**, and the sequential ene products **19** and **20**, depending on the electron-withdrawing groups at the terminus. Derivatives of malonate **9a–c** led exclusively to **15** and **16**, whereas those of acetylacetone **9f** gave **17b** and **18b**. Lewis acid catalyzed reaction of **9g/9h** afforded mainly **19b**. The ratio of the diastereomeric pairs **15/16**, **17/18**, and **19/20** with de values = 74.0–84.0% at 180 °C and 82.0–95.0% at 25 °C is governed by the preference of an equatorial orientation of the methyl group at C-5 in the proposed chairlike transition state and the steric demand of the electron-withdrawing groups in the enophile. The ene adducts are of value as decalin precursors in the synthesis of natural products.

The development of regio- and stereoselective C–C bond-forming reactions is a key objective in organic synthesis. The intramolecular ene reaction has recently received considerable attention[2] and offers a valuable method for the formation of carbo- and heterocyclic cyclopentanes.[2,3] However, with unreactive enes and enophiles, the ene reaction is unsatisfactory, since harsh reaction conditions are required and yields and selectivities are generally low. Structurally modified enes[4] and enophiles as well as the elegant activation of the enophile by means of Lewis acids[5] can be useful to increase the reactivity in ene reactions. Applications of these concepts have been proven particularly successful in the diastereoselective formation of cyclopentanes.[2,3]

In the course of an investigation toward the synthesis of enantiomerically pure sesquiterpenoid natural products, we became interested in the diastereoselective formation of trans-substituted cyclohexanes of type **2**. Retrosynthetic analysis shows that it should be possible to synthesize cyclohexanes **2** by intramolecular ene reactions of 1,7-dienes **1**. In contrast to the intramolecular ene reaction of 1,6-dienes, little is known about this type of ene reaction. To our knowledge, the first example of an intramolecular ene reaction of a 1,7-diene was reported by Huntsman et al.[6] Reaction of **3** at 490 °C yielded disubstituted cyclohexane **4** in 25% yield probably as a mixture of diastereomers. From this and other studies[2,6] on the intramolecular ene cyclization of 1,7-dienes, it is clear that thermal ene reactions of nonactivated 1,7-dienes proceed non-



Scheme I. LUMO Energies of Selected Alkenes and Alkynes[8] (1 eV = 96.5 kJ = 23 kcal)



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